# 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 |
| Public contact | Dr. med. Ulrike Gnad-Vogt, CureVac AG, +49 707198830, info@curevac.com |
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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<br>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<br>Units: years | | | |
| median | 81 | 60 | 66 |
| full range (min-max) | 61 to 83 | 56 to 72 | 52 to 69 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | 2 |
| Male | 3 | 3 | 1 |
| NSCLC Stage at Study Entry<br>Units: Subjects | | | |
| IIIB | 1 | 1 | 0 |
| IV | 2 | 2 | 3 |
| Histology of tumor<br>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<br>Units: Subjects | | | |
| Caucasian | 3 | 3 | 3 |
| ECOG score<br>Units: Subjects | | | |
| ECOG 0 | 2 | 1 | 3 |
| ECOG 1 | 1 | 2 | 0 |
| ECOG 2 | 0 | 0 | 0 |
| Previous Treatment for NSCLC<br>Units: Subjects | | | |
| Previous oncologic Treatment | 3 | 3 | 3 |

| **Reporting group values** | Phase IIa | Total | |
|---|---|---|---|
| Number of subjects | 37 | 46 | |
| Age categorical<br>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<br>Units: years | | | |
| median | 65 | | |
| full range (min-max) | 38 to 79 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 15 | 17 | |
| Male | 22 | 29 | |
| NSCLC Stage at Study Entry<br>Units: Subjects | | | |
| IIIB | 5 | 7 | |
| IV | 32 | 39 | |
| Histology of tumor<br>Units: Subjects | | | |
| Adenocarcinoma | 22 | 27 | |
| Squamous | 10 | 13 | |
| Large Cell | 3 | 3 | |
| Mixed | 1 | 2 | |
| Not recorded | 1 | 1 | |
| Race<br>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<br>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<br>subjects affected / exposed<br>occurrences (all)<br><br>Paraesthesia<br>subjects affected / exposed<br>occurrences (all)<br><br>Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all) | 6 / 37 (16.22%)<br>11<br><br>3 / 37 (8.11%)<br>3<br><br>0 / 37 (0.00%)<br>0<br><br>2 / 37 (5.41%)<br>2 | | |
| Blood and lymphatic system disorders<br>Eosinophilia<br>subjects affected / exposed<br>occurrences (all)<br><br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 37 (0.00%)<br>0<br><br>2 / 37 (5.41%)<br>2 | | |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all) | 5 / 37 (13.51%)<br>5 | | |
| Eye disorders<br>Erythema of eyelid<br>subjects affected / exposed<br>occurrences (all) | 0 / 37 (0.00%)<br>0 | | |
| Gastrointestinal disorders<br>Abdominal distension<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all) | 0 / 37 (0.00%)<br>0<br><br>3 / 37 (8.11%)<br>3<br><br>2 / 37 (5.41%)<br>2 | | |

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

| | | | |
|---|---|---|---|
| Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all)<br><br>Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all) | 3 / 37 (8.11%)<br>4<br><br>4 / 37 (10.81%)<br>4<br><br>3 / 37 (8.11%)<br>3<br><br>2 / 37 (5.41%)<br>2 | | |
| Infections and infestations<br>Gangrene<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Bronchitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 37 (0.00%)<br>0<br><br>4 / 37 (10.81%)<br>4<br><br>2 / 37 (5.41%)<br>2 | | |
| Metabolism and nutrition disorders<br>Anorexia<br>subjects affected / exposed<br>occurrences (all) | 4 / 37 (10.81%)<br>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.<br>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.<br>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.<br>If a patient was hospitalized for disease progression, this was no longer to be considered an AE or SAE.<br>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.<br>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.<br>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<br>hypothesis was only supported in the published medical literature.<br>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.<br>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