CYP2D6: gefitinib 4871/4872/4873

AUC = area under the concentration-time curve, CI = confidence interval, Cl_{or} = oral clearance, EM = extensive metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), IM = intermediate metaboliser (gene dose 0.5-1) (decreased CYP2D6 enzyme activity), NS = non-significant, OR = odds ratio, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose ≥ 3) (increased CYP2D6 enzyme activity)

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

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)).
Studies showed effects of CYP2D6 gene variants on gefitinib kinetics. However, the studies showing clinical effects of CYP2D6 gene variants (increased incidence of hepatotoxicity and rash in IM), also showed that these clinical effects were reversible and could be managed well. For this reason, it is acceptable not to prevent these clinical effects, but to manage them in the patients developing these clinical effects. For this reason, the KNMP Pharmacogenetics Working Group decides that the CYP2D6-gefitinib interactions do not necessitate adjustment of therapy (yes/no-interactions).
A more detailed justification of choices per CYP2D6 phenotype or phenotype group is given below.
IM and PM:

There are significant kinetic effects for both PM and IM. The AUC doubled for PM. However, there is no evidence that gefitinib has a narrow therapeutic range. 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.

For IM, Suzumura 2012 and Takimoto 2013 did not find an increased risk of grade ≥ 2 hepatotoxicity 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 (SPC'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. Suzumura 2012 found an increased risk of grade ≥ 2 rash for IM. However, the authors 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 and Hirose 2016 did not find an increased risk of diarrhoea.

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.

UM: There is no literature on the use of gefitinib by UM. In practice, an alternative is only chosen if gefitinib has been proved ineffective. Gefitinib concentrations are rarely determined, as the analytical method for gefitinib detection is not generally available.

You can find an overview of the observed kinetic and clinical consequences per phenotype in the background information text of the gene-drug interactions on 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 definitions for EM, PM, IM and UM. As a result, the definitions of EM, PM, IM and UM in the table below can differ from the definitions used by the authors in the articles.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr>
<td>ref. 1
Hirose T et al. Association of pharmacokinetics and pharmacogenomics with safety and efficacy 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

IM: AA</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 elevation 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.
Medicines affecting CYP3A4, proton-pump inhibitors and histamine H2 receptor antagonists were excluded, but medicines affecting CYP2D6 were 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 determined.

Genotyping:
- 12x *1/*1
- 16x gene dose 1.5 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 1.5 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 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</td></tr>
</table>
</td>
<td>Author’s conclusion: ”The pharmacokinetics and pharmacogenomics were not associated with significantly different toxicities, response rates, or survival times with gefitinib.”

AUC gefitinib versus *1/*1:
IM (+ PM): 130%</td>
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<table>
<tr><td>ref. 1, continuation</td><td></td><td>was not homozygous for a variant CYP2D6 allele.

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 1.5 or 1.0 will be predominantly gene dose 1.5 (*1/*10).</td><td></td></tr>
<tr><td>ref. 2
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

IM: D</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 or 1 (10x gene dose 2, 36x gene dose 1.5, 8x gene dose 1 (*1/*5 or *2/*5), 1x gene dose 1 or 1.5 (*1/*14))
- 5x IM (3x *10/*10, 2x *5/*10)

Results:
<table>
<tr><td colspan="3">Results compared to gene dose 2, 1.5 or 1:</td></tr>
<tr><td></td><td>IM</td><td>value for gene dose 2, 1.5 or 1</td></tr>
<tr><td rowspan="2">hepatotoxicity grade ≥ 3</td><td>OR = 14.5 (95% CI: 1.6-346.5) (S)</td><td rowspan="2">27.3% of patients</td></tr>
<tr><td>21% of the patients with hepatotoxicity grade ≥ 3 was CYP2D6 IM (*10/*10 or *5/*10).</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. These are the most common alleles in this Japanese population. *4 and *41 were not found in this patient group.</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>
<tr><td>ref. 3
Kobayashi H et al. Relationship among</td><td>3</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).</td><td>Author’s conclusion: ”The side effects from gefitinib were</td></tr>
</table>

<table>
<tr>
<td>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.

ref. 3, continuation</td>
<td>EM+IM: AA</td>
<td>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 0.5-1.5 (11x gene dose 1.5, 6x gene dose 1, 2x gene dose 0,5)

Results:
<table>
<tr><td colspan="3">Results compared to gene dose 2:</td></tr>
<tr><td></td><td>gene dose 0.5-1.5</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>
NOTE: genotyping was performed for *5 and *10. These are the most common alleles in this Japanese population.</td>
<td>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>
<tr>
<td>ref. 4
Takimoto T et al. Polymorphisms of CYP2D6 gene and gefitinib-induced hepatotoxicity.
Clinical Lung Cancer 2013;14:502-7.
PubMed PMID: 23664723.</td>
<td>3

IM: AA

EM+IM: B</td>
<td>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 EM (11x *1/*1, 5x *1/*2 and 1x *1/*39)
- 38x EM+IM (24x EM (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)

EM+IM versus EM:
- 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 EM+IM patients among 7 patients using CYP3A4 inhibitors again developed hepatotoxicity on re-initiation of lower-dose gefitinib while none of the 3 EM patients did (S)

NOTE: genotyping was performed for *2, *4, *5, *10 and *39. These are the most common alleles in this Japanese population.</td>
<td>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.’</td>
</tr>
<tr>
<td>ref. 5
Suzumura T et al. Reduced CYP2D6 function is associated with gefitinib-induced rash in</td>
<td>3</td>
<td>206 patients were treated with gefitinib. Relevant co-medication was not excluded. DNA genotyping was mainly performed using formaldehyde-fixed paraffin-embedded tissue:
- 156x EM+IM (*1/*1, *1/*2, *2/*2, *1/*10, *2/*10, *1/*14A, *1/not known or *2/not known)
- 50x IM (*10/*10)</td>
<td>Author’s conclusion: ‘The frequency of rash was significantly higher in patients with reduced CYP-2D6 activity who</td>
</tr>
</table>

patients with non-small cell lung cancer. BMC Cancer 2012;12:568. PubMed PMID: 23207012. **ref. 5, continuation**	IM: C	IM versus EM+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.	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. 6 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 EM (*1/*1) - 7x IM (5x 1/*4, 2x*1/*5) - 1x PM (*4/*4) PM versus IM versus EM: - Decreased Cl_{or} (54 versus 79 versus 118 L/hour) (S for IM versus EM and for IM+PM versus EM) NOTE: genotyping was performed for *3 to *6. These are the most common alleles in this European population.	Authors' conclusion: 'The CYP2D6 genotype was slightly but significantly related to gefitinib clearance (P = 0.04).'
ref. 7 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 EM+IM (4x EM (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 EM+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. 8 SPC Iressa (gefitinib) 18-07-18.		<u>Dose</u>: No specific dose adjustment is recommended in patients with known CYP2D6 poor metaboliser genotype, but these	

ref. 8, continuation	PM: A	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 extensive 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 average exposures that could be achieved by individuals with no active CYP2D6 may be clinically relevant since adverse effects are related to dose and exposure.	

Risk group	CYP3A4 inhibitors, IM with CYP2D6 inhibitors

Comments:

- 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: 23 July 2018.

	Genotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
Dutch Pharmacogenetics Working Group decision	IM	4 D	yes	no	19 November 2018
	PM	3 A	yes	no	
	UM	-	yes	no	

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.