

*Farmacokinetiek en genetica
bij TKI behandeling*

Nielka van Erp



LEIDS UNIVERSITAIR MEDISCH CENTRUM



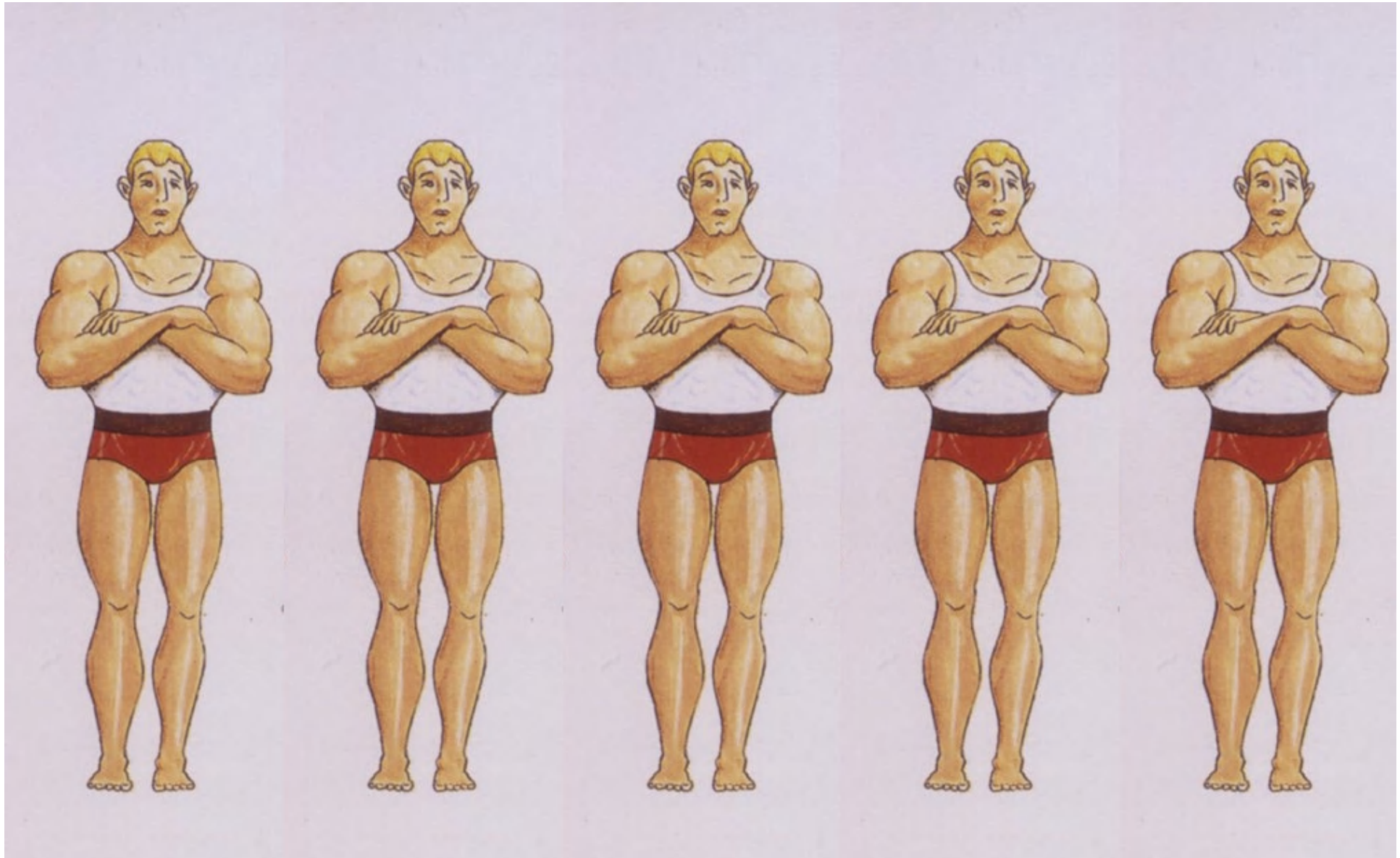
Werkgroep Immunotherapie Nederland
voor Oncologie

Patiënten reageren verschillend:

- Toxiciteit
- Antitumor activiteit

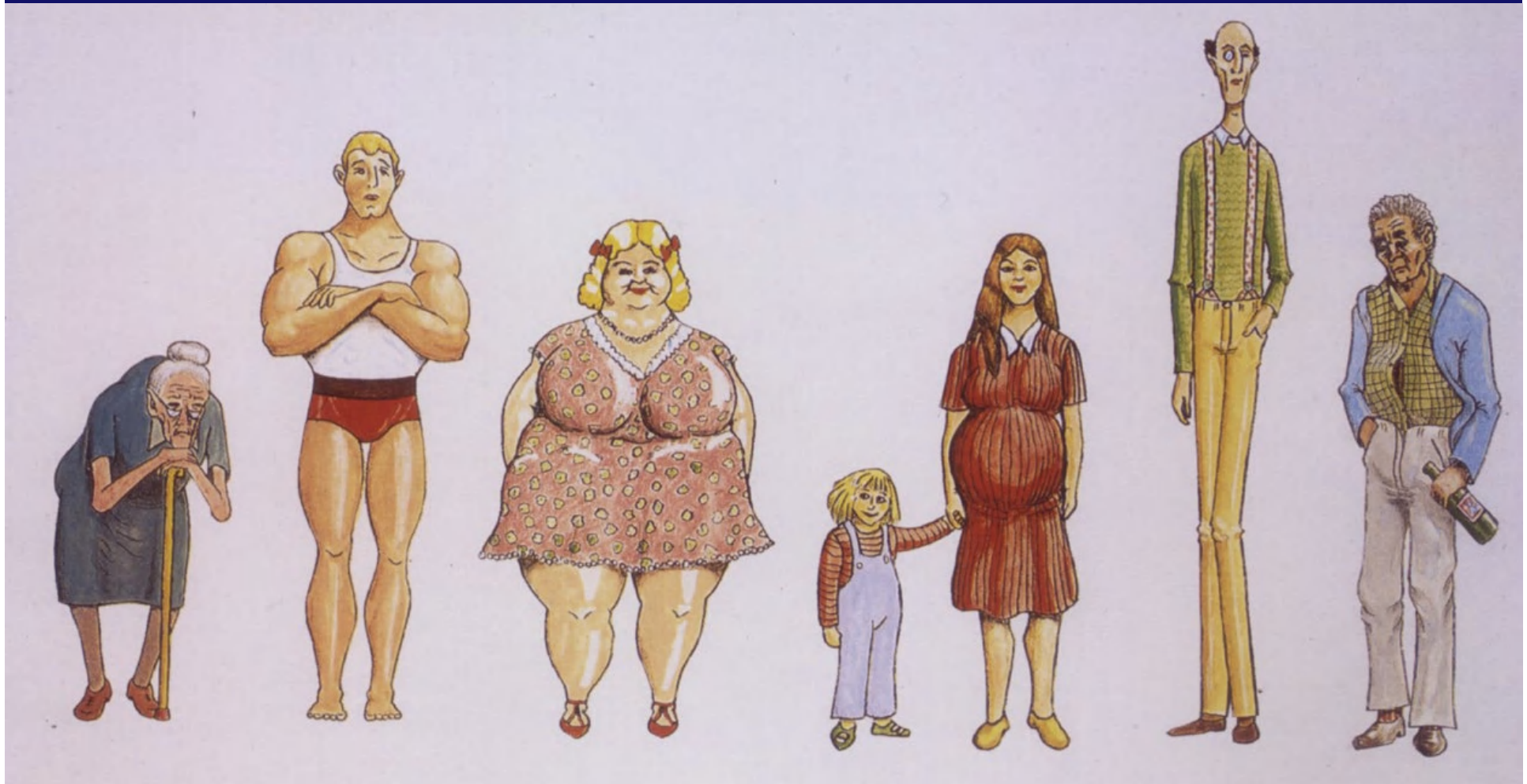


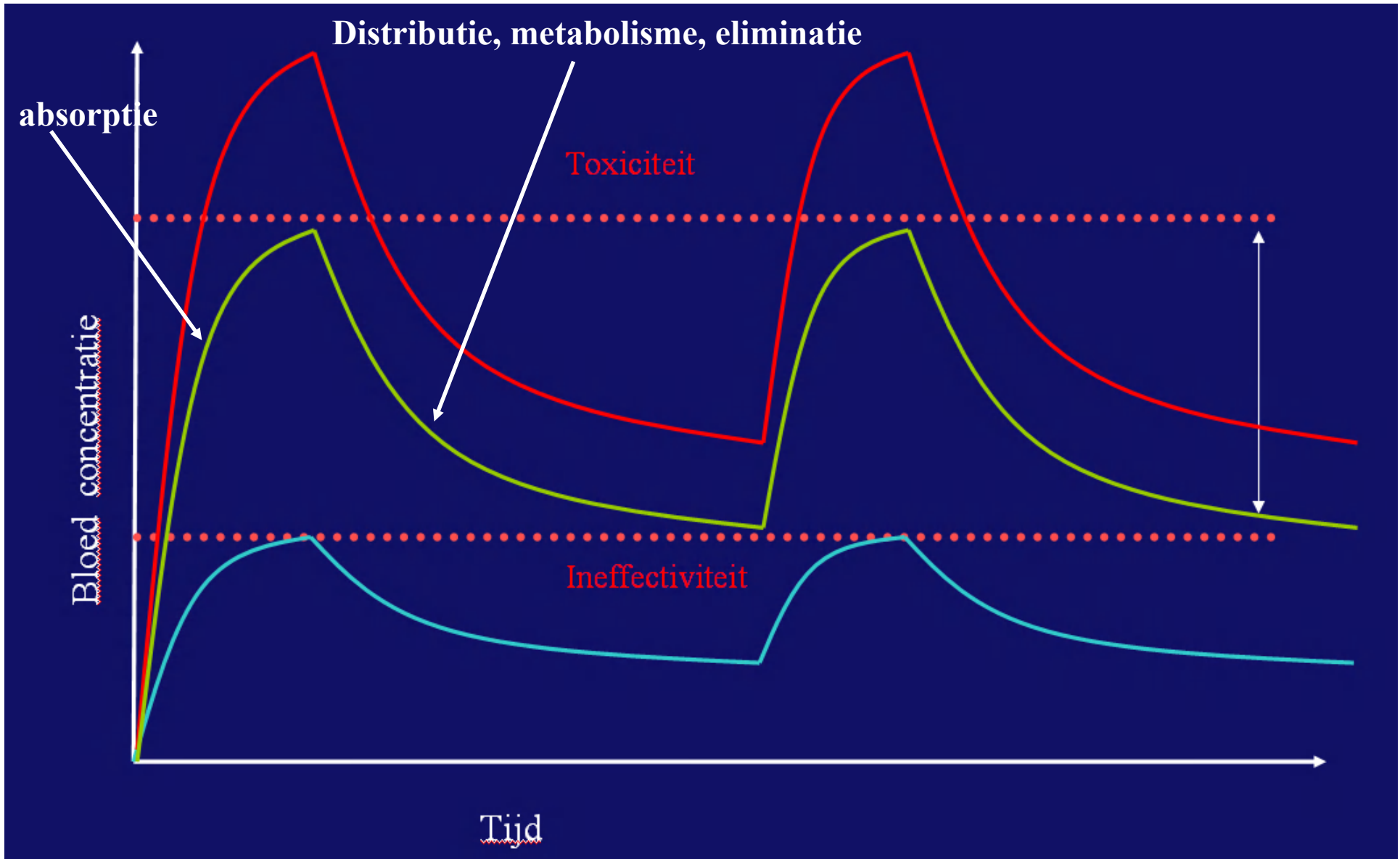
In de ideale wereld: 1 pill suits all



Interpatient variabiliteit:

- Genetische verschillen
- Farmacokinetische verschillen





Traditionele dosis individualisatie binnen de oncologie: mg / BSA

Rationale:

Correlatie lichaamsopp \leftrightarrow distributie en / of eliminatie

Echter:

- Matige correlatie
- Correlatie onbekend



Doel:

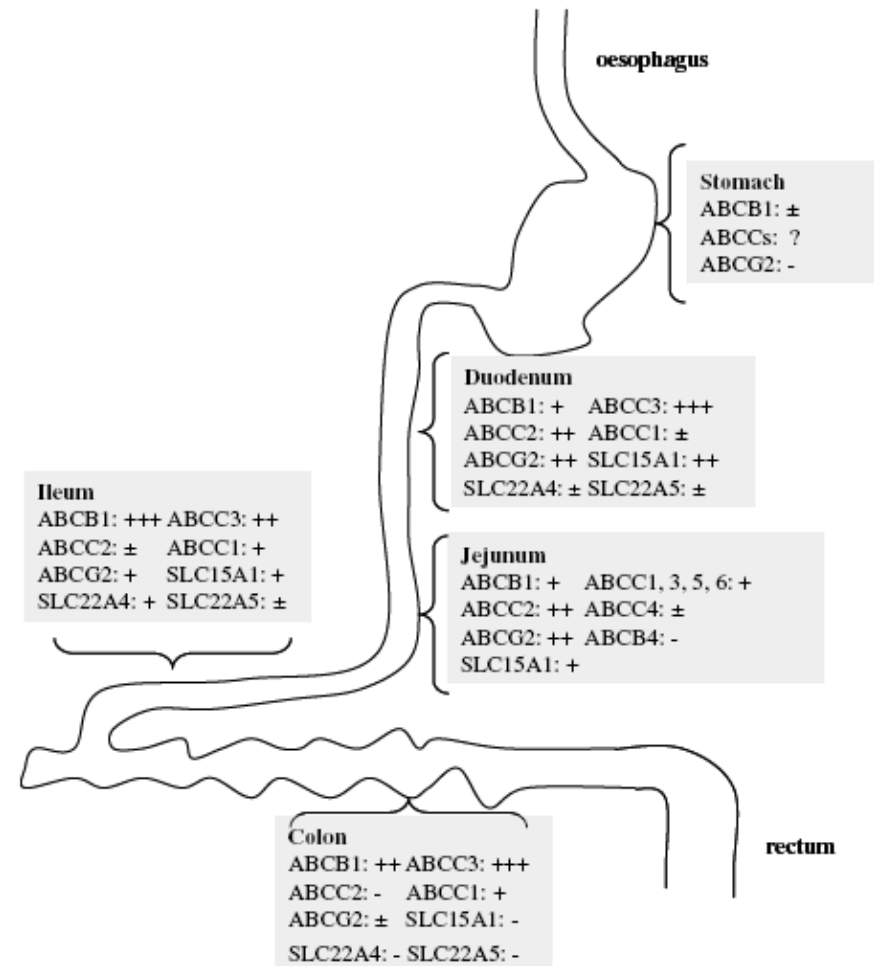
Interpatient variabiliteit in geneesmiddel blootstelling reduceren

Alternatieven voor dosis individualisatie op BSA:

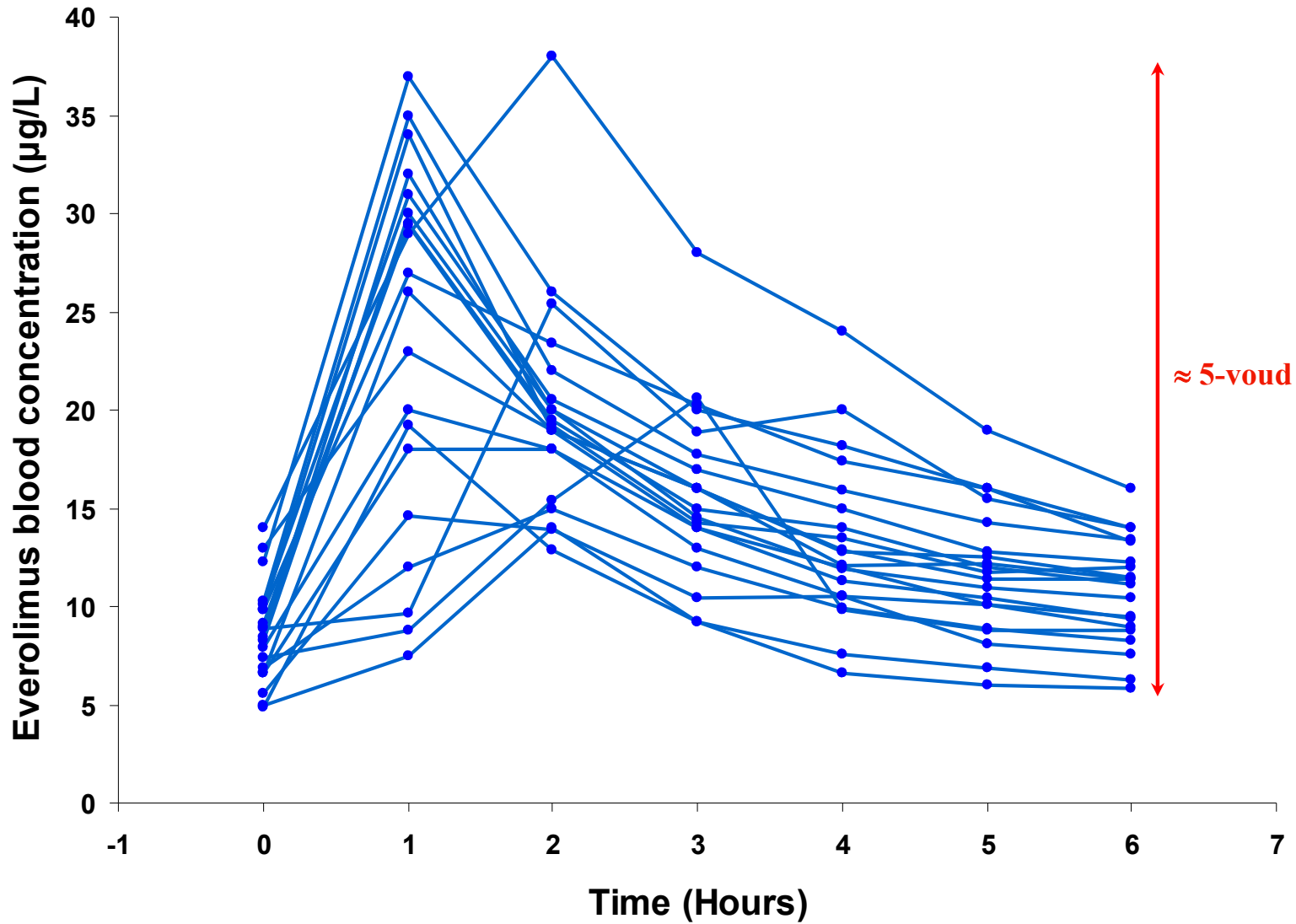
- Toxicity adjusted dose
- Biomarker - Farmacodynamisch eindpunt
- Therapeutic Drug Monitoring - Farmacokinetisch eindpunt
- Dosis / therapieselectie o.b.v. patiëntkarakteristieken (incl. genotypering)

Oorzaak extra variatie:

- Afgifte geneesmiddel uit toedieningsvorm
- Opname vanuit het MD-kanaal
- Invloed voedsel / pH
- Genotype transporters / enzymen
- Fenotype transporters / enzymen



Cancer Treat Rev; Oostendorp et al. (2009) 35(2) 137-47



Definitie:

Bepalen en interpreteren van geneesmiddelconcentraties in patiëntmateriaal op basis waarvan de dosis kan worden aangepast voor de individuele patiënt.

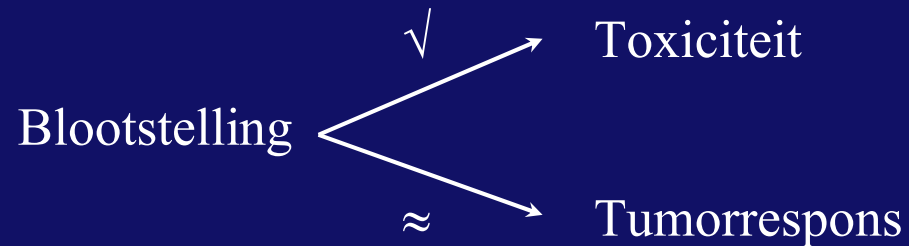
Doel:

Dosisindividualisatie teneinde vermindering toxiciteit, verbetering effectiviteit

Meerwaarde TDM vastgesteld:

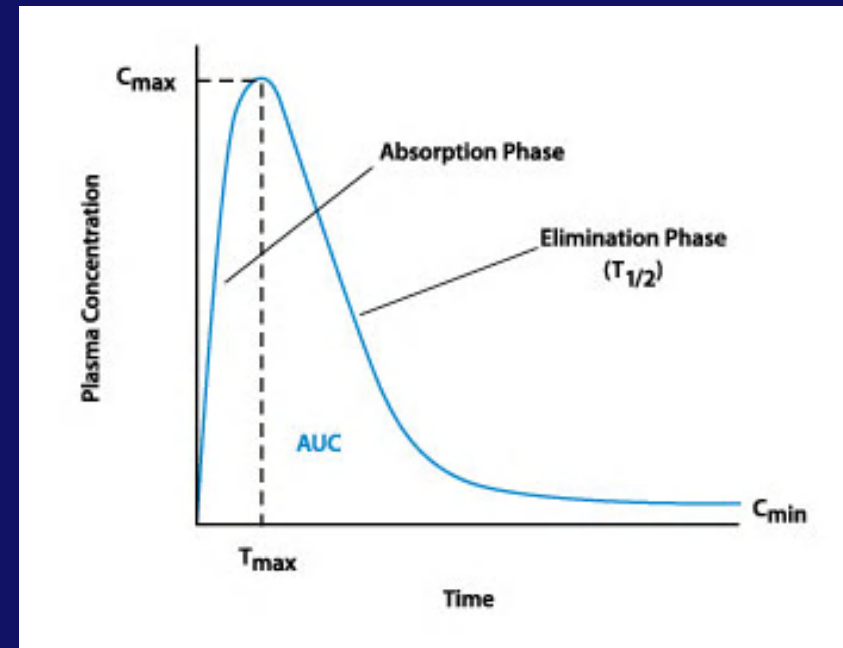
Aminoglycosiden, lithium, anti-epileptica, anti-HIV therapie, immunosuppressive therapie ...

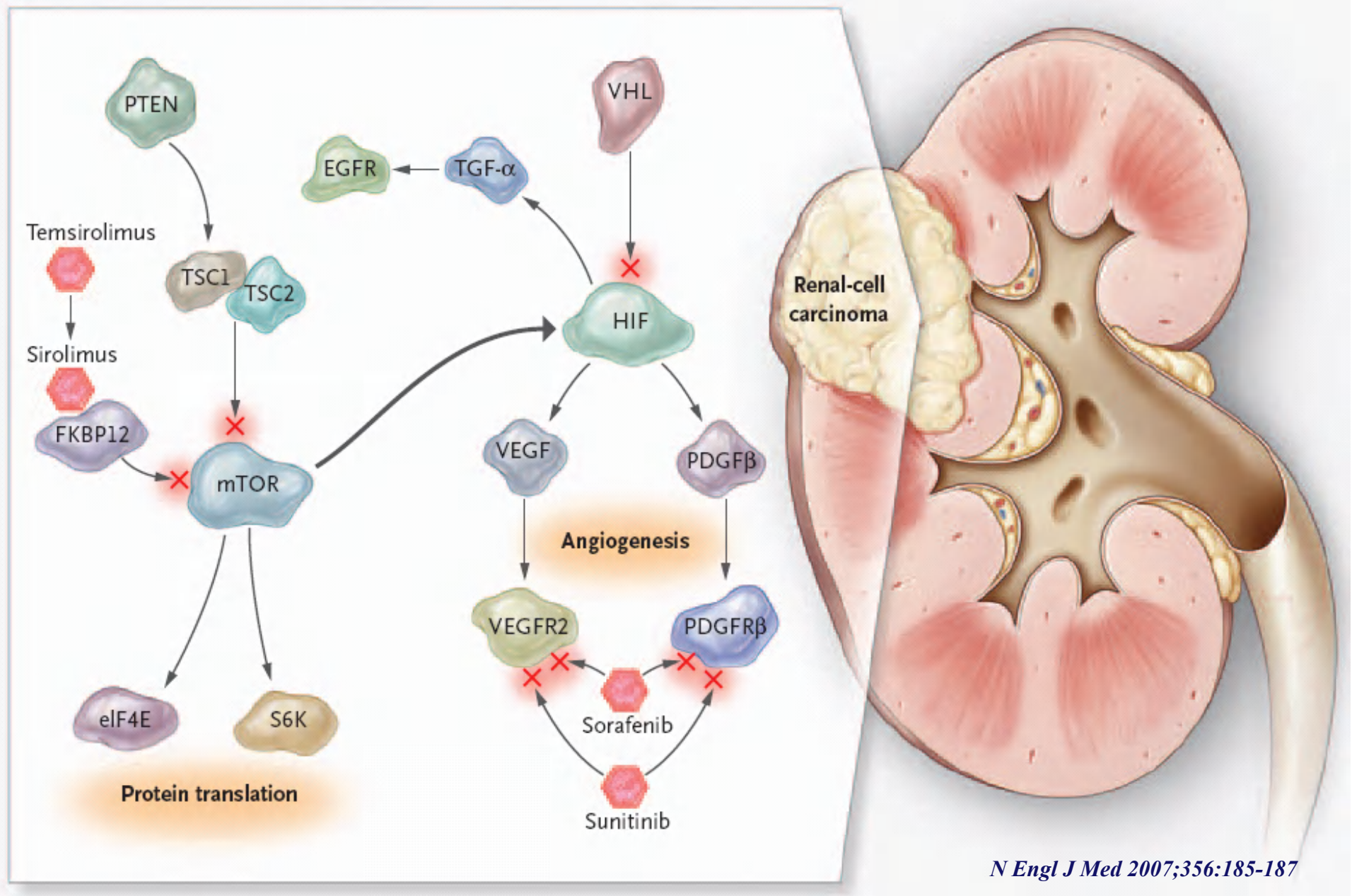
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2. Smalle therapeutische breedte
3. Grote interpatient variabiliteit met relatief kleine intrapatient variabiliteit in farmacokinetiek
4. Geen eenvoudige klinische / laboratorium determinanten aanwezig waarop de dosis kan worden aangepast
5. De mate van dosisaanpassing aan de hand van geneesmiddelspiegels kan eenvoudig worden bepaald en is gevalideerd
6. Geneesmiddel wordt meerdere malen toegediend
7. Geschikte analytische methode aanwezig voor geneesmiddelanalyse



Reden \approx blootstellen en tumorrespons

- Tumor heterogeniteit
 - Resistente tumorcellen voor therapie
 - Farmacokinetiek op tumorcelniveau
- Relatie AUC – tumorrespons is lastiger vast te stellen
- Relatie concentratie geneesmiddel serum/bloed \leftrightarrow tumorcel veelal onbekend



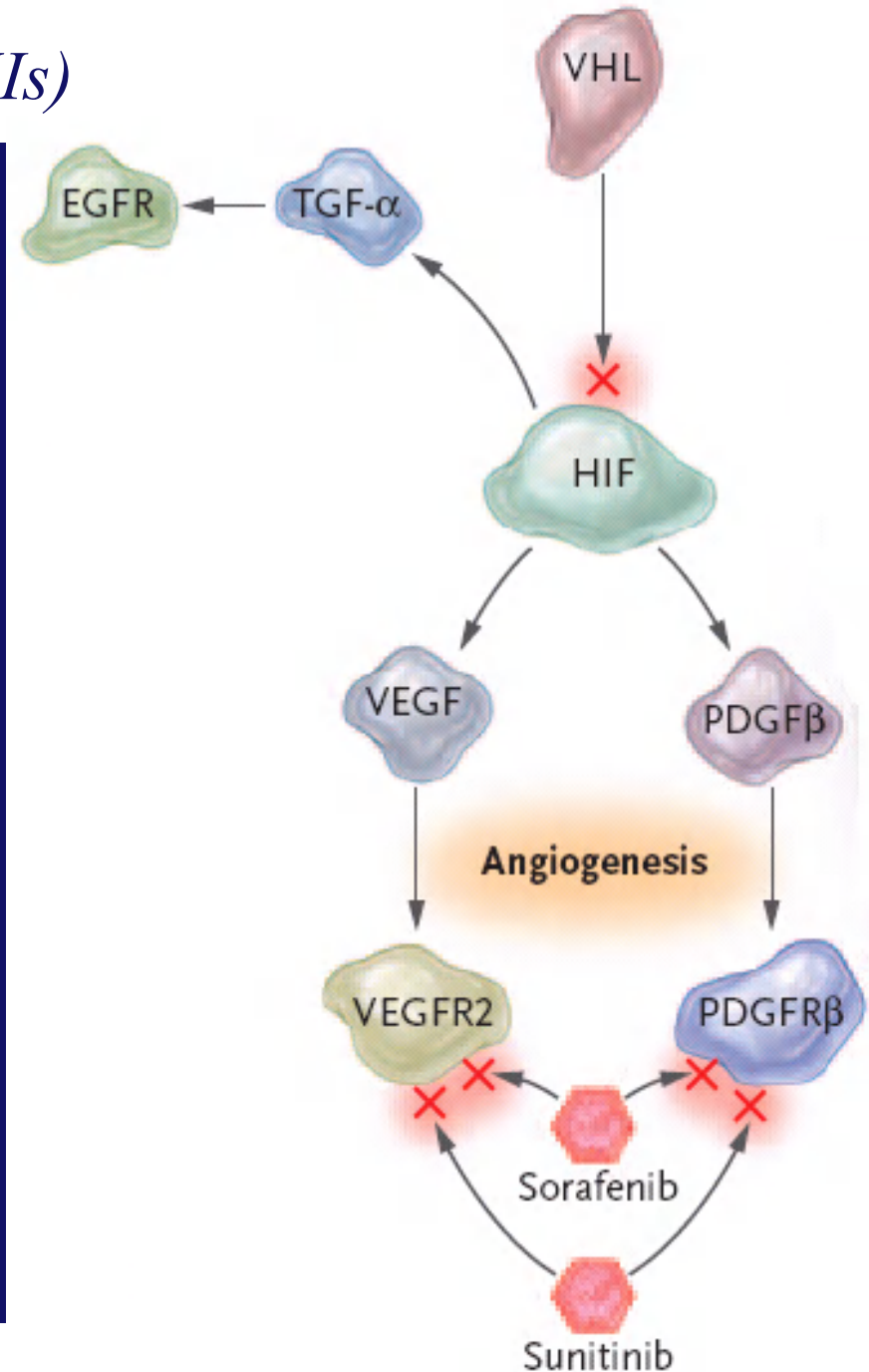


Geregistreerde TKIs

- Sunitinib (Sutent; Pfizer)
- Sorafenib (Nexavar; Bayer)

TKIs in fase III

- Pazopanib (Votrient; GSK)
- Axitinib (AG-013736; Pfizer)



	F (%)	Eiwitbinding (%)	Tmax (hr)	t _{1/2} (hr)	AUC _{0-24hr} (ug*hr/mL)
Sunitinib	unknown	~ 95	6 - 12	40 - 60	1.11
Sorafenib	unknown	> 99	3	25 - 48	143.4
Axitinib	unknown	unknown	2 - 6	2 - 5	0.46
Pazopanib	14 - 39	> 99	2 - 8	30.9	1037

*Cancer Treat Rev; van Erp et al (2009) 35(8) 692-706
 Clin Cancer Res; Hurwitz et al (2009) 15(12) 4220-4227
 JCO; Rugo et al (2005) 23(24) 5474 – 5483
 FDA registration information*

	Enzymen fase I	Enzyme fase II	Transporters
Sunitinib	CYP3A4		ABCB1, ABCG2
Sorafenib	CYP3A4	UGT1A9	ABCB1, ABCG2
Axitinib	Major CYP3A4 Minor CYP1A2		unknown
Pazopanib	Major CYP3A4 Minor CYP1A2, CYP2C8		ABCB1, ABCG2

*Cancer Treat Rev; van Erp et al (2009) 35(8) 692-706
 Clin Cancer Res; Hurwitz et al (2009) 15(12) 4220-4227
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Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study

Richard A. Larson,¹ Brian J. Druker,² Francois Guilhot,³ Stephen G. O'Brien,⁴ Gilles J. Riviere,⁵ Tillmann Krahnke,⁶ Insa Gathmann,⁶ and Yanfeng Wang,⁷ for the IRIS (International Randomized Interferon vs STI571) Study Group

¹University of Chicago, IL; ²Oregon Health and Science University Cancer Institute, Portland; ³Clinical Investigational Center Inserm, Centre Hospitalier Universitaire (CHU), Poitiers, France; ⁴University of Newcastle, Newcastle, United Kingdom; ⁵Novartis Pharma, Rueil-Malmaison, France; ⁶Novartis Pharma, Basel, Switzerland; and ⁷Novartis Pharmaceuticals, East Hanover, NJ

Imatinib at 400 mg daily is standard treatment for chronic myeloid leukemia in chronic phase. We here describe the correlation of imatinib trough plasma concentrations (C_{\min}) with clinical responses, event-free survival (EFS), and adverse events (AEs). Trough level plasma samples were obtained on day 29 (steady state, $n = 351$). Plasma concentrations of imatinib and its metabolite CGP74588 were determined by liquid chromatography/mass spectrometry. The overall mean (\pm SD, CV%) steady-state C_{\min} for imatinib and CGP74588

were 979 ng/mL (\pm 530 ng/mL, 54.1%) and 242 ng/mL (\pm 106 ng/mL, 43.6%), respectively. Cumulative estimated complete cytogenetic response (CCyR) and major molecular response (MMR) rates differed among the quartiles of imatinib trough levels ($P = .01$ for CCyR, $P = .02$ for MMR). C_{\min} of imatinib was significantly higher in patients who achieved CCyR (1009 ± 544 ng/mL vs 812 ± 409 ng/mL, $P = .01$). Patients with high imatinib exposure had better rates of CCyR and MMR and EFS. An exploratory analysis demonstrated that imatinib trough levels

were predictive of higher CCyR independently of Sokal risk group. AE rates were similar among the imatinib quartile categories except fluid retention, rash, myalgia, and anemia, which were more common at higher imatinib concentrations. These results suggest that an adequate plasma concentration of imatinib is important for a good clinical response. This study is registered at <http://clinicaltrials.gov> as NCT00333840. (Blood. 2008;111:4022-4028)

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Imatinib Plasma Levels Are Correlated With Clinical Benefit in Patients With Unresectable/Metastatic Gastrointestinal Stromal Tumors

George D. Demetri, Yanfeng Wang, Elisabeth Wehrle, Amy Racine, Zariana Nikolova, Charles D. Blanke, Heikki Joensuu, and Margaret von Mehren

A B S T R A C T

Purpose

To study the pharmacokinetics (PK) of imatinib (IM) in patients with advanced GI stromal tumors (GISTs) treated in a randomized phase II study and to explore the potential relationship between IM plasma levels and long-term clinical outcomes.

Patients and Methods

Patients were randomly assigned to receive IM at 400 mg versus 600 mg daily. IM plasma levels were analyzed in a subset of patients ($n = 73$) for whom PK data on day 1 and at steady-state (SS, day 29) were available. IM PK was evaluated using a population PK approach. The relationship between IM plasma exposure and clinical outcome was explored by grouping patients into quartiles according to IM trough concentration (C_{\min}). The clinical outcome parameters evaluated include overall objective benefit rate (OOBR; complete response plus partial response plus stable disease) time to progression (TTP), and *KIT* genotyping.

Results

IM PK exposure showed a high inter-patient variability, and clinical outcomes were correlated with IM trough levels at SS. The median TTP was 11.3 months for patients in the lowest C_{\min} quartile (Q1, $< 1,110$ ng/mL) compared with more than 30 months for Q2 to Q4 ($P = .0029$). OOBR was also inferior in Q1 patients. In patients with GIST with *KIT* exon 11 mutations ($n = 39$), the OOBR was 67% for Q1 patients versus 100% for all others ($P = .001$).

Conclusion

In patients with advanced GIST, IM trough levels at SS were associated with clinical benefit. Patients with IM C_{\min} below 1,100 ng/mL showed a shorter TTP and lower rate of clinical benefit (OOBR). Further studies are justified to test whether monitoring IM plasma levels might optimize clinical outcomes for patients with GIST.

From the Ludwig Center, Dana-Farber/Harvard Cancer Center, and Harvard Medical School, Boston, MA; Oncology Business Unit, Novartis Pharmaceuticals Corp, Florham Park, NJ; Oncology Business Unit and Biostatistics, Novartis Pharmaceuticals AG, Basel, Switzerland; British Columbia Cancer Agency, University of British Columbia, Vancouver, British Columbia, Canada; Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland; and Fox Chase Cancer Center, Philadelphia, PA.

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Supported in part by Novartis Pharmaceuticals Corp, Oncology Business Unit, Florham Park, NJ. Additional philanthropic support for this work has been provided by the Virginia and Daniel K. Ludwig Trust for Cancer Research and the Stutman Gastrointestinal Stromal Tumor Cancer Research Fund (G.D.D.).

Presented in part at the 44th Annual Meeting of the American Society of Clinical Oncology, May 30-June 3, 2008, Chicago, IL, as well as the Gastrointestinal Cancer Symposium of the American Society of Clinical Oncology, the American Gastroenterological Association, the American Society for

Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta-analysis

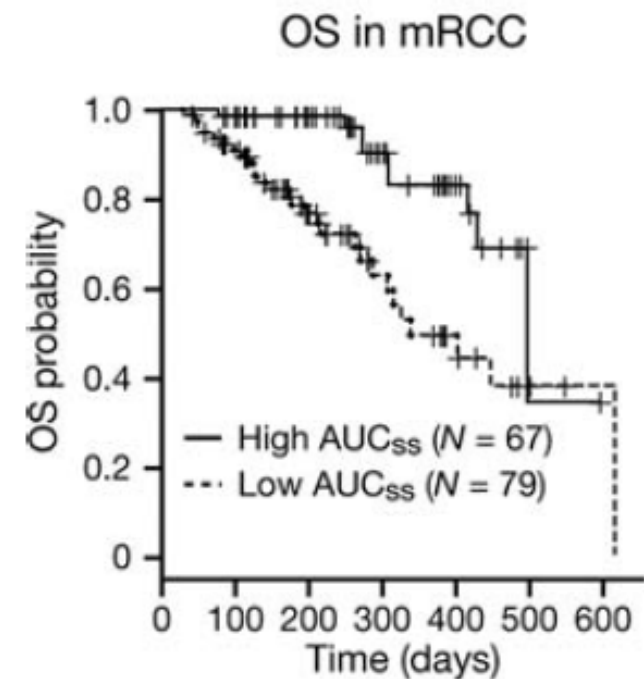
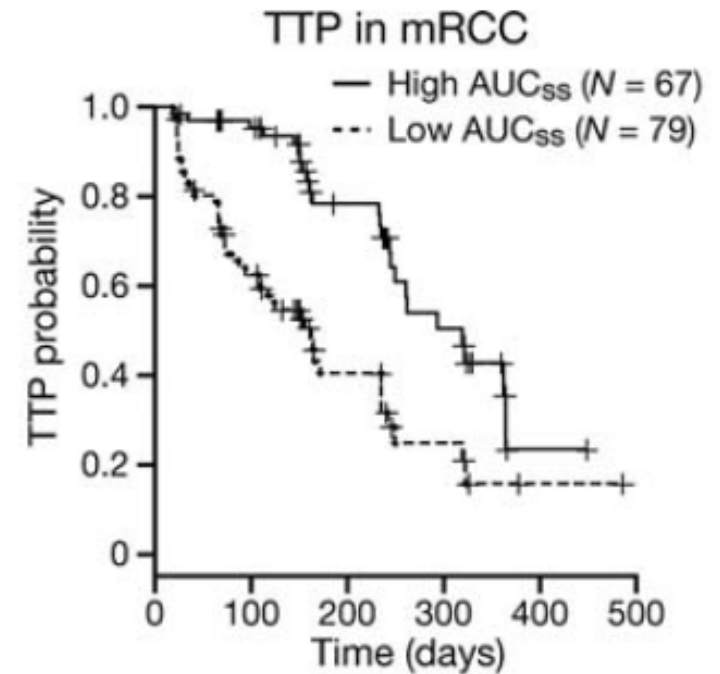
**Brett E. Houk · Carlo L. Bello · Bill Poland ·
Lee S. Rosen · George D. Demetri ·
Robert J. Motzer**

LU
MC *Relatie “exposure – efficacy”*

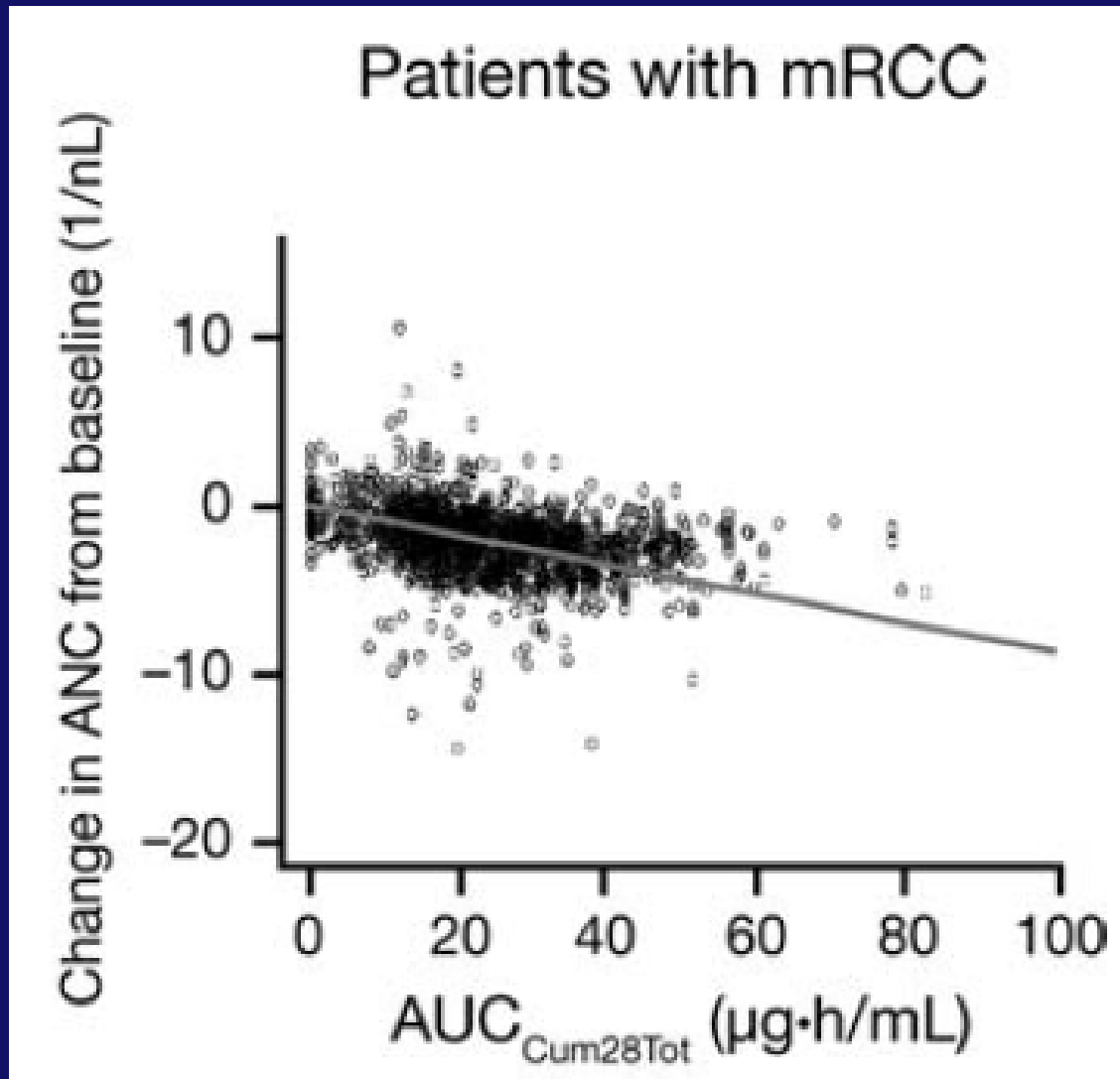
Hogere blootstelling → langere TTP en OS

Hogere blootstelling gedefinieerd:

$AUC_{ss} > \text{mediane } AUC_{ss} (> 0.8 \text{ ug*hr/mL})$



Relatie “exposure – neutrophile counts”

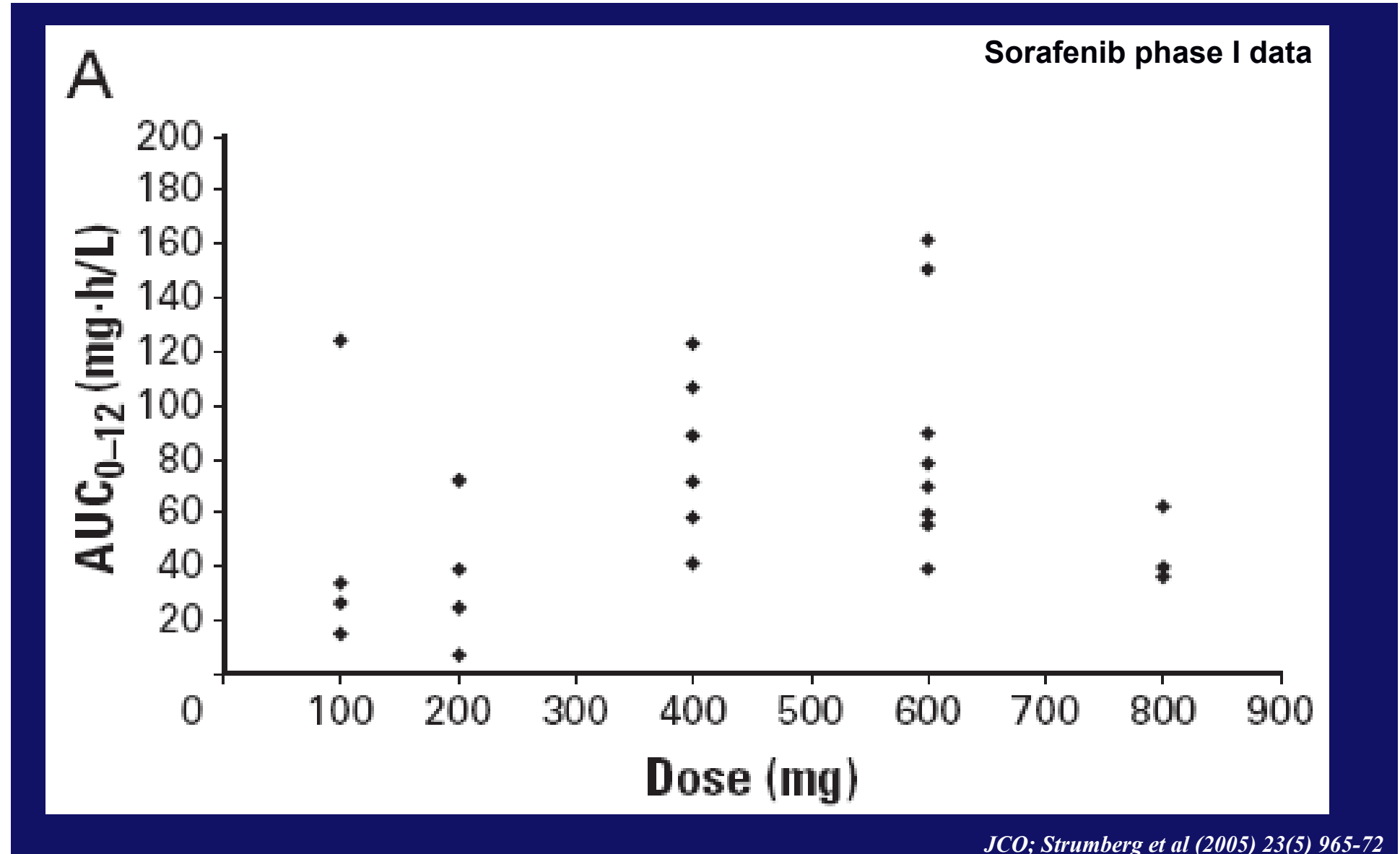


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5. De mate van dosisaanpassing aan de hand van geneesmiddelspiegels kan eenvoudig worden bepaald en is gevalideerd

- Doseringen TKIs op MTD
 - relatief snel toxiciteit

- Hogere blootstelling lijkt beter effectief
 - Retrospectieve analyses doen het vermoeden
 - Prospectief mogelijk de oorzaak van falen gefitinib / slagen erlotinib bij NSCLC

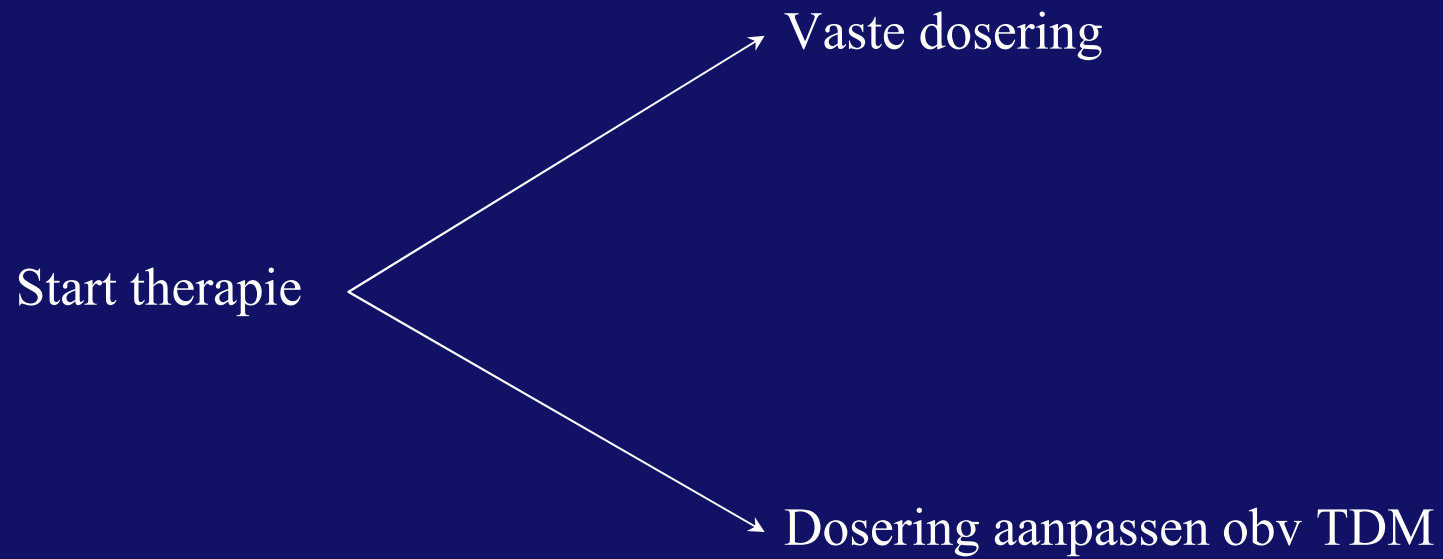
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JCO; Strumberg et al (2005) 23(5) 965-72

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- TKIs lijken goede kandidaten voor TDM
- Prospectieve validatie rol TDM noodzakelijk
- Onderzoek continueren naar eenvoudigere wijzen van dosisindividualisatie:
 - Biomarkers
 - Mogelijkheden om meest geschikte dosis voor start therapie vast te stellen

Vaststellen juiste dosis voor start therapie



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Werkgroep Immunotherapie Nederland
voor Oncologie

Predictive factors for severe toxicity of sunitinib in unselected patients with advanced renal cell cancer

AAM van der Veldt¹, E Boven¹, HH Helgason², M van Wouwe¹, J Berkhof³, G de Gast², H Mallo², CN Tillier¹, AJM van den Eertwegh¹ and JBAG Haanen^{*,2}

¹Department of Medical Oncology, VU University medical center, Amsterdam, The Netherlands; ²Department of Medical Oncology, the Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; ³Epidemiology and Biostatistics, VU University medical center, Amsterdam, The Netherlands

Sunitinib has been registered for the treatment of advanced renal cell cancer (RCC). As patient inclusion was highly selective in previous studies, experience with sunitinib in general oncological practice remains to be reported. We determined the efficacy and safety of sunitinib in patients with advanced RCC included in an expanded access programme. ECOG performance status > 1, histology other than clear cell and presence of brain metastases were no exclusion criteria. Eighty-two patients were treated: 23% reached a partial response, 50% had stable disease, 20% progressed and six patients were not evaluable. Median progression-free survival (PFS) was 9 months and median overall survival (OS) was 15 months. Importantly, 47 patients (57%) needed a dose reduction, 35 (43%) because of treatment-related adverse events, 10 (12%) because of continuous dosing, and two because of both. Stomatitis, fatigue, hand–foot syndrome and a combination of grade 1–2 adverse events were the most frequent reasons for dose reduction. In 40 patients (49%), there was severe toxicity, defined as dose reduction or permanent discontinuation, which was highly correlated with low body surface area, high age and female gender. On the basis of age and gender, a model was developed that could predict the probability of severe toxicity.

British Journal of Cancer (2008) **99**, 259–265. doi:10.1038/sj.bjc.6604456 www.bjcancer.com

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Pharmacogenetic Pathway Analysis for Determination of Sunitinib-Induced Toxicity

Nielka P. van Erp, Karel Eechoute, Astrid A. van der Veldt, John B. Haanen, An K.L. Reyners, Ron H.J. Mathijssen, Epie Boven, Tahar van der Straaten, Renée F. Baak-Pablo, Judith A.M. Wessels, Henk-Jan Guchelaar, and Hans Gelderblom

From the Departments of Clinical Pharmacy & Toxicology and Clinical Oncology, Leiden University Medical Center, Leiden; Department of Medical Oncology, Erasmus University Medical Center, Rotterdam; Department of Medical Oncology, Vrije Universiteit University Medical Center; Department of Medical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam; and the Department of Medical Oncology, University Medical Center Groningen, Groningen, the Netherlands.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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The Acknowledgment and Appendix are included in the full-text version

A B S T R A C T

Purpose

To identify genetic markers in the pharmacokinetic and pharmacodynamic pathways of sunitinib that predispose for development of toxicities: thrombocytopenia, leukopenia, mucosal inflammation, hand-foot syndrome, and any toxicity according to National Cancer Institute Common Toxicity Criteria higher than grade 2.

Patients and Methods

A multicenter pharmacogenetic association study was performed in 219 patients treated with single-agent sunitinib. A total of 31 single nucleotide polymorphisms in 12 candidate genes, together with several nongenetic variants, were analyzed for a possible association with toxicity. In addition, genetic haplotypes were developed and related to toxicity.

Results

The risk for leukopenia was increased when the G allele in *CYP1A1* 2455A/G (odds ratio [OR], 6.24; $P = .029$) or the T allele in *FLT3* 738T/C (OR, 2.8; $P = .008$) were present or CAG in the *NR1I3* (5719C/T, 7738A/C, 7837T/G) haplotype (OR, 1.74; $P = .041$) was absent. Any toxicity higher than grade 2 prevalence was increased when the T allele of vascular endothelial growth factor receptor 2 1191C/T (OR, 2.39; $P = .046$) or a copy of TT in the *ABCG2* (−15622C/T, 1143C/T) haplotype (OR, 2.63; $P = .016$) were present. The risk for mucosal inflammation was increased in the presence of the G allele in *CYP1A1* 2455A/G (OR, 4.03; $P = .021$) and the prevalence of hand-foot syndrome was increased when a copy of TTT in the *ABCB1* (3435C/T, 1236C/T, 2677G/T) haplotype (OR, 2.56; $P = .035$) was present.

Conclusion

This exploratory study suggests that polymorphisms in specific genes encoding for metabolizing enzymes, efflux transporters, and drug targets are associated with sunitinib-related toxicities. A better understanding of genetic and nongenetic determinants of sunitinib toxicity should help to optimize drug treatment in individual patients.

Selected toxicities → placebo controlled study

- Objectivity
- Clinical impact

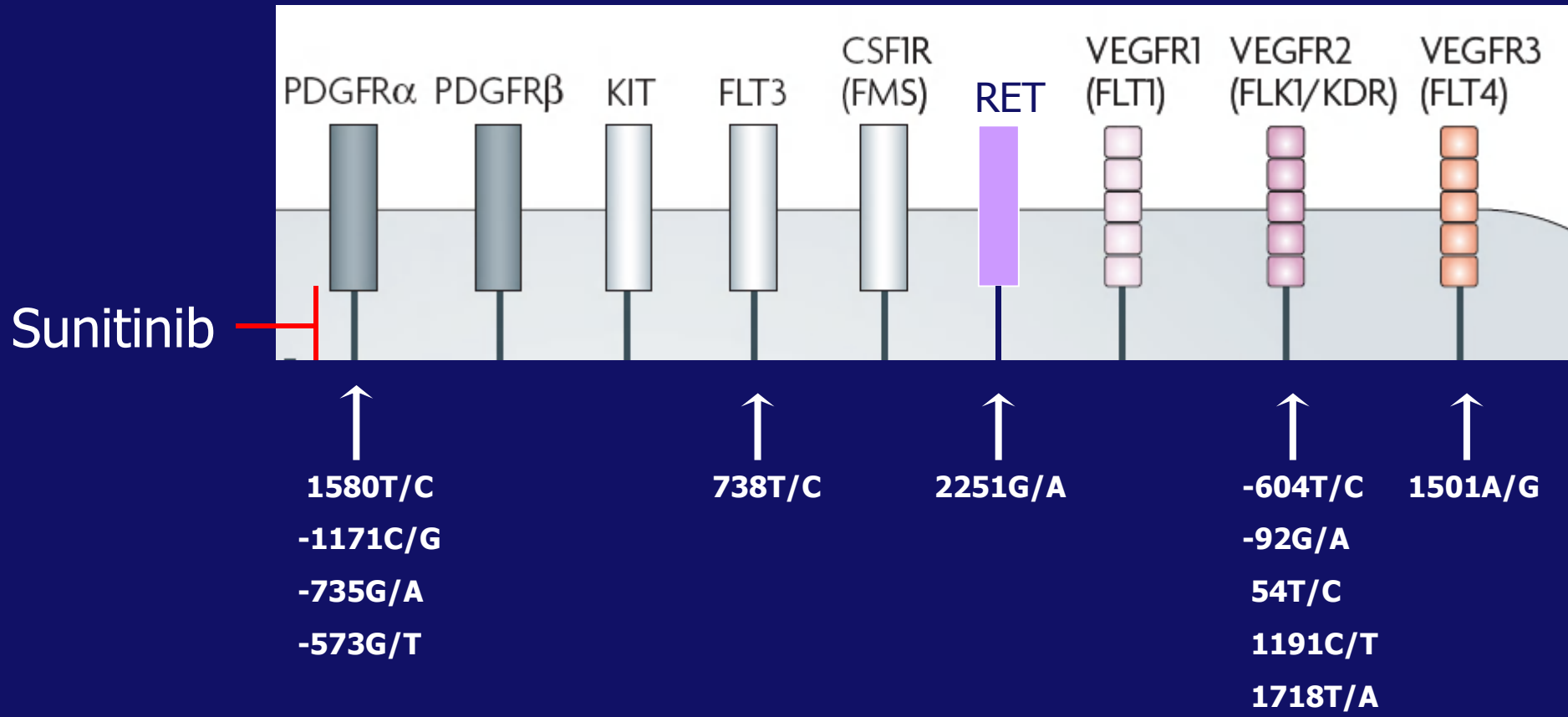
Thrombocytopenia

Leucopenia

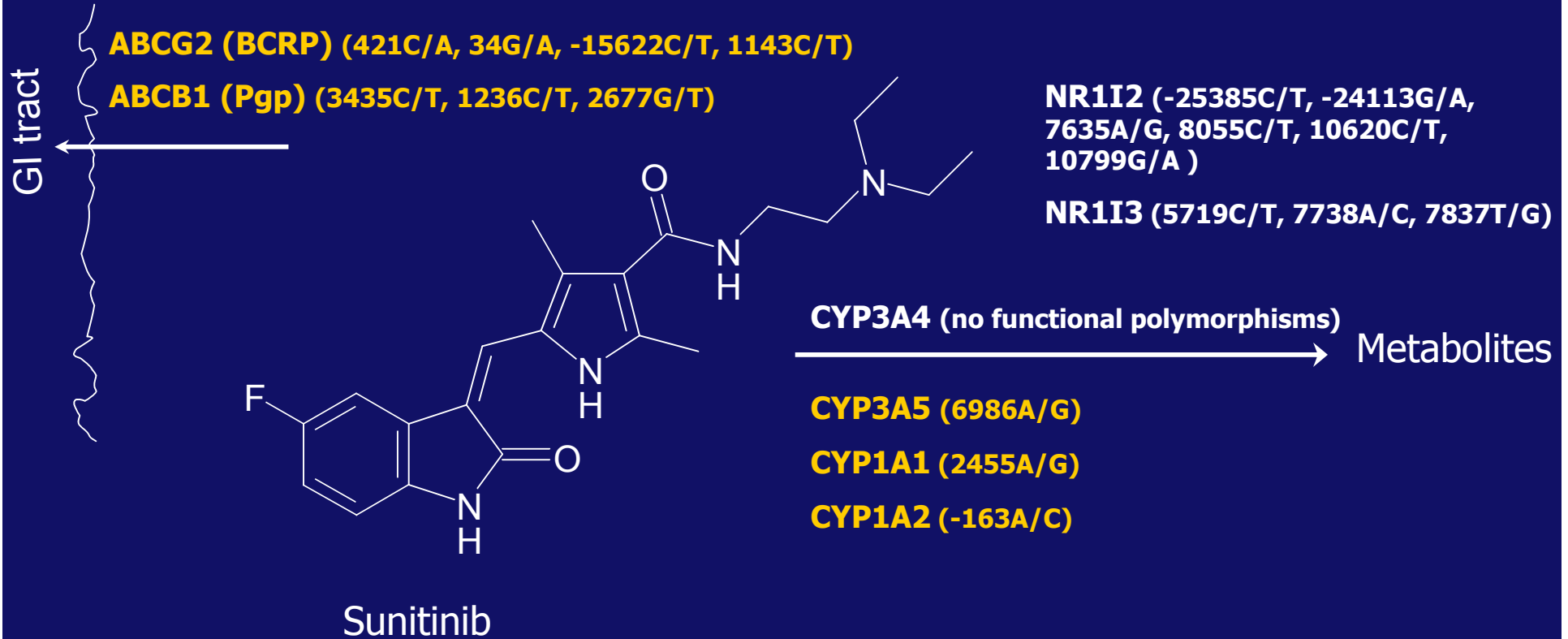
Mucosal inflammation

Hand-Foot syndrome

‘Any toxicity’ according to Common Terminology Criteria > grade 2



Adapted from Faivre Nat Rev Drug Discov 2007



Leukopenia

- CYP1A1 2455A/G OR= 6.24
- FLT3 738T/C OR= 2.8
- NR1I3 haplotype OR= 1.74

Any toxicity > grade 2

- VEGFR2 1191C/T OR= 2.39
- ABCG2 haplotype OR= 2.63

Mucosal inflammation

- CYP1A1 2455A/G OR= 4.03

Handfoot syndrome

- ABCB1 haplotype OR= 2.56

- Geen farmacogenetisch associatie onderzoek uitgevoerd voor sorafenib
- Validatie resultaten farmacogenetische studie met sunitinib:
 - Farmacokinetiek
 - Prospectieve validatie in onafhankelijk cohort
- Verfijning dosisindividualisatie
 - Biomarkers
 - Genotypering
 - Patiëntkarakteristieken
 - Fenotypering

