Clinical trial results:
Phase I/II study of Induction Chemotherapy with weekly RAD001, Carboplatine and Paclitaxel in Unresectable or Inoperable Locally Advanced Head and Neck Squamous Cell Carcinoma (HNSCC)

Summary

EudraCT number	2008-005702-39
Trial protocol	FR
Global end of trial date	31 January 2013

Results information

Result version number	v1 (current)
This version publication date	23 July 2016
First version publication date	23 July 2016

Trial information

Trial identification

Sponsor protocol code	O08-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01333085
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GERCOR
Sponsor organisation address	151 rue du faubourg Saint Antoine, PARIS, France, 75011
Public contact	Regulatory affairs, GERCOR, 33 1 40 29 85 00, regulatory.affairs@gercor.com.fr
Scientific contact	coordinating investigator, Pr Sandrine FAIVRE, 33 1 40 29 85 00, regulatory.affairs@gercor.com.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	31 January 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2013
Global end of trial reached?	Yes
Global end of trial date	31 January 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I:
To determine the safety profile of weekly RAD001 in combination with carboplatin and paclitaxel in chemonaive patients with unresectable or inoperable locally advanced HNSCC.

Phase II: To assess anti-tumor activity of the combination in these patients.

Protection of trial subjects:

Premedication
Administration of paclitaxel should be preceded by an anti-allergic premedication with solumedrol 80 mg IV and polaramine 5 mg IV, and an anti-emetic prophylaxis at the discretion of the investigator.

Dose adjustments:
Doses will be reduced for hematological and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI CTCAE version 3.0.
Except for nausea and vomiting, dose reductions are definitive. A maximum of 2 dose reductions are allowed. First dose reduction has to be done on RAD001 and the second one on carboplatin and/or paclitaxel. Patients who should experience a third dose reduction must be dropped out of study. Anemia should be treated according to investigator’s discretion. No dose reduction is allowed, but erythropoietin use is permitted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2009
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: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	35
From 65 to 84 years	14
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patient enrollment occurred from 15 October 2009 (first patient was treated in phase I) to 20 November 2012 (laste patient enrolled in phase II).
This study was conducted in France in five centers (Hôpital Beaujon - Clichy; Hôpital St Joseph, Institut Curie - Paris; Centre Léon Bérard Lyon; Institut Claudius Regaud -Toulouse)

Pre-assignment

Screening details:

Patient with inoperable Locally Advanced Head and Neck Squamous cell carcinoma.
Phase I (permitted to identify the recommended dose level): 7 patients were enrolled: 4 at dose level 1 (RAD001 30mg) and 3 at dose level 2 (RAD001 50mg).
Phase II: 43 patients were enrolled at dose RAD001 50mg.

Period 1

Period 1 title	Paclitaxel - Carboplatin - RAD001 50mg (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Paclitaxel - Carboplatin - RAD001 50mg

Arm description:

Patients received in first-line 9 weekly cycles of RAD001 (50mg) in combination with carboplatin (AUC2) and paclitaxel (60mg/m²).
Recommended dose was RAD001 50mg

Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel: 60mg/m² IV in 1 hour
Before infusion of paclitaxel at D1, D8, D15 a premedication was recommended with one injection of 5 mg polaramine.

Investigational medicinal product name	Carboplatin AUC2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin AUC2 in 1 hour
Dose of carboplatin is calculated according to creatinine clearance estimated by Calvert formula and area under curve (AUC).

Investigational medicinal product name	RAD001
Investigational medicinal product code	
Other name	Everolimus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

RAD001 is presented as 10mg tablets. It was orally administrated weekly at a dose of 50mg. It was swallowed 1 hour before or 2 hours after lunch with a glass of water.

Number of subjects in period 1[1]	Paclitaxel - Carboplatin - RAD001 50mg
Started	46
Completed	41
Not completed	5
Physician decision	1
Intercurrent medical event	1
Death (related to cancer)	1
Adverse event, non-fatal	1
Patient choice	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 50 patients were included in phase I and phase II.
4 patients treated at dose level RAD001 30mg and 3 patients at dose level RAD001 50mg, permitted to identify the recommended dose level (RAD001 50mg)
46 patients treated at the dose level recommended (3 patients phase I and 43 patients phase II) were evalauted (overall period)

Baseline characteristics

Reporting groups	
Reporting group title	Paclitaxel - Carboplatin - RAD001 50mg
Reporting group description:	
Analysis of the data's, including the patients treated at recommended dose of RAD001 (50mg/week). (3 patients in phase I and 43 patients in phase II).	

Reporting group values	Paclitaxel - Carboplatin - RAD001 50mg	Total	
Number of subjects	46	46	
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)	31	31	
From 65-84 years	14	14	
85 years and over	1	1	
Age continuous Units: years			
median	0		
standard deviation	± 0	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	37	37	
T-stage Units: Subjects			
T1	2	2	
T2	6	6	
T3	2	2	
T4a	31	31	
T4b	4	4	
Tx	1	1	
Missing	0	0	
N-stage Units: Subjects			
N1	6	6	
N2a	3	3	
N2b	5	5	
N2c	14	14	
N3	13	13	
Nx	4	4	
Missing	1	1	

Stade Units: Subjects			
IVa	30	30	
IVb	16	16	
Missing	0	0	
Grade Units: Subjects			
Well	16	16	
Moderately	18	18	
Poorly	7	7	
Not evaluable	4	4	
Missing	1	1	
Side Units: Subjects			
Left	23	23	
Right	17	17	
Both	6	6	
Missing	0	0	
Node Units: Subjects			
Yes	40	40	
No	6	6	
Missing	0	0	
Tumor Site Units: Subjects			
Oral cavity	13	13	
Hypopharynx	5	5	
Larynx	4	4	
Oropharynx	24	24	
Missing	0	0	
ECOG - Performance status Units: Subjects			
ECOG - PS=0	22	22	
ECOG - PS=1	18	18	
ECOG - PS=2	6	6	
Missing	0	0	

End points

End points reporting groups

Reporting group title	Paclitaxel - Carboplatin - RAD001 50mg

Reporting group description:

Patients received in first-line 9 weekly cycles of RAD001 (50mg) in combination with carboplatin (AUC2) and paclitaxel (60mg/m²).
Recommended dose was RAD001 50mg

Subject analysis set title	Clinical Toxicity, all Grade
Subject analysis set type	Full analysis

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0. Clinical toxicty at the recommended dose (RAD001, 50mg)

Subject analysis set title	Clinical Toxicity, Grade 1-2
Subject analysis set type	Full analysis

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0 Clinical toxicity at the recommended dose (RAD001,50mg)

Subject analysis set title	Clinial Toxicity, Grade 3-4
Subject analysis set type	Full analysis

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0 Clinical toxicity at the recommended dose (RAD001, 50mg)

Subject analysis set title	Biological Toxicity, All Grade
Subject analysis set type	Full analysis

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0 At recommended dose (RAD001, 50mg)

Subject analysis set title	Biological Toxicity, Grade 0-1
Subject analysis set type	Full analysis

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0 At the recommended dose (RAD001, 50mg)

Subject analysis set title	Biological Toxicity, grade 3-4
Subject analysis set type	Full analysis

Subject analysis set description:

The adverse events were assessed using the terminology Criteria for adverse Event (CTCAE) version 3.0 At the recommended dose RAD001, 50mg

Primary: Objective Response Rate

End point title	Objective Response Rate[1]

End point description:

All eligible patients will be included in the response rate calculation. Objective response rate was according to RECIST criteria.
The subset that will be assigned a response category (CR, PR, SD or PD) are all patients who have received at least one treatment and have their disease re-evaluated.

End point type	Primary

End point timeframe:

Evaluation at 11 weeks after first administration.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Results of phase II trial will be given as response rates with 95% confidence intervals.

End point values	Paclitaxel - Carboplatin - RAD001 50mg			
Subject group type	Reporting group			
Number of subjects analysed	41[2]			
Units: subjects				
Complete response (CR)	1			
Partial response (PR)	30			
Stable disease (SD)	9			
Progressive disease	1			

Notes:

[2] - 5 patients were not included in efficacity analysis, being not evaluable for tumor response.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Adverse Event at RAD001 50mg

End point title	Clinical Adverse Event at RAD001 50mg

End point description:

All patients will be evaluable for toxicity from the time of their first treatment with RAD001, carboplatin and paclitaxel. Safety evaluations were conducted at least weekly until 2 weeks after the end of therapy and included assessments of laboratory parameters and clinical adverse reactions. Clinical adverse events were graded according to the NCI-CTCAE grading system version 3.0.

End point type	Secondary

End point timeframe:

From inclusion to 14 days after radiation therapy completion

End point values	Clinical Toxicity, all Grade	Clinical Toxicity, Grade 1-2	Clinial Toxicity, Grade 3-4	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	46	46	46	
Units: subject				
Nausea	16	16	0	
Vomiting	9	9	0	
Mucositis	13	13	0	
Constipation	11	11	0	
Alopecia	14	14	0	
Oedema	2	2	0	
Asthenia	31	27	4	
Neuropathy	3	3	0	
Hand foot syndrome	2	2	0	
Rash	12	11	1	
Acnea	5	5	0	
Cough	6	6	0	
Dyspnea	9	8	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Biological Adverse Events at RAD001 50mg

End point title	Biological Adverse Events at RAD001 50mg

End point description:

All patients will be evaluable for toxicity from the time of their first treatment with RAD001, carboplatin and paclitaxel. Safety evaluations were conducted at least weekly until 2 weeks after the end of therapy and included assessments of laboratory parameters and clinical adverse reactions. Clinical adverse events were graded according to the NCI-CTCAE grading system version 3.0.

End point type	Secondary

End point timeframe:

From the randomisation to 14 days after radiation therapy completion

End point values	Biological Toxicity, All Grade	Biological Toxicity, Grade 0-1	Biological Toxicity, grade 3-4	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	46	46	46	
Units: Subject				
Leucopenia	39	26	13	
Neutropenia	40	16	24	
Anemia	43	35	8	
Thrombocytopenia	37	31	6	
Hyperglycemia	38	36	2	
Hypercholesterolemia	27	27	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of CAPRA study in the expression of biomarkers (Ki67 and p-S6K)

End point title	Effect of CAPRA study in the expression of biomarkers (Ki67 and p-S6K)

End point description:

End point type	Secondary

End point timeframe:

Biopsie specimens obtained before treatment (baseline) and post treatment (Post-CAPRA).

End point values	Paclitaxel - Carboplatin - RAD001 50mg			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: subject	46			

Attachments (see zip file)	CAPRA biomarkers in biopsies results.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose taken to 14 days after radiation therapy completion

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Paclitaxel - carboplatin- RAD001 (50mg)

Reporting group description:

Forty-six patients were evaluable for toxicity.

Serious adverse events	Paclitaxel - carboplatin- RAD001 (50mg)		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 46 (43.48%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Platelet count decreased	Additional description: grade 4 et grade 2		
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased	Additional description: grade 4		
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Hemorrhage tumoral	Additional description: grade 3		
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Stroke	Additional description: grade 3 et grade 2		

subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever	Additional description: grade 1		
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Edema of the uvula	Additional description: grade 2		
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain	Additional description: grade 3		
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oral hemorrhage	Additional description: grade 2		
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure	Additional description: grade 5 (death not related to treatment)		
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea	Additional description: grade 2		

subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis	Additional description: grade 2		
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Febrile syndrome	Additional description: grade 1		
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia	Additional description: grade 3		
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abscess	Additional description: gastrostrostomy tube abscess grade 2		
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalemia	Additional description: grade 4		
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Paclitaxel - carboplatin- RAD001 (50mg)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 46 (100.00%)		
Nervous system disorders			
Oedema			

subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	0		
Neuropathy			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	31 / 46 (67.39%)		
occurrences (all)	0		
Hand foot syndrome			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Leucopenia			
subjects affected / exposed	39 / 46 (84.78%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	40 / 46 (86.96%)		
occurrences (all)	0		
Anemia			
subjects affected / exposed	43 / 46 (93.48%)		
occurrences (all)	0		
Thrombocytopenia			
subjects affected / exposed	37 / 46 (80.43%)		
occurrences (all)	0		
Hyperglycemia			
subjects affected / exposed	38 / 46 (82.61%)		
occurrences (all)	0		
hypercholesterolemia			
subjects affected / exposed	27 / 46 (58.70%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	16 / 46 (34.78%)		
occurrences (all)	0		
Vomiting			

subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	0		
Mucositis management			
subjects affected / exposed	13 / 46 (28.26%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	11 / 46 (23.91%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 46 (13.04%)		
occurrences (all)	0		
Dyspnea			
subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	14 / 46 (30.43%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	12 / 46 (26.09%)		
occurrences (all)	0		
Acnea			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2010	Precision concerning inclusion and exclusion criteria.
14 April 2011	Prolongation of the trial

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported