UGT1A1: sacituzumab govitecan 8510 to 8513

*1/*28 = genotype leading to a reduced UGT1A1 activity, *28/*28 = genotype leading to a strongly reduced UGT1A1 activity, CTCAE = Common Terminology Criteria for Adverse Events, IM = IM OTHER = intermediate metaboliser, genotype otherwise = *1 in combination with an allele with reduced activity other than *28 (e.g. *1/*6), NS = non-significant, PM = PM, OTHER = poor metaboliser, genotype otherwise = two alleles with reduced activity of which at least one other than *28 (e.g. *6/*28 or *6/*6), popPK model = population pharmacokinetic model, S = significant, SmPC = Summary of Product Characteristics, UGT = uridine diphosphate glucuronosyltransferase,
UGT1A1*1 = TA_6 = [$A(TA)_6TAA$] = wild-type, UGT1A1*28 = TA_7 = [$A(TA)_7TAA$] (reduced UGT1A1 activity), UGT1A1*36 = TA_5 = [$A(TA)_5TAA$] (increased UGT1A1 activity), UGT1A1*37 = TA_8 = [$A(TA)_8TAA$] (UGT1A1 activity more strongly reduced than for *28), UGT1A1*6 = gene variant in Asians, reduced activity, comparable to *28.

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, then the health care professional should consider the next best option.

Conclusion and justification of choices

Sacituzumab govitecan releases the active metabolite SN-38, which is inactivated by glucuronidation, predominantly by UGT1A1.
The SmPCs indicate a higher risk of grade ≥3 adverse events in patients with *28/*28 and *1/*28 genotypes and suggest this might also be the case in patients with reduced UGT1A1 activity due to other gene variants (PM OTHER and IM OTHER). For *28/*28 and *1/*28, this was confirmed for diarrhoea in Ocean 2017, but only for a dose of 8 mg/kg, not for the registered dose of 10 mg/kg. Two other studies also found numerically higher incidences of adverse events for *28/*28 (Loriot 2024 and Rugo 2022) and *1/*28 (Rugo 2022). However, a modelling study did not find a difference in the predicted AUC of free SN-38 over the first treatment cycle between the genotype groups. Because of the observed clinical effects, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction and that action is needed for *28/*28 and PM OTHER (yes/no-interactions). However, because *1/*28 is the major group among White populations including the Dutch population, sacituzumab govitecan therapy will be optimised based mainly on *1/*28, which has a comparable UGT1A1 activity as IM OTHER. For this reason, the KNMP Pharmacogenetics Working Group does not recommend adjustment of therapy or patient monitoring for *1/*28 and IM OTHER (yes/no-interactions).
Both SmPCs recommend only close monitoring of patients with known reduced UGT1A1 activity for adverse reactions. An a priori dose reduction could prevent serious adverse events, but might decrease effectiveness of sacituzumab govitecan. Loriot 2024 found that the majority of *28/*28 (57%) did not require a dose reduction due to treatment-related adverse events. This was confirmed by the absence of a difference in the calculated median dose intensity between the UGT1A1 genotypes in this study. In addition, Rugo 2022 found median progression-free survival to be numerically higher in patients with dose reductions or dose interruptions due to adverse events than in patients without (8.3 versus 4.6 months for dose reductions and 5.7 versus 4.2 months for dose interruptions). Finally, although there were indications for a higher rate of sacituzumab govitecan discontinuation due to treatment-related adverse events in *28/*28, this rate remained low (6-7%) (Loriot 2024 and Rugo 2022). For these reasons, the KNMP Pharmacogenetics Working Group indeed decided to only recommend close monitoring for adverse events and no dose reduction for *28/*28 and PM OTHER.
You can find an overview of the observed kinetic and clinical effects 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.

Mechanism

Sacituzumab govitecan is an antibody-drug conjugate composed of an antibody with binding affinity for trophoblast cell-surface antigen-2 (Trop-2), coupled to SN-38, the active metabolite of irinotecan, via hydrolysable linkers. Because of its hydrolysable linkers, sacituzumab govitecan releases SN-38 both intra- and extracellularly in Trop-2 expressing tumours. SN-38 is glucuronidated to the inactive metabolite SN-38-glucuronide by glucuronosyltransferases. SN-38 is predominantly metabolised by UGT1A1 and also by UGT1A6, UGT1A7, UGT1A9 and UGT1A10.
A UGT1A1 genetic polymorphism may change the plasma and local concentration of SN-38 and SN-38 glucuronide.

	Genotype	Code	Gene- drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	*1/*28	4 D	Yes	No	27 January 2025
	*28/*28	4 D	Yes	Yes	
	IM	0 D	Yes	No	
	PM	0 D	Yes	Yes	

Recommendation concerning pre-emptive genotyping, including justification of choices

The KNMP Pharmacogenetics Working Group does not recommend genotyping of UGT1A1 before starting sacituzumab govitecan.
The clinical implication of the gene-drug interaction scores 3 out of the maximum of 10 points. Pre-emptive genotyping is considered to be beneficial for scores ranging from 3 to 5 points (see below and the clinical implication score tables at the end of this risk analysis). However, the KNMP Pharmacogenetics Working Group decided not to follow the clinical implication score for sacituzumab govitecan. Because the therapeutic recommendation for sacituzumab govitecan (to closely monitor for adverse events) does not prevent any severe adverse event, genotyping does not prevent any adverse event. Therefore, the clinical impact of genotyping before start of sacituzumab govitecan is either absent or very limited. For this reason, the KNMP Pharmacogenetics Working Group decided not to recommend genotyping before start of sacituzumab govitecan, i.e. decided to recommend the same as the Dutch SmPC of sacituzumab govitecan.
The rationale for the (sub)scores on the clinical implication score is indicated below:
The SmPCs and one study indicate a higher risk of grade ≥3 adverse events in patients with *28/*28 and *1/*28 genotypes (code D corresponding to CTCAE grade 3). This results in 1 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 (1 point for code D or E (CTCAE grade 3 or 4)).
Only one study confirmed an increased risk of serious adverse events (code D corresponding to CTCAE grade 3) (Ocean 2017). This results in 1 out of the maximum of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (1 points for one publications with level of evidence score ≥ 3).
Because the therapeutic recommendation to closely monitor patients for serious adverse events does not prevent a severe adverse event, but might only prevent it from becoming even more severe, genotyping of patients will not prevent any severe adverse event. This results in 0 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) to prevent one clinical effect code ≥ D (grade ≥ 3) (only points for NNG ≤ 1000).
The Dutch SmPC of sacituzumab govitecan mentions an increased risk of serious haematologic adverse events for *28/*28 (and *1/*28), but indicates that when unknown, no testing of UGT1A1 status is required. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype being mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).

Literature

The table below follows KNMP nomenclature for UGT1A1 polymorphisms. The nomenclature used in the table below may therefore differ from the nomenclature used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Sathe AG et al. Population pharmacokinetics of sacituzumab govitecan in patients with metastatic triple-negative breast cancer and other solid tumors. Clin Pharmacokinet 2024;63:669-81. PMID: 38578394.	4	Pharmacokinetics was analysed in 529 sacituzumab govitecan treated patients (276 of the patients from the IMMU-132-01 study (Ocean 2017) and all 253 patients from the ASCENT study (Rugo 2022)), followed by the development of population pharmacokinetic (popPK) models for sacituzumab govitecan and free SN-38. UGT1A1 genotype was known for 472 patients (226 from the IMMU-132-01 study and 246 from the ASCENT study). Free and total SN-38 in the serum samples were determined. Subsequently, the concentration of sacituzumab govitecan was determined from the calculated concentration of bound SN-38, assuming a constant mean number of 8 SN-38 groups per sacituzumab govitecan molecule (this number actually decreases in time due to the hydrolysis of sacituzumab govitecan). The popPK model was first developed for sacituzumab govitecan and the model for free SN-38 was developed from this by incorporating formation of free SN-38 driven by total amount of sacituzumab govitecan following first-order kinetics. Goodness-of-fit plots indicated no meaningful bias in the popPK models. The prediction-corrected visual predictive checks showed lack of model misspecification with good concordance between observed and simulated percentiles for sacituzumab govitecan, but a slight underprediction of the 5th percentile of the observed concentrations during the distribution phase for free SN-38.	Authors' conclusion: 'Mild-to-moderate renal impairment, mild hepatic impairment, age, sex, baseline albumin level, tumor type, UGT1A1 genotype, or Trop-2 expression did not have a clinically relevant impact on exposure for any of the three analytes (sacituzumab govitecan, free SN-38, and total antibody). These analyses support the approved sacituzumab govitecan dosing regimen of 10 mg/kg as intravenous infusion on days 1 and 8 of 21-day cycles and did not identify a need for dose adjustment

<table>
<tr>
<td>ref. 1, continuation</td>
<td>*1/*28: A

*28/*28: AA</td>
<td>Relevant comedication was not excluded, but only 1% of patients used a UGT1A1 inducer and only 3% a UGT1A1 inhibitor. In addition, no significant effect of inducer or inhibitor use was observed.

Genotyping:
- 204x *1/*1
- 195x *1/*28
- 66x *28/*28
- 7x *1/*1 (*1/*36 or *36/*36) or *1/*28 (*28/*36) or IM (*1/*37) or PM (*28/*37)

Results:
<table>
<tr><td colspan="3">Results compared to *1/*1:</td></tr>
<tr><td></td><td>*1/*28</td><td>*28/*28</td></tr>
<tr><td>popPK model for sacituzumab govitecan</td><td colspan="2">UGT1A1 genotype had no effect (NS)</td></tr>
<tr><td>popPK model for free SN-38</td><td colspan="2">UGT1A1 genotype had no effect (NS)</td></tr>
<tr><td>predicted AUC over the first treatment cycle of sacituzumab govitecan</td><td>x 0.972 (S)</td><td>NS</td></tr>
<tr><td>predicted AUC over the first treatment cycle of free SN-38</td><td>NS</td><td>NS</td></tr>
</table>
</td>
<td>based on evaluated covariates or disease characteristics.’</td>
</tr>
<tr>
<td>ref. 2
Loriot Y et al. TROPHY-U-01, a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors: updated safety and efficacy outcomes.
Ann Oncol 2024;35:392-401.
PMID: 38244927.</td>
<td>3</td>
<td>106 patients with urothelial carcinoma were treated with sacituzumab govitecan (SG) 10 mg/kg intravenously on days 1 and 8 of 21-day cycles until progression, unacceptable toxicity, or withdrawal of informed consent. Hematopoietic growth factors or blood transfusions were allowed as clinically indicated. 22% of patients received granulocyte colony-stimulating factor (G-CSF) as primary prophylaxis and 23% as secondary prophylaxis. Median follow-up was 10.5 months (range 0.3-40.9 months). At data cut-off, 88% of treated patients had discontinued treatment due to death (79%), completion of 2-year follow-up (4%), loss to follow-up (3%), or withdrawal of consent (3%).
Efficacy was evaluated using computed tomography (CT) or magnetic resonance imaging (MRI) scans, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria, to classify tumour response and progression-free survival.
Objective response was defined as complete response + partial response. Clinical benefit was defined as complete response + partial response + stable disease during ≥ 6 months.
All patients who received ≥1 dose of sacituzumab govitecan were included in the evaluation of adverse events.
There was no requirement for tumour Trop-2 expression for enrolment. Patients with known Gilbert syndrome were excluded. This indicates that patients in which the *28/*28 genotype has phenotypic consequences in everyday life (and so the *28/*28 patients expected to be most likely to show phenotypic consequences also during drug treatment) were excluded. It is not stated whether UGT1A1 inducers and inhibitors were excluded.

Genotyping:
- 45x *1/*1
- 47x *1/*28
- 14x *28/*28

Results:
<table>
<tr><td>Results compared to *1/*1 (differences larger than 1.5 times</td></tr>
</table>
</td>
<td>Authors’ conclusion: ‘Adverse event incidence varied across UGT1A1 subgroups; however, discontinuation rates remained relatively low for all groups.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td>*28/*28: AA

*1/*28: AA</td>
<td>
are reported below, significance was not determined for adverse events, so NS indicates significance not determined for the adverse event outcomes):
<table>
<tr><th></th><th>*28/*28</th><th>*1/*28</th><th>value for *1/*1</th></tr>
<tr><td>objective response rate</td><td>NS</td><td>NS</td><td>22%</td></tr>
<tr><td>clinical benefit rate</td><td>NS</td><td>NS</td><td>33%</td></tr>
<tr><td>median progression free survival</td><td>NS</td><td>NS</td><td>5 months</td></tr>
<tr><td>median overall survival</td><td>NS</td><td>NS</td><td>11 months</td></tr>
<tr><td>treatment-related adverse event rate</td><td>NS</td><td>NS</td><td>93%</td></tr>
<tr><td>treatment-related adverse event grade ≥ 3 rate</td><td>NS</td><td>NS</td><td>62%</td></tr>
<tr><td>treatment-related death rate</td><td>NS
Note: the only patient with a treatment-related death (due to febrile neutropenia-related sepsis) was *1/*1.</td><td>NS</td><td>2%</td></tr>
<tr><td>rate of SG discontinuation due to treatment-related adverse events</td><td>x 2.1 (NS)</td><td>NS</td><td>6.7%</td></tr>
<tr><td>rate of SG dose reduction due to treatment-related adverse events</td><td>NS
Note: the rate was 43% for *28/*28.</td><td>NS</td><td>38%</td></tr>
<tr><td>rate of SG interruption due to treatment-related adverse events</td><td>x 1.7 (NS)</td><td>NS</td><td>42%</td></tr>
</table>
Note: Genotyping was for *28. This is the most important gene variant in this population from the USA and France.
</td>
<td></td>
</tr>
<tr>
<td>ref. 3
Rugo HS et al. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. NPJ Breast Cancer 2022;8:98. PMID: 36038616.</td>
<td>3</td>
<td>250 patients with breast cancer were treated with sacituzumab govitecan (SG) 10 mg/kg intravenously on days 1 and 8 of 21-day cycles until disease progression, unacceptable toxicity, withdrawal from the trial, or death. Severe neutropenia and non-neutropenic toxicities were managed with dose delays or reductions and medications (granulocyte colony-stimulating factor (G-CSF) for neutropenia and loperamide for diarrhoea). Prophylactic growth factors at study start were not allowed, and anti-diarrhoea prophylaxis was not recommended. 49% of patients received G-CSF, 29% for secondary prophylaxis and 30% as treatment). Median follow-up from study enrollment was 17.7 months (range 5.8-28.1 months). At data cutoff, 7% of patients remained on treatment. The primary reason for discontinuation was disease progression (86%). No treatment-related deaths were reported. Median progression-free survival was numerically higher in patients with dose reductions or dose interruptions than in patients without (8.3 versus 4.6 months for dose reductions and 5.7 versus 4.2 months for dose interruptions).
All patients who received ≥1 dose of sacituzumab govitecan were included in the evaluation of adverse events.
UGT1A1 inducers and inhibitors were not excluded nor corrected for, but they were used with caution.

Genotyping:</td>
<td>Authors' conclusion: 'Patients with UGT1A1 *28/*28 genotype versus those with 1/*28 and *1/*1 genotypes had higher rates of grade ≥3 SG-related neutropenia (59% vs 47% and 53%), febrile neutropenia (18% vs 5% and 3%), anemia (15% vs 6% and 4%), and diarrhea (15% vs 9% and 10%), respectively. Individuals with UGT1A1 *28/*28 genotype should be monitored closely; active monitoring and routine adverse event management allow optimal therapeutic exposure of SG.'</td>
</tr>
</table>

<table>
<tr>
<td>ref. 3, continuation</td>
<td>*28/*28: AA

*1/*28: AA</td>
<td>- 113x *1/*1
- 96x *1/*28
- 34x *28/*28
- 7x other genotype

Results:
<table>
<tr><td colspan="4">Results compared to *1/*1 (except for the median dose intensity, differences equal to or larger than 1.5 times are reported below, significance was not determined, so NS indicates significance not determined):</td></tr>
<tr><td></td><td>*28/*28</td><td>*1/*28</td><td>value for *1/*1</td></tr>
<tr><td>median SG dose intensity</td><td>x 1.00 (NS)</td><td>x 1.00 (NS)</td><td>99.8%</td></tr>
<tr><td>rate of SG dose reduction due to treatment-related adverse events</td><td>x 1.9 (NS)</td><td>NS</td><td>18%</td></tr>
<tr><td>time to first dose reduction</td><td>x 0.67 (NS)</td><td>NS</td><td>2.7 months</td></tr>
<tr><td rowspan="2">rate of SG discontinuation due to treatment-related adverse events</td><td>x 3 (NS)</td><td>x 0.5 (NS)</td><td>2%</td></tr>
<tr><td colspan="2">There were no discontinuations due to SG-related neutropenia, febrile neutropenia, or diarrhoea.</td></tr>
<tr><td>treatment-related neutropenia grade ≥3 rate</td><td>NS</td><td>NS</td><td>53%</td></tr>
<tr><td>treatment-related febrile neutropenia rate</td><td>x 6.6 (NS)</td><td>x 2.0 (NS)</td><td>2.7%</td></tr>
<tr><td>treatment-related leukopenia grade ≥3 rate</td><td>x 1.7 (NS)</td><td>NS</td><td>8.8%</td></tr>
<tr><td>treatment-related anaemia grade ≥3 rate</td><td>x 3.3 (NS)</td><td>NS</td><td>4.4%</td></tr>
<tr><td>treatment-related diarrhoea grade ≥3 rate</td><td>x 1.5 (NS)</td><td>NS</td><td>9.7%</td></tr>
<tr><td>other treatment-related adverse events, including nausea, vomiting, constipation, fatigue, alopecia, and decreased appetite</td><td colspan="2">no effect of UGT1A1 phenotype</td><td></td></tr>
</table>
Note: Genotyping was by Sanger sequencing. Therefore, all gene variants present were identified in this population from the USA, Canada, Belgium, France, Germany, Italy, Spain, and the United Kingdom.</td>
<td>Median dose intensity compared to *1/*1:
*1/*28: 100%
*28/*28: 100%</td>
</tr>
<tr>
<td>ref. 4
Ocean AJ et al. Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate for the treatment of diverse epithelial cancers: Safety</td>
<td>3</td>
<td>146 patients with epithelial cancers were treated with sacituzumab govitecan (SG) 8 mg/kg (n = 69) or 10 mg/kg (n = 77) intravenously on days 1 and 8 of 21-day cycles until disease progression or unacceptable toxicity. Dosing was delayed, with or without subsequent reductions, for adverse events grade ≥3 (haematologic or non-haematologic). Prophylactic use of antiemetics or antidiarrheal medications was prohibited. Hematopoietic growth factor support was allowed for neutropenia prophylactically after cycle 1 for part of the patients and after the first dose for the other patients. 22% of patients in the 8-mg/kg</td>
<td>Authors' conclusion: 'Dose-limiting neutropenia after the first cycle was not correlated with SN-38 in serum or with UGT1A1 genotype.'</td>
</tr>
</table>

<table>
<tr>
<td>and pharmaco-kinetics.
Cancer 2017;123:3843-54.
PMID: 28558150.

ref. 4, continuation</td>
<td>*28/*28: D
*1/*28: D</td>
<td>group and 26% in the 10-mg/kg group received at least one haematologic cytokine support treatment. Treatment was permanently discontinued for delays >3 weeks. Patients received a median of 9 doses (ranges, 1-35 and 1-30 doses at 8 and 10 mg/kg, respectively), and 35 patients were continuing treatment at the cutoff date. Most patients received more than 1 cycle of treatment (>2 doses) (93% and 92% at 8 and 10 mg/kg, respectively). Study discontinuation due to adverse events and to treatment-related adverse events in the 8-mg/kg group was 8.6% and 2.5%, respectively, and in the 10-mg/kg group 10.3% and 7.2%, respectively,.
All patients who received ≥1 dose of sacituzumab govitecan were included in the evaluation.
There was no requirement for tumour Trop-2 expression for enrolment. Patients with known Gilbert syndrome were excluded. This indicates that patients in which the *28/*28 genotype has phenotypic consequences in everyday life (and so the *28/*28 patients expected to be most likely to show phenotypic consequences also during drug treatment) were excluded. It is not stated whether UGT1A1 inducers and inhibitors were excluded.

Genotyping:
- 63x *1/*1
- 64x *1/*28
- 19x *28/*28

Results:
<table>
<tr><td colspan="4">Results compared to *1/*1 (differences equal to or larger than 1.5 times are reported below, significance was only determined for part of the outcomes and only for *28/*28 versus *1/*28 versus *1/*1, so NS for the separate genotypes indicates significance not determined):</td></tr>
<tr><td></td><td>*28/*28</td><td>*1/*28</td><td>value for *1/*1</td></tr>
<tr><td rowspan="3">neutropenia grade ≥3 rate</td><td>x 1.5 (NS)</td><td>NS</td><td rowspan="3">38%</td></tr>
<tr><td colspan="2">NS for *28/*28 versus *1/*28 versus *1/*1</td></tr>
<tr><td colspan="2">Results were also NS for *28/*28 versus *1/*28 versus *1/*1 for patients who only received 10 mg/kg.</td></tr>
<tr><td>rate of onset of neutropenia grade ≥3 in the first cycle</td><td>x 1.8 (NS)</td><td>NS</td><td>17%</td></tr>
<tr><td rowspan="3">rate of onset of neutropenia grade ≥3 in the first two cycles</td><td>x 1.9 (NS)</td><td>NS</td><td rowspan="3">30%</td></tr>
<tr><td colspan="2">trend for significance for *28/*28 versus *1/*28 versus *1/*1 (p = 0.073) (NS)</td></tr>
<tr><td colspan="2">Results were NS for *28/*28 versus *1/*28 versus *1/*1 for patients who only received 10 mg/kg.</td></tr>
<tr><td rowspan="3">diarrhoea grade 3 rate
(diarrhoea grade 4 was not observed)</td><td>x 2.0 (NS)</td><td>x 0.6 (NS)</td><td rowspan="3">8%</td></tr>
<tr><td colspan="2">S for *28/*28 versus *1/*28 versus *1/*1</td></tr>
<tr><td colspan="2">Results were NS for *28/*28 versus *1/*28 versus *1/*1 for the 10-mg/kg subgroup.</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

ref. 4, continuation		Note: It was not reported which gene variants were determined, but only *28 was reported, so genotyping was probably only for *28. This is the most important gene variant in this population from the USA.	
ref. 5 SmPC Trodelvy (sacituzumab govitecan) 11-08-23.	0 *28/*28: D PM: D *1/*28: D	<u>Warnings</u>: *Use in patients with reduced UGT1A1 activity* SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via uridine diphosphate-glucuronosyl transferase (UGT1A1). Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous for UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anaemia and are at increased risk for other adverse reactions following initiation of sacituzumab govitecan treatment. Approximately 20% of the Black population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT-1A1*28 allele. Decreased function alleles other than UGT1A1 *28 may be present in certain populations. Patients with known reduced UGT1A1 activity should be closely monitored for adverse reactions. When unknown, no testing of UGT1A1 status is required as the management of adverse reactions including the recommended dose modifications will be the same for all patients. <u>Adverse events</u>: *Use in patients with reduced UGT1A1 activity* The incidence of Grade 3-4 neutropenia was 60.6% (43/71) in patients homozygous for the UGT1A1*28 allele, 52.9% (144/272) in patients heterozygous for the UGT1A1*28 allele, and 49.1% (140/285) in patients homozygous for the wild-type allele. The incidence of Grade 3-4 febrile neutropenia was 14.1% (10/71) in patients homozygous for the UGT1A1*28 allele, 5.9% (16/272) in patients heterozygous for the UGT1A1*28 allele, and 4.6% (13/285) in patients homozygous for the wild-type allele. The incidence of Grade 3-4 anaemia was 15.5% (11/71) in patients homozygous for the UGT1A1*28 allele, 7.4% (20/272) in patients heterozygous for the UGT1A1*28 allele, and 8.1% (23/285) in patients homozygous for the wild-type allele. Compared to patients homozygous for the wild-type allele, earlier median onset of neutropenia and anaemia was observed in patients homozygous for the UGT1A1*28 allele and in patients heterozygous for the UGT1A1*28 allele.	
ref. 6 SmPC Trodelvy (sacituzumab govitecan) 02-03-23 (USA).	0 *28/*28: D	<u>Warnings</u>: *Increased risk of adverse reactions in patients with reduced UGT1A1 activity* Patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia; and may be at increased risk for other adverse reactions when treated with Trodelvy. The incidence of neutropenia and anemia was analyzed in 948 patients who received Trodelvy and had UGT1A1 genotype results. In patients homozygous for the UGT1A1 *28 allele (n=112), the incidence of Grade 3-4 neutropenia was 58%. In patients heterozygous for the UGT1A1*28 allele (n=420), the incidence of Grade 3-4 neutropenia was 49%. In patients homozygous for the wild-type allele (n=416), the incidence of Grade 3-4 neutropenia was 43%. In patients homozygous for the UGT-1A1 *28 allele, the incidence of Grade 3-4 anemia was 21%. In patients heterozygous for the UGT1A1*28 allele, the incidence	

ref. 6, continuation	*1/*28: D PM: D IM: D	of Grade 3-4 anemia was 10%. In patients homozygous for the wild-type allele, the incidence of Grade 3-4 anemia was 9%. The median time to first neutropenia including febrile neutropenia was 9 days in patients homozygous for the UGT1A1*28 allele, 15 days in patients heterozygous for the UGT1A1*28 allele, and 20 days in patients homozygous for the wild-type allele. The median time to first anemia was 21 days in patients homozygous for the UGT1A1*28 allele, 25 days in patients heterozygous for the UGT1A1*28 allele, and 28 days in patients homozygous for the wild-type allele. Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue Trodelvy based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 enzyme activity. Clnical pharmacology: *Pharmacogenomics* SN-38 is metabolized via UGT1A1. Genetic variants of the UGT-1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous or heterozygous for the UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia from Trodelvy compared to individuals who are wildtype (*1/*1). Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele (*28/*28). Approximately 40% of the Black or African American population, 50% of the White population, and 25% of the East Asian population are heterozygous for the UGT1A1*28 allele (*1/*28). Decreased function alleles other than UGT1A1*28 may be present in certain populations.	

Risk group	*28/*28 with UGT1A1 inhibitors (e.g. ketoconazole and gemfibrozil)

Comments

-

PICO

P(atient / person)	non-UGT1A1 *1/*1 individuals
I(ntervention)	sacituzumab govitecan
C(omparison / Control)	UGT1A1 *1/*1 individuals
O(utcome)	kinetic and/or clinical effects

In- and exclusion criteria
Literature table
Inclusion:

- According to PICO
- Relevant case reports
- Exception made for this risk analysis: study with pharmacokinetic modelling of data from other studies
- SmPCs (NL and USA) if they contain relevant information

Exclusion:

- Animal studies
- In vitro studies
- Reviews that are not meta-analyses and other not-original studies

Comments
Inclusion:

- Other guidelines

- Cost-effectiveness studies for genotype-guided therapy

General background text of the gene

Inclusion:

- Articles with information relevant for the general background text of the gene (e.g. information on gene variant frequency in the Netherlands)

Search terms

Pubmed

Date	Search terms
13-8-2024	("sacituzumab govitecan" [Supplementary Concept] OR "sacituzumab govitecan" OR sacituzumab) AND ("UGT1A1 enzyme" [Supplementary Concept] OR UGT1A1 OR 1A1) AND (English[lang] OR German[lang] OR Dutch[lang])

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+	3+
Corresponding Clinical Implication Score:		Beneficial
Recommendation after taking additional considerations into account:		No recommendation to genotype.