Consideration of UGT1A1: Irinotecan as a future CPIC guideline

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Many thanks to Federico Innocenti MD and Ryan Nelson, PharmD for slides and discussion.

CPIC®
Clinical Pharmacogenetics Implementation Consortium

Irinotecan

Semi-synthetic camptothecin analogue

i.v. formulation, Camptosar® (Pfizer)

Topoisomerase I poison

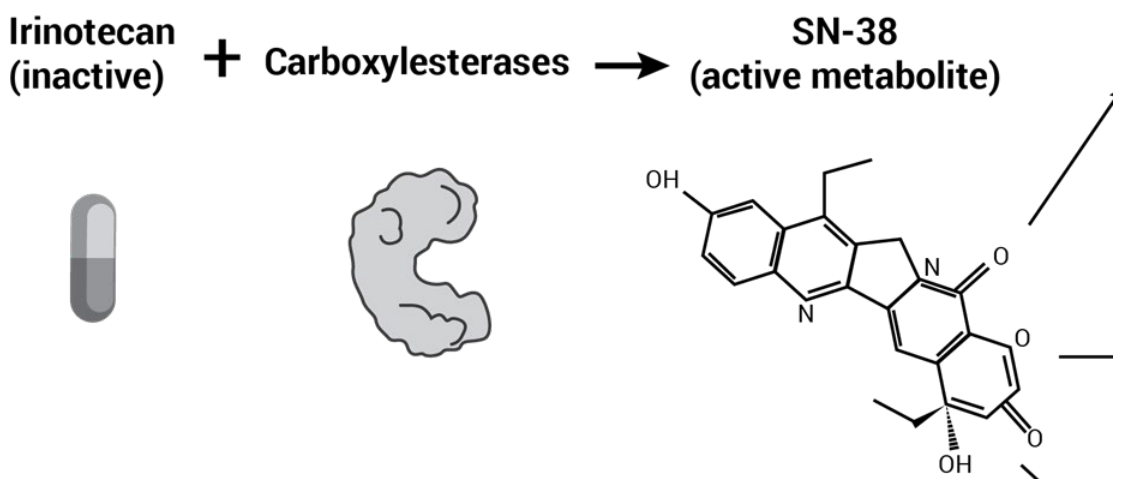
Advanced/metastatic colorectal cancer (mCRC), esophageal, small cell lung cancer, gliomas, and other solid tumors

mCRC therapy

- Initial (1st line)
  - + 5-fluorouracil (5FU)/Leucovorin (LV) (FOLFIRI) + bevacuzimab
- After 1st progression: refractory to oxaliplatin- or 5FU-based therapies (2nd line)
  - Single agent +/- cetuximab
  - FOLFIRI +/- cetuximab
- After 1st or 2nd progression: refractory to irinotecan-based therapy (≥2nd line)
  - Single agent + cetuximab

Schedule: weekly, biweekly, or every 3 wks

Doses: 125 to 350 mg/m^2



Irinotecan dose-limiting toxicities

Severe neutropenia (up to 50% CTC grade≥3)[1,2]

- major risk factor for infection-related morbidity and mortality

Severe diarrhea (up to 40% CTC grade≥3) [1,2]

Both reversible & not cumulative

Life-threatening, require hospitalization, dose reduction &/or treatment delays

They can impair success of treatment; knowing who is at high risk of toxicities could improve clinical utility of irinotecan

[1] Rougier Semin. Oncol. 1996; **23**: 34–41.
[2] Rothenberg Semin Oncol 1998; **25**: 39–46.

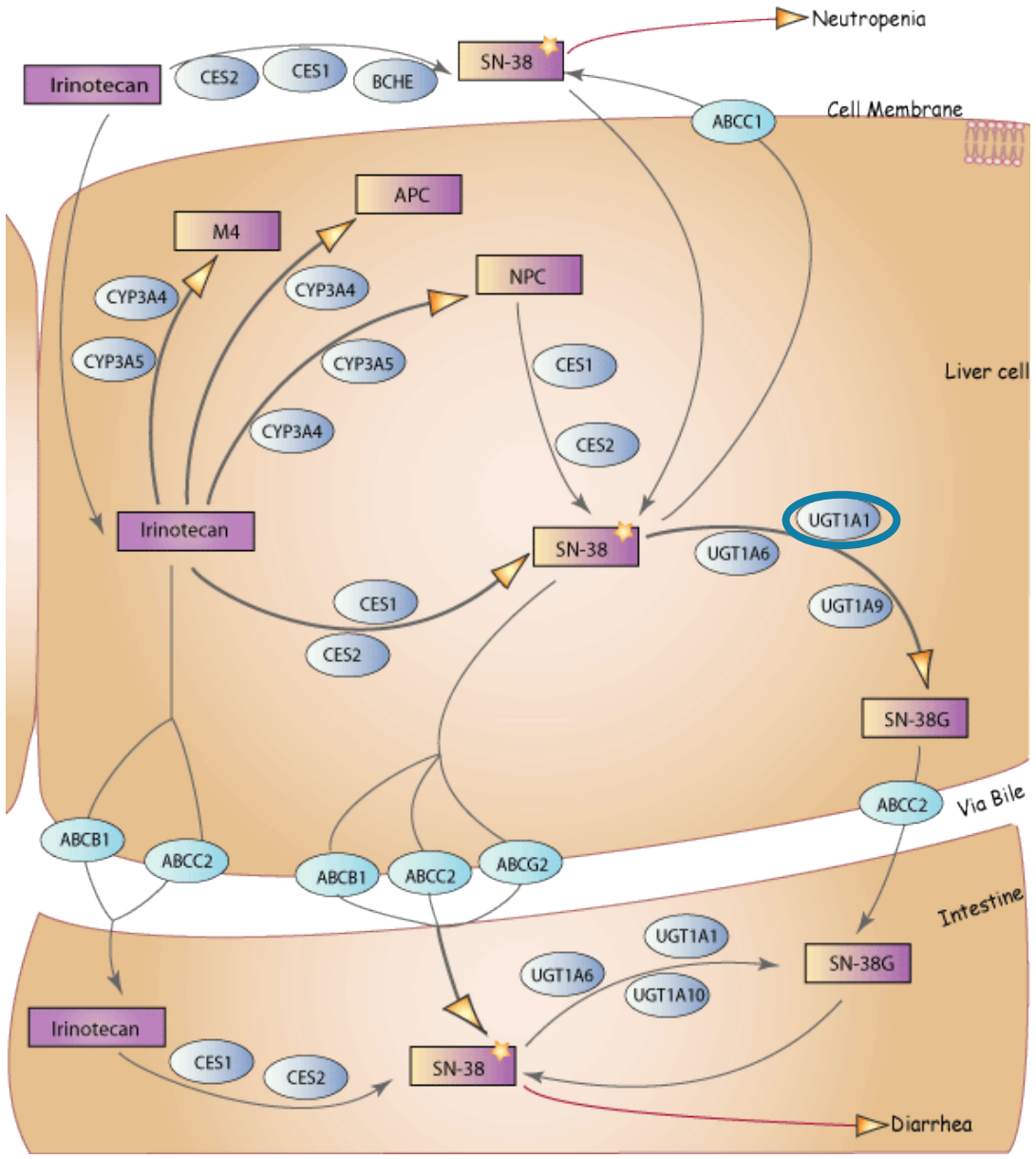
Irinotecan metabolism pathway

Irinotecan activated by conversion to SN-38

SN-38: active metabolite 100-1,000x activity

SN-38 inactivated by glucuronidation to SN-38-glucuronide (SN-38G)

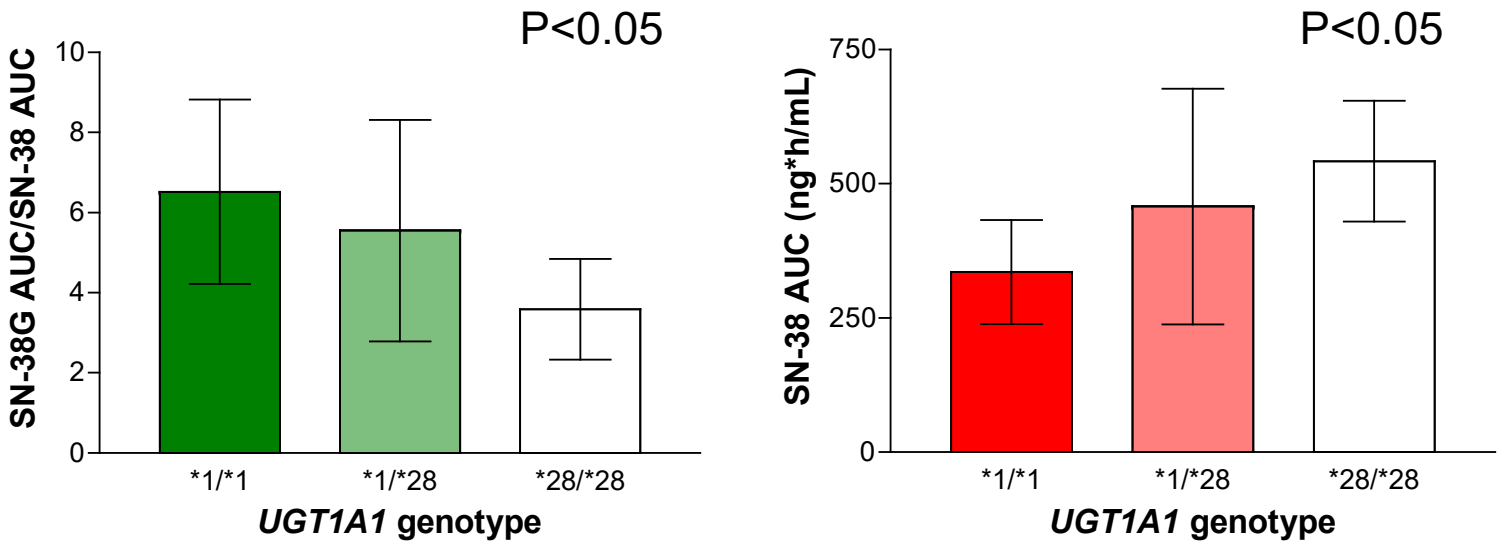
SN-38 glucuronidation rate varies greatly among people and has been associated with irinotecan toxicities.



www.pharmgkb.org

*UGT1A1*28* associated w/ reduced SN-38 glucuronidation & elevated SN-38 exposure

Patients with solid tumors or lymphoma (Phase I); single agent
350 mg/m^2 irinotecan, every 3 wks

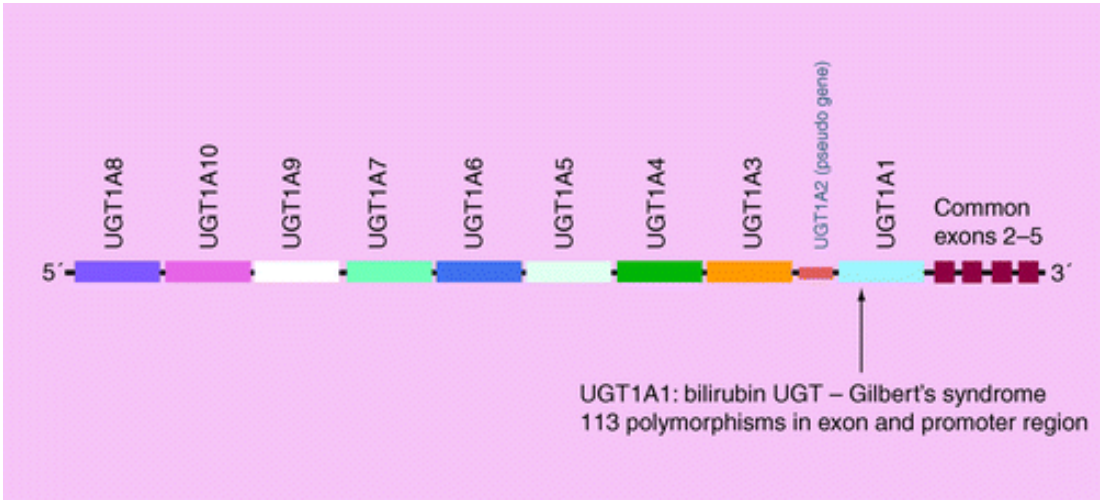


SN-38 glucuronidation decreases and SN-38 exposure increases with the number of (TA)7 alleles.

Innocenti JCO 2004

UDP-glucuronosyltransferase 1A1 (UGT1A1)

***UGT1A* locus**
Chr 2q37
Cluster of 13 genes
9 unique first exons
4 pseudoexons
Liver: 1A1, 1A3, 1A4, 1A6, 1A9
Esophagus: 1A7, 1A8, 1A10
Stomach: 1A7, 1A10
Colon: 1A8, 1A10
Bile ducts: 1A10



Strassburg 2008

***UGT1A1*:** TATA box TA repeat polymorphism, (TA)5, (TA)6, (TA)7, (TA)8

f(Eur)=0.61

f(Eur)=0.39

Missense variants with functional consequence also exist

Desai et al 2003

Ethnic differences in *UGT1A1*

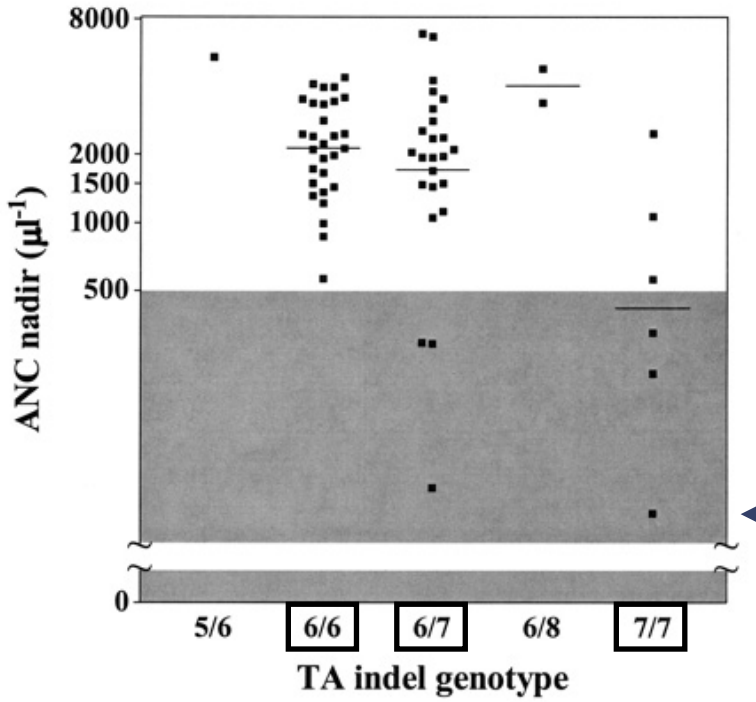
	European	African	East Asian
**28* allelic frequency	39%	45%	8-15%
**28/*28* frequency	15%	20%	1-2%
**6* allelic frequency	0%	0%	12-18%
**6/*6* frequency	0%	0%	2-3%

- *UGT1A1*6* = c.211G>A; Glv→Arg αα71 (non-synonymous SNP)
- 50% reduced *in vitro* clearance of SN-38 to SN-38G; reduced Vmax
- Together *UGT1A1*6* & **28* may predict irinotecan-induced toxicity in East Asians

Kaniwa et al 2005, Zhang et al 2007, Gagne et al 2002

*UGT1A1*28* increases risk of neutropenia

Patients with solid tumors or lymphoma; 350 mg/m^2 irinotecan, every 3 wks



Correlation between absolute neutrophil count (ANC) nadir (log scale) and *UGT1A1*28* genotype (*P*=0.001).

ANC nadir decreases with the number of *UGT1A1*28* alleles.

Grade 4 neutropenia (shaded area)

Innocenti JCO 2004

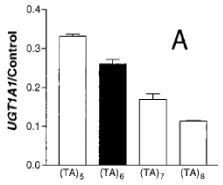
From basic genetics to a clinical trial and label change

Gilbert's syndrome and UGT1A1*28

1995
Bosma

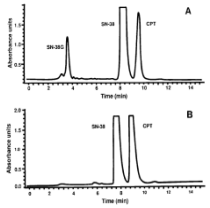
UGT1A1*28 molecular effect

1998
Beutler



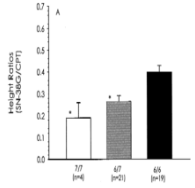
UGT1A1: metabolic gene of irinotecan

1998
Iyer



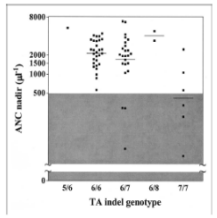
UGT1A1*28 and irinotecan metabolism

1999
Iyer



UGT1A1*28 and clinical validation

1998-2004
Innocenti



FDA revised drug label

2005

FDA approves changes to Camptosar® package insert (2005)

population is homozygous for the UGT1A1*28 allele. In a prospective study, in which irinotecan was administered as a single-agent on a once-every-3-week schedule, patients

Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1*28 allele (see DOSAGE AND ADMINISTRATION). Heterozygous patients (carriers of one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

A reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele (See CLINICAL PHARMACOLOGY and WARNINGS). The appropriate dose reduction in this patient population is not known.

Is Irinotecan/UGT1A1 ‘ready’ for a CPIC guideline?

Number of independent studies: inconsistent replication

Phenotypic consequence	P	Ethnicity	No. of patients	Reference
↑ Severe toxicity	<0.001	Asian	118	Ando et al 2000
↑ SN-38 AUC (& neutropenia)	0.001	White	20	Iyer et al 2000
Altered toxicity	NS	White	51	Font et al 2003
↑ Severe diarrhea	0.005	White	95	Marcuello et al 2004
↑ Severe neutropenia	0.001	White	75	Rouits et al 2004
↑ Relative extent of glucuronidation	0.022	White	94	Paoluzzi et al 2004
↑ SN-38 AUC & neutropenia	0.01	White & other	65	Innocenti et al 2004
↑ SN-38 AUC & neutropenia	0.02	White	30	Mathijssen et al 2004
Altered Pharmacokinetics	NS	Asian	29	Zhou et al 2005
Altered response & toxicity	NS	White & Black	67	Carlini et al 2005
Altered response & toxicity	NS	White	25	Soepenberg et al 2005

Smith, Toxicology in Vitro 2005

Factors that contribute to lack of reproducibility among genetic association studies

Variation in power between studies

- Small effect size, limited sample size (especially important for alleles with low frequency)

Misclassification of outcome

Heterogeneity of effect size among studies

- Variation in the prevalence of an environmental factor

Allelic heterogeneity

- When many causative alleles are present in the studied gene

Publication bias

Failure to attribute results to chance

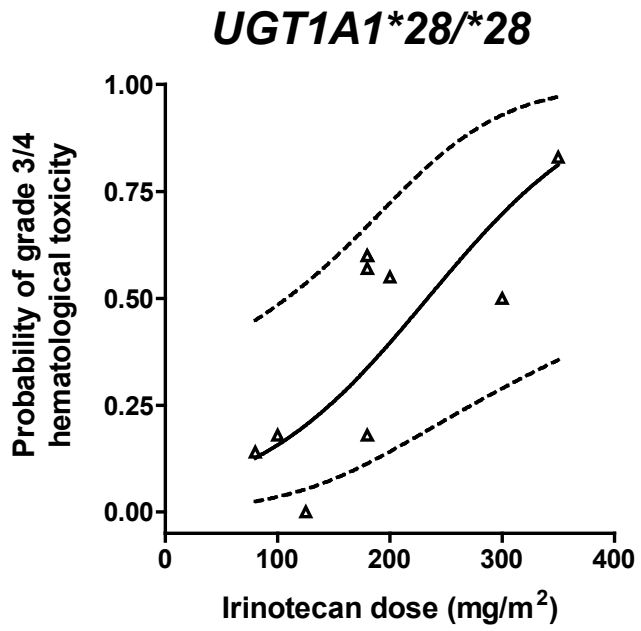
Population stratification

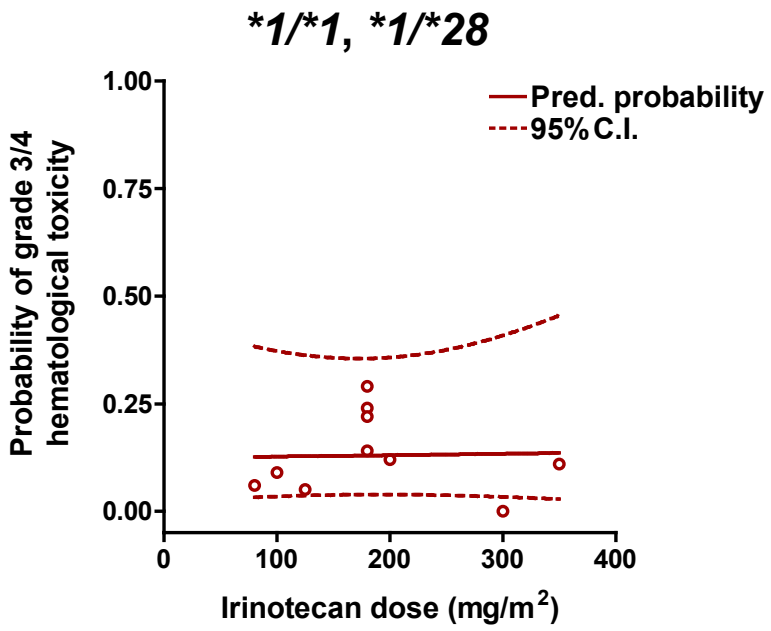
- When population consists of a mixture of two or more subpopulations that have different allele frequencies and risks (for genetic or environmental reasons)

Colhoun et al Lancet 2003

Association between *28/*28 & hematologic toxicity: irinotecan dose

Dose (continuous): generalized linear mixed model





Slope = 0.012 P=0.03

Hoskins et al JNCI 2007

- Are there different maximum tolerated doses based on UGT1A1 genotype?
- What about with different schedules and/or combination therapy?
- Is genotype-specific dosing effective for cancer control?

- Is testing routinely available?

- Have other guideline bodies considered irinotecan/UGT1A1?

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

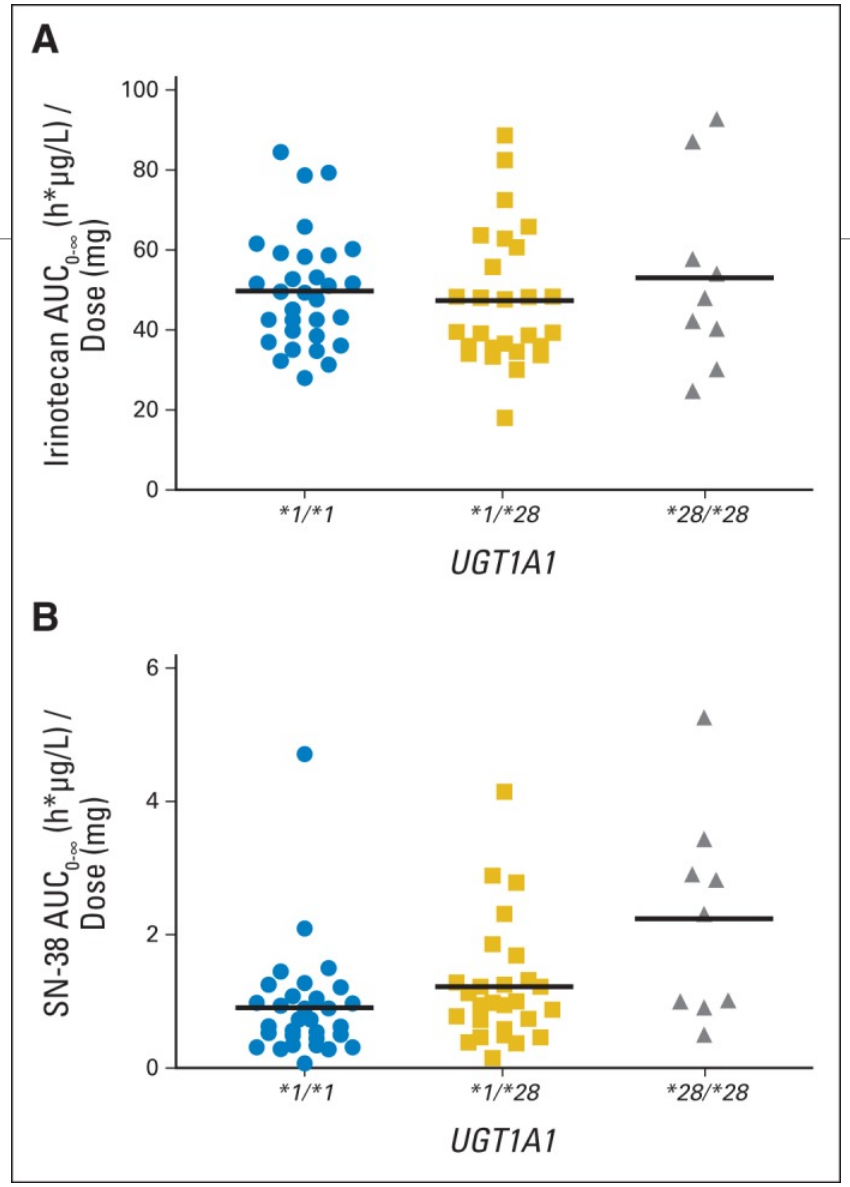
Dose-Finding and Pharmacokinetic Study to Optimize the Dosing of Irinotecan According to the *UGT1A1* Genotype of Patients With Cancer

Federico Innocenti, Richard L. Schilsky, Jacqueline Ramírez, Linda Janisch, Samir Undevia, Larry K. House, Soma Das, Kehua Wu, Michelle Turcich, Robert Marsh, Theodore Karrison, Michael L. Maitland, Ravi Salgia, and Mark J. Ratain

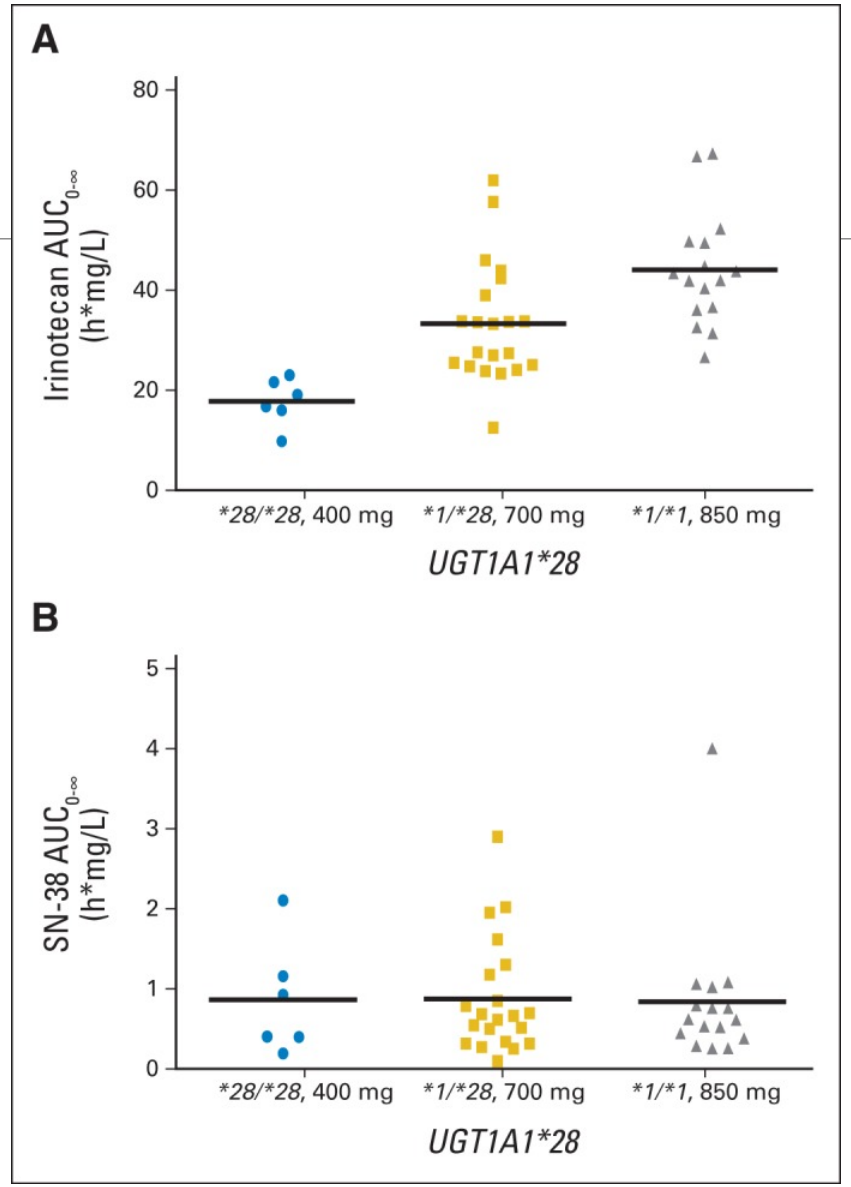
See accompanying editorial on page 2287

PI: Innocenti

Genotype



MTD



- Are there different maximum tolerated doses based on UGT1A1 genotype?
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VOLUME 28 · NUMBER 5 · FEBRUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Genotype-Driven Phase I Study of Irinotecan Administered in Combination With Fluorouracil/Leucovorin in Patients With Metastatic Colorectal Cancer

Giuseppe Toffoli, Erika Cecchin, Giampiero Gasparini, Mario D'Andrea, Giuseppe Azzarello, Umberto Basso, Enrico Mini, Sergio Pessa, Elena De Mattia, Giovanni Lo Re, Angela Buonadonna, Stefania Nobili, Paolo De Paoli, and Federico Innocenti

Table 2. Dose Escalation and DLT of Increased Irinotecan Doses in Patients Treated With FOLFIRI

Irinotecan Dose (mg/m^2)	No. of *1/*1 Patients	DLT		No. of *1/*28 Patients	DLT	
		No. of Patients With DLT	Type of DLT		No. of Patients With DLT	Type of DLT
215	4*	0		6	1	Grade 3 nausea, diarrhea, anorexia, and asthenia
260	12†	1	Grade 4 thrombocytopenia, grade 3 diarrhea	4‡	0	
310	6	1	Grade 3 stomatitis, grade 4 pancytopenia§	10	0	
370	10	0		4	2	Grade 4 neutropenia and leucopenia, grade 3 asthenia
420	3	2	Grade 3 anorexia, grade 4 asthenia, grade 3 diarrhea	—		

Cancer Therapy: Clinical

Clinical Cancer Research

Genotype-Guided Dosing Study of FOLFIRI plus Bevacizumab in Metastatic Colorectal Cancer Patients

Giuseppe Toffoli[1], Manish R. Sharma[2], Elena Marangon[1], Bianca Posocco[1], Elizabeth Gray[3], Quan Mai[4], Angela Buonadonna[1], Blase N. Polite[2], Gianmaria Miolo[1], Gianna Tabaro[1], and Federico Innocenti[5]

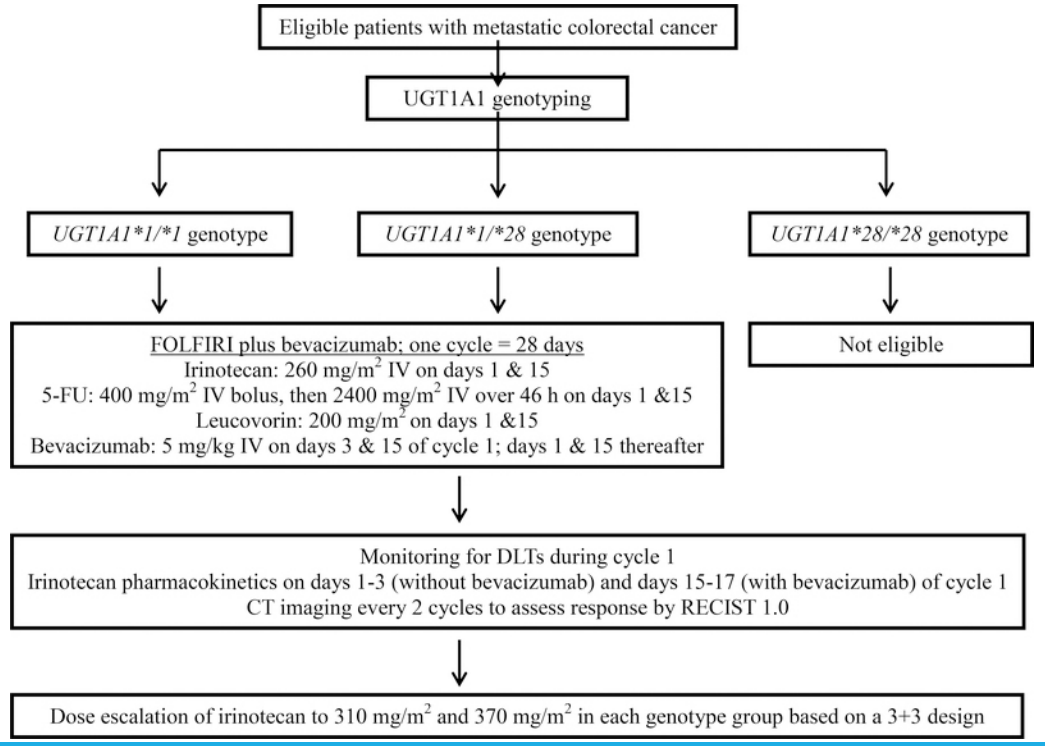


Table 2. Dose escalation of irinotecan and observed DLTs in patients treated with FOLFIRI plus bevacizumab

Irinotecan dose (mg/m^2)	*1/*1 patients (DLTs)	*1/*28 patients (DLTs)
260	10 (1) Grade 3 diarrhea	10 (2) Grade 3 arrhythmia Grade 4 neutropenia
310	10 (2) Grade 3 diarrhea × 2	10 (4) Grade 3 diarrhea Grade 3 mucositis Grade 4 neutropenia × 2
370	4 (2) Grade 3 nausea/vomiting Grade 5 neutropenic sepsis	3 (2) Grade 3 diarrhea Grade 4 neutropenia × 2

- Are there different maximum tolerated doses based on UGT1A1 genotype?
- What about with different schedules and/or combination therapy?
- Is genotype-specific dosing effective for cancer control?

- Is testing routinely available?

- Have other guideline bodies considered irinotecan/UGT1A1?

A *UGT1A1* Genotype-Guided Dosing Study of Modified FOLFIRINOX in Previously Untreated Patients With Advanced Gastrointestinal Malignancies

Manish R. Sharma, MD[1]; Smita S. Joshi, MD [1]; Theodore G. Karrison, PhD[2]; Kenisha Allen, MSN[1]; Grace Suh, MD[3]; Robert Marsh, MD[4]; Mark F. Kozloff, MD[5]; Blase N. Polite, MD, MPP [1]; Daniel V. T. Catenacci, MD[1]; and Hedy L. Kindler, MD[1]

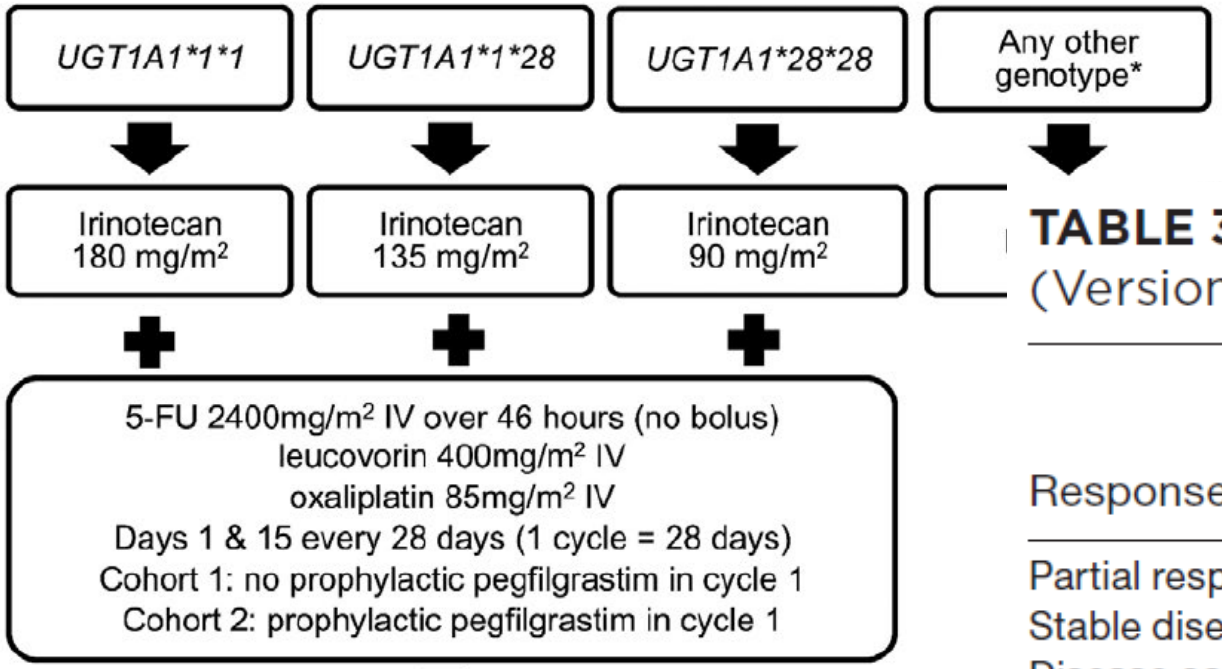


TABLE 3. Best Patient Response by RECIST Criteria (Version 1.1)

Response	Pancreatic Cancer (n = 37)	Biliary Tract Cancer (n = 29)	Gastric Cancer (n = 4)
Partial response	14 (38%)	6 (21%)	3 (75%)
Stable disease	14 (38%)	14 (48%)	1 (25%)
Disease control	28 (76%)	20 (69%)	4 (100%)
Progressive disease	4 (11%)	7 (24%)	0
Not evaluable	5 (14%)	2 (7%)	0

Data are presented as n (%).

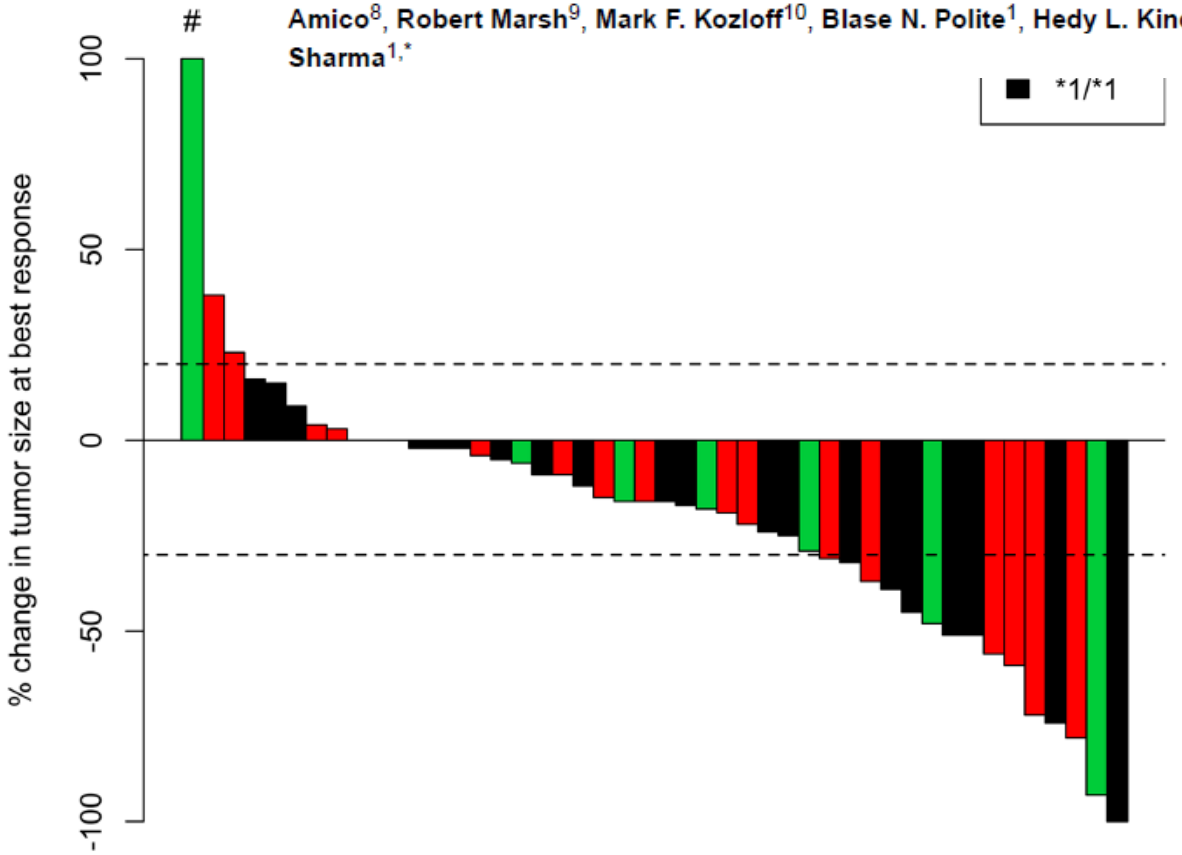
Cancer 2019;125:1629-1636

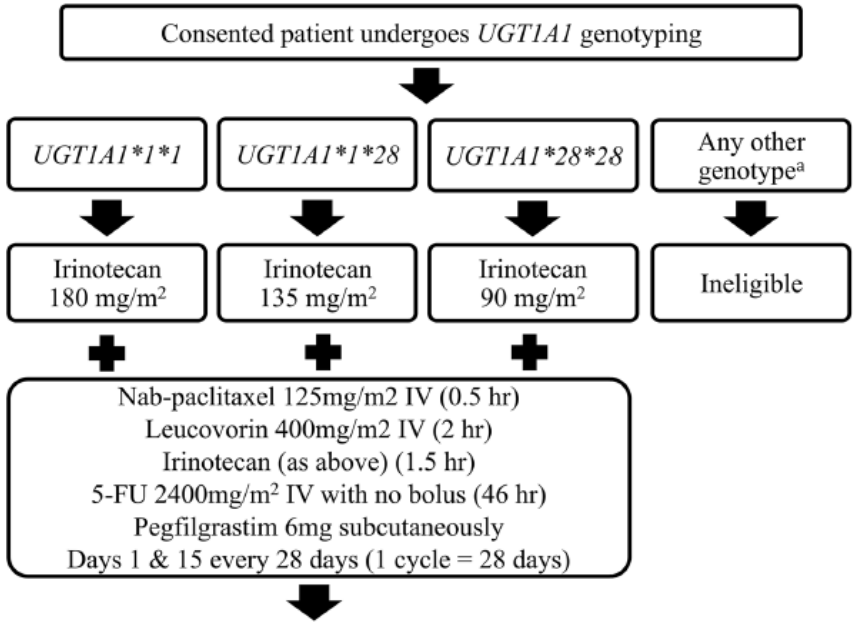
Clin Cancer Res. 2020 January 01; 26(1): 18–24. doi:10.1158/1078-0432.CCR-19-1483.

Clinical assessment of 5-fluorouracil/leucovorin, nab-paclitaxel, and irinotecan (FOLFIRABRAX) in untreated gastrointestinal cancer patients using UGT1A1 genotype-guided dosing

Smita S. Joshi[1], Daniel V.T. Catenacci[1], Theodore G. Karrison[2], Jaclyn D. Peterson[1], Mark M. Zalupski[3], Amikar Sehdev[4], James Wade[5], Ahad Sadiq[6], Vincent Picozzi[7], Andrea Amico[8], Robert Marsh[9], Mark F. Kozloff[10], Blase N. Polite[1], Hedy L. Kindler[1], Manish R. Sharma[1,*]

UGT1A1	1/1	1/28	28/28
CR/PR %	30%	32%	29%
SD %	48%	47%	57%





A Multicenter Clinical Phase II Study of FOLFOXIRI Plus Bevacizumab as First-line Therapy in Patients With Metastatic Colorectal Cancer: QUATTRO Study

Eiji Oki,[1] Takeshi Kato,[2] Hideaki Bando,[3] Takayuki Yoshino,[3] Kei Muro,[4] Hiroya Taniguchi,[4] Yoshinori Kagawa,[5] Kentaro Yamazaki,[6] Tatsuro Yamaguchi,[7] Akihito Tsuji,[8] Shigeyoshi Iwamoto,[9] Goro Nakayama,[10] Yasunori Emi,[11] Tetsuo Touyama,[12] Masato Nakamura,[13] Masahito Kotaka,[14] Hideki Sakisaka,[15] Takeharu Yamanaka,[16] Akiyoshi Kanazawa[17]

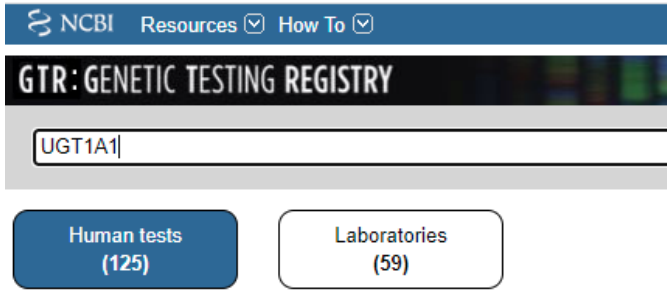
Clin Colorectal Cancer 2018;17:147-155

Table 6 The Incidence Rate of Neutropenia (Grade 4) and Febrile Neutropenia Before Cycle 3 by *UGT1A1* Genotype

UGT1A1 Genotype	n	Incidence Rate, n (%)	*P* Value (Vs. Wild Type)[a]
Neutropenia (Grade 4)			
All	69	22 (31.9)	
Wild type	30	4 (13.3)	
Heterozygote (**1/*6* or **1/*28*)	39	18 (46.2)	.004
**1/*6*	24	10 (41.7)	.028
**1/*28*	15	8 (53.3)	.010
Febrile neutropenia			
All	69	13 (18.8)	
Wild type	30	3 (10.0)	
Heterozygote (**1/*6* or **1/*28*)	39	10 (25.6)	.128
**1/*6*	24	8 (33.3)	.046
**1/*28*	15	2 (13.3)	1.000

[a]The Fisher exact test was performed for comparison between *UGT1A1* wild type and heterozygote.

- Are there different maximum tolerated doses based on UGT1A1 genotype?
- What about with different schedules and/or combination therapy?
- Is genotype-specific dosing effective for cancer control?
- Is testing routinely available?

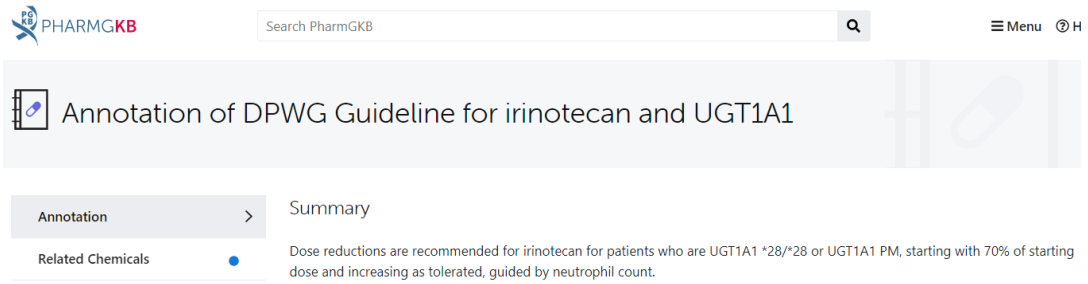


- Have other guideline bodies considered irinotecan/UGT1A1?

Dutch PGx Working Group

KNMP
Dutch PGx Working Group

- *6, *28, and *37 have sufficient evidence to be implemented into clinical care
- Initial literature search Sept, 2006. FU Oct 2008, March 2014, July 2017 and March 2021.
- Given the >>> papers, only included >25 subjects with one or more *28 alleles.
- **There is strong evidence that the **28* and/or **6* variants are associated with an increased risk of grade ≥ 3 toxicity. All nine meta-analyses [22–30] investigating adverse events and 16 [19,21,31–44] of the 23 [20,45–50] included studies have reported this increased risk. In addition, all seven meta-analyses and three studies investigating the effect of **28/*28* and/or **6/*6* and/or **6/*28* compared with all other genotypes, found that this risk was also increased for **28/*28* and/or PM patients compared to all other patients [23–25,28–30,37,42,44]. With regard to efficacy, four [23,51–53] of the five [24] meta-analyses and eight [32,34,37–39,41,49,50] of the ten [43,44] studies did not show the **28* and/or **6* variants to be associated with increased effectiveness of treatment. In summary, for **28/*28* and PM there is ample evidence for an increased risk of serious adverse events at normal doses (also when compared to all other genotypes/phenotypes), while convincing evidence for an increased efficacy has not been demonstrated**



KNMP

UGT1A1: irinotecan

Recommendation concerning pre-emptive genotyping, including justification of choices:

The KNMP Pharmacogenetics Working Group considers genotyping before starting irinotecan to be essential for drug safety. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection.

The clinical implication of the gene-drug interaction scores 8 out of the maximum of 10 points (with pre-emptive genotyping considered to be essential for scores ranging from 6 to 10 points):

The risk of serious life-threatening toxicity is increased for patients with a genotype resulting in diminished UGT1A1 enzyme activity (*28/*28 and PM). This toxicity can be fatal (grade 5) (Rouits 2004). This results in the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (2 points for CTCAE grade 5).

The increased risk for serious life-threatening toxicity (code E corresponding to grade 4) has been shown in 14 studies and 9 meta-analyses. This results in the maximum score of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for three or more publications with level of evidence score ≥ 3).

The number needed to genotype was deduced to be 41, using the data on Whites in the second largest meta-analysis (Liu 2017) and the prevalence of *28/*28 in the Dutch population. For White patients, Liu 2017 found only the risk for severe neutropenia to be increased for *28/*28 compared to *1/*1+*1/*28, not the risk for severe diarrhoea. In the 12

	Genotype	Code	Gene- drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	*1/*28	4 F	Yes	No	7 June 2021
	*28/*28	4 F	Yes	Yes	
	IM	4 E	Yes	No	
	PM	4 E	Yes	Yes	

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+	8+
Corresponding Clinical Implication Score:		Essential

KNMP

UGT1A1: irinotecan

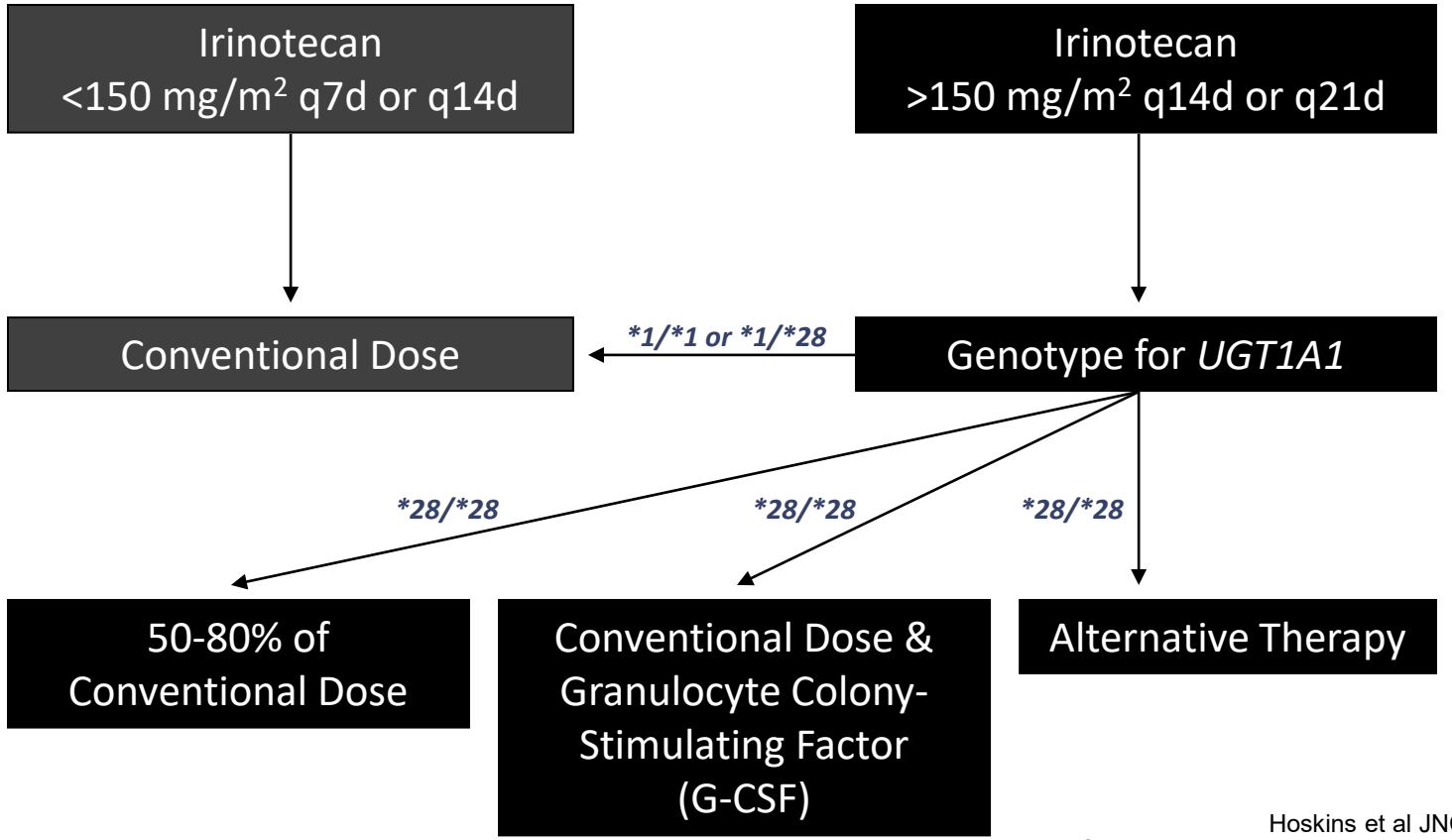
Diplotype	Dose adjustment?	Rationale
*1/*28	No	most prevalent diplotype in caucasians
*28/*28	Yes, 70% of normal dose followed by tapering in response of tolerability and neutrophile counts	

PGx-Based Recommendations for Irinotecan/UGT1A1

Comparison of PGx Recommendations Between Guideline and Administrative Authorities		
	Topic, Artifact, or Statement	**Irinotecan**
CPIC	**CPIC level**	A
	CPIC clinical recommendations	**NR**
FDA	**PGx associations with sufficient evidence to allow their use in guiding therapy management**	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (severe neutropenia). Consider reducing the starting dosage by one level and modify the dosage based on individual patient tolerance for **28/*28* (PMs).
	Associations with data to suggest a potential impact on drug safety or response	NR
DPWG	**Recommendations**	***UGT1A1 *1/*28* : No action is needed for this gene-drug interaction**. ***UGT1A1 *28/*28*** : Start with 70% of the standard dose. If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.
NCCN	**Recommendations**	Irinotecan should be used with caution in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for *UGT1A1*. Guidelines for use in clinical practice have not been established.
EMA	**Recommendations**	An initial dose reduction from 80 to 60 mg/m^2 is recommended in patients with *UGT1A1 *28/*28* (PMs).
RNPGx / GPCO-Unicancer	**Recommendations (French)**	Pre-treatment UGT1A1 genotyping is strongly recommended. An initial 25-30% dose reduction is recommended for *28/*28 patients. Pre-treatment testing is not recommended for irinotecan <180 mg/m2 because haematological and GI toxicities are quite similar regardless of the genotype for low irinotecan doses
AIOM and SIF	**Recommendations (Italian)**	An initial 30% dose reduction is recommended for *28/*28 patients.

https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2020.pdf, CAMPTOSAR Drug Label, 2020, https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/pharmacogenomics-working-party, https://www.nccn.org, https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

Suggested decision tree for dosing irinotecan



Hoskins et al JNCI 2007
Obradovic et al Pharmacogenomics 2008

UGT1A1 Clinical Decision Support

Irinotecan Dosing Recommendations Based on *UGT1A1* Genotype/Phenotype [a]			
***UGT1A1* Result**	**UGT1A1 Phenotype**	**Implications**	**Dosing Recommendations**
**1/*1*	Normal metabolizer	No influence on SN-38 plasma concentrations	Consider usual irinotecan dosage and titrate based on response
**1/*6* **1/*28*	Intermediate metabolizer	Risk of toxicity due to elevated SN-38 plasma concentrations	Consider usual irinotecan dosage and titrate based on response
**6/*6* **6/*28* **28/*28*	Poor metabolizer	Risk of toxicity due to elevated SN-38 plasma concentrations	For irinotecan doses ≥250 mg/m^2, consider a 30% reduction of the usual starting dosage and titrate based on response For irinotecan doses <250 mg/m^2, consider the usual irinotecan dosage and titrate based on response The FDA drug label provides additional guidance for drug dosing
[a] Weight, liver function, previous irinotecan exposure, and other patient characteristics may influence drug selection and dosage.			

https://www.knmp.nl/downloads/pharmacogenetic-recommendations-august-2020.pdf

It is time to start working on this guideline!

Active FDA + EMA label for irinotecan/UGT1A1
30+ clinical studies to assess
Toxicity and Efficacy data to consider
Growing use of oncology preemptive PGx panel testing
Already provisional CPIC level A and PharmGKB level 1A

Gateway to future, broader guidance around UGT1A PGx