425P : Cetuximab could be administered once every two weeks instead of once weekly

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INTRODUCTION

Cetuximab (CTX): anti-EGFR monoclonal antibody (mAb) approved in metastatic colorectal cancer (mCRC). Target-mediated drug disposition (TMDD) models (1,2) are used to describe mAb target-mediated pharmacokinetics (TMPK)

Objectives: to investigate :

- TMPK of cetuximab
- Relationship between target occupancy of EGFR and progression free survival (PFS)
- Alteration of dosing regimen

MATERIALS & METHODS

- Multicenter phase II study (*ClinicalTrials.gov identifier: NCT00559741*) (3,4) evaluating FOLFIRI-CTX regimens in patients with mCRC *(n=91)*
- Cetuximab administration: loading dose of 400mg/m² followed by a 250mg/m² weekly doses
- PK analysis :
  - Concentration of cetuximab in blood sample *(n=1296)*→ ELISA technique
  - a 2-compartment quasi-steady-state (QSS) TMDD model (fig.1) using population approach (5)

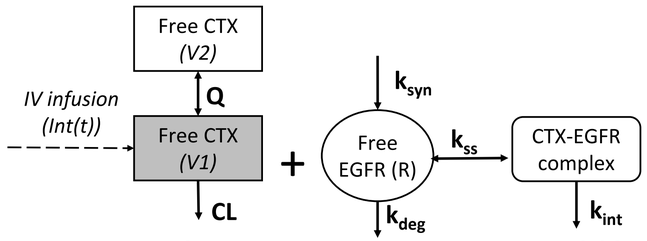

Figure 1 : Structure of a two-compartment QSS TMDD model for CTX and EGFR interaction in mCRC patients. (adapted from Gibiansky)

- Survival analysis : Kaplan-Meier method and using cox proportional-hazards models (6)
- Model-based simulation for several dosing regimens by using Simulx software (7)

RESULTS

Table 1 : Population PK parameters of CTX in mCRC patients

Parameters	Estimates	RSE (%)
Population parameters		
V1 (L)	2,7	3,8
Q (L.day^{-1})	1,0	1,2
V2 (L)	4,6	6,5
CL (L.day^{-1})	0,4	4,7
R_0 (nM)	3,2	8,2
k_{int} (day^{-1})	4,0	21,3
k_{deg} (day^{-1})	11,1	1,9
K_{SS} (nM)	0,7	4,7
Between subject variability		
ω_V	0,3	9,5
ω_{V2}	0,5	12,2
ω_{CL}	0,3	9,5
ω_{R0}	0,3	20,7
Error model parameter		
σ_{prop}	0,2	2,3

V1 and V2 : volumes of the central and peripheral compartment ; Q : intercompartmental clearance constant; CL: clearance of free CTX, K_{SS} : steady-state rate constant; k_{deg} and k_{syn}: the EGFR degradation and synthesis rate constant of the free EGFR; k_{int}, the complex internalisation rate constant; R_0 is the baseline of EGFR

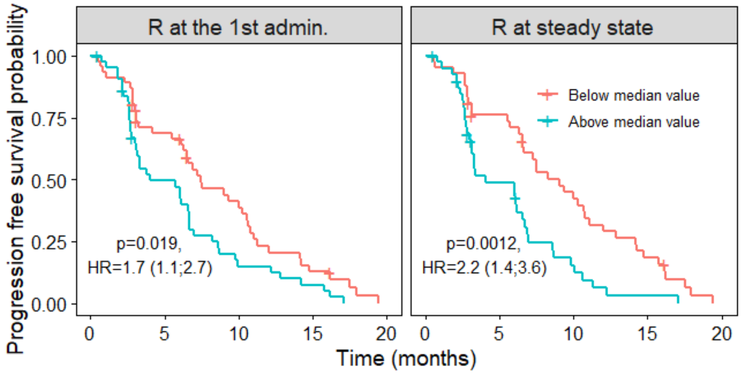

Figure 2 : Kaplan-Meier curves of PFS according R at the 1st administration and at steady state

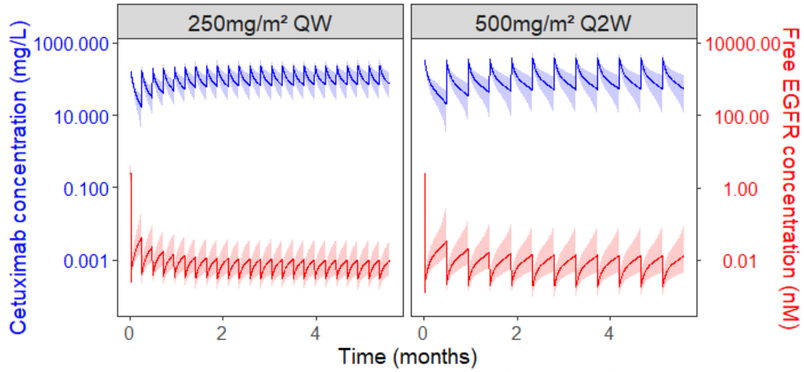

Figure 3 : Model-based Simulation of CTX and free EGFR

CONCLUSIONS

Quantification of the EGFR kinetics influence PFS.

Our simulations suggested that a **500mg/m² Q2W regimen could be used instead of 250mg/m²QW** in most patients.

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DISCLOSURE STATEMENT

S. Lobet has no conflicts of interest to disclose and benefits from a PhD grant from the *Conseil général d'Indre-et-Loire* and *labex MabImprove*.