Clinical trial results:
Evaluation de l’intérêt d’un dosage des anticorps anti-cetuximab dans la prise en charge thérapeutique des patients présentant un cancer colique ou des voies aéro-digestives supérieures et candidats à un traitement par cetuximab

Summary

EudraCT number	2009-016968-37
Trial protocol	FR
Global end of trial date	29 May 2013

Results information

Result version number	v1 (current)
This version publication date	22 September 2019
First version publication date	22 September 2019
Summary attachment (see zip file)	IgES Article (soumission British J Clin Pharmacol.pdf)

Trial information

Trial identification

Sponsor protocol code	IgES

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01436617
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Centre François Baclesse
Sponsor organisation address	3 avenue général Harris, caen, France, 14076
Public contact	Centre François Baclesse Jean-Michel GRELLARD, Centre François Baclesse Dr Radj GERVAIS, 33 0231455002, jm.grellard@baclesse.unicancer.fr
Scientific contact	Centre François Baclesse Jean-Michel GRELLARD, Centre François Baclesse Dr Radj GERVAIS, 0231455002 231455002, r.gervais@baclesse.unicancer.fr

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to validate the utility of IgE anti-cetuximab in the treatment strategy to identify patients at risk for a severe allergic reaction to cetuximab (grade 3 or 4 of the classification of NCI) and thus reduce the incidence of severe reactions.

Protection of trial subjects:

For the duration of the treatment, the patients performed the standard monitoring.
- For IgE negative patients (absence of anti-cetuximab antibodies): The first product administration was under standard surveillance
- For IgE-positive patients (presence of cetuximab antibodies) not treated with cetuximab: No specific surveillance for cetuximab administration was performed.

- For IgE positive patients treated with cetuximab:
The first two injections were performed with the safety conditions deemed necessary by the referring physician (at best in the intensive care unit).

Special case of patients who had a severe allergic reaction:
For patients who had an allergic reaction after the injection, a tryptase and histamine assay was performed according to the usual protocol used for any allergic reaction or supposedly as such. Skin tests were performed in the weeks following the allergic episode. A basophil degranulation test could also be offered to patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 January 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 300
Worldwide total number of subjects	300
EEA total number of subjects	300

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	195
From 65 to 84 years	105
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

After collection of signed informed consent, verification of all selection criteria and before starting treatment, inclusion of the patient has been completed

Pre-assignment

Screening details:

Patients eligible for the trial and having signed their consent to participate performed a blood test (2 dry tubes) in the weeks prior to the start of treatment.

Patients were seen in consultation with their referring physician before the start of treatment, once the results of the specific IgE assay (positive / negative) were available and the

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Negativ IgE group

Arm description:

For IgE-negative patients, there should be no change in the initial treatment.

Arm type	Standard survey
Investigational medicinal product name	cetuximab
Investigational medicinal product code	L01XC06
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m²

Arm title	Positiv IgE test

Arm description:

For IgE-positive patients, the indication for cetuximab was to be reviewed multidisciplinary meeting. If the indication of treatment with cetuximab was maintained, the first two administrations should be performed with the safety conditions deemed necessary by the referring physician (at best in the intensive care unit).

Arm type	Additional monitoring

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Negativ IgE group	Positiv IgE test
Started	234	66
Completed	208	38
Not completed	26	28
Physician decision	26	28

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	300	300	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	198	198	
From 65-84 years	102	102	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	57	57	
Male	243	243	

End points

End points reporting groups

Reporting group title	Negativ IgE group

Reporting group description:

For IgE-negative patients, there should be no change in the initial treatment.

Reporting group title	Positiv IgE test

Reporting group description:

For IgE-positive patients, the indication for cetuximab was to be reviewed multidisciplinary meeting. If the indication of treatment with cetuximab was maintained, the first two administrations should be performed with the safety conditions deemed necessary by the referring physician (at best in the intensive care unit).

Subject analysis set title	Incidence
Subject analysis set type	Full analysis

Subject analysis set description:

The incidence of allergic reactions in IgE-negative patients is 1.5%, 95% Confidence Interval (CI) = [0.2 - 5.2].

If we compare this incidence of 1.5% to the incidence observed in the historical Lower Norman cohort (11/213 = 5.2%) using a Fisher exact test under a unilateral alpha risk of 5 %: odd-ratio (OR) = 0.27, p-value = 0.062

The incidence of severe allergic reactions to cetuximab (grade 3-4) in IgE-positive patients whose indication was maintained: 13.2%, 95% CI = [4.4 - 28.8]

There are significantly more severe allergic reactions to cetuximab in patients with a dosage ≥30 UAE (13.2%) compared to patients <30 UAE (1.4%), all regions, p. value = 0.0027.

There is no significant difference observed between the percentage of severe allergic reactions according to the presence of an atopic or non-atopic site, the age (in years), the sex or the location of the cancer (ORL vs COLON).

Primary: Incidence

End point title	Incidence

End point description:

End point type	Primary

End point timeframe:

After 2 cycles of cetuximab

End point values	Negativ IgE group	Positiv IgE test		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	38		
Units: percentage				
number (not applicable)	1.5	13.2		

Statistical analyses

Statistical analysis title	Incidence of severe allergic reactions (grade 3 +)
Comparison groups	Negativ IgE group v Positiv IgE test
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
After 2 cycles of cetuximab	
Assessment type	Systematic

Dictionary used	
Dictionary name	NCI CTCAE
Dictionary version	3

Reporting groups	
Reporting group title	Negativ Ige group
Reporting group description: -	
Reporting group title	Positiv IgE group
Reporting group description: -	

Serious adverse events	Negativ Ige group	Positiv IgE group	
Total subjects affected by serious adverse events			
subjects affected / exposed	65 / 208 (31.25%)	26 / 34 (76.47%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Vascular disorders			
hemoptysis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Agitation			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
allergic reaction			
subjects affected / exposed	0 / 208 (0.00%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			

subjects affected / exposed	1 / 208 (0.48%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Canula dysfunction			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusion			
subjects affected / exposed	2 / 208 (0.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine renal clearance increased			
subjects affected / exposed	0 / 208 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 208 (1.44%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Decanulation			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
deffective pick-line			
subjects affected / exposed	0 / 208 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
deshydratation			
subjects affected / exposed	0 / 208 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			

subjects affected / exposed	5 / 208 (2.40%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	5 / 208 (2.40%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hematuria			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 208 (0.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	5 / 208 (2.40%)	4 / 34 (11.76%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speak disorder			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	0 / 208 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			

subjects affected / exposed	1 / 208 (0.48%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Desaturation			
subjects affected / exposed	2 / 208 (0.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnea			
subjects affected / exposed	2 / 208 (0.96%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	2 / 208 (0.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	4 / 208 (1.92%)	3 / 34 (8.82%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
General physical condition decreased			
subjects affected / exposed	8 / 208 (3.85%)	5 / 34 (14.71%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
decompensation			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Extrasystoles			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infarction			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tachycardy			
subjects affected / exposed	0 / 208 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal compression			
subjects affected / exposed	0 / 208 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anemia			
subjects affected / exposed	1 / 208 (0.48%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	4 / 208 (1.92%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hemorrhage			
subjects affected / exposed	0 / 208 (0.00%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	2 / 208 (0.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasogastric tube pose			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occlusion			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Icterus			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Deramatitis			

subjects affected / exposed	3 / 208 (1.44%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Edema	Additional description: due to cirrhosis		
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 208 (0.48%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Insufficiency			
subjects affected / exposed	2 / 208 (0.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	6 / 208 (2.88%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis shock			
subjects affected / exposed	2 / 208 (0.96%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	2 / 208 (0.96%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			
subjects affected / exposed	0 / 208 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

weight loss			
subjects affected / exposed	0 / 208 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Negativ Ige group	Positiv IgE group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 208 (2.88%)	6 / 34 (17.65%)	
Cardiac disorders			
Hypertension			
subjects affected / exposed	1 / 208 (0.48%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Hypotension			
subjects affected / exposed	2 / 208 (0.96%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Tachycardia			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Anaphylactic reaction			
subjects affected / exposed	1 / 208 (0.48%)	3 / 34 (8.82%)	
occurrences (all)	1	3	
Lumbar pain			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Flush			
subjects affected / exposed	2 / 208 (0.96%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Skills			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	1 / 208 (0.48%)	1 / 34 (2.94%)	
occurrences (all)	1	1	

Sweat			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	2 / 208 (0.96%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Thoracic pain			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Dyspnea			
subjects affected / exposed	1 / 208 (0.48%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Acnea			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	1 / 208 (0.48%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 208 (0.48%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	1 / 208 (0.48%)	1 / 34 (2.94%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2011	New investigator site and modification of an inclusion criteria
25 May 2011	ICF modification
15 September 2011	New investigator site
10 March 2012	Population increase

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27662818