# Clinical trial results:
# Phase II multicenter randomized, double blind, placebo controlled study assessing the efficacy of buparlisib (BKM120) plus paclitaxel vs. placebo plus paclitaxel in patients with platinum pre-treated recurrent or metastatic head and neck squamous cell carcinoma

## Summary

| | |
|---|---|
| EudraCT number | 2013-000744-26 |
| Trial protocol | HU ES IT GB DE IE PL FR |
| Global end of trial date | 30 March 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 April 2018 |
| First version publication date | 15 April 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CBKM120H2201 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01852292 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Novartis Pharma, AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com |

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 | 30 March 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 March 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To estimate the efficacy of buparlisib in combination with paclitaxel in terms of progression-free survival (PFS) according to local radiological assessment and Response Evaluation Criteria In Solid Tumors (RECIST) 1.1.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 October 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 2 |
| Country: Number of subjects enrolled | Canada: 10 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | Hungary: 20 |
| Country: Number of subjects enrolled | India: 14 |
| Country: Number of subjects enrolled | Ireland: 1 |
| Country: Number of subjects enrolled | Italy: 21 |
| Country: Number of subjects enrolled | Japan: 3 |
| Country: Number of subjects enrolled | Korea, Republic of: 5 |
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Russian Federation: 11 |
| Country: Number of subjects enrolled | Spain: 11 |
| Country: Number of subjects enrolled | Switzerland: 4 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | United States: 11 |
| Country: Number of subjects enrolled | Taiwan: 14 |
| Country: Number of subjects enrolled | Thailand: 8 |

| | |
|---|---|
| Worldwide total number of subjects | 158 |
| EEA total number of subjects | 76 |

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 117 |
| From 65 to 84 years | 41 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Planned: 150; Analyzed: 158. Patients were randomized to receive treatment with buparlisib 100 mg daily (n=79) or placebo (n=79) in combination with paclitaxel.

### Pre-assignment

Screening details:

One hundred and fifty-eight patients were randomized in a 1:1 ratio to treatment with buparlisib plus paclitaxel or placebo plus paclitaxel, with stratification according to number of prior lines of treatment in the recurrent/metastatic setting (1 vs.2) and the region of Investigator site (North America vs. Rest of the World).

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Buparlisib + Paclitaxel |

Arm description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib 100 mg daily and paclitaxel 80 mg/m^2 weekly.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Buparlisib |
| Investigational medicinal product code | BKM120 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Buparlisib was supplied as 10-mg, and 50-mg hard gelatin capsules. Buparlisib was administered orally once daily on a continuous dosing schedule starting on Day 1.

| | |
|---|---|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel was administered weekly (Days 1, 8, 15 and 22 of a 28-day cycle) as an intravenous infusion at a dose of 80 mg/m^2 on a continuous dosing schedule.

| | |
|---|---|
| **Arm title** | Buparlisib matching placebo + Paclitaxel |

Arm description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib matching placebo 100 mg daily and paclitaxel 80 mg/m^2 weekly.

| | |
|---|---|
| Arm type | Placebo |

| | |
|---|---|
| Investigational medicinal product name | Buparlisib matching placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Buparlisib matching placebo was supplied as 10-mg, and 50-mg hard gelatin capsules. Buparlisib matching placebo was administered orally once daily on a continuous dosing schedule starting on Day 1.

| | |
|---|---|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel was administered weekly (Days 1, 8, 15 and 22 of a 28-day cycle) as an intravenous infusion at a dose of 80 mg/m^2 on a continuous dosing schedule.

| **Number of subjects in period 1** | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel |
|---|---|---|
| Started | 79 | 79 |
| Completed | 0 | 0 |
| Not completed | 79 | 79 |
| Adverse event, serious fatal | 9 | 8 |
| Physician decision | 6 | 2 |
| Study terminated by Sponsor | - | 1 |
| Adverse event, non-fatal | 8 | 11 |
| Non-compliance with study treatment | 1 | - |
| Patient/guardian decision | 8 | 4 |
| Progressive disease | 42 | 52 |
| Untreated - did not receive study drug | 3 | 1 |
| Protocol deviation | 2 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Buparlisib + Paclitaxel |
| Reporting group description: | |
| Patients who were randomized to this arm on a 1:1 randomization, took buparlisib 100 mg daily and paclitaxel 80 mg/m^2 weekly. | |

| | |
|---|---|
| Reporting group title | Buparlisib matching placebo + Paclitaxel |
| Reporting group description: | |
| Patients who were randomized to this arm on a 1:1 randomization, took buparlisib matching placebo 100 mg daily and paclitaxel 80 mg/m^2 weekly. | |

| Reporting group values | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel | Total |
|---|---|---|---|
| Number of subjects | 79 | 79 | 158 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 59 | 58 | 117 |
| From 65-84 years | 20 | 21 | 41 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 58.0 | 58.2 | |
| standard deviation | ± 9.44 | ± 9.44 | - |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 14 | 11 | 25 |
| Male | 65 | 68 | 133 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic or Latino\| | 3 | 0 | 3 |
| East Asian\| | 12 | 9 | 21 |
| Southeast Asian\| | 4 | 9 | 13 |
| South Asian\| | 6 | 5 | 11 |
| Russian\| | 7 | 4 | 11 |
| Mixed ethnicity\| | 1 | 2 | 3 |
| Not reported\| | 13 | 10 | 23 |
| Unknown\| | 3 | 6 | 9 |
| Other\| | 30 | 34 | 64 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Buparlisib + Paclitaxel |

Reporting group description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib 100 mg daily and paclitaxel 80 mg/m^2 weekly.

| | |
|---|---|
| Reporting group title | Buparlisib matching placebo + Paclitaxel |

Reporting group description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib matching placebo 100 mg daily and paclitaxel 80 mg/m^2 weekly.

### Primary: Progression Free Survival (PFS) per Investigator assessment

| | |
|---|---|
| End point title | Progression Free Survival (PFS) per Investigator assessment |

End point description:

PFS was defined as the time from the date of randomization to the date of the event, defined as the first radiologically documented disease progression per RECIST v 1.1 or death due to any cause. If a patient has not progressed or died at the analysis cut-off date or when the patient receives further anti-neoplastic therapy, PFS was censored on the date of the last adequate tumor assessment before the earlier of the cut-off date or start of the further anti-neoplastic therapy date.

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

End point timeframe:

4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years

| End point values | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 79 | 79 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.63 (3.52 to 5.32) | 3.45 (2.17 to 3.71) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Analysis of Double Criteria for PFS |
| Comparison groups | Buparlisib + Paclitaxel v Buparlisib matching placebo + Paclitaxel |

| | |
|---|---|
| Number of subjects included in analysis | 158 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.646 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.44 |
| upper limit | 0.94 |

## Secondary: Overall Survival (OS)

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

End point description:

Overall survival (OS) was defined as the time from date of randomization to date of death due to any cause. If a patient was not known to have died by the date of analysis cut-off, OS was censored at the date of last contact.

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

End point timeframe:

4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years

| **End point values** | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 79 | 79 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 10.41 (7.29 to 12.78) | 6.54 (5.26 to 8.77) | | |

### Statistical analyses

| **Statistical analysis title** | Analysis of Double Criteria for Overall survival |
|---|---|
| Comparison groups | Buparlisib + Paclitaxel v Buparlisib matching placebo + Paclitaxel |
| Number of subjects included in analysis | 158 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.72 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 1.04 |

## Secondary: Overall Response Rate (ORR) as per local radiological assessment

| End point title | Overall Response Rate (ORR) as per local radiological assessment |
|---|---|

End point description:

ORR: Percentage of patients with best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1.

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

End point timeframe:

4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years

| End point values | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 79 | 79 | | |
| Units: Percentage of participants | | | | |
| median (confidence interval 95%) | 39.2 (28.4 to 50.9) | 13.9 (7.2 to 23.5) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Response (TTR) as per local radiological assessment

| End point title | Time to Response (TTR) as per local radiological assessment |
|---|---|

End point description:

TTR is the time from date of randomization until first documented response (CR or PR, which has to be confirmed subsequently) according to RECIST v1.1.

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

End point timeframe:

4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years

| End point values | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 79[1] | 79[2] | | |
| Units: months | | | | |
| median (full range (min-max)) | 1.02 (0.8 to 9.2) | 0.99 (0.8 to 5.1) | | |

Notes:

[1] - n for responders = 31

[2] - n for responders = 11

### Statistical analyses

No statistical analyses for this end point

### Secondary: Disease Control Rate (DCR) as per local radiological assessment

| End point title | Disease Control Rate (DCR) as per local radiological assessment |
|---|---|

End point description:

DCR is the the proportion of patients with a best overall response of CR, PR or stable disease (SD), according to RECIST v1.1.

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

End point timeframe:

4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years

| End point values | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 79 | 79 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 72.2 (60.9 to 81.7) | 69.6 (58.2 to 79.5) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DoR) as per local investigator

| End point title | Duration of Response (DoR) as per local investigator |
|---|---|

End point description:

DoR is the time from the date of the first documented response (CR or PR, which had to be confirmed subsequently) to the date of the first radiologically documented disease progression or death due to disease according to RECIST v1.1 .

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

End point timeframe:

4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years

| End point values | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 79[3] | 79[4] | | |
| Units: months | | | | |
| median (full range (min-max)) | 3.06 (2.1 to 9.6) | 4.17 (2.7 to 5.6) | | |

Notes:

[3] - n for responders = 17

[4] - n for responders = 4

### Statistical analyses

No statistical analyses for this end point

## Secondary: Health-related quality of life (HRQoL):Time to 10% definitive deterioration in the global health status/Quality of life per EORTC-QLQ-C30

| End point title | Health-related quality of life (HRQoL):Time to 10% definitive deterioration in the global health status/Quality of life per EORTC-QLQ-C30 |
|---|---|

End point description:

A summary of EORTC-QLQ-C30 scores by time window. Time to deterioration is the number of days between the date of randomization and the date of the assessment at which definitive deterioration is seen. Definitive Deterioration in global health status and symptoms was defined as a decrease in the subscale score by at least 10% compared to baseline, with no later increase above this threshold observed during the course of the study. If a patient had not had an event prior to analysis cut-off or start of another anticancer therapy, time to deterioration was censored at the date of the last quality of life (QoL) evaluation.

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

End point timeframe:

Baseline, every 6 weeks starting from cycle 2 day 15 up to 3.5 years

| End point values | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 79 | 79 | | |
| Units: months | | | | |

| | | | | |
|---|---|---|---|---|
| median (confidence interval 95%) | 3.0 (1.6 to 4.9) | 3.5 (2.1 to 4.3) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Health-related quality of life (HRQoL):Time to 10% definitive deterioration in the head and neck cancer symptoms scales for pain, speech problems, swallowing and sense problems per EORTC-QLQ-HN35

| | |
|---|---|
| End point title | Health-related quality of life (HRQoL):Time to 10% definitive deterioration in the head and neck cancer symptoms scales for pain, speech problems, swallowing and sense problems per EORTC-QLQ-HN35 |

End point description:

A summary of EORTC-QLQ-HN35 scores by time window. Time to deterioration is the number of days between the date of randomization and the date of the assessment at which definitive deterioration is seen. Definitive Deterioration in global health status and symptoms was defined as an increase in the subscale score of at least 10% compared to baseline, with no later decrease above this threshold observed during the course of the study. If a patient had not had an event prior to analysis cut-off or start of another anticancer therapy, time to deterioration was censored at the date of the last quality of life (QoL) evaluation.

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

End point timeframe:

Baseline, every 6 weeks starting from cycle 2 day 15 up to 3.5 years

| End point values | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 79 | 79 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Pain Subscale\| | 5.8 (4.2 to 7.3) | 5.3 (3.2 to 6.8) | | |
| Speech problems\| | 5.6 (4.1 to 6.9) | 4.2 (2.2 to 5.4) | | |
| Swallowing\| | 5.1 (3.7 to 7.2) | 4.6 (2.8 to 6.7) | | |
| Sense Problems\| | 5.1 (3.1 to 7.3) | 4.6 (2.9 to 6.5) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for AUC0-24 and AUClast

| End point title | Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for AUC0-24 and AUClast[5] |
|---|---|

End point description:

To characterize the pharmacokinetics of buparlisib given in combination with paclitaxel for AUC0-24 and AUClast. At a 100 mg QD dose these primary PK parameters were determined for buparlisib.

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

End point timeframe:

6 Full PK samples over 24hrs at Day 15 of Cycle 1 (steady state)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: There was no statistical analysis planned for this endpoint.

| End point values | Buparlisib + Paclitaxel | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 79[6] | | | |
| Units: ng*hr/mL | | | | |
| median (full range (min-max)) | | | | |
| AUC0-24\| | 25628.56 (13651.75 to 33375.10) | | | |
| AUClast\| | 25734.33 (13651.75 to 33306.37) | | | |

Notes:

[6] - n = 4

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for Cmax

| End point title | Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for Cmax[7] |
|---|---|

End point description:

To characterize the pharmacokinetics of buparlisib given in combination with paclitaxel for Cmax.

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

End point timeframe:

At a 100 mg QD dose this primary PK parameter was determined for buparlisib.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: There was no statistical analysis planned for this endpoint.

| End point values | Buparlisib + Paclitaxel | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 79[8] | | | |
| Units: ng/mL | | | | |
| median (full range (min-max)) | 1775.00 (834.00 to | | | |

| | |
|---|---|
| | 2180.00) |

Notes:

[8] - n = 4

### Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for Tmax

| | |
|---|---|
| End point title | Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for Tmax[9] |

End point description:

To characterize the pharmacokinetics of buparlisib given in combination with paclitaxel for Tmax.

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

End point timeframe:

At a 100 mg QD dose this primary PK parameter was determined for buparlisib.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis planned for this endpoint.

| End point values | Buparlisib + Paclitaxel | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 79[10] | | | |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | 2.42 (1.00 to 4.00) | | | |

Notes:

[10] - n = 4

### Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for CL/F

| | |
|---|---|
| End point title | Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for CL/F[11] |

End point description:

To characterize the pharmacokinetics of buparlisib given in combination with paclitaxel for CL/F.

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

End point timeframe:

At a 100 mg QD dose this primary PK parameter was determined for buparlisib.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical analysis planned for this endpoint.

| End point values | Buparlisib + Paclitaxel | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 79[12] | | | |
| Units: L/hr | | | | |
| median (full range (min-max)) | 4.14 (3.00 to 7.33) | | | |

Notes:

[12] - n = 4

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit up to approximately 3.5 yrs.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Buparlisib + Paclitaxel |

Reporting group description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib 100 mg daily and paclitaxel 80 mg/m^2 weekly.

| | |
|---|---|
| Reporting group title | Buparlisib matching placebo + Paclitaxel |

Reporting group description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib matching placebo 100 mg daily and paclitaxel 80 mg/m^2 weekly.

| Serious adverse events | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 43 / 76 (56.58%) | 37 / 78 (47.44%) | |
| number of deaths (all causes) | 16 | 17 | |
| number of deaths resulting from adverse events | 2 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tumour haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 76 (3.95%) | 5 / 78 (6.41%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Tumour invasion | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Arterial rupture | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Face oedema | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 4 / 78 (5.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |

| | | | |
|---|---|---|---|
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory arrest | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Upper airway obstruction | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aggression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device connection issue | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural discharge | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Post procedural fistula | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraplegia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 3 / 78 (3.85%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Blindness | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Aorto-oesophageal fistula | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 3 / 78 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal obstruction | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral cavity fistula | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hypercalcaemia of malignancy | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Anal abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Candida sepsis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest wall abscess | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 6 / 78 (7.69%) | |
| occurrences causally related to treatment / all | 2 / 6 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Post procedural infection | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Septic shock | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 3 / 78 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 3 | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 78 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 2 / 78 (2.56%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 78 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Buparlisib + Paclitaxel | Buparlisib matching placebo + Paclitaxel | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 76 / 76 (100.00%) | 75 / 78 (96.15%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 2 / 78 (2.56%) | |
| occurrences (all) | 5 | 2 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 11 / 76 (14.47%) | 6 / 78 (7.69%) | |
| occurrences (all) | 13 | 8 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 20 / 76 (26.32%) | 15 / 78 (19.23%) | |
| occurrences (all) | 27 | 19 | |
| Face oedema | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 4 / 78 (5.13%) | |
| occurrences (all) | 2 | 4 | |
| Fatigue | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 31 / 76 (40.79%) | 16 / 78 (20.51%) | |
| occurrences (all) | 45 | 19 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 4 / 78 (5.13%) | |
| occurrences (all) | 2 | 4 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 10 / 78 (12.82%) | |
| occurrences (all) | 5 | 12 | |
| Pyrexia | | | |
| subjects affected / exposed | 12 / 76 (15.79%) | 16 / 78 (20.51%) | |
| occurrences (all) | 16 | 23 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Catarrh | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 4 / 78 (5.13%) | |
| occurrences (all) | 1 | 4 | |
| Cough | | | |
| subjects affected / exposed | 17 / 76 (22.37%) | 18 / 78 (23.08%) | |
| occurrences (all) | 18 | 20 | |
| Dysphonia | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 4 / 78 (5.13%) | |
| occurrences (all) | 3 | 4 | |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 76 (10.53%) | 13 / 78 (16.67%) | |
| occurrences (all) | 10 | 17 | |
| Epistaxis | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 4 / 78 (5.13%) | |
| occurrences (all) | 7 | 5 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 7 / 78 (8.97%) | |
| occurrences (all) | 1 | 7 | |
| Hiccups | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 3 / 78 (3.85%) | |
| occurrences (all) | 9 | 3 | |
| Oropharyngeal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 76 (6.58%) | 6 / 78 (7.69%) | |
| occurrences (all) | 5 | 6 | |
| Pneumonitis | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 3 / 78 (3.85%) | |
| occurrences (all) | 4 | 3 | |
| Productive cough | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 3 / 78 (3.85%) | |
| occurrences (all) | 5 | 3 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 13 / 76 (17.11%) | 9 / 78 (11.54%) | |
| occurrences (all) | 17 | 10 | |
| Depression | | | |
| subjects affected / exposed | 13 / 76 (17.11%) | 7 / 78 (8.97%) | |
| occurrences (all) | 16 | 7 | |
| Insomnia | | | |
| subjects affected / exposed | 10 / 76 (13.16%) | 6 / 78 (7.69%) | |
| occurrences (all) | 13 | 6 | |
| Mood altered | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 5 / 78 (6.41%) | |
| occurrences (all) | 4 | 5 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 4 / 78 (5.13%) | |
| occurrences (all) | 6 | 4 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 7 / 78 (8.97%) | |
| occurrences (all) | 8 | 8 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 1 / 78 (1.28%) | |
| occurrences (all) | 6 | 1 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 1 / 78 (1.28%) | |
| occurrences (all) | 6 | 1 | |
| Blood glucose increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 76 (3.95%) | 4 / 78 (5.13%) | |
| occurrences (all) | 4 | 5 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 5 / 78 (6.41%) | |
| occurrences (all) | 5 | 5 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 8 / 76 (10.53%) | 7 / 78 (8.97%) | |
| occurrences (all) | 9 | 8 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 4 / 78 (5.13%) | |
| occurrences (all) | 5 | 7 | |
| Weight decreased | | | |
| subjects affected / exposed | 19 / 76 (25.00%) | 9 / 78 (11.54%) | |
| occurrences (all) | 27 | 11 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 3 / 78 (3.85%) | |
| occurrences (all) | 18 | 3 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 6 / 78 (7.69%) | |
| occurrences (all) | 6 | 7 | |
| Dysgeusia | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 1 / 78 (1.28%) | |
| occurrences (all) | 4 | 1 | |
| Headache | | | |
| subjects affected / exposed | 14 / 76 (18.42%) | 6 / 78 (7.69%) | |
| occurrences (all) | 17 | 6 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 18 / 78 (23.08%) | |
| occurrences (all) | 7 | 21 | |
| Paraesthesia | | | |
| subjects affected / exposed | 8 / 76 (10.53%) | 9 / 78 (11.54%) | |
| occurrences (all) | 11 | 12 | |
| Peripheral sensory neuropathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 76 (7.89%) | 3 / 78 (3.85%) | |
| occurrences (all) | 6 | 3 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 29 / 76 (38.16%) | 32 / 78 (41.03%) | |
| occurrences (all) | 39 | 42 | |
| Leukopenia | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 13 / 78 (16.67%) | |
| occurrences (all) | 15 | 28 | |
| Neutropenia | | | |
| subjects affected / exposed | 23 / 76 (30.26%) | 10 / 78 (12.82%) | |
| occurrences (all) | 49 | 21 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 2 / 78 (2.56%) | |
| occurrences (all) | 7 | 2 | |
| Constipation | | | |
| subjects affected / exposed | 14 / 76 (18.42%) | 8 / 78 (10.26%) | |
| occurrences (all) | 15 | 9 | |
| Diarrhoea | | | |
| subjects affected / exposed | 26 / 76 (34.21%) | 13 / 78 (16.67%) | |
| occurrences (all) | 50 | 23 | |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 2 / 78 (2.56%) | |
| occurrences (all) | 4 | 2 | |
| Dysphagia | | | |
| subjects affected / exposed | 9 / 76 (11.84%) | 5 / 78 (6.41%) | |
| occurrences (all) | 10 | 5 | |
| Nausea | | | |
| subjects affected / exposed | 19 / 76 (25.00%) | 13 / 78 (16.67%) | |
| occurrences (all) | 22 | 19 | |
| Odynophagia | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 1 / 78 (1.28%) | |
| occurrences (all) | 5 | 1 | |
| Oral pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 76 (5.26%) | 1 / 78 (1.28%) | |
| occurrences (all) | 4 | 1 | |
| Stomatitis | | | |
| subjects affected / exposed | 23 / 76 (30.26%) | 10 / 78 (12.82%) | |
| occurrences (all) | 30 | 13 | |
| Vomiting | | | |
| subjects affected / exposed | 19 / 76 (25.00%) | 11 / 78 (14.10%) | |
| occurrences (all) | 25 | 15 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 24 / 76 (31.58%) | 15 / 78 (19.23%) | |
| occurrences (all) | 25 | 15 | |
| Dry skin | | | |
| subjects affected / exposed | 8 / 76 (10.53%) | 2 / 78 (2.56%) | |
| occurrences (all) | 8 | 2 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 1 / 78 (1.28%) | |
| occurrences (all) | 9 | 1 | |
| Erythema | | | |
| subjects affected / exposed | 8 / 76 (10.53%) | 2 / 78 (2.56%) | |
| occurrences (all) | 8 | 3 | |
| Onycholysis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 4 / 78 (5.13%) | |
| occurrences (all) | 0 | 4 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 0 / 78 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 8 / 76 (10.53%) | 3 / 78 (3.85%) | |
| occurrences (all) | 10 | 4 | |
| Rash | | | |
| subjects affected / exposed | 14 / 76 (18.42%) | 11 / 78 (14.10%) | |
| occurrences (all) | 18 | 14 | |
| Rash maculo-papular | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 76 (6.58%) | 3 / 78 (3.85%) | |
| occurrences (all) | 8 | 3 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 6 / 78 (7.69%) | |
| occurrences (all) | 0 | 7 | |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 3 / 78 (3.85%) | |
| occurrences (all) | 4 | 3 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 5 / 78 (6.41%) | |
| occurrences (all) | 0 | 5 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 2 / 78 (2.56%) | |
| occurrences (all) | 5 | 2 | |
| Myalgia | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 1 / 78 (1.28%) | |
| occurrences (all) | 4 | 2 | |
| Neck pain | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 7 / 78 (8.97%) | |
| occurrences (all) | 7 | 7 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 5 / 78 (6.41%) | |
| occurrences (all) | 1 | 5 | |
| Pain in jaw | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 1 / 78 (1.28%) | |
| occurrences (all) | 5 | 1 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 4 / 78 (5.13%) | |
| occurrences (all) | 5 | 4 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 6 / 78 (7.69%) | |
| occurrences (all) | 2 | 6 | |
| Respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 76 (6.58%) | 2 / 78 (2.56%) | |
| occurrences (all) | 5 | 4 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 4 / 78 (5.13%) | |
| occurrences (all) | 1 | 4 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 23 / 76 (30.26%) | 14 / 78 (17.95%) | |
| occurrences (all) | 34 | 15 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 47 / 76 (61.84%) | 27 / 78 (34.62%) | |
| occurrences (all) | 95 | 46 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 8 / 78 (10.26%) | |
| occurrences (all) | 2 | 10 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 3 / 78 (3.85%) | |
| occurrences (all) | 5 | 3 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 4 / 78 (5.13%) | |
| occurrences (all) | 7 | 5 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 3 / 78 (3.85%) | |
| occurrences (all) | 9 | 3 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | 6 / 78 (7.69%) | |
| occurrences (all) | 12 | 7 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 6 / 78 (7.69%) | |
| occurrences (all) | 8 | 8 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 3 / 76 (3.95%) | 5 / 78 (6.41%) | |
| occurrences (all) | 3 | 7 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 10 December 2013 | Amendment 1 introduced the following changes: • Added pharmacokinetics (PK) sampling collection in a subset of patients in order to characterize the PK of buparlisib given in combination with paclitaxel. Aim: to assess if patients treated with buparlisib are exposed to the drug within the targeted range. The inclusion of this assessment was based on findings that emerged from Study CBEZ235A2118, which investigated the use of the same combination. The collection of additional PK data was to provide more information in support of this study indication and also to obtain a more robust population PK model based on several indications currently in clinical development using the same regimen. Objectives and statistical plan were updated accordingly. • Reduced the amount of tumor tissue required at Baseline for HPV and PI3K pathway determination Novartis had adopted the use of a more sensitive platform requiring smaller amount of DNA compared to the one previously used. The list of biomarkers being assessed was not changed. •Allowed confirmation of an adequate amount of tumor tissue for enrollment by central or local pathologist in order to accelerate the turnaround time for eligibility decision making process and eventually to start the study treatment earlier. • Mild and asymptomatic transaminase elevations at Baseline are a common finding in this patient population even in the absence of liver metastasis (e.g. related to concomitant medications, prior treatment/surgery, underlying disease, fatty liver, etc.). Therefore, the upper limit for aspartate aminotransferase (AST)/alanine aminotransferase (ALT) in patients without liver metastases was slightly increased to allow 1.5x upper limit of normal (ULN) for study inclusion. The ULN for bilirubin remained unchanged |
| 02 July 2015 | Amendment 2 issued when recruitment was 100% complete, introduced the following change(s):<br>• Provided additional guidance to Investigators regarding management of liver toxicities:<br>o Clarification of the management of AST or ALT side effects<br>o New section added "Management of hepatotoxicity (ALT and/or AST >3. 0x ULN and total bilirubin >2.0x ULN) in patients receiving buparlisib/placebo" including detailed liver event follow-up assessments and close monitoring measures<br>• Addition of hepatotoxicity follow-up testing/procedures<br>• Clarification provided in the data analysis to reflect the change in wording for number of events needed for final PFS and final OS analyses<br>• Update of the clinical background section on liver toxicity to align with the protocol amendment rationale.<br>• Clarification of laboratory parameters collection plan and viral hepatitis testing.<br>• Clarification of the wording for the number of PFS events required for the PFS analysis and for the number of deaths to be observed for the planned final Overall Survival analyses. |

| | |
|---|---|
| 30 August 2016 | The main purposes of this protocol amendment 3 were to:<br>• Provide a clarification on the measures to follow when a patient exhibits suicidal ideation regardless of the response to question 9 of the Patient Health Questionnaire-9 (PHQ-9) questionnaire (as has been described in the BKM120 Investigator's Brochure Ed. 8.0).<br>• Unblind patients' treatment considering that all planned analyses (final PFS analysis & final OS analysis) have been completed. The study was to be closed after LPLV.<br>• Reduce assessment schedule for patients still on study treatment. Tumor assessment will be performed per local clinical practices & safety evaluation will be done per revised visit schedule.<br>• For patients who are still on study treatment & are considered benefiting from study drug (s), study treatment will continue to be provided on or off this study. Treatment for these patients can also be managed according to local clinical practices per Investigator discretion. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported