CYP2D6: gefitinib 4634-4636

AUC = area under the concentration-time curve, CI = confidence interval, Cl_{or} = oral clearance, IM = intermediate metaboliser (gene dose 0.25-1) (decreased CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, OR = odds ratio, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, SmPC = Summary of Product Characteristics, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (increased CYP2D6 enzyme activity)

Brief summary and justification of choices:

Gefitinib is mainly metabolised by CYP3A4 and to a lesser extent by CYP2D6. Gefitinib is converted by CYP2D6 to O-desmethylgefitinib, which is 14x less active than gefitinib.

Genetic variants in CYP2D6 can result in a decreased CYP2D6 enzyme activity (intermediate metabolisers (IM)), an absent CYP2D6 enzyme activity (poor metabolisers (PM)) or an increased CYP2D6 enzyme activity (ultra-rapid metabolisers (UM)).

IM and PM: Studies showed effects of CYP2D6 gene variants on gefitinib kinetics (Nio 2022, Chhun 2009, and Swaisland 2006). However, the studies showing CYP2D6 gene variants to affect adverse events (increased incidence of hepatotoxicity and rash in IM), also showed that these clinical effects were reversible and could be managed well (Kwok 2022, Sugiyama 2015, and Suzumura 2012). For this reason, it is acceptable not to prevent these clinical effects, but to manage them in the patients developing these clinical effects. The only study that investigated effectiveness found a decrease in median progression free survival for *10-allele carriers (NM+IM) versus non-carriers (Fan 2022). However, there is no study confirming this result for IM versus NM or for PM versus NM. The only other study investigating response found no effect of CYP2D6 genotype (Hirose 2016). The KNMP Pharmacogenetics Working Group considers confirmation of these results to be necessary, because, especially for an oncolytic with a relatively low incidence of adverse events necessitating pausing of therapy, higher exposure would be expected to result in higher instead of lower effectiveness. For these reasons, the KNMP Pharmacogenetics Working Group decided that the CYP2D6 IM-gefitinib and CYP2D6 PM-gefitinib interactions do not necessitate adjustment of therapy (yes/no-interactions).

UM: There is no literature on the use of gefitinib by UM. However, since an increase in exposure is observed for IM and PM, a decreased in exposure is expected in UM. The minimum effective trough concentration of gefitinib has been determined to be 200 µg/L (tdm-monografie.org, accessed 23 January 2025). Therefore, based on theoretical grounds, the risk of ineffectiveness is increased in UM. For this reason, the KNMP Pharmacogenetics Working Group decided that the CYP2D6 UM-gefitinib interaction requires action (yes/yes-interaction). The recommendation is to perform therapeutic drug monitoring and to either increase the gefitinib dose or choose an alternative when the gefitinib trough concentrationbepaal is below 200 µg/L. Erlotinib is not metabolised by CYP2D6.

A more detailed justification of choices for IM and PM is given below:

There are significant kinetic effects for both PM and IM (Nio 2022, Chhun 2009, and Swaisland 2006). The exposure doubled for PM (Chhun 2009 and Swaisland 2006). However, there is no evidence that gefitinib has a narrow therapeutic range. No upper limit of the therapeutic range has been defined for gefitinib (tdm-monografie.org, accessed 23 January 2025). In addition, gefitinib was safe in clinical studies at a dose twice the standard dose of 250 mg/day.

No research into the clinical effects has been performed for PM. There is limited evidence for clinical effects for IM (Kwok 2022, Sugiyama 2015, and Suzumura 2012).

For IM, Suzumura 2012 and Takimoto 2013 did not find an increased risk of grade ≥ 2 hepatotoxicity and Kwok 2022 and Hirose 2016 did not find an increased risk of hepatotoxicity. Takimoto, 2013 found an elevated risk on re-initiation of gefitinib in IM patients using CYP3A4 inhibitors. However the use of CYP3A4 inhibitors is not recommended in patients using gefitinib. Sugiyama 2015 found an increased risk of hepatotoxicity grade ≥ 3 for IM (OR = 14.5). However, the authors indicated that this side effect could be well managed. 44% of all patients with gefitinib-induced hepatotoxicity did not develop a second episode of grade ≥ 3 hepatotoxicity upon re-initiation of gefitinib. It has not been determined whether this percentage is similar for IM patients. In addition, none of 9 patients including 2 IM redeveloped severe hepatotoxicity after being switched to erlotinib. Although erlotinib is reported to give a lower risk of severe hepatotoxicity, it does not give a lower risk of total severe toxicity than gefitinib, indicating the risk of severe skin rash and severe diarrhoea to be increased in erlotinib users compared to gefitinib users (SmPC's of gefitinib and erlotinib). For this reason, it is not known whether IM and PM patients would benefit from a priori avoiding gefitinib and choosing erlotinib instead.

Hirose 2016 found no increased risk of rash for IM. Kwok 2022 found an increased risk of rash and Suzumura 2012 found an increased risk of grade ≥ 2 rash for IM. However, the Suzumura 2012 stated that this side effect could generally be controlled. Adjusting the therapy will therefore not generally be necessary for IM. Erlotinib, which is not metabolised by CYP2D6, was associated with a twofold higher incidence of grade ≥ 2 rash in the same study. Erlotinib therefore does not seem an appropriate alternative for patients with rash. It is uncertain whether efficacy would be retained when the dose of gefitinib would be reduced. Two studies found associations between rash and survival.
For IM, Suzumura 2012 did not find a significantly increased risk of grade ≥ 2 diarrhoea, Hirose 2016 did not find an increased risk of diarrhoea and Kwok 2022 did not find an increased risk of gastrointestinal side effects.
This means that there is no evidence of an increased risk of unacceptable side effects in IM patients. There are no data at all for PM. Moreover, there is no evidence of positive effects of an alternative or dose reduction.
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.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping before starting gefitinib to be potentially beneficial for drug efficacy. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the KNMP Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 0 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points) (see also the clinical implication score tables at the end of this risk analysis):
For gefitinib, action is only needed for UM. However, since there are no studies investigating UM using gefinitib, no severe clinical effects were observed in UM using gefitinib. This results in a score of 0 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (only points for CTCAE grade ≥ 3).
The lack of a severe clinical effect also results in a score of 0 of the maximum of 3 points for the second and third criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 and the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3).
The Summary of Product Characteristics (SmPC) of gefitinib does not mention the CYP2D6 UM phenotype. This results in 0 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC.

The table below uses the KNMP definitions for NM, PM, IM and UM. As a result, the definitions of NM, PM, IM and UM in the table below can differ from the definitions used by the authors in the articles.

Source	Code	Effect	Comments
ref. 1 Fan R et al. Effects of p450 polymorphisms on the clinical outcomes of gefitinib treatment in patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer. Genet Test Mol Biomarkers 2022;26:582-8. PMID: 36577124.	3	112 patients with EFGR mutation positive non-small cell lung cancer were treated with gefitinib. The median follow-up period was 10 months (1-48 months). Comedication with CYP2D6 inhibitors was not excluded. In addition, gene mutation of EGFR was determined in tumour tissue, and plasma samples for detection of CYP2D6 gene variants were not reported, suggesting that CYP2D6 gene variants were also detected in tumour tissue. Deletion of CYP2D6 genes has been shown previously in tumour tissue, which would result in part of *1/*10 being detected as either *1/*1 or *10/*10. Indeed, observed prevalences of *1/*1 and *10/*10 were slightly higher (31% versus 27% and 27% versus 23%, respectively) and observed prevalence of *1/*10 slightly lower (42% versus 50%) in this patient group than calculated based on *10-frequency. For this reason, it cannot be excluded that for part of the patients, the determined genotype differed from the germline genotype (with the latter determining CYP2D6 activity in metabolising organs, like liver and gut). Multivariate analysis, adjusting for sex, age, smoking history, drinking history, EGFR mutation status and tumour node stage, was performed. Genotyping:	Author's conclusion: "Genotypes of the drug-metabolizing enzymes rs1065852 (CYP2D6 *10) and rs2242480 (CYP3A4 *1G) have an impact on the prognosis of patients with non-small cell lung cancer treated with gefitinib."

<table>
<tr><td>ref. 1, continuation</td><td>IM+NM: E</td><td>- 35x *1/*1 (gene dose 2)
- 47x *1/*10 (gene dose 1.25)
- 30x IM (*10/*10, gene dose 0.5)

Results:<table><tr><td colspan="2">Median progression free survival compared to *1/*1 (median progression free survival of 350 days):</td></tr><tr><td rowspan="2">IM+*1/*10</td><td>x 0.82 (S)</td></tr><tr><td>CYP2D6 IM+*1/*10 was an independent factor for a worse prognosis (HR = 1.61; 95% CI: 1.01-2.58 (S)).</td></tr></table>
NOTE: Genotyping was performed for *10.This is the most important gene variant in this Chinese population.</td><td></td></tr>
<tr><td>ref. 2
Nio Y et al.
Pharmacokinetics of gefitinib in elderly patients with EGFR-mutated advanced non-small cell lung cancer: a prospective study.
BMC Pulm Med 2022;22:454.
PMID: 36451169.</td><td>3

IM: A</td><td>18 patients, aged 75 years or older, received a single dose of 250 mg gefitinib. All patients had adequate liver and kidney function.
Comedication affecting CYP3A4, such as proton-pump inhibitors and histamine H2 receptor antagonists, was excluded, but comedication affecting CYP2D6 was not.
The authors indicate that analyses were exploratory.

Genotyping:
- 4x *1/*1 (gene dose 2)
- 9x gene dose 1.25 or 1 (8x *1/*10 and 1x *1/*5)
- 5x IM (*10/*10 or *5/*10, gene dose 0.5 or 0.25)

Results:<table><tr><td colspan="4">Results compared to *1/*1:</td></tr><tr><td></td><td>IM</td><td>gene dose 1.25 or 1</td><td>value for *1/*1</td></tr><tr><td rowspan="2">$AUC_{0\text{-}48h}$ gefitinib</td><td>x 2.28</td><td>x 1.72</td><td rowspan="2">5.52 µM.h</td></tr><tr><td colspan="2">S for IM versus (gene dose 1.25 or 1) versus *1/*1.</td></tr><tr><td rowspan="2">$AUC_{0\text{-}48h}$ O-desmethyl-gefitinib</td><td>x 0.11</td><td>x 0.24</td><td rowspan="2">28.2 µM.h</td></tr><tr><td colspan="2">S for IM versus (gene dose 1.25 or 1) versus *1/*1.</td></tr></table>
NOTE: Genotyping was for *5 and *10. These are the most important gene variants alleles in this Japanese population.</td><td>Author’s conclusion: ”The CYP2D6 genotype was associated with CYP2D6-mediated metabolism of gefitinib to O-desmethyl gefitinib.”

AUC gefitinib versus *1/*1:
IM (gene dose 0.5 or 0.25): 228%</td></tr>
<tr><td>ref. 3
Kwok WC et al.
Association of genetic polymorphisms of CYP3A4 and CYP-2D6 with gefitinib-induced toxicities.
Anticancer Drugs 2022;33:1139-44.
PMID: 35946566.</td><td>3</td><td>151 patients were treated with gefitinib. CYP2D6 *8 genotyping results were missing for 2 patients and CYP2D6 *10 genotyping results for 20 patients.
Cutaneous adverse events occurred in 74% of patients (grade 3 in 2% of patients), gastrointestinal adverse events in 35% (no grade 3 or 4), and hepatotoxicity in 34% (grade 3 in 5% of patients). In the majority of cases the severity of the adverse event was grade 1.
Comedication affecting CYP3A4 or CYP2D6 was not excluded.
Analysis was by univariate logistic regression. Multivariate analysis of hepatotoxicity adjusted for the presence of liver metastasis.

Genotyping:<table><tr><td>*4</td><td>*8</td><td>*10</td><td>*41</td></tr><tr><td>- 150x no *4</td><td>- 143x no *8</td><td>- 29x no *10</td><td>- 140x no *41</td></tr><tr><td>- 1x *4 heterozygote</td><td>- 5x *8 heterozygote</td><td>- 65x *10 heterozygote</td><td>- 11x *41 heterozygote</td></tr><tr><td></td><td>- 1x *8/*8</td><td>- 37x *10/*10</td><td></td></tr></table></td><td>Author’s conclusion: ”CYP2D6*41 CT, CYP2D6*10 AA and CYP3A4*1/*1G TT genotypes may be associated with increased risks of gefitinib-induced toxicities in the liver, skin and gastrointestinal tract.”</td></tr>
</table>

<table>
<tr>
<td>ref. 3, continuation</td>
<td>IM: AA
PM: AA

IM: B

NM: B</td>
<td>Results:
<table>
<tr><td colspan="3">Results compared to no *4, no *8, no *10 (for cutaneous adverse events), *10/*10 (for hepatotoxicity or gastro-intestinal adverse events), or no *41:</td></tr>
<tr><td></td><td>genotype</td><td></td></tr>
<tr><td rowspan="7">cuta-neous adverse events</td><td>*4 heterozygote</td><td>NS</td></tr>
<tr><td>*8 heterozygote</td><td>NS</td></tr>
<tr><td>*8/*8</td><td>NS</td></tr>
<tr><td>*10 heterozygote</td><td>NS</td></tr>
<tr><td>*10/*10</td><td>OR = 3.368 (95% CI: 1.000-11.345) (S)</td></tr>
<tr><td colspan="2">Note: There were no indications for a gene-dose effect. The ratios of the percentage of patients with cutaneous adverse events were 1.7:2.5:1 for *10/*10:*10 heterozygote:no *10.</td></tr>
<tr><td>*41 heterozygote</td><td>NS</td></tr>
<tr><td rowspan="6">gastro-intesti-nal adverse events</td><td>*4 heterozygote</td><td>NS</td></tr>
<tr><td>*8 heterozygote</td><td>NS</td></tr>
<tr><td>*8/*8</td><td>NS</td></tr>
<tr><td>*10 heterozygote</td><td>trend for a smaller risk of gastrointestinal adverse events (p = 0.064) (NS)</td></tr>
<tr><td>*1/*1</td><td>NS</td></tr>
<tr><td>*41 heterozygote</td><td>NS</td></tr>
<tr><td rowspan="7">hepato-toxicity</td><td>*4 heterozygote</td><td>NS</td></tr>
<tr><td>*8 heterozygote</td><td>NS</td></tr>
<tr><td>*8/*8</td><td>NS</td></tr>
<tr><td>*10 heterozygote</td><td>NS</td></tr>
<tr><td>*1/*1</td><td>NS</td></tr>
<tr><td rowspan="2">*41 heterozygote</td><td>OR = 3.818 (95% CI: 1.062-13.722) (S)</td></tr>
<tr><td>Results were similar after adjustment for the pre-sence of liver metastasis (OR = 3.773 (95% CI: 1.046-13.610) (S)).</td></tr>
</table>

NOTE: Genotyping was for *3, *4, *6, *8, *10, and *41. Together with *5, these are the most common alleles in this Chinese population. *3 and *6 were not found in this patient group.</td>
<td></td>
</tr>
<tr>
<td>ref. 4
Hirose T et al. Association of phar-macokinetics and pharmacogenomics with safety and effi-cacy of gefitinib in patients with EGFR mutation positive advanced non-small cell lung cancer. Lung Cancer 2016;93:69-76. PubMed PMID: 26898617.</td>
<td>3</td>
<td>33 patients were treated with gefitinib 250 mg/day.
Skin toxicity occurred in 68% of patients, diarrhoea in 46%, and liver toxicity in 63%. In the majority of cases the severity of the adverse event was grade 1. Eight patients had eleva-tion of aminotransferase grade 3 and one patient died of drug-induced interstitial lung disease. No other patients had toxicity grade ≥ 3.
A partial or complete response occurred in 82.9% of patients and 88.6% had either a response or stable disease.
Comedication affecting CYP3A4, such as proton-pump inhi-bitors and histamine H2 receptor antagonists, was excluded, but comedication affecting CYP2D6 was not.
The authors indicate that the number of patients in the study was too small for the association of pharmacogenomics with the toxicity and efficacy of gefitinib to be precisely determi-ned.

Genotyping:
- 12x *1/*1</td>
<td>Author’s conclusion: ”The pharmacokine-tics and pharmaco-genomics were not associated with significantly different toxicities, response rates, or survival times with gefitinib.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 4, continuation</td>
<td>IM: AA</td>
<td>
- 16x gene dose 1.25 or 1 (*1/*10 or *1/*36)
- 5x IM or PM (*10/*10, *10/*36 or *36/*36)

Results:
<table>
<tr><td colspan="4">Results compared to *1/*1:</td></tr>
<tr><td></td><td>IM or PM</td><td>gene dose 1.25 or 1</td><td>value for *1/*1</td></tr>
<tr><td>skin toxicity</td><td colspan="2">no difference between groups (NS)</td><td></td></tr>
<tr><td>diarrhoea</td><td colspan="2">no difference between groups (NS)</td><td></td></tr>
<tr><td>liver toxicity</td><td colspan="2">no difference between groups (NS)</td><td></td></tr>
<tr><td>% of patients with response</td><td colspan="2">no difference between groups (NS)</td><td></td></tr>
<tr><td>% of patients with response or stable disease</td><td colspan="2">no difference between groups (NS)</td><td></td></tr>
<tr><td>$AUC_{0\text{-}24h}$ gefitinib (at day 1)</td><td>x 1.30 (NS)</td><td>x 1.14 (NS)</td><td>4738 ng.h/ml</td></tr>
<tr><td rowspan="2">gefitinib trough concentration (at day 8)</td><td>x 1.65 (NS)</td><td>x 1.16 (NS)</td><td rowspan="2">371 ng/ml</td></tr>
<tr><td colspan="2">Trend for (IM or PM) versus (gene dose 1.5, 1.25 or 1) versus *1/*1 (p = 0.10).</td></tr>
<tr><td colspan="4">This study did not find a correlation of adverse events or efficacy with AUC, trough concentration or maximum concentration of gefitinib either.
The patient with interstitial lung disease had the highest AUC and maximum concentration and the one but highest trough concentration of all patients. This patient was not homozygous for a variant CYP2D6 allele.</td></tr>
</table>

NOTE: Genotyping was performed for *10 and *36. Together with *5, these are the most common alleles in this Japanese population.
NOTE: The frequency of *10 is more than 10-fold higher in Japanese than the frequency of *36. So, IM or PM will most likely be only IM (no *36/*36) and gene dose 1.25 or 1.0 will be predominantly gene dose 1.25 (*1/*10).
</td>
<td>AUC gefitinib versus *1/*1:
IM (+ PM): 130%</td>
</tr>
<tr>
<td>ref. 5
Sugiyama E et al. Impact of single nucleotide polymorphisms on severe hepatotoxicity induced by EGFR tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring EGFR mutations. Lung Cancer 2015;90:307-13. PubMed PMID: 26323212.</td>
<td>4</td>
<td>
60 patients were treated with gefitinib.
Severe hepatotoxicity developed in 19 patients (32%) after a median time of 1.8 months (range 0.1-9.7 months). According to the Common Terminology Criteria for Adverse Events, severe hepatotoxicity was defined as grade 3 or higher transaminase elevation (alanine aminotransferase (ALT) ≥ 210 U/L or aspartate aminotransferase (AST) ≥ 165 U/L) and any grade of total bilirubin elevation (≥ 1.2 mg/dL), or a grade 2 or higher transaminase elevation (ALT ≥ 126 U/L or AST ≥ 99 U/L) and a grade 2 or higher total bilirubin elevation (≥ 1.8 mg/dL).
Skin rash developed in 80% of patients and diarrhoea in 20%, but all cases were grade 1.
Relevant co-medication and patients with a history of liver disease were excluded.
Associations with severe hepatotoxicity were evaluated using multivariate logistic regression analysis.

Genotyping:
- 55x gene dose 2, 1.5, 1.25 or 1 (10x gene dose 2, 36x gene dose 1.25 (*1/*10 or *2/*10), 8x gene dose 1 (*1/*5 or *2/*5), 1x gene dose 1 or 1.5 (*1/*14))
</td>
<td>Author’s conclusion: ”Evaluation of SNPs in CYP3A5 and CYP2D6 can effectively predict severe hepatotoxicity induced by gefitinib. Erlotinib can be used as an alternative treatment for patients who develop gefitinib-induced severe hepatotoxicity.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 5, continuation</td>
<td>IM: D</td>
<td>- 5x IM (3x *10/*10, 2x *5/*10)

Results:
<table>
<tr><td colspan="3">Results compared to gene dose 2, 1.5, 1.25 or 1:</td></tr>
<tr><td></td><td>IM</td><td>value for gene dose 2, 1.5, 1.25 or 1</td></tr>
<tr><td>hepatotoxicity grade ≥ 3</td><td>OR = 14.5 (95% CI: 1.6-346.5) (S)

21% of the patients with hepatotoxicity grade ≥ 3 was CYP2D6 IM (*10/*10 or *5/*10).</td><td>27.3% of patients</td></tr>
<tr><td colspan="3">9 of 16 patients (56%) with severe hepatotoxicity developed severe hepatotoxicity again after re-administration of gefitinib.
9 patients including 2 CYP2D6 IM (*10/*10 or *5/*10) were switched to erlotinib, either after the first (n = 3) or second episode (n = 6) of gefitinib-induced severe hepatotoxicity. None of these patients developed severe hepatotoxicity on erlotinib. One patient with a PM phenotype for both CYP3A5 and UGT1A1 and without a CYP2D6 *10/*10 or *5/*10 genotype exhibited a grade 3 elevation in total bilirubin after switching to erlotinib.</td></tr>
</table>
NOTE: genotyping was performed for *2, *4, *5, *10, *14 and *41. In 2015, *14 included both *14a (now termed *114) and *14b (now termed *14). These are the most common alleles in this Japanese population. *4 and *41 were not found in this patient group.</td>
<td></td>
</tr>
<tr>
<td>ref. 6
Kobayashi H et al. Relationship among gefitinib exposure, polymorphisms of its metabolizing enzymes and transporters, and side effects in Japanese patients with non-small-cell lung cancer.
Clin Lung Cancer 2015;16:274-81.
PubMed PMID: 25554506.</td>
<td>3

NM+IM: AA</td>
<td>28 patients were treated with gefitinib 250 mg/day.
Plasma samples for determination of gefitinib pharmacokinetics were obtained in steady state (at day 14 of therapy).
A total of 55% of patients developed hepatotoxicity (39% grade 1, 3% grade 2, 10% grade 3, and 3% grade 4).
A total of 48% of patients developed diarrhoea (32% grade 1, 13% grade 2, and 3% grade 3).
A total of 65% of patients developed skin rash (29% grade 1 and 36% grade 2).
Relevant co-medication was not excluded.

Genotyping:
- 9x gene dose 2
- 19x gene dose 0.25-1.25 (11x gene dose 1.25, 3x gene dose 1, 3x gene dose 0.5, 2x gene dose 0.25)

Results:
<table>
<tr><td colspan="3">Results compared to gene dose 2:</td></tr>
<tr><td></td><td>gene dose 0.25-1.25</td><td>value for gene dose 2</td></tr>
<tr><td>hepatotoxicity</td><td>NS</td><td>44% of patients</td></tr>
<tr><td>diarrhoea</td><td>NS</td><td>56% of patients</td></tr>
<tr><td>skin rash</td><td>NS</td><td>44% of patients</td></tr>
<tr><td>median $AUC_{0\text{-}24h}$ gefitinib</td><td>x 1.14 (NS)</td><td>9757 ng.h/ml</td></tr>
<tr><td>median gefitinib trough concentration</td><td>x 1.47 (NS)</td><td>245 ng/ml</td></tr>
<tr><td colspan="3">This study found a correlation of hepatotoxicity and diarrhoea, but not of skin rash, with AUC and trough concentration of gefitinib.</td></tr>
</table></td>
<td>Author’s conclusion: ”The side effects from gefitinib were related to exposure but not genetic polymorphism. Therefore, therapeutic drug monitoring after beginning gefitinib therapy rather than the analysis of polymorphism before initiating therapy might be beneficial.”</td>
</tr>
</table>

ref. 6, continuation		NOTE: genotyping was performed for *5 and *10. These are the most common alleles in this Japanese population.	
ref. 7 Takimoto T et al. Polymorphisms of CYP2D6 gene and gefitinib-induced hepatotoxicity. Clinical Lung Cancer 2013;14:502-7. PubMed PMID: 23664723.	3 IM: AA NM+IM: B	55 patients developed hepatotoxicity (grade ≥ 2 transaminase elevation) as a result of 250 mg/day gefitinib therapy. 30 of the patients had ≥ 3 hepatotoxicity. Relevant co-medication was not excluded. 8 patients used CYP3A4 inhibitors and 5 patients used CYP2D6 inhibitors. Genotyping: - 17x NM (11x *1/*1, 5x *1/*2 and 1x *1/*39) - 38x NM+IM (24x NM (19x *1/*10, 5x *2/*10) + 14x IM (4x *1/*5, 1x *5/*10, 9x *10/*10)) Patients with hepatotoxicity versus the general population: - No difference in the frequency of individual genotypes and of all genotypes including *5 and *10 combined (NS) NM+IM versus NM: - No difference in the time to hepatotoxicity (NS) - No difference in the severity of hepatotoxicity (NS) - No difference in the incidence of hepatotoxicity after re-initiation of lower-dose gefitinib (NS) - All 4 NM+IM patients among 7 patients using CYP3A4 inhibitors again developed hepatotoxicity on re-initiation of lower-dose gefitinib while none of the 3 NM patients did (S) NOTE: genotyping was performed for *2, *4, *5, *10 and *39. These are the most common alleles in this Japanese population.	Authors' conclusion: 'Reduced function of CYP2D6 may partly account for gefitinib-induced hepatotoxicity when CYP3A4 is inhibited. Erlotinib could be safely used in patients with decreased CYP2D6 activity even after they experienced gefitinib-induced hepatotoxicity.'
ref. 8 Suzumura T et al. Reduced CYP2D6 function is associated with gefitinib-induced rash in patients with non-small cell lung cancer. BMC Cancer 2012;12:568. PubMed PMID: 23207012.	3 IM: C	206 patients were treated with gefitinib. Relevant co-medication was not excluded. DNA genotyping was mainly performed using formaldehyde-fixed paraffin-embedded tissue: - 156x NM+IM (*1/*1, *1/*2, *2/*2, *1/*10, *2/*10, *1/*14A, *1/not known or *2/not known) - 50x IM (*10/*10) IM versus NM+IM: - Increased risk of grade ≥ 2 rash (OR = 2.3; 95% CI: 1.1-4.8) (S) - No increased risk of grade ≥ 2 diarrhoea and of grade ≥ 2 liver impairment (NS) The authors reported that the side effects in the study were generally controllable, apart from interstitial lung disease. The authors also stated that two recent studies found an association between rash and survival for gefitinib monotherapy. NOTE: genotyping was performed for *2, *10, *14a and *14b. Together with *5, these are the most common alleles in this Japanese population.	Author's conclusion: 'The frequency of rash was significantly higher in patients with reduced CYP-2D6 activity who treated with gefitinib compared to patients with functional CYP2D6. CYP2D6 phenotypes are a risk factor for the development of rash in response to gefitinib therapy.'
ref. 9 Chhun S et al. Gefitinib-phenytoin interaction is not correlated with the C-erythromycin breath test in healthy male volunteers. Br J Clin Pharmacol 2009;68:226-37. Pubmed PMID: 19694743.	3 IM: A PM: AA	17 healthy volunteers received a single dose of gefitinib 250 mg. Relevant co-medication was excluded. Genotyping: - 9x NM (*1/*1) - 7x IM (5x 1/*4, 2x*1/*5) - 1x PM (*4/*4) PM versus IM versus NM: - Decreased Cl_{or} (54 versus 79 versus 118 L/hour) (S for IM versus NM and for IM+PM versus NM) NOTE: genotyping was performed for *3 to *6. These are the	Authors' conclusion: 'The CYP2D6 genotype was slightly but significantly related to gefitinib clearance (P = 0.04).' Cl_{or} gefitinib versus NM: IM 67% PM: 46%

ref. 9, continuation		most common alleles in this European population.	
ref. 10 Swaisland HC et al. Exploring the relationship between expression of cytochrome P450 enzymes and gefitinib pharmacokinetics. Clin Pharmacokinet 2006;45:633-44. Pubmed PMID: 16719544.	3 PM: A	30 genotype-selected, healthy volunteers were given a single dose of gefinitib 250 mg. Relevant co-medication was excluded. Genotypes: - 15x NM+IM (4x NM (3x *1/*2, 1x *2/*41) + 11x IM (7x *1/*4, 2x *2/*4, 1x *1/*3, 1x *2/*5)) - 15x PM (8x *4/*4, 2x *4/*5, 2x *3/*4, 1x *4/*6, 1x *3/*5, 1x *4/*4x2) PM versus NM+IM: - Gefitinib AUC increased by 114% (from 1430 to 3060 ng.hour/mL) (S) - Oral clearance decreased by 53% (from 2910 to 1360 mL/min) (S) - Gefitinib $t_{1/2}$ increased by 46% (from 23.3 to 34.1 hours) (NS) - The metabolite O-desmethylgefitinib was not detectable for PM Four mild adverse events were reported, all in the PM group. The investigators did not consider these to be caused by gefitinib. There were no clinically relevant changes in lab values, vital signs and ECGs. The authors stated that gefitinib 250 mg/day and 500 mg/day were found to be safe in extensive clinical studies. NOTE: genotyping was performed for *2 to *6, *9, *10, *41 and gene duplication. These are the most common alleles in this European population.	Authors' conclusion: 'The lack of measurable levels of O-desmethylgefitinib in poor CYP2D6 metabolisers confirms that production of this metabolite is mediated by CYP-2D6. Although higher exposure to gefitinib occurs in individuals who are poor CYP2D6 metabolisers, genotyping prior to initiation of therapy and dosage adjustment are not warranted.'
ref. 11 SmPC Iressa (gefitinib) 17-07-2023.	0 PM: A	Dose: No specific dose adjustment is recommended in patients with known CYP2D6 poor metaboliser genotype, but these patients should be closely monitored for adverse events. Warning: In individual patients with CYP2D6 poor metaboliser genotype, treatment with a potent CYP3A4 inhibitor might lead to increased plasma levels of gefitinib. At initiation of treatment with a CYP3A4 inhibitor, patients should be closely monitored for gefitinib adverse reactions. Pharmacokinetics: The role of CYP2D6 in the metabolic clearance of gefitinib has been evaluated in a clinical trial in healthy volunteers genotyped for CYP2D6 status. In poor metabolisers no measurable levels of O-desmethylgefitinib were produced. The levels of exposure to gefitinib achieved in both the normal and the poor metaboliser groups were wide and overlapping, but the mean exposure to gefitinib was 2-fold higher in the poor metaboliser group. The higher mean exposure that could be achieved by individuals with no active CYP2D6 may be clinically relevant since adverse effects are related to dose and exposure.	exposure gefitinib versus NM: PM: 200%
ref. 12 SmPC Iressa (gefitinib), USA, 05-05-21.	0 PM: A	Pharmacokinetics: *CYP2D6 poor metabolizer*: CYP2D6 metabolizes gefitinib to O-desmethyl gefitinib in vitro. In healthy CYP2D6 poor metabolizers, O-desmethyl gefitinib concentration was not measurable and the mean exposure to gefitinib was 2-fold higher as compared to the normal metabolizers. This increase in exposure in CYP2D6 poor metabolizers may be clinically important because some adverse drug reactions are related to higher exposure of	exposure gefitinib versus NM: PM: 200%

ref. 12, continuation		gefitinib. No dose adjustment is recommended in patients with a known CYP2D6 poor metabolizer genotype, but these patients should be closely monitored for adverse reactions. The impact of CYP2D6 inhibiting drugs on gefitinib pharmacokinetics has not been evaluated. However, similar precautions should be used when administering CYP2D6 inhibitors with Iressa because of the possibility of increased exposure in these patients. An exploratory exposure response analysis showed an increase in the incidence of interstitial lung disease (ILD) with a greater than 2-fold increase in the gefitinib exposure.	

Risk group	CYP3A4 inhibitors, IM with CYP2D6 inhibitors

Comments:

- The study of Chen 2024 (Chen YR et al. Effect of genetic polymorphisms on the pharmacokinetics of gefitinib in healthy Chinese volunteers. Xenobiotica 2024;54:38-44. PMID: 38085693) was not included in the risk analysis, because only the effect of a gene variant not affecting CYP2D6 activity (rs1058164, which is both present in alleles with normal activity (*1 and *2) and in alleles with reduced or absent activity (e.g. *4, *8, and *10)) was investigated. The effect of *10 was not investigated, because there was a deviation from Hardy-Weinberg equilibrium for the causative gene variant.
  The study of Zhang 2018 (Zhang H et al. Association of variability and pharmacogenomics with bioequivalence of gefitinib in healthy male subjects. Front Pharmacol 2018;9:849. PMID: 30131694) was not included in the risk analysis, because only the effect of gene variants not affecting CYP2D6 activity (rs135840, rs1058164, rs1080989, rs1081003, rs1985842, rs2004511, rs2267447, rs28371702, rs28588594 and rs28735595) was investigated. Also rs1058164 for which the authors found an association with a high exposure does not affect CYP2D6 activity (see the comment above).
- The drug-drug interaction of CYP3A4 inhibitors with tyrosine kinase inhibitors (excl. ima/sora/vandetanib) in the G-Standaard (6858) recommends that CYP3A4 inhibitors are preferably switched in patients using a combination of gefitinib and CYP3A4 inhibitors. However, this therapeutic recommendation is only for strong CYP3A4 inhibitors, not moderately potent CYP3A4 inhibitors used in Takimoto, 2013 (amlodipine, nifedipine and diltiazem).

Date of literature search: 12 September 2024.

	Genotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	IM	4 E	yes	no	27 January 2025
	PM	3 A	yes	no	
	UM	-	yes	yes	

UM: signaal bij eerste uitgifte

Mechanism:
Gefitinib is mainly metabolised by CYP3A4 and to a lesser extent by CYP2D6. Gefitinib is converted by CYP2D6 to O-desmethylgefitinib, which is 14x less active than gefitinib. O-desmethylgefitinib is the primary metabolite in plasma.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	0+
Corresponding Clinical Implication Score:		Potentially beneficial