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Protocol

The CetuxIMAX protocol: a non-interventional, uncontrolled, and non-comparative multicentric study for exploring the pharmacokinetics/pharmacodynamics relationships of cetuximab in head and neck cancer patients

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ABSTRACT

Background: In a previous pilot-study, a link between Cetuximab exposure levels (i.e., trough levels above 34 mg/ml) and clinical outcome in head and neck cancer patients was found. Considering the high inter-individual variability in Cetuximab plasma levels, lack of efficacy could thus be linked to inadequate exposure levels, rather than issues with signalling pathways at the tumor level.
Methods: The CetuxIMAX study is a non-interventional, uncontrolled, and non-comparative multicentric study in patients with recurrent or metastatic head and neck squamous cell carcinoma, and treated by any Cetuximab-based regimen. A total of 122 patients will be enrolled in this study. The primary endpoint is the estimation of receiver operating characteristic (ROC) and area under the ROC curve (AUROC) of Cetuximab trough plasma level for the disease control rate (DCR). Pharmacokinetics samples will be collected at first cycle, when steady-state is reached, and during maintenance phase to monitor the Cetuximab levels throughout time. Standard PK modelling using population-approach will be performed to identify individual PK parameters and enable further simulations of exposure levels throughout the different cycles. Univariate and multivariable statistical analysis aiming at exploring any association between Cetuximab exposure levels and clinical outcome will be performed.
Conclusions: Should the target therapeutic window associated with efficacy be confirmed with Cetuximab in head/neck cancer patients, this could pave the way for PK-guided dosing next. Based upon single point PK sampling, pop-PK modelling could help personalizing dosing or scheduling, to ensure an optimal toxicity-efficacy ratio with Cetuximab.
Trial Registration: Trial registration number is NCT 04218136.

Keywords: Cetuximab, Pharmacokinetics, Head and neck cancer, Modelling

INTRODUCTION

PK of Cetuximab, promises and pitfalls

Only about 30-50% of cancer patients show clinical benefit upon Cetuximab administration, despite large resources spent for bio-guided administration such as K-Ras and N-Ras mutational status determination. Pilot studies in colorectal and head and neck cancer patients have suggested that Cetuximab pharmacokinetics (PK), i.e. clearance values, could predict clinical outcome such as progression-free survival.[1,2] However, determining

Cetuximab plasma clearance requires time-consuming PK modelling performed by trained operators, thus making it difficult to implement in routine clinical practice next. In addition, thus far most PK studies with Cetuximab were based upon time- consuming, labor-intensive and operator-dependent enzyme-linked immunosorbent assay (ELISA) determination of drug plasma levels, an analytical method that fails to meet the requirements of daily practice for performing therapeutic drug monitoring

Pilot-study: trough levels could help predicting clinical outcome with Cetuximab

Our group has developed an original, fast, low cost and semi-automated mass spectrometry method to assay Cetuximab in plasma. A pilot study aimed to evaluate the analytical performance of a liquid chromatography /mass spectrometry method as a part of a "real world" study, for primarily evaluating the inter-patient variability in exposure levels (i.e., peak observed, both in the peak concentrations (C_{max}) and in C_{min}. Most interestingly, despite the limited number of patients enrolled, a statistically significant association was found between exposure levels and clinical outcome (DCR). This association was even more significant on C_{min} (49.0±16.3 µg/ml versus 25.8±17 µg/ml, $p<0.01$, t test), thus suggesting that simple trough levels monitoring could help predicting efficacy. Receive operating characteristics (ROC) analysis further determined a threshold level (i.e., 34 µg/ml) with acceptable specificity (78%) and sensitivity (87%).[3]

Further analysis on survival showed that although not statistically significant, a trend toward longer both progression-free survival (H.R.=0.84; 0.32-2.1 n.s.) and overall survival (HR=0.78; 0.45-2.45 n.s.) was observed in the subsets with high (>34 µg/ml) and low (<34 µg/ml) trough concentrations, respectively (SMARTc, unpublished data).

Rationale for the CetuxIMAX protocol

Despite promising results, this pilot study had several flaws, such as its monocentric design, its small sample size, and lack of proper PK modelling. Still, although preliminary, these real-world data suggested that Cetuximab trough levels could be indeed a predictive marker of therapeutic efficacy and that in addition to tumor characteristics, simple therapeutic drug monitoring could help forecasting clinical outcome or enable PK-guided dose adaptation in patients with inadequate drug levels.

Here, the CetuxIMAX study aims to confirm or refine the efficacy threshold previously identified in a larger, multicentric study, with full PK modelling support. In addition, this study aims to investigate on other putative metrics of exposure (i.e., C_{max}, AUC) potentially associated with the clinical outcome of Cetuximab in head and neck cancer patients.

METHODS

Study design

The CetuxIMAX study is a non-interventional, uncontrolled, and non-comparative low-risk multicentric study promoted by the University Hospitals of Marseille (APHM, France). The study aims at comparing Cetuximab plasma levels, and to confirm the putative link between exposure levels and clinical outcome in adult patient with recurrent/metastatic head and neck squamous cell carcinoma. Up to 122 patients will be enrolled, involving 15 recruiting sites in France (university-hospitals, comprehensive cancer centres and private clinics). The complete list of recruiting centres for CetuxIMAX is available upon request to corresponding author. Head-neck cancer patients scheduled for Cetuximab regimen are eligible to participate to this study. PK exploration will be performed on biological samples taken as part of routine care during the treatment period. Treatment will be administered following standard guidelines in head and neck cancers, and participation to this study will not change the current routine care corresponding to state-of-the-art clinical practice in this setting.

Trial status

The study is registered as NCT 04218136 at ClinicalTrials.gov. Recruitment started on 26 December 2019, and the inclusion period is expected to stop at the end of February 2023. Audit will be performed by the Direction de la Recherche Clinique et de l'Innovation (Direction of Clinical Research and Innovation) of the promoter (i.e., Assistance Publique Hôpitaux de Marseille, France) on a twice a year basis.

Recruitment and patients' eligibility

This study should include patients aged 18 to 75 years, who suffer from recurrent or metastatic head and neck squamous cell carcinoma only (i.e., oral cavity, oropharynx, and hypopharynx cancers), and treated by any Cetuximab-based regimen per current local practice. All patients must sign the standard non-opposition form of the institute to be collected by investigators. Initially, only patient treated by the "EXTREM" protocol (i.e., 400 mg/m^2 at C1D1 and 250 mg/m^2 weekly (QW) of Cetuximab in combination with 1000 mg/m2 every 3 weeks (Q3W) day 1-4 of 5-fluorouracil and 100 mg/m^2 (or equivalent) Q3W of cisplatin or carboplatin during 6 cycles of 21 days) were eligible. Next, the protocol was amended (21 February 2021) to further include patients treated by all Cetuximab-based regimen as several studies have recently shown the superiority of other treatment regimen such as TPEx protocol as compared with the EXTREM protocol indeed.[4,5] Were excluded, all patients currently participating in a study with another investigational agent, minor patients, or patients over the age of 75 years, pregnant or breast-feeding women, and

patients with any contra-indication to Cetuximab in the summary of product characteristics.

Study objectives

Primary endpoint

The primary endpoint is the estimation of ROC and AUROC of Cetuximab trough plasma level for the disease control rate (DCR). DCR is a composite criteria encapsulating complete response, partial response, and stable disease following RECIST 1.1 criteria. Cetuximab trough plasma levels are referred to as C_{min}. Response evaluation will be performed by each center's radiologist, at 3-4 months depending on the regimen (i.e., 3 months after starting treatment in patients following EXTREME protocol and 4 months in patients treated with TPEx).

Secondary endpoints

Secondary endpoints included: estimation of receiver operating characteristics (ROC) of Cetuximab trough levels (C_{min}) for progression-free survival (PFS), estimation of ROC of Cetuximab peak plasma levels (C_{max}) for DCR and PFS, estimation of ROC of Cetuximab trough and peak plasma level for treatment- related toxicity, and additional endpoints include identification of individual PK parameters of Cetuximab (i.e., total plasma clearance, half-life, V_d) and full pharmacokinetics/ pharmacodynamics (PK/PD) modelling. For the secondaries endpoints, the following definitions will be retained: Cetuximab peak plasma levels (C_{max}) defined as the plasma value measured when infusion stops– progression-free survival (PFS) defined as the time from baseline evaluation until first event (death due to any cause, or progression defined following response evaluation criteria in solid tumors (RECIST) 1.1) – treatment-related toxicity (i.e., common terminology criteria for adverse events (CTCAE) 6.0 grading) – identification of Cetuximab individual PK parameters (i.e., clearance value, volume of distribution, plasma half-life), based upon measured C_{max} and C_{min} levels and published PK-population mean values and Bayesian estimation using SAEM algorithm implemented on the Monolix® software (Lixoft, France) – global plasma exposure of Cetuximab (i.e., area under the curve (AUC) and mean steady-state concentrations (mean Css)) simulated from individual pharmacokinetics parameters – PK/PD model of Cetuximab in head and neck cancer patients and dedicated algorithm for future decision-making (i.e., adaptative dosing to reach the exposure target). Monitoring of toxicities will primarily focus on typical Cetuximab-related side-effects such as skin toxicities, hypomagnesemia, and hyper-sensitivity reactions (HSR).

Primary objective

The primary objective is to compare estimation or ROC and area under the ROC (AUROC) of Cetuximab C_{min} following DCR patients' status.

Secondary objectives

Secondary objectives of the study were: to confirm the optimal cut-off value of trough plasma level of Cetuximab for the DCR previously identified in a former proof-of-concept study (i.e., 34 μg/ml of Cetuximab [3]), or to identify an alternate cut-off to be used next; to identify the optimal cut-off values of C_{min}/C_{max} predictive of Cetuximab-related toxicities; to estimate the technical performance (sensitivity, specificity) and predictive values (positive predictive value and negative predictive value) of the optimal cut- off of C_{min} for the DCR; to assess the predictive performance of C_{max} for the DCR (using the estimation of the ROC curve, the calculation of the AUROC, the optimal cut-off value, the sensitivity, specificity, positive predictive value, and negative predictive value) as previously described for trough level; to assess the predictive performance of C_{min}, C_{max}, and total plasma exposure (i.e., plasma AUC obtained by modelling using a PK-population approach and Bayesian estimation of each patient's individual PK parameters, or mean Css values) for the progression free survival, and the incidence and severity of the adverse events (patients will be categorized as "severe toxicities" (i.e., at least one toxicity ≥grade 3 CTCAE grading) or "no severe toxicities" (i.e., no toxicity or toxicities <grade 3 CTCAE grading); and to develop an algorithm (PK/PD-based model) dedicated to future Cetuximab adaptative dosing strategies improving the probability that patients will be in the optimal target exposure level associated with efficacy.

Treatment

Patients will receive 400 mg/m^2 of Cetuximab during day one of cycle one, and 250 mg/m^2 each week thereafter (QW). Should patients respond to the treatment, a maintenance phase will start, following standard local practice. As a non-interventional study, no change in patient's care will be made because of this study, and all treatments (i.e., 5-FU and Cisplatin) will be administered following current guidelines in head and neck cancer.

PK study

Cetuximab plasma levels monitoring should be performed in a longitudinal fashion (i.e., thrice during the treatment period), using blood samples already taken for routine care. Samples will be collected at first cycle, when steady state is reached (i.e., after the third cycle), and during maintenance phase to evaluate the exposure levels throughout time. The plasma exposure during the first cycle is evaluated by measuring C_{max} after the first administration and C_{min} immediately before the second administration. The exposure at steady state is evaluated through C_{max} and C_{min} levels measured at C3D15 (i.e., just before RECIST evaluation for response). Finally, for patients who will be in maintenance phase, long term exposure will be evaluated with C_{max} and C_{min} collected 2 months after that the maintenance has begun. Samples collection is summarized in Figure 1.

Bioanalysis of Cetuximab plasma levels will be performed using liquid chromatography in tandem with mass spectrometry detection after a preliminary step of enzymatic digestion and measurement of prototypic peptides as previously described.[6] This method has been fully validated following European Medical Agency (EMA) guidelines for mass spectrometry bioanalytical methods.[7] Bioanalysis will be performed in an ISO-15189 labelled hospital laboratory. All samples will be stored at the Clinical Pharmacokinetic laboratory of La Timone University Hospital of Marseille prior analysis.

Individual PK parameters will be computed using a Bayesian estimate and reference populations parameters following standard compartmental analysis on Monolix® (Lixoft, France). A dosing algorithm will be built next and parametrized using appropriate modelling software (i.e., Monolix®, R (R-Project, Austria)). A subgroup analysis will be carried out according to the protocol followed by the patients.

Collection of clinical data and other biological data

No additional clinic visits or consultations are required for this study apart from the ones scheduled as part of routine care. Patients will be followed up during their routine visits/consultations, with data collection starting with Baseline values recorded for biological (e.g., complete blood count, creatinine clearance (CKD-EPI formula), liver function tests, albumin, protein, magnesium) and clinical (weight, height, ECOG performance status, number and type of previous treatment line, and baseline tumor size).

Response will be evaluated at about 12 weeks after start of Cetuximab treatment, and every 2 at 3 months during Cetuximab maintenance phase following routine care. Efficacy will be assessed upon PET-scan imaging following standard RECIST criteria. Treatment-related side effects will be monitored and graded following standard CTCAE V6.0. grading.

Investigators, coordinator, and biologists will have access to the database encapsulating both biological and clinical data that will be implemented on the promoter's site (i.e., Assistance Publique Hôpitaux de Marseille). Figure 2 displays the flow diagram of the CetuxIMAX study.

Sample size and statistical analysis

The calculation of the sample size was based from the primary endpoint, i.e. AUROC representing the diagnostic performance of Cetuximab C_{min} for the DCR as defined above. We estimated in our eligible population, that 30% will show disease control and 70% will not. This estimation was extrapolated from several studies showing DCR ranging from 41,9% to 53,6% in 1st and 2d line setting.[8-11] With respect to the fact in the present study, we expect including a large proportion of patients in 3^{d} up to 5thline of treatment, DCR was rather set at 30%.

The following assumptions were then considered: 30% of DCR in the study population, AUROC set at 0.81, degree of precision for a 95% confidence interval (CI) set as 0.10 (i.e., width of 95% CI=0.2), and alpha risk set at 0.05.[3]

The number of required subjects is then n=99.[12] Considering a usual 10% lost to follow up or un-useable/missing data, we should then include a total of n=110 subjects in 15 recruiting centres. Of note, if we use the PASS (version 16) method and not the canonical Zhou method, we obtain a slightly higher sample size (i.e., 110 plus 10% for non-useable data) resulting in a total of n=122 patients to be included. This discrepancy comes from the fact that formulas or rounding can markedly differ from one method to another. To be more consistent and robust, a total of n=122 patients is expected to be enrolled in this study.

Univariate and multivariable statistical analysis aiming at exploring any association between Cetuximab exposure levels and clinical outcome (i.e., response, toxicity, PFS) will be conducted using plasma concentrations and AUC obtained during the first administration, before response evaluation and during the maintenance phase. Qualitative variable will be represented using number and proportions. Quantitative variable will be represented using means and standard deviations, or medians and quartiles. The number and the proportion of missing data will be determined for each variable. The normality of these parameters will be evaluated using standard Shapiro tests.

Considering the primary endpoint, two groups of subjects will be defined based on the DCR criteria (i.e., presence/absence). The main analysis will focus on the study of C_{min} predictive performance for the DCR, estimating the ROC curve and the AUROC by the nonparametric method of Hanley, as well as its 95% confidence interval.[13] The optimal threshold will be determined.[12] Sensitivity, specificity, and predictive values will be estimated, as well as 95% CI.

Considering the secondaries endpoints, different tests will be performed depending on the variable type. For binary variable, ROC curves, and AUROC will be calculated by the nonparametric method of Hanley, as well as their 95% confidence intervals.[13] Optimal threshold will be determined.[12] The Younden index will be provided. Sensitivity, specificity and predictive values will be estimated, as well as their 95% confidence interval. For time to event variables (e.g., PFS), time-dependent ROC analysis for censored survival data will be performed.[14] The final analysis of the data will be carried out using the statistical package for the social sciences (SPSS) v17.0. software (SPSS, USA).

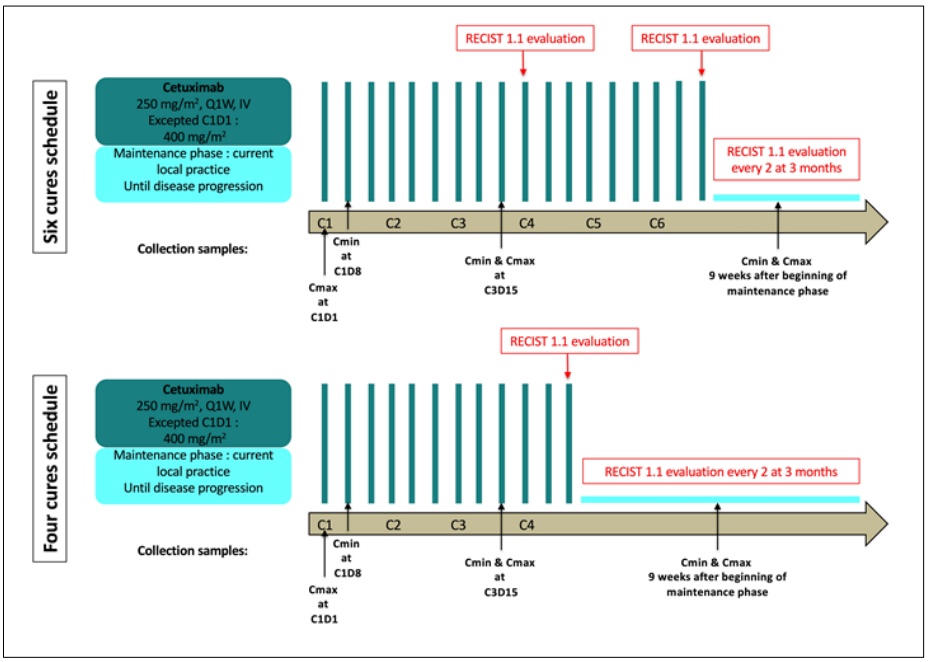

Figure 1: PK Sampling during the study.

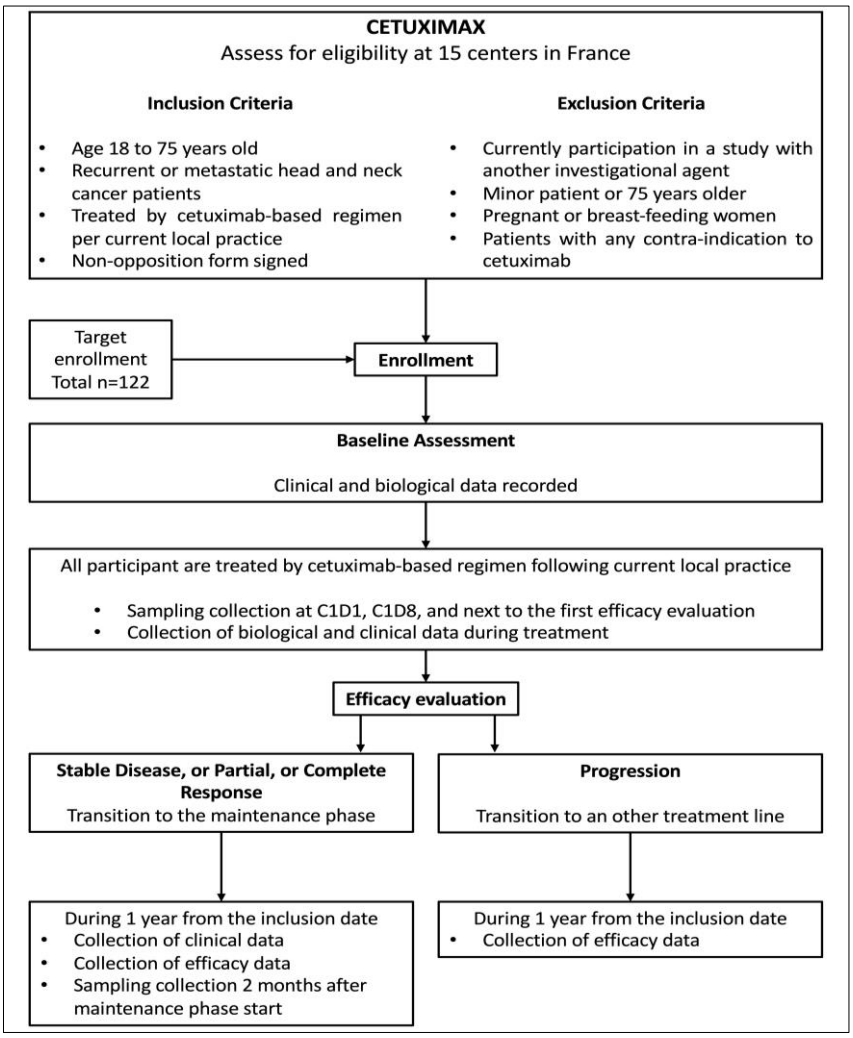

Figure 2: Flow diagram of the trial.

Ethics and dissemination

Research ethic approval

This study will be conducted in accordance with the declaration of Helsinki and the good clinical practice. The study was fully approved by the ethic committee of the institution (registered as 2019-A02422-55) and finally registered as NCT 04218136.

Dissemination of results

Results will be presented at national and international conferences and published in a peer- reviewed journal, on behalf of all collaborators. All participating sites and Investigators will be acknowledged in related publications and scientific presentations.

DISCUSSION

Despite the rise of bioguided medicine, the development of innovative treatments in cancer too often fails to translate into meaningful clinical benefit for the patients. The issue of poor PK and inadequate drug levels has been neglected for too long.[15] CetuxIMAX is a non-interventional, uncontrolled, and non-comparative study evaluating in head and neck cancer patients, the predictive value of trough plasma levels of Cetuximab associated to clinical benefit. Of note, no limitation in previously lines of treatment has been made, making heavily pre-treated patients eligibles in this trial. Due to this absence of limitation, efficacy in the CetixIMAX study is expected to be lower than usually reported in 1st line or 2^{d} line therapy.[16] To take this specificity into account, here we have set the expected DCR at 30% because a large proportion of patients are expected to be heavily pre-treated (i.e., up to the 5th line). To the best of our knowledge, CetuxIMAX is the first prospective and multicentric study investigating on a possible association between Cetuximab plasma exposure and clinical outcome (efficacy, toxicity) in this setting. One of the possible weakness of this PK/PD study is the fact that Cetuximab is not given as a single agent, because this drug will be constantly associated with cytotoxics (i.e., platinum derivatives and 5-FU with the TPEx regimen or docetaxel with the EXTREME regimen). To lift possible confounding factors, monitoring of side-effects will primarily focus on typical Cetuximab-induced toxicities such as skin toxicities, hypomagnesemia or HSR – whereas the associated cytotoxics are more likely to trigger ototoxicity, renal toxicity, neutropenia or neuro-toxicity. In addition, multivariate analysis will help to better understand the role each of the regimen (i.e., EXTREME versus TPEx) plays in treatment efficacy.

Currently, for recurrent and metastatic head and neck cancers, Cetuximab-based regimen are supplanted by immunotherapy-based regimens.[17] However, considering the rising number of studies showing the high inter-individual variability observed in Cetuximab levels both in head and neck cancers and colorectal cancers, one can hypothesize that PK, and therefore dosing, could be an actionable item to improve the risk-benefit ratio of this drug.[1-3,18] Should the large inter-patient variability in exposure levels and the determination of a cut-off level in plasma concentration required to achieve clinical benefit be both confirmed in the CetuxIMAX trial, then it will pave the way for implementing PK-guided dosing of this major drug. Ideally, once treatment has been initiated using standard dosing (i.e., 250 mg/m^2 QW or 500 mg/m^2 Q2W), a single measurement of Cetuximab trough levels should help predicting whether the patient will respond, or not. Using pop-PK modelling and with respect to the therapeutic window to reach, it will be then possible to personalize either dosing or scheduling, to maintain the patient within an optimal exposure (i.e., associated with maximal efficacy and limited toxicities).

The perspectives of the CetuxIMAX trial are to implement, in an ancillary study, further testing including search for mutations on the *FCyR* gene such as *FcR2A* and *FcR3A*, plus gene polymorphisms such as the *K/K* variant on the *EGFR* gene, all possibly impacting on PK/PD endpoints with Cetuximab.[19] Finally, once a dosing-algorithm will have been built, a future comparative phase-2 trial should be performed to compare the toxicity-efficacy ratio of standard dosing Cetuximab with that of PK-guided dosing in patients with head and neck cancer.

CONCLUSION

The CetuxIMAX trial aims to decipher the exposure-effects relationships with Cetuximab in head and neck cancer patients. This study will pave the way for future comparative trials to further test whether PK-guided dosing or scheduling of Cetuximab will perform better than standard dosing in terms of toxicity-efficacy ratio.

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Conflict of interest: None declared
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