Clinical trial results:
Safety and efficacy phase I/IIa trial of an RNActive®-derived cancer vaccine in stage IIIB/IV non small cell lung cancer (NSCLC)

Summary

EudraCT number	2008-007785-39
Trial protocol	DE
Global end of trial date	25 February 2014

Results information

Result version number	v1 (current)
This version publication date	21 July 2016
First version publication date	21 July 2016

Trial information

Trial identification

Sponsor protocol code	CV-9201-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00923312
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CureVac AG
Sponsor organisation address	Paul-Ehrlich-Str. 15, Tübingen, Germany, 72076
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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	06 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2014
Global end of trial reached?	Yes
Global end of trial date	25 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I part:
Primary: Determination of recommended dose (RD) for exploration in the phase IIa part of the study.
Secondary: Assessment of safety of the treatment regimen, evaluation of induction of immune response, and assessment of antitumor activity

Phase IIa part:
Primary: Assessment of safety and tolerability of the treatment regimen
Secondary: Evaluation of induction of immune response, assessment of antitumor activity, correlation between tumor-associated antigen (TAA) expression and survival, progression, and/or immunological response.

Protection of trial subjects:

Throughout Phase I, information regarding any serious adverse event (SAE) and potential dose-limiting toxicity (DLT) was sent to the Cohort Review Committee (CRC) on a continuous basis. After completion of each cohort in Phase I, the CRC evaluated safety data and made the decision on whether to open the study to the next dose level. Patient data were evaluated for the occurrence of a DLT in order to ascertain the recommended dose (RD) for Phase IIa. The investigator was responsible for reporting all adverse events (AE) observed or described by the patient, regardless of their relatedness to study drug or clinical significance.
Vaccinations were administered on an out-patient basis. During Phase I, patients were monitored for 6 hours following the administration of each vaccination. Vital signs had to have returned to pre-vaccination values before the patient was released. Patients were monitored at hospitals for these 6 hours with an emergency team and equipment available in case of any hypersensitivity reactions or any other medical problems. In the phase IIa part of the trial, patients were monitored at the study site up to the time when vital signs had returned to pre-vaccination values, but at least for 2 hours. If patients experienced AEs related to study drug it was at the discretion of the investigator to extend the on-site monitoring.
One of the potential risks of vaccination was the induction of autoimmune disease. As a precaution, special monitoring for autoimmunity was implemented.
In addition, patients with a documented history of active autoimmune disorders requiring systemic immunosuppressive therapy (except stabilized autoimmune thyroiditis) were excluded from this trial.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	30 June 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Switzerland: 14
Worldwide total number of subjects	46
EEA total number of subjects	32

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)	22
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 46 patients were enrolled between 30 June 2009 and 26 January 2011. 9 patients were enrolled into the dose-finding Phase I part, with 3 patients in each cohort. 37 patients were enrolled into the Phase IIa part at the recommended dose.
Twelve investigational centers each enrolled at least 1 patient (Germany: 10; Switzerland: 2).

Pre-assignment

Screening details:

Stage IIIB/IV NSCLC, life expectancy > 6 m., ECOG 0 – 1. Stable disease or objective response according to RECIST 1.0, after initial chemotherapy, or chemo-radiotherapy for advanced, unresectable disease. Cancer therapies to be completed 4 weeks prior to study treatment. Age 18-75 y. Adequate organ function: bone marrow, hepatic, renal, cardiac

Pre-assignment period milestones

Number of subjects started	55[1]
Number of subjects completed	46

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Progression of Disease: 2
Reason: Number of subjects	Brain metastases: 2
Reason: Number of subjects	Low lymphocytes: 3
Reason: Number of subjects	Consent withdrawn by subject: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 55 subjects were screened and 9 dropped out before start of treatment. 46 were treated/enrolled.

Period 1

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

Blinding implementation details:

This was an open-label Phase I/IIa study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I - Cohort I

Arm description:

Patients in cohort I received the lowest dose level (400 µg mRNA per vaccination time point).

Arm type	Verum
Investigational medicinal product name	CV9201
Investigational medicinal product code	CV9201
Other name	messenger ribonucleic acid (mRNA)
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Dosage: 400 µg mRNA (80 µg of each of five components of CV9201) per vaccination time point (= Dose Level I)
Administration in Phase I: Each component was given separately as one intradermal injection, i.e. five intradermal injections were performed per vaccination time point in weeks 1, 3, 7, 11, and 15.

Arm title	Phase I - Cohort II

Arm description:

Patients in cohort II received the mid dose level (800 µg mRNA per vaccination time point).

Arm type	Verum
Investigational medicinal product name	CV9201
Investigational medicinal product code	CV9201
Other name	messenger ribonucleic acid (mRNA)
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Dosage: 800 µg mRNA (160 µg of each of five components of CV9201) per vaccination time point (= Dose Level II)
Administration in Phase I: Each component was given separately as one intradermal injection, i.e. five intradermal injections were performed per vaccination time point in weeks 1, 3, 7, 11, and 15.

Arm title	Phase I - Cohort III

Arm description:

Patients in cohort III received the highest dose level (1600 µg mRNA per vaccination time point, which is equivalent to the recommended dose).

Arm type	Verum
Investigational medicinal product name	CV9201
Investigational medicinal product code	CV9201
Other name	messenger ribonucleic acid (mRNA)
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Dosage: 1600 µg mRNA (320 µg of each of five components of CV9201) per vaccination time point (= Dose Level III)
Administration in Phase I: Each component was given separately as one intradermal injection, i.e. five intradermal injections were performed per vaccination time point in weeks 1, 3, 7, 11, and 15.

Arm title	Phase IIa

Arm description:

Patients in Phase IIa were treated with the recommended dose level of CV9201 (1600 µg mRNA per vaccination time point).

Arm type	Verum
Investigational medicinal product name	CV9201
Investigational medicinal product code	CV9201
Other name	messenger ribonucleic acid (mRNA)
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Dosage: 1600 µg mRNA (320 µg of each of five components of CV9201) per vaccination time point (This was the Recommended Dose determined during dose-finding Phase I part of the study.)
Administration in Phase IIa: Each component was given separately as two intradermal injections, i.e. ten intradermal injections were performed per vaccination time point in weeks 1, 2, 3, 5 and 7.

Number of subjects in period 1	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III
Started	3	3	3
Treatment period completed	1	1	1
Completed	1	1	1
Not completed	2	2	2
Consent withdrawn by subject	-	-	-
Progression of Disease	2	2	2
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Phase IIa
Started	37
Treatment period completed	30
Completed	30
Not completed	7
Consent withdrawn by subject	1
Progression of Disease	5
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Phase I - Cohort I
Reporting group description:	
Patients in cohort I received the lowest dose level (400 µg mRNA per vaccination time point).	
Reporting group title	Phase I - Cohort II
Reporting group description:	
Patients in cohort II received the mid dose level (800 µg mRNA per vaccination time point).	
Reporting group title	Phase I - Cohort III
Reporting group description:	
Patients in cohort III received the highest dose level (1600 µg mRNA per vaccination time point, which is equivalent to the recommended dose).	
Reporting group title	Phase IIa
Reporting group description:	
Patients in Phase IIa were treated with the recommended dose level of CV9201 (1600 µg mRNA per vaccination time point).	

Reporting group values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III
Number of subjects	3	3	3
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	2	1
From 65-84 years	2	1	2
85 years and over	0	0	0
Age continuous Units: years			
median	81	60	66
full range (min-max)	61 to 83	56 to 72	52 to 69
Gender categorical Units: Subjects			
Female	0	0	2
Male	3	3	1
NSCLC Stage at Study Entry Units: Subjects			
IIIB	1	1	0
IV	2	2	3
Histology of tumor Units: Subjects			
Adenocarcinoma	2	2	1
Squamous	1	1	1
Large Cell	0	0	0

Mixed	0	0	1
Not recorded	0	0	0
Race Units: Subjects			
Caucasian	3	3	3
ECOG score Units: Subjects			
ECOG 0	2	1	3
ECOG 1	1	2	0
ECOG 2	0	0	0
Previous Treatment for NSCLC Units: Subjects			
Previous oncologic Treatment	3	3	3

Reporting group values	Phase IIa	Total	
Number of subjects	37	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)	18	22	
From 65-84 years	19	24	
85 years and over	0	0	
Age continuous Units: years			
median	65		
full range (min-max)	38 to 79	-	
Gender categorical Units: Subjects			
Female	15	17	
Male	22	29	
NSCLC Stage at Study Entry Units: Subjects			
IIIB	5	7	
IV	32	39	
Histology of tumor Units: Subjects			
Adenocarcinoma	22	27	
Squamous	10	13	
Large Cell	3	3	
Mixed	1	2	
Not recorded	1	1	
Race Units: Subjects			
Caucasian	37	46	
ECOG score			

Units: Subjects			
ECOG 0	20	26	
ECOG 1	16	19	
ECOG 2	1	1	
Previous Treatment for NSCLC Units: Subjects			
Previous oncologic Treatment	37	46	

End points

End points reporting groups

Reporting group title	Phase I - Cohort I
Reporting group description:	
Patients in cohort I received the lowest dose level (400 µg mRNA per vaccination time point).	
Reporting group title	Phase I - Cohort II
Reporting group description:	
Patients in cohort II received the mid dose level (800 µg mRNA per vaccination time point).	
Reporting group title	Phase I - Cohort III
Reporting group description:	
Patients in cohort III received the highest dose level (1600 µg mRNA per vaccination time point, which is equivalent to the recommended dose).	
Reporting group title	Phase IIa
Reporting group description:	
Patients in Phase IIa were treated with the recommended dose level of CV9201 (1600 µg mRNA per vaccination time point).	
Subject analysis set title	Treated Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The treated Population comprises all patients who received any study vaccinations.	
Subject analysis set title	Evaluable Population for Determination of Recommended Dose
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who received the planned treatment up to week 3 and were followed up to week 5, or who experienced a DLT until the week 5 visit.	
Subject analysis set title	Evaluable Population for Immune Response
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who received treatment at least up to week 7 and underwent tumor specific immune assessment at baseline and after week 7, or demonstrated prior immune response.	
Subject analysis set title	Evaluable Population for Tumor Marker Response
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who received treatment at least up to week 7 and underwent tumor marker assessment at baseline, and at end of treatment were considered evaluable for tumor marker response.	
Subject analysis set title	Evaluable Population for RECIST Response
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with measurable disease according to RECIST who underwent a disease assessment within 4 weeks prior to treatment initiation and at least once during study, and those who discontinued early due to disease progression.	

Primary: Phase I Secondary: Occurrence of a Dose Limiting Toxicity (DLT)

End point title	Phase I Secondary: Occurrence of a Dose Limiting Toxicity (DLT)[1][2]
End point description:	
Primary endpoint was the occurrence of a Dose Limiting Toxicity (DLT) between treatment initiation and the Week 5 visit in patients evaluable for determination of the recommended dose. A DLT was defined as one of the following NCI-CTCAE graded treatment-related events: grade 3 and/or 4 neutropenia with fever and/or infection, a non-hematological toxicity ≥ grade 3, an autoimmunity/allergy ≥ grade 2, or a dosing delay > 48 hours due to toxicity.	
End point type	Primary

End point timeframe:

From treatment initiation and the Week 5 visit.

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: No statistical Analysis has been done. Only descriptive.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical Analysis has been done. Only descriptive.

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Evaluable Population for Determination of Recommended Dose
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	3	3	3	9
Units: dose limiting toxicity	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Primary/Phase I Secondary: Treatment-related adverse events (AEs) and laboratory abnormalities

End point title	Phase II Primary/Phase I Secondary: Treatment-related adverse events (AEs) and laboratory abnormalities[3]

End point description:

Primary safety endpoint for Phase IIa and secondary safety endpoint for Phase I:
• Incidence and severity of treatment-related AEs and laboratory abnormalities, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 3.0 criteria

End point type	Primary

End point timeframe:

• Treatment related AEs/SAEs were to be reported from Baseline until 30 days after last vaccination
• Laboratory Parameters were assessed from Baseline until Week 26

Notes:

[3] - 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: No statistical Analysis has been done. Only descriptive.

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Phase IIa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	37
Units: Treatment related AEs	18	24	76	543

End point values	Treated Population			

Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Treatment related AEs	661			

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Primary/Phase I Secondary: Occurrence of serious AEs

End point title	Phase II Primary/Phase I Secondary: Occurrence of serious

End point description:

Primary safety endpoint for Phase IIa and secondary safety endpoint for Phase I: Occurrence of serious AEs

End point type	Primary

End point timeframe:

AEs were reported from the time the patient signed the ICF through 30 days after the last vaccination. Treatment-related AEs were to be reported up to Week 52.

Notes:

[4] - 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: No statistical Analysis has been done. Only descriptive.

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Phase IIa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	37
Units: Total Number of SAEs in all subjects				
Grade 1	0	0	0	0
Grade 2	0	1	0	2
Grade 3	0	0	0	4
Grade 4	0	0	0	2
Grade 5	0	0	0	3

End point values	Treated Population			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Total Number of SAEs in all subjects				
Grade 1	0			
Grade 2	3			
Grade 3	4			
Grade 4	2			
Grade 5	3			

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Primary/Phase I Secondary: Occurrence of treatment discontinuation due to AEs

End point title	Phase II Primary/Phase I Secondary: Occurrence of treatment discontinuation due to AEs[5]

End point description:

Primary safety endpoint for Phase IIa and secondary safety endpoint for Phase I

End point type	Primary

End point timeframe:

AEs were reported from the time the patient signed the ICF through 30 days after the last vaccination.

Notes:

[5] - 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: No statistical Analysis has been done. Only descriptive.

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Phase IIa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	37
Units: Subjects who discontinued because of AE	2	1	1	2

End point values	Treated Population			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Subjects who discontinued because of AE	6			

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Primary/Phase I Secondary: Incidence of development of autoimmune antibodies

End point title	Phase II Primary/Phase I Secondary: Incidence of development of autoimmune antibodies[6]

End point description:

Primary safety endpoint for Phase IIa and secondary safety endpoint for Phase I. Patients with a shift of parameters from normal at baseline to abnormal during the study were assessed.

End point type	Primary

End point timeframe:

Autoimmune antibodies were assessed at Baseline, Week 5 and Week 26.

Notes:

[6] - 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: No statistical Analysis has been done. Only descriptive.

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Phase IIa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	37
Units: Subj. with shift in parameters				
Rheumatoid factor	0	1	0	3
TSH	0	2	1	6
Antithyroglobuline	0	0	0	4
Anti-Nuclear Antibodies	0	0	1	4
Anti-Smooth Muscle Antibodies	0	0	0	0

End point values	Treated Population			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Subj. with shift in parameters				
Rheumatoid factor	4			
TSH	9			
Antithyroglobuline	4			
Anti-Nuclear Antibodies	5			
Anti-Smooth Muscle Antibodies	0			

Statistical analyses

No statistical analyses for this end point

Primary: Phase II Primary/Phase I Secondary: Incidence of treatment-emergent autoimmune disease

End point title	Phase II Primary/Phase I Secondary: Incidence of treatment-emergent autoimmune disease[7]

End point description:

Primary safety endpoint for Phase IIa and secondary safety endpoint for Phase I: Incidence of treatment-emergent autoimmune disease.

End point type	Primary

End point timeframe:

AEs were reported from the time the patient signed the ICF through 30 days after last vaccination. Treatment-related AEs were to be reported up to Week 52.

Notes:

[7] - 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: No statistical Analysis has been done. Only descriptive.

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Phase IIa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	37
Units: Subjects with out-of-range values				
ANA increased	0	0	1	2
TSH increased	0	0	0	1

Hypothyroidism	0	0	0	1

End point values	Treated Population			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Subjects with out-of-range values				
ANA increased	3			
TSH increased	1			
Hypothyroidism	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I/Phase II: Objective disease response in patients evaluable for RECIST response

End point title	Phase I/Phase II: Objective disease response in patients evaluable for RECIST response

End point description:

Objective disease Response was assessed in patients evaluable for RECIST response i.e. those patients who underwent a baseline disease assessment within 4 weeks prior to treatment initiation, and had at least one disease assessment on study.

End point type	Secondary

End point timeframe:

Objective disease response until Week 52

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Phase IIa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	21
Units: Subjects				
Response	0	0	0	0

End point values	Evaluable Population for RECIST Response			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Subjects				
Response	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I/Phase II: Progression-free survival

End point title	Phase I/Phase II: Progression-free survival

End point description:

The progression-free survival was defined as: (a) the interval from the date of first vaccination and the date of death or progression, whichever came first, and (b) the interval from the date of initiation of initial chemotherapy and the date of death or progression, whichever came first. The PFS of the patients who had not progressed was censored at Week 52.

End point type	Secondary

End point timeframe:

a) From Initiation of vaccine until Week 52
b) From Initiation of initial chemotherapy until Week 52

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Phase IIa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	37[8]
Units: Median time (months)				
median (confidence interval 95%)				
a) From Initiation of vaccine until Week 52	2.1 (1.2 to 12.2)	2.5 (1.5 to 6.3)	2.3 (0.5 to 3.3)	5 (1.8 to 6.3)
b) From Initiation of initial chemotherapy until W	9 (6 to 39.8)	5.7 (5.7 to 16.7)	7.1 (4.7 to 7.1)	10.3 (8 to 11.2)

Notes:

[8] - a) Number of subjects: 37
b) Number of subjects: 36

End point values	Treated Population			
Subject group type	Subject analysis set			
Number of subjects analysed	46[9]			
Units: Median time (months)				
median (confidence interval 95%)				
a) From Initiation of vaccine until Week 52	2.7 (1.9 to 5.8)			
b) From Initiation of initial chemotherapy until W	10 (7.1 to 10.9)			

Notes:

[9] - a) Number of subjects: 46
b) Number of subjects: 45

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I/Phase II: CEA/CYFRA 21-1 tumor marker levels

End point title	Phase I/Phase II: CEA/CYFRA 21-1 tumor marker levels

End point description:

Evaluation of changes in CEA and CYFRA 21-1 tumor marker levels during the course of treatment was summarized. Number of patients with a maximum change by 10% or more from baseline.

End point type	Secondary

End point timeframe:

Samples were taken at baseline, Week 11 (in Phase I only), at EOT, and during the Follow-up period at the Week 26 and Week 52 visits.

End point values	Evaluable Population for Tumor Marker Response			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: Subjetcs				
a) CEA: Increasing Tumor Marker ≥ 10%	16			
b) CEA: Stable Tumor Marker	7			
c) CEA: Decreasing Tumor Marker ≥ 10%	15			
d) CYFRA 21-1: Increasing Tumor Marker ≥ 10%	25			
e) CYFRA 21-1: Stable Tumor Marker	7			
f) CYFRA 21-1: Decreasing Tumor Marker ≥ 10%	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I/Phase II: Evaluation of influence of tumor-associated antigen expression in tumor specimens on survival/progression/immunological response

End point title	Phase I/Phase II: Evaluation of influence of tumor-associated antigen expression in tumor specimens on survival/progression/immunological response

End point description:

Correlations were made between tumor-associated antigen (TAA) expression of each antigen and survival, progression, and immunological response.

End point type	Secondary

End point timeframe:

Pre-treatment until end of follow-up period (week 52).

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Phase IIa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	30
Units: occurrence of variables per patient	2	3	3	30

End point values	Evaluable Population for Tumor Marker Response			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: occurrence of variables per patient	38			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I/Phase II: Proportion of patients with vaccine antigen-specific cellular and humoral immune response

End point title	Phase I/Phase II: Proportion of patients with vaccine antigen-specific cellular and humoral immune response

End point description:

Proportion of patients with vaccine antigen-specific cellular and humoral immune response (ELISpot, ICS tetramer, and ELISA assessment of immune reaction to vaccine antigens) was evaluated.

End point type	Secondary

End point timeframe:

At Weeks 5 and 9 (Phase I only), and at end of treatment, compared to baseline.

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Phase IIa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	31
Units: Overall immune response	2	2	0	20

End point values	Evaluable Population for Immune Response			

Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: Overall immune response	24			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I/Phase II: Regulatory T-cell levels

End point title	Phase I/Phase II: Regulatory T-cell levels

End point description:

Evolution of regulatory T cell levels in peripheral blood during the course of treatment.

End point type	Secondary

End point timeframe:

At Weeks 5 and 9 (Phase I only), and at end of treatment, compared to baseline.

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Phase IIa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	3	31
Units: Subjects with change in Tregs				
1 time point increased	0	1	1	8
2 time points increased	0	1	0	7
3 time points increased	1	0	0	0
1 time point decreased	0	2	1	9
2 time points decreased	0	1	2	14
3 time points decreased	1	0	0	0

End point values	Evaluable Population for Immune Response			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: Subjects with change in Tregs				
1 time point increased	10			
2 time points increased	8			
3 time points increased	1			
1 time point decreased	12			
2 time points decreased	17			
3 time points decreased	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase I/Phase II: Overall Survival

End point title	Phase I/Phase II: Overall Survival

End point description:

Overall survival was measured from initiation of vaccine and from initiation of initial chemotherapy until either death or last follow-up at Week 52 or Week 52 + 2 years.

End point type	Secondary

End point timeframe:

from a) initiation of vaccine and from b) initiation of initial chemotherapy
until either Week 52 or Week 52 + 2 years

End point values	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III	Phase IIa
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	37[10]
Units: Median time (months)				
median (confidence interval 95%)				
a) from initiation of vaccine	34.8 (5.5 to 38.2)	7.4 (6.1 to 12.2)	18.8 (12.5 to 35.2)	10.8 (8.1 to 16.7)
b) from initiation of initial chemotherapy	39.6 (12.4 to 65.8)	16.4 (9.3 to 17.8)	23 (16.3 to 40)	17.2 (13.6 to 23.4)

Notes:

[10] - a) Number of subjects: 37
b) Number of subjects: 36

End point values	Treated Population			
Subject group type	Subject analysis set			
Number of subjects analysed	46[11]			
Units: Median time (months)				
median (confidence interval 95%)				
a) from initiation of vaccine	11.5 (8.5 to 18.8)			
b) from initiation of initial chemotherapy	18.8 (14.2 to 25.7)			

Notes:

[11] - a) Number of subjects: 46
b) Number of subjects: 45

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

52 weeks, at the following visits, Phase I: week 1, 3, 5, 7, 9, 11, 15, 2 weeks post last treatment, 26, 52; Phase II: week 1, 2, 3, 5, 7, 2 weeks post last treatment, 26, 52

Adverse event reporting additional description:

AEs were determined at each visit incl. EOT visit up to 30 days post last injection; at Week 26 and 52 only those considered related to study drug. During the follow-up period, all treatment-related AEs were followed until resolution. Those occurring between the EOT visit and Week 52 were documented only if treatment-related.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12

Reporting groups

Reporting group title	Phase I - Cohort I

Reporting group description:

Patients receiving 400 µg of CV9201 at week 1, 3, 5, 7, 9, 11, 15

Reporting group title	Phase I - Cohort II

Reporting group description:

Patients receiving 800 µg of CV9201 at week 1, 3, 5, 7, 9, 11, 15

Reporting group title	Phase I - Cohort III

Reporting group description:

Patients receiving 1600 µg of CV9201 at week 1, 3, 5, 7, 9, 11, 15

Reporting group title	Phase IIa-recommended dose

Reporting group description:

Patients receiving 1600 µg of CV9201 at week 1, 2, 3, 5, 7

Serious adverse events	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial tachycardia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic Infection			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase IIa-recommended dose		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 37 (16.22%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial tachycardia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Musculoskeletal and connective tissue disorders			

Bone Pain			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic Shock			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Neutropenic Infection			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Phase I - Cohort I	Phase I - Cohort II	Phase I - Cohort III
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
General disorders and administration			

site conditions			
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Chills			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	1	1	1
Injection site erythema			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
occurrences (all)	16	19	57
Injection site hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Injection site pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	3
Injection site discoloration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Disease progression			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Feeling cold			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Dysphonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	9
Dyspnea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Investigations			
Heart rate irregular			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Antinuclear antibody increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	12

Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Erythema of eyelid			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	3
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Hyperhydrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gangrene			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Phase IIa-recommended dose		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 37 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Surgical and medical procedures			

Tooth extraction			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	5		
Chills			
subjects affected / exposed	7 / 37 (18.92%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	12 / 37 (32.43%)		
occurrences (all)	22		
Injection site erythema			
subjects affected / exposed	28 / 37 (75.68%)		
occurrences (all)	350		
Injection site hypersensitivity			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	8		
Injection site pruritus			
subjects affected / exposed	9 / 37 (24.32%)		
occurrences (all)	39		
Pyrexia			
subjects affected / exposed	9 / 37 (24.32%)		
occurrences (all)	18		
Injection site discoloration			
subjects affected / exposed	6 / 37 (16.22%)		
occurrences (all)	24		
Disease progression			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
Asthenia			

subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Feeling cold			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Injection site swelling			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Dysphonia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Dyspnea			
subjects affected / exposed	5 / 37 (13.51%)		
occurrences (all)	6		
Investigations			
Heart rate irregular			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
Antinuclear antibody increased			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 37 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	6 / 37 (16.22%) 11 3 / 37 (8.11%) 3 0 / 37 (0.00%) 0 2 / 37 (5.41%) 2		
Blood and lymphatic system disorders Eosinophilia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0 2 / 37 (5.41%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	5 / 37 (13.51%) 5		
Eye disorders Erythema of eyelid subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0 3 / 37 (8.11%) 3 2 / 37 (5.41%) 2		

Nausea subjects affected / exposed occurrences (all)	10 / 37 (27.03%) 11		
Vomiting subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 3		
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3		
Diarrhoea subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3		
Skin and subcutaneous tissue disorders Hyperhydrosis subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 6		
Erythema subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Night sweats subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 3		
Pruritus subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Rash subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		

Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 4 4 / 37 (10.81%) 4 3 / 37 (8.11%) 3 2 / 37 (5.41%) 2		
Infections and infestations Gangrene subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0 4 / 37 (10.81%) 4 2 / 37 (5.41%) 2		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2009	Protocol Amendment 1 was generated to ensure compliance with several deficiency requests received from the Paul-Ehrlich-Institute upon their review of the Initial Clinical Trial Application. One exclusion criteria had to be modified to exclude patients with any kind of brain metastases (symptomatic or asymptomatic). The patient observation after administration of each vaccination had to be described and it had to be specified that all treated patients, also those whose treatment was prematurely stopped, would be followed until Week 52. The stopping rules for the entire trial were added to the protocol and defined to be: ≥ 2 DLTs out of 2 to 6 patients in the first dose level (DL); unacceptable toxicity; new available data which may have led to a negative benefit risk assessment; and unsatisfactory enrollment. Also, the role of the Data Safety Monitoring Board (DSMB) was further defined and included decision-making authority for stopping the trial. It was defined that Phase I safety data had to be submitted to the German authority to decide on start of the Phase IIa part of the study. In addition to the changes resulting from the deficiency request, the recall skin test was removed due to the limited sensitivity of this assay, the urine pregnancy test was replaced by a serum pregnancy test, and an additional safety laboratory was added to the Week 26 visit. Amendment 1 was only submitted in Germany.
06 August 2009	Protocol Amendment 2 was generated following discussion with the German Authority and included changes to the Inclusion and Exclusion Criteria and further clarification of the safety and efficacy assessments. The DSMB was renamed to CRC (Cohort Review Committee). The CRC as the new name was better aligned with the role of the committee in this study, and was a more common and accepted name for this type of oncology Phase I/IIa study. The exclusion criteria that were removed included the presence of mild allergy requiring seasonal (non-steroidal) medication, treatment of controlled pleural effusion by puncture, and specific radiation doses for tumor treatment. Patients with known brain metastasis and those who were > 75 years of age were to be excluded. If a patient was hospitalized for disease progression, this was no longer to be considered an AE or SAE. Amendment 2 was not submitted. Amendment 1 and 2 were combined to Amendment 3 and submitted in Germany and Switzerland.
24 September 2009	Protocol Amendment 3 included the list of changes noted previously for Protocol Amendment 1 (required by the German Regulatory Authority, only implemented in Germany), and Protocol Amendment 2. Amendment 3 was submitted to the Swiss and German Regulatory Authority. The exclusion criteria that were removed included the presence of mild allergy requiring seasonal (non-steroidal) medication, treatment of controlled pleural effusion by puncture, and specific radiation doses for tumor treatment. Patients with brain metastases and those who were > 75 years of age were to be excluded. If a patient was hospitalized for disease progression, this was no longer to be considered an AE or SAE. The DSMB was renamed to the CRC as the new name was better aligned with the role of the committee in this study, and was a more common and accepted name for this type of oncology Phase I/IIa study.

25 May 2010	Protocol Amendment 4 was implemented prior to starting Phase IIa. The duration of treatment with CV9201 was shortened to 7 weeks (Weeks 1, 2, 3, 5, and 7) leading to more frequent vaccinations in order to induce an immune response as quickly as possible since a considerable amount of time appears to be necessary to establish a persistent immune response. The CV9201 vaccine, which had been administered at the same location at each vaccination visit during Phase I, was now to be administered using an alternating pattern. CV9201 was to be applied intradermally into the thigh and upper arm of either side (4 sites in total) with each drug product component administered in 2 injections per treatment day, one into the thigh and one into the upper arm of the same side. The injection site for each component was to be alternating between the body halves for different treatment days. The rationale for this was that choosing 2 different injection sites per antigen should increase the number of lymph nodes exposed to the vaccine. Since recent preclinical results suggested that the immune response positively correlated with the number of lymph nodes being exposed to the vaccine, it was expected that this would contribute to efficacy. Prior to this preclinical data, this hypothesis was only supported in the published medical literature. The Phase IIa Week 5 procedures were revised to include autoimmunity assessments and blood sampling for immune response monitoring. Post vaccination monitoring was reduced to at least 2 hours at the study site, due to the good tolerability shown in Phase I. Patients who had progressive disease, and therefore needed other anticancer treatment (e.g., chemo- or radiotherapy), were no longer to be discontinued from the study. Patients were still prohibited from receiving treatment with other biological anti-cancer agents and/or cancer vaccines.
19 April 2011	Protocol Amendment 5 was implemented to prolong the Survival Follow-Up period to 2 years and to include additional plasma testing on previously collected blood samples, that would allow judging the immune response to CV9201 more explicitly. Testing was for antibodies against other tumor specific antigens, vaccine specific antibody responses, and the induction of epitope spreading.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported