

GPCO

unicancer

2023

16 & 17 novembre

STRASBOURG

Hôpital Hautepierre

XIX^{ES} JOURNÉES

DU GROUPE DE
PHARMACOLOGIE
CLINIQUE
ONCOLOGIQUE

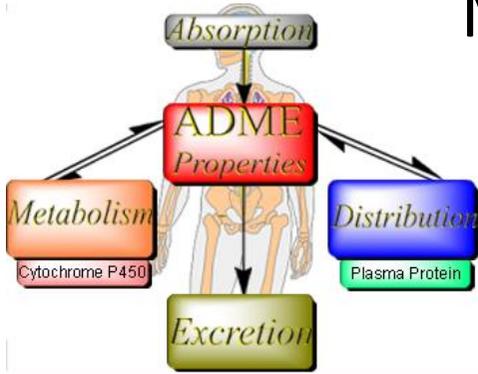


Développement d'un modèle PBPK de prédiction des interactions médicamenteuses : application aux associations atypiques entre iBRAf et iMEK.

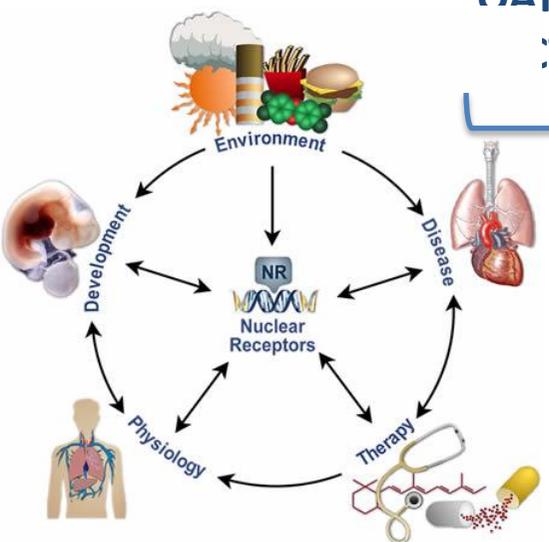
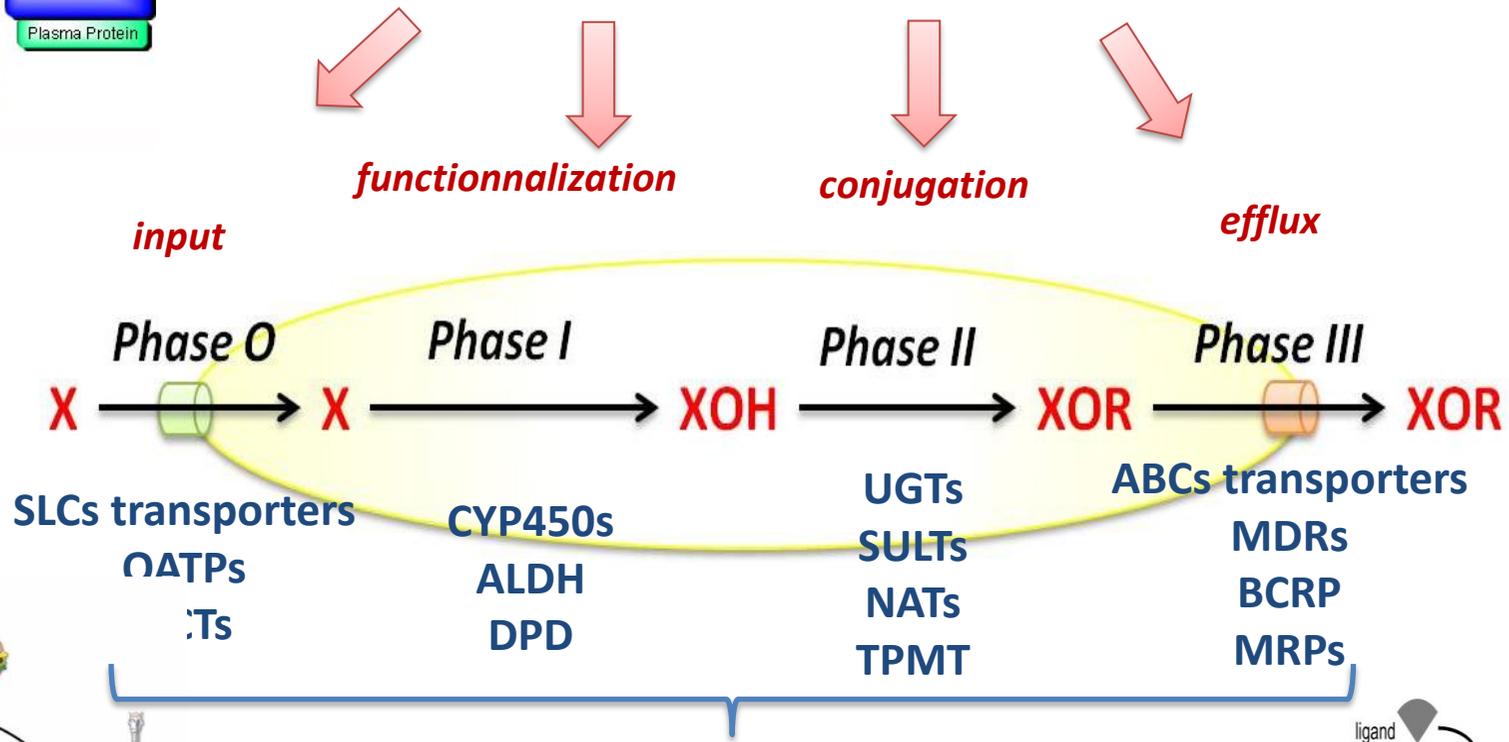
Yoena ROBERT, Alice MATHEUX, Mathilde ROBIN, Fanny LEENHARDT, Céline GONGORA, Philippe POURQUIER, Alexandre EVRARD, Litaty MBATCHI.



Molecular determinants of pharmacokinetics

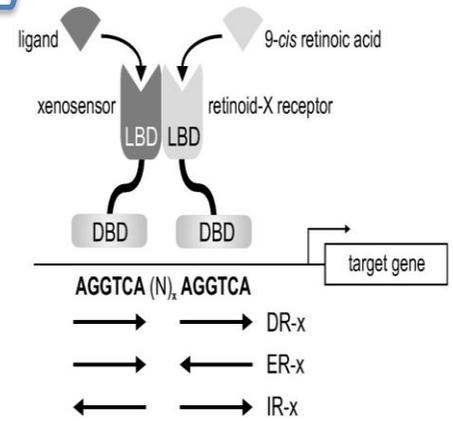


Responsive and adaptative process of DMET genes

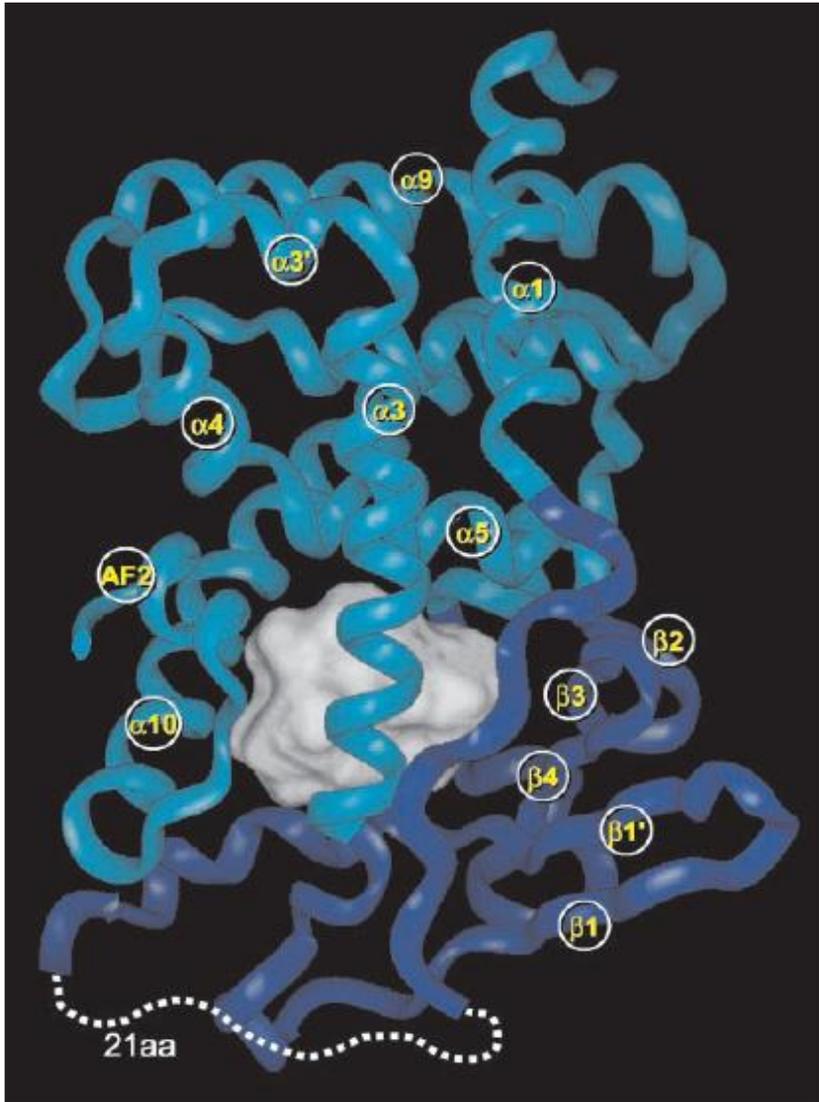


PXR (NR112) : Pregnane X Receptor
 CAR (NR113) : Constitutive Androstane Receptor
 AhR : Aryl hydrocarbhone Receptor

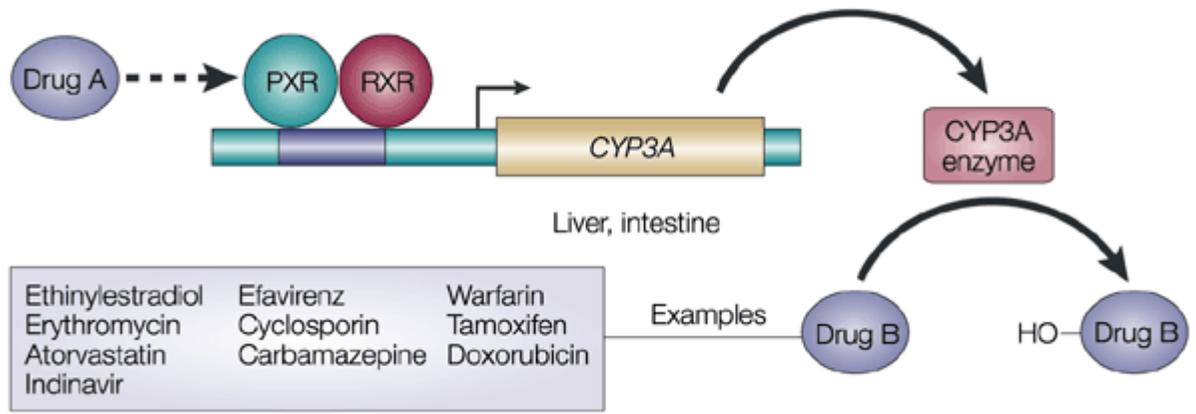
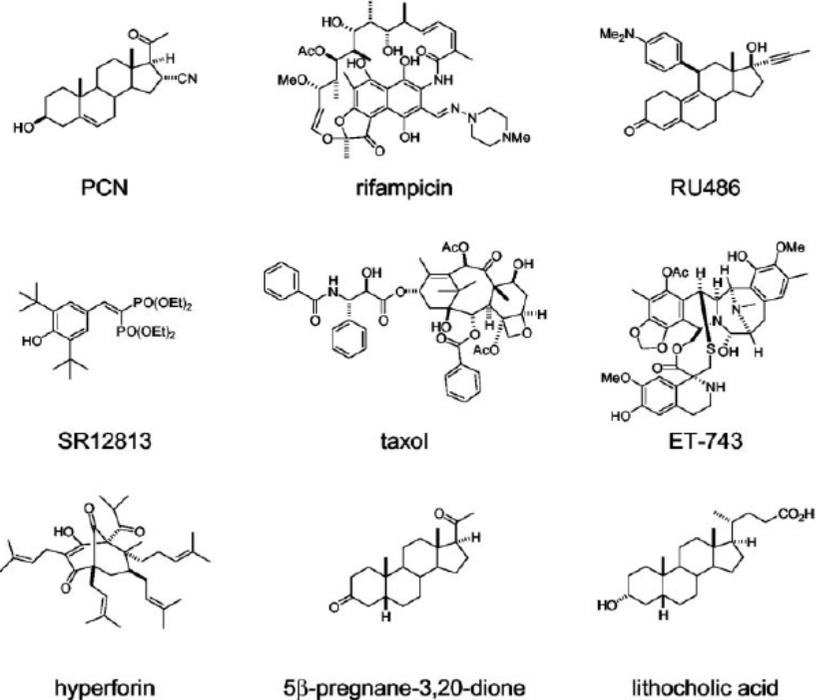
Drug-drug interactions
 Chemoresistance



PXR « sentinelle moléculaire »...ou récepteur poubelle !



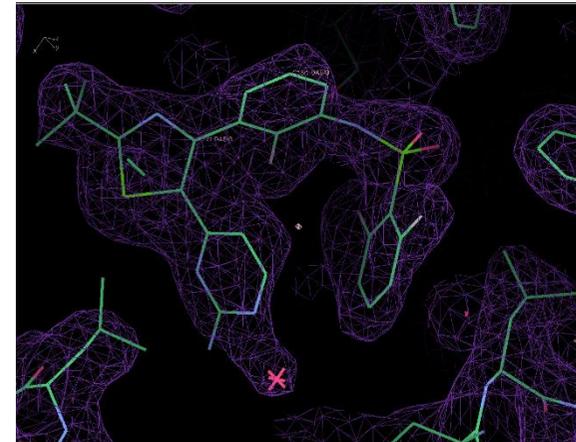
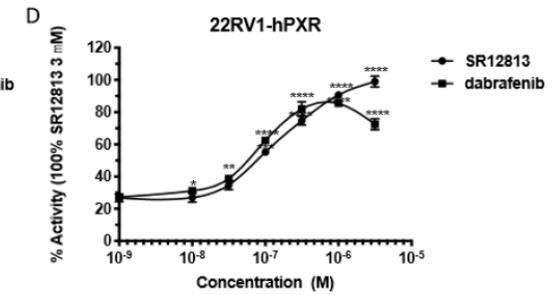
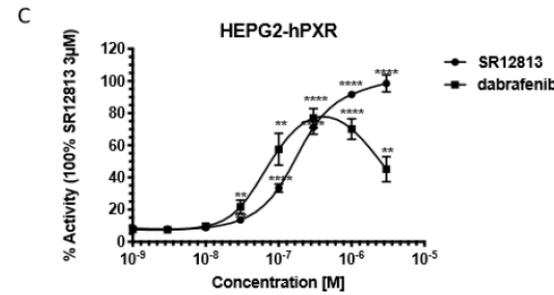
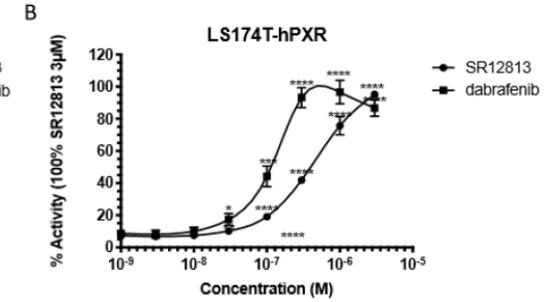
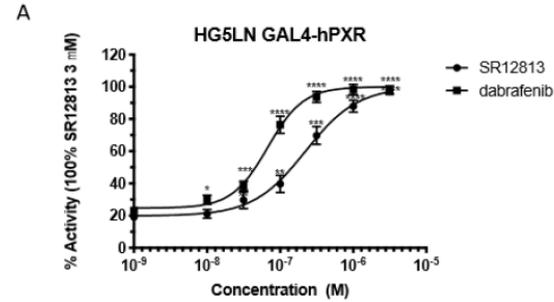
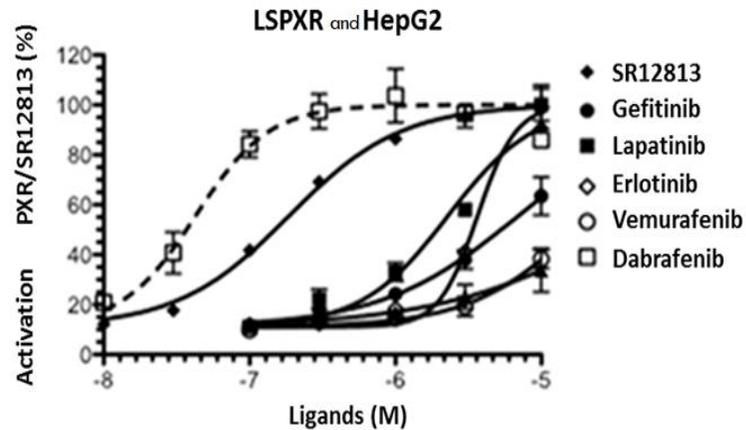
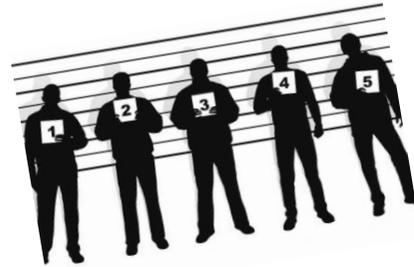
Kliwer et al., Endocrine Reviews 2002



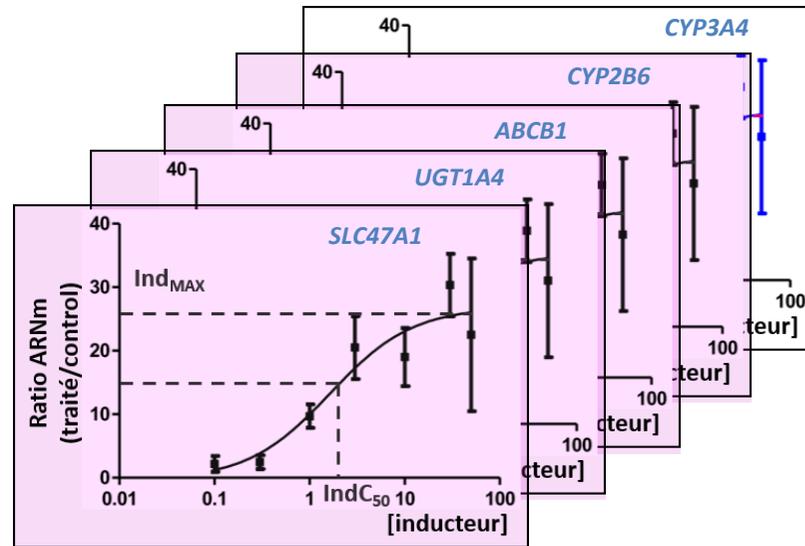
The Anti-Cancer Drug Dabrafenib Is a Potent Activator of the Human Pregnane X Receptor

Cells 2020, 9, 1641; doi:10.3390/cells9071641

Nicolas Creusot ^{1,†} , Matthieu Gassiot ^{1,†}, Elina Alaterre ¹, Barbara Chiovarina ¹, Marina Grimaldi ¹, Abdelhay Boulahtouf ¹, Lucia Toporova ¹, Sabir Martine Daujat-Chavanieu ² , Alice Matheux ¹, Roger Rahmani ³, Alexandre Evrard ¹, Philippe Pourquier ^{1,*} , and Patrick Balaguer



Méthodologie de prédiction de l'induction enzymatique



Transcriptomique

Modèles basiques (données *in vitro*)

Is increase in mRNA > a predefined threshold^[a]?

Or, is the calculated R value < 1/1.1 (i.e., 0.9)?

$$R_3 = 1 / (1 + d \times E_{max} \times [I] / (EC_{50} + [I]))^{[c]}$$

Limites actuelles :

Induction considérée du point de vue de l'enzyme induite, souvent le CYP3A4 => vision restrictive

Modèles mécanistiques (données *in vitro* + *in vivo*)

$AUC_{RATIO} < 0,8 \Rightarrow$ induction

Estimate AUCR of a sensitive probe substrate using

→ a mechanistic static model^[e]

$$AUC_{RATIO} = \frac{1}{C_g \times (1 - F_g) + F_g} \times \frac{1}{C_h \times f_m + (1 - f_m)}$$

→ or a dynamic model, including PBPK^[f]

Physiologically Based Pharmacokinetics

➔ Remettre PXR au cœur du processus : approche globale (déclencheur unique, conséquences multiples)

Workflow du projet

Cultures primaires d'hépatocytes

Société Biopredict : 3 séries (3 donneurs distincts) ; exposition : 72h



Transcriptome (RNASeq)

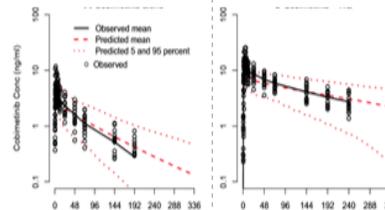
Plate-forme Data Analysis Core - Institut du cerveau (PARIS)

Image globale de l'adaptation du réseau de gènes cibles, à 1 phénomène unique (l'activation de PXR)

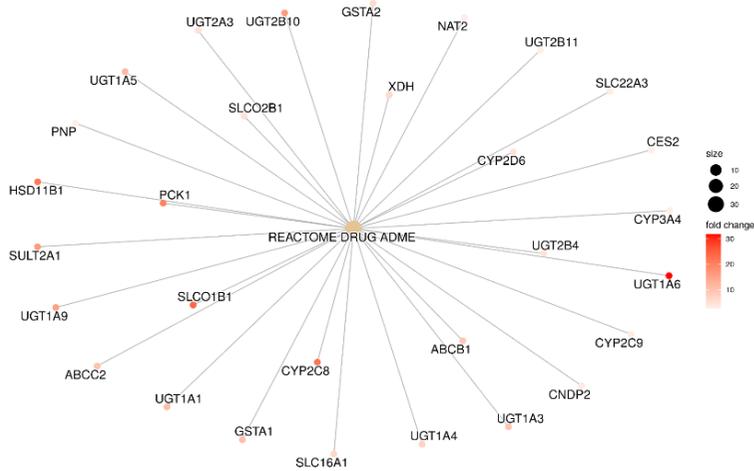
Modèle PBPK

Modification de l'abondance des Enzymes et Transporteurs impliqués dans le métabolisme du médicament « victime » de l'interaction médicamenteuse

SIMULATION DE PROFILS PK POUR PREDIRE L'INTERACTION



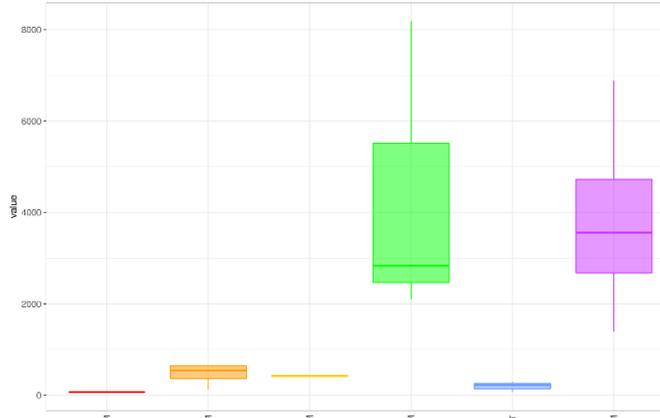
Données transcriptomiques



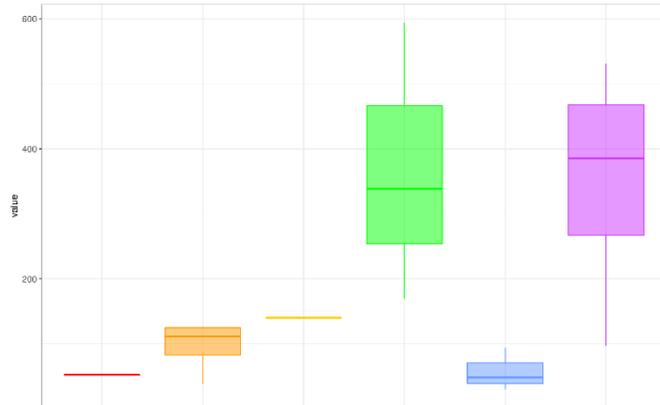
SampleGroup

-  Dabrafenib_0;01µM
-  Dabrafenib_0;1µM
-  Dabrafenib_100µM
-  Dabrafenib_50µM
-  NT
-  Rifampicine_10µM

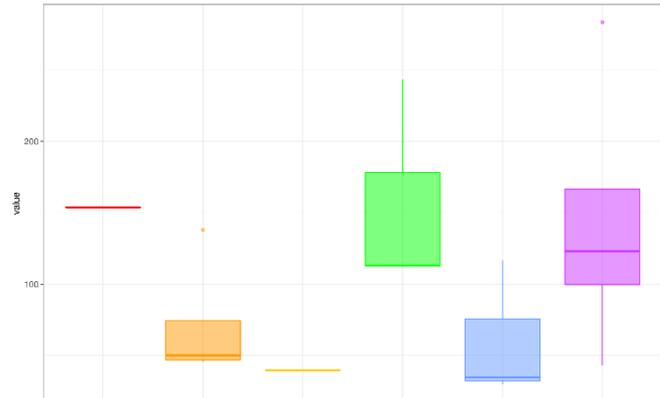
CYP3A4 gene cpm expression levels



UGT1A4 gene cpm expression levels



ABCB1 gene cpm expression levels



FeatureID	D50_FC	R10_FC
ABCB1	2,63	2,36
ABCC2	2,14	2,17
CYP1A1	4,77	1,11
CYP1A2	7,19	-1,26
CYP2A6	25,62	17,86
CYP2B6	32,19	14,19
CYP2C8	12,69	4,50
CYP2C9	2,25	1,97
CYP3A4	17,13	17,38
CYP3A5		
CYP3A7	2,80	4,34
SLC16A1	2,08	1,17
SLC19A2	3,77	1,11
SLC47A1	6,72	1,27
SLC51A	4,26	1,21
SLC51B	128,55	11,42
SLCO1B1	5,11	1,31
SLCO2B1	2,18	1,45
SLCO4C1	7,08	1,14
UGT1A1	4,54	2,36
UGT1A3	3,29	3,09
UGT1A4	5,38	5,66
UGT1A5	10,05	10,42
UGT1A6	4,05	2,11
UGT1A9	3,20	1,85
UGT2B1		
UGT2B1		
UGT2B4		



Ind_{MAX}
Ind_{C₅₀}

Stratégie de validation des modèles PBPK



(± webplotdigitizer)

Logiciel de PBPK (Physiologically based pharmacokinetic)

MODÈLES DU DABRAFENIB

Modulation des valeurs IndMax/IndC50

MODÈLES DES VICTIMES

midazolam, warfarin

SIMULATION DES INTERACTIONS dabrafenib/victimes

Confrontation avec les données cliniques
Choix du meilleur modèle de dabrafenib

APPLICATION DU MODÈLE D'INDUCTION SÉLECTIONNÉ

Simulation d'associations atypiques :
dabrafenib/cobimetinib
dabrafenib /binimetinib

[Clinical Trial](#) > [Clin Pharmacol Drug Dev.](#) 2021 Sep;10(9):1054-1063. doi: 10.1002/cpdd.937. Epub 2021 May 1.

Evaluation of the Effects of Repeat-Dose Dabrafenib on the Single-Dose Pharmacokinetics of Rosuvastatin (OATP1B1/1B3 Substrate) and Midazolam (CYP3A4 Substrate)

Noelia Nebot¹, Christina S Won², Victor Moreno³, Eva Muñoz-Couselo⁴, Dung-Yang Lee¹, Eduard Gasal¹, Emmanuel Bouillaud⁵

[Controlled Clinical Trial](#) > [J Clin Pharmacol.](#) 2015 Apr;55(4):392-400. doi: 10.1002/jcph.437. Epub 2014 Dec 30.

Assessment of the drug interaction potential and single- and repeat-dose pharmacokinetics of the BRAF inhibitor dabrafenib

A Benjamin Suttle¹, Kenneth F Grossmann, Daniele Ouellet, Lauren E Richards-Peterson, Gursel Aktan, Michael S Gordon, Patricia M LoRusso, Jeffrey R Infante, Sunil Sharma, Kari Kendra, Manish Patel, Shubham Pant, Hendrik-Tobias Arkenau, Mark R Middleton, Samuel C Blackman, Jeff Botbyl, Stanley W Carson

Intégration des données transcriptomiques dans SimCYP

Simcyp Version 22 Release 1 : MDZ_DABRA_1

File Options Tools View Licensing Notifications Help Resources

Open Save Clear Simulation Prediction Annotation Projects OC Workflow LSA GSA P.E. CTPE CPE Batch VBE Real Time Results CSS

Workspace MDZ_DABRA_1

Population Wsp-Healthy Vol...
Substrate R_warfarin_2023
Inhibitor 1 DABRAFENIB_8...
Inhibitor 2 Wsp-Atazanavir

Phys Chem and Blood Binding
Absorption
Distribution
Elimination
Interaction
Transport (Permeability Ltd. Organs)
Custom Lua Models
PD Basic 1
Setup

PKPD Parameters Profiles
Outputs
Trial Design

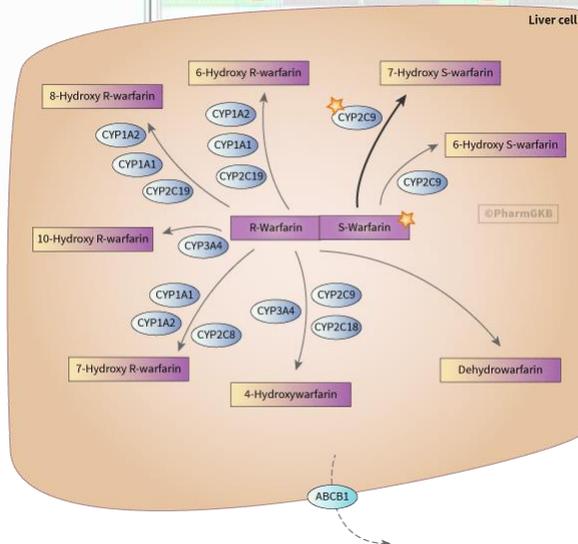
DABRAFENIB_8_TR_Ind50-0.05

CYP UGT Esterases FMO Cytosolic Enzymes Transporters

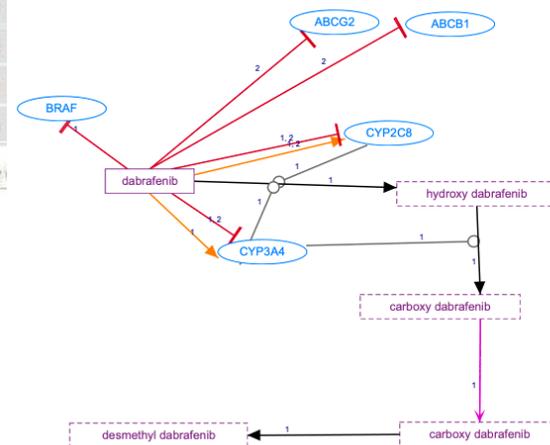
Consider Competitive Inhibition Protection Effect on MBI

Co-administration of Multiple Inducers and/or Suppressors
Default Additive Multiplicative

Enzyme	Competitive Inhibition			Mechanism-Based Inhibition				Induction/Suppression								
	Ki	f _{unc}		K _{app}	kinact	Slope	f _{unc}	Ind _{max} ^A	CV (%)		Ind _{max} ^A	CV (%)	IndC ₅₀ ^A	CV (%)	f _{unc}	γ
CYP1A2	1E+06	1		1E+06	0	0	1	0	30		7.2	30	0.05	30	1	1
CYP2A6	1E+06	1		1E+06	0	0	1	0	30		25.6	30	0.05	30	1	1
CYP2B6	1E+06	1		1E+06	0	0	1	0	30		32.2	30	0.05	30	1	1
CYP2C8	4.1	1		1E+06	0	0	1	0	30		12.7	30	0.05	30	1	1
CYP2C9	1E+06	1		1E+06	0	0	1	0	30		2.2	30	0.05	30	1	1
CYP2C18	1E+06	1		1E+06	0	0	1	0	30		1	30	1E+06	30	1	1
CYP2C19	1E+06	1		1E+06	0	0	1	0	30		1	30	1E+06	30	1	1
CYP2D6	1E+06	1		1E+06	0	0	1	0	30		1	30	1E+06	30	1	1
CYP2E1	1E+06	1		1E+06	0	0	1	0	30		1	30	1E+06	30	1	1
CYP2J2	1E+06	1		1E+06	0	0	1	0	30		1	30	1E+06	30	1	1



and here is already calibrated against the



Validation du modèle PK du dabrafénib

doi: 10.1111/1346-8138.14210

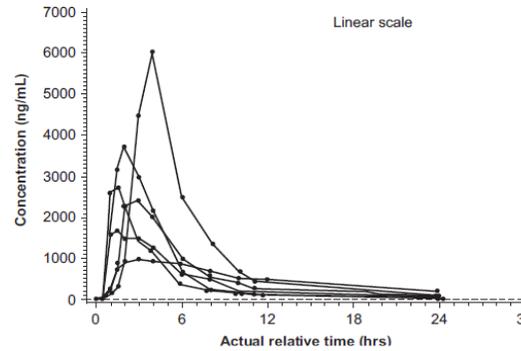
Journal of Dermatology 2018; 45: 397–407

ORIGINAL ARTICLE

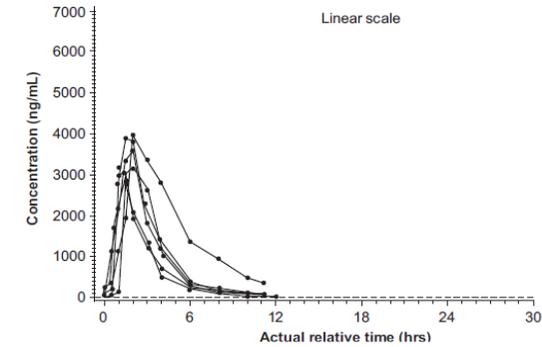
Phase 1/2 study assessing the safety and efficacy of dabrafenib and trametinib combination therapy in Japanese patients with *BRAF* V600 mutation-positive advanced cutaneous melanoma

Naoya YAMAZAKI,¹ Arata TSUTSUMIDA,¹ Akira TAKAHASHI,¹ Kenjiro NAMIKAWA,¹ Shusuke YOSHIKAWA,² Yutaka FUJIWARA,³ Shunsuke KONDO,⁴ Akihira MUKAIYAMA,⁵ Fanghong ZHANG,⁵ Yoshio KIYOHARA²

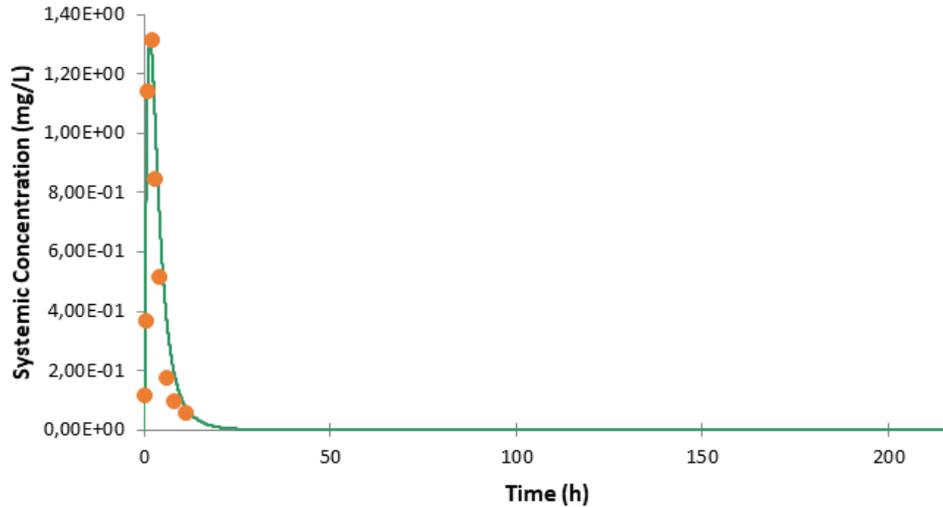
(a) Dabrafenib: Day 1



(b) Dabrafenib: Day 21

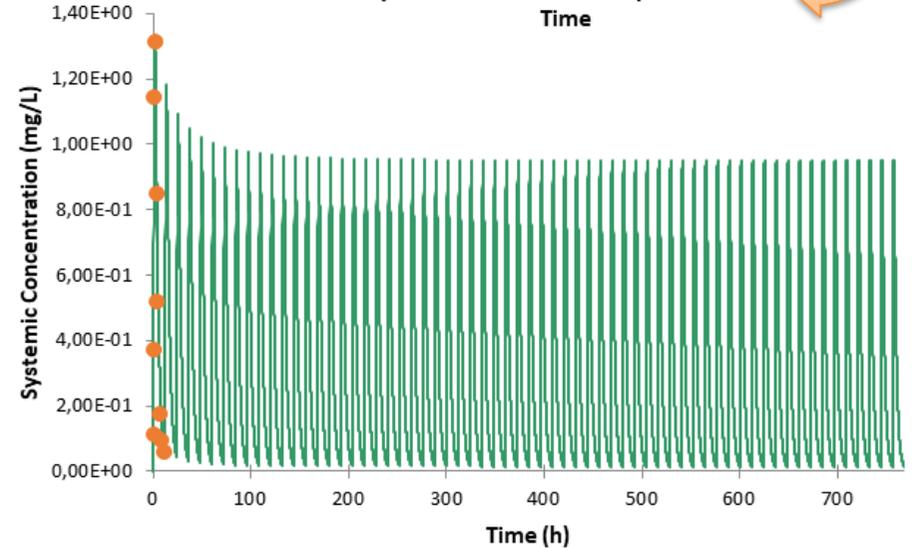


Mean Values of Systemic concentration in plasma of DABRAFENIB Time



— CSys ● Subject 1 : DV 1

Mean Values of Systemic concentration in plasma of DABRAFENIB over Time



— CSys ● Subject 1 : DV 1

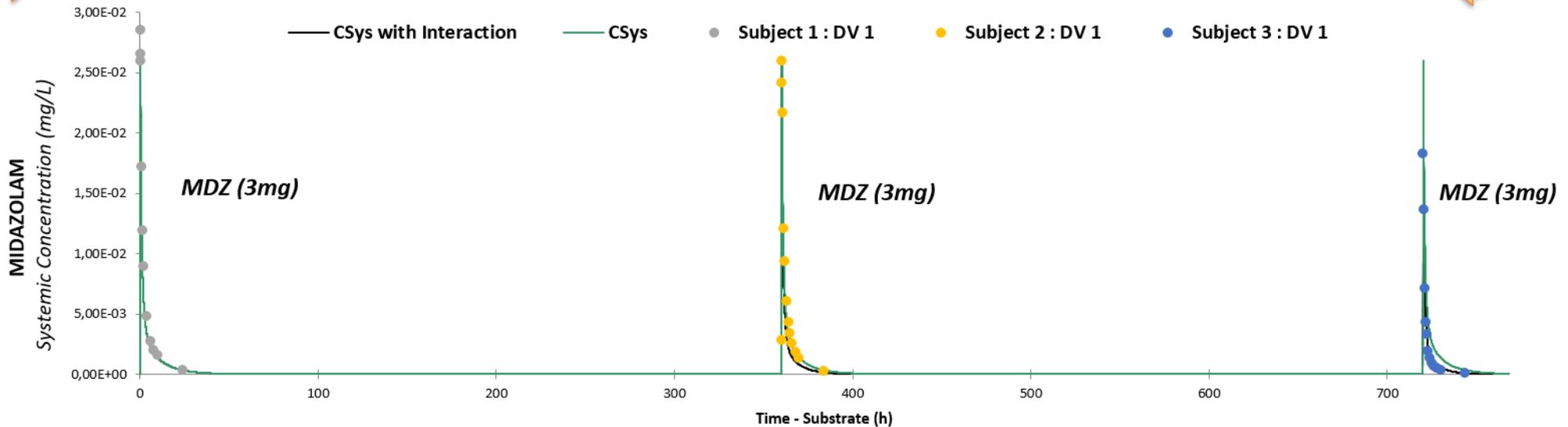
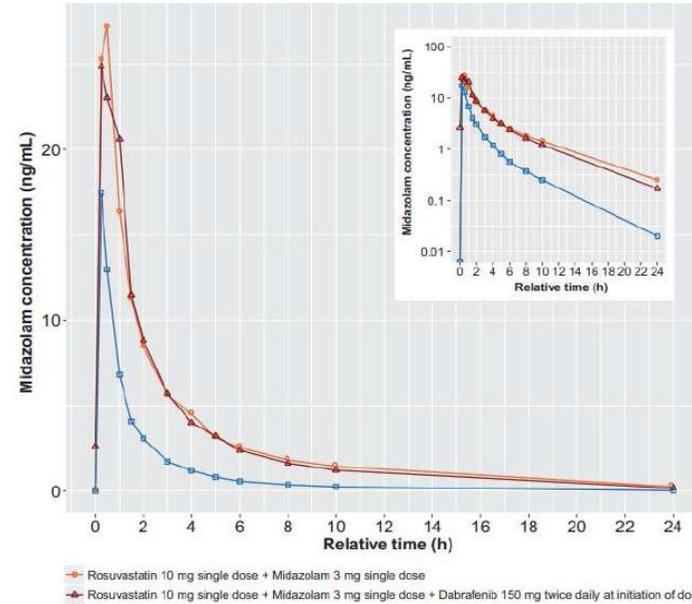
Validation du modèle d'induction sur le midazolam

Clinical Trial > Clin Pharmacol Drug Dev. 2021 Sep;10(9):1054-1063. doi: 10.1002/cpdd.937.

Epub 2021 May 1.

Evaluation of the Effects of Repeat-Dose Dabrafenib on the Single-Dose Pharmacokinetics of Rosuvastatin (OATP1B1/1B3 Substrate) and Midazolam (CYP3A4 Substrate)

Noelia Nebot¹, Christina S Won², Victor Moreno³, Eva Muñoz-Couselo⁴, Dung-Yang Lee¹, Eduard Gasal¹, Emmanuel Bouillaud⁵



A partir de J15 : DABRAFENIB 150mgx2/j

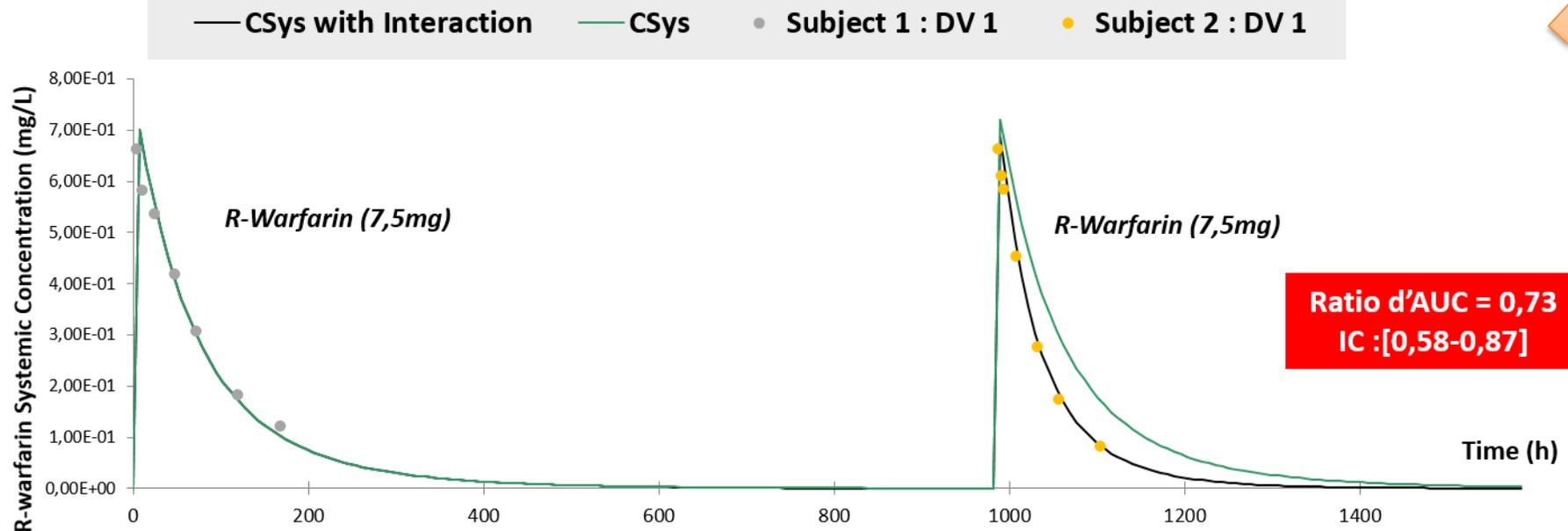
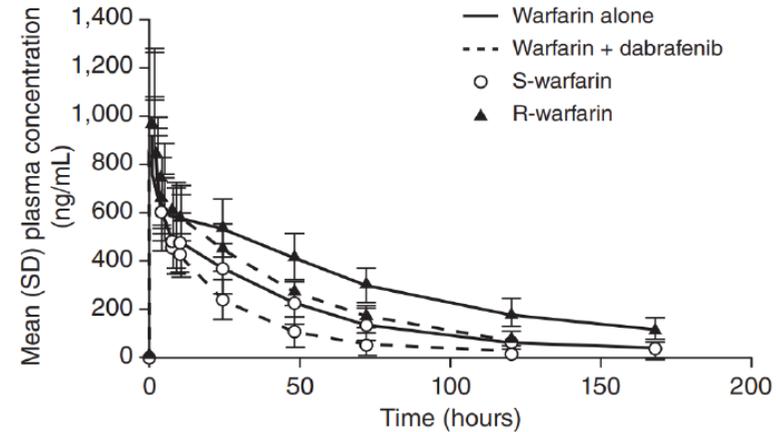
Validation du modèle d'induction sur la R-warfarin

Controlled Clinical Trial > J Clin Pharmacol. 2015 Apr;55(4):392-400. doi: 10.1002/jcph.437.

Epub 2014 Dec 30.

Assessment of the drug interaction potential and single- and repeat-dose pharmacokinetics of the BRAF inhibitor dabrafenib

A Benjamin Suttle¹, Kenneth F Grossmann, Daniele Ouellet, Lauren E Richards-Peterson, Gursel Aktan, Michael S Gordon, Patricia M LoRusso, Jeffrey R Infante, Sunil Sharma, Kari Kendra, Manish Patel, Shubham Pant, Hendrik-Tobias Arkenau, Mark R Middleton, Samuel C Blackman, Jeff Botbyl, Stanley W Carson



A partir de J15 : DABRAFENIB 150mgx2/j

Application aux associations atypiques iBRAF/iMEK

BJC

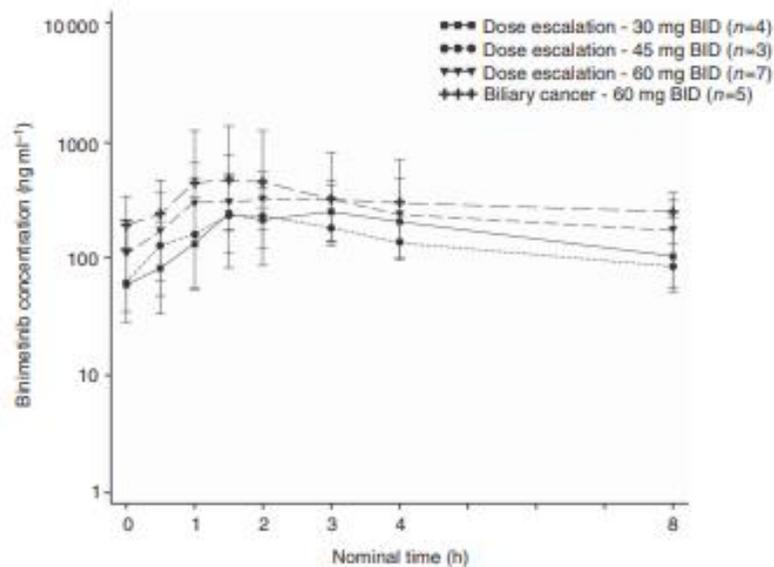
British Journal of Cancer (2017) 116, 575–583 | doi: 10.1038/bjc.2017.10



Keywords: binimetinib; MEK162; MEK inhibitor; gastrointestinal cancers; colorectal cancers; clinical trial

A phase 1 dose-escalation and expansion study of binimetinib (MEK162), a potent and selective oral MEK1/2 inhibitor

Johanna C Bendell^{1*}, Milind Javle², Tarios S Bekaii-Saab³, Richard S Finn⁴, Zev A Wainberg⁴, Daniel A Laheru⁵, Colin D Weekes⁶, Benjamin R Tan⁷, Gazala N Khan⁸, Mark M Zalupski⁹, Jeffrey R Infante¹, Suzanne Jones¹⁰, Kyriakos P Papadopoulos¹¹, Anthony W Tolcher¹¹, Renae E Chavira¹², Janna L Christy-Bittel^{12,13}, Emma Barrett^{12,13} and Amita Patnaik¹¹



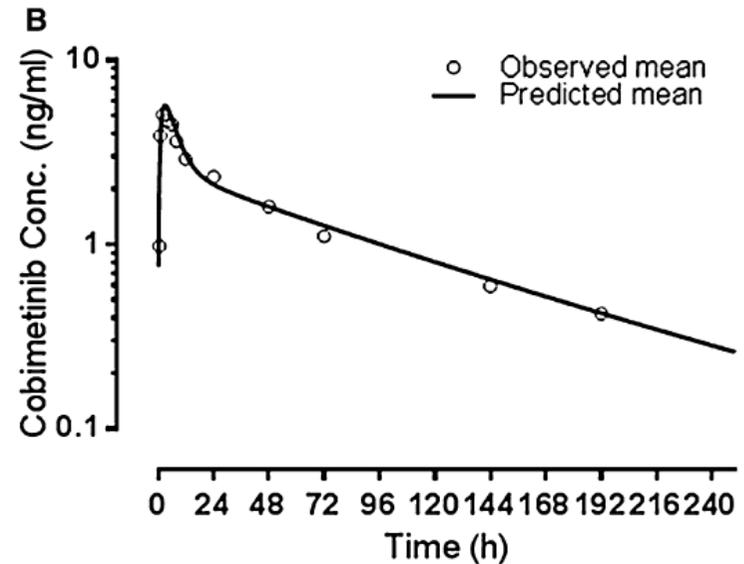
Clin Pharmacokinet (2016) 55:1435–1445
DOI 10.1007/s40262-016-0412-5



ORIGINAL RESEARCH ARTICLE

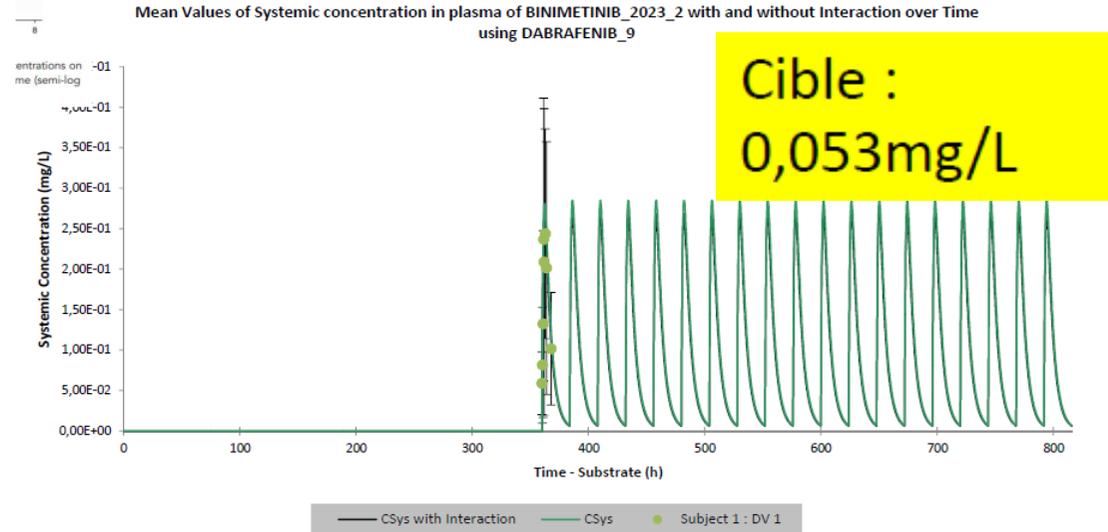
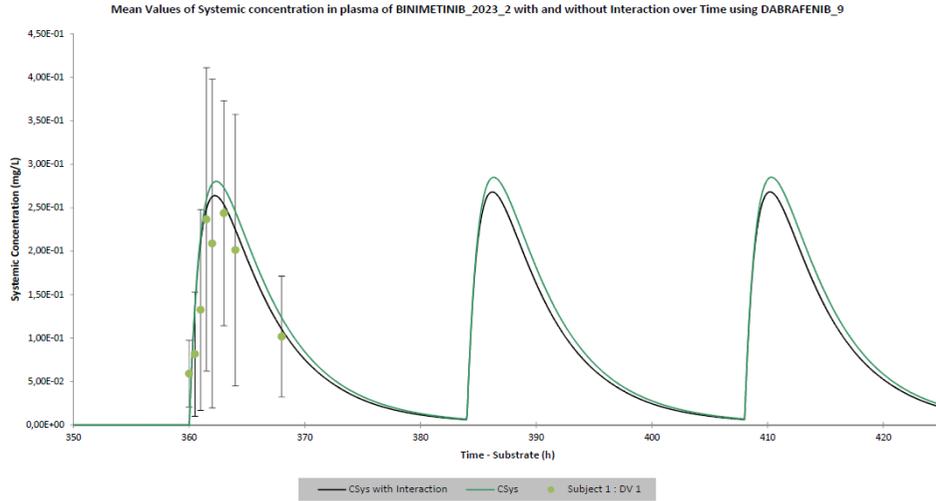
Evaluation of Cytochrome P450 3A4-Mediated Drug–Drug Interaction Potential for Cobimetinib Using Physiologically Based Pharmacokinetic Modeling and Simulation

Nageshwar R. Budha¹ · Tao Ji¹ · Luna Musib¹ · Steve Eppler¹ · Mark Dresser¹ · Yuan Chen² · Jin Y. Jin¹



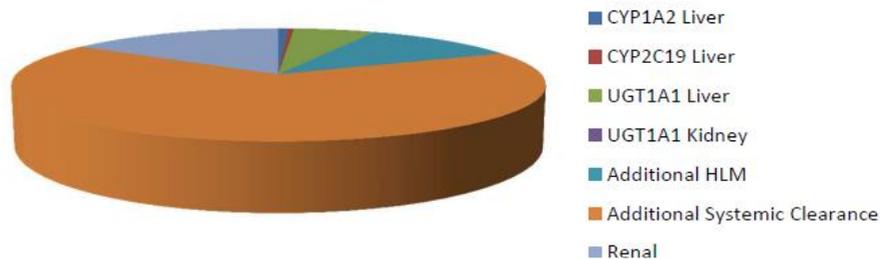
Simulation du traitement binimétinib/dabrafénib

BINIMETINIB 60mg/j
DABRAFENIB 150mg x2/j

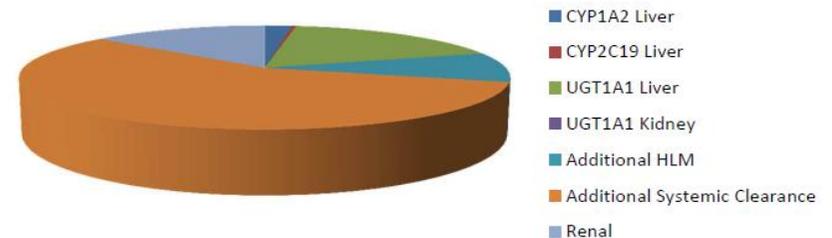


Légère diminution de l'exposition au binimétinib en dose unique et à l'équilibre

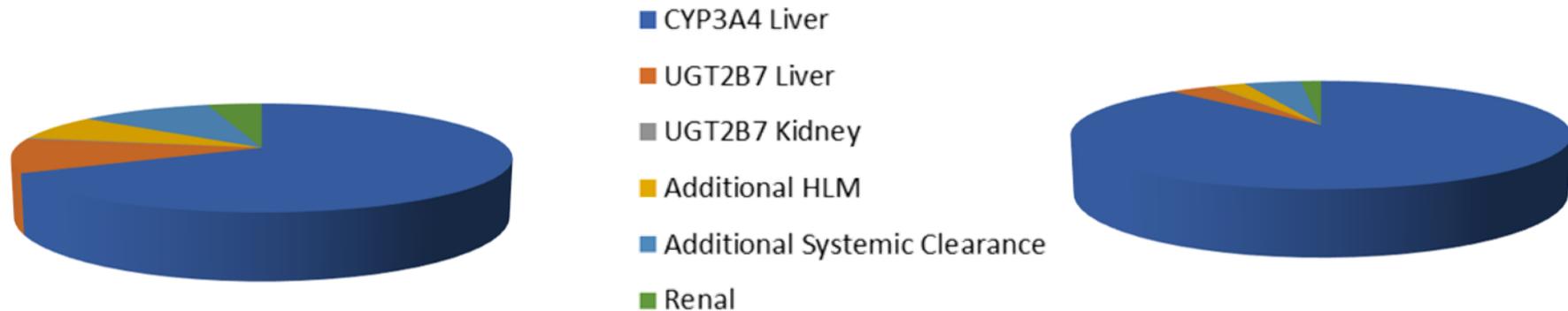
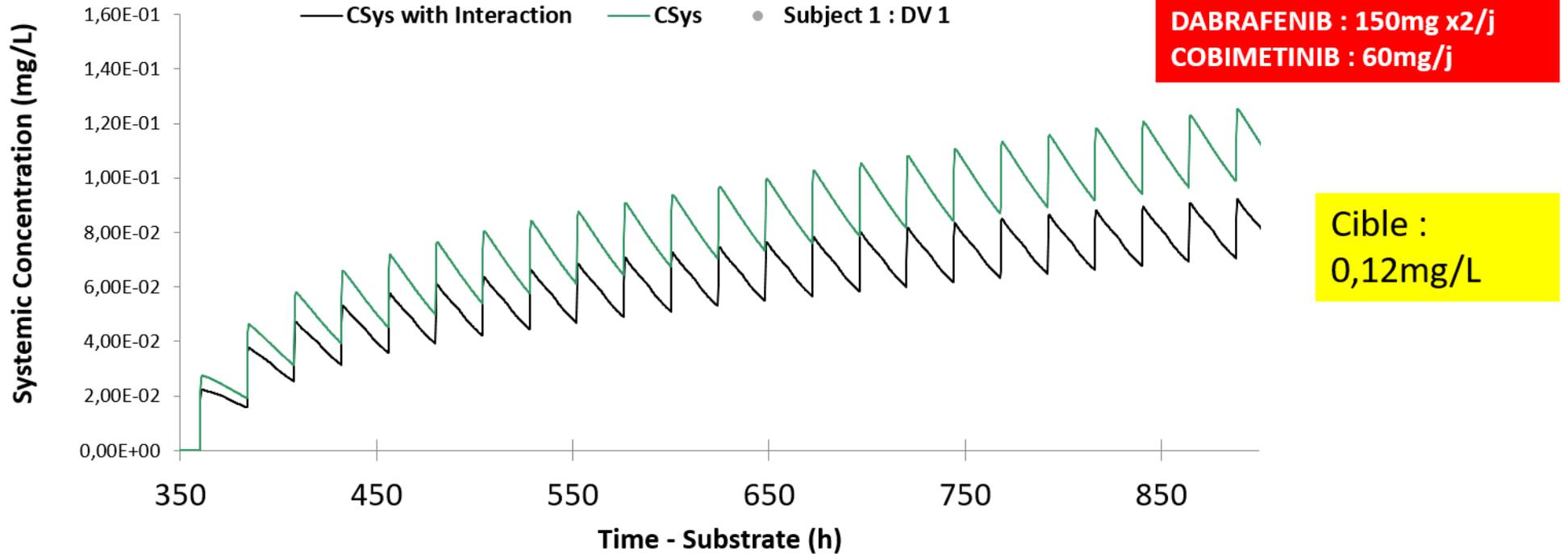
Median % fm and fe in relation to systemic clearance in absence of inhibitors



Median % fm and fe in relation to systemic clearance in presence of inhibitor



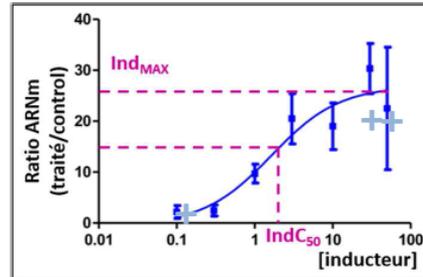
Simulation du traitement cobimetinib/dabrafénib



Diminution de l'exposition au cobimetinib en dose unique et à l'équilibre

Conclusions / Perspectives

Premier transcriptome de culture primaire d'hépatocytes réalisé pour un inducteur



Limites de l'expérience actuelle : peu de donneurs, peu de concentrations

Elargir l'analyse

Approfondir les connaissances sur l'induction au niveau fondamental

Comparaison des niveaux d'induction
entre gène cibles, entre inducteurs ?

FeatureID	D50_FC	R10_FC
ABCB1	2,63	2,36
ABCC2	2,14	2,17
CYP1A1	4,77	1,11
CYP1A2	7,19	-1,26
CYP2A6	25,62	17,86
CYP2B6	32,19	14,19
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CYP2C9	2,25	1,97
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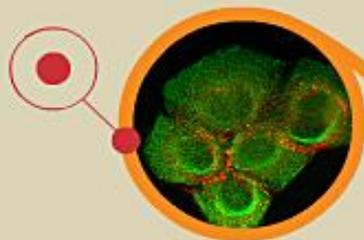
Compréhension et interregulation
du réseau DMET
(Drug Metabolizing Enzymes and Transporters)

Collaboration J. Colinge



32

- ✓ Simulation des stratégies posologiques basées sur des réalités physiologiques
- ✓ Arguments rationnels pour le choix d'associations atypiques



Céline GONGORA (dir)

Ileana CORBEAU

Alexandre EVRARD

Alexandra FAUVRE

Véronique GARAMBOIS

Aurélie GARCIN

Nadine HOUEDE

Laura JEANSON

Christel LARBOURET

Fanny LEENHARDT

Candice MARCHIVE

Litaty MBATCHI

Philippe POURQUIER

Mathilde ROBIN

Diego TOSI

Nadia VIE

Stefan NICOLESCU



+ Collab. P. Balaguer