



## Clinical trial results: Lurbinectedin Monotherapy in Patients with Progressive Malignant Pleural Mesothelioma. A Multicenter, Single-arm Phase II Trial Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2017-001016-11 |
| Trial protocol           | IT             |
| Global end of trial date | 22 March 2021  |

### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 28 September 2022 |
| First version publication date | 28 September 2022 |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | SAKK17/16 |
|-----------------------|-----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03213301 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                            |
|------------------------------|------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Swiss Group for Clinical Cancer Research (SAKK)                                                            |
| Sponsor organisation address | Effingerstrasse 33, Bern, Switzerland, 3008                                                                |
| Public contact               | Head Regulatory Affairs, Swiss Group for Clinical Cancer Research (SAKK), +41 31 508 41 51, sakkcc@sakk.ch |
| Scientific contact           | Head Regulatory Affairs, Swiss Group for Clinical Cancer Research (SAKK), +41 31 508 41 51, sakkcc@sakk.ch |

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                       | 11 June 2021  |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 22 March 2021 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 22 March 2021 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To assess efficacy and safety of lurbinectedin monotherapy in patients with progressive malignant mesothelioma

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continuous assessment of laboratory values and vital signs.

Background therapy:

All patients received standard antiemetic prophylaxis 30 minutes before each lurbinectedin treatment infusion, as follows: (i) Corticosteroids (dexamethasone i.v. at least 8 mg or equivalent; if institutional standard antiemetic dose is higher, institutional dose is allowed), (ii) Serotonin (5-HT<sub>3</sub>) antagonists (ondansetron at least 8 mg i.v. or equivalent).

If necessary, during treatment and in addition to the above, the duration of treatment with 5-HT<sub>3</sub> antagonists and/or dexamethasone could be extended. Additional antiemetic agents (with the exception of aprepitant or equivalents) could be administered as appropriate.

Evidence for comparator:

N/A; single arm study

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 06 October 2017 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Italy: 17       |
| Country: Number of subjects enrolled | Switzerland: 25 |
| Worldwide total number of subjects   | 42              |
| EEA total number of subjects         | 17              |

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          | 0 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 0  |
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 10 |
| From 65 to 84 years       | 32 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The recruitment phase started September 28th, 2017 and was completed October 25th, 2018 after recruitment of 42 out of 39 planned patients. Twenty-five patients were enrolled at six sites in Switzerland and 17 patients at three sites in Italy.

### Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fulfils all inclusion criteria and not any of the exclusion criteria, he/she was enrolled.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Baseline                    |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Lurbinectedin - Treatment arm |
|------------------|-------------------------------|

Arm description:

Lurbinectedin, 3.2 mg/m<sup>2</sup> by intravenous infusion on day one every three weeks (q3w) until disease progression, unacceptable toxicity or patient's withdrawal of consent.

|                                        |                            |
|----------------------------------------|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | Lurbinectedin              |
| Investigational medicinal product code |                            |
| Other name                             | Zepsyre, Zepzelca, PM01183 |
| Pharmaceutical forms                   | Infusion                   |
| Routes of administration               | Intravenous use            |

Dosage and administration details:

3.2 mg/m<sup>2</sup> by intravenous infusion on day one every three weeks (q3w)

|                                       |                               |
|---------------------------------------|-------------------------------|
| <b>Number of subjects in period 1</b> | Lurbinectedin - Treatment arm |
| Started                               | 42                            |
| Completed                             | 42                            |

### Period 2

|                              |                             |
|------------------------------|-----------------------------|
| Period 2 title               | Treatment                   |
| Is this the baseline period? | No                          |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

## Arms

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Lurbinectedin - Treatment arm |
|------------------|-------------------------------|

### Arm description:

Lurbinectedin, 3.2 mg/m<sup>2</sup> by intravenous infusion on day one every three weeks (q3w) until disease progression, unacceptable toxicity or patient's withdrawal of consent.

After treatment discontinuation patients were followed up for up to two years.

|                                        |                            |
|----------------------------------------|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | Lurbinectedin              |
| Investigational medicinal product code |                            |
| Other name                             | Zepsyre, Zepzelca, PM01183 |
| Pharmaceutical forms                   | Infusion                   |
| Routes of administration               | Intravenous use            |

### Dosage and administration details:

3.2 mg/m<sup>2</sup> by intravenous infusion on day one every three weeks (q3w)

| <b>Number of subjects in period 2</b> | Lurbinectedin - Treatment arm |
|---------------------------------------|-------------------------------|
| Started                               | 42                            |
| Completed                             | 0                             |
| Not completed                         | 42                            |
| Physician decision                    | 2                             |
| Consent withdrawn by subject          | 7                             |
| Treatment delay >6 weeks              | 1                             |
| Progressive disease                   | 32                            |

## Baseline characteristics

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### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Lurbinectedin - Treatment arm |
|-----------------------|-------------------------------|

Reporting group description:

Lurbinectedin, 3.2 mg/m<sup>2</sup> by intravenous infusion on day one every three weeks (q3w) until disease progression, unacceptable toxicity or patient's withdrawal of consent.

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| Reporting group values                | Lurbinectedin - Treatment arm | Total |  |
|---------------------------------------|-------------------------------|-------|--|
| Number of subjects                    | 42                            | 42    |  |
| Age categorical<br>Units: Subjects    |                               |       |  |
| Adults (18-64 years)                  | 10                            | 10    |  |
| From 65-84 years                      | 32                            | 32    |  |
| Gender categorical<br>Units: Subjects |                               |       |  |
| Female                                | 7                             | 7     |  |
| Male                                  | 35                            | 35    |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                        |                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                  | Lurbinectedin - Treatment arm                         |
| Reporting group description:<br>Lurbinectedin, 3.2 mg/m <sup>2</sup> by intravenous infusion on day one every three weeks (q3w) until disease progression, unacceptable toxicity or patient's withdrawal of consent.                                                                                   |                                                       |
| Reporting group title                                                                                                                                                                                                                                                                                  | Lurbinectedin - Treatment arm                         |
| Reporting group description:<br>Lurbinectedin, 3.2 mg/m <sup>2</sup> by intravenous infusion on day one every three weeks (q3w) until disease progression, unacceptable toxicity or patient's withdrawal of consent.<br>After treatment discontinuation patients were followed up for up to two years. |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                             | FAS                                                   |
| Subject analysis set type                                                                                                                                                                                                                                                                              | Full analysis                                         |
| Subject analysis set description:<br>Defined as all patients who received at least one dose of trial treatment, excluding patients with major eligibility violations.                                                                                                                                  |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                             | PPS                                                   |
| Subject analysis set type                                                                                                                                                                                                                                                                              | Per protocol                                          |
| Subject analysis set description:<br>Defined as a subset of patients of the FAS population excluding patients with major protocol violations.                                                                                                                                                          |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                             | FAS   Subgroup Immunotherapy - Prior Immunotherapy    |
| Subject analysis set type                                                                                                                                                                                                                                                                              | Sub-group analysis                                    |
| Subject analysis set description:<br>Subgroup of patients in FAS receiving prior immunotherapy.                                                                                                                                                                                                        |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                             | FAS   Subgroup Immunotherapy - No Prior Immunotherapy |
| Subject analysis set type                                                                                                                                                                                                                                                                              | Sub-group analysis                                    |
| Subject analysis set description:<br>Subgroup of patients in FAS receiving no prior immunotherapy.                                                                                                                                                                                                     |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                             | PPS   Subgroup Immunotherapy - Prior Immunotherapy    |
| Subject analysis set type                                                                                                                                                                                                                                                                              | Sub-group analysis                                    |
| Subject analysis set description:<br>Subgroup of patients in PPS receiving prior immunotherapy.                                                                                                                                                                                                        |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                             | PPS   Subgroup Immunotherapy - No prior Immunotherapy |
| Subject analysis set type                                                                                                                                                                                                                                                                              | Sub-group analysis                                    |
| Subject analysis set description:<br>Subgroup of patients in PPS receiving no prior immunotherapy.                                                                                                                                                                                                     |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                             | FAS   Subgroup Histological type - Epithelioid        |
| Subject analysis set type                                                                                                                                                                                                                                                                              | Sub-group analysis                                    |
| Subject analysis set description:<br>Subgroup of patients in FAS with histological type at initial diagnosis = Epithelioid                                                                                                                                                                             |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                             | FAS   Subgroup Histological type - Non-Epithelioid    |
| Subject analysis set type                                                                                                                                                                                                                                                                              | Sub-group analysis                                    |
| Subject analysis set description:<br>Subgroup of patients in FAS with histological type at initial diagnosis = Non-epithelioid                                                                                                                                                                         |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                             | PPS   Subgroup Histological type - Epithelioid        |
| Subject analysis set type                                                                                                                                                                                                                                                                              | Sub-group analysis                                    |
| Subject analysis set description:<br>Subgroup of patients in PPS with histological type at initial diagnosis = Epithelioid                                                                                                                                                                             |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                             | PPS   Subgroup Histological type - Non-epithelioid    |

|                                                                                           |                                                  |
|-------------------------------------------------------------------------------------------|--------------------------------------------------|
| Subject analysis set type                                                                 | Sub-group analysis                               |
| Subject analysis set description:                                                         |                                                  |
| Subgroup of patients in PPS with histological type at initial diagnosis = Non-epithelioid |                                                  |
| Subject analysis set title                                                                | FAS   Subgroup Prior PT-Pemetrexed - <6 months   |
| Subject analysis set type                                                                 | Sub-group analysis                               |
| Subject analysis set description:                                                         |                                                  |
| Subgroup of patients in FAS with prior platinum-pemetrexed chemotherapy in <6 months      |                                                  |
| Subject analysis set title                                                                | FAS   Subgroup Prior PT-Pemetrexed - ≥6 months   |
| Subject analysis set type                                                                 | Sub-group analysis                               |
| Subject analysis set description:                                                         |                                                  |
| Subgroup of patients in FAS with prior platinum-pemetrexed chemotherapy in ≥6 months      |                                                  |
| Subject analysis set title                                                                | PPS   Subgroup Prior PT-Pemetrexed - <6 months   |
| Subject analysis set type                                                                 | Sub-group analysis                               |
| Subject analysis set description:                                                         |                                                  |
| Subgroup of patients in PPS with prior platinum-pemetrexed chemotherapy in <6 months      |                                                  |
| Subject analysis set title                                                                | PPS   Subgroup Prior PT-Pemetrexed - ≥6 months   |
| Subject analysis set type                                                                 | Sub-group analysis                               |
| Subject analysis set description:                                                         |                                                  |
| Subgroup of patients in PPS with prior platinum-pemetrexed chemotherapy in ≥6 months      |                                                  |
| Subject analysis set title                                                                | FAS   Subgroup Subsequent treatment received     |
| Subject analysis set type                                                                 | Sub-group analysis                               |
| Subject analysis set description:                                                         |                                                  |
| Subgroup of patients in FAS starting subsequent systemic further treatment.               |                                                  |
| Subject analysis set title                                                                | FAS   Subgroup Subsequent treatment not received |
| Subject analysis set type                                                                 | Sub-group analysis                               |
| Subject analysis set description:                                                         |                                                  |
| Subgroup of patients in FAS not starting subsequent systemic further treatment.           |                                                  |
| Subject analysis set title                                                                | PPS   Subgroup Subsequent treatment received     |
| Subject analysis set type                                                                 | Sub-group analysis                               |
| Subject analysis set description:                                                         |                                                  |
| Subgroup of patients in PPS starting subsequent systemic further treatment.               |                                                  |
| Subject analysis set title                                                                | PPS   Subgroup Subsequent treatment not received |
| Subject analysis set type                                                                 | Sub-group analysis                               |
| Subject analysis set description:                                                         |                                                  |
| Subgroup of patients in PPS not starting subsequent systemic further treatment.           |                                                  |

### Primary: PE || Progression-free survival (PFS) at 12 weeks

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | PE    Progression-free survival (PFS) at 12 weeks <sup>[1]</sup> |
|-----------------|------------------------------------------------------------------|

End point description:

PFS is defined as time from registration to one of the following events, whichever occurs first: (i) Relapse or progression according to the modified RECIST criteria for malignant pleural mesothelioma (ii) Death due to any cause. Patients not experiencing an event will be censored at the date of last evaluable tumor assessment before starting a subsequent treatment, if any.

p-value for FAS = 0.015; p-value for PPS = 0.024

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

PFS at 12 +/- 2 weeks.

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: This was a single arm study, no comparison groups were available. However, the null hypothesis was rejected as the lower of the 90%CI of the primary endpoint calculated using the



uniformly minimum variance unbiased estimator (UMVUE) was over 35% (null hypothesis).

| End point values                 | FAS                  | PPS                  |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 42                   | 41                   |  |  |
| Units: % patients with PFS       |                      |                      |  |  |
| number (confidence interval 90%) | 52.4 (38.7 to 63.6)  | 51.6 (37.5 to 62.7)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SE || Progression-free survival

|                                                                                                              |                                 |
|--------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                              | SE    Progression-free survival |
| End point description:<br>Kaplan-Meier analysis. Number of events 39/42 (FAS) and 38/41 (PPS), respectively. |                                 |
| End point type                                                                                               | Secondary                       |
| End point timeframe:<br>From registration until death or progressive disease (PD).                           |                                 |

| End point values                          | FAS                  | PPS                  |  |  |
|-------------------------------------------|----------------------|----------------------|--|--|
| Subject group type                        | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed               | 42                   | 41                   |  |  |
| Units: Progression-free survival (months) |                      |                      |  |  |
| median (confidence interval 95%)          | 4.1 (2.6 to 5.5)     | 3.4 (2.6 to 5.5)     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SE || Objective Response

|                                                                         |                          |
|-------------------------------------------------------------------------|--------------------------|
| End point title                                                         | SE    Objective Response |
| End point description:<br>CR - Complete response; PR - Partial response |                          |
| End point type                                                          | Secondary                |
| End point timeframe:<br>From registration until CR or PR.               |                          |

| End point values                 | FAS                  | PPS                  |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 42                   | 41                   |  |  |
| Units: % patients with CR or PR  |                      |                      |  |  |
| number (confidence interval 95%) | 4.8 (0.6 to 16.2)    | 4.9 (0.6 to 16.5)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: SE || Disease control (DC) at 12 weeks

|                                                                                                                                                                                             |                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| End point title                                                                                                                                                                             | SE    Disease control (DC) at 12 weeks |
| End point description:<br>Disease control defined as CR (complete response), PR (partial response) or SD (stable disease) at week 12.<br>(FAS: CR=1; PR=1; SD=20); (PPS: CR=1; PR=1; SD=19) |                                        |
| End point type                                                                                                                                                                              | Secondary                              |
| End point timeframe:<br>At 12 weeks.                                                                                                                                                        |                                        |

| End point values                 | FAS                  | PPS                  |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 42                   | 41                   |  |  |
| Units: % patients with DC        |                      |                      |  |  |
| number (confidence interval 95%) | 52.4 (36.4 to 68.0)  | 51.2 (35.1 to 67.1)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: SE || Duration of disease control

|                                                                                                                                            |                                   |
|--------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| End point title                                                                                                                            | SE    Duration of disease control |
| End point description:<br>Kaplan-Meier analysis of duration of DC.<br>(FAS: 20 events [1 death, 19 PD]), (PPS: 20 events [1 death, 19 PD]) |                                   |
| End point type                                                                                                                             | Secondary                         |
| End point timeframe:<br>From registration until death or progressive disease.                                                              |                                   |

| End point values                 | FAS                  | PPS                  |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 20 <sup>[2]</sup>    | 20 <sup>[3]</sup>    |  |  |
| Units: Duration of DC (months)   |                      |                      |  |  |
| number (confidence interval 95%) | 6.6 (5.2 to 7.4)     | 6.6 (5.2 to 7.4)     |  |  |

Notes:

[2] - 20 patients with DC at 12 weeks.

[3] - 20 patients with DC at 12 weeks.

## Statistical analyses

No statistical analyses for this end point

## Secondary: SE || Overall survival (OS)

|                                                                                                                      |                             |
|----------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                      | SE    Overall survival (OS) |
| End point description:                                                                                               |                             |
| Median follow-up time =32.8 months (95%CI: 28.5 – 39.0).<br>(FAS 36/42 events [deaths]); (FAS 35/41 events [deaths]) |                             |
| End point type                                                                                                       | Secondary                   |
| End point timeframe:                                                                                                 |                             |
| From registration until death.                                                                                       |                             |

| End point values                 | FAS                  | PPS                  |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 42                   | 41                   |  |  |
| Units: OS (months)               |                      |                      |  |  |
| median (confidence interval 95%) | 11.5 (8.8 to 13.9)   | 11.9 (8.5 to 14.7)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: SE || Overall survival - OS at fixed timepoints

|                                                |                                                 |
|------------------------------------------------|-------------------------------------------------|
| End point title                                | SE    Overall survival - OS at fixed timepoints |
| End point description:                         |                                                 |
| Estimates of OS rate at 3, 6, 9 and 12 months. |                                                 |
| End point type                                 | Secondary                                       |
| End point timeframe:                           |                                                 |
| At 3, 6, 9, 12 months.                         |                                                 |

| End point values                 | FAS                  | PPS                  |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 42                   | 41                   |  |  |
| Units: % patients                |                      |                      |  |  |
| number (confidence interval 95%) |                      |                      |  |  |
| 3 months                         | 95.2 (82.3 to 98.8)  | 95.1 (85.2 to 98.4)  |  |  |
| 6 months                         | 73.8 (57.7 to 84.6)  | 73.2 (59.8 to 82.7)  |  |  |
| 9 months                         | 64.3 (47.9 to 76.7)  | 63.4 (49.7 to 74.3)  |  |  |
| 12 months                        | 47.6 (32.1 to 61.6)  | 48.8 (35.5 to 60.8)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: SE || Time to treatment failure (TTF)

|                                                                                                           |                                       |
|-----------------------------------------------------------------------------------------------------------|---------------------------------------|
| End point title                                                                                           | SE    Time to treatment failure (TTF) |
| End point description:                                                                                    |                                       |
| Kaplan-Meier Analysis of time to treatment failure from registration.<br>(FAS: 42 events; PPS: 41 events) |                                       |
| End point type                                                                                            | Secondary                             |
| End point timeframe:                                                                                      |                                       |
| From registration until end of treatment due to any reason.                                               |                                       |

| End point values                          | FAS                  | PPS                  |  |  |
|-------------------------------------------|----------------------|----------------------|--|--|
| Subject group type                        | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed               | 42                   | 41                   |  |  |
| Units: Time to treatment failure (months) |                      |                      |  |  |
| median (confidence interval 95%)          | 2.5 (0.9 to 3.6)     | 2.3 (0.9 to 3.8)     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: PE || Progression-free survival (PFS) at 12 weeks - Subgroup analyses

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | PE    Progression-free survival (PFS) at 12 weeks - Subgroup analyses |
|-----------------|-----------------------------------------------------------------------|

End point description:

PFS as defined before. Subgroup analyses.

|                        |                     |
|------------------------|---------------------|
| End point type         | Other pre-specified |
| End point timeframe:   |                     |
| PFS at 12 +/- 2 weeks. |                     |

| End point values                 | FAS   Subgroup Immunotherapy - Prior Immunotherapy | FAS   Subgroup Immunotherapy - No Prior Immunotherapy | PPS   Subgroup Immunotherapy - Prior Immunotherapy | PPS   Subgroup Immunotherapy - No prior Immunotherapy |
|----------------------------------|----------------------------------------------------|-------------------------------------------------------|----------------------------------------------------|-------------------------------------------------------|
| Subject group type               | Subject analysis set                               | Subject analysis set                                  | Subject analysis set                               | Subject analysis set                                  |
| Number of subjects analysed      | 10                                                 | 32                                                    | 9                                                  | 32                                                    |
| Units: % patients with PFS       |                                                    |                                                       |                                                    |                                                       |
| number (confidence interval 95%) | 70 (32.9 to 89.2)                                  | 61.4 (42.1 to 75.9)                                   | 66.7 (28.2 to 87.8)                                | 61.4 (42.1 to 75.9)                                   |

| End point values                 | FAS   Subgroup Histological type - Epithelioid | FAS   Subgroup Histological type - Non-Epithelioid | PPS   Subgroup Histological type - Epithelioid | PPS   Subgroup Histological type - Non-epithelioid |
|----------------------------------|------------------------------------------------|----------------------------------------------------|------------------------------------------------|----------------------------------------------------|
| Subject group type               | Subject analysis set                           | Subject analysis set                               | Subject analysis set                           | Subject analysis set                               |
| Number of subjects analysed      | 33                                             | 9                                                  | 33                                             | 8                                                  |
| Units: % patients with PFS       |                                                |                                                    |                                                |                                                    |
| number (confidence interval 95%) | 63.6 (44.9 to 77.5)                            | 62.5 (22.9 to 86.1)                                | 63.6 (44.9 to 77.5)                            | 57.1 (17.2 to 83.7)                                |

| End point values                 | FAS   Subgroup Prior PT-Pemetrexed - <6 months | FAS   Subgroup Prior PT-Pemetrexed - ≥6 months | PPS   Subgroup Prior PT-Pemetrexed - <6 months | PPS   Subgroup Prior PT-Pemetrexed - ≥6 months |
|----------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| Subject group type               | Subject analysis set                           | Subject analysis set                           | Subject analysis set                           | Subject analysis set                           |
| Number of subjects analysed      | 14                                             | 28                                             | 11                                             | 27                                             |
| Units: % patients with PFS       |                                                |                                                |                                                |                                                |
| number (confidence interval 95%) | 53.8 (24.8 to 76.0)                            | 67.9 (47.3 to 81.8)                            | 53.8 (24.8 to 76.0)                            | 66.7 (45.7 to 81.1)                            |

## Statistical analyses

|                            |                                       |
|----------------------------|---------------------------------------|
| Statistical analysis title | Subgroup analysis Immunotherapy (FAS) |
|----------------------------|---------------------------------------|

Statistical analysis description:

The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks.

|                                         |                                                                                                            |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------|
| Comparison groups                       | FAS   Subgroup Immunotherapy - Prior Immunotherapy v FAS   Subgroup Immunotherapy - No Prior Immunotherapy |
| Number of subjects included in analysis | 42                                                                                                         |
| Analysis specification                  | Pre-specified                                                                                              |
| Analysis type                           | other                                                                                                      |
| P-value                                 | = 0.628                                                                                                    |
| Method                                  | Logrank                                                                                                    |

|                                                                                                                                          |                                                                                                            |
|------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                        | Subgroup analysis Immunotherapy (PPS)                                                                      |
| Statistical analysis description:<br>The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks. |                                                                                                            |
| Comparison groups                                                                                                                        | PPS   Subgroup Immunotherapy - Prior Immunotherapy v PPS   Subgroup Immunotherapy - No prior Immunotherapy |
| Number of subjects included in analysis                                                                                                  | 41                                                                                                         |
| Analysis specification                                                                                                                   | Pre-specified                                                                                              |
| Analysis type                                                                                                                            | other                                                                                                      |
| P-value                                                                                                                                  | = 0.775                                                                                                    |
| Method                                                                                                                                   | Logrank                                                                                                    |

|                                                                                                                                          |                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                        | Subgroup analysis Histological type (FAS)                                                           |
| Statistical analysis description:<br>The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks. |                                                                                                     |
| Comparison groups                                                                                                                        | FAS   Subgroup Histological type - Epithelioid v FAS   Subgroup Histological type - Non-Epithelioid |
| Number of subjects included in analysis                                                                                                  | 42                                                                                                  |
| Analysis specification                                                                                                                   | Pre-specified                                                                                       |
| Analysis type                                                                                                                            | other                                                                                               |
| P-value                                                                                                                                  | = 0.952                                                                                             |
| Method                                                                                                                                   | Logrank                                                                                             |

|                                                                                                                                          |                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                        | Subgroup analysis Histological type (PPS)                                                           |
| Statistical analysis description:<br>The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks. |                                                                                                     |
| Comparison groups                                                                                                                        | PPS   Subgroup Histological type - Epithelioid v PPS   Subgroup Histological type - Non-epithelioid |
| Number of subjects included in analysis                                                                                                  | 41                                                                                                  |
| Analysis specification                                                                                                                   | Pre-specified                                                                                       |
| Analysis type                                                                                                                            | other                                                                                               |
| P-value                                                                                                                                  | = 0.744                                                                                             |
| Method                                                                                                                                   | Logrank                                                                                             |

|                                                                                                                                          |                                                                                                 |
|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                        | Subgroup analysis Prior Pt-Pemetrexed (FAS)                                                     |
| Statistical analysis description:<br>The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks. |                                                                                                 |
| Comparison groups                                                                                                                        | FAS   Subgroup Prior PT-Pemetrexed - <6 months v FAS   Subgroup Prior PT-Pemetrexed - ≥6 months |
| Number of subjects included in analysis                                                                                                  | 42                                                                                              |
| Analysis specification                                                                                                                   | Pre-specified                                                                                   |
| Analysis type                                                                                                                            | other                                                                                           |
| P-value                                                                                                                                  | = 0.381                                                                                         |
| Method                                                                                                                                   | Logrank                                                                                         |

|                                                                                                                                          |                                                                                                 |
|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                        | Subgroup analysis Prior Pt-Pemetrexed (PPS)                                                     |
| Statistical analysis description:<br>The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks. |                                                                                                 |
| Comparison groups                                                                                                                        | PPS   Subgroup Prior PT-Pemetrexed - <6 months v PPS   Subgroup Prior PT-Pemetrexed - ≥6 months |
| Number of subjects included in analysis                                                                                                  | 38                                                                                              |
| Analysis specification                                                                                                                   | Pre-specified                                                                                   |
| Analysis type                                                                                                                            | other                                                                                           |
| P-value                                                                                                                                  | = 0.428                                                                                         |
| Method                                                                                                                                   | Logrank                                                                                         |

|                                                                                |                                                   |
|--------------------------------------------------------------------------------|---------------------------------------------------|
| <b>Other pre-specified: PE    Progression-free survival (PFS) at 12 weeks</b>  |                                                   |
| End point title                                                                | PE    Progression-free survival (PFS) at 12 weeks |
| End point description:<br>PFS as defined before. Using Kaplan Meier Estimator. |                                                   |
| End point type                                                                 | Other pre-specified                               |
| End point timeframe:<br>At 12 weeks.                                           |                                                   |

|                                  |                      |                      |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| <b>End point values</b>          | FAS                  | PPS                  |  |  |
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 42                   | 41                   |  |  |
| Units: % patients with PFS       |                      |                      |  |  |
| number (confidence interval 90%) | 63.5 (49.7 to 74.4)  | 62.5 (48.6 to 73.7)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: SE || Progression-free survival - PFS at fixed timepoints

End point title SE || Progression-free survival - PFS at fixed timepoints

End point description:

Kaplan-Meier analysis.

End point type Other pre-specified

End point timeframe:

At 3, 6, 9, 12 months.

| End point values                 | FAS                  | PPS                  |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed      | 42                   | 41                   |  |  |
| Units: % patients with PFS       |                      |                      |  |  |
| number (confidence interval 95%) |                      |                      |  |  |
| 3 months                         | 58.4 (41.8 to 71.7)  | 57.3 (43.4 to 69.0)  |  |  |
| 6 months                         | 30.5 (17.1 to 44.9)  | 31.3 (19.6 to 43.6)  |  |  |
| 9 months                         | 12.7 (4.7 to 24.9)   | 13.0 (5.8 to 23.3)   |  |  |
| 12 months                        | 3.4 (0.3 to 14.1)    | 3.5 (0.5 to 12.0)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: SE || Progression-free survival - Subgroup analyses

End point title SE || Progression-free survival - Subgroup analyses

End point description:

Kaplan-Meier analysis for subgroups.

End point type Other pre-specified

End point timeframe:

From registration until death or progressive disease (PD).

| End point values                          | FAS   Subgroup<br>Immunotherapy - Prior<br>Immunotherapy | FAS   Subgroup<br>Immunotherapy - No Prior<br>Immunotherapy | PPS   Subgroup<br>Immunotherapy - Prior<br>Immunotherapy | PPS   Subgroup<br>Immunotherapy - No prior<br>Immunotherapy |
|-------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------|
| Subject group type                        | Subject analysis set                                     | Subject analysis set                                        | Subject analysis set                                     | Subject analysis set                                        |
| Number of subjects analysed               | 10                                                       | 32                                                          | 9                                                        | 32                                                          |
| Units: Progression-free survival (months) |                                                          |                                                             |                                                          |                                                             |



|                                  |                  |                  |                  |                  |
|----------------------------------|------------------|------------------|------------------|------------------|
| number (confidence interval 95%) | 3.2 (1.4 to 5.8) | 4.1 (2.3 to 6.4) | 3.2 (1.4 to 5.8) | 4.1 (2.3 to 6.4) |
|----------------------------------|------------------|------------------|------------------|------------------|

| End point values                          | FAS   Subgroup Histological type - Epithelioid | FAS   Subgroup Histological type - Non-Epithelioid | PPS   Subgroup Histological type - Epithelioid | PPS   Subgroup Histological type - Non-epithelioid |
|-------------------------------------------|------------------------------------------------|----------------------------------------------------|------------------------------------------------|----------------------------------------------------|
| Subject group type                        | Subject analysis set                           | Subject analysis set                               | Subject analysis set                           | Subject analysis set                               |
| Number of subjects analysed               | 33                                             | 9                                                  | 33                                             | 8                                                  |
| Units: Progression-free survival (months) |                                                |                                                    |                                                |                                                    |
| number (confidence interval 95%)          | 4.1 (2.5 to 6.4)                               | 3.7 (1.1 to 5.5)                                   | 4.1 (2.5 to 6.4)                               | 3.2 (1.1 to 5.5)                                   |

| End point values                          | FAS   Subgroup Prior PT-Pemetrexed - <6 months | FAS   Subgroup Prior PT-Pemetrexed - ≥6 months | PPS   Subgroup Prior PT-Pemetrexed - <6 months | PPS   Subgroup Prior PT-Pemetrexed - ≥6 months |
|-------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| Subject group type                        | Subject analysis set                           | Subject analysis set                           | Subject analysis set                           | Subject analysis set                           |
| Number of subjects analysed               | 14                                             | 28                                             | 14                                             | 27                                             |
| Units: Progression-free survival (months) |                                                |                                                |                                                |                                                |
| number (confidence interval 95%)          | 3.0 (1.3 to 5.5)                               | 4.3 (2.6 to 6.6)                               | 3.0 (1.3 to 5.5)                               | 4.4 (2.5 to 6.6)                               |

## Statistical analyses

| Statistical analysis title                                                                                           | Subgroup analysis Immunotherapy (FAS)                                                                      |
|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Statistical analysis description:<br>Comparisons of PFS between subgroups were investigated using the log rank test. |                                                                                                            |
| Comparison groups                                                                                                    | FAS   Subgroup Immunotherapy - Prior Immunotherapy v FAS   Subgroup Immunotherapy - No Prior Immunotherapy |
| Number of subjects included in analysis                                                                              | 42                                                                                                         |
| Analysis specification                                                                                               | Pre-specified                                                                                              |
| Analysis type                                                                                                        | other                                                                                                      |
| P-value                                                                                                              | = 0.508                                                                                                    |
| Method                                                                                                               | Logrank                                                                                                    |

| Statistical analysis title                                                                                           | Subgroup analysis Immunotherapy (PPS)                                                                      |
|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Statistical analysis description:<br>Comparisons of PFS between subgroups were investigated using the log rank test. |                                                                                                            |
| Comparison groups                                                                                                    | PPS   Subgroup Immunotherapy - Prior Immunotherapy v PPS   Subgroup Immunotherapy - No prior Immunotherapy |

|                                         |               |
|-----------------------------------------|---------------|
| Number of subjects included in analysis | 41            |
| Analysis specification                  | Pre-specified |
| Analysis type                           | other         |
| P-value                                 | = 0.555       |
| Method                                  | Logrank       |

|                                                                                 |                                                                                                     |
|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                               | Subgroup analysis Histological type (FAS)                                                           |
| Statistical analysis description:                                               |                                                                                                     |
| Comparisons of PFS between subgroups were investigated using the log rank test. |                                                                                                     |
| Comparison groups                                                               | FAS   Subgroup Histological type - Epithelioid v FAS   Subgroup Histological type - Non-Epithelioid |
| Number of subjects included in analysis                                         | 42                                                                                                  |
| Analysis specification                                                          | Pre-specified                                                                                       |
| Analysis type                                                                   | other                                                                                               |
| P-value                                                                         | = 0.986                                                                                             |
| Method                                                                          | Logrank                                                                                             |

|                                                                                 |                                                                                                     |
|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                               | Subgroup analysis Histological type (PPS)                                                           |
| Statistical analysis description:                                               |                                                                                                     |
| Comparisons of PFS between subgroups were investigated using the log rank test. |                                                                                                     |
| Comparison groups                                                               | PPS   Subgroup Histological type - Epithelioid v PPS   Subgroup Histological type - Non-epithelioid |
| Number of subjects included in analysis                                         | 41                                                                                                  |
| Analysis specification                                                          | Pre-specified                                                                                       |
| Analysis type                                                                   | other                                                                                               |
| P-value                                                                         | = 0.916                                                                                             |
| Method                                                                          | Logrank                                                                                             |

|                                                                                 |                                                                                                 |
|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                               | Subgroup analysis Prior Pt-Pemetrexed (FAS)                                                     |
| Statistical analysis description:                                               |                                                                                                 |
| Comparisons of PFS between subgroups were investigated using the log rank test. |                                                                                                 |
| Comparison groups                                                               | FAS   Subgroup Prior PT-Pemetrexed - <6 months v FAS   Subgroup Prior PT-Pemetrexed - ≥6 months |
| Number of subjects included in analysis                                         | 42                                                                                              |
| Analysis specification                                                          | Pre-specified                                                                                   |
| Analysis type                                                                   | other                                                                                           |
| P-value                                                                         | = 0.402                                                                                         |
| Method                                                                          | Logrank                                                                                         |

|                                                                                 |                                             |
|---------------------------------------------------------------------------------|---------------------------------------------|
| <b>Statistical analysis title</b>                                               | Subgroup analysis Prior Pt-Pemetrexed (PPS) |
| Statistical analysis description:                                               |                                             |
| Comparisons of PFS between subgroups were investigated using the log rank test. |                                             |

|                                         |                                                                                                 |
|-----------------------------------------|-------------------------------------------------------------------------------------------------|
| Comparison groups                       | PPS   Subgroup Prior PT-Pemetrexed - <6 months v PPS   Subgroup Prior PT-Pemetrexed - ≥6 months |
| Number of subjects included in analysis | 41                                                                                              |
| Analysis specification                  | Pre-specified                                                                                   |
| Analysis type                           | other                                                                                           |
| P-value                                 | = 0.387                                                                                         |
| Method                                  | Logrank                                                                                         |

### Other pre-specified: SE || Overall survival - Subgroup analyses

|                        |                                            |
|------------------------|--------------------------------------------|
| End point title        | SE    Overall survival - Subgroup analyses |
| End point description: | Kaplan-Meier analyses for subgroups.       |
| End point type         | Other pre-specified                        |
| End point timeframe:   | From registration until death.             |

| End point values                 | FAS   Subgroup Immunotherapy - Prior Immunotherapy | FAS   Subgroup Immunotherapy - No Prior Immunotherapy | PPS   Subgroup Immunotherapy - Prior Immunotherapy | PPS   Subgroup Immunotherapy - No prior Immunotherapy |
|----------------------------------|----------------------------------------------------|-------------------------------------------------------|----------------------------------------------------|-------------------------------------------------------|
| Subject group type               | Subject analysis set                               | Subject analysis set                                  | Subject analysis set                               | Subject analysis set                                  |
| Number of subjects analysed      | 10                                                 | 32                                                    | 9                                                  | 32                                                    |
| Units: Overall survival (months) |                                                    |                                                       |                                                    |                                                       |
| median (confidence interval 95%) | 10.8 (2.5 to 13.3)                                 | 12.0 (8.1 to 22.4)                                    | 11.1 (2.5 to 14.7)                                 | 12.0 (8.1 to 22.4)                                    |

| End point values                 | FAS   Subgroup Histological type - Epithelioid | FAS   Subgroup Histological type - Non-Epithelioid | PPS   Subgroup Histological type - Epithelioid | PPS   Subgroup Histological type - Non-epithelioid |
|----------------------------------|------------------------------------------------|----------------------------------------------------|------------------------------------------------|----------------------------------------------------|
| Subject group type               | Subject analysis set                           | Subject analysis set                               | Subject analysis set                           | Subject analysis set                               |
| Number of subjects analysed      | 33                                             | 9                                                  | 33                                             | 8                                                  |
| Units: Overall survival (months) |                                                |                                                    |                                                |                                                    |
| median (confidence interval 95%) | 12.4 (8.1 to 15.5)                             | 10.0 (2.9 to 30.9)                                 | 12.4 (8.1 to 15.5)                             | 9.8 (2.9 to 30.9)                                  |

| End point values            | FAS   Subgroup Prior PT-Pemetrexed - <6 months | FAS   Subgroup Prior PT-Pemetrexed - ≥6 months | PPS   Subgroup Prior PT-Pemetrexed - <6 months | PPS   Subgroup Prior PT-Pemetrexed - ≥6 months |
|-----------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| Subject group type          | Subject analysis set                           | Subject analysis set                           | Subject analysis set                           | Subject analysis set                           |
| Number of subjects analysed | 14                                             | 28                                             | 14                                             | 27                                             |

|                                  |                   |                     |                   |                    |
|----------------------------------|-------------------|---------------------|-------------------|--------------------|
| Units: Overall survival (months) |                   |                     |                   |                    |
| median (confidence interval 95%) | 8.8 (3.2 to 11.1) | 14.2 (10.0 to 22.4) | 8.8 (3.2 to 11.1) | 14.7 (8.8 to 22.5) |

## Statistical analyses

|                                                                                |                                                                                                            |
|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                              | Subgroup analysis Immunotherapy (FAS)                                                                      |
| Statistical analysis description:                                              |                                                                                                            |
| Comparisons of OS between subgroups were investigated using the log rank test. |                                                                                                            |
| Comparison groups                                                              | FAS   Subgroup Immunotherapy - Prior Immunotherapy v FAS   Subgroup Immunotherapy - No Prior Immunotherapy |
| Number of subjects included in analysis                                        | 42                                                                                                         |
| Analysis specification                                                         | Pre-specified                                                                                              |
| Analysis type                                                                  | other                                                                                                      |
| P-value                                                                        | = 0.063                                                                                                    |
| Method                                                                         | Logrank                                                                                                    |

|                                                                                |                                                                                                            |
|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                              | Subgroup analysis Immunotherapy (PPS)                                                                      |
| Statistical analysis description:                                              |                                                                                                            |
| Comparisons of OS between subgroups were investigated using the log rank test. |                                                                                                            |
| Comparison groups                                                              | PPS   Subgroup Immunotherapy - Prior Immunotherapy v PPS   Subgroup Immunotherapy - No prior Immunotherapy |
| Number of subjects included in analysis                                        | 41                                                                                                         |
| Analysis specification                                                         | Pre-specified                                                                                              |
| Analysis type                                                                  | other                                                                                                      |
| P-value                                                                        | = 0.075                                                                                                    |
| Method                                                                         | Logrank                                                                                                    |

|                                                                                |                                                                                                     |
|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                              | Subgroup analysis Histological type (FAS)                                                           |
| Statistical analysis description:                                              |                                                                                                     |
| Comparisons of OS between subgroups were investigated using the log rank test. |                                                                                                     |
| Comparison groups                                                              | FAS   Subgroup Histological type - Non-Epithelioid v FAS   Subgroup Histological type - Epithelioid |
| Number of subjects included in analysis                                        | 42                                                                                                  |
| Analysis specification                                                         | Pre-specified                                                                                       |
| Analysis type                                                                  | other                                                                                               |
| P-value                                                                        | = 0.385                                                                                             |
| Method                                                                         | Logrank                                                                                             |

|                                                                                |                                           |
|--------------------------------------------------------------------------------|-------------------------------------------|
| <b>Statistical analysis title</b>                                              | Subgroup analysis Histological type (PPS) |
| Statistical analysis description:                                              |                                           |
| Comparisons of OS between subgroups were investigated using the log rank test. |                                           |

|                                         |                                                                                                     |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------|
| Comparison groups                       | PPS   Subgroup Histological type - Epithelioid v PPS   Subgroup Histological type - Non-epithelioid |
| Number of subjects included in analysis | 41                                                                                                  |
| Analysis specification                  | Pre-specified                                                                                       |
| Analysis type                           | other                                                                                               |
| P-value                                 | = 0.478                                                                                             |
| Method                                  | Logrank                                                                                             |

|                                                                                |                                                                                                 |
|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                              | Subgroup analysis Prior Pt-Pemetrexed (FAS)                                                     |
| Statistical analysis description:                                              |                                                                                                 |
| Comparisons of OS between subgroups were investigated using the log rank test. |                                                                                                 |
| Comparison groups                                                              | FAS   Subgroup Prior PT-Pemetrexed - <6 months v FAS   Subgroup Prior PT-Pemetrexed - ≥6 months |
| Number of subjects included in analysis                                        | 42                                                                                              |
| Analysis specification                                                         | Pre-specified                                                                                   |
| Analysis type                                                                  | other                                                                                           |
| P-value                                                                        | = 0.003                                                                                         |
| Method                                                                         | Logrank                                                                                         |

|                                                                                |                                                                                                 |
|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                              | Subgroup analysis Prior Pt-Pemetrexed (PPS)                                                     |
| Statistical analysis description:                                              |                                                                                                 |
| Comparisons of OS between subgroups were investigated using the log rank test. |                                                                                                 |
| Comparison groups                                                              | PPS   Subgroup Prior PT-Pemetrexed - <6 months v PPS   Subgroup Prior PT-Pemetrexed - ≥6 months |
| Number of subjects included in analysis                                        | 41                                                                                              |
| Analysis specification                                                         | Pre-specified                                                                                   |
| Analysis type                                                                  | other                                                                                           |
| P-value                                                                        | = 0.003                                                                                         |
| Method                                                                         | Logrank                                                                                         |

|                                                                                             |                                                                 |
|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| <b>Other pre-specified: SE    Overall survival - Subgroup analysis Subsequent treatment</b> |                                                                 |
| End point title                                                                             | SE    Overall survival - Subgroup analysis Subsequent treatment |
| End point description:                                                                      |                                                                 |
| Subgroup analysis for patients starting further systemic treatment.                         |                                                                 |
| End point type                                                                              | Other pre-specified                                             |
| End point timeframe:                                                                        |                                                                 |
| From registration until death.                                                              |                                                                 |

| <b>End point values</b>     | FAS  <br>Subgroup<br>Subsequent<br>treatment<br>received | FAS  <br>Subgroup<br>Subsequent<br>treatment not<br>received | PPS  <br>Subgroup<br>Subsequent<br>treatment<br>received | PPS  <br>Subgroup<br>Subsequent<br>treatment not<br>received |
|-----------------------------|----------------------------------------------------------|--------------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------|
| Subject group type          | Subject analysis set                                     | Subject analysis set                                         | Subject analysis set                                     | Subject analysis set                                         |
| Number of subjects analysed | 28                                                       | 14                                                           | 28                                                       | 13                                                           |
| Units: Number of patients   | 28                                                       | 14                                                           | 28                                                       | 13                                                           |

## Statistical analyses

|                                                                                     |                                                                                                 |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                   | Hazard ratio (OS / Subsequent treatment) - FAS                                                  |
| Statistical analysis description:<br>Effect of systemic subsequent treatment on OS. |                                                                                                 |
| Comparison groups                                                                   | FAS   Subgroup Subsequent treatment received v FAS   Subgroup Subsequent treatment not received |
| Number of subjects included in analysis                                             | 42                                                                                              |
| Analysis specification                                                              | Pre-specified                                                                                   |
| Analysis type                                                                       | other                                                                                           |
| P-value                                                                             | = 0.699                                                                                         |
| Method                                                                              | Regression, Cox                                                                                 |
| Parameter estimate                                                                  | Hazard ratio (HR)                                                                               |
| Point estimate                                                                      | 0.851                                                                                           |
| Confidence interval                                                                 |                                                                                                 |
| level                                                                               | 95 %                                                                                            |
| sides                                                                               | 2-sided                                                                                         |
| lower limit                                                                         | 0.375                                                                                           |
| upper limit                                                                         | 1.931                                                                                           |

|                                                                                     |                                                                                                 |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                   | Hazard ratio (OS / Subsequent treatment) - PPS                                                  |
| Statistical analysis description:<br>Effect of systemic subsequent treatment on OS. |                                                                                                 |
| Comparison groups                                                                   | PPS   Subgroup Subsequent treatment received v PPS   Subgroup Subsequent treatment not received |
| Number of subjects included in analysis                                             | 41                                                                                              |
| Analysis specification                                                              | Pre-specified                                                                                   |
| Analysis type                                                                       | other                                                                                           |
| P-value                                                                             | = 0.84                                                                                          |
| Method                                                                              | Regression, Cox                                                                                 |
| Parameter estimate                                                                  | Hazard ratio (HR)                                                                               |
| Point estimate                                                                      | 0.917                                                                                           |
| Confidence interval                                                                 |                                                                                                 |
| level                                                                               | 95 %                                                                                            |
| sides                                                                               | 2-sided                                                                                         |
| lower limit                                                                         | 0.396                                                                                           |
| upper limit                                                                         | 2.123                                                                                           |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From registration up to 30 days after last dose of study medication or until the start of a new antitumor therapy, whichever occurred first.

Adverse event reporting additional description:

Recording during the follow-up period, except for new malignancies or congenital abnormalities, only for events with possible relationship to the study drug.

Safety was assessed with the safety set, defined as all patients who took at least one dose of the trial treatment after registration.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 25.0   |

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Safety analysis set |
|-----------------------|---------------------|

Reporting group description:

Safety set, defined as all patients who took at least one dose of the trial treatment after registration.

| Serious adverse events                               | Safety analysis set |  |  |
|------------------------------------------------------|---------------------|--|--|
| Total subjects affected by serious adverse events    |                     |  |  |
| subjects affected / exposed                          | 9 / 42 (21.43%)     |  |  |
| number of deaths (all causes)                        | 36                  |  |  |
| number of deaths resulting from adverse events       | 0                   |  |  |
| Investigations                                       |                     |  |  |
| Neutrophil count decreased                           |                     |  |  |
| subjects affected / exposed                          | 1 / 42 (2.38%)      |  |  |
| occurrences causally related to treatment / all      | 1 / 1               |  |  |
| deaths causally related to treatment / all           | 0 / 0               |  |  |
| Platelet count decreased                             |                     |  |  |
| subjects affected / exposed                          | 1 / 42 (2.38%)      |  |  |
| occurrences causally related to treatment / all      | 1 / 1               |  |  |
| deaths causally related to treatment / all           | 0 / 0               |  |  |
| Blood and lymphatic system disorders                 |                     |  |  |
| Febrile neutropenia                                  |                     |  |  |
| subjects affected / exposed                          | 3 / 42 (7.14%)      |  |  |
| occurrences causally related to treatment / all      | 3 / 3               |  |  |
| deaths causally related to treatment / all           | 0 / 0               |  |  |
| General disorders and administration site conditions |                     |  |  |



|                                                 |                                                            |  |  |
|-------------------------------------------------|------------------------------------------------------------|--|--|
| Fatigue                                         |                                                            |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)                                             |  |  |
| occurrences causally related to treatment / all | 1 / 1                                                      |  |  |
| deaths causally related to treatment / all      | 0 / 0                                                      |  |  |
| Pyrexia                                         |                                                            |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)                                             |  |  |
| occurrences causally related to treatment / all | 1 / 1                                                      |  |  |
| deaths causally related to treatment / all      | 0 / 0                                                      |  |  |
| Gastrointestinal disorders                      |                                                            |  |  |
| Vomiting                                        |                                                            |  |  |
| subjects affected / exposed                     | 2 / 42 (4.76%)                                             |  |  |
| occurrences causally related to treatment / all | 2 / 2                                                      |  |  |
| deaths causally related to treatment / all      | 0 / 0                                                      |  |  |
| Hepatobiliary disorders                         |                                                            |  |  |
| Cholangitis                                     |                                                            |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)                                             |  |  |
| occurrences causally related to treatment / all | 1 / 1                                                      |  |  |
| deaths causally related to treatment / all      | 0 / 0                                                      |  |  |
| Infections and infestations                     |                                                            |  |  |
| Infection                                       |                                                            |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)                                             |  |  |
| occurrences causally related to treatment / all | 1 / 1                                                      |  |  |
| deaths causally related to treatment / all      | 0 / 0                                                      |  |  |
| Pneumonia                                       |                                                            |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)                                             |  |  |
| occurrences causally related to treatment / all | 1 / 1                                                      |  |  |
| deaths causally related to treatment / all      | 0 / 0                                                      |  |  |
| Subdiaphragmatic abscess                        | Additional description: Sub-diaphragmatic fluid collection |  |  |
| subjects affected / exposed                     | 1 / 42 (2.38%)                                             |  |  |
| 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 %

| <b>Non-serious adverse events</b>                                   | Safety analysis set |  |  |
|---------------------------------------------------------------------|---------------------|--|--|
| Total subjects affected by non-serious adverse events               |                     |  |  |
| subjects affected / exposed                                         | 42 / 42 (100.00%)   |  |  |
| Investigations                                                      |                     |  |  |
| Neutrophil count decreased                                          |                     |  |  |
| subjects affected / exposed                                         | 14 / 42 (33.33%)    |  |  |
| occurrences (all)                                                   | 24                  |  |  |
| Weight decreased                                                    |                     |  |  |
| subjects affected / exposed                                         | 4 / 42 (9.52%)      |  |  |
| occurrences (all)                                                   | 5                   |  |  |
| Alanine aminotransferase increased                                  |                     |  |  |
| subjects affected / exposed                                         | 10 / 42 (23.81%)    |  |  |
| occurrences (all)                                                   | 12                  |  |  |
| Blood bilirubin increased                                           |                     |  |  |
| subjects affected / exposed                                         | 3 / 42 (7.14%)      |  |  |
| occurrences (all)                                                   | 4                   |  |  |
| Blood creatinine increased                                          |                     |  |  |
| subjects affected / exposed                                         | 4 / 42 (9.52%)      |  |  |
| occurrences (all)                                                   | 5                   |  |  |
| Gamma-glutamyltransferase increased                                 |                     |  |  |
| subjects affected / exposed                                         | 6 / 42 (14.29%)     |  |  |
| occurrences (all)                                                   | 8                   |  |  |
| Lymphocyte count decreased                                          |                     |  |  |
| subjects affected / exposed                                         | 23 / 42 (54.76%)    |  |  |
| occurrences (all)                                                   | 23                  |  |  |
| Blood urea increased                                                |                     |  |  |
| subjects affected / exposed                                         | 5 / 42 (11.90%)     |  |  |
| occurrences (all)                                                   | 6                   |  |  |
| White blood cell count decreased                                    |                     |  |  |
| subjects affected / exposed                                         | 12 / 42 (28.57%)    |  |  |
| occurrences (all)                                                   | 17                  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |  |  |
| Tumour pain                                                         |                     |  |  |
| subjects affected / exposed                                         | 3 / 42 (7.14%)      |  |  |
| occurrences (all)                                                   | 3                   |  |  |
| Vascular disorders                                                  |                     |  |  |

|                                                                                                                                  |                        |  |  |
|----------------------------------------------------------------------------------------------------------------------------------|------------------------|--|--|
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                                                                 | 5 / 42 (11.90%)<br>10  |  |  |
| Superficial vein thrombosis<br>subjects affected / exposed<br>occurrences (all)                                                  | 3 / 42 (7.14%)<br>3    |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                                         | 3 / 42 (7.14%)<br>3    |  |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)                                                | 3 / 42 (7.14%)<br>6    |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)                              | 18 / 42 (42.86%)<br>26 |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                                                             | 6 / 42 (14.29%)<br>10  |  |  |
| General disorders and administration<br>site conditions<br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 4 / 42 (9.52%)<br>4    |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                                                                      | 32 / 42 (76.19%)<br>38 |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                                                                      | 5 / 42 (11.90%)<br>10  |  |  |
| Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all)                                                       | 7 / 42 (16.67%)<br>8   |  |  |
| Gastrointestinal disorders<br>Abdominal pain                                                                                     |                        |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 5 / 42 (11.90%)  |  |  |
| occurrences (all)                               | 6                |  |  |
| Constipation                                    |                  |  |  |
| subjects affected / exposed                     | 12 / 42 (28.57%) |  |  |
| occurrences (all)                               | 21               |  |  |
| Diarrhoea                                       |                  |  |  |
| subjects affected / exposed                     | 5 / 42 (11.90%)  |  |  |
| occurrences (all)                               | 7                |  |  |
| Dysphagia                                       |                  |  |  |
| subjects affected / exposed                     | 3 / 42 (7.14%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| Stomatitis                                      |                  |  |  |
| subjects affected / exposed                     | 3 / 42 (7.14%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Nausea                                          |                  |  |  |
| subjects affected / exposed                     | 25 / 42 (59.52%) |  |  |
| occurrences (all)                               | 36               |  |  |
| Vomiting                                        |                  |  |  |
| subjects affected / exposed                     | 11 / 42 (26.19%) |  |  |
| occurrences (all)                               | 12               |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Cough                                           |                  |  |  |
| subjects affected / exposed                     | 11 / 42 (26.19%) |  |  |
| occurrences (all)                               | 13               |  |  |
| Dyspnoea                                        |                  |  |  |
| subjects affected / exposed                     | 12 / 42 (28.57%) |  |  |
| occurrences (all)                               | 15               |  |  |
| Psychiatric disorders                           |                  |  |  |
| Insomnia                                        |                  |  |  |
| subjects affected / exposed                     | 3 / 42 (7.14%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Renal and urinary disorders                     |                  |  |  |
| Chronic kidney disease                          |                  |  |  |
| subjects affected / exposed                     | 10 / 42 (23.81%) |  |  |
| occurrences (all)                               | 10               |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |

|                                                                        |                        |  |  |
|------------------------------------------------------------------------|------------------------|--|--|
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)  | 6 / 42 (14.29%)<br>6   |  |  |
| Metabolism and nutrition disorders                                     |                        |  |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 14 / 42 (33.33%)<br>16 |  |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)      | 5 / 42 (11.90%)<br>6   |  |  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)   | 6 / 42 (14.29%)<br>7   |  |  |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)    | 5 / 42 (11.90%)<br>5   |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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|-----|
| n/a |
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Notes: