# Clinical trial results:
# A Randomized, Multicenter, Double-Blind Phase 2 Study of Palbociclib Plus Cetuximab Versus Cetuximab for the Treatment of Human Papillomavirus-Negative, Cetuximab Naïve Patients With Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck After Failure of One Prior Platinum-Containing Chemotherapy Regimen

## Summary

| | |
|---|---|
| EudraCT number | 2015-000515-41 |
| Trial protocol | CZ HU ES PL SK IT |
| Global end of trial date | 02 September 2022 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 September 2023 |
| First version publication date | 21 September 2023 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | A5481044 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02499120 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Pfizer, Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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 | 02 September 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 02 September 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this Phase 2 study was to compare the efficacy and safety of palbociclib in combination with cetuximab versus cetuximab in HPV negative, cetuximab naïve subjects with R/M SCCHN after failure of 1 platinum containing regimen.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of subjects.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 10 September 2015 |
| 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 | Czechia: 1 |
| Country: Number of subjects enrolled | Hungary: 4 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | Japan: 10 |
| Country: Number of subjects enrolled | Korea, Republic of: 5 |
| Country: Number of subjects enrolled | Mexico: 7 |
| Country: Number of subjects enrolled | Poland: 5 |
| Country: Number of subjects enrolled | Romania: 9 |
| Country: Number of subjects enrolled | Russian Federation: 9 |
| Country: Number of subjects enrolled | Serbia: 8 |
| Country: Number of subjects enrolled | Slovakia: 4 |
| Country: Number of subjects enrolled | Spain: 9 |
| Country: Number of subjects enrolled | Taiwan: 13 |
| Country: Number of subjects enrolled | Ukraine: 24 |
| Country: Number of subjects enrolled | United States: 16 |
| Worldwide total number of subjects | 125 |
| EEA total number of subjects | 33 |

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) | 88 |
| From 65 to 84 years | 37 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 125 subjects were randomized; among them, 124 subjects received study treatments. One (1) subject in the palbociclib + cetuximab treatment group was randomized but not treated.

### 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, Carer |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Palbociclib + Cetuximab |

Arm description:

Subjects received Palbociclib, 125 mg, orally once daily (QD) with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute intravenous (IV) infusion followed by 250 mg/m2 weekly infused over 60 minutes.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Palbociclib 125 mg was administered QD with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute IV infusion followed by 250 mg/m2 weekly infused over 60 minutes.

| | |
|---|---|
| Investigational medicinal product name | Palbociclib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Palbociclib 125 mg was administered QD with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute intravenous (IV) infusion followed by 250 mg/m2 weekly infused over 60 minutes.

| | |
|---|---|
| **Arm title** | Placebo + Cetuximab |

Arm description:

Subjects received Placebo orally QD with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute IV infusion followed by 250 mg/m2 weekly infused over 60 minutes.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo was administered orally QD with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute IV infusion followed by 250 mg/m2 weekly infused over 60 minutes.

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo was administered orally QD with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute IV infusion followed by 250 mg/m2 weekly infused over 60 minutes.

| **Number of subjects in period 1** | Palbociclib + Cetuximab | Placebo + Cetuximab |
|---|---|---|
| Started | 65 | 60 |
| Received treatment | 64 | 60 |
| Completed | 0 | 0 |
| Not completed | 65 | 60 |
| Adverse event, serious fatal | 52 | 43 |
| Consent withdrawn by subject | 2 | 5 |
| Participant refused further follow-up | 1 | - |
| Unspecified | 9 | 10 |
| Lost to follow-up | 1 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Palbociclib + Cetuximab |
| Reporting group description: | |
| Subjects received Palbociclib, 125 mg, orally once daily (QD) with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute intravenous (IV) infusion followed by 250 mg/m2 weekly infused over 60 minutes. | |
| Reporting group title | Placebo + Cetuximab |
| Reporting group description: | |
| Subjects received Placebo orally QD with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute IV infusion followed by 250 mg/m2 weekly infused over 60 minutes. | |

| Reporting group values | Palbociclib + Cetuximab | Placebo + Cetuximab | Total |
|---|---|---|---|
| Number of subjects | 65 | 60 | 125 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 50 | 38 | 88 |
| From 65-84 years | 15 | 22 | 37 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 58.3 | 60.9 | |
| standard deviation | ± 10.2 | ± 10.1 | - |
| Sex: Female, Male<br>Units: Subjects | | | |
| FEMALE | 8 | 4 | 12 |
| MALE | 57 | 56 | 113 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White\| | 47 | 46 | 93 |
| Black\| | 1 | 1 | 2 |
| Asian\| | 15 | 13 | 28 |
| Other\| | 2 | 0 | 2 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Palbociclib + Cetuximab |
| Reporting group description: | |
| Subjects received Palbociclib, 125 mg, orally once daily (QD) with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute intravenous (IV) infusion followed by 250 mg/m2 weekly infused over 60 minutes. | |
| Reporting group title | Placebo + Cetuximab |
| Reporting group description: | |
| Subjects received Placebo orally QD with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute IV infusion followed by 250 mg/m2 weekly infused over 60 minutes. | |

### Primary: Overall Survival (OS)

| | |
|---|---|
| End point title | Overall Survival (OS) |
| End point description: | |
| OS was defined as the time from the date of randomization to the date of death due to any cause. OS (in months) was calculated as (date of death − randomization date +1)/30.4. For subjects lacking survival data beyond the date of their last follow-up, the OS time was censored on the last date they were known to be alive. Subjects lacking survival data beyond randomization had their OS times be censored at randomization. Estimates of OS and its 95% confidence interval were determined using Kaplan-Meier method. The analysis population was intent-to-treat (ITT) population, which included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline up to primary completion date (PCD) (about 34 months) | |

| End point values | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 60 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.7 (7.3 to 13.9) | 7.8 (6.7 to 10.6) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical analysis on OS |
| Comparison groups | Palbociclib + Cetuximab v Placebo + Cetuximab |

| | |
|---|---|
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.18 [1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.536 |
| upper limit | 1.253 |

Notes:

[1] - 1-sided p-value was from the log-rank test stratified by stratification factors ECOG (Eastern Cooperative Oncology Group) per randomization.

## Secondary: Percentage of Subjects with Objective Response (OR)

| | |
|---|---|
| End point title | Percentage of Subjects with Objective Response (OR) |

End point description:

OR was defined as the overall complete response (CR) or partial response (PR) according to the RECIST version 1.1. Objective response rate (ORR) was defined as the proportion of patients with best overall response (BOR) of CR or PR relative to all randomized. The analysis population was ITT population, which included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized.

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

End point timeframe:

Baseline up to PCD (about 34 months)

| End point values | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 60 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 27.7 (17.3 to 40.2) | 25.0 (14.7 to 37.9) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Clinical Benefit Response (CBR)

| | |
|---|---|
| End point title | Percentage of Subjects with Clinical Benefit Response (CBR) |

End point description:

CBR was defined as the overall CR, PR, or stable disease>=24 weeks according to the RECIST version 1.1. Clinical benefit response rate (CBRR) was defined as the proportion of patients with CR, PR, or stable disease>= 24 weeks relative to all randomized patients and randomized patients with measurable disease at baseline. The analysis population was ITT population, which included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were

randomized.

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

End point timeframe:

Baseline up to PCD (about 34 months)

| **End point values** | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 60 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 36.9 (25.3 to 49.8) | 36.7 (24.6 to 50.1) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression Free Survival (PFS)

| End point title | Progression Free Survival (PFS) |
|---|---|

End point description:

PFS which was defined as the time from the date of randomization to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever was earlier. Estimates of the PFS curves from the Kaplan Meier method were presented. The analysis population was IT population, which included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or received a different drug from that to which they were randomized.

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

End point timeframe:

Baseline up to PCD (about 34 months)

| **End point values** | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 60 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.9 (3.6 to 5.6) | 4.6 (2.3 to 5.5) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical analysis on PFS |
|---|---|
| Comparison groups | Palbociclib + Cetuximab v Placebo + Cetuximab |

| | |
|---|---|
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4953 [2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.669 |
| upper limit | 1.495 |

Notes:

[2] - 1-sided p-value was from the log-rank test stratified by stratification factors ECOG per randomization.

## Secondary: Duration of Response (DR)

| | |
|---|---|
| End point title | Duration of Response (DR) |

End point description:

DR was defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or to death due to any cause, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. DR was calculated as [the date response ended (ie, date of PD or death) – first CR or PR date + 1)]/30.4. DR was only calculated for the subgroup of all ITT subjects with an objective tumor response.

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

End point timeframe:

Baseline up to PCD (about 34 months)

| End point values | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 15 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.6 (3.7 to 7.7) | 7.4 (3.6 to 99999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs)

| | |
|---|---|
| End point title | Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) |

End point description:

TEAEs were defined as adverse events (AEs) which occurred for the first time during the effective duration of treatment or AEs that increased in severity during treatment. Serious AEs (SAEs) were defined as any untoward medical occurrence at any dose that resulted in death; was life-threatening (immediate risk of death); required inpatient hospitalization or caused prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduction normal life functions). AEs included SAEs and non-serious AEs. Causality to study

treatment was determined by the investigator. Severity was graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The analysis population included all subjects who received a t least 1 dose of study medication, with treatment assignments designated according to actual study treatment received.

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

End point timeframe:

From the first dose through and including 28 calendar days after the last administration of the study treatment (up to 6.9 years)

| **End point values** | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 60 | | |
| Units: subjects | | | | |
| AEs (all causality)\| | 61 | 56 | | |
| AEs (treatment-related)\| | 58 | 48 | | |
| SAEs (all causality)\| | 25 | 19 | | |
| SAEs (treatment-related)\| | 7 | 2 | | |
| Grade 3 or 4 AEs (all causality)\| | 33 | 19 | | |
| Grade 5 AEs (all causality)\| | 15 | 11 | | |
| Grade 3 or 4 AEs (treatment-related)\| | 34 | 10 | | |
| Grade 5 AEs (treatment-related)\| | 1 | 0 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects with Laboratory Abnormalities

| End point title | Number of Subjects with Laboratory Abnormalities |
|---|---|

End point description:

The hematology, chemistry and coagulation tests were included in the laboratory examination. Hematology evaluation included hemoglobin, platelets, white blood cell, absolute neutrophils, absolute lymphocytes. Chemistry evaluation included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, sodium, potassium, magnesium, chloride, total calcium, total bilirubin, blood urea nitrogen (BUN) or urea, creatinine, uric acid, glucose (non-fasted), albumin, phosphorus or phosphate and hemoglobin A1c (HbA1c). Coagulation evaluation included activated partial thromboplastin time/partial thromboplastin time, international normalized ratio (INR) or prothrombin time. The analysis population included all subjects with at least 1 observation of the laboratory test while on study treatment or during lag time.

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

End point timeframe:

From the Screening (Day -28) through and including 28 calendar days after the last administration of the study treatment (up to 7 years)

| End point values | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 62 | 59 | | |
| Units: Subjects | 61 | 55 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)

| End point title | Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) |
|---|---|

End point description:

The EORTC QLQ-C30 is a 30 item questionnaire composed of 5 multi-item functional subscales, 3 multi-item symptom scales, a global health/quality of life (QOL) subscale, and 6 single items assessing other cancer related symptoms. The questionnaire employed twenty-eight 4 point Likert scales with responses from "not at all" to "very much" and two 7 point Likert scales for global health and overall QOL. For functional and global QOL scales, higher scores represented a better level of functioning and were converted to a 0 to 100 scale. For symptom oriented scales, a higher score represented more severe symptoms. Negative changes from baseline indicate deterioration in functioning / global QoL scales and improvement in symptom scales. The analysis population included all ITT subjects, who had both baseline and at least 1 follow-up patient reported outcome (PRO) assessment before treatment discontinuation.

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

End point timeframe:

Baseline up to PCD (about 34 months)

| End point values | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 57 | 55 | | |
| Units: units on a scale | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Global health status / QOL\| | 2.819 (-1.49 to 7.13) | 2.687 (-1.70 to 7.08) | | |
| Functional scale: Physical functioning\| | 0.736 (-3.26 to 4.73) | -0.463 (-4.59 to 3.66) | | |
| Functional scale: Role functioning\| | -0.407 (-5.91 to 5.09) | -1.600 (-7.28 to 4.08) | | |
| Functional scale: Cognitive functioning\| | -1.466 (-5.14 to 2.21) | -1.230 (-5.06 to 2.59) | | |
| Functional scale: Social functioning\| | 1.239 (-4.43 to 6.90) | 2.082 (-3.76 to 7.92) | | |
| Symptom scale/item: Fatigue\| | -2.788 (-7.04 to 1.46) | -5.124 (-9.50 to -0.75) | | |
| Symptom scale/item: Nausea and vomiting\| | -0.869 (-2.63 to 0.90) | -1.040 (-2.82 to 0.74) | | |
| Symptom scale/item: Pain\| | -5.977 (-11.06 to -0.90) | -6.096 (-11.32 to -0.87) | | |

| | | | | |
|---|---|---|---|---|
| Symptom scale/item: Dyspnoea\| | 3.074 (-2.15 to 8.30) | 5.086 (-0.27 to 10.45) | | |
| Symptom scale/item: Insomnia\| | -4.623 (-10.33 to 1.08) | -5.018 (-10.88 to 0.84) | | |
| Symptom scale/item: Appetite loss\| | 2.247 (-3.89 to 8.38) | -0.687 (-7.04 to 5.67) | | |
| Symptom scale/item: Constipation\| | -4.120 (-10.30 to 2.06) | -1.326 (-7.72 to 5.07) | | |
| Symptom scale/item: Diarrhoea\| | 4.255 (1.34 to 7.17) | 1.744 (-1.24 to 4.73) | | |
| Symptom scale/item: Financial difficulties\| | -5.258 (-11.61 to 1.10) | -0.273 (-6.83 to 6.29) | | |
| Functional scale: Emotional functioning\| | 4.155 (0.13 to 8.18) | 3.560 (-0.57 to 7.69) | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer Head and Neck Module 35 (EORTC QLQ H&N35)**

| | |
|---|---|
| End point title | Change from Baseline in European Organization for Research and Treatment of Cancer Head and Neck Module 35 (EORTC QLQ H&N35) |

End point description:

The EORTC QLQ H&N35 is designed to be used together with the core QLQ C30. The recall period for the items in the module was "the past week". Items hn1 to hn30 were scored on 4 point Likert type categorical scales ("not at all", "a little", "quite a bit", "very much"). Items hn31 to hn35 had a "no/yes" response format. The scores were transformed into 0 to 100 scales, with a high score implying a high level of symptoms.Negative changes from baseline indicate deterioration in functioning / global QoL scales and improvement in symptom scales. The analysis population included all ITT subjects, who had both baseline and at least 1 follow-up PRO assessment before treatment discontinuation.

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

End point timeframe:

Baseline up to PCD (about 34 months)

| **End point values** | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 57 | 55 | | |
| Units: units on a scale | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Symptom scale/item: Pain\| | -3.565 (-8.56 to 1.43) | -0.407 (-5.54 to 4.73) | | |
| Symptom scale/item: Swallowing\| | -4.344 (-8.79 to 0.10) | -1.469 (-6.03 to 3.09) | | |
| Symptom scale/item: Senses problems\| | -1.582 (-7.22 to 4.05) | -1.879 (-7.72 to 3.96) | | |
| Symptom scale/item: Speech problems\| | -4.541 (-9.21 to 0.13) | -2.691 (-7.51 to 2.13) | | |
| Symptom scale/item: Trouble with social eating\| | -5.550 (-10.14 to -0.96) | -0.709 (-5.42 to 4.01) | | |

| | | | | |
|---|---|---|---|---|
| Symptom scale/item: Trouble with social contact\| | -1.265 (-5.68 to 3.15) | 3.452 (-1.14 to 8.04) | | |
| Symptom scale/item: Less sexuality\| | -3.323 (-11.44 to 4.80) | 4.904 (-3.72 to 13.53) | | |
| Symptom scale/item: Teeth\| | -1.586 (-8.91 to 5.74) | -1.880 (-9.29 to 5.53) | | |
| Symptom scale/item: Opening mouth\| | 0.347 (-5.29 to 5.99) | 0.215 (-5.56 to 5.99) | | |
| Symptom scale/item: Dry mouth\| | -6.300 (-10.50 to -2.10) | 3.444 (-0.82 to 7.71) | | |
| Symptom scale/item: Sticky saliva\| | -3.912 (-9.70 to 1.88) | 4.680 (-1.22 to 10.58) | | |
| Symptom scale/item: Coughing\| | -3.988 (-8.67 to 0.69) | -1.717 (-6.48 to 3.04) | | |
| Symptom scale/item: Felt ill\| | 1.320 (-4.22 to 6.86) | 0.124 (-5.45 to 5.70) | | |
| Symptom scale/item: Pain killers\| | -13.184 (-24.49 to -1.88) | -11.393 (-23.02 to 0.24) | | |
| Symptom scale/item: Nutritional supplements\| | 0.351 (-7.19 to 7.89) | -4.370 (-12.23 to 3.49) | | |
| Symptom scale/item: Feeding tube\| | -6.364 (-9.58 to -3.15) | -0.107 (-3.30 to 3.08) | | |
| Symptom scale/item: Weight loss\| | -17.723 (-27.23 to -8.21) | -9.470 (-19.16 to 0.22) | | |
| Symptom scale/item: Weight gain\| | -3.030 (-10.08 to 4.02) | 5.159 (-1.96 to 12.27) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Summary of PFS and OS for P16 Negative (%Positive tumor cells < 70%)

| End point title | Summary of PFS and OS for P16 Negative (%Positive tumor cells < 70%) |
|---|---|

End point description:

A central test was defined as the tumor tissue-based p16 IHC test performed at a central laboratory (Ventana). The analysis of concordance between HPV status as assessed by local or central laboratory included the number and percentage of subjects with p16 detected or not detected at the central laboratory, given that all local testing must have been negative for HPV in order for the subject to be eligible for the study. Initial analysis of the p16 status was based on the conventional cutoff of 70% p16-positive tumor cells to call out cases that might be considered HPV-positive. P16 expression was scored as positive if strong and diffuse nuclear and cytoplasmic staining was present in at least 70% of the tumor cells. The analysis population included all subjects treated with cetuximab in combination with placebo or palbociclib who had at least 1 baseline biomarker assessment.

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

End point timeframe:

Screening

| End point values | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 54 | 48 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| PFS\| | 3.7 (3.2 to 5.6) | 5.0 (1.3 to 7.2) | | |
| OS\| | 9.9 (7.1 to 13.9) | 8.0 (7.0 to 14.7) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Trough plasma concentration (Ctrough) and within-participant mean steady-state pre-dose concentration (WPM-Ctrough) at steady state for Palbociblib

| End point title | Trough plasma concentration (Ctrough) and within-participant mean steady-state pre-dose concentration (WPM-Ctrough) at steady state for Palbociblib[3] |
|---|---|

End point description:

Ctrough is steady-state pre-dose concentration, which was observed directly from data. WPM-Ctrough is within-subject mean steady-state pre-dose concentration. For palbociclib, a steady-state trough was to be defined as a pre-dose plasma concentration following at least 7 consecutive days of 125 mg daily dose without dosing interruption and the time window for the PK collection was to be between 24 hr +/- 2 hr and 24 min post-dose the day prior to PK collection and no more than 1 hr post-dose on the day of PK collection. The analysis population included all as-treated subjects, who were treated with the study treatments and had a t least measured plasma concentration for at least 1 analyte (palbociclib and/or cetuximab)

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

End point timeframe:

Pre-dose of Day 15 in Cycle 1 and Cycle 2

Notes:

[3] - 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: 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.

| End point values | Palbociclib + Cetuximab | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 57 | | | |
| Units: nanograms per millilitre (ng/ml) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Ctrough Cycle 1 Day 15\| | 69.75 (± 28.208) | | | |
| Ctrough Cycle 2 Day 15\| | 67.79 (± 28.905) | | | |
| WPM-Ctrough\| | 71.64 (± 30.183) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Summary of PFS and OS Based on Investigator Assessment by Rb Expression >= 1%

| End point title | Summary of PFS and OS Based on Investigator Assessment by Rb Expression >= 1% |
|---|---|

End point description:

Rb expression in the palbociclib and cetuximab treatment group, the relationship of the biomarkers (individually) with PFS and OS were explored using graphical methods such as box plots, at baseline. The tumors of subjects were Rb-positive, which was defined by Rb IHC with>=1% positive tumor cells. The analysis population included all subjects treated with cetuximab in combination with placebo or palbociclib who had at least 1 baseline biomarker assessment.

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

End point timeframe:

Screening

| End point values | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 57 | 53 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| PFS\| | 3.9 (3.5 to 6.2) | 4.6 (2.6 to 5.6) | | |
| OS\| | 10.5 (7.1 to 15.6) | 7.8 (6.9 to 11.8) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Ctrough and Cendinf, WPM-Ctrough and WPM-Cendinf at steady state for Serum Cetuximab

| End point title | Ctrough and Cendinf, WPM-Ctrough and WPM-Cendinf at steady state for Serum Cetuximab |
|---|---|

End point description:

Ctrough is steady-state pre-dose concentration. Cendinf is steady-state end-of-infusion concentration. Ctrough and Cendinf were observed directly from data. WPM-Ctrough and WPM-Cendinf are within-subject mean steady-state pre-dose concentration and end-of-infusion concentration. Acceptance criteria for a steady-state Cendinf was defined as a PK sample that was 1) collected after at least 3 consecutive weeks of cetuximab IV infusions without interruption or prior dose reduction and 2) was collected at the end of cetuximab infusion time +/- 10% of the actual duration of the cetuximab infusion. The analysis population included all as-treated subjects, who were treated with the study treatments and had at least measured plasma concentration for at least 1 analyte (palbociclib and/or cetuximab)

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

End point timeframe:

Pre-dose and end-of infusion of Day 15 in Cycle 1 and Cycle 2

| End point values | Palbociclib + Cetuximab | Placebo + Cetuximab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 57 | 57 | | |
| Units: ng/ml | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Ctrough Cycle 1 Day 15\| | 39706.407 (± 92) | 42914.095 (± 62) | | |
| Ctrough Cycle 2 Day 15\| | 54005.307 (± 74) | 52995.663 (± 71) | | |
| WPM-Ctrough\| | 45605.949 (± 83) | 46796.538 (± 63) | | |
| Cendinf Cycle 1 Day 15\| | 145748.275 (± 43) | 137185.479 (± 61) | | |
| Cendinf Cycle 2 Day 15\| | 149155.706 (± 38) | 153310.061 (± 39) | | |
| WPM-Cendinf\| | 149119.179 (± 36) | 148063.341 (± 39) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose through and including 28 calendar days after the last administration of the study treatment (up to 6.9 years).

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. An event may be categorized as serious in 1 subject and as non-serious in another subject, or 1 subject may have experienced both a serious and non-serious event during the study. Total number at risk below refers to the number of subjects evaluable for SAEs or AEs.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

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

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo + Cetuximab |

Reporting group description:

Subjects received Placebo orally QD with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute IV infusion followed by 250 mg/m2 weekly infused over 60 minutes.

| | |
|---|---|
| Reporting group title | Palbociclib + Cetuximab |

Reporting group description:

Subjects received Palbociclib, 125 mg, orally once daily (QD) with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle in combination with Cetuximab, 400 mg/m2 initial dose as a 120-minute intravenous (IV) infusion followed by 250 mg/m2 weekly infused over 60 minutes.

| Serious adverse events | Placebo + Cetuximab | Palbociclib + Cetuximab | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 19 / 60 (31.67%) | 25 / 64 (39.06%) | |
| number of deaths (all causes) | 43 | 52 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disease progression | | | |
| subjects affected / exposed | 6 / 60 (10.00%) | 7 / 64 (10.94%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Death | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal obstruction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac arrest | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 2 / 64 (3.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (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 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (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 | | | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 4 / 64 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Abscess | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo + Cetuximab | Palbociclib + Cetuximab | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 53 / 60 (88.33%) | 55 / 64 (85.94%) | |
| Investigations | | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 11 / 64 (17.19%) | |
| occurrences (all) | 0 | 26 | |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 5 / 64 (7.81%) | |
| occurrences (all) | 6 | 5 | |
| Neutrophil count decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 60 (0.00%) | 9 / 64 (14.06%) | |
| occurrences (all) | 0 | 25 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 5 / 64 (7.81%) | |
| occurrences (all) | 3 | 6 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 2 / 64 (3.13%) | |
| occurrences (all) | 7 | 5 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 1 / 64 (1.56%) | |
| occurrences (all) | 8 | 5 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 10 / 64 (15.63%) | |
| occurrences (all) | 0 | 21 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 5 / 64 (7.81%) | |
| occurrences (all) | 4 | 5 | |
| Hypotension | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 3 / 64 (4.69%) | |
| occurrences (all) | 4 | 3 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 6 / 64 (9.38%) | |
| occurrences (all) | 5 | 10 | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 60 (10.00%) | 3 / 64 (4.69%) | |
| occurrences (all) | 7 | 4 | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 5 / 64 (7.81%) | |
| occurrences (all) | 0 | 12 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 19 / 64 (29.69%) | |
| occurrences (all) | 0 | 53 | |
| Lymphopenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 60 (1.67%) | 7 / 64 (10.94%) | |
| occurrences (all) | 1 | 22 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 13 / 64 (20.31%) | |
| occurrences (all) | 0 | 39 | |
| Anaemia | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | 23 / 64 (35.94%) | |
| occurrences (all) | 9 | 47 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | 9 / 64 (14.06%) | |
| occurrences (all) | 11 | 17 | |
| Fatigue | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | 8 / 64 (12.50%) | |
| occurrences (all) | 11 | 8 | |
| Asthenia | | | |
| subjects affected / exposed | 7 / 60 (11.67%) | 5 / 64 (7.81%) | |
| occurrences (all) | 10 | 7 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 6 / 60 (10.00%) | 8 / 64 (12.50%) | |
| occurrences (all) | 10 | 9 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 4 / 64 (6.25%) | |
| occurrences (all) | 0 | 7 | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 9 / 64 (14.06%) | |
| occurrences (all) | 12 | 11 | |
| Constipation | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 7 / 64 (10.94%) | |
| occurrences (all) | 6 | 7 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 4 / 64 (6.25%) | |
| occurrences (all) | 2 | 4 | |
| Dysphagia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 60 (8.33%) | 9 / 64 (14.06%) | |
| occurrences (all) | 6 | 16 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 3 / 64 (4.69%) | |
| occurrences (all) | 5 | 4 | |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | 4 / 64 (6.25%) | |
| occurrences (all) | 8 | 4 | |
| Productive cough | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 6 / 64 (9.38%) | |
| occurrences (all) | 4 | 6 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 13 / 60 (21.67%) | 14 / 64 (21.88%) | |
| occurrences (all) | 22 | 23 | |
| Dry skin | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 9 / 64 (14.06%) | |
| occurrences (all) | 2 | 12 | |
| Pruritus | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 7 / 64 (10.94%) | |
| occurrences (all) | 5 | 11 | |
| Rash | | | |
| subjects affected / exposed | 21 / 60 (35.00%) | 27 / 64 (42.19%) | |
| occurrences (all) | 35 | 42 | |
| Musculoskeletal and connective tissue disorders | | | |
| Neck pain | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 5 / 64 (7.81%) | |
| occurrences (all) | 4 | 8 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 60 (10.00%) | 4 / 64 (6.25%) | |
| occurrences (all) | 6 | 4 | |
| Paronychia | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | 2 / 64 (3.13%) | |
| occurrences (all) | 8 | 3 | |

| | | | |
|---|---|---|---|
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 4 / 64 (6.25%) | |
| occurrences (all) | 5 | 4 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | 11 / 64 (17.19%) | |
| occurrences (all) | 10 | 25 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 6 / 64 (9.38%) | |
| occurrences (all) | 1 | 7 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 6 / 64 (9.38%) | |
| occurrences (all) | 1 | 8 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 0 / 64 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 3 / 64 (4.69%) | |
| occurrences (all) | 10 | 3 | |
| Decreased appetite | | | |
| subjects affected / exposed | 10 / 60 (16.67%) | 12 / 64 (18.75%) | |
| occurrences (all) | 10 | 19 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 09 April 2015 | 1. Protocol Summary/Study Design/ Tumor Assessment Requirements Flowchart/Sections 3 Study Design, 7.1.1.2 Post-Baseline Tumor Assessments: Removed statement concerning continuous treatment beyond RECIST-defined disease progression (agreement between Sponsor and FDA). 2. Protocol Summary, Study Design/Section 3 Study Design/Section 4.3 Randomization Criteria/Section 5.1 Allocation to Treatment/9.2.1 Analysis of Primary Endpoint: Clarified stratification terminology from checkpoint inhibitors to immunotherapy. 3. Schedule of Activities/Tumor Assessment Requirements Flowchart/Sections 7.1.1.1 Screening/Baseline Tumor Assessments and 7.1.1.2 Post-Baseline Tumor Assessments: Added CT or MRI scan of the chest and abdomen (including the liver) to support PFS secondary endpoint. 4. Clarification of Inclusion Criteria # 9 for patients aged 20 years old or greater as applicable by local country regulations. 5. Section 5.5.3.1.1 Cetuximab Hypersensitivity Reactions: Simplified wording for cetuximab retreatment after Grade 2 hypersensitivity reactions. 6. Section 5.5.3.1.4 Cetuximab Gastrointestinal Adverse Events: Added "Patients experiencing treatment-related Grade 4 vomiting or diarrhea should have their cetuximab and palbociclib/placebo treatments permanently discontinued." 7. Section 5.5.3.2.1 Palbociclib/Placebo Dosing Interruptions/Delays: Added "Patients experiencing treatment-related Grade 4 vomiting, diarrhea, or hypertension should have their palbociclib/placebo and cetuximab treatments permanently discontinued." Removed "≥" from Grade 3 non-hematologic bullet point (5th bullet point). Added bullet point "Grade 4 non-hematologic toxicities (see exceptions of vomiting, diarrhea, or hypertension above)." 8. Required Protocol Template updates in Adverse Event Reporting section and Communication of Results by Pfizer section. |
| 31 March 2016 | 1. Schedule of Activities/Tumor Assessment Requirements Flowchart: 29Jul2015 PCL removal of the phrase "on Day 1 of event cycles" for Disease Assessment to align with Section 7.1.1, Tumor Assessment. 2. Schedule of Activities, footnote c/Section 6.2, Active Treatment Phase: Add vital signs for any new cycle Day 1 procedures. 3. Schedule of Activities, footnote l/Section 6.3, End of Treatment Visit/Section 7.3.1, Laboratory Safety Assessments: included patients starting post-study anticancer therapy for 8 week chemistry panel analysis. 4. Schedule of Activities, footnote n /Abbreviations/Section 7.3.1, Laboratory Safety Assessments: 21Oct2015 PCL added aPTT as acceptable coagulation parameter. 5. Schedule of Activities, footnote y/Section 5.8, Concomitant Treatments: Added further clarification for patients beginning new therapy before the 28-day time period is complete. 6. Schedule of Activities, footnote z/Section 7.7, Patient Reported Outcomes: Added further clarification for patients starting post-study anticancer therapy. 7. Tumor Assessment Requirements Flowchart, footnote d/Section 7.1.1 Tumor Assessment: Removed the phrase "and pelvis". 8. Section 4.2 Exclusion Criteria: Removed the phrase "or requirement for a feeding tube" and clarified inability to swallow capsules for Exclusion Criterion # 5. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported