Oncolytica voor niet-oncologen: Tyrosine kinase inhibitors

3-9-2015

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Radboudumc

Disclosure belangen Annelieke Willemsen

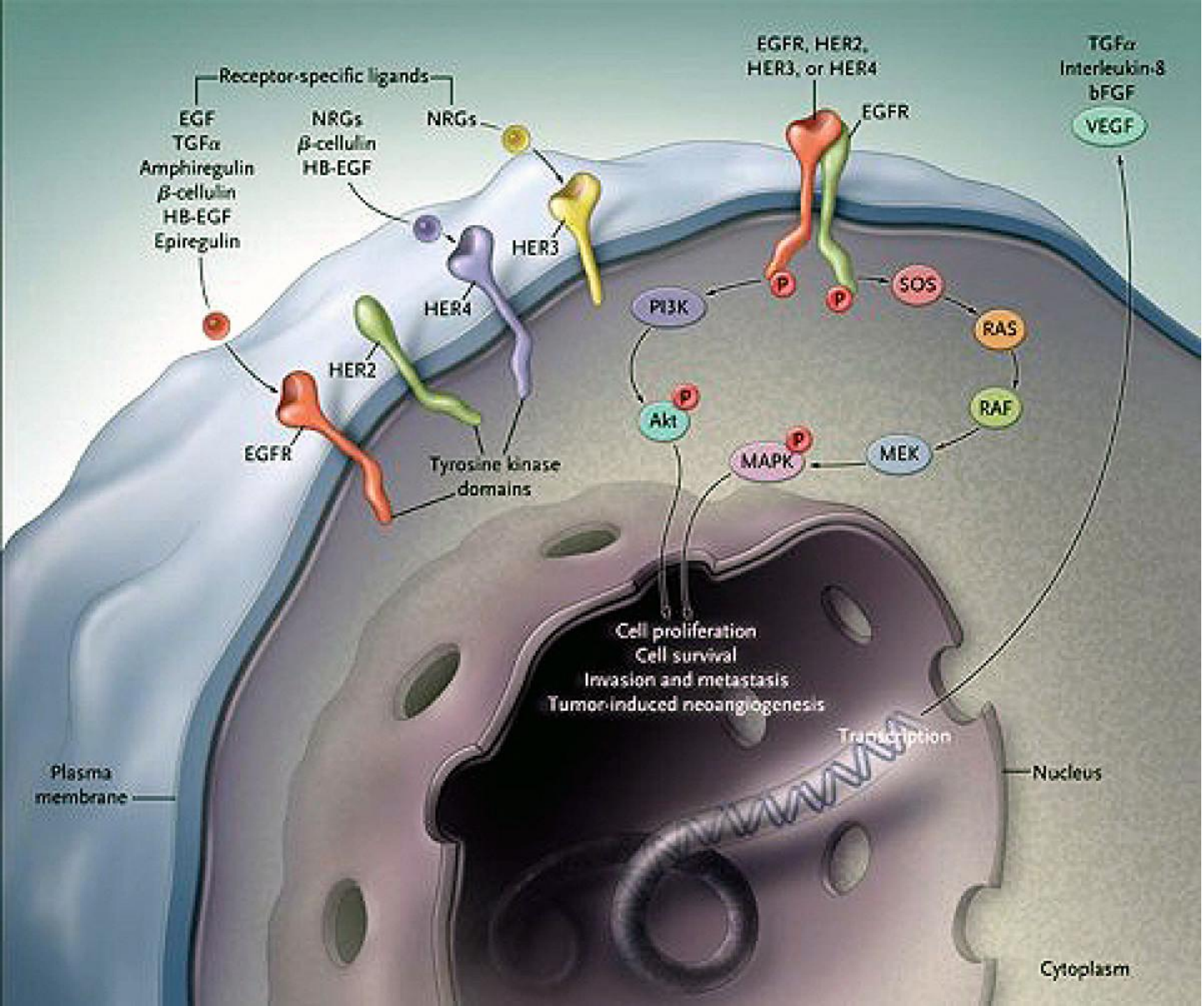
(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Geen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• • • •

Disclosure belangen Nielka van Erp

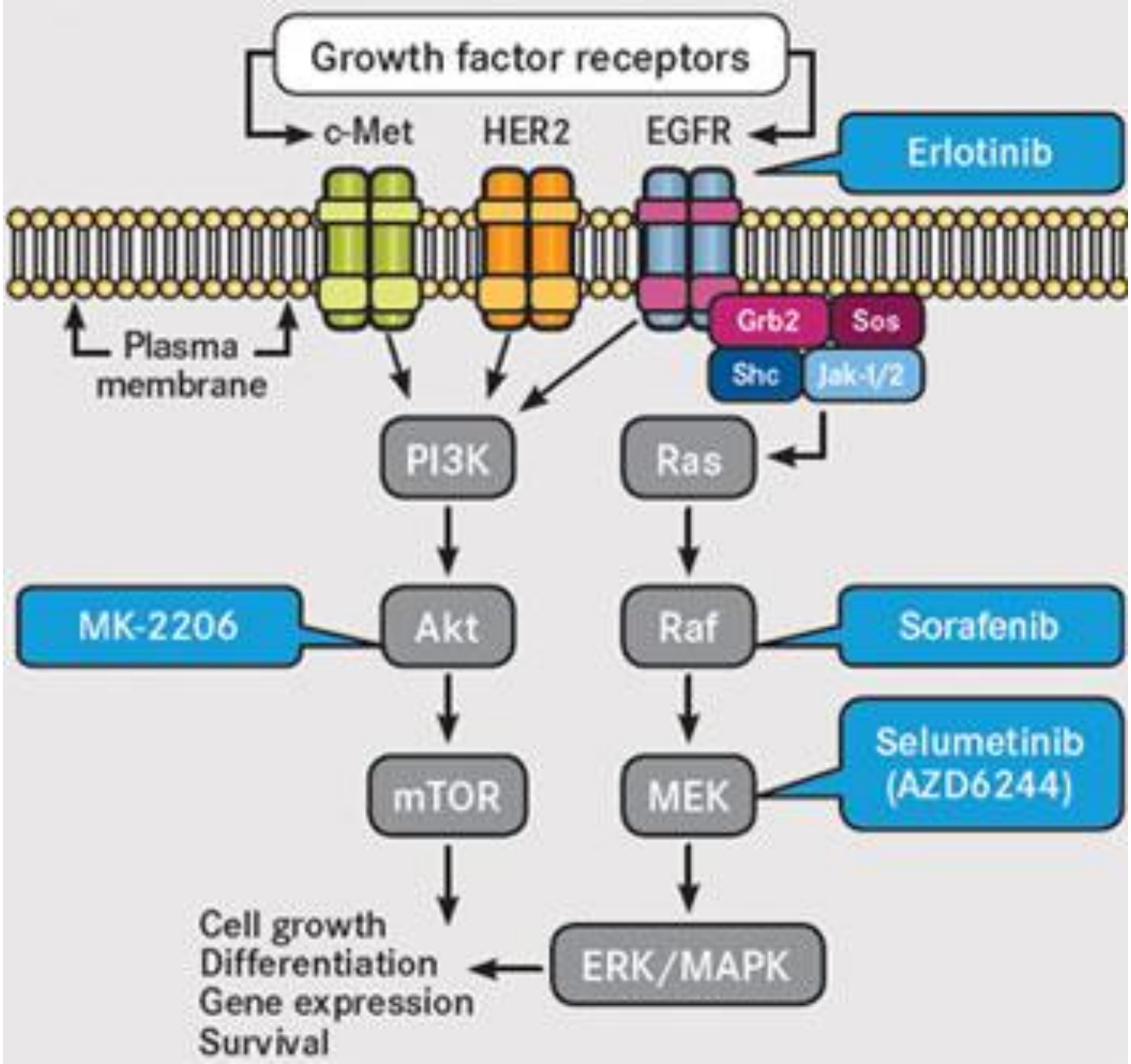
(potentiële) belangenverstrengeling	Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Novartis, GSK, Janssen-Cilag, Astellas
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• Onderzoeksgeld

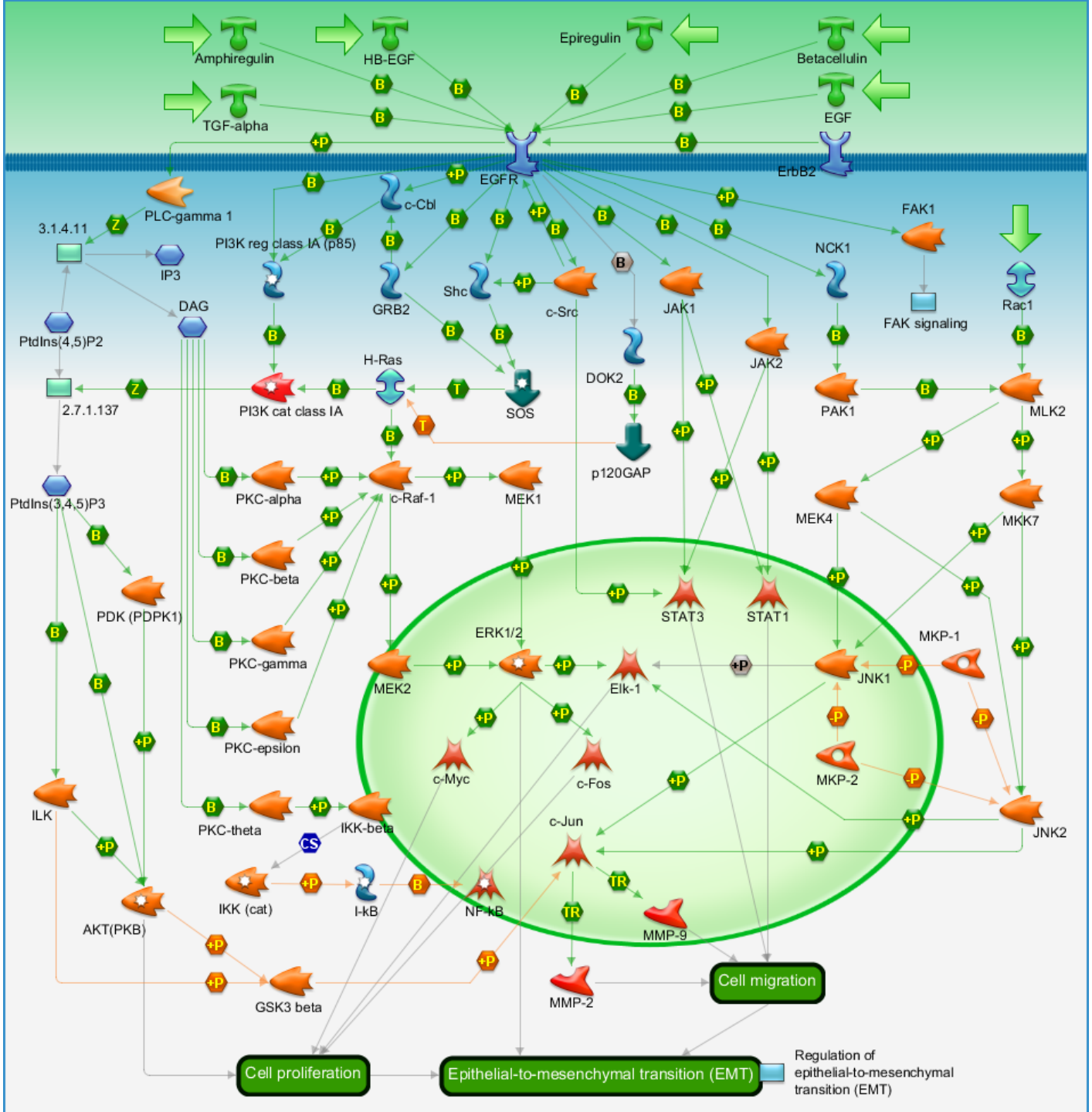
Tyrosine kinase inhibitors

Time magazine, mei 2001

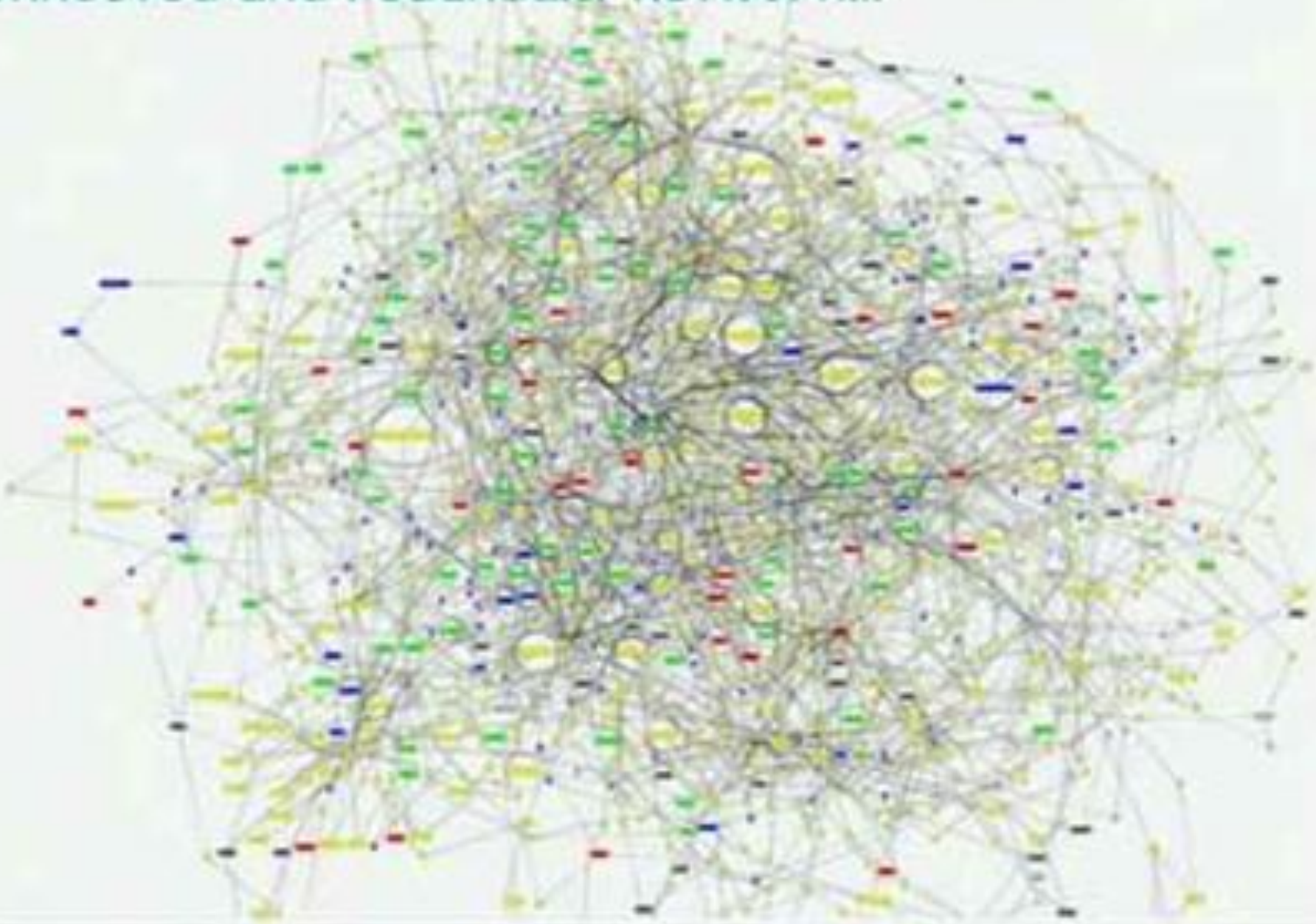


Katzel *Journal of Hematology & Oncology* 2009 **2**:2


Growth factor receptors
c-Met
HER2
EGFR
Erlotinib
Plasma membrane
Grb2
Sos
Shc
Jak-1/2
PI3K
Ras
MK-2206
Akt
Raf
Sorafenib
mTOR
MEK
Selumetinib (AZD6244)
ERK/MAPK
Cell growth
Differentiation
Gene expression
Survival


Amphiregulin
HB-EGF
Epiregulin
Betacellulin
TGF-alpha
EGF
ErbB2
EGFR
PLC-gamma 1
3.1.4.11
IP3
DAG
PtdIns(4,5)P2
2.7.1.137
PtdIns(3,4,5)P3
PDK (PDPK1)
ILK
AKT(PKB)
GSK3 beta
c-Cbl
PI3K reg class IA (p85)
GRB2
Shc
c-Src
JAK1
JAK2
FAK1
FAK signaling
NCK1
Rac1
DOK2
p120GAP
H-Ras
PI3K cat class IA
SOS
PAK1
MLK2
MEK4
MKK7
PKC-alpha
PKC-beta
PKC-gamma
PKC-epsilon
PKC-theta
c-Raf-1
MEK1
MEK2
ERK1/2
Elk-1
STAT3
STAT1
MKP-1
MKP-2
JNK1
JNK2
c-Myc
c-Fos
c-Jun
IKK-beta
IKK (cat)
I-kB
NF-kB
MMP-9
MMP-2
Cell migration
Cell proliferation
Epithelial-to-mesenchymal transition (EMT)
Regulation of epithelial-to-mesenchymal transition (EMT)

Cancer signaling is not linear…. It is a highly inter-connected and redundant network…



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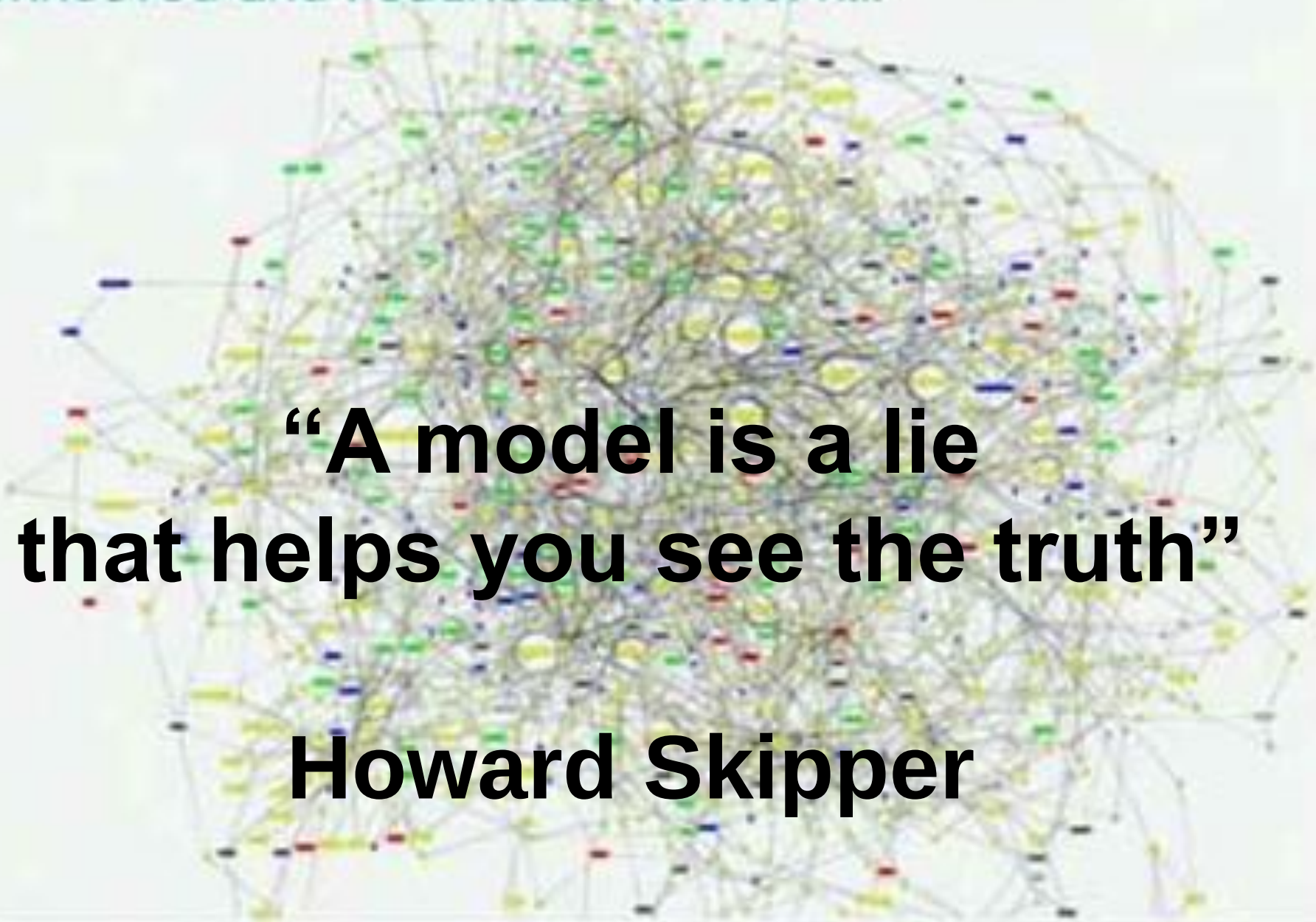


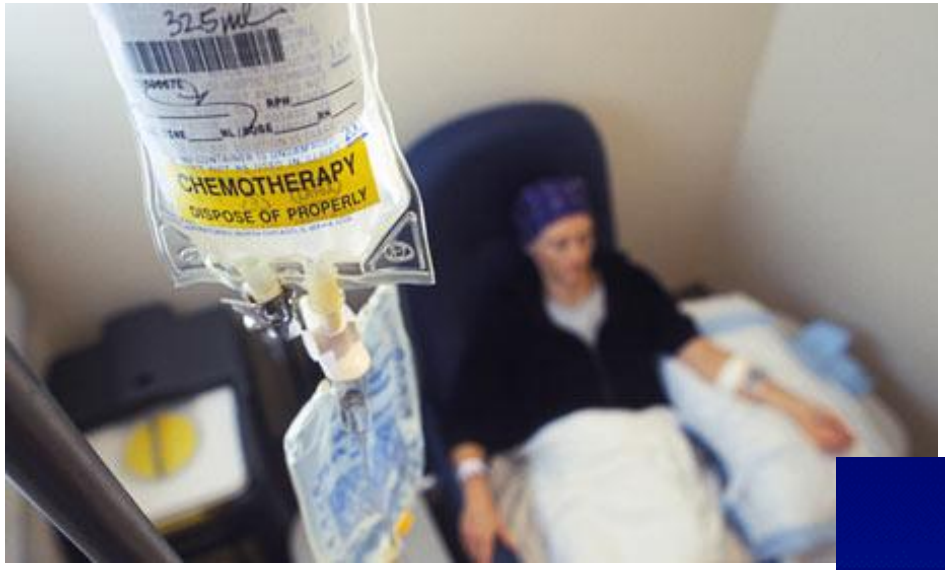
"A model is a lie that helps you see the truth"

Howard Skipper

Targeted therapy

- (relatief) Selectief (TKI<mAB)
- Soms indrukwekkende respons in subset van patiënten
- Minder systemische bijwerkingen
- Kan kwaliteit van leven doen verbeteren

Toedieningswijze



Dosering

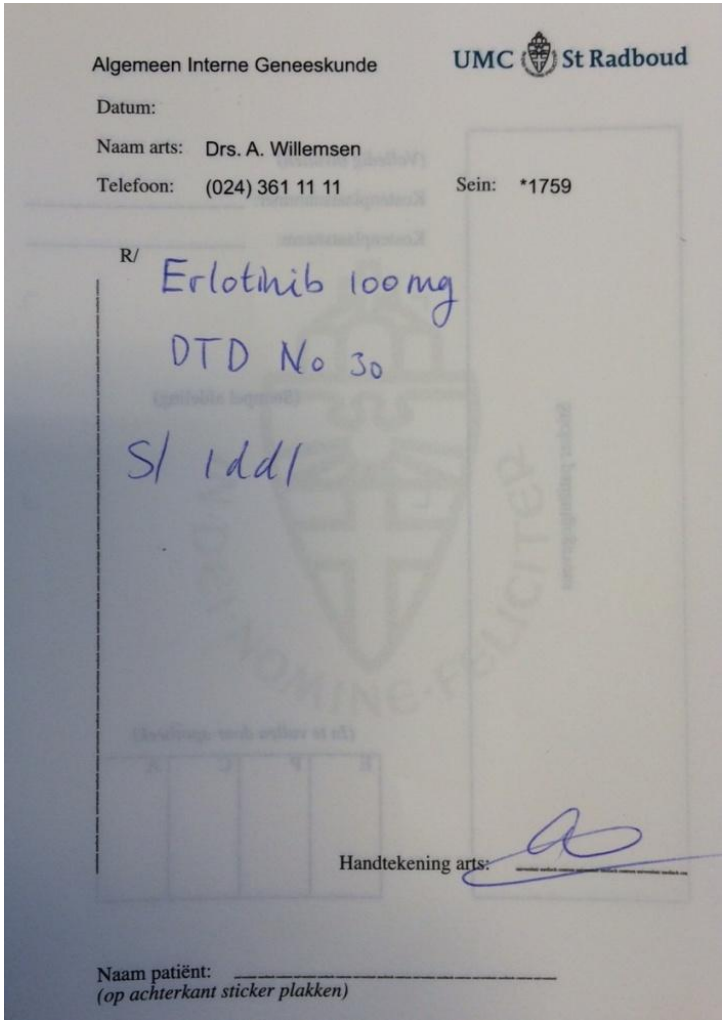
Adjusting Chemotherapy Dose to Account For Reduced Renal Function: An Example

- Cisplatin, 50 mg/m² IV; renal excretion fraction ~ 35%
- Patient BSA = 1.7 m²; GFR = 40 mL/min
- Standard dose = 50 mg/m² x 1.7 m² = 85 mg
- Adjustment factor $= 1 - \left[0.35 \times \frac{120 - 40}{120} \right]$
  $= 1 - [\, 0.35 \times 2/3 \,]$
  $\sim 1 - 0.23$
  $= 0.77$
- Adjusted dose = 85 x 0.77 ~ 65 mg

Frequentie

Toedieningswijze

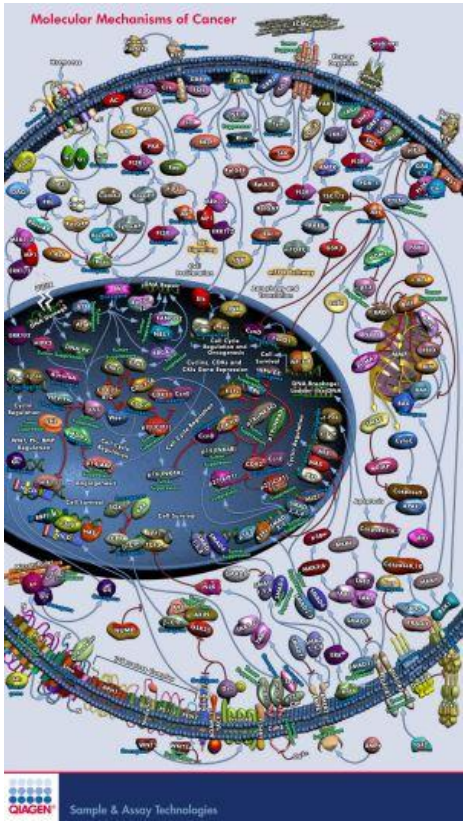
Dosering



Frequentie

Belangrijke pathways voor therapie

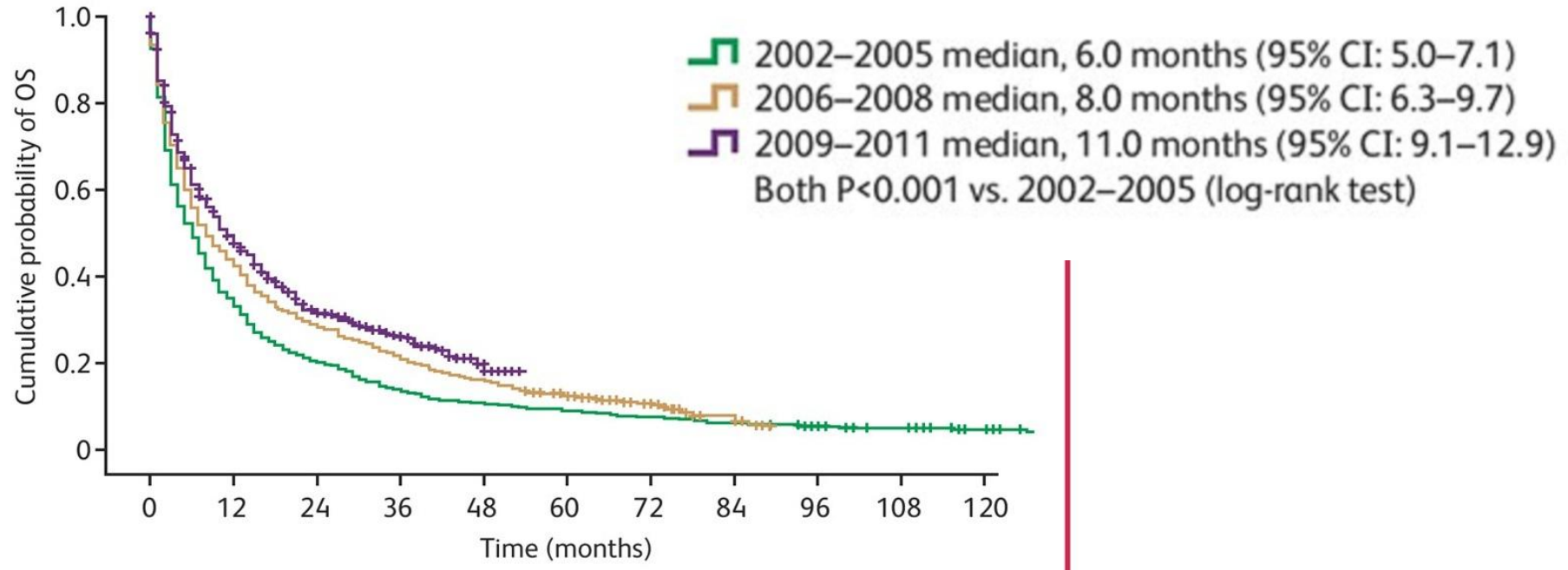
- VEGF (vascular endothelial growth factor): angiogeneseremmers: sunitinib, sorafenib, pazopanib, regorafenib, axitinib
- EGFR (epidermal growth factor receptor): gefitinib, erlotinib, afatinib
- Melanoom:
  - BRAF: vemurafenib, dabrafenib
  - MEK: trametinib
- MET/RET: vandetanib, cabozantinib
- ALK: crizotinib




SUCCESS

Angiogeneseremmers bij niercelcarcinoom

Figure 3. Kaplan–Meier estimates of OS in Norwegian patients diagnosed with mRCC between the periods 2002–2005, 2006–2008, and 2009–2011.

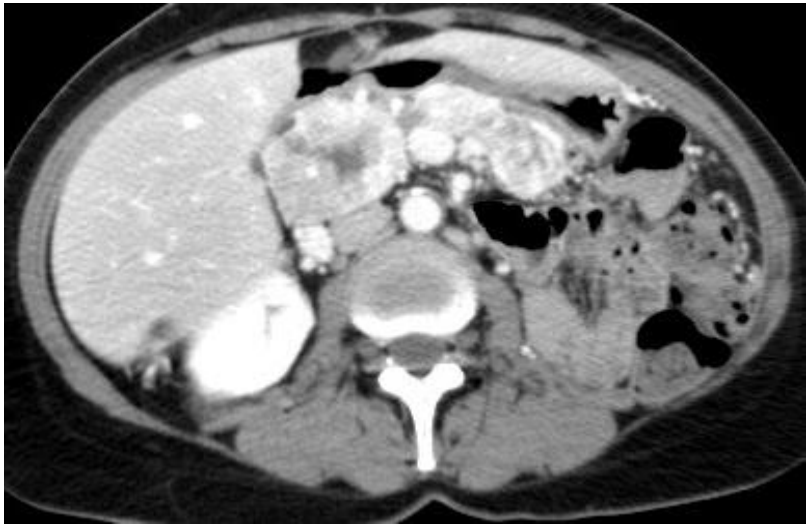


Overall Survival According to Predictive Factors

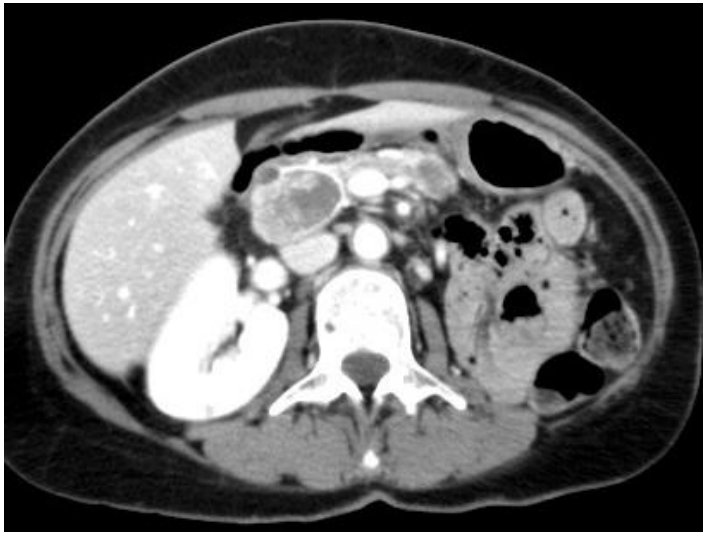
- Multivariate analysis (Table 2) showed that median adjusted OS was significantly longer in RCC patients diagnosed from both 2009–2011 (hazard ratio [HR]=0.838, 95% CI: 0.764–0.920) and 2006–2008 (HR=0.880, 95% CI: 0.809–0.959) compared with 2002–2005.

Klepp, JCO 2015: 33;7

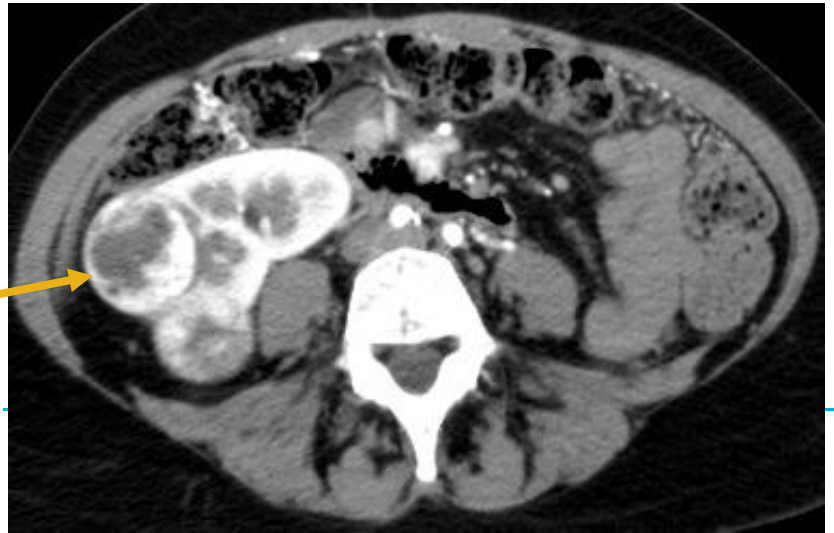
Sunitinib bij pt met niercelcarcinoom

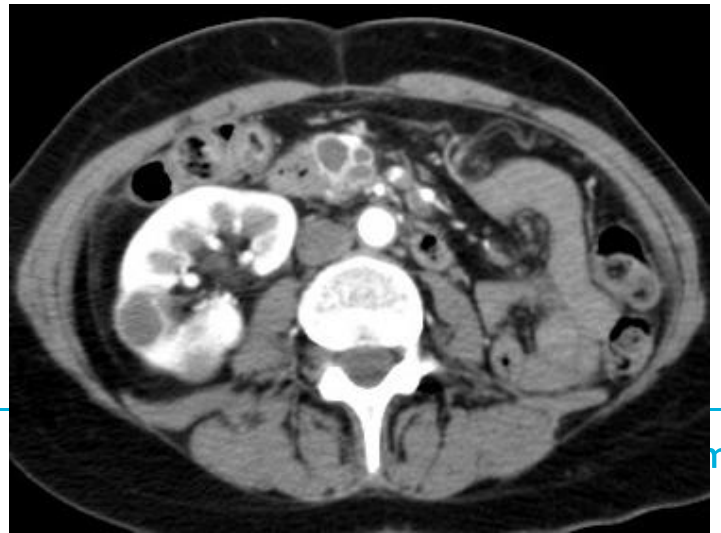


Juni



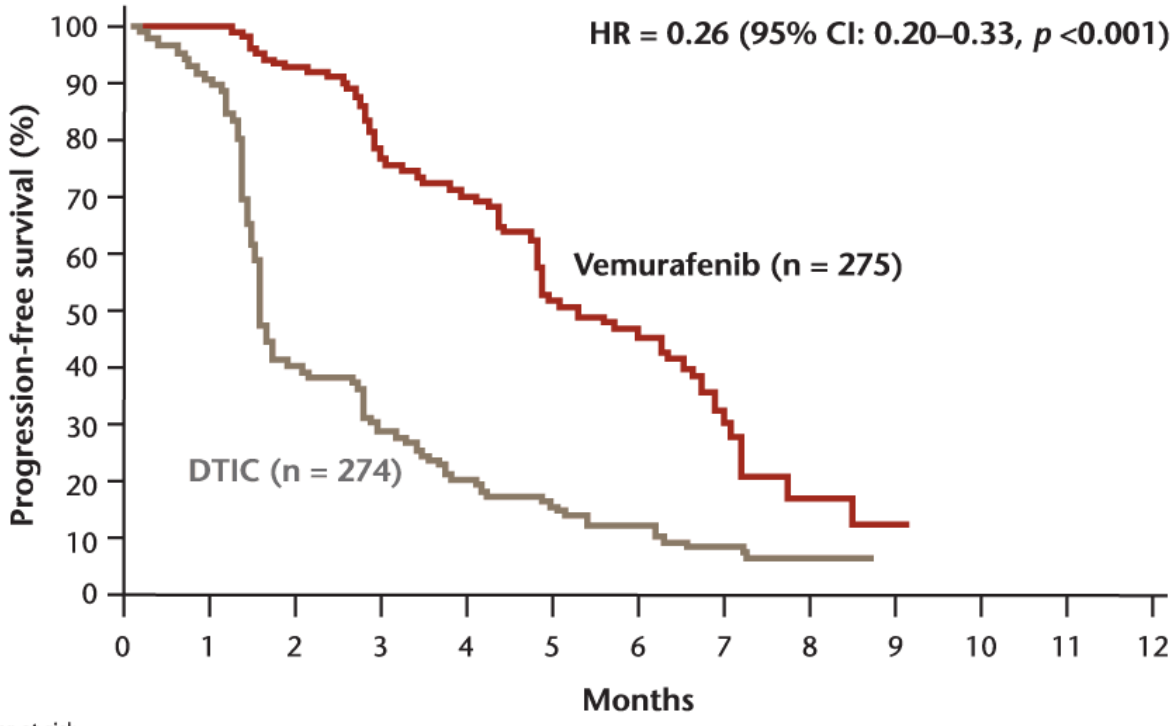
Oktober





Melanoom: vemurafenib

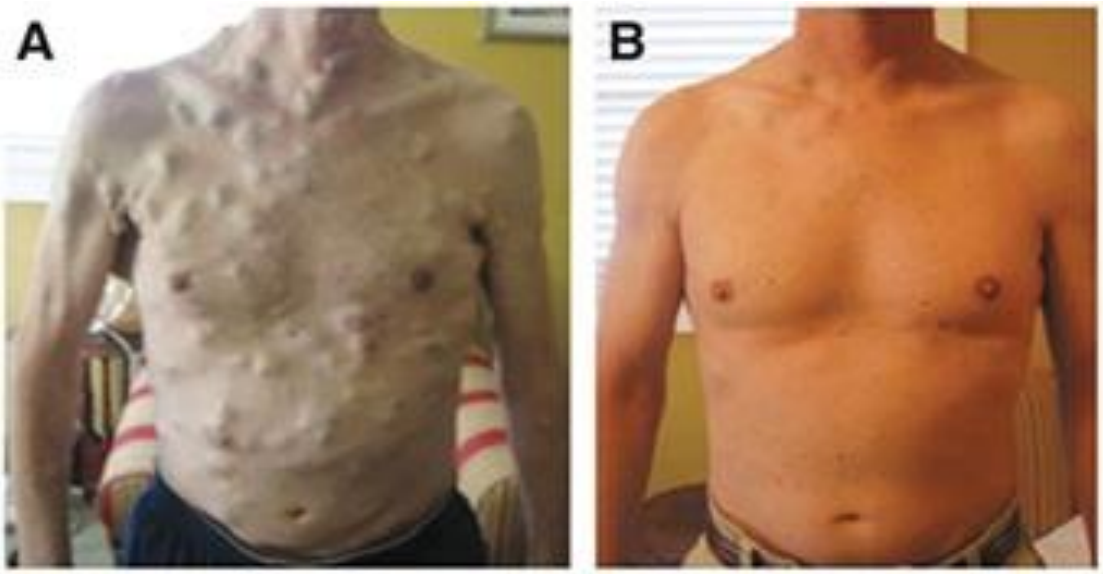
Figure 3. BRIM-3 progression-free survival[45]



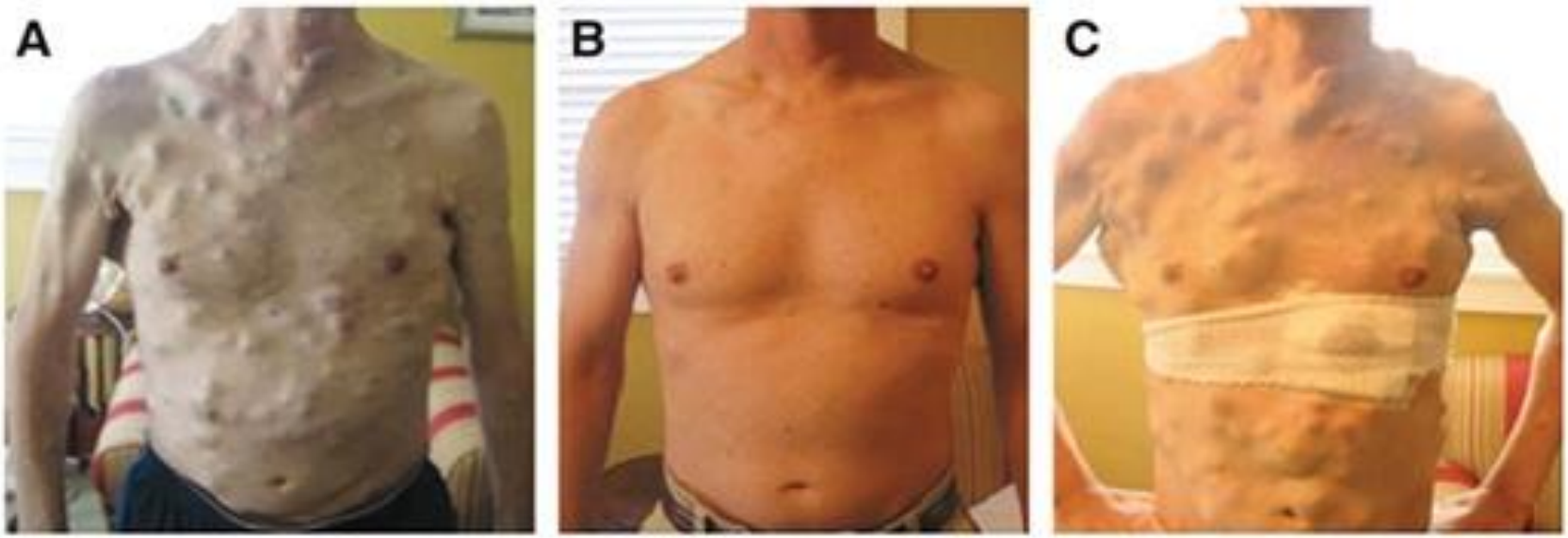
CI = confidence interval; DTIC = dacarbazine; HR = hazard ratio

McArthur, Lancet Onc 2014

Melanoom: vemurafenib



Melanoom: vemurafenib



A) A metastatic melanoma patient prior to therapy. B) Same patient after 15 weeks of therapy with the $BRAF^{V600E}$-inhibitor PLX4032 C) Same patient 23 weeks after therapy[1].

FRIENDLY FIRE

Toxiciteit

- Veel graad 1 toxiciteit: niet ernstig, wel veel impact
- Gezien chronisch gebruik van zeer groot belang

- Bijwerkingen behandelen
- Praten over QOL
- Samen beslissen
- Drug holidays, dosis aanpassingen

- Alleen zo kan patiënt op therapie blijven en profiteren van behandeling

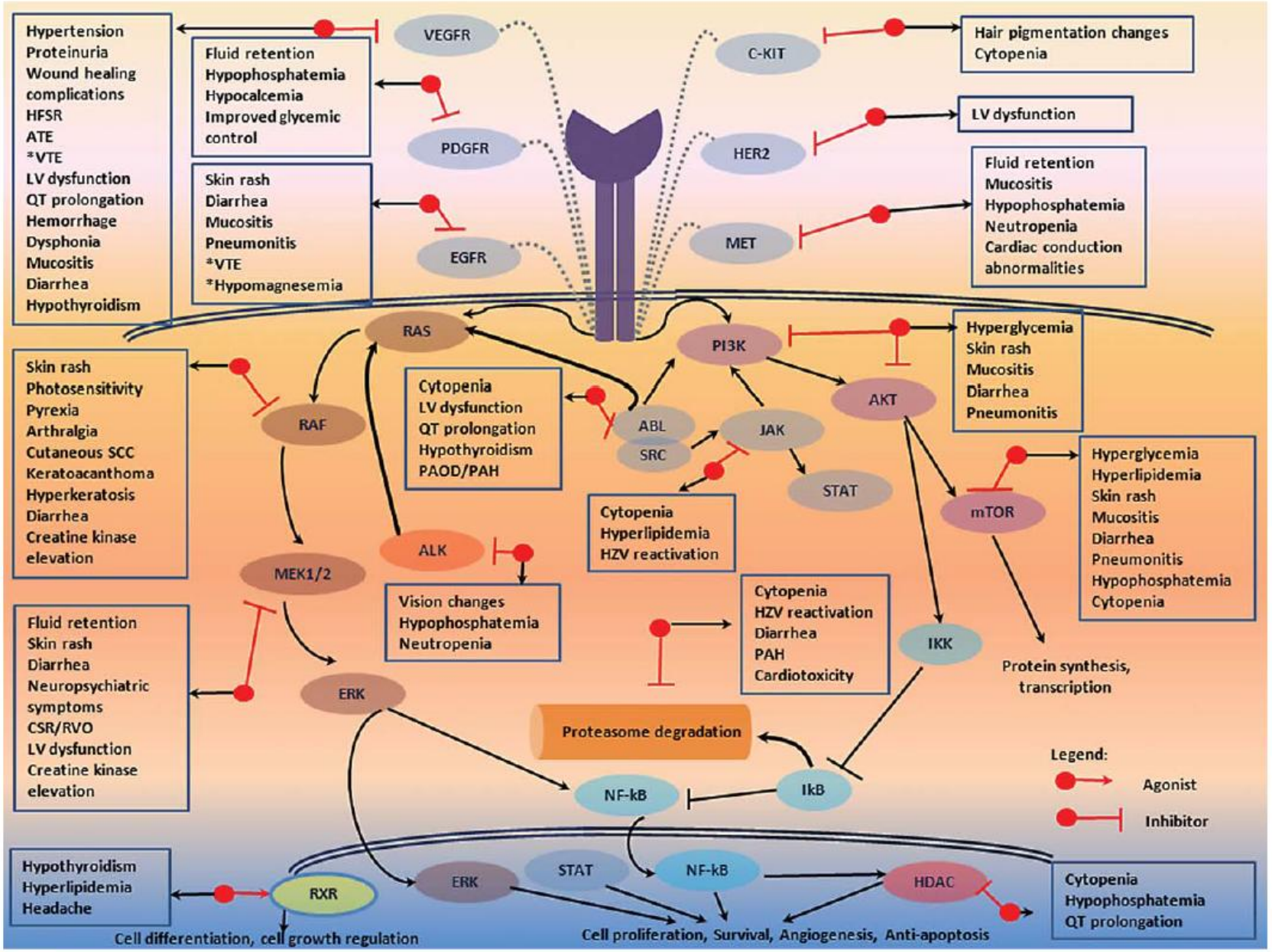
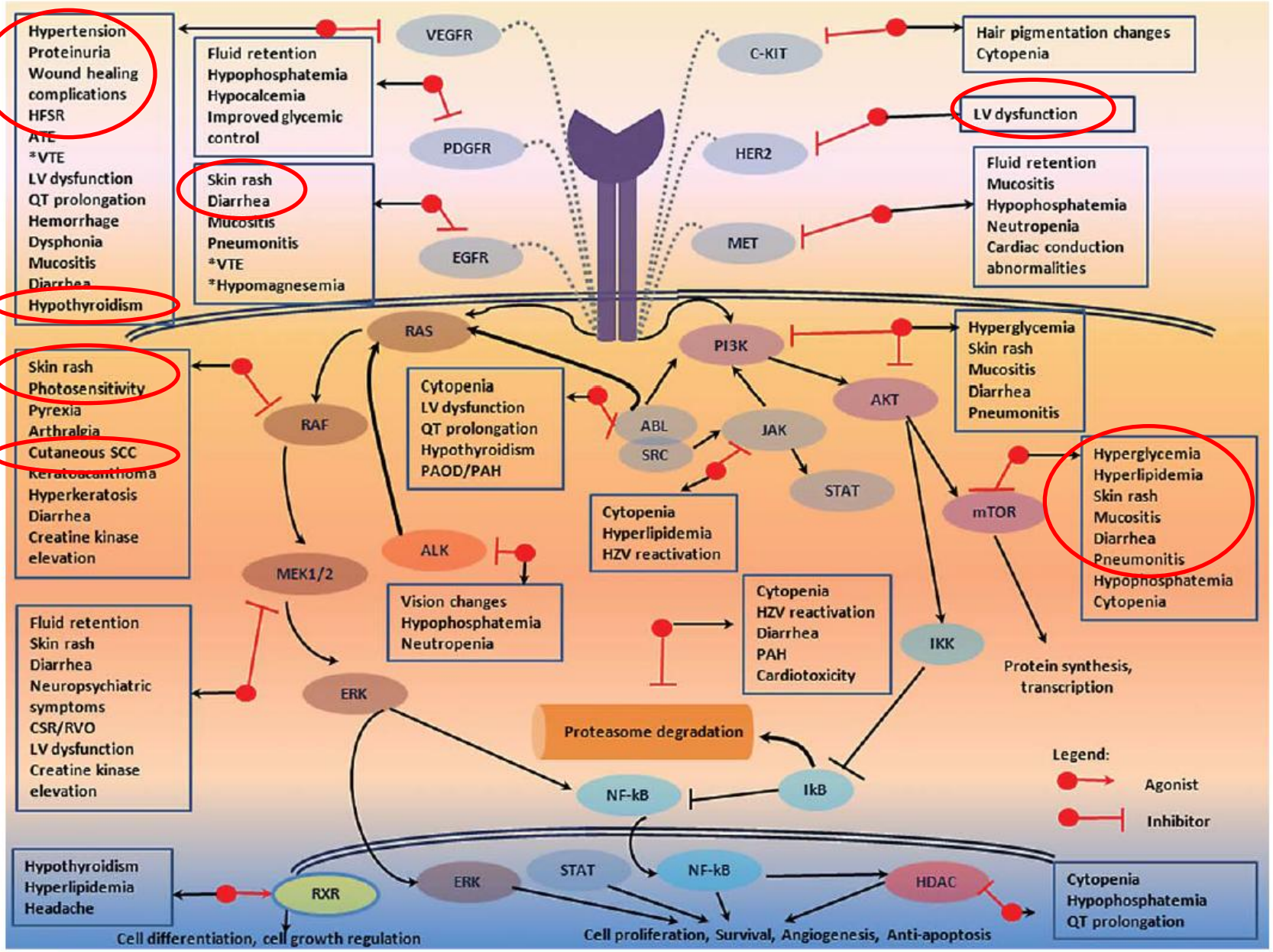


FIGURE 1. Toxicities Associated With Signal Transduction Inhibitors. *Associated predominantly with monoclonal antibodies. ATE indicates arterial thromboembolism; CSR, central serous retinopathy; HZV, herpes zoster virus; LV, left ventricular; PAH, pulmonary arterial hypertension; PAOD, progressive arterial occlusive disease; RVO, retinal vein occlusion; SCC, squamous cell cancer; VTE, venous thromboembolism.

Dy, CA cancer journal clinicians, 2013;63:249-279



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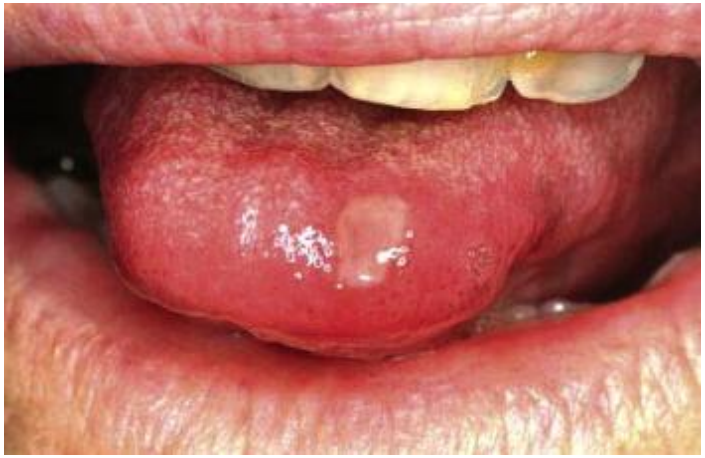
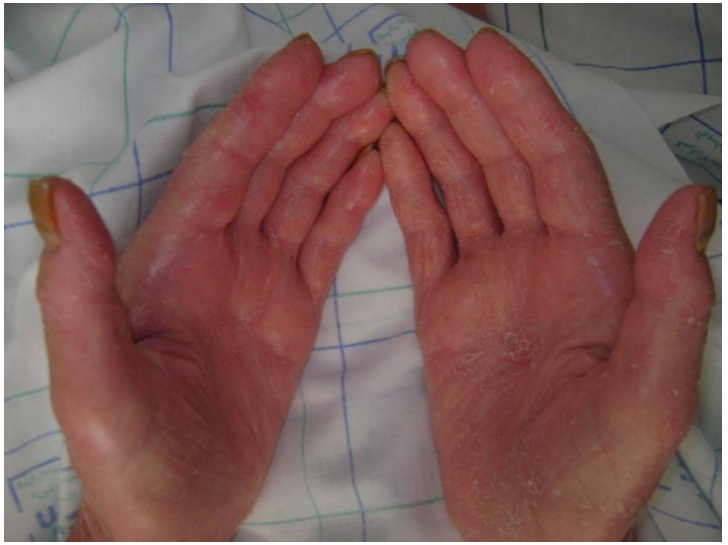
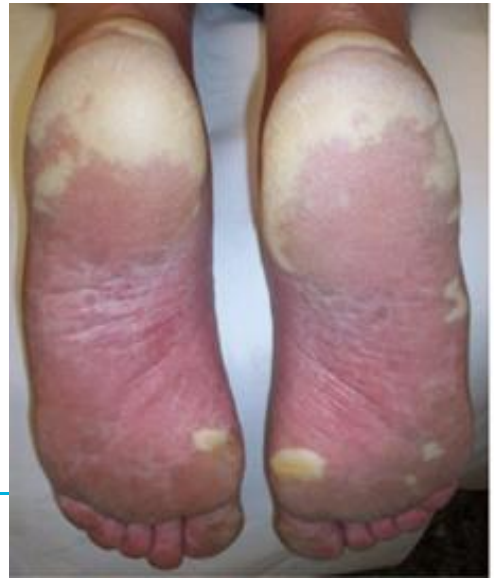
VEGF TKI: angiogeneseremmers

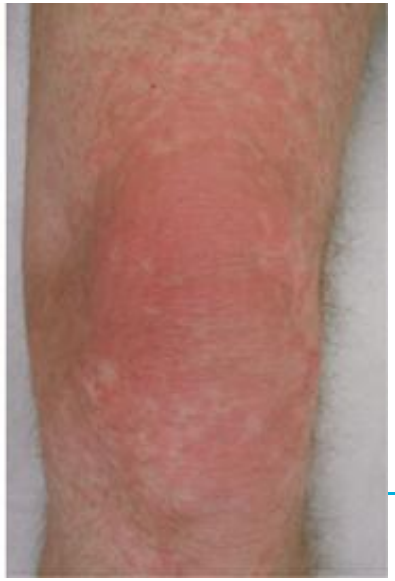
sunitinib – pazopanib – sorafenib – axitinib - regorafenib

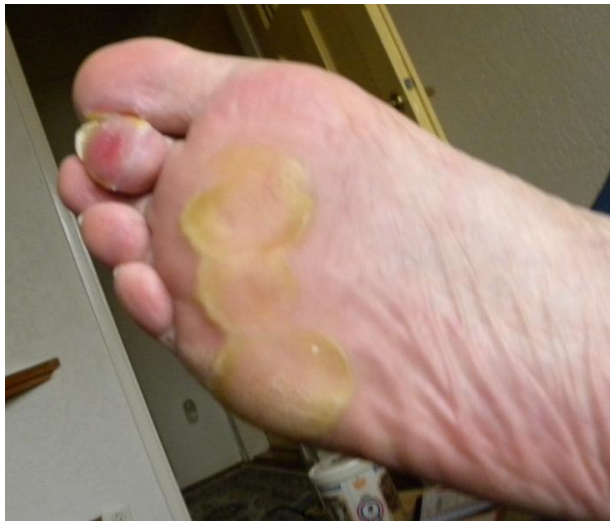
- Gastro-intestinaal: **mucositis** – maagpijn– diarree – obstipatie – anorexie
- Huid: uitslag – **hand voet syndroom** – jeuk– alopecia – huid, haar en nagel veranderingen
- Hart/vaten: **hypertensie** – daling linker ventrikel functie
- Bloed: neutropenie – trombopenie - anemie – leverenzymstoornissen
- Andere: vermoeidheid – smaakverandering- hoofdpijn – **hypothyreoïdie** – oedeem
- Mogelijk ook cognitieve bijwerkingen











Haar depigmentatie bij sunitinib

Remming c-KIT
> ↓ melanine synthese
> depigmentatie haar

Angiogeneseremmers, behandeling toxiciteit

- Handvoet syndroom:
  - met name druk verlaging: podotherapeut, zooltjes
  - Vet houden: cetomacrogol vaseline
  - Topicale steroiden
  - Dosis interruptie

- Hypertensie:
  - Calciumantagonist
  - Combineren met ACE-remmer, betablokker

Angiogeneseremmers: ernstige toxiciteit

- Hepatotoxiciteit[1]:
  - graad 3/4: 5%
  - leverfalen: 0,8%
- Congestief hartfalen[2]: 1,2%
- Wondgenezingsproblematiek → indicatie voor interruptie rondom chirurgische procedures

- Fatale adverse events[3]: bloeding, hartfalen, leverfalen, GI perforatie (?)

1: Iacovelli, BJCP 2014, 2: Ghatalia CROH 2015, 3: Sivendran Canc Tr Rev 2012

EGFR remmers

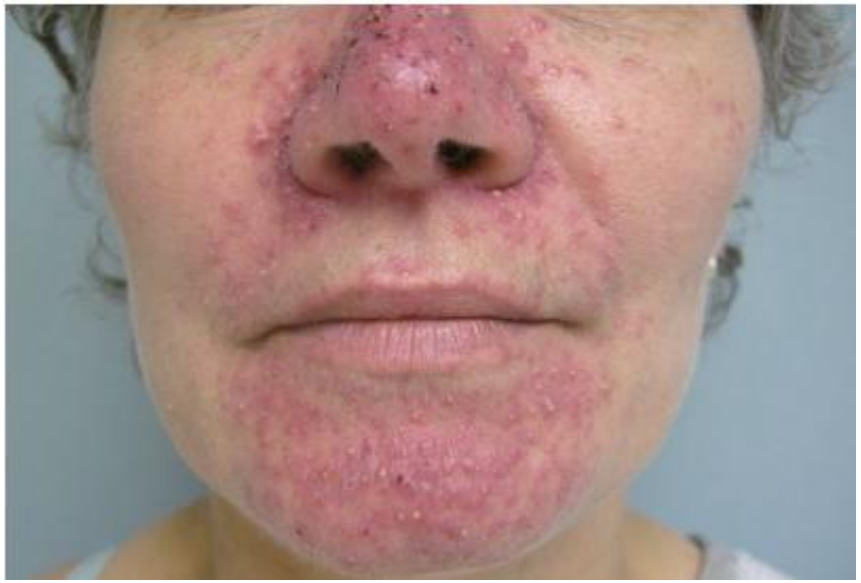
gefitinib – erlotinib – afatinib

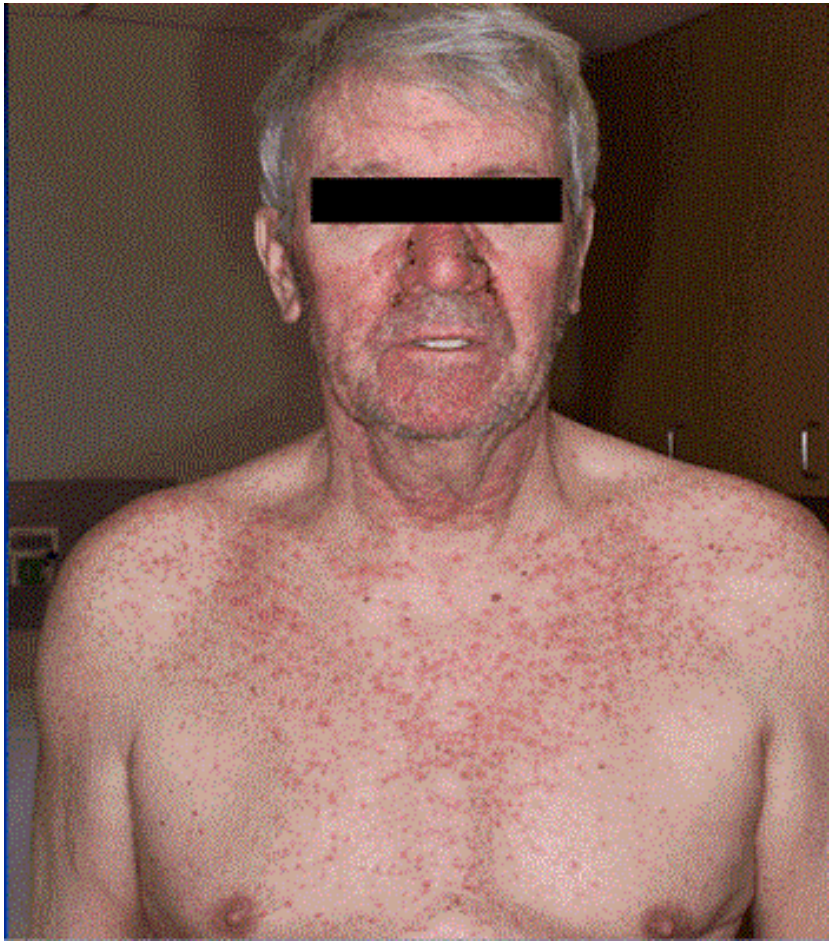
- EGFR essentiële rol in
  - epidermale homeostase door regulatie keratinocyt functie
    → acneiform rash (50-80%): papels en pustels
    schedel, gelaat, nek, thorax

  - epitheel van mucosa
    → diarree (>50%)

Gerber, AAFP 2008. Dy , 2013

EGFR remmers, huidtoxiciteit





EGFR remmers: behandeling toxiciteit

- Huidtoxiciteit:
  - Topicale of systemische antibiotica:
    bv doxycycline, minocycline
  - Topicale steroiden
  - Topicale retinoiden (adapaleen en tretinoïne)

- Diarree:
  - vaak self-limiting
  - symptomatisch: loperamide

Melanoom

- Vemurafenib:
  - Huidtoxiciteit:
    - hyperkeratose, keratoacanthoom
    - plaveiselcelcarcinoom huid
      - tgv reactieve activatie MAPK pathway
      - locale therapieen (chrirugie, cryotherapie, fotodynamische therapie)

    dDit geremd door combinatietherapie met MEK-remmer!
  - Verlengd QT (> cave comedicatie)

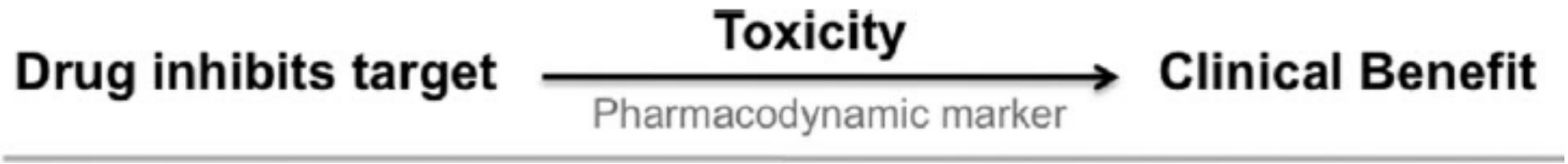
- MEK remmers:
  - Verminderde linker ventrikelfunctie
  - Retinal vein occlusion, retina loslating

brouwerij

TROOST

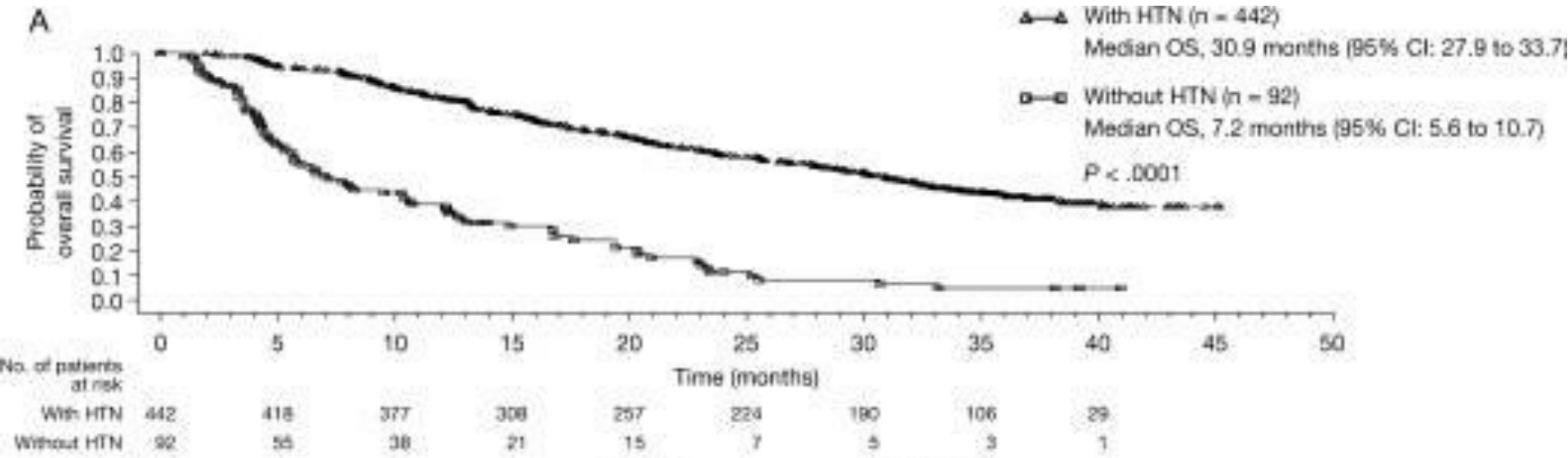
Toxiciteit

- On target effects vs off target effects
- Mechanism-based toxicity:



Dienstmann, The Oncologist 2011; 16: 1729-1740

Hypertensie bij sunitinib



Rini et al. JNCI 2011; 103: 763

Radboudumc

Hypothyreoïdie bij sunitinib

Table 3. Multitargeted tyrosine kinase inhibitors and efficacy according to hypothyroidism development

Disease, study design	*n* of patients	Hypothyroidism prevalence	Response	Survival
Renal cell carcinoma				
Sunitinib, retrospective [72]	40	Any time, 70%	No data	Median PFS: No TFT abn, 3.6 mos; TFT abn, 10.3 mos. Median OS: No TFT abn, 6.6 mos; TFT abn, 18.2 mos
Sunitinib, retrospective [77]	111	Within 180 days, 52%	No data	Median PFS: No TFT abn, 481 days; TFT abn, 575 days
Sunitinib, prospective [78]	22	Any time, 59%	No data	Median PFS: No hypoT, 7.03 mos; hypoT, 8.55 mos
Sunitinib or sorafenib, prospective [79]	78 (37 in sunitinib group)	Within 60 days, 36%	No hypoT, 3.3%; hypoT, 28.3%	Median PFS: No hypoT, 10.8 mos; hypoT, 17 mos. Median OS: No hypoT, 13.9 mos; hypoT, not reached

Abbreviations: hypoT, hypothyroidism; OS, overall survival; PFS, progression-free survival; TFT abn, thyroid function test abnormality.

Dienstmann, The Oncologist 2011; 16: 1729-1740

EGFR inhibitors: overall survival ahv rash

- Niet-kleincellig longcarcinoom, erlotinib:
  - Geen rash: 1.5 mnd
  - Graad 1 rash: 8.5 mnd
  - Graad 2 rash: 19.6 mnd
- Hoofd/hals kanker, erlotinib:
  - Geen rash: 4 mnd
  - Graad 1 rash: 5 mnd
  - Graad 2 rash: 7.4 mnd
- Pancreascarcinoom, gemcitabine + erlotinib:
  - Graad 0 of 1: 5 mnd
  - Graad 2 rash: 10.1 mnd
- Colorectaal carcinoom:
  - Bij cetuximab en panitumumab duidelijk effect

Dienstmann, The Oncologist 2011; 16: 1729-1740

Uitdagingen/toekomst

- Optimaliseren
  - Bijwerkingen management
  - Therapeutic drug monitoring
- Theragnostics: juiste drug bij juiste patiënt
  - ‘driver’ mutaties, pharmacogenomics, molecular imaging
- Tumor response assessment
  - Vroeg vaststellen met functionele imaging?
- Resistentie
  - Combinatietherapieen
- Tumor heterogeniteit
  - De ene meta is de andere niet
- Kosten!

Tyrosinekinaseremmers (-Nib)

Stofnaam	Specialité (EMA- registratie)
Afatinib	**Giotrif (09-2013)**
Axitinib	**Inlyta (09-2012)**
bosutinib	Bosulif (03-2013)
Cabozantinib	**Cometriq (03-2014)**
Crizotinib	**Xalkori (10-2012)**
Dabrafenib	**Tafinlar (08-2013)**
Dasatinib	Sprycel (22-2006)
Everolimus	**Tarceva (09-2005)**
Gefitinib	**Iressa (06-2009)**
Imatinib	**Glivec (11-2001)**
Lapatinib	**Tyverb (06-2008)**
Nilotinib	Tasigna (11-2007)
Pazopanib	**Votrient (06-2010)**
Ponatinib	Iclusig (07-2013)
Regorafenib	**Stivarga (08-2013)**
ruxolitinib	Jakavi (08-2012)
Sorafenib	**Nexavar (07-2006)**
Sunitinib	**Sutent (07-2006)**
Vandetanib	**Caprelsa (02-2012)**
Vemurafenib	**Zelboraf (02-2012)**

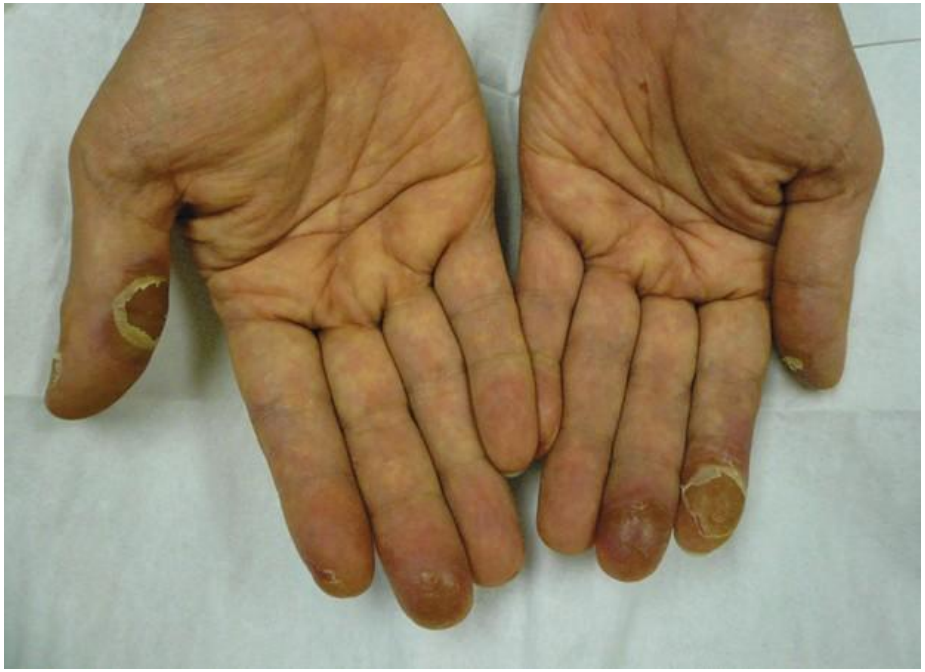
Tyrosinekinaseremmers (-Nib)			
Stofnaam	target	t½	Dosis
Afatinib	EGFR	37 hr	40 mg 1 dd
Axitinib	VEGFR 1-3	2-5 hr	5 mg 2 dd
Cabozantinib	MET, VEGFR 2	120 hr	140 mg 1 dd
Crizotinib	ALK, MET	42 hr	250 mg 2 dd
Dabrafenib	BRAF	8 hr	150 mg 2 dd
Erlotinib	EGFR	36 hr	150 mg 1 dd
Gefitinib	EGFR	48 hr	250 mg 1 dd
Imatinib	Bcr-Abl, cKIT, PDGFRα,β	18 hr	400 mg 1 dd
Lapatinib	EGFR, HER2	24 hr	1250 mg 1 dd
Pazopanib	cKIT, PDGFRα,β, VEGFR 1,2,3	31 hr	800 mg 1 dd
Regorafenib	BRAF, cKIT, PDGFRα,β, RAF, RET, TEK, VEGFR 1-3	20-40 hr	160 mg 1 dd (3op 1af)
Sorafenib	cKIT, FLT3, PDGFR,β RAF-kinases, VEGFR 1-3	25-48 hr	400 mg 2 dd
Sunitinib	cKIT, CSFR, FLT3, PDGFRα,β, RET, VEGFR 1-3	40-60 hr	50 mg 1 dd (4op 2af)
Vandetanib	EGFR, RET, VEGFR 2	480 hr	300 mg 1 dd
Vemurafenib	BRAF	57 hr	960mg 2 dd

In de ideale wereld: 1 pill / dose suits all

In werkelijkheid zijn we verschillend

Variatie

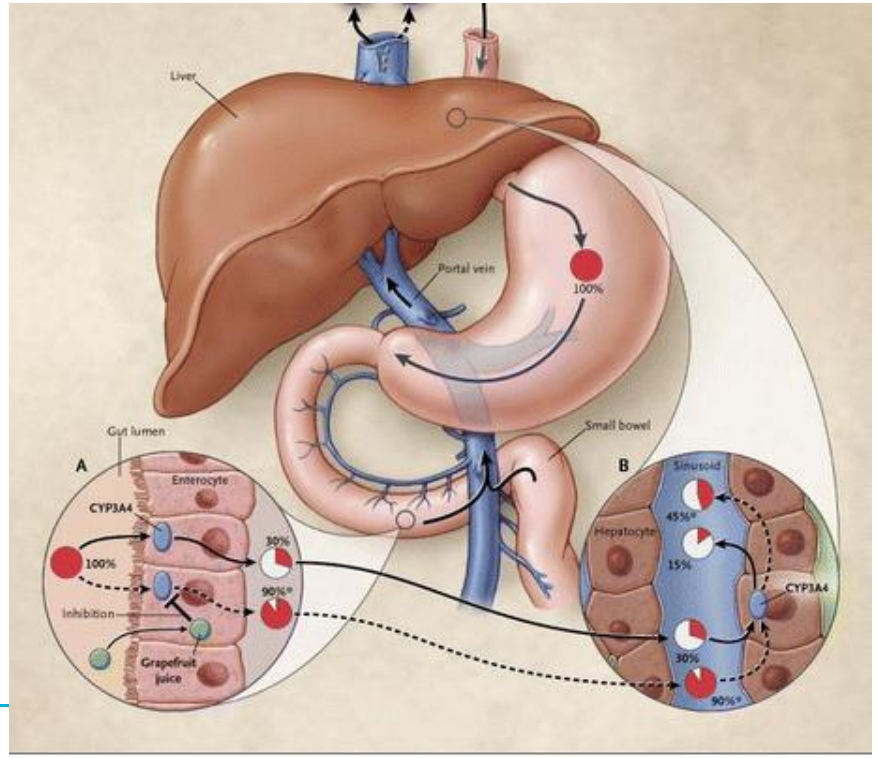
- Patiënten reageren verschillend:
  - Toxiciteit
  - Antitumor activiteit



Introductie extra variabiliteit bij orale oncolytica

Oorzaak extra variatie:

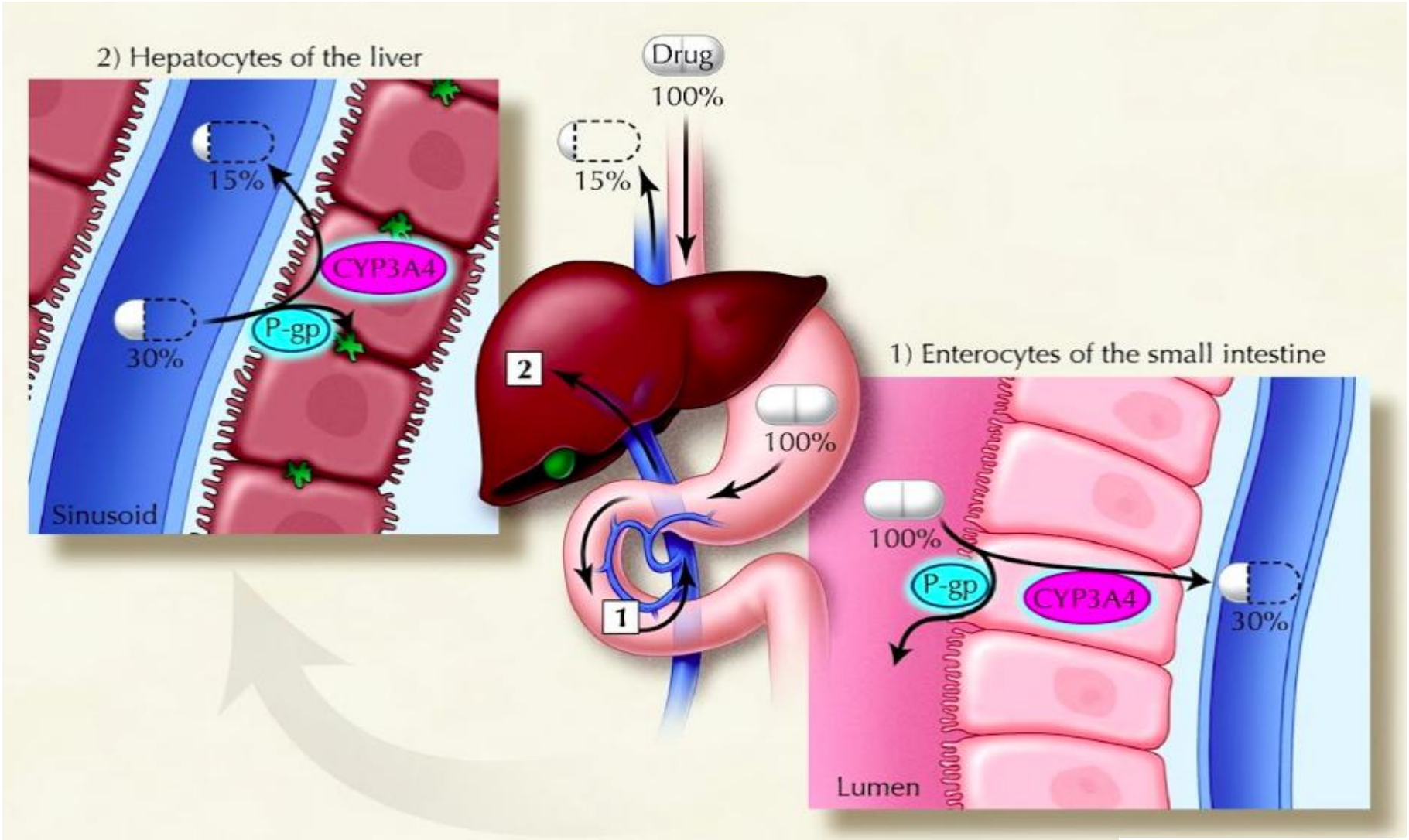
- Afgifte geneesmiddel uit toedieningsvorm
- Opname vanuit het MD-kanaal
- Invloed voedsel / pH
- Genotype transporters / enzymen
- Fenotype transporters / enzymen



Adapted from: NEJM; Wilkinson (2005) 352: 2211-2221

Grote rol voor CYP3A4 en Pgp

Nib – gemetaboliseerd door cytochroom P450 (m.n. CYP3A4)
Nib – affiniteit voor ATP Binding Cassette transporters



Metabolisme Tyrosinekinaseremmers (-Nib)		
Stofnaam	Belangrijke enzymen	Minder belangrijke enzymen
Afatinib	-	-
Axitinib	CYP3A4	CYP1A2, CYP2C19, UGT
Cabozantinib	CYP3A4	
Crizotinib	CYP3A4	CYP2D6, CYP2C19
Dabrafenib	CYP3A4, CYP2C8	
Erlotinib	CYP3A4	CYP1A1, CYP1A2, CYP2D6, CYP2C8
Gefitinib	CYP3A4	CYP2D6, CYP1A1
Imatinib	CYP3A4	CYP2D6, CYP2C9, CYP2C19
Lapatinib	CYP3A4	CYP2C8, CYP2C19, CYP2C9, CYP1A2, CYP2D6
Pazopanib	CYP3A4	CYP1A2, CYP2C8
Regorafenib	CYP3A4	UGT
Sorafenib	CYP3A4, UGT1A9	
Sunitinib	CYP3A4	CYP1A2
Vandetanib	CYP3A4	FMO-1,3
Vemurafenib	CYP3A4	

Veranderde absorptie:

pazopanib ~200% ↑

erlotinib ~100% ↑

Lapatinib ~425% ↑

axitinib ~19% ↑

Vemurafenib ???

sorafenib ~30% ↓

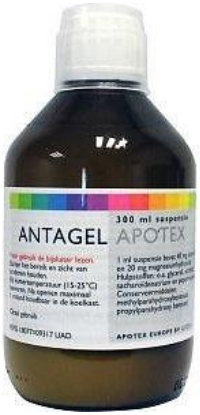
imatinib ~0%

sunitinib ~0%

gefitinib ~0%

Radboudumc

Veranderde absorptie:



pazopanib ~40% ↓

gefitinib ~47% ↓

erlotinib ~44% ↓

vemurafenib ↑↑↑

imatinib ↑↑↑

gefitinib ↑↑↑

pazopanib ↑↑↑

axitinib ↑↑↑

sorafenib ↑↑↑

erlotinib ↑↑↑

sunitinib ↑↑↑

nilotinib ↑↑↑

Veranderde omzetting door:

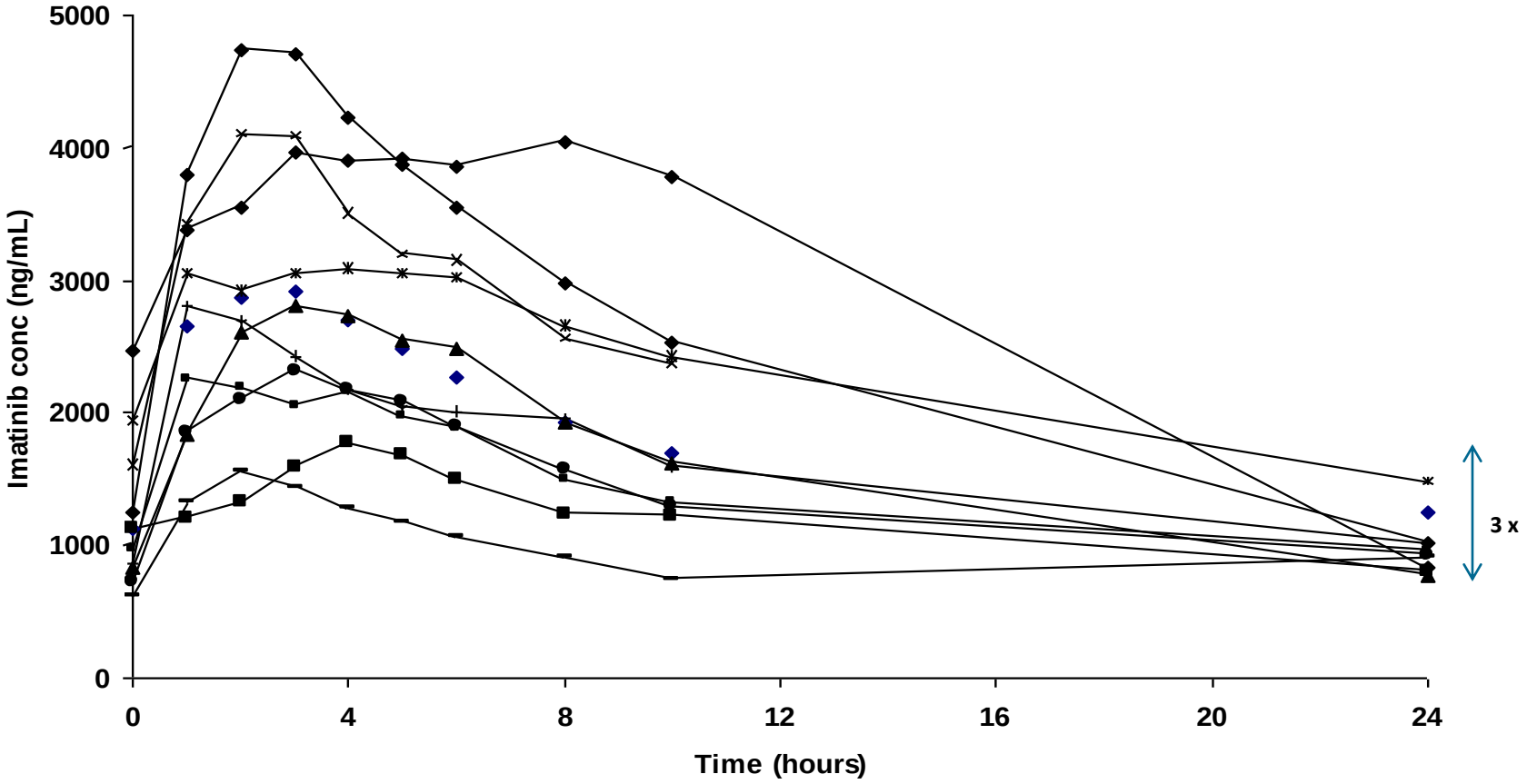
Andere geneesmiddelen

Veranderde omzetting door:

Kruidengeneesmiddelen

Allerlei factoren waarvan het effect onbekend is

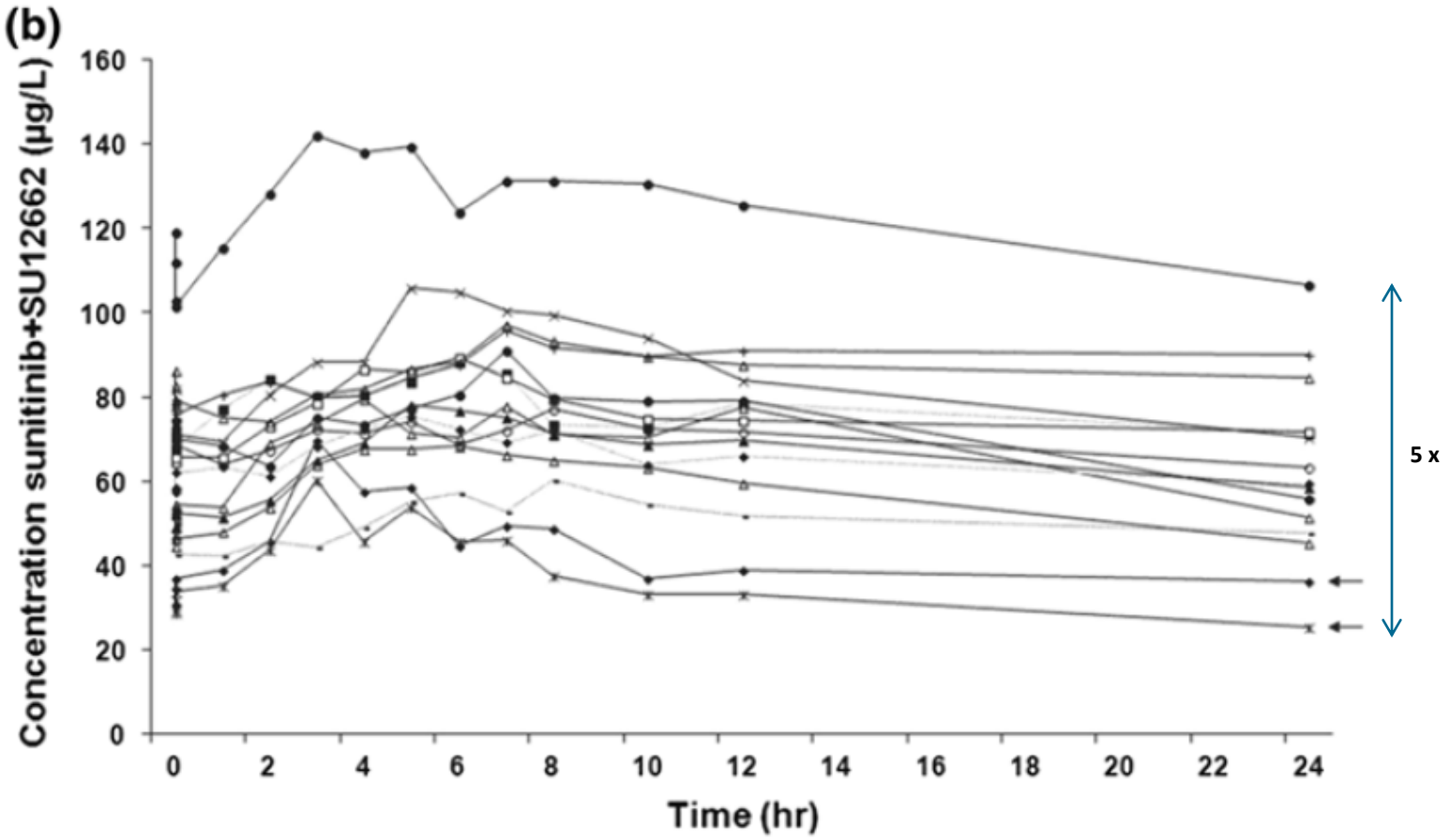
Imatinib



Radboudumc

Data Clin Cancer Res; van Erp et al. (2007) 13 (24) 7394-7400

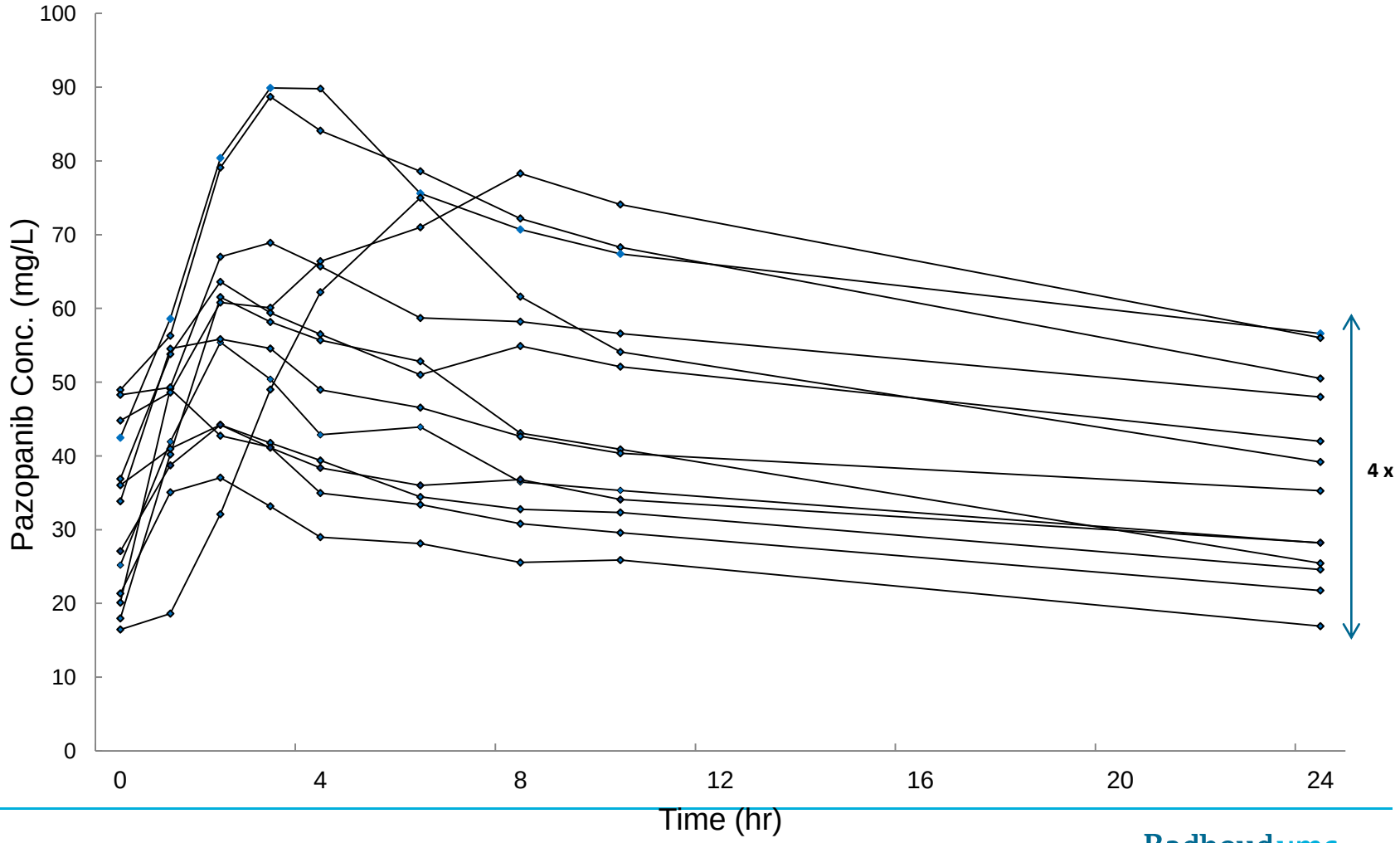
Sunitinib



Radboudumc

Cancer Chemother Pharmacol (2014) Jan;73(1):87-96; de Wit et al.

Pazopanib



Radboudumc

Data: Ther Drug Monitoring (2014) Sept (Epub).de Wit et al.

Farmacokinetische variatie TKIs

Drug	Dosage per Day	Interpatient Variations (fold or CV*) AUC	Trough Level
Hormones			
Tamoxifen†	20 mg		26-fold[28]
Letrozole	2.5 mg	40%[29]	12-fold[30]
Anastrozole	1 mg	25%[31]	11-fold[32]
Bicalutamide	50 mg	25%[33]	
Abiraterone	1,000 mg	58%[34]	
Tyrosine kinase inhibitors			
Imatinib	400 mg	25%[35]	16-fold[36]
Nilotinib	400 mg bd	51.9%[37]	51.3%[37]
Gefitinib	250 mg	15-fold[38]	23-fold[39]
Erlotinib	150 mg	64%[40]	51%[40]
Sunitinib	50 mg	41%[41]	54%[41]
Sorafenib	400 mg bd	39-82%[42]	11-fold[43]
Temsirolimus	25 mg	26%[44]	
Monoclonal antibodies			
Cetuximab	400 mg/m^2	39%[45]	6-fold[46]
Trastuzumab	6 mg/kg	10-35%[47]	>10-fold[48]
Rituximab	375 mg/m^2	6.2-fold[49]	23-fold[50]
Bevacizumab	10 mg/kg	2.4-fold[18]	

Gao B. et al, J Clin Oncol. 2012 30(32): 4017-25

VOLUME 27 · NUMBER 19 · JULY 1 2009

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

From the Ludwig Center, Dana-Farber/Harvard Cancer Center, and Harvard Medical School, Boston, MA; Oncology

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

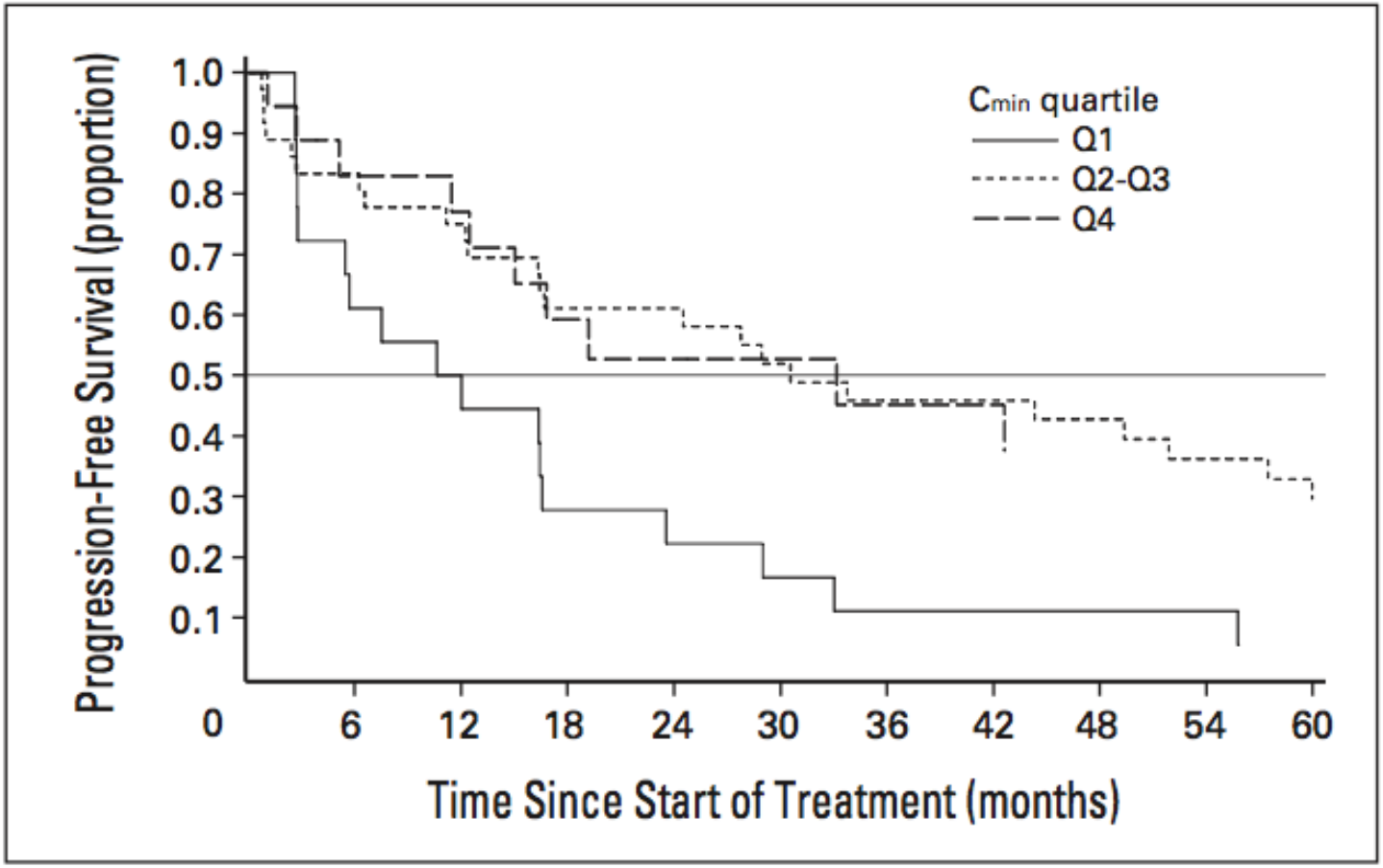


Fig 3. Time to progression by imatinib day 29 trough level (C_{min}) quartile (Q).

FULL PAPER

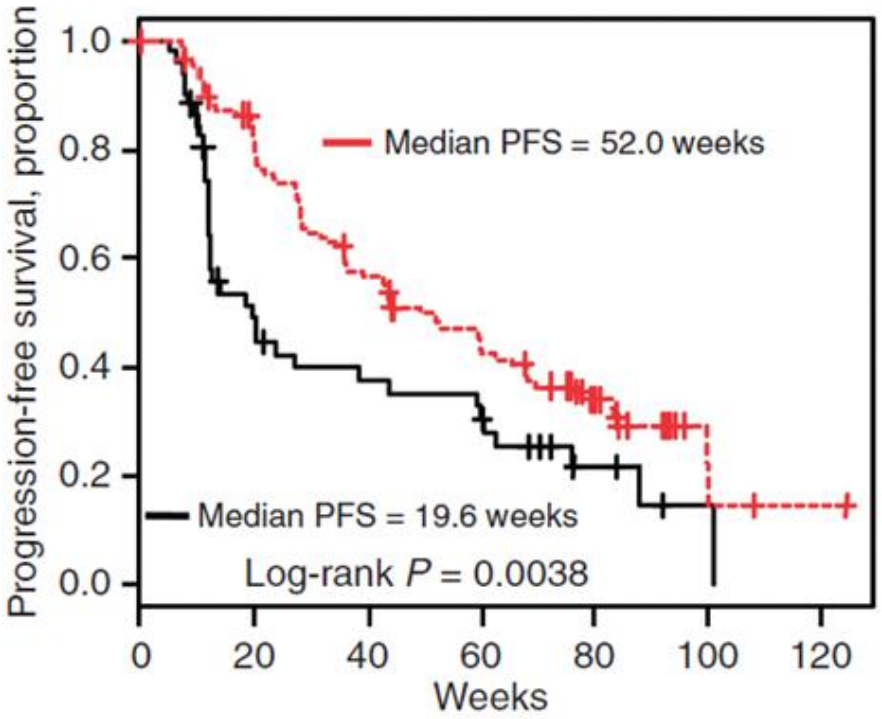
BJC

British Journal of Cancer (2014) 111, 1909–1916 | doi: 10.1038/bjc.2014.503

Keywords: pazopanib; trough concentration; renal cell carcinoma; progression-free survival; blood pressure

Relationships between pazopanib exposure and clinical safety and efficacy in patients with advanced renal cell carcinoma

A B Suttle*[,1], H A Ball[2], M Molimard[3], T E Hutson[4], C Carpenter[1,5], D Rajagopalan[2], Y Lin[2], S Swann[2], R Amado[2] and L Pandite[1]



ORIGINAL ARTICLE

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

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

Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial

Brian I Rini, Bohuslav Melichar, Takeshi Ueda, Viktor Grünwald, Mayer N Fishman, José A Arranz, Angel H Bair, Yazdi K Pithavala, Glen I Andrews, Dmitri Pavlov, Sinil Kim, Eric Jonasch

Blootstelling – response relatie

Clin Pharmacokinet (2014) 53:305–325
DOI 10.1007/s40262-014-0137-2

REVIEW ARTICLE

Practical Guidelines for Therapeutic Drug Monitoring of Anticancer Tyrosine Kinase Inhibitors: Focus on the Pharmacokinetic Targets

Huixin Yu · Neeltje Steeghs · Cynthia M. Nijenhuis · Jan H. M. Schellens · Jos H. Beijnen · Alwin D. R. Huitema

REVIEWS
Drug Discovery Today • Volume 20, Number 1 • January 2015

ELSEVIER

This is a comprehensive review of the evidence for dose individualization of TKIs used for the treatment of solid tumors. Current data suggest that, for imatinib, sunitinib, pazopanib, and axitinib, treatment could be optimized by dose individualization.

CrossMark

Reviews • FOUNDATION REVIEW

Individualized dosing of tyrosine kinase inhibitors: are we there yet?

Djoeke de Wit[1], Henk-Jan Guchelaar[1], Jan den Hartigh[1], Hans Gelderblom[2] and Nielka P. van Erp[3]

[1] Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands
[2] Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands
[3] Department of Clinical Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands

Djoeke de Wit is currently a pharmacist in the Department of Clinical Pharmacy & Toxicology, Leiden University Medical Centre (LUMC), Leiden, The Netherlands. She is a PhD candidate working in the field of pharmacology and oncology. She focuses on the

Opinie

COMMENTAAR

Bloedspiegelbepaling van orale doelgerichte antikankermedicatie

Nielka P. van Erp en Winette T.A. van der Graaf

OPINIE

- TKIs waarbij meerwaarde TDM retrospectief is vastgesteld incl. streefwaarden:
  - Imatinib
  - Sunitinib
  - Pazopanib

- TKIs waarbij meerwaarde TDM nog moet worden vastgesteld:
  - Concentratie vaststellen bij
    - Onverklaarde toxiciteit
    - Onverklaard uitblijven effectiviteit
    - Mogelijke interacties
    - Therapieontrouw

Vragen?