Etudes pharmacocinétiques lors du développement d'un médicament anticancéreux

Etienne CHATELUT, PharmD, PhD
Université de Toulouse,
IUCT-oncopole

Plan

- Préclinique
- Méthodologies cliniques
  - Essais: phase 1 … et autres
  - Méthodes d'analyse des données (Conc. Plasm. Vs. temps)
- PK de population
- Post-AMM

Rappels PK

- Elimination: CL
- Distribution: Vd
- Absorption: F (thérapie ciblée, petite molécule)

- Paramètres graphiques:
  - Cmax
  - AUC = F x Dose / CL (cytotoxiques: =Dose/CL)
  - T1/2 = Ln2 x Vd / CL (Mab)

Différents médicaments anticancéreux: « enjeux PKs » différents

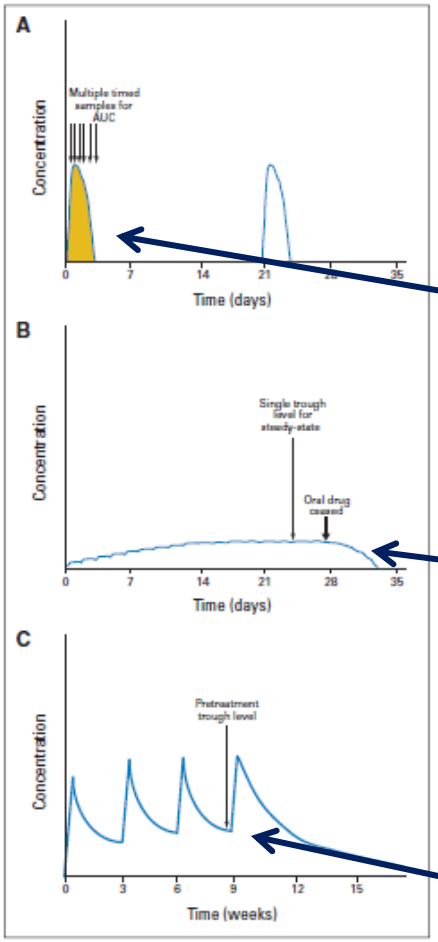


Fig 1. Representation of the blood concentration over time of various anticancer agents with differing pharmacokinetics profile. (A) Traditional cytotoxic agent given by three weekly intravenous injections. The description of systemic exposure requires multiple timed blood samples to define the area under the time-concentration curve (AUC). (B) Targeted agent given orally daily. Steady state can be described by a single trough sample. (C) Monoclonal antibody (mAB) given by intermittent infusions. Owing to the long half-life of most mABs, a pretreatment trough level may adequately describe drug exposure.

Evidence for Therapeutic Drug Monitoring of Targeted Anticancer Therapies

Bo Gao, Shang Yeap, Arthur Clements, Bavanthi Balakrishnar, Mark Wong, and Howard Gurney

AUC = Dose / CL

$C_{moy,ss} = AUC/\tau = F \times Dose / CL$

$C_{min,ss} \approx C_{moy,ss}$

Cmin,ss = f(Dose, T1/2)

PK et préclinique

- Animal
  - Rat: iv, (oral), doses différentes, unique et répétées, ^{14}C
  - Autres: singe
  - Voie(s) d'élimination principale(s)
- In vitro
  - Hépatocytes en culture (humains et animaux), microsomes (CYP), Caco-2 (ABC transporteurs)
  - Fixation aux protéines plasmatiques

PK et Etudes cliniques: objectifs

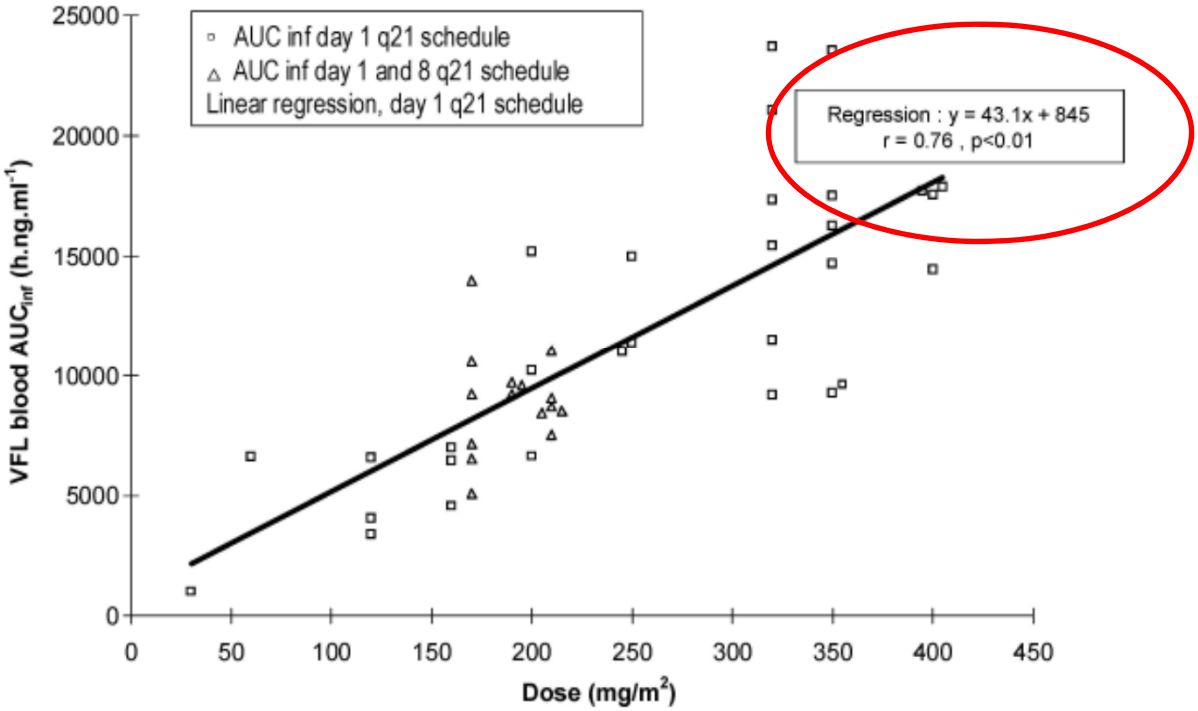
- Schémas d'administration (paramètres moyens)
  - Voie d'administration: F
  - Rythme des administrations: T1/2
- Doses (valeurs individuelles, variabilité)
  - mg/m^2, mg/kg, mg: CL
  - Adaptation des doses
    - Sous groupes: insuffisants hépatiques, …
    - Doses individualisées

Phase 1 (« first-in-man ») et PK

- Linéarité de la PK:
  - Paramètres PK indépendants de la dose: CL/F indépendant de la dose
  - Paramètres graphiques (mg/L) proportionnels à la dose: AUC vs. Dose
- Variabilité inter-individuelle
  - CV (%): écart-type / moyenne
  - Focus sur la CL, CL/F (Dose/AUC)
- Méthodologie
  - Nombreux prélèvements sanguins

Exemple: phase 1 vinflunine

R^2=0.58



Phase(s) 1-2

- Extension de la cohorte à la dose recommandée
- Concentrations à l'état d'équilibre (Css, AUCτ,ss)
- Exemple: un ITK

Phase 1-2 association

2 cytotoxiques, cytotoxique et thér. ciblée, 2 thér. ciblées

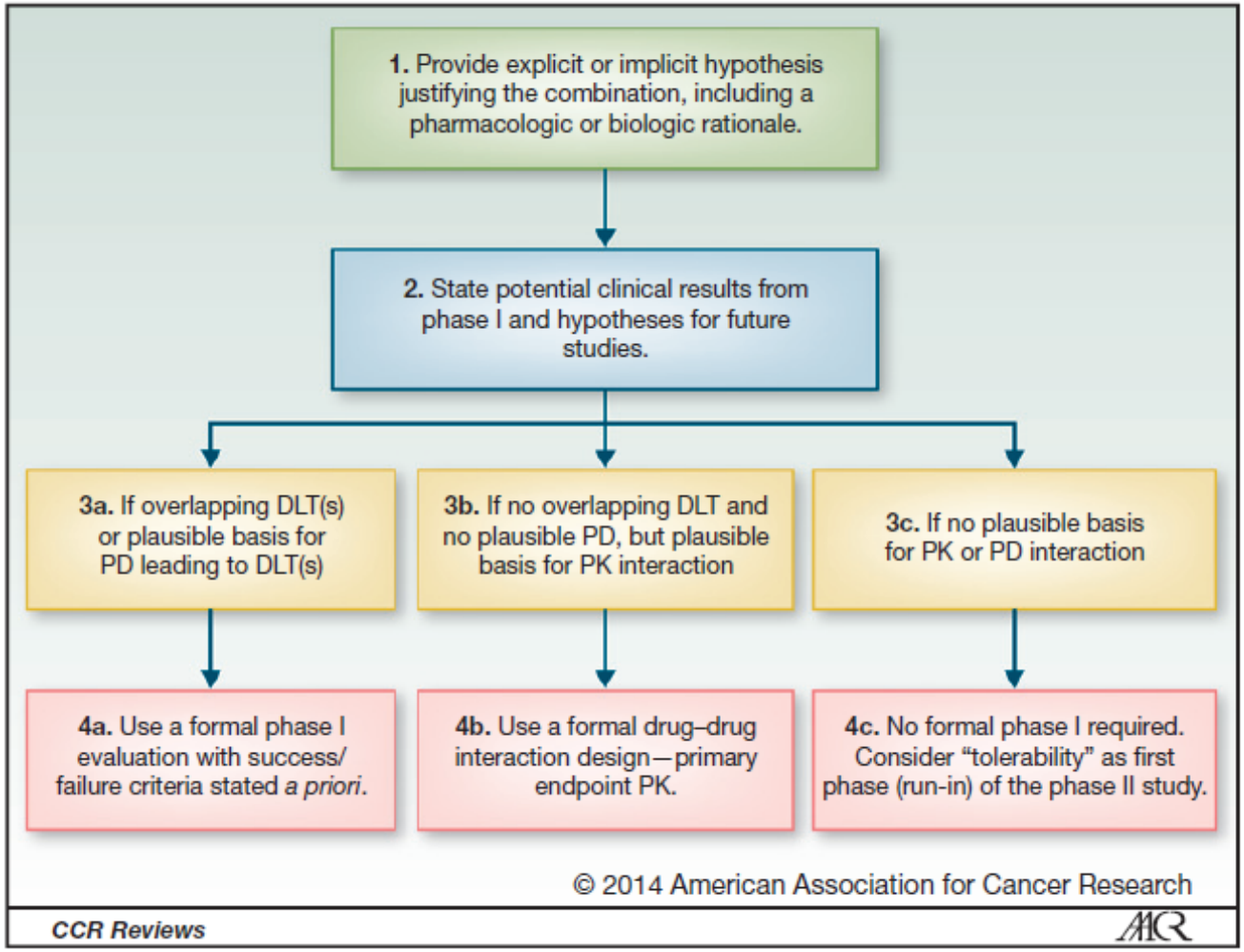


Figure 1. Process for determination of the phase I combination trial design. PD, pharmacodynamic; PK, pharmacokinetic.

Paller CG, …, Ratain MJ, Clin Cancer Res

PK dans des sous-groupes

- Insuffisants rénaux
- Insuffisants hépatiques
- (Personnes âgées)
- Pédiatrie: phase 1 …

- Interactions médicamenteuses: rifampicine, itraconazole: thérapies ciblées vs. cytotoxiques

Approche standard: méthode en « deux étapes »

- Essai clinique spécifique: 4 sous-groupes de volontaires ayant fonction rénale normale, altérée (80, 50, 30 mL/min/1,73 m^2), insuffisance rénale complète [www.emea]
- Détermination puis Comparaison des paramètres PK: clairance d'élimination du médicament (CL)
- RCP: ex. topotecan (Hycantin):
- La dose recommandée de topotécan en monothérapie pour les patients ayant un carcinome de l'ovaire ou un cancer du poumon à petites cellules, dont la clairance de la créatinine est comprise entre 20 et 39 ml/min, est de 0,75 mg/m2/jour pendant 5 jours consécutifs.

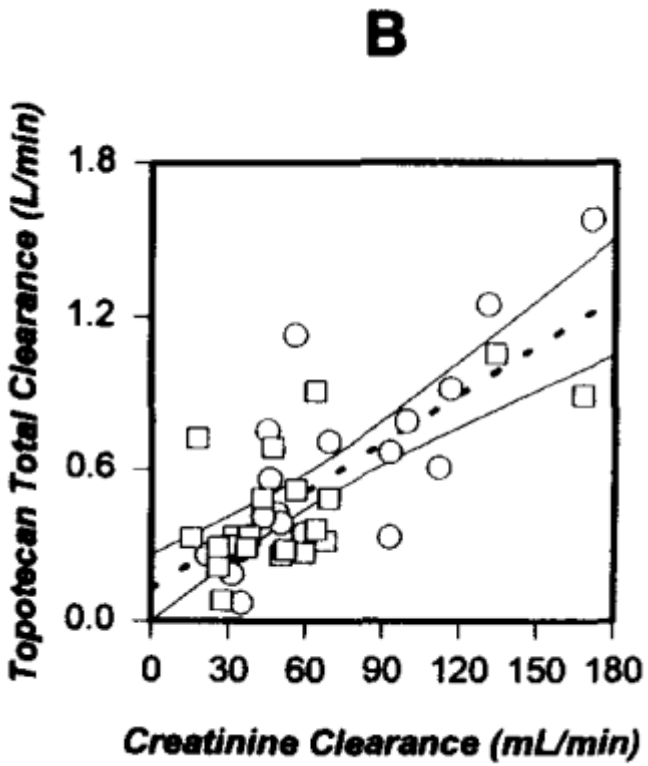
Ex. Topotecan et insuffiance rénale

[O'Reilly JCO 1996]

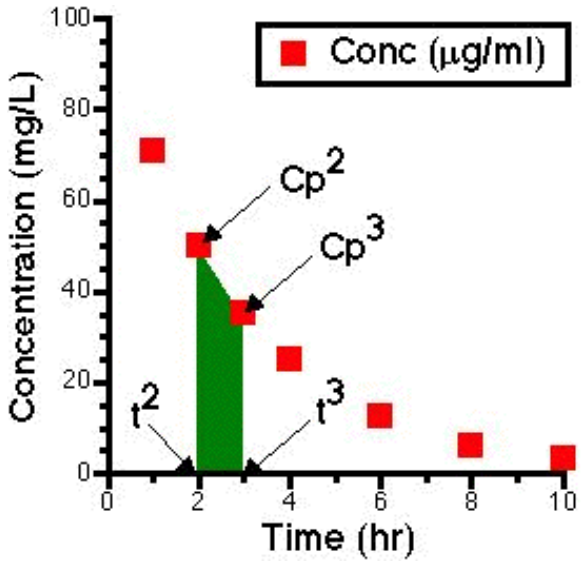
Table 6. Pharmacokinetics of Topotecan

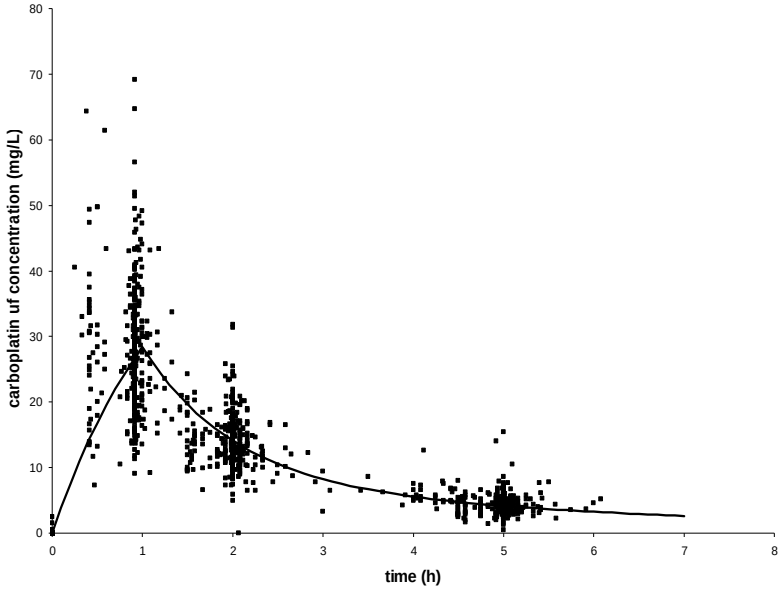
	Treatment Group by CrCl (mL/min)			
	≥ 60*	40-59*	20-39*	< 20†
Topotecan total $t_{1/2}\beta$ (min)‡	152	187	306	184
Topotecan total clearance (L/min/m²)	0.4 ± 0.18	0.27 ± 0.11	0.14 ± 0.05	0.34 0.17, 0.51
Topotecan total Vss (L/m²)	83 ± 3.4	68 ± 7.3	56 ± 9.1	69 59, 79
Topotecan lactone $t_{1/2}\beta$ (min)‡	92	142	200	55§
Topotecan lactone clearance (L/min/m²)	1.68 ± 0.13	1.02 ± 0.47	0.46 ± 0.19	0.84 0.57, 1.12
Topotecan lactone Vss (L/m²)	111 ± 7.4	136 ± 3.8	118 ± 4.6	76 110.9, 41.2
Topotecan total renal clearance (L/min/m²)	0.07 ± 0.05	0.04 ± 0.02	0.02 ± 0.01	0.01§
Topotecan total renal excretion (%)	18.3 ± 0.6	19.8 ± 0.4	11.8 ± 0.3	3.6 2.5, 4.8
Lactone/total AUC (%)	30 ± 2.7	28 ± 0.4	32 ± 3.5	36 30, 42

*Mean ± SD.
†Mean and patient values.
‡Harmonic mean half life.



two stage method vs. Pop PK





- First stage: simple and robust mathematic allowing to determine individual PK parameter: e.g., trapezoidal rule for clearance (CL)
- Second stage: statistics: e.g. comparison of mean CL between subgroups of patients differing by (e.g.) hepatic function

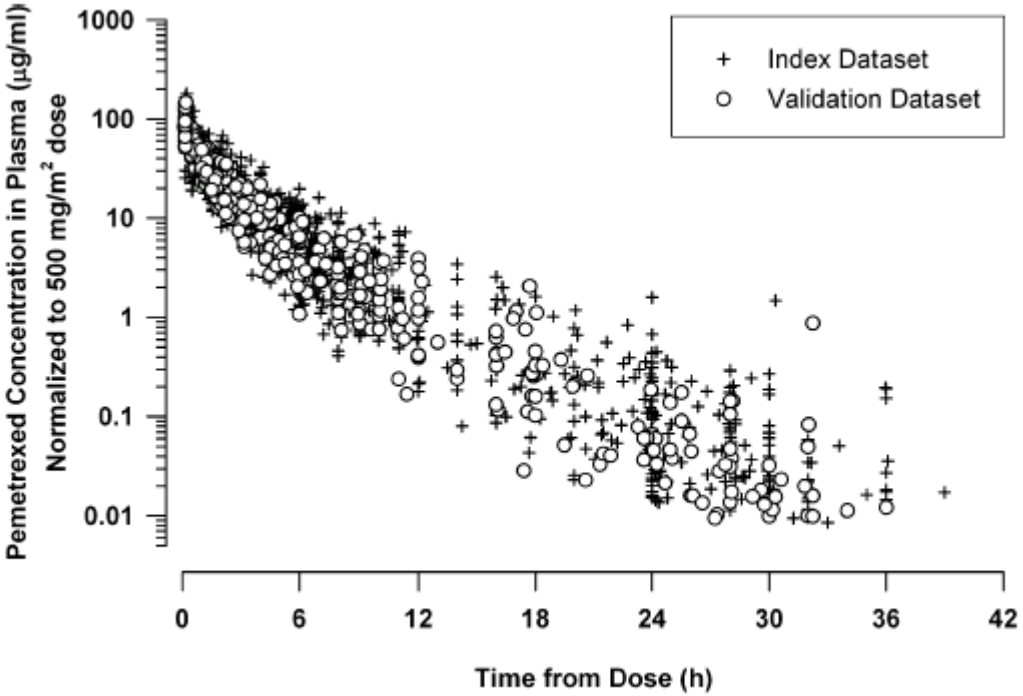
- Unit of analysis: PK data from all patients by modeling (PK model, inter- and intra-individual variability models) ; few samples (e.g., 1-3) per patient is possible
- Considering patients' characteristics (covariate) to decrease unexplained interindividual variability

Jane E Latz · Ajai Chaudhary · Atalanta Ghosh
Robert D Johnson

Population pharmacokinetic analysis of ten phase II clinical trials of pemetrexed in cancer patients

[Cancer Chemoth Pharmacol 2006]

Fig. 1 Pemetrexed concentration in plasma versus time from start of infusion (all doses, normalized to 500 mg/m^2)



The analyses included data from 287 patients (441 cycles) enrolled in 10 studies as summarized in Table 1.

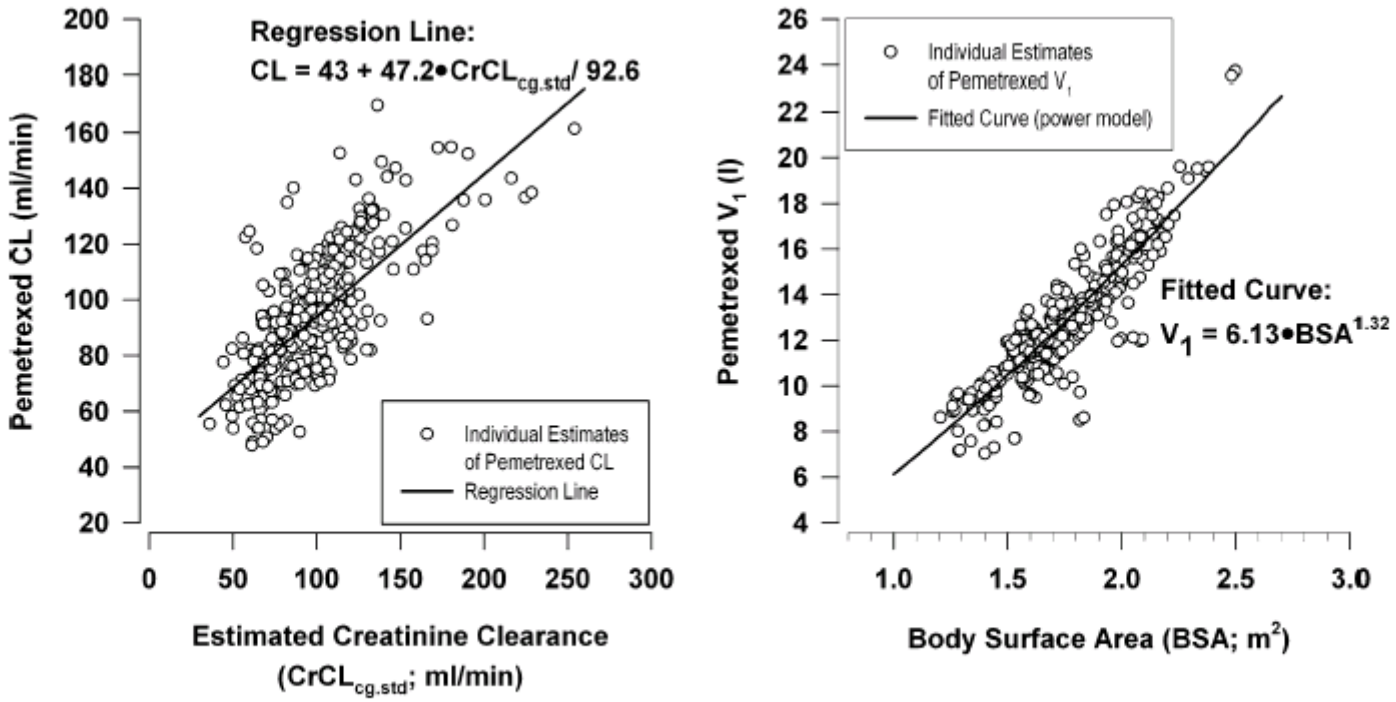


Fig. 2 Relationship between estimated creatinine clearance ($CrCL_{cg.std}$) and pemetrexed clearance (CL) (*left panel*) and body surface area (BSA) and pemetrexed central volume of distribution (V_1) (*right panel*)

RCP : Chez les patients ayant une clairance de la créatinine < 45 ml/min, l'utilisation du pemetrexed n'est pas recommandée chez ces patients

Post-AMM

- Carboplatine (AUC-dosing), 5-FU (Déficit en DPD)
- ITK: imatinib (TDM)
- Mab (cétuximab, relation PK-PD)
- Immunothérapie ???

A Universal Formula Based on Cystatin C to Perform Individual Dosing of Carboplatin in Normal Weight, Underweight, and Obese Patients

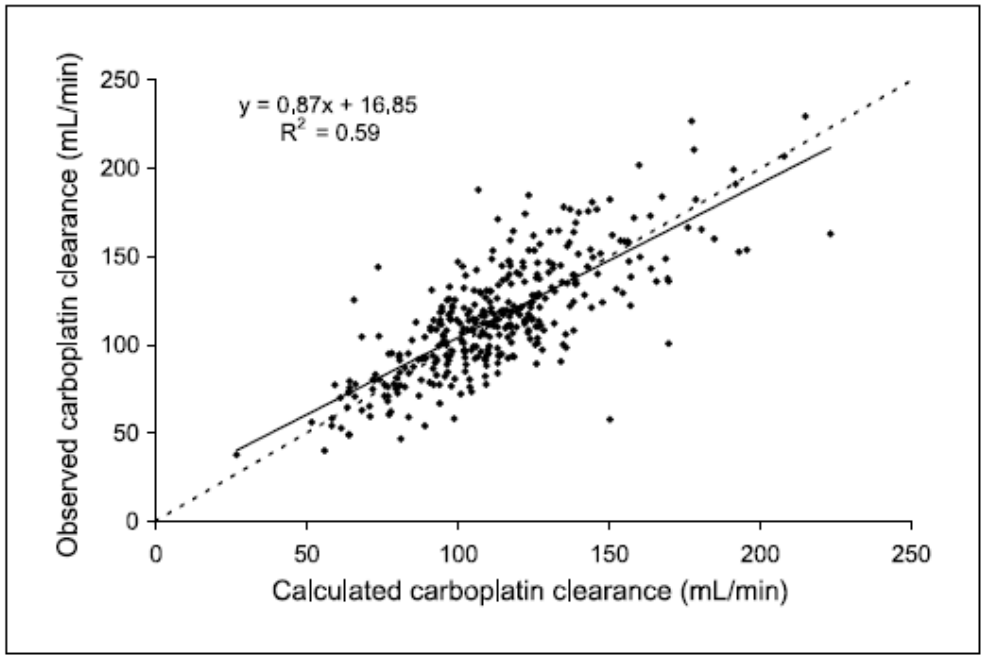
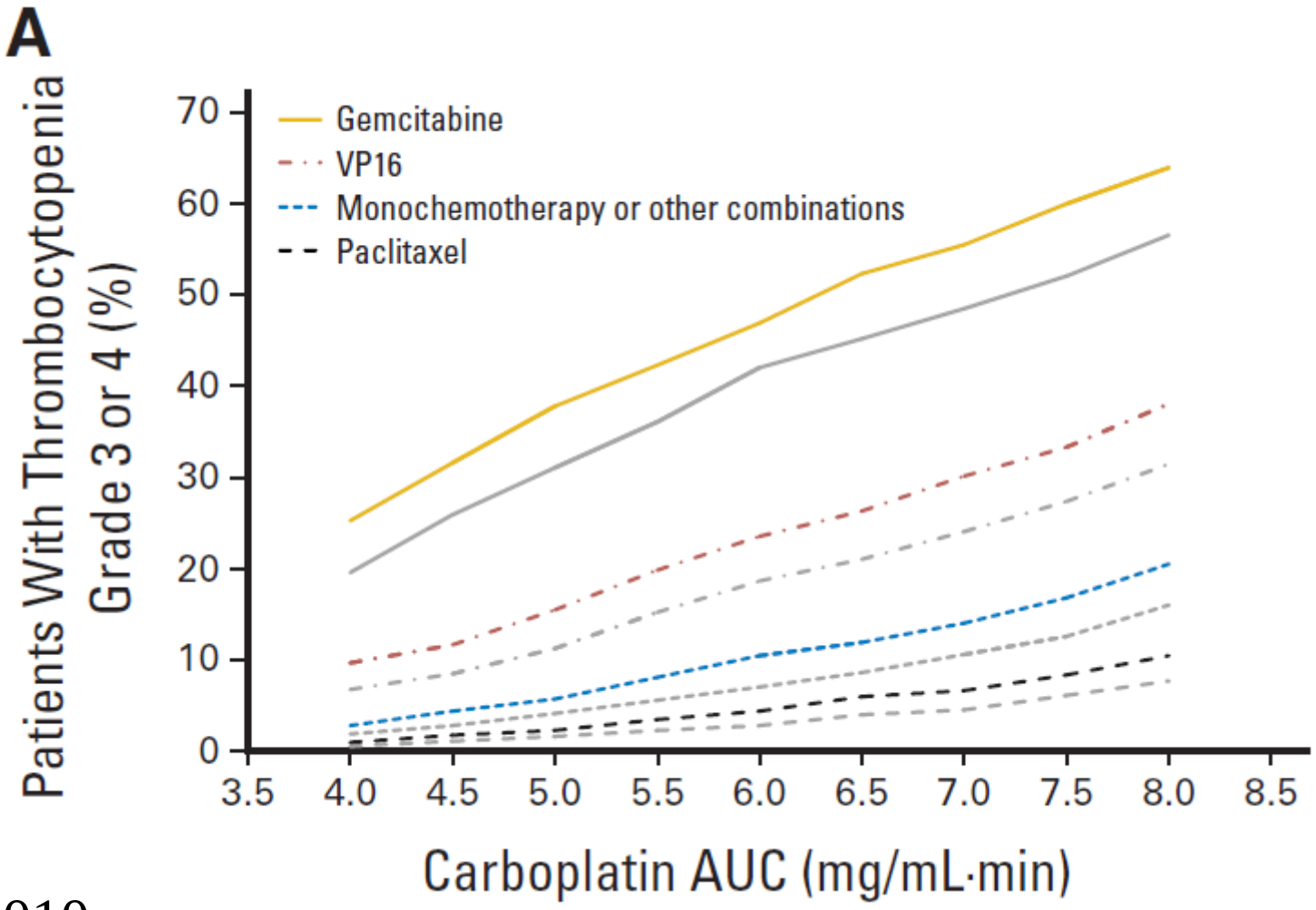


Fig. 2. Correlation between *observed* carboplatin CL and value calculated according to the modified Thomas formula: CL (mL/min) = 117.8. $(Scr/75)^{-0.450}$. $(cysC/1.0)^{-0.385}$. $(ABW/65)^{+0.504}$. $(age/56)^{-0.366}$. 0.847^{SEX}, with sex = 0 if male, 1 if female, Scr in μmol/L, cysC in mg/L, ABW in kilograms, and age in y.

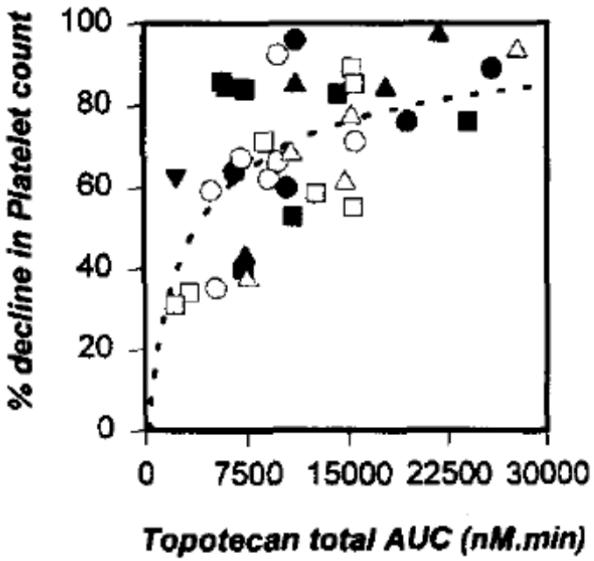
Clin Cancer Res 2009

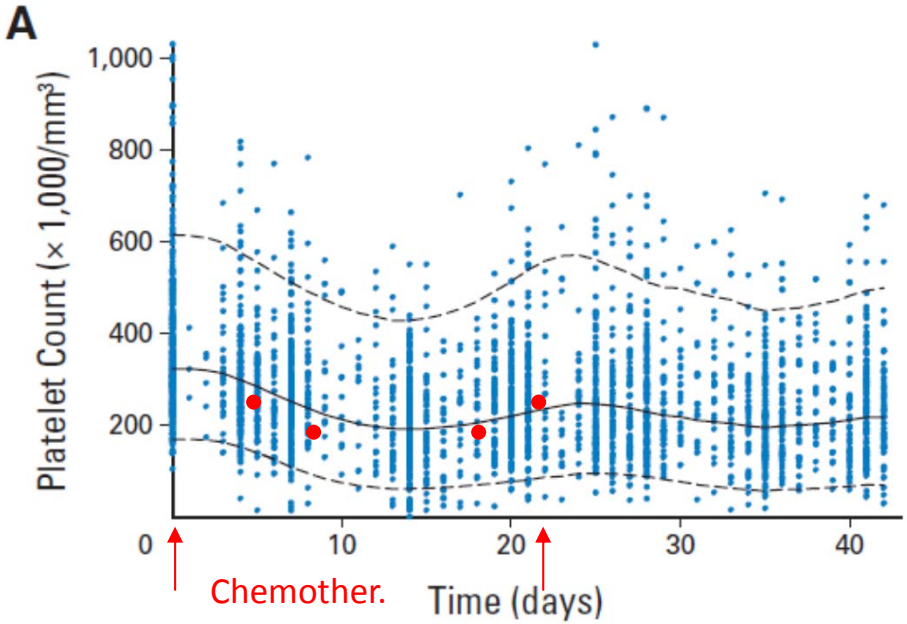
Fig 4. Simulated percentage of patients experiencing hematotoxicity according to the final models obtained with the whole data set. (A) Thrombocytopenia grade 3 or 4. Gold, red, and blue indicate previous chemotherapy; gray indicates no chemotherapy. (B) Neutropenia grade 4. VP16, etoposide; AUC, area under the curve.



JCO 2010

two stage method vs. Pop PK-PD





- First stage: determination of individual AUC, and specific end-point toxic (e.g., percentage of decrease in platelet count = nadir vs. pre-chemotherapy [O'Reilly, J Clin Oncol 1996])
- Second stage: comparison %platelet vs. AUC (Hill function)

- Unit of analysis: PD data from all patients by modeling (PK-PD model, inter- and intra-individual variability models) ; Some blood count may be missing
- To explain interindividual variability of thrombopenia: e.g. carboplatin: age, pharmacogenetics, … by considering individual PK data [Schmitt, J Clin Oncol 2010]

DihydroPyrimidine Dehydrogenase (DPD) evaluation before 5-FU treatment

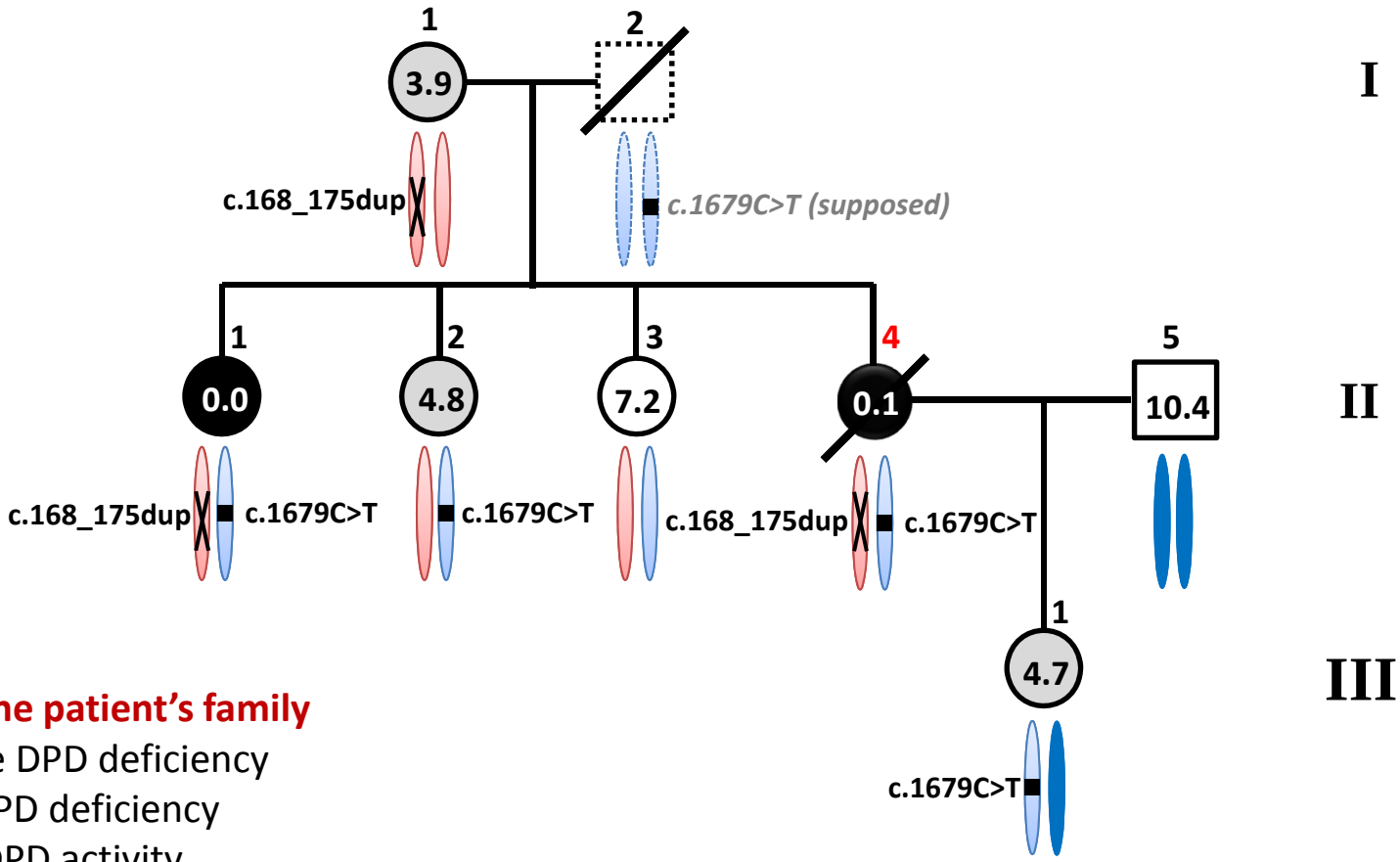
- DPYD Genotype:
  - C.1905 + 1G>A, c.1679T>G, and c.2846A>T
- DPD Phenotype:
  - Plasma ratio UH_2/U: cut off value of 6

Clin Pharmacol Ther 2015:

Genotyping of a Family With a Novel Deleterious *DPYD* Mutation Supports the Pretherapeutic Screening of DPD Deficiency With Dihydrouracil/Uracil Ratio

F Thomas[1,2], I Hennebelle[1,2], C Delmas[1,2], I Lochon[1,2], C Dhelens[3], C Garnier Tixidre[4], A Bonadona[5], N Penel[6], A Goncalves[7], JP Delord[2,8], C Toulas[9] and E Chatelut[1,2]

Validation of phenotype test (UH_2/U) by comparison with genotype



Pedigree of the patient's family

● = complete DPD deficiency
= partial DPD deficiency
= normal DPD activity
= individuals not tested

Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia

Stephane Picard,[1,2,3] Karine Titier,[1,2,3] Gabriel Etienne,[4] Emmanuelle Teilhet,[1,2,3] Dominique Ducint,[1,2,3] Marie-Agnes Bernard,[1] Regis Lassalle,[1] Gerald Marit,[2,5,6] Josy Reiffers,[4] Bernard Begaud,[1,2,3] Nicholas Moore,[1,2,3] Mathieu Molimard,[1,2,3] and Francois-Xavier Mahon[2,5,6]

Blood 2007

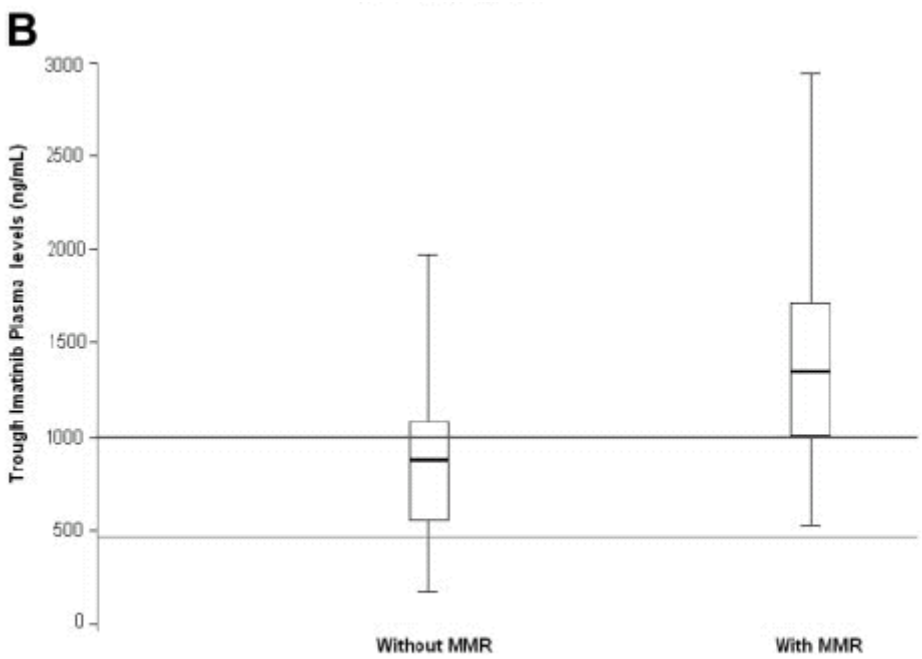


Figure 1. Trough plasma imatinib threshold for major molecular response (MMR).(A) Receiver operating characteristic (ROC) curve analysis. Regarding

PK (GIST)

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

JCO mai 2009

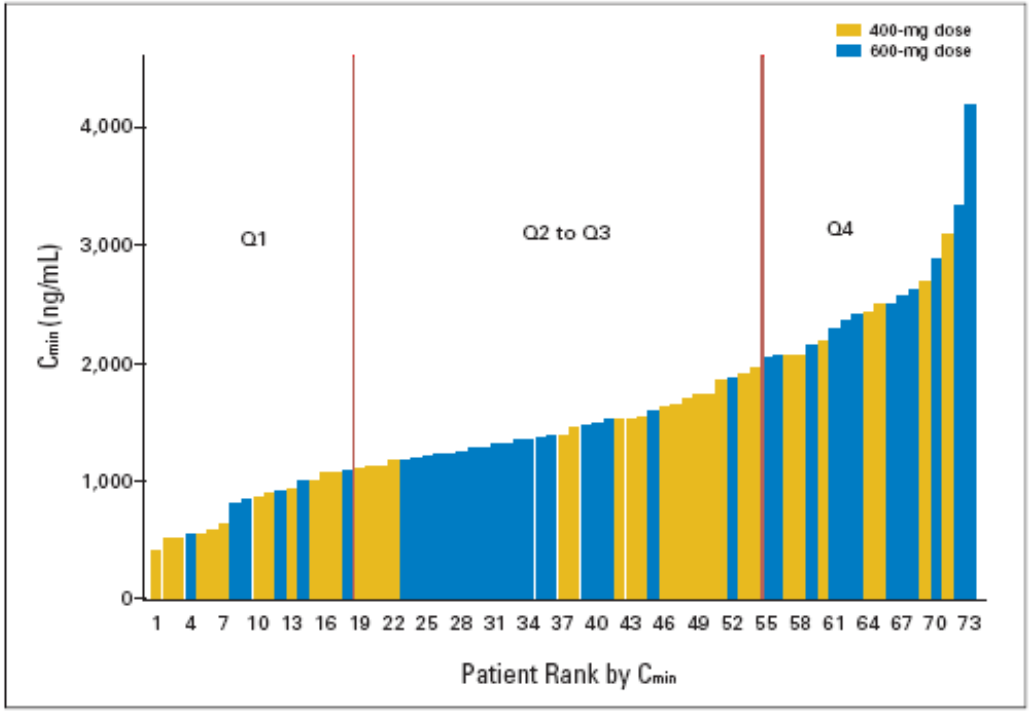


Fig 2. Distribution of imatinib trough concentration (C_{min}) at steady-state (day 29) for 400-mg and 600-mg daily doses combined. For the 36 patients in the 400-mg dose group, 12 patients were in quartile 1 (Q1), 17 were in Q2-Q3, and seven were in Q4, whereas for the 37 patients in the 600-mg dose group, six were in Q1, 19 were in Q2-Q3, and 12 were in Q4. The vertical lines represent 25% and 75% percentiles (ie, 1,100 and 2,040 ng/mL), respectively, dividing the population into three groups: Q1 (414 to 1,110 ng/mL; n = 18), Q2-Q3 (1,110 to 2,040 ng/mL; n = 36), and Q4 (2,041 to 4,182 ng/mL; n = 19).

PK-PD (GIST)

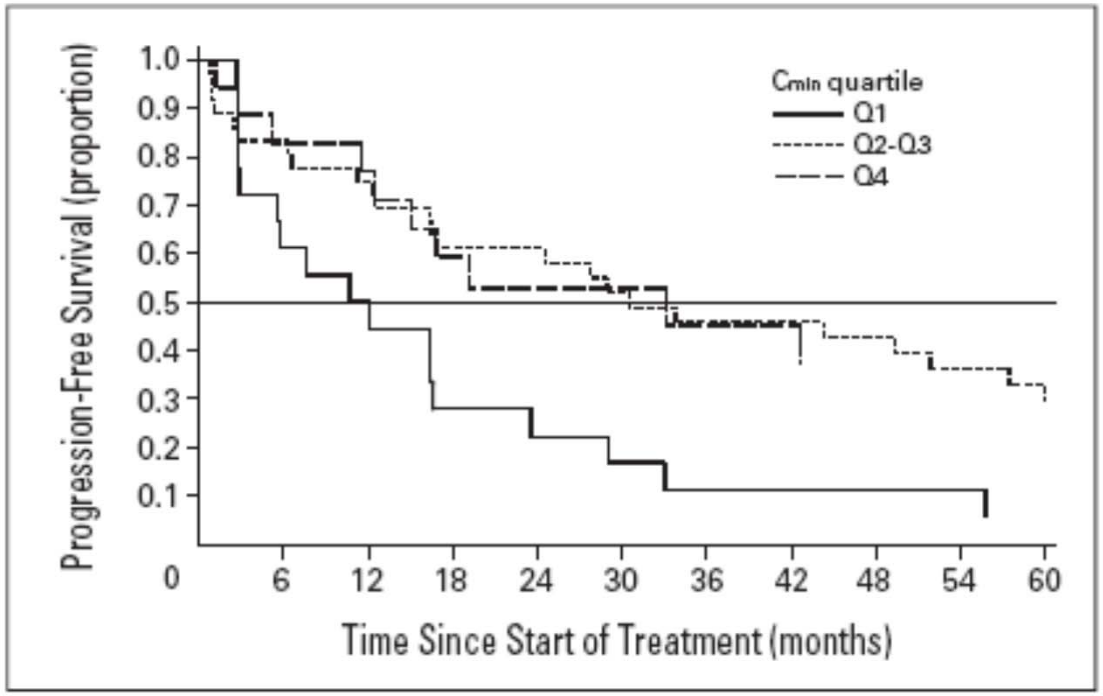


Fig 3. Time to progression by imatinib day 29 trough level (C_{min}) quartile (Q).

Conclusion: PK et développement MAC

- Précliniques et cliniques
- Médicaments: Cytoxiques vs. Thérapies ciblée
- Méthodologies: approche standard vs. Pharmacocinétique de population
- Pré-AMM vs. Post-AMM