



## Clinical trial results:

### Abscopal Effect of Radiotherapy and Nivolumab in anti-PD1 Pretreated Relapsed or Refractory classical Hodgkin Lymphoma - An international multicenter Phase II trial

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2017-003334-82 |
| Trial protocol           | DE NO NL AT    |
| Global end of trial date | 04 May 2024    |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 21 May 2025  |
| First version publication date | 21 May 2025  |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | Uni-Koeln-3140 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03480334 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | University of Cologne   |
| Sponsor organisation address | Albertus-Magnus-Platz , Cologne, Germany, 50923   |
| Public contact               | German Hodgkin Study Group (GHSG), Trial Coordination Center, +49 22147888200, ghsg@uk-koeln.de |
| Scientific contact           | German Hodgkin Study Group (GHSG), Trial Coordination Center, +49 22147888200, ghsg@uk-koeln.de |

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                       | 01 November 2024 |
| Is this the analysis of the primary completion data? | No               |

|                                  |             |
|----------------------------------|-------------|
| Global end of trial reached?     | Yes         |
| Global end of trial date         | 04 May 2024 |
| Was the trial ended prematurely? | Yes         |

Notes:

## General information about the trial

Main objective of the trial:

The primary aim of this international, prospective, multicenter phase II proof-of-concept trial is to demonstrate the efficacy of the experimental treatment strategy. The combination of immune checkpoint inhibition with nivolumab and immunogenic radiotherapy is expected to act synergistically, offering a well-tolerated and effective therapeutic approach in patients with relapsed or refractory Hodgkin lymphoma previously treated with an anti-pD1 antibody. The study is specifically designed to assess the abscopal effect of localized radiotherapy directed at a single lesion.

Protection of trial subjects:

Participants give their written informed consent to participate in the trial. They may discontinue trial treatment at any time at their own request. Protocol treatment must be stopped in the event of pregnancy in a female participant, unless re-consent for continuation is obtained. Treatment may also be terminated at the discretion of the treating physician in cases of unacceptable toxicity, disease progression (PD), or serious comorbid conditions.

Early termination of the entire trial may be initiated by the trial chairman if:

- the formal stopping criterion regarding the primary endpoint is met,
- participant safety is at risk,
- the risk-benefit ratio for patients changes significantly,
- the trial medication can no longer be justifiably used,
- the sponsor (represented by the trial chairman) deems discontinuation necessary for safety reasons,
- the trial proves unfeasible due to low recruitment or major shifts in the treatment landscape or sequencing for relapsed/refractory Hodgkin lymphoma (rrHL).

An independent Data Monitoring Committee (DMC) oversees trial progress and patient safety. The GHSG Trial Coordination Center ensures that the DMC receives all necessary information. Regular safety analyses are conducted for all patients (FAS) to monitor:

- Study eligibility,
- Disease progression, relapse, and mortality during and after treatment,
- Adverse events (AEs) and serious adverse events (SAEs).
- Cases of early treatment discontinuation are documented and analyzed for safety assessment and to identify patients who may need to be replaced in the Abscopal Response Analysis Set (ARAS).

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 05 December 2019 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety           |
| Long term follow-up duration                              | 1 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | Norway: 2      |
| Country: Number of subjects enrolled | Austria: 5     |
| Country: Number of subjects enrolled | Germany: 15    |
| Worldwide total number of subjects   | 26             |
| EEA total number of subjects         | 26             |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                      | 20 |
| From 65 to 84 years                       | 5  |
| 85 years and over                         | 1  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 26 patients were enrolled at 15 European sites before the trial was closed to recruitment on September 30, 2023. Originally, 29 evaluable patients were planned, but after positive interim results and changes in clinical practice during the COVID-19 pandemic, recruitment slowed considerably.

### Pre-assignment

Screening details:

1 patient had a screening failure and could not be included in the trial

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Stage-2 (overall period)    |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|           |         |
|-----------|---------|
| Arm title | Stage-2 |
|-----------|---------|

Arm description:

This trial is a single-arm two-stage phase II study.

|  |  |
|--|--|
| Arm type                               | single-arm                                   |
| Investigational medicinal product name | Nivolumab                                    |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder and solvent for solution for infusion |
| Routes of administration               | Intravenous use                              |

Dosage and administration details:

Therapy began as soon as possible after the patient has been enrolled and preferably started on a Wednesday (w1d1) to allow timely initiation of RT on day 6 of treatment week 1 (w1d6). Patients received 240 mg nivolumab i.v. in 2-weekly intervals usually in an outpatient setting. The first infusion was administered over 60 minutes while consecutive infusions were administered over 30 minutes if no infusion related reaction was observed. Subjects were dosed no less than 12 days from the previous dose of drug and subsequent infusions should not have been delayed unnecessarily or without medical reasons. The patient should have been observed for 60 minutes following the first infusion of nivolumab. During this observation period, the i.v. line should have remained patent to allow administration of i.v. drugs if necessary. In case an infusion-related reaction have occurred after reduction to 30 minutes infusion duration, the following nivolumab infusions had to be administered over 60 min.

|   |         |
|---|---------|
| <b>Number of subjects in period 1<sup>[1]</sup></b> | Stage-2 |
| Started   | 25      |
| Completed   | 25      |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One patient could not be included in the trial due to a screening failure.

## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Stage-2 |
|-----------------------|---------|

Reporting group description:

The reporting group consists of all patients evaluated in the final analysis. This corresponds to the Full Analysis Set (FAS), which includes all patients who qualify for enrollment into the trial and received at least 1 dose of the study drug. The FAS contains 25 patients.

| Reporting group values                             | Stage-2  | Total |  |
|--|----------|-------|--|
| Number of subjects                                 | 25       | 25    |  |
| 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)                               | 20       | 20    |  |
| From 65-84 years                                   | 4        | 4     |  |
| 85 years and over                                  | 1        | 1     |  |
| Not recorded                                       | 0        | 0     |  |
| Age continuous                                     |          |       |  |
| Units: years                                       |          |       |  |
| median   | 37       |       |  |
| full range (min-max)                               | 25 to 90 | -     |  |
| Gender categorical                                 |          |       |  |
| Units: Subjects                                    |          |       |  |
| Female   | 10       | 10    |  |
| Male   | 15       | 15    |  |
| Not recorded                                       | 0        | 0     |  |
| Stage  |          |       |  |
| Units: Subjects                                    |          |       |  |
| Stage I  | 0        | 0     |  |
| Stage II   | 3        | 3     |  |
| Stage III  | 11       | 11    |  |
| Stage IV   | 11       | 11    |  |
| B-Symptoms   |          |       |  |
| Units: Subjects                                    |          |       |  |
| Weight loss > 10%                                  | 3        | 3     |  |
| Unclear fever > 38°                                | 0        | 0     |  |
| Night sweats                                       | 1        | 1     |  |
| not recorded                                       | 21       | 21    |  |
| GHSG stage   |          |       |  |
| Units: Subjects                                    |          |       |  |
| IIA  | 2        | 2     |  |
| IIB  | 1        | 1     |  |

|   |    |    |  |
|---|----|----|--|
| IIIA  | 9  | 9  |  |
| IIIB  | 2  | 2  |  |
| IVA   | 11 | 11 |  |
| ECOG performance status                       |    |    |  |
| Units: Subjects                               |    |    |  |
| normal activity, no symptoms                  | 16 | 16 |  |
| able to work, symptoms apparent               | 6  | 6  |  |
| able to care for her-/himself                 | 3  | 3  |  |
| Concomitant disease                           |    |    |  |
| Any clinically relevant concomitant diseases? |    |    |  |
| Units: Subjects                               |    |    |  |
| yes   | 22 | 22 |  |
| no  | 3  | 3  |  |
| Body mass index (BMI)                         |    |    |  |
| Units: kg/m <sup>2</sup>                      |    |    |  |
| median  |    |    |  |
| full range (min-max)                          |    | -  |  |

### Subject analysis sets

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type  | Full analysis           |

Subject analysis set description:

The full analysis set (FAS) consists of all patients who qualify for enrollment into the trial and receive at least one dose of study drug.

|                            |                                       |
|----------------------------|---------------------------------------|
| Subject analysis set title | Abscopal response analysis set (ARAS) |
| Subject analysis set type  | Per protocol                          |

Subject analysis set description:

The ARAS consists of all FAS subjects who meet all evaluability criteria and none of the exclusion criteria stated below:

Evaluability Criteria: Patient received one initial nivolumab dose before and at least 3 doses after the first fraction of RT, RT was timed and performed according to protocol.

Exclusion Criteria: First Nivolumab dose more than 6 weeks after the scheduled treatment-interval of the last anti-PD1 infusion outside the trial, Less than 4 Nivolumab doses before week 12, RT start before the first nivolumab dose, RT start after the second nivolumab dose, >3 calendar days between any two consecutive RT treatment days, Less than 9 or more than 12 single RT doses, No Non-RTL outside the 10% isodose of RT, Start of non-study treatment before completion of RE-6 examinations.

One patient withdrew informed consent and had no post-baseline assessment and was excluded from the ARAS.

| Reporting group values                             | Full Analysis Set (FAS) | Abscopal response analysis set (ARAS) |  |
|--|-------------------------|---------------------------------------|--|
| Number of subjects                                 | 25                      | 24                                    |  |
| 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)                               | 20                      | 19                                    |  |
| From 65-84 years                                   | 4                       | 4                                     |  |
| 85 years and over                                  | 1                       | 1                                     |  |

|              |   |   |  |
|--------------|---|---|--|
| Not recorded | 0 | 0 |  |
|--------------|---|---|--|

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| Age continuous<br>Units: years<br>median<br>full range (min-max)                    | 37<br>25 to 90       | 37<br>25 to 90       |  |
| Gender categorical<br>Units: Subjects   |                      |                      |  |
| Female  | 10                   | 10                   |  |
| Male  | 15                   | 14                   |  |
| Not recorded  | 0                    | 0                    |  |
| Stage<br>Units: Subjects  |                      |                      |  |
| Stage I   | 0                    | 0                    |  |
| Stage II  | 3                    | 3                    |  |
| Stage III   | 11                   | 10                   |  |
| Stage IV  | 11                   | 11                   |  |
| B-Symptoms<br>Units: Subjects   |                      |                      |  |
| Weight loss > 10%   | 3                    | 3                    |  |
| Unclear fever > 38°   | 0                    | 0                    |  |
| Night sweats  | 1                    | 1                    |  |
| not recorded  | 21                   | 21                   |  |
| GHSg stage<br>Units: Subjects   |                      |                      |  |
| IIA   | 2                    | 2                    |  |
| IIB   | 1                    | 1                    |  |
| IIIA  | 9                    | 8                    |  |
| IIIB  | 2                    | 2                    |  |
| IVA   | 11                   | 11                   |  |
| ECOG performance status<br>Units: Subjects  |                      |                      |  |
| normal activity, no symptoms  | 16                   | 15                   |  |
| able to work, symptoms apparent   | 6                    | 6                    |  |
| able to care for her-/himself   | 3                    | 3                    |  |
| Concomitant disease   |                      |                      |  |
| Any clinically relevant concomitant diseases?                                       |                      |                      |  |
| Units: Subjects   |                      |                      |  |
| yes   | 22                   | 22                   |  |
| no  | 3                    | 2                    |  |
| Body mass index (BMI)<br>Units: kg/m <sup>2</sup><br>median<br>full range (min-max) | 23.3<br>17.7 to 41.9 | 23.3<br>17.7 to 41.9 |  |

## End points

### End points reporting groups

|   |                                       |
|---|---------------------------------------|
| Reporting group title   | Stage-2                               |
| Reporting group description:<br>This trial is a single-arm two-stage phase II study.  |                                       |
| Subject analysis set title  | Full Analysis Set (FAS)               |
| Subject analysis set type   | Full analysis                         |
| Subject analysis set description:<br>The full analysis set (FAS) consists of all patients who qualify for enrollment into the trial and receive at least one dose of study drug.  |                                       |
| Subject analysis set title  | Abscopal response analysis set (ARAS) |
| Subject analysis set type   | Per protocol                          |
| Subject analysis set description:<br>The ARAS consists of all FAS subjects who meet all evaluability criteria and none of the exclusion criteria stated below:<br>Evaluability Criteria: Patient received one initial nivolumab dose before and at least 3 doses after the first fraction of RT, RT was timed and performed according to protocol.<br>Exclusion Criteria: First Nivolumab dose more than 6 weeks after the scheduled treatment-interval of the last anti-PD1 infusion outside the trial, Less than 4 Nivolumab doses before week 12, RT start before the first nivolumab dose, RT start after the second nivolumab dose, >3 calendar days between any two consecutive RT treatment days, Less than 9 or more than 12 single RT doses, No Non-RTL outside the 10% isodose of RT, Start of non-study treatment before completion of RE-6 examinations.<br>One patient withdrew informed consent and had no post-baseline assessment and was excluded from the ARAS. |                                       |

### Primary: Abscopal response rate (ARR)

|  |                              |
|--|------------------------------|
| End point title  | Abscopal response rate (ARR) |
| End point description:<br>The primary objective was to assess the ARR to localized RT combined with 4–6 doses of the study drug. An ARR ≤5% was considered insignificant, while an ARR of around 30% suggested a promising systemic effect in heavily pre-treated HL patients. Efficacy benchmarks were evaluated using Simon's optimal two-stage design. The null hypothesis (H0: ARR-6 < 5%) was tested against a one-sided alternative with a significance level of 5%. The probability of not rejecting H0 when the true ARR-6 was 30% was controlled at <5%. In stage 2, the UMVUE and two-sided 90% confidence limits for ARR-6 were calculated according to Koyama and Chen. The one-sided 95% confidence interval was obtained by setting the upper limit to 1. H0 was rejected if the lower limit exceeded 5%. Based on stage-1 results, the test had 100% power regardless of the final number of evaluable patients in stage 2. |                              |
| End point type   | Primary                      |
| End point timeframe:<br>Prerequisite of primary endpoint assessment is the first restaging which was performed and documented between weeks 12 – 14, after the last nivolumab dose administered before week 12 after start of treatment.   |                              |

| End point values                | Full Analysis Set (FAS) | Abscopal response analysis set (ARAS) |  |  |
|---------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type              | Subject analysis set    | Subject analysis set                  |  |  |
| Number of subjects analysed     | 25                      | 24                                    |  |  |
| Units: point estimate (95% CIs) |                         |                                       |  |  |
| yes                             | 11                      | 11                                    |  |  |
| no                              | 13                      | 13                                    |  |  |
| not applicable                  | 1                       | 0                                     |  |  |



## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Primary efficacy endpoint analysis                              |
| Comparison groups                       | Abscopal response analysis set (ARAS) v Full Analysis Set (FAS) |
| Number of subjects included in analysis | 49  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[1]</sup>  |
| Parameter estimate                      | point estimate (UMVUE)  |
| Point estimate                          | 45.8  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 1-sided   |
| lower limit                             | 31.5  |

Notes:

[1] - The primary endpoint (ARR-6) was estimated using the uniformly minimum variance unbiased estimator (UMVUE) according to Koyama and Chen (2008), consistent with Simon's optimal two-stage design. A one-sided 95% CI with an upper limit of 1 was also calculated as required for hypothesis testing.

## Secondary: Remission status

|  |                  |
|--|------------------|
| End point title  | Remission status |
| End point description:<br>The overall remission status (CR, PR, SD, PD) was listed for each subject and summarized per investigator. |                  |
| End point type   | Secondary        |
| End point timeframe:<br>Consecutive restaging examination over the course of therapy with nivolumab doses (RE-6)                     |                  |

|                             |                                       |  |  |  |
|-----------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>     | Abscopal response analysis set (ARAS) |  |  |  |
| Subject group type          | Subject analysis set                  |  |  |  |
| Number of subjects analysed | 24                                    |  |  |  |
| Units: subjects             |                                       |  |  |  |
| Complete remission (CR)     | 1                                     |  |  |  |
| Partial remission (PR)      | 8                                     |  |  |  |
| Stable disease (SD)         | 6                                     |  |  |  |
| Progressive disease (PD)    | 9                                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of response (DOR)

|                 |                            |
|-----------------|----------------------------|
| End point title | Duration of response (DOR) |
|-----------------|----------------------------|

End point description:

For subjects who survive without PD, the DOR was censored on the date of their last tumor assessment. Subjects who started subsequent therapy without a prior reported PD were censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy. This endpoint will only be evaluated in subjects with CR or PR.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

DOR was defined as the time from first response (CR or PR) to the date of first objectively documented disease progression (PD) or death due to any cause, whichever occurs first.

| End point values              | Full Analysis Set (FAS) | Abscopal response analysis set (ARAS) |  |  |
|-------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type            | Subject analysis set    | Subject analysis set                  |  |  |
| Number of subjects analysed   | 25                      | 24                                    |  |  |
| Units: subjects               |                         |                                       |  |  |
| median (full range (min-max)) | 10.7 (2.8 to 19.4)      | 10.7 (2.8 to 19.4)                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Failure-free survival (FFS)

|                 |                             |
|-----------------|-----------------------------|
| End point title | Failure-free survival (FFS) |
|-----------------|-----------------------------|

End point description:

Failure-free survival (FFS) was calculated as time between the initiation of treatment with nivolumab within the trial and the date of first progression, relapse, death, or administration of any anti-cancer drug other than nivolumab or radiotherapy. If none of these events have occurred, FFS was censored on the date of the last documented staging or follow-up.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

One-year FFS (as reported) and 18-months FFS rates

| End point values                 | Full Analysis Set (FAS) | Abscopal response analysis set (ARAS) |  |  |
|----------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type               | Subject analysis set    | Subject analysis set                  |  |  |
| Number of subjects analysed      | 25                      | 24                                    |  |  |
| Units: percent                   |                         |                                       |  |  |
| number (confidence interval 95%) | 6.4 (2.7 to             | 6.4 (2.7 to                           |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival (PFS)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression-free survival (PFS) |
|-----------------|---------------------------------|

End point description:

Progression-free survival (PFS) was calculated for each as time between the initiation of treatment with nivolumab within the trial and the date of first progression, relapse or death. In cases of continuing response, PFS will be censored at the date of the last documented follow-up.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

One-year PFS rates (as reported) and 18-months PFS rates

| End point values                 | Full Analysis Set (FAS) | Abscopal response analysis set (ARAS) |  |  |
|----------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type               | Subject analysis set    | Subject analysis set                  |  |  |
| Number of subjects analysed      | 25                      | 24                                    |  |  |
| Units: percent                   |                         |                                       |  |  |
| number (confidence interval 95%) | 8.3 (3.4 to 13.2)       | 8.3 (3.4 to 13.2)                     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall survival (OS) |
|-----------------|-----------------------|

End point description:

Overall survival (OS) was calculated for each patient as time between the initiation of treatment with nivolumab within the trial and the date of death. In patients alive by the time of analysis, OS was censored at the date of the last documented information on survival status.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

One-year OS rates (as reported) and 18-months OS rates

| <b>End point values</b>          | Full Analysis Set (FAS) | Abscopal response analysis set (ARAS) |  |  |
|----------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type               | Subject analysis set    | Subject analysis set                  |  |  |
| Number of subjects analysed      | 25                      | 24                                    |  |  |
| Units: percent                   |                         |                                       |  |  |
| number (confidence interval 95%) | 19.9 (14.7 to 27.4)     | 19.9 (14.7 to 27.4)                   |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All events from first dose up to 125 days after treatment end must be reported. Events beyond 125 days must be reported only if a causal relationship to study treatment is suspected.

Adverse event reporting additional description:

During the period, every adverse event has to be documented, independent of the investigator's opinion whether there is a causative relation with therapy or not.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 10.1 |
|--------------------|------|

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Safety analysis set (SAS) |
|-----------------------|---------------------------|

Reporting group description:

The safety analysis set (SAS) consists of all patients of the FAS who had at least one valid post-baseline safety assessment. In this trial all patients who were included in the FAS were also included in the SAS (N=25).

| Serious adverse events                               | Safety analysis set (SAS)  |  |  |
|--|--|--|--|
| Total subjects affected by serious adverse events    |  |  |  |
| subjects affected / exposed                          | 6 / 25 (24.00%)  |  |  |
| number of deaths (all causes)                        | 5  |  |  |
| number of deaths resulting from adverse events       | 0  |  |  |
| Blood and lymphatic system disorders                 |  |  |  |
| Blood and lymphatic disorders                        | Additional description: Includes Neutropenia   |  |  |
| subjects affected / exposed                          | 2 / 25 (8.00%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 2  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| General disorders and administration site conditions |  |  |  |
| General disorders                                    | Additional description: Includes: Malaise, reduced general condition, Migraine with aura |  |  |
| subjects affected / exposed                          | 3 / 25 (12.00%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 3  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| Gastrointestinal disorders                           |  |  |  |
| Gastrointestinal disorder                            | Additional description: Includes: SAPO virus infection, diarrhea, nausea, exicosis       |  |  |
| subjects affected / exposed                          | 5 / 25 (20.00%)  |  |  |
| occurrences causally related to treatment / all      | 3 / 8  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |

|   |   |  |  |
|---|---|--|--|
| Infections and infestations                     |   |  |  |
| Infections and infestations                     | Additional description: Includes: lung infection, fever |  |  |
| subjects affected / exposed                     | 4 / 25 (16.00%)   |  |  |
| occurrences causally related to treatment / all | 0 / 4   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |

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

| Non-serious adverse events                            | Safety analysis set (SAS)                    |  |  |
|---|--|--|--|
| Total subjects affected by non-serious adverse events |  |  |  |
| subjects affected / exposed                           | 24 / 25 (96.00%)                             |  |  |
| Cardiac disorders                                     |  |  |  |
| Cardiac disorders                                     |  |  |  |
| subjects affected / exposed                           | 1 / 25 (4.00%)                               |  |  |
| occurrences (all)                                     | 2  |  |  |
| Nervous system disorders                              |  |  |  |
| Nervous system disorders                              | Additional description: Includes: Neuropathy |  |  |
| subjects affected / exposed                           | 1 / 25 (4.00%)                               |  |  |
| occurrences (all)                                     | 3  |  |  |
| Blood and lymphatic system disorders                  |  |  |  |
| Anemia  |  |  |  |
| subjects affected / exposed                           | 2 / 25 (8.00%)                               |  |  |
| occurrences (all)                                     | 27   |  |  |
| Leukopenia  |  |  |  |
| subjects affected / exposed                           | 2 / 25 (8.00%)                               |  |  |
| occurrences (all)                                     | 33   |  |  |
| Neutropenia   |  |  |  |
| subjects affected / exposed                           | 2 / 25 (8.00%)                               |  |  |
| occurrences (all)                                     | 2  |  |  |
| Thrombocytopenia                                      |  |  |  |
| subjects affected / exposed                           | 1 / 25 (4.00%)                               |  |  |
| occurrences (all)                                     | 3  |  |  |
| General disorders and administration site conditions  |  |  |  |
| Allergic reaction                                     |  |  |  |
| subjects affected / exposed                           | 1 / 25 (4.00%)                               |  |  |
| occurrences (all)                                     | 1  |  |  |
| Toothache   |  |  |  |

|  |  |  |  |
|--|--|--|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 25 (4.00%)<br>1                                |  |  |
| Gastrointestinal disorders                       |  |  |  |
| Gastrointestinal disorders                       | Additional description: Includes: Nausea, vomiting |  |  |
| subjects affected / exposed<br>occurrences (all) | 5 / 25 (20.00%)<br>21                              |  |  |
| Mucositis  |  |  |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 25 (8.00%)<br>21                               |  |  |
| Hepatobiliary disorders                          |  |  |  |
| Hepatobiliary disorders                          |  |  |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 25 (8.00%)<br>22                               |  |  |
| Respiratory, thoracic and mediastinal disorders  |  |  |  |
| Respiratory, thoracic and mediastinal disorders  |  |  |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 25 (16.00%)<br>8                               |  |  |
| Skin and subcutaneous tissue disorders           |  |  |  |
| Skin and subcutaneous tissue disorders           |  |  |  |
| subjects affected / exposed<br>occurrences (all) | 11 / 25 (44.00%)<br>36                             |  |  |
| Renal and urinary disorders                      |  |  |  |
| Renal and urinary tract disorders                |  |  |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 25 (8.00%)<br>3                                |  |  |
| Musculoskeletal and connective tissue disorders  |  |  |  |
| Muscle, bone and joint disorders                 |  |  |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 25 (16.00%)<br>19                              |  |  |
| Infections and infestations                      |  |  |  |
| Fever  |  |  |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 25 (12.00%)<br>3                               |  |  |
| Infections                                       |  |  |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 25 (12.00%)<br>6                               |  |  |





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 13 August 2019   | Amendment to the protocol, Amendment to other documents appended to the initial application form, Amendment to other documents or information (SmPC-Update), SmPC-Update with effect on the ICF: Correction of the laboratory address for the accompanying program   |
| 17 February 2020 | Amendment of the protocol, Amendment of other documents or information (SmPC-Update): <ul style="list-style-type: none"><li>- The quality of life (QoL) analyses, originally planned as secondary endpoints, were added as secondary objectives</li><li>- The procedure for the assessment and reporting of adverse events was clarified</li><li>- The anticipated end of the study was added</li><li>- The definition of women of childbearing potential (WOCBP) and postmenopausal women was specified</li><li>- An incorrect description of the patient population was corrected</li></ul>  |
| 29 July 2020     | Amendment to the protocol, Amendment to other documents or information (SmPC-Update and Informed Consent Form): <ul style="list-style-type: none"><li>- incorrect definition of postmenopausal status for distinguishing WOCBP was corrected</li><li>- potential study termination for feasibility reasons was clarified</li><li>- Information on DMC involvement in the decision to proceed to stage 2 recruitment was added</li><li>- planned publication process was clarified</li><li>- clinical relevance of a potentially positive study outcome was described</li><li>- treatment schedule including possible delays in the initiation of radiotherapy (RT) was detailed</li><li>- Compliance with current GCP and European data protection regulations was elaborated</li><li>- reference to the respective patient information sheet regarding details of the scientific support program was added</li><li>- Information on patient insurance coverage abroad was added</li></ul> |
| 18 June 2021     | Amendment to the protocol, Amendment to other documents or information (SmPC-Update): <ul style="list-style-type: none"><li>- continuation of study recruitment in phase 2 (previously reported in 05/2020)</li><li>- relevant inclusion criterion was adjusted</li><li>- interval between the last anti-PD1 dose outside and the first dose within the study was modified</li><li>- Inclusion of patients with well-controlled HIV infection under adequate antiretroviral therapy was allowed</li></ul>  |
| 30 August 2022   | Amendment to the protocol, Amendment to other documents or information: <ul style="list-style-type: none"><li>- Adjustment of timelines</li><li>- Revision of inclusion/exclusion criteria</li><li>- General wording of the medication supply</li><li>- Editorial and organizational adjustments</li></ul>   |
| 06 February 2023 | Amendment to information in the CT application form, Amendment to the protocol, Amendment to other documents appended to the initial application form (Informed Consent Form update, SmPC Update, Additional Information for patients who have already been briefed): <ul style="list-style-type: none"><li>- adverse reaction eosinophilia was listed with a changed frequency (occasional instead of rare)</li><li>- adverse reaction "renal failure (including acute renal failure)" was replaced in the OPDIVO® October 2022 prescribing information by "renal failure (including acute kidney injury)"</li></ul>  |

|                 |   |
|-----------------|---|
| 17 January 2024 | Amendment to the protocol, Amendment to other documents appended to the initial application form (SmPC-Update, Additional Information for patients who have already been briefed): <ul style="list-style-type: none"> <li>- Adjustment of timelines due to the shortened study duration</li> <li>- Revision of the statistical section based on the actual sample size of 26 patients</li> <li>- Editorial adjustments</li> </ul> |
|-----------------|---|

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported