

UTILITY OF SERUM ANTI-CETUXIMAB IGE LEVELS TO IDENTIFY PATIENTS AT A HIGH RISK OF SEVERE HYPERSENSITIVITY REACTION TO CETUXIMAB

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Competing Interest

KBL had a consulting or advisory role for Sanofi and Merck Serono. FDF received honoraria from Roche, Sanofi, Amgen and Merck Serono. MPG had a consulting or advisory role for Roche, Sanofi, Amgen and GlaxoSmithKline. RS had a consulting or advisory role for Roche. All the remaining authors have declared no conflicts of interests.

ABSTRACT

Aim: Cetuximab is an anti-EGFR antibody used for the treatment of metastatic colorectal cancer and head and neck cancer. Hypersensitivity reactions (HSR) are associated with cetuximab use. The aim of the study was to evaluate the utility of anti-cetuximab IgE detection in order to identify patients at risk of HSR to cetuximab.

Methods: We included patients ready to receive a first cetuximab infusion in a prospective cohort carried out at 9 French centers. Pre-treatment anti-cetuximab IgE levels were measured. We compared the proportion of severe HSR in the low anti-cetuximab IgE levels (≤ 29 IgE Arbitrary Units (EAU)) subgroup with that in a historical cohort of 213 patients extracted from a previous study.

Results: Of the 301 assessable patients (mean age: 60.9 ± 9.3 years, head-and-neck cancer: 77%), 66 patients (22%) had high anti-cetuximab IgE levels, and 247 patients received cetuximab (including 38 with high anti-cetuximab levels). Severe HSR occurred in 8 patients (5 grade 3; 3 grade 4). The proportion of severe HSR was lower in the low anti-cetuximab IgE levels subgroup vs. the historical cohort [3/209 (1.4%) vs. 11/213 (5.2%), OR, 0.27, 95% CI, 0.07 to 0.97], and higher in high vs. low anti-cetuximab IgE levels subgroup [5/38 (13.2%) vs. 3/209 (1.4%); OR, 10.4, 95% CI, 2.4 to 45.6]. Patients with severe HSR had higher anti-cetuximab IgE levels than patients without reaction (median, 45 vs. 2 EAU, $P = 0.006$).

Conclusions: Detection of pretreatment anti-cetuximab IgE is feasible and helpful to identify patients at risk of severe cetuximab-induced HSR.

LIGANDS	
Cetuximab	EGF
Histamine	
TARGETS	
EGFR	
RAS family	RAF family

These Tables of Links list key protein targets and ligands in this article that are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al., 2016), and are permanently archived in The Concise Guide to PHARMACOLOGY 2015/16 (^{a,b,c,d,e} Alexander et al., 2015a,b,c,d,e).*

What is already known about this subject:

- Hypersensitivity reactions (HSR) are not rare and are potentially life-threatening adverse events associated with cetuximab.
- HSR appears to be an IgE-mediated anaphylactic mechanism because of a cross-reactivity with galactose- α -1,3 galactose present on cetuximab.
- High pretreatment levels of anti-cetuximab IgE have been observed in patients who experienced HSR.

What this study adds:

- HSRs reported in the study were immediate-onset episodes, implying the presence of pre-existing anti-cetuximab IgEs
- A strong association is prospectively verified between the presence of circulating anti-cetuximab IgE and the risk of HSR
- Anti-cetuximab IgE detection could be helpful to physicians in order to identify patients at higher risk of severe HSR

INTRODUCTION

Cetuximab is a chimeric IgG1 monoclonal antibody directed against the EGF receptor (EGFR). Currently, it is used in daily practice for metastatic colorectal cancer_and for locally advanced or metastatic head and neck cancer [1-5]. Hypersensitivity reactions (HSR) are adverse events often associated with cetuximab use [6]. The frequency of severe HSR to cetuximab was found to be <5% [1, 2, 5, 7], although it appears to vary according to the geographical region. A higher incidence of 14 to 30% has been observed in Arkansas, North Carolina, and Tennessee in the USA [8-11], and even fatal reactions have been reported [12-15].

Several approaches have been attempted to identify patients at a higher risk of HSR to cetuximab. Smokers, men, and patients with a history of allergy were suggested to be at a higher risk of HSR [10, 16], while no clear relationship was found with tumor location [10-12, 16, 17]. Importantly, the link between these factors and the risk of HSR to cetuximab is not strong enough to help clinicians identify patients at a high risk of severe HSR [17].

High pretreatment levels of anti-cetuximab IgE have been observed in patients who experienced HSR at the first cetuximab administration [8]. The basis for the HSR appears to be an IgE-mediated anaphylactic mechanism because of a cross-reactivity with galactose- α -1,3 galactose (alpha-gal), an oligosaccharidic epitope that is present on cetuximab [18].

In a previous retrospective study, conducted on patients treated between October 2005 and March 2009 at our center, we described the standardization of an ELISA

test to detect serum anti-cetuximab IgE [19]. In that historical cohort, the overall rate of severe HSR reactions was 5.2% (11/213 patients). Statistical analysis indicated a cut-off value of 29 anti-cetuximab IgE arbitrary units (EAU) above which patients may be considered at a higher risk of severe HSR to cetuximab [19].

The present study was conducted prospectively to evaluate the utility of pre-treatment measurement of serum anti-cetuximab IgE levels in patients naive to cetuximab to identify those who may be at a high risk of severe HSR.

METHODS

Study design

This was a multicenter, prospective, diagnostic trial carried out between January 2010 and February 2013, at 9 centers across France. Patients receiving a first infusion of cetuximab were included and classified according to their pre-treatment levels of serum anti-cetuximab IgE.

The primary objective was to compare the proportion of severe HSR at the first infusion of cetuximab in patients with low levels of anti-cetuximab IgE, to that observed in the historical cohort of 213 patients treated with cetuximab without prior testing for their anti-cetuximab IgE levels [19]. Secondary objectives were to compare the proportion of severe HSR to cetuximab between patients with low or high levels of anti-cetuximab IgE, and to examine the association of previously reported risk factors for HSR to cetuximab in the present prospective cohort.

All patients provided a written informed consent before undergoing any study-specific procedures. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the local Ethics Committee [Comité de Protection des Personnes (CPP) Nord-Ouest III, Caen, France]. This study is registered with ClinicalTrials.gov (NCT01436617) and with EudraCT (2009-016968-37).

Anti-cetuximab IgE assay

The detection of anti-cetuximab IgE was centralized at the Laboratory of Immunology and Immunopathology, Caen University Hospital, Caen, France, and was performed using an enzyme-linked immunosorbent assay (ELISA) as previously described [19]. The results were expressed as EAU using a standard calibration established with a control serum containing known concentration of anti-cetuximab IgE antibodies. The lower limit of quantification (LOQ) was between 3 to 5 EAU according to the batch of calibration serum. Consequently when results were lower to the LOQ, they were given as LOQ/2. According to the ROC analysis performed in the historical cohort, a cutoff value of 29 EAU had been previously selected in order to predict severe HSR with a sensitivity of 87.5% and a specificity of 82.1% [19]. The calculated positive predictive value and negative predictive value of the test were 33.3% and 98.5%, respectively. Anti-cetuximab IgE levels ≤ 29 were defined as low, and levels > 29 EAU as high.

Patients and treatment

Inclusion criteria for patients were age ≥ 18 years, histologically confirmed colon or head-and-neck cancer, naive to cetuximab, and adequate liver, renal, and bone marrow functions to receive cetuximab and associated treatments. Cetuximab infusion, premedication, and concomitant treatments were applied according to the recommended protocols at each participating center. The serum anti-cetuximab IgE levels were determined in all patients before cetuximab infusion, and patients were excluded if these data were not available. Concerning the historical cohort, the premedication usually administrated before the cetuximab infusion was made up of a combination of corticosteroids and antihistamine.

The treating physician was informed of each patient's anti-cetuximab IgE levels before the first administration of cetuximab. Patients with low IgE levels were administered cetuximab according to the center's standard procedures. For patients with high IgE levels, the decision of cetuximab treatment was reevaluated in a multidisciplinary oncology experts meeting. In case of patients with high IgE levels, the two possible options were to provide cetuximab treatment as planned, or suggest another equally effective or less effective treatment. In all cases, the options and their consequences were clearly explained to the patient, who was then allowed to choose between the treatments. If the patient consented to receive cetuximab treatment, the first and second (if applicable) infusions were monitored closely by a physician, with resuscitation equipment readily available in case of an HSR.

Clinical data

For each patient, data were collected on the following parameters: weight, age at cetuximab administration, site of primary tumor, date of diagnosis, previous tumor treatments, concomitant and previous medications, and location of metastases in case of metastatic disease. In addition, history of allergy (against drug, food, or insects), asthma, eczema, allergic rhinitis, and shock or angioedema were recorded.

In case of a HSR to cetuximab, the time interval between the beginning of the infusion and reaction, the clinical manifestation of the HSR, as well as the details of its management were recorded. Serum assays for histamine and tryptase were performed.

Case definition and grading system

HSRs to cetuximab were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0, in the same manner as in our previous retrospective cohort study [19]. The grades for all HSR were described by an independent clinician blinded to the anti-cetuximab IgE levels and to the grades given by the investigators. Severe HSR were defined as grades 3, 4, or 5.

Statistical Design and Analyses

All HSR proportions were analyzed in patients who received cetuximab. A cohort of interest was defined as patients with low pretreatment levels of anti-cetuximab IgE (≤ 29 EAU). The study was designed to test whether the proportion of severe HSR (grade 3 or above) in the cohort of interest would be lower than that observed in the

historical cohort ($11/213 = 5.2\%$) in which the pretreatment anti-cetuximab IgE levels had not been determined prior to treatment. In the studies that have assessed the indications for treatment with cetuximab, the minimal reported rate of severe HSR was 1.2% [1, 2, 5, 7]. Assuming that the severe HSR proportion in the cohort of interest would be equal or lower to this proportion of 1.2% (*i.e.* lower by at least 4-percent compared with the historical cohort), 135 patients would be needed in the cohort of interest from Basse Normandie to detect this reduction as significant with a one-sided Fisher's exact test ($\alpha = 5\%$, $\beta = 20\%$). Given that 75% of the patients from Basse Normandie had low pretreatment levels of anti-cetuximab IgE, the required overall sample size was increased to 180 patients from Basse Normandie. Secondly, the protocol was amended to open new investigator centres in different geographical areas to assess if the rate of HSR depended on the geographical region [1, 2, 5, 7-11, 20, 21]. Assuming that 80% of the study patients would be from Basse Normandie, the number of patients to enrol was therefore increased to 225 patients. Additionally, we had to be taken into account that cetuximab treatment was not continued for 20% of recruited patients. Thus at least 285 patients had to be enrolled.

The comparison of the rate of severe HSR in the present prospective cohort with that in the historical cohort was done in a stepwise manner. In the first step, reflecting the primary objective, the proportion of severe HSR in the cohort of interest specifically from the region of Basse-Normandie was compared by a one-sided Fisher's exact test with the one observed in the historical cohort which had been entirely constituted from this region. Secondly, it was compared between the cohort of interest from Basse-Normandie and that from outside this region by a two-sided Fisher's exact

test. Lastly, if no geographical disparity is found in the second step, then the severe HSR rate would be compared between the entire cohort of interest from the present prospective cohort and the historical cohort by a one-sided Fisher's exact test. The odds ratio (OR) of the rate of severe HSR in a given cohort of interest to that in the historical cohort was determined with a two-sided 95% confidence interval (CI). The sensitivity and the negative predictive value (NPV) of anti-cetuximab IgE assay associated with the risk of severe HSR were estimated with exact binomial 95% CI. As it was possible for patients with high levels of anti-cetuximab IgE, not to receive cetuximab, specificity and positive predictive value could not be calculated.

The following factors that have been reported as possibly related to the occurrence of a severe HSR were investigated as described below. Mean age was compared by a Student's *t* test, levels of anti-cetuximab IgE by a Mann-Whitney *U* test, and qualitative factors (gender, history of allergy, premedication, and site of cancer) were compared by a Fisher's exact test. *P*-values and CI are two-sided unless otherwise specified. Significance was set at $P \leq 0.05$. The statistical software R version 3.0.1 (R foundation for statistical computing, Vienna, Austria) was used for all analyses.

RESULTS

Patient population

Three hundred and three patients were included in the study (Figure 1). Of these patients, 2 patients were excluded because of either previous cetuximab treatment or lack of data on pretreatment anti-cetuximab IgE levels. Of the 301 assessable patients, 66 patients (21.9%) had anti-cetuximab IgE levels (>29 EAU) and 38 (57.6%) received cetuximab. Two hundred and thirty five patients had low anti-cetuximab IgE levels (≤ 29 EAU) of which 209 (88.9%) received cetuximab.

Concerning the main cohort of interest, 138 patients from Basse-Normandie who had low levels of anti-cetuximab IgE were treated with cetuximab.

The baseline characteristics of the present study population were similar to those of the historical cohort [19], except for the site of tumor (Table 1). The proportion of patients treated with cetuximab for head-and-neck cancer was relatively higher in the present prospective cohort than in the historical cohort probably because of the more recent addition of this type of tumor to cetuximab indications.

Hypersensitivity reactions to cetuximab

Among the 247 patients who received cetuximab for the first time, 12 patients (4.9%) experienced a HSR, of which 8 patients (3.2%) had a severe reaction (5 grade 3, and 3 grade 4 reaction). There were no deaths due to a HSR to cetuximab. All HSRs occurred within one hour after the beginning the first cetuximab administration. The 12 cases of HSR to cetuximab and their management are described in Table 2.

Anti-cetuximab IgE levels and risk of hypersensitivity reaction to cetuximab

Primary objective

The proportion of severe HSR to cetuximab in the cohort of interest (low levels subgroup) from the Basse-Normandie region was non significantly lower than that in the historical cohort conducted in the same region ($2/138 = 1.4\%$ vs. $11/213 = 5.2\%$, one-sided $P = 0.060$; OR, 0.27, 95% CI, 0.06 to 1.24; two-sided $P = 0.087$), indicating a decrease of 3.8% in the observed rate of severe HSR.

Secondary objectives

There was no geographical disparity in the proportion of severe HSR between the cohort of interest from Basse-Normandie and that from outside this region ($2/138 = 1.4\%$ vs. $1/71 = 1.4\%$, $P = 1$). Moreover, the characteristics of the patients in these two populations were not different. These results allowed to compare the HSR rate in the entire population with the historical cohort conducted only in the Basse-Normandie region. The overall severe HSR rate in the cohort of interest from the entire study population was lower as compared with the historical cohort ($3/209 = 1.4\%$ vs. $11/213 = 5.2\%$, one-sided $P = 0.029$; OR, 0.27, 95% CI, 0.07 to 0.97; two-sided $P = 0.053$, Figure 2).

The proportion of severe HSR in patients with high levels of anti-cetuximab IgE was significantly higher than that in those with low levels ($5/38 = 13.2\%$ vs. $3/209 = 1.4\%$, $P = 0.0027$; OR, 10.4, 95% CI, 2.4 to 45.6).

The sensitivity and the NPV of anti-cetuximab IgE assay associated with the risk of severe HSR were $5/8 = 63\%$ (95% CI, 24 to 91%) and $206/209 = 98.6\%$ (95% CI, 95.9 to 99.7%), respectively. In the historical cohort, the sensitivity and the NPV were 87.5% and 98.5% respectively.

Nineteen patients did not finally receive the drug due to high anti-cetuximab IgE level: anti-cetuximab IgE levels of these patients were not significantly different than levels of patients with a high level who were treated (median, 55 EAU; interquartile range 39.5 – 122.5 vs 57.5 EAU; interquartile range 35 – 101.8, respectively, $P = 0.49$).

Patients with severe HSR had significantly higher levels of anti-cetuximab IgE than patients without severe HSR (median, 45 EAU; interquartile range, 3.5 – 220.5 vs. 2 EAU; interquartile range, 1 – 12, $P = 0.0059$).

Factors related to severe hypersensitivity reactions

A comparison of various characteristics between patients who did not have a severe HSR and those who did (Table 3) revealed that high levels of anti-cetuximab IgE was the only factor significantly associated with the occurrence of severe HSR to cetuximab. No significant association was noted between severe HSR and gender, age, history of allergies or tumor localization (Table 3). Further, none of these factors was found to be related to HSR of any severity grade (data not shown).

DISCUSSION

This is the first large-scale prospective study to confirm the strong association between the presence of circulating anti-cetuximab IgE before the first infusion of cetuximab, and the occurrence of hypersensitivity reactions to cetuximab. It demonstrates that assaying for pre-existing anti-cetuximab IgEs could help assess the risk of HSR and to tailor the therapeutic strategy accordingly. These considerations are clinically meaningful because prevention of severe allergic reactions to cetuximab is a major challenge, and also a financial burden, especially in regions with high incidence [14, 22].

The study was powered to detect a difference of at least 4% decrease in the proportion of severe HSRs between patients with low pretreatment anti-cetuximab IgE levels from the present prospective cohort and the historical cohort that had not

been prospectively screened for pre-sensitization to cetuximab [19]. However, the calculated difference was a decrease of 3.8%, after verifying lack of geographical disparity. Although our statistical assumptions concerning the main objective were not fully reached (expected at least a decrease of 4%, observed a decrease of 3.8%), the decrease in the severe HSR rate remains of clinical interest.

This study confirms that severe HSR to cetuximab is not a rare adverse event. In the historical cohort, the proportion was of 5.2%, an intermediate between low rates from the pivotal studies of cetuximab (1%–3.5%) [1, 2, 5, 7], and the high rates described in some areas such as North Carolina or Tennessee (up to 22%) [9, 10]. In the present prospective study, we noted an overall low rate of severe HSR of 3.2%, accounting for 1.4% or 13.2% in subgroups of cetuximab-treated patients with low or high levels of anti-cetuximab IgE, respectively. This observed overall proportion is indeed biased because some patients with high levels of anti-cetuximab IgE declined cetuximab treatment (19/66), notably patients with an alternative treatment option. Considering the severe HSR rate of 13.2% observed in the group of patients with high levels of anti-cetuximab IgE, we can speculate that between 2 and 3 (19×0.132) severe HSR were avoided in the 19 untreated patients with high pretreatment levels of anti-cetuximab IgE and that 7 to 8 severe HSR (57×0.132) could have been avoided if all patients with high pretreatment levels of anti-cetuximab IgE had received an alternative treatment.

Analysis of various patient characteristics did not show a correlation of any with the risk of HSR, except for high levels of pre-existing anti-cetuximab IgEs. The results of this study do not support the indications from previous studies, such as that of

association of HSR with allergies, head-and-neck cancer, or male gender [10-12, 16]. Indeed, several reports have described a higher incidence of HSR to cetuximab in patients treated for head-and-neck cancer or lung cancer [10-12], but these patients are usually more likely to have symptoms such as dyspnea or bronchospasm, which are confounding symptoms for HSR.

In our study, patients who had severe HSR had in fact received appropriate premedication, but this did not seem to prevent HSR to cetuximab unlike in previous studies [9, 23]. Given the mechanism of HSR involving pre-existing IgE, it is not surprising that premedication with corticosteroids and antihistamine was not sufficient to avoid anaphylactic reaction in patients with high anti-cetuximab IgE concentration.

The results presented here support the notion that cetuximab HSR is an IgE-mediated anaphylactic reaction in a pre-sensitized individual [24]. All HSRs reported here were immediate-onset, implying the presence of pre-existing IgEs [25].

The negative predictive value of testing for anti-cetuximab IgE would permit a better selection of patients for cetuximab treatment, so that patients with high IgE levels will not be exposed to the risk of a potentially fatal HSR. Therefore, rather than denying this treatment, it would be advisable to test for pre-sensitization to cetuximab and then provide the treatment taking all the necessary precautionary measures, especially during the first infusion. It is often the element of surprise that can cost the life of patients experiencing severe reactions [12, 13, 17]. Thus, screening for

patients at a high risk of severe reactions would allow a better management of these cases.

In conclusion, anti-cetuximab IgE detection appears to be an effective tool to help clinicians predict allergic accidents to cetuximab, and should be considered as a part of a comprehensive approach to personalized cancer treatment. In addition to testing for *RAS* and *RAF* mutations to predict the effectiveness of treatment with cetuximab in colon cancer, assaying anti-cetuximab IgE levels will predict a patient's tolerance to treatment [26, 27] and avoid fatal events.

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REFERENCES

1. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Raben D, Jassem J, Ove R, Kies MS, Baselga J, Youssoufian H, Amellal N, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006; 354: 567-78.
2. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351: 337-45.
3. Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, Idziaszczyk S, Harris R, Fisher D, Kenny SL, Kay E, Mitchell JK, Madi A, Jasani B, James MD, Bridgewater J, Kennedy MJ, Claes B, Lambrechts D, Kaplan R, Cheadle JP. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011; 377: 2103-14.
4. Sobrero AF, Maurel J, Fehrenbacher L, Scheithauer W, Abubakr YA, Lutz MP, Vega-Villegas ME, Eng C, Steinhauer EU, Prausova J, Lenz HJ, Borg C, Middleton G, Kroning H, Luppi G, Kisker O, Zubel A, Langer C, Kopit J, Burris HA, 3rd. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; 26: 2311-9.
5. Vermorken JB, Mesia R, Rivera F, Remenar E, Kaweckki A, Rottey S, Erfan J, Zabolotnyy D, Kienzer HR, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, De Raucourt D, Bokemeyer C, Schueler A, Amellal N, Hitt R. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008; 359: 1116-27.

6. Patel DD, Goldberg RM. Cetuximab-associated infusion reactions: pathology and management. *Oncology (Williston Park)* 2006; 20: 1373-82; discussion 82, 92-4, 97.
7. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, Vynnychenko I, Park K, Yu CT, Ganul V, Roh JK, Bajetta E, O'Byrne K, de Marinis F, Eberhardt W, Goddemeier T, Emig M, Gatzemeier U. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet* 2009; 373: 1525-31.
8. Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, Murphy BA, Satinover SM, Hosen J, Mauro D, Slebos RJ, Zhou Q, Gold D, Hatley T, Hicklin DJ, Platts-Mills TA. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med* 2008; 358: 1109-17.
9. Keating K, Walko C, Stephenson B, O'Neil BH, Weiss J. Incidence of cetuximab-related infusion reactions in oncology patients treated at the University of North Carolina Cancer Hospital. *J Oncol Pharm Pract* 2013.
10. O'Neil BH, Allen R, Spigel DR, Stinchcombe TE, Moore DT, Berlin JD, Goldberg RM. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. *J Clin Oncol* 2007; 25: 3644-8.
11. Hansen NL, Chandiramani DV, Morse MA, Wei D, Hedrick NE, Hansen RA. Incidence and predictors of cetuximab hypersensitivity reactions in a North Carolina academic medical center. *J Oncol Pharm Pract* 2011; 17: 125-30.
12. Grandvuillemin A, Disson-Dautriche A, Miremont-Salame G, Fourrier-Reglat A, Sgro C. Cetuximab infusion reactions: French pharmacovigilance database analysis. *J Oncol Pharm Pract* 2013; 19: 130-7.

13. Pointreau Y, Commins SP, Calais G, Watier H, Platts-Mills TA. Fatal infusion reactions to cetuximab: role of immunoglobulin e-mediated anaphylaxis. *J Clin Oncol* 2012; 30: 334; author reply 35.
14. Tronconi MC, Sclafani F, Rimassa L, Carnaghi C, Personeni N, Santoro A. Fatal infusion reaction to cetuximab: the need for predictive risk factors and safer patient selection. *J Clin Oncol* 2011; 29: e680-1.
15. Dupont B, Mariotte D, Moldovan C, Grellard JM, Vergnaud MC, Laroche D, Gervais R. Case Report About Fatal or Near-Fatal Hypersensitivity Reactions to Cetuximab: Anticetuximab IgE as a Valuable Screening Test. *Clin Med Insights Oncol* 2014; 8: 91-4.
16. Hopps S, Medina P, Pant S, Webb R, Moorman M, Borders E. Cetuximab hypersensitivity infusion reactions: Incidence and risk factors. *J Oncol Pharm Pract* 2013; 19: 222-7.
17. Dupont B, Mariotte D, Clarisse B, Galais MP, Bouhier-Leporrier K, Grellard JM, Le Mauff B, Reimund JM, Gervais R. Risk factors associated with hypersensitivity reactions to cetuximab: anti-cetuximab IgE detection as a valuable screening test. *Future Oncol* 2014; 10.
18. Saleh H, Embry S, Nauli A, Atyia S, Krishnaswamy G. Anaphylactic reactions to oligosaccharides in red meat: a syndrome in evolution. *Clin Mol Allergy* 2012; 10: 5.
19. Mariotte D, Dupont B, Gervais R, Galais MP, Laroche D, Tranchant A, Comby E, Bouhier-Leporrier K, Reimund JM, Le Mauff B. Anti-cetuximab IgE ELISA for identification of patients at a high risk of cetuximab-induced anaphylaxis. *MAbs* 2011; 3: 396-401.

20. Herbst RS, Arquette M, Shin DM, Dicke K, Vokes EE, Azarnia N, Hong WK, Kies MS. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. *J Clin Oncol* 2005; 23: 5578-87.
21. Pfister DG, Su YB, Kraus DH, Wolden SL, Lis E, Aliff TB, Zahalsky AJ, Lake S, Needle MN, Shaha AR, Shah JP, Zelefsky MJ. Concurrent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregionally advanced, squamous cell head and neck cancer: a pilot phase II study of a new combined-modality paradigm. *J Clin Oncol* 2006; 24: 1072-8.
22. Foley KA, Wang PF, Barber BL, Long SR, Bagalman JE, Wagner V, Song X, Zhao Z. Clinical and economic impact of infusion reactions in patients with colorectal cancer treated with cetuximab. *Ann Oncol* 2010; 21: 1455-61.
23. Siena S, Glynne-Jones R, Adenis A, Thaler J, Preusser P, Aguilar EA, Aapro MS, Loos AH, Esser R, Wilke H. Reduced incidence of infusion-related reactions in metastatic colorectal cancer during treatment with cetuximab plus irinotecan with combined corticosteroid and antihistamine premedication. *Cancer* 2010; 116: 1827-37.
24. Galili U. Anti-Gal: an abundant human natural antibody of multiple pathogeneses and clinical benefits. *Immunology* 2013; 140: 1-11.
25. Yamaguchi K, Watanabe T, Satoh T, Ishiguro M, Izawa M, Inoshiri S, Sugihara K, Sakata Y. Severe infusion reactions to cetuximab occur within 1 h in patients with metastatic colorectal cancer: results of a nationwide, multicenter, prospective registry study of 2126 patients in Japan. *Jpn J Clin Oncol* 2014; 44: 541-6.

26. De Roock W, Claes B, Bernasconi D, De Schutter J, Biesmans B, Fountzilas G, Kalogeras KT, Kotoula V, Papamichael D, Laurent-Puig P, Penault-Llorca F, Rougier P, Vincenzi B, Santini D, Tonini G, Cappuzzo F, Frattini M, Molinari F, Saletti P, De Dosso S, Martini M, Bardelli A, Siena S, Sartore-Bianchi A, Tabernero J, Macarulla T, Di Fiore F, Gangloff AO, Ciardiello F, Pfeiffer P, Qvortrup C, Hansen TP, Van Cutsem E, Piessevaux H, Lambrechts D, Delorenzi M, Tejpar S. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol* 2010; 11: 753-62.
27. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ, Zalcborg JR. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008; 359: 1757-65.

Table 1. Baseline Patient Characteristics

	Historical cohort <i>N</i> = 213	Present prospective cohort Patients receiving cetuximab <i>N</i> = 247	Overall population <i>N</i> = 301
Age , years, (mean ± SD)	62.1 ± 10	61.1 ± 9.1	60.9 ± 9.3
Male	159 (76.6%)	197 (79.8%)	244 (81.1%)
History of allergy	36 (16.9%)	30 (12.1%)	41 (13.6%)
Type of cancer			
Head-and-neck cancer	100 (46.9%)	189 (76.5%)	232 (77.1%)
Colon cancer	107 (50.2%)	58 (23.5%)	69 (22.9%)

Data are presented as *N* (%) unless otherwise specified.

Table 2. Description of the cases of hypersensitivity reactions to cetuximab

Time (min)	IgE Value (EAU)	Anti-cetuximab IgE assay	Histamine (Normal <6 nmol/L)	Tryptase (Normal <12.5 µg/L)	Treatment* Medications
35	9	Low	ND	ND	-
15	1.5	Low	3.1	5.2	-
40	15	Low	9.3	27.8	-
15	39	High	ND	ND	CORT
40	1.5	Low	3.8	5.1	CORT, TER, IPR
15	35	High	83.3	13.7	-
20	55	High	1.3	2	CORT, DEX, TER, IPR
25	2.5	Low	12	ND	CORT, DEX
15	490	High	ND	ND	DEX, CORT, TER
15	134	High	661	31.6	CORT, EPI
<1	480	High	100	64	CORT, EPI, TER
30	4	Low	20.8	8.6	EPI

Cases	Localization	Premedication dexchlorpheniramine + corticosteroids	Grade
A	Colon	Yes	1
B	Colon	Yes	1
C	Head-and-neck	Only dexchlorpheniramine	2
D	Head-and-neck	Yes	2
E	Colon	Yes	3
F	Head-and-neck	Yes	3
G	Head-and-neck	Yes	3
H	Colon	Yes	3
I	Head-and-neck	Yes	3
J	Head-and-neck	Yes	4
K	Head-and-neck	Yes	4
L	Head-and-neck	Yes	4

* Treatment administered in addition to cetuximab infusion stop. In patient A, cetuximab infusion was stopped temporarily and resumed. ND, Not Determined.

CORT: corticosteroids; DEX: dexchlorpheniramine; TER: terbutaline; IPR: ipratropium; EPI: epinephrine; SD: standard deviation.

Table 3. Univariate analysis of factors related to the occurrence of a severe hypersensitivity reaction to cetuximab

	No severe HSR <i>N</i> =239	Severe HSR Grade 3 or 4 <i>N</i> =8	<i>P</i>
Age, years, <i>mean</i> ± <i>SD</i>	61.1 ± 8.9	62 ± 12.9	0.85
Male	191 (79.9%)	6 (75%)	0.67
History of allergy	28 (11.7%)	2 (25%)	0.25
Type of cancer			
Head-and-neck cancer	183 (76.6%)	6 (75%)	1
Premedication			
Dexchlorpheniramine	216 (91.5%)	8 (100%)	1
Corticosteroids	232 (98.3%)	8 (100%)	1
Anti-cetuximab IgE assay			
High	33 (13.8%)	5 (62.5%)	0.0027

HSR, hypersensitivity reaction, *SD* Standard Deviation

Data are presented as *N* (%) unless otherwise specified.

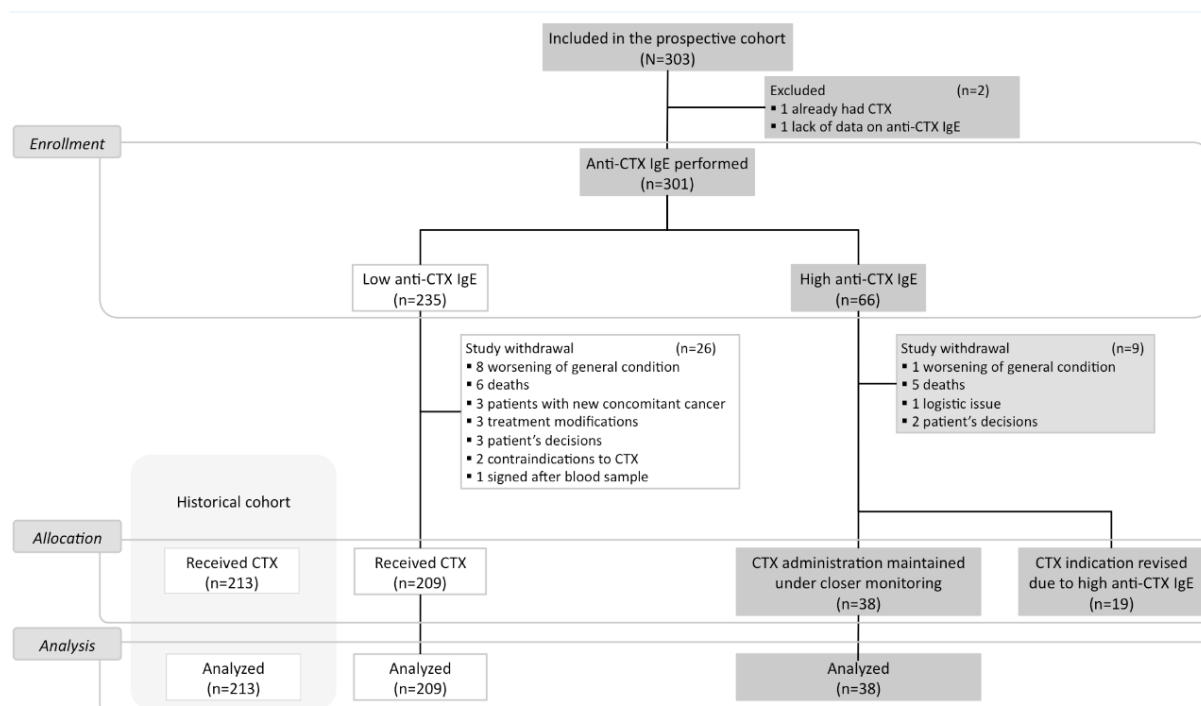


Figure 1. Study flowchart

CTX: Cetuximab; IgE: Immunoglobulin E

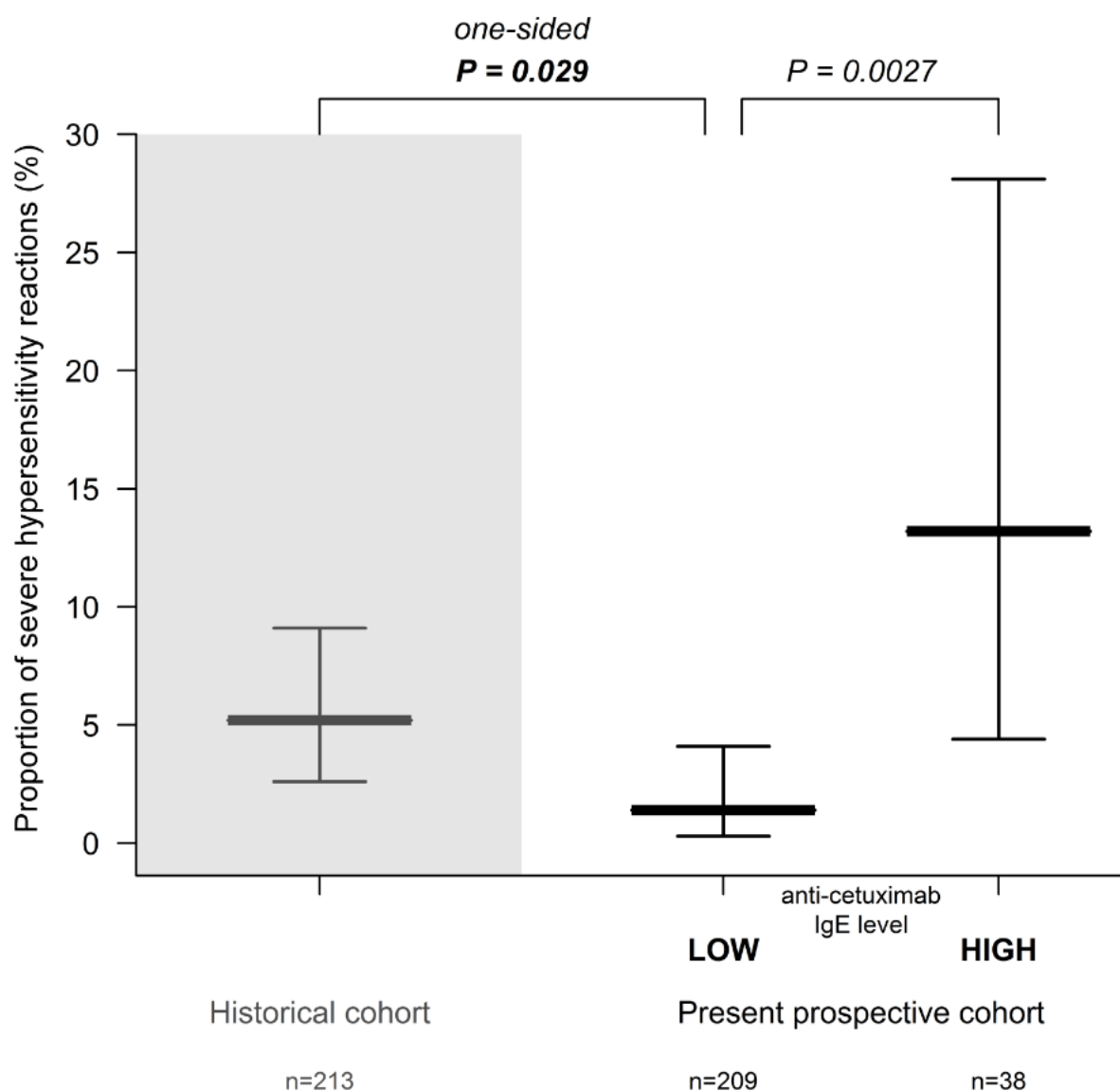


Figure 2. Proportion of severe hypersensitivity reactions to cetuximab.

Proportion of severe hypersensitivity reactions (bold line) and two-sided 95% confidence interval (thin line) in the historical retrospective cohort and the present prospective cohort, according to the levels of anti-cetuximab IgE (low levels, ≤ 29 , or high levels, > 29 EAU).