NOVARTIS

PIQRAY® (alpelisib)

1 Tradename

PIQRAY® 200MG DAILY DOSE PACK

PIQRAY® 250MG DAILY DOSE PACK (200mg + 50mg)

PIQRAY® 300MG DAILY DOSE PACK (150mg + 150mg)

2 Description and composition

Pharmaceutical form

Film-coated tablets

- 50 mg: Light pink, unscored, round and curved with beveled edges, imprinted with "L7" on one side and "NVR" on the other side.
- 150 mg: Pale red, unscored, ovaloid and curved with beveled edges, imprinted with "UL7" on one side and "NVR" on the other side.
- 200 mg: Light red, unscored, ovaloid and curved with beveled edges, imprinted with "YL7" on one side and "NVR" on the other side.

Active substance

Film-coated tablets containing alpelisib

Excipients

Film-coated tablet core: Microcrystalline cellulose, mannitol, sodium starch glycolate, hypromellose and magnesium stearate.

Coating material: Hypromellose, titanium dioxide, macrogol / polyethylene glycol (PEG), talc, iron oxide red, and iron oxide black.

Information might differ in some countries.

3 Indications

Piqray® is an α-specific class I phosphatidylinositol-3-kinase (PIK3CA) inhibitor indicated for the treatment of postmenopausal women, and men, with hormone receptor positive, HER2-negative, advanced breast cancer with a PIK3CA mutation in combination with fulvestrant after disease progression following an endocrine-based regimen.

4 Dosage regimen and administration

Treatment with Piqray should be initiated by a physician experienced in the use of anticancer therapies.

Dosage regimen

General target population

Patients with HR positive, HER2 negative advanced breast cancer should be selected for treatment with Piqray, based on the presence of a PIK3CA mutation in tumor or plasma specimens, using a validated test. If a mutation is not detected in a plasma specimen, test tumor tissue if available.

There was no treatment benefit demonstrated in patients without PIK3CA mutations in the phase III clinical study (see section 12 clinical studies).

The recommended dose of Piqray is 300 mg (2×150 mg film-coated tablets) taken orally, once daily on a continuous basis. Piqray should be taken immediately following food, at approximately the same time each day (see section 11 Clinical pharmacology and section 8 Interactions). The maximum recommended daily dose of Piqray is 300 mg. If a dose of Piqray is missed, it can be taken immediately following food and within 9 hours after the time it is usually administered. After more than 9 hours, the dose should be skipped for that day. On the next day, Piqray should be taken at its usual time. If the patient vomits after taking the Piqray dose, the patient should not take an additional dose on that day and should resume the usual dosing schedule the next day, at the usual time.

When co-administered with Piqray, the recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15 and, 29, and once monthly thereafter. Please refer to the full prescribing information of fulvestrant.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Dosing modifications may be necessary to improve tolerability.

Dosing modifications

The recommended daily dose of Piqray is 300 mg. Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dosing interruption, reduction, and/or discontinuation of Piqray. If dosing reduction is required, the dosing reduction guidelines for ADRs are listed in Table 4-1. A maximum of 2 dosing reductions are recommended, after which the patient should be discontinued from treatment with Piqray. Dosing reduction should be based on worst preceding toxicity.

Table 4-1 Recommended Dosing reduction guidelines for adverse drug reactions for Piqray[1]

Piqray dose level	Dose and schedule	Number and strength of tablets
Starting dose	300 mg/day continuously	2 x 150 mg tablets
First dose reduction	250 mg/day continuously	1 x 200 mg tablet and 1 x 50 mg tablet
Second dose reduction	200 mg/day continuously	1 x 200 mg tablet
[1]Only one dose reduction is permitted for pancreatitis.		

Tables 4-2, 4-3, 4-4 and 4-5 summarize recommendations for dosing interruption, reduction or discontinuation of Piqray in the management of specific ADRs. Clinical judgment of the treating physician, including confirmation of laboratory values if deemed

necessary, should guide the management plan of each patient based on the individual benefit/risk assessment for treatment with Piqray.

Hyperglycaemia

Consultation with a Healthcare Professional (HCP) with experience in the management of hyperglycemia should be considered and lifestyle changes as per local guidelines (e.g. American Diabetes Association (ADA)), including exercise and dietary advice should be recommended/reinforced (e.g. small frequent meals, low carbohydrate, high fiber, low processed food intake, three macronutrient balanced meals and 2 optional small snacks rather than one large meal).

In patients with risk factors for hyperglycemia, monitor fasting glucose more closely and as clinically indicated (see section 6 Warnings and precautions).

Table 4-2 Dosing Modification and Management for Hyperglycaemia[1]

Fasting Glucose (FG)[2]	**Recommendation**
Dose modifications and management should only be based on fasting glucose (plasma/blood) values.	
> ULN - 160 mg/dL or > ULN - 8.9 mmol/L	No Piqray dose adjustment required. Initiate or intensify oral anti-diabetic treatment[2].
>160 - 250 mg/dL or > 8.9 - 13.9 mmol/L.	No Piqray dose adjustment required. Initiate or intensify oral anti-diabetic treatment[2]. If FG does not decrease to ≤160 mg/dL or 8.9 mmol/L within 21 days with appropriate oral anti-diabetic treatment[2,3], reduce Piqray dose by 1 dose level, and follow FG value specific recommendations.
> 250 - 500 mg/dL or > 13.9 - 27.8 mmol/L	Interrupt Piqray. Initiate or intensify oral anti-diabetic treatment[2] and consider additional anti-diabetic medications such as insulin[3] for 1-2 days until hyperglycemia resolves, as clinically indicated. Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances). If FG decreases to ≤160 mg/dL or 8.9 mmol/L within 3 to 5 days under appropriate anti-diabetic treatment, resume Piqray at next lower dose level. If FG does not decrease to ≤160 mg/dL or 8.9 mmol/L within 3 to 5 days under appropriate anti-diabetic treatment, consultation with a physician with expertise in the treatment of hyperglycemia is recommended. If FG does not decrease to ≤160 mg/dL or 8.9 mmol/L within 21 days following appropriate anti-diabetic treatment[2,3], permanently discontinue Piqray treatment.

> 500 mg/dL or > 27.8 mmol/L	Interrupt Piqray Initiate or intensify appropriate anti-diabetic treatment[23] (administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances)), re-check within 24 hours and as clinically indicated. If FG decreases to (≤ 500 mg/dL) or (≤ 27.8 mmol/L), then follow FPG value specific recommendations for (<500 mg/dL). If FG is confirmed at > 500 mg/dL or (> 27.8 mmol/L), permanently discontinue Piqray treatment.

[1] Fasting Glucose levels reflect hyperglycemia grading according to CTCAE Version 4.03. CTCAE=Common Terminology Criteria for Adverse Events.

[2] Applicable anti-diabetic medications, like metformin, SGLT2 inhibitors or insulin sensitizers (such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors), should be initiated and respective prescribing information should be reviewed for dosing and dose titration recommendations, including local diabetic treatment guidelines. Metformin was recommended in the phase III clinical study with the following guidance [6]: Metformin 500 mg once daily should be initiated. Based on tolerability, metformin dose may be increased to 500 mg bid, followed by 500 mg with breakfast, and 1000 mg with dinner, followed by further increase to 1000 mg bid if needed (see section 6 Warnings and precautions).

[3] As recommended in the phase III clinical study, insulin may be used for 1-2 days until hyperglycemia resolves. However, this may not be necessary in the majority of alpelisib-induced hyperglycemia, given the short half-life of alpelisib and the expectation of glucose levels normalizing after interruption of Piqray

Rash

Oral antihistamine administration may be considered prophylactically, at the time of initiation of treatment with Piqray. Based on the severity of rash, Piqray may require dose interruption, reduction, or discontinuation as described in Table 4-3 (see section 7 Adverse drug reactions).

Table 4-3 Dosing Modification and Management for Rash[1]

Grade	Recommendation
All Grades	Consultation with a dermatologist should always be considered.
Grade 1 (<10% body surface area (BSA) with active skin toxicity)	No Piqray dose adjustment required. Initiate topical corticosteroid treatment. Consider adding oral antihistamine treatment to manage symptoms. If active rash is not improved within 28 days of appropriate treatment, add a low dose systemic corticosteroid.
Grade 2 (10-30% BSA with active skin toxicity)	No Piqray dose adjustment required. Initiate or intensify topical corticosteroid and oral antihistamine treatment. Consider low dose systemic corticosteroid treatment. If rash improves to Grade 1 ≤ within 10 days, systemic corticosteroid may be discontinued.
Grade 3 (e.g: severe rash not responsive to medical management). (>30% BSA with active skin toxicity)	Interrupt Piqray until rash improves to Grade ≤1. Initiate or intensify topical/systemic corticosteroid and anti-histamine treatment. Once rash improves to Grade ≤1, resume Piqray at next lower dose level.
Grade 4 (e.g: severe bullous, blistering or exfoliating skin conditions). (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	Permanently discontinue Piqray.
[1] *Grading according to CTCAE Version 5.0*	

Table 4-4 Dosing modification and management for diarrhea or colitis[1]

Grade[1]	Recommendation
Grade 1	No Piqray dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	Interrupt Piqray dose until improvement to Grade ≤1, then resume Piqray at same dose level. For recurrent Grade ≥2, interrupt Piqray dose until improvement to Grade ≤1, then resume Piqray at the next lower dose level. Initiate or intensify appropriate medical therapy and monitor as clinically indicated[2].
Grade 3	Interrupt Piqray dose until improvement to Grade ≤1, then resume Piqray at the next lower dose level. Initiate or intensify appropriate medical therapy and monitor as clinically indicated[2,3].
Grade 4	Permanently discontinue Piqray[3].

[1] Grading according to CTCAE Version 5.0.
[2] For Grade 2 and 3 colitis consider additional treatment, such as steroids.
[3] For Grade 3 and 4 diarrhea, patients should additionally be managed according to local standard of care, including electrolyte monitoring, administration of antiemetics and antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.

Other toxicities

Table 4-5 Dosing Modification and Management for other toxicities (excluding hyperglycemia, rash and diarrhea)[1]

Grade	Recommendation
Grade 1 or 2	No Piqray dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated[2,3].
Grade 3	Interrupt Piqray dose until improvement to Grade ≤1, then resume Piqray at the next lower dose level[2].
Grade 4	Permanently discontinue Piqray.

[1] Grading according to CTCAE Version 5.0 .

[2] For Grade 2 and 3 pancreatitis, interrupt Piqray dose until improvement to Grade ≤1 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity recurs, permanently discontinue Piqray treatment.

[3] For Grade 2 total bilirubin elevation, interrupt Piqray dose until improvement to Grade ≤1 and resume at the same dose if improved in ≤14 days or resume at the next lower dose level if improved in >14 days.

Refer to the full prescribing information for fulvestrant for dose modification guidelines in the event of toxicity and other relevant safety information.

Special populations

Renal impairment

Based on population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild or moderate renal impairment (see section 11 Clinical pharmacology). Caution should be used in patients with severe renal impairment as there is no experience with Piqray in this population (see section 11 Clinical pharmacology).

Hepatic impairment

Based on a hepatic impairment study in non-cancer subjects with impaired hepatic function, no dose adjustment is necessary in patients with mild, moderate and severe hepatic impairment (Child-Pugh class A, B or C, respectively) (see section 11 Clinical pharmacology).

Refer to the full prescribing information of fulvestrant for dose modifications related to hepatic impairment.

Pediatric patients (below 18 years)

The safety and efficacy of Piqray in pediatric patients have not been established.

Geriatric patients (65 years or above)

No dosage regimen adjustment is required in patients 65 years or above (see section 12 Clinical studies).

Method of administration

Piqray tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). Tablets that are broken, cracked, or otherwise not intact should not be ingested.

5 Contraindications

Piqray is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

6 Warnings and precautions

Hypersensitivity (including anaphylactic reaction)

Serious hypersensitivity reactions (including anaphylactic reaction and anaphylactic shock), manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever or tachycardia were reported in patients treated with Piqray in clinical studies (see section 7 Adverse drug reactions). Angioedema has been reported in the post marketing setting in patients treated with Piqray (see section 7 Adverse drug reactions). The incidence of Grade 3 and 4 hypersensitivity reactions was 0.7%.

Piqray should be permanently discontinued and should not be re- introduced in patients with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

Severe cutaneous reactions

Severe cutaneous reactions have been reported with Piqray. In the Phase III clinical study, Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) were reported in 1 (0.4%) and
3 (1.1%) patients, respectively. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in the post marketing setting (see section 7 Adverse drug reactions).

Piqray treatment should not be initiated in patients with history of severe cutaneous reactions.

Patients should be advised of the signs and symptoms of severe cutaneous reactions (eg. a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash). If signs or symptoms of severe cutaneous reactions are present, Piqray should be interrupted until the etiology of the reaction has been determined. A consultation with a dermatologist is recommended. If a severe cutaneous reaction is confirmed, Piqray should be permanently discontinued. Piqray should not be reintroduced in patients who have experienced previous severe cutaneous reactions. If a severe cutaneous reaction is not confirmed, Piqray may require treatment interruption, dose reduction, or treatment discontinuation as described in Table 4-3 Dose Modification and Management for rash (see section 4 Dosage and administration).

Hyperglycaemia

Severe hyperglycemia, in some cases associated with hyperglycemic hyperosmolar nonketotic syndrome (HHNKS) or ketoacidosis, has been observed in patients treated with Piqray. Some cases of ketoacidosis with fatal outcome have been reported in the post marketing setting.

Hyperglycaemia, including ketoacidosis, was reported in patients treated with Piqray. Hyperglycemia was reported in 64.8% of patients treated with Piqray in the phase III clinical study. Grade 2 (fasting glucose 160 to 250 mg/dL), 3 (fasting glucose >250 to 500 mg/dL) or 4 (fasting glucose > 500 mg/dL) hyperglycaemia were reported in 15.8%, 33.1% and 3.9% of patients, respectively, in phase III clinical study. Ketoacidosis was reported in 0.7% of patients (n = 2) treated with Piqray.

In the phase III clinical study, patients with a history of diabetes mellitus intensified anti-diabetic medication(s) while on treatment with Piqray; therefore, these patients require monitoring and possibly intensified anti-diabetic treatment. Patients with poor glycemic control may be at a higher risk of developing severe hyperglycemia and associated complications. Patients with risk factors for hyperglycemia such as obesity (BMI ≥30), elevated FPG or HbA1c at or above the upper limit of normal, or age ≥75 are at a higher risk of developing severe hyperglycemia. Schedule for monitoring fasting glucose is presented in

Table 6-1.

Patients should be advised of the signs and symptoms of hyperglycaemia (e.g. excessive thirst, urinating more often than usual or higher amount of urine than usual, increased appetite with weight loss). If signs or symptoms of hyperglycaemia are present, Piqray may require treatment interruption, dose reduction, or treatment discontinuation as described in Table 4-2.

The safety of PIQRAY in patients with Type 1 and uncontrolled Type 2 diabetes has not been established as these patients were excluded from the SOLAR-1 trial. Patients with a medical history of Type 2 diabetes were included.

In patients with hyperglycemia, 163/187 (87.2%) were managed with anti-diabetic medication and 142/187 (75.9%) reported use of metformin as single agent or in combination with other anti-diabetic medication. The maximum dose of metformin recommended in phase III clinical study was 2,000 mg per day.

In patients with hyperglycemia of at least Grade 2 (FPG 160 to 250 mg/dL), median time to improvement by at least 1 Grade of the first event was 8 days (95% CI of 8 to 10 days). In all patients with elevated FPG, who continued fulvestrant treatment after discontinuing Piqray, all FPG levels returned to baseline (normal).

Based on the severity of the hyperglycemia, Piqray may require dose interruption, reduction, or discontinuation as described in Table 4-2 Dose Modification and Management for hyperglycemia. (see section 4 Dosage regimen and administration).

Table 6-1 Schedule of fasting glucose monitoring

	Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with Piqray	**Recommended schedule of monitoring of fasting glucose and HbA1c levels in patients with diabetes, pre-diabetes, BMI ≥30 or age ≥75 years treated with Piqray**
At screening, before initiating treatment with Piqray	Test for fasting plasma glucose (FPG), HbA1c, and optimize the patient's level of blood glucose.	
After initiating treatment with Piqray	Monitor/self-monitor fasting glucose at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated, according to the instructions of a healthcare professional*.	Monitor/self-monitor fasting glucose more frequently for the first few weeks of treatment. Then continue to monitor fasting glucose as frequently as needed to manage hyperglycemia according to the instructions of a healthcare professional*.
	HbA1c should be monitored every 3 months as clinically indicated.	
If hyperglycemia develops after initiating treatment with Piqray	Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels.	
	During treatment with antidiabetic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks, and monitor fasting glucose according to the instructions of a healthcare professional with expertise in the treatment of hyperglycemia.	

** All glucose monitoring should be performed at the physician's discretion as clinically indicated.*

Pneumonitis

Pneumonitis including serious cases of pneumonitis/acute interstitial lung disease have been reported in Piqray treated patients in clinical studies. The incidence of Grade 3 pneumonitis was 0.4%. No Grade 4 events were observed.

Patients should be advised to promptly report any new or worsening respiratory symptoms (e.g. cough, dyspnea, hypoxia). In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, Piqray treatment should be interrupted immediately and the patient should be evaluated for pneumonitis.

A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non- specific respiratory signs and symptoms such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations.

Piqray should be permanently discontinued in all patients with confirmed pneumonitis.

Diarrhea or colitis

Severe diarrhea and clinical consequences, such as dehydration and acute kidney injury, have been reported during treatment with Piqray in clinical studies (see section 7 Adverse drug reactions). In the phase III clinical study, Grade 2 and 3 diarrhea was reported in 18.3% and 6.7% of patients, respectively. There were no reported cases of Grade 4 diarrhea. Among patients with Grade 2 or 3 diarrhea, median time to onset was 46 days (range: 1 to 442 days).

Colitis has been reported in the post marketing setting in patients treated with Piqray (see section 7 Adverse drug reactions).

In the phase III clinical study, dose reductions of Piqray were required in 6% of patients and 2.8% of patients permanently discontinued Piqray due to diarrhea.

Patients should be monitored for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Based on the severity of the diarrhea or colitis, Piqray may require dose interruption, reduction, or discontinuation as described in Table 4-4 (see section 4 Dosage regimen and administration).

Patients should be advised to notify their healthcare provider if diarrhea or additional symptoms of colitis occur while taking Piqray. Patients should be managed according to local standard of care medical management, including electrolyte monitoring, administration of anti-emetics and anti-diarrheal medications and/or fluid replacement and electrolyte supplements, as clinically indicated. In case of colitis, additional treatment, such as steroids, may be considered as clinically indicated.

Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, Piqray can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of alpelisib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes including embryo-fetal mortality (post-implantation loss), reduced fetal weights, and increased incidences of fetal malformations at maternal exposures based on area under the curve (AUC) that were ≥ 0.8 times the exposure in humans at the recommended dose of 300 mg/day. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Piqray and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use condoms and effective contraception during treatment with Piqray and for 1 week after the last dose.

Refer to the Full Prescribing Information of fulvestrant for pregnancy and contraception information.

7 Adverse drug reactions

Summary of the safety profile

SOLAR-1 safety information:

The overall safety evaluation of Piqray is based on data from the phase III clinical study of 572 patients (571 post-menopausal women and 1 male) who were randomized in a 1:1 ratio to receive Piqray plus fulvestrant or placebo plus fulvestrant; 284 of whom received Piqray at the recommended starting dose of 300 mg dose in combination with fulvestrant, using the proposed treatment regimen.

The median duration of exposure to Piqray plus fulvestrant was 8.2 months with 59.2% patients exposed for >6 months.

Piqray dose reductions due to adverse events (AEs), regardless of causality occurred in 57.7% of patients receiving Piqray plus fulvestrant and in 4.5% of patients receiving placebo plus fulvestrant. Permanent discontinuations due to AEs were reported in 25% of patients receiving Piqray plus fulvestrant and 4.5% of patients receiving placebo and/or fulvestrant. The most common AEs leading to treatment discontinuation of both Piqray and/or fulvestrant were hyperglycemia (6.3%), rash (3.2%), diarrhea (2.8%), and fatigue (2.1%).

On-treatment deaths, regardless of causality, were reported in 7 patients (2.5%) treated with Piqray plus fulvestrant vs. 12 patients (4.2%) treated with placebo plus fulvestrant. In Piqray plus fulvestrant treated patients, disease progression (5 patients, 1.8%) was the most frequent cause of death; the others were one each for cardio-respiratory arrest and second primary malignancy, neither of which were considered related to treatment with Piqray.

The most common ADRs in Piqray plus fulvestrant treated patients (reported at a frequency ≥20% and for which the frequency for Piqray plus fulvestrant exceeds the frequency for placebo plus fulvestrant) were hyperglycemia, diarrhea, rash, nausea, fatigue and asthenia, decreased appetite, stomatitis, vomiting and weight decreased.

The most common Grade 3/4 ADRs (reported at a frequency ≥2% in the Piqray plus fulvestrant arm and for which the frequency for Piqray plus fulvestrant exceeds the frequency for placebo plus fulvestrant) were hyperglycaemia, rash and maculo-papular rash, fatigue, diarrhea, lipase increased, hypertension, hypokalaemia, anaemia, weight decreased, gamma-glutamyltransferase increased, lymphopenia, nausea, stomatitis, alanine aminotransferase increased and mucosal inflammation.

Tabulated summary of adverse drug reactions from clinical studies

ADRs from the phase III clinical study (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, ADRs are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each ADR is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Adverse drug reactions observed in the phase III clinical study

Adverse drug reactions	Piqray + Fulvestrant N= 284 n (%) All Grades	Placebo + Fulvestrant N= 287 n (%) All Grades	Piqray + Fulvestrant N= 284 n (%) Grades 3/4	Placebo + Fulvestrant N=287 n (%) Grades 3/4	Frequency category for Piqray + Fulvestrant All Grades
Blood and lymphatic system disorders					
Anaemia	29 (10.2)	15 (5.2)	11 (3.9)	3 (1.0)	Very common
Lymphopenia	14 (4.9)	3 (1.0)	7 (2.5)	3 (1.0)	Common
Thrombocytopenia	6 (2.1)	0	2 (0.7)	0	Common
Eye disorders					
Vision blurred	14 (4.9)	2 (0.7)	1 (0.4)	0	Common
Dry eye	10 (3.5)	1 (0.3)	0	0	Common
Gastrointestinal disorders					

Diarrhoea	164 (57.7)	45	19 (6.7)	1 (0.3)	Very common
Nausea	127 (44.7)	64	7 (2.5)	1 (0.3)	Very common
Stomatitis[1]	85 (29.9)	18 (6.3)	7 (2.5)	0	Very common
Vomiting	77 (27.1)	28 (9.8)	2 (0.7)	1 (0.3)	Very common
Abdominal pain	47 (16.5)	32	4 (1.4)	3 (1.0)	Very common
Dyspepsia	32 (11.3)	16 (5.6)	0	0	Very common
Toothache	12 (4.2)	6 (2.1)	1 (0.4)	0	Common
Gingivitis	10 (3.5)	2 (0.7)	1 (0.4)	0	Common
Cheilitis	8 (2.8)	0	0	0	Common
Gingival pain	8 (2.8)	0	0	0	Common
Pancreatitis	1 (0.4)	0	1 (0.4)	0	Uncommon

Adverse drug reactions	**Piqray + Fulvestrant N= 284 n (%) All Grades**	**Placebo + Fulvestrant N= 287 n (%) All Grades**	**Piqray + Fulvestrant N= 284 n (%) Grades 3/4**	**Placebo + Fulvestrant N=287 n (%) Grades 3/4**	**Frequency category for Piqray + Fulvestrant All Grades**
General disorders and administrative site conditions					
Fatigue[2]	120 (42.3)	83 (28.9)	15 (5.3)	3 (1.0)	Very common
Mucosal inflammation	54 (19.0)	3 (1.0)	6 (2.1)	0	Very common
Peripheral oedema	43 (15.1)	15 (5.2)	0	1 (0.3)	Very common
Pyrexia	41 (14.4)	14 (4.9)	2 (0.7)	1 (0.3)	Very common
Mucosal dryness [3]	33 (11.6)	12 (4.2)	1 (0.4)	0	Very common
Oedema [4]	17 (6.0)	1 (0.3)	0	0	Common
Immune system disorders					
Hypersensitivity [5]	10 (3.5)	0	2 (0.7)	0	Common
Infections and infestations					
Urinary tract infection[6]	29 (10.2)	15 (5.2)	2 (0.7)	3 (1.0)	Very common
Investigations					
Weight decreased	76 (26.8)	6 (2.1)	11 (3.9)	0	Very common
Blood creatinine increased	29 (10.2)	4 (1.4)	5 (1.8)	0	Very common
Gamma- glutamyltransferase increased	27 (9.5)	20 (7.0)	11 (3.9)	14 (4.9)	Common
Alanine aminotransferase increased	23 (8.1)	16 (5.6)	7 (2.5)	6 (2.1)	Common
Lipase increased	18 (6.3)	11 (3.8)	14 (4.9)	10	Common
Glycosylated haemoglobin increased	9 (3.2)	0	0	0	Common
Metabolism and nutrition disorders					
Hyperglycaemia	184 (64.8)	29 (10.1)	105 (37.0)	2 (0.7)	Very common
Decreased appetite	101 (35.6)	30 (10.5)	2 (0.7)	1 (0.3)	Very common
Hypokalemia	28 (9.9)	5 (1.7)	12 (4.2)	1 (0.3)	Common

Hypocalcaemia	12 (4.2)	4 (1.4)	3 (1.1)	1 (0.3)	Common
Dehydration	10 (3.5)	4 (1.4)	1 (0.4)	3 (1.0)	Common
Ketoacidosis [7]	2 (0.7)	0	2 (0.7)	0	Uncommon
Musculoskeletal and connective tissue disorders					
Muscle spasms	19 (6.7)	11 (3.8)	0	0	Common
Myalgia	19 (6.7)	8 (2.8)	1 (0.4)	0	Common
Osteonecrosis of jaw	12 (4.2)	4 (1.4)	4 (1.4)	2 (0.7)	Common
Nervous system disorders					
Headache	51 (18.0)	38 (13.2)	2 (0.7)	0	Very common
Dysgeusia [8]	51 (18.0)	10 (3.5)	1 (0.4)	0	Very common
Psychiatric disorders					
Insomnia	21 (7.4)	12 (4.2)	0	0	Common

Adverse drug reactions	**Piqray + Fulvestrant N= 284 n (%) All Grades**	**Placebo + Fulvestrant N= 287 n (%) All Grades**	**Piqray + Fulvestrant N= 284 n (%) Grades 3/4**	**Placebo + Fulvestrant N=287 n (%) Grades 3/4**	**Frequency category for Piqray + Fulvestrant All Grades**
Renal and Urinary disorders					
Acute kidney injury	15 (5.3)	2 (0.7)	5 (1.8)	1 (0.3)	Common
Respiratory, thoracic and mediastinal disorders					
Pneumonitis [9]	5 (1.8)	1 (0.3)	1 (0.4)	1 (0.3)	Common
Skin and subcutaneous tissue disorders					
Rash [10]	147 (51.8)	21 (7.3)	56 (19.7)	1 (0.3)	Very common
Alopecia	56 (19.7)	7 (2.4)	0	0	Very common
Pruritus	52 (18.3)	17 (5.9)	2 (0.7)	0	Very common
Dry skin [11]	51 (18.0)	11 (3.8)	1 (0.4)	0	Very common
Erythema [12]	17 (6.0)	2 (0.7)	2 (0.7)	0	Common
Dermatitis [13]	10 (3.5)	3 (1.0)	2 (0.7)	0	Common
Palmar-plantar erythrodysaesthesia syndrome	5 (1.8)	1 (0.3)	0	0	Common
Erythema multiforme	3 (1.1)	0	2 (0.7)	0	Common
Stevens-Johnson syndrome	1 (0.4)	0	1 (0.4)	0	Uncommon
Vascular disorders					
Hypertension	24 (8.5)	15 (5.2)	13 (4.6)	9 (3.1)	Common
Lymphoedema	15 (5.3)	6 (2.1)	0	0	Common

[1] *Stomatitis: also includes aphthous ulcer and mouth ulceration*

[2] *Fatigue: also includes asthenia*

[3] *Mucosal dryness: also includes dry mouth, vulvovaginal dryness*

[4] *Oedema: also includes face swelling, face oedema, eyelid oedema*

[5] *Hypersensitivity: also includes allergic dermatitis*

[6] *Urinary tract infection: also includes single case of urosepsis*

[7] *Ketoacidosis: also includes diabetic ketoacidosis (see section 6 Warnings and precautions)*

[8] *Dysgeusia : also includes ageusia, hypogeusia*

[9] *Pneumonitis: also includes interstitial lung disease*

[10] *Rash: also includes rash maculo-papular, rash macular, rash generalized, rash-papular, rash pruritic*

[11] *Dry skin: also includes skin fissures, xerosis, xeroderma*

[12] *Erythema: also includes erythema generalised*

[13] *Dermatitis: also includes dermatitis acneiform*

Table 7-2 Laboratory abnormalities observed in the phase III study

Laboratory abnormalities	Piqray + Fulvestrant N= 284 n (%) All Grades	Placebo + Fulvestrant N= 287 n (%) All Grades	Piqray + Fulvestrant N= 284 n (%) Grades 3/4	Placebo + Fulvestrant N=287 n (%) Grades 3/4	Frequency category for Piqray + Fulvestrant All Grades
Hematological parameters					
Lymphocyte count decreased	147 (51.8)	116 (40.4)	23 (8.1)	13 (4.5)	Very common
Hemoglobin decreased	118 (41.5)	83 (28.9)	12 (4.2)	3 (1.0)	Very common
Activated partial thromboplastin time increased	60 (21.1)	45 (15.7)	2 (0.7)	1 (0.3)	Very common
Platelet count decreased	39 (13.7)	17 (5.9)	3 (1.1)	0	Very common
Biochemical parameters					
Glucose plasma increased	223 (78.5)	99 (34.5)	110 (38.7)	3 (1.0)	Very common
Creatinine increased	190 (66.9)	71 (24.7)	8 (2.8)	2 (0.7)	Very common
Gamma-glutamyl transferase increased	148 (52.1)	127 (44.3)	30 (10.6)	29 (10.1)	Very common
Alanine aminotransferase increased	124 (43.7)	99 (34.5)	10 (3.5)	7 (2.4)	Very common
Lipase increased	119 (41.9)	73 (25.4)	19 (6.7)	17 (5.9)	Very common
Calcium corrected decreased	76 (26.8)	57 (19.9)	6 (2.1)	4 (1.4)	Very common
Glucose plasma decreased	73 (25.7)	40 (13.9)	1 (0.4)	0	Very common
Albumin decreased	39 (13.7)	22 (7.7)	0	0	Very common
Potassium decreased	39 (13.7)	8 (2.8)	16 (5.6)	2 (0.7)	Very common
Magnesium decreased	31 (10.9)	12 (4.2)	1 (0.4)	0	Very common

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Piqray via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Table 7-3 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Gastrointestinal disorders
Colitis
Metabolism and nutrition disorders
Hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS)
Skin and subcutaneous tissue disorders
Angioedema
Drug reaction with eosinophilia and systemic symptoms (DRESS)

Description of selected ADRs and treatment recommendations, where applicable

Hyperglycaemia

In the phase III clinical study, hyperglycaemia (fasting glucose > 160 mg/dL) was reported in 184 (64.8%) of patients. An event of hyperglycaemia resolved to ≤Grade 1 ((fasting glucose < 160 mg/dL)) in 166 (88.8%) of the 187 patients. Dose interruptions and adjustments due to hyperglycaemic events were reported in 26.8% and 28.9% of patients, respectively, in the Piqray plus fulvestrant arm. Hyperglycaemic events leading to discontinuation of Piqray and/or fulvestrant were reported in 19 (6.7 %) patients.

Based on baseline FPG and HbA1c values, 56% of patients were considered pre-diabetic (FPG >100 to 126 mg/dL (5.6 to 6.9 mmol/L) and/or HbA1c 5.7 to 6.4%) and 4.2% of patients were considered diabetic (FPG ≥126 mg/dL (≥7.0 mmol/L) and/or HbA1c ≥6.5 %). There were no patients with type 1 diabetes mellitus based on reported medical history. Among those pre-diabetic patients at baseline, 74.2% experienced hyperglycaemia (any Grade) when treated with Piqray. Among the patients who had Grade ≥2 (FPG 160 to 250 mg/dL) hyperglycaemia, the median time to first occurrence of Grade ≥2 (FPG >160 to 250 mg/dL) hyperglycaemia was 15 days (range: 5 days to 517 days) (based on laboratory findings). The median duration of Grade 2 (FPG >160 to 250 mg/dL) or higher hyperglycaemia (based on laboratory findings) was 10 days (95% CI: 8 to 13 days).

Rash

In the phase III clinical study, rash events (including rash maculo-papular, rash macular, rash generalized, rash papular, rash pruritic, dermatitis and dermatitis acneiform) were reported in 153 (53.9%) patients. Rash may be accompanied by pruritus and dry skin in some cases. Rash was predominantly mild or moderate (Grade 1 or 2) and responsive to therapy. Maximum Grade 2 and 3 rash events were reported in 13.7% and 20.1% of patients, respectively. There were no Grade 4 cases of rash reported. Among the patients with Grade 2 or 3 rash, the median time to first onset of Grade 2 or 3 rash was 12 days (range: 2 days to 220 days). Dose interruptions and dose adjustments due to rash were reported in 21.8% and 9.2% of patients, respectively, in the Piqray plus fulvestrant arm.

Topical corticosteroid treatment should be initiated at the first signs of rash and oral corticosteroids should be considered for moderate to severe rashes. Additionally, antihistamines are recommended to manage symptoms of rash. In the Phase III study, among the patients who developed a rash, 73.9% (113/153) reported use of at least one topical corticosteroid and 67.3% (103/153) of at least one oral antihistamine. Systemic corticosteroid were administered for rash events in 23% (66/284) of patients. Of the patients who received systemic corticosteroids, 55% (36/66) received oral corticosteroids for rash. At least one event of rash resolved in the majority of the patients, 141 out of 153 patients (92%). Discontinuation of Piqray and/or fulvestrant treatment due to rash events occurred in 12 patients (4.2%).

A subgroup of 86 patients received anti rash treatment, including anti-histamines, prior to onset of rash. In these patients, rash was reported less frequently than in the overall population, for all Grades rash (26.7% vs 53.9%), Grade 3 rash (11.6% vs 20.1%) and rash leading to permanent discontinuation of Piqray (3.5% vs 4.2%). Accordingly, antihistamines may be initiated prophylactically, at the time of initiation of treatment with Piqray. Based on the severity of rash, Piqray may require dose interruption, reduction, or discontinuation as described in Table 4-3 Dose Modification and Management for rash (see section 4 Dosage

regimen and administration).

GI toxicity (nausea, diarrhea, vomiting)

In the phase III study, diarrhea, nausea and vomiting were (see Table 7-1 Adverse drug reactions) reported in 57.7%, 44.7% and 27.1% of the patients, respectively, and led to discontinuation of Piqray and/or fulvestrant in 8 (2.8%), 5 (1.8%) and 3 (1.1%) of the patients, respectively.

Anti-emetics (e.g. ondansetron) and anti-diarrheal medications (e.g. loperamide) were used in 27/149 (18.1%) and 104/164 (63.4%) of patients to manage symptoms.

Osteonecrosis of the jaw (ONJ)

In the phase III clinical study, ONJ was reported in 4.2% patients (12/284) in the Piqray plus fulvestrant arm compared to 1.4% patients (4/287) in the placebo plus fulvestrant arm. All patients experiencing ONJ were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid) or RANK-ligand inhibitors (e.g. denosumab). Therefore, in patients receiving Piqray and bisphosphonates or RANK-ligand inhibitors, an increased risk of development of ONJ cannot be excluded.

8 Interactions

The elimination of alpelisib is majorly driven by non-hepatic hydrolysis , mediated by multiple enzymes (esterases, amidases, choline esterase) and to a lesser degree, CYP3A4 mediated metabolism (hydroxylation). The contribution of hepatobiliary export or intestinal secretion via BCRP in human is considered to be low.

Medicinal products that may increase alpelisib plasma concentrations

BCRP inhibitors

Alpelisib is a sensitive substrate for BCRP *in vitro*, predominantly expressed in the liver, intestine, and at blood-brain barrier. Absorption of alpelisib will not be affected by BCRP inhibition due to saturation of the transporter in the intestine. However, due to the involvement of BCRP in the hepatobiliary export and intestinal secretion of alpelisib, caution is advised when co-administering Piqray with a BCRP inhibitor (e.g. eltrombopag, lapatininb, pantoprazole), as inhibition of BCRP in the liver and in the intestine after absorption may lead to an increase in systemic exposure of Piqray.

Medicinal products that may decrease alpelisib plasma concentrations

CYP3A4 inducers

Administration of 600 mg once daily rifampin, a strong CYP3A4 inducer, for 7 days, before co-administration with a single oral 300 mg alpelisib dose on Day 8, decreased alpelisib Cmax by 38% and AUC by 57% in healthy adults (N = 25). Administration of 600 mg once daily rifampin for 15 days, coadministered with daily 300 mg alpelisib starting from Day 8 to Day 15 decreased the steady state alpelisib Cmax by 59% and AUC by 74%.

Co-administration with a strong CYP3A4 inducer decreases alpelisib area under the curve (AUC) (see section 11 Clinical Pharmacology), which may reduce alpelisib efficacy. Co-administration of alpelisib with strong CYP3A4 inducers (e.g., apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John’s wort) should be avoided and selection

of an alternative concomitant medicinal product, with no or minimal potential to induce CYP3A4, should be considered (see section 11 Clinical pharmacology).

Medicinal products whose plasma concentrations may be altered by alpelisib

CYP3A4 substrates

No dose adjustment is required when co-administering Piqray with CYP3A4 substrates (e.g. everolimus, midazolam).

Caution is recommended when Piqray is used in combination with CYP3A4 substrates that also possess an additional time-dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (e.g. rifampicin, ribociclib, encorafenib). Systemic exposures of such CYP3A4 auto-inhibitors and auto-inducers may be decreased and increased, respectively, when Piqray is co-administered, based on PBPK simulations.

CYP2C9 substrates with narrow therapeutic index

In vitro evaluations indicated that the pharmacological activity may be reduced by the CYP2C9 induction effects of alpelisib. Based on PBPK modeling data with sensitive CYP2C9 substrate warfarin, after co-administration of alpelisib (300 mg once daily for 20 days), AUC and Cmax ratios of warfarin were estimated to be 0.91 and 0.99, respectively, indicating no or weak induction potential of alpelisib on CYP2C9.

However, in the absence of clinical data, caution is recommended. Closely monitor when Piqray is used in combination with CYP2C9 substrates where decreases in the plasma concentration of CYP2C9 substrates may reduce activity of these drugs.

CYP2B6 sensitive substrates with narrow therapeutic index

Static mechanistic assessment with sensitive CYP2B6 substrates such as bupropion, a reduction of exposure by up to 3-fold can be expected when co-administered with alpelisib based on *in vitro* assessment, no clinical study was performed. Sensitive CYP2B6 substrates (e.g. bupropion) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with Piqray, as Piqray may reduce the clinical activity of such drugs.

Drug-food interactions

In healthy subjects, co-administration of alpelisib with food resulted in an increased AUC of alpelisib by 77% (see section 4 Dosage regimen and administration and section 11 Clinical Pharmacology). Therefore, Piqray should be taken immediately after food, at approximately same time each day (see section 4 Dosage regimen and administration).

Hormonal contraceptives

It is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

Based on animal data and its mechanism of action, Piqray can cause fetal harm when administered to a pregnant woman.

There are no adequate and well-controlled studies in pregnant women. Embryo-fetal

development studies in rats and rabbits have demonstrated that oral administration of alpelisib during organogenesis induced embryo-toxicity, feto-toxicity, and teratogenicity. In rats and rabbits, following prenatal exposure to alpelisib, increased incidences of post-implantation loss, reduced fetal weights, and increased incidences of fetal abnormalities were observed starting at doses below (see animal data) the exposure in humans at the highest recommended dose of 300 mg.

Piqray should not be used during pregnancy unless the benefits to the mother outweigh the risk to the fetus. If Piqray is used during pregnancy, the patient should be advised of the potential risk to the fetus.

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of alpelisib up to 30 mg/kg/day, during the period of organogenesis.

In rats, oral administration of alpelisib was associated with maternal body weight loss or stagnation, low food consumption and embryonal death at 30 mg/kg/day, approximately 3.2 times (based on AUC) the exposure in humans at the highest recommended dose of 300 mg. Low maternal body weight gain, increased incidences of enlarged brain ventricle in the fetuses, reduced fetal weight, decreased bone ossification and skeletal malformations were seen at 10 mg/kg/day, that is equal to approximately 0.9 times below the exposure in humans at the highest recommended dose.

In rabbits, at doses of ≥25 mg/kg/day, maternal body weight loss with reduced food intake was observed. At 15mg/kg/day, slight transient body weight loss was observed. At ≥ 15 mg/kg/day increased embryo-fetal deaths and malformations were observed, mostly related to the tail and head, and were associated with increased serum glucose levels in dams. At 25 mg/kg/day, reduced mean fetal weight was observed. The dose of 15 mg/kg/day dose in rabbits is equivalent to approximately 5.5 times (based on AUC) the exposure achieved at the highest recommended human dose.

In rats and rabbits, no fetal effects were observed at 3 mg/kg/day, and considered to be the no-observable-adverse-effect-level (NOAEL) for fetal abnormalities. The maternal systemic exposures (AUC) at the NOAEL were 0.12 (rats) or 0.86 (rabbits) times the exposure in humans at the highest recommended dose of 300 mg.

9.2 Lactation

Risk summary

It is not known if alpelisib is transferred into human or animal milk after administration of Piqray. There are no data on the effects of alpelisib on the breastfed child or the effects of alpelisib on milk production.

Because of the potential for serious adverse drug reactions in the breastfed child from Piqray, it is recommended that women should not breastfeed during treatment and for at least 4 days after the last dose of Piqray.

9.3 Females and males of reproductive potential

Pregnancy testing

The pregnancy status for females of reproductive potential should be verified prior to starting treatment with Piqray.

Contraception

Females of reproductive potential should be advised that animal studies and the mechanism of action have shown that alpelisib can be harmful to the developing fetus. Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using Piqray during treatment and for at least 1 week after stopping treatment with alpelisib. It is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives.

Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during sexual intercourse while taking Piqray and for at least 1 week after stopping treatment with Piqray.

Infertility

There are no clinical data available on the effect of Piqray on fertility. Based on repeat dose toxicity studies in animals, Piqray may impair fertility in males and females of reproductive potential (see section 13 Non-clinical safety data). In fertility studies conducted in male and female rats, similar effects were observed (see section 13 Non-clinical safety data).

10 Overdosage

There is limited experience of overdose with Piqray in clinical studies. In the clinical studies, Piqray was administered at doses up to 450 mg once daily.

In cases where accidental overdosage of Piqray was reported in the clinical studies, the adverse events associated with the overdose were consistent with the known safety profile of Piqray and included hyperglycemia, nausea, asthenia and rash.

General symptomatic and supportive measures should be initiated in all cases of overdosage where necessary. There is no known antidote for Piqray.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Antineoplastic agents, other antineoplastic agents L01EM03.

Mechanism of action (MOA)

Alpelisib is an α specific class I phosphatidylinositol3kinase (PI3Kα) inhibitor.

Class I PI3K lipid kinases are key components of the PI3K/AKT/mTOR signaling pathway.

Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα manifested by increased lipid kinase activity, growth-factor independent activation of Akt-signaling, cellular transformation and the generation of tumors in a diverse array of preclinical models.

In vitro, alpelisib treatment potently inhibited the phosphorylation of PI3K downstream targets Akt as well as its various downstream effectors in breast cancer cells and showed selectivity towards cell lines harboring a PIK3CA mutation .

In vivo, alpelisib showed good tolerability as well as dose-and time-dependent inhibition of the PI3K/Akt pathway and dose-dependent tumor growth inhibition in relevant tumor xenograft models, including models of breast cancer.

PI3K inhibition by alpelisib treatment has been shown to induce an increase in ER transcription in breast cancer cells, therefore, sensitizing these cells to estrogen receptor (ER) inhibition by fulvestrant treatment. Combination of alpelisib and fulvestrant demonstrated increased anti-tumor activity than either treatment alone in xenograft models derived from ER+, PIK3CA mutated breast cancer cell lines (MCF-7 and KPL1).

Pharmacodynamics (PD)

In biochemical assays, alpelisib inhibited wild type PIK3α (IC_{50}=4.6 nmol/L) and its 2 most common somatic mutations (H1047R, E545K) (IC_{50}~4 nmol/L) more potently than the PI3Kδ (IC_{50}=290 nmol/L) and PI3Kγ (IC_{50}=250 nmol/L) isoforms and showed significantly reduced activity against PI3Kβ (IC_{50}=1156 nmol/L).

The potency and selectivity of alpelisib was confirmed at the cellular level in mechanistic and relevant tumor cell lines.

Cardiac electrophysiology

Serial, triplicate ECGs were collected following a single dose and at steady-state to evaluate the effect of alpelisib on the QTcF interval in patients with advanced cancer. A pharmacokinetic-pharmacodynamic analysis included a total of 134 patients treated with alpelisib at doses ranging from 30 to 450 mg.
The analysis demonstrates the absence of a clinically significant QTcF prolongation at the recommended 300 mg dose with or without fulvestrant. The estimated mean change from baseline in QTcF was <10 msecs (7.2 ms; 90% CI: 5.62, 8.83) at the observed geometric-mean Cmax at steady-state (2900 ng/mL) following single agent administration at the recommended 300 mg dose.

Pharmacokinetics (PK)

The pharmacokinetics of alpelisib were investigated in patients under an oral dosing regimen ranging from 30 to 450 mg daily. Healthy subjects received single oral doses ranging from 300 mg to 400 mg. The PK was mostly comparable in both oncology patients and healthy subjects.

Absorption

Following oral administration of alpelisib, median time to reach peak plasma concentration (Tmax) ranged between 2.0 to 4.0 hours, independent of dose, time or regimen. Based on absorption modelling bioavailability was estimated to be very high (>99%) under fed conditions but lower under fasted conditions (~68.7% at a 300 mg dose). Steady-state plasma levels of alpelisib after daily dosing can be expected to be reached on day 3 following onset of therapy in most patients.

Food effect

Alpelisib absorption is affected by food. In healthy volunteers after a single 300 mg oral dose of alpelisib, compared to the fasted state, a high-fat high-calorie (HFHC) meal (985 calories with 58.1 g of fat) increased AUCinf by 73% and Cmax by 84%, and a low-fat low-calorie

(LFLC) meal (334 calories with 8.7 g of fat) increased AUCinf by 77% and Cmax by 145%. No significant difference was found for AUCinf between LFLC and HFHC with a geometric mean ratio of 0.978 [CI: 0.876, 1.09] showing that neither fat content nor overall caloric intake has a considerable impact on absorption. The increase in gastrointestinal solubility by bile, secreted in response to food intake, is considered to be the driver of the food effect. Hence, Piqray should be taken immediately after food, at approximately the same time each day.

Acid reducing agents

The co-administration of the H2 receptor antagonist ranitidine in combination with a single 300 mg oral dose of alpelisib slightly reduced the bioavailability of alpelisib and decreased overall exposure of alpelisib. In the presence of a LFLC meal, AUCinf was decreased on average by 21% and Cmax by 36% with ranitidine. In the absence of food, the effect was more pronounced with a 30% decrease in AUCinf and a 51% decrease in Cmax with ranitidine compared to the fasted state without co-administration of ranitidine. Piqray can be co-administered with drugs that are acid-reducing agents, if Piqray is taken immediately after food. Population pharmacokinetic analysis showed no significant effect on the PK of Piqray by co-administration of acid reducing agents including proton pump inhibitors, H2 receptor antagonists and antacids.

Distribution

Alpelisib moderately binds to protein with a free fraction of 10.8% regardless of concentration. Alpelisib was equally distributed between red blood cells and plasma with a mean *in vivo* blood-to-plasma ratio of 1.03. There was no evidence for distribution into red blood cells caused by metabolites. Alpelisib did not penetrate the blood-brain-barrier in rats. As alpelisib is a substrate of human efflux transporters, penetration of the blood-brain-barrier is not expected to occur in human. The volume of distribution of alpelisib at steady-state (Vss/F) is estimated at 114 L (intersubject CV% 46%).

Biotransformation/metabolism

In vitro studies demonstrated that formation of the hydrolysis metabolite BZG791 by chemical and enzymatic amide hydrolysis was a major metabolic pathway, followed by CYP3A4 mediated hydroxylation. Alpelisib hydrolysis occurs systemically by both chemical decomposition and enzymatic hydrolysis via ubiquitously expressed, high-capacity enzymes (esterases, amidases, choline esterase) not limited to the liver. CYP3A4-mediated metabolites and glucuronides amounted to ~15% of the dose BZG791 accounted for ~40-45% of the dose. The rest of the dose, which was found as unchanged alpelisib in urine and feces, was either excreted as alpelisib or non-absorbed.

Elimination

Alpelisib exhibits low clearance with 9.2 L/hr (CV% 21%) based on population PK analysis under fed conditions. The population derived half-life, independent of dose and time, was 8 to 9 hours at steady state of 300mg, once daily.

In human mass-balance study, after oral administration, alpelisib and its metabolites were primarily found in the feces (81.0%), as alpelisib or metabolized as BZG791. Excretion in the urine is minor (13.5%), with 2% of unchanged alpelisib. Following single oral dose of [^{14}C]-alpelisib, 94.5% of the total administered radioactive dose was recovered within 8 days.

Linearity/non-linearity

The pharmacokinetics were found to be linear with respect to dose and time under fed conditions between 30 and 450 mg. After multiple doses, Alpelisib exposure (AUC) at steady- state is only

slightly higher than that of a single dose with an average accumulation of 1.3 to 1.5 with a daily dosing regimen.

Metabolic interaction

Based on the results of metabolic *in vitro* induction and inhibition studies, alpelisib may induce the metabolic clearance of co-medications metabolized by CYP2B6, CYP2C9 and CYP3A4 and may inhibit the metabolic clearance of co-medications metabolized CYP3A4 (time-dependent inhibition) if sufficiently high concentrations are achieved *in vivo*.

In a drug-drug interaction study, co-administration of alpelisib with everolimus, a sensitive CYP3A4 substrate, confirmed that there are no clinically significant pharmacokinetic interactions (increase in AUC by 11.2%) between alpelisib and CYP3A4 substrates. No change in everolimus exposure was observed at alpelisib doses ranging from 250 to 300 mg, also confirmed by PBPK modeling with everolimus and midazolam (≤ 15% increase in AUC). Due to the concurrent induction and time-dependent inhibition by alpelisib, PBPK simulations with substrates of CYP3A4 that also possess an additional time-dependent inhibition and induction potential on CYP3A4 that affects their own metabolism predict changes in exposure (decrease or increase) less than 2-fold, depending on the substrate.

In a drug-drug interaction study, co-administration of alpelisib with rifampin, a strong CYP3A4 inducer, confirmed that there is a clinically significant pharmacokinetic interaction between alpelisib and strong CYP3A4 inducers leading to a decrease in AUC by 57% and 74% for a single 300 mg dose and a repeated 300 mg dose of alpelisib, respectively (see section 8 Interactions).

CYP2C9 substrates

In lieu of a clinical study, PBPK modeling showed that AUC and Cmax ratios of warfarin (10 mg single dose) were estimated to be 0.91 and 0.99, respectively, after repeated co-administration of alpelisib (300 mg), indicating no or weak induction potential of alpelisib on CYP2C9.

Transporter-based interaction

Alpelisib showed only weak in vitro inhibition towards the ubiquitously expressed efflux transporters (P-gp, BCRP, MRP2, BSEP), solute carrier transporters at the liver inlet (OATP1B1, OATP1B3, OCT1) and solute carrier transporters in the kidney (OAT1, OAT3, OCT2, MATE1, MATE2K). As unbound systemic steady state concentrations (or concentrations at the liver inlet) at both the therapeutic dose and maximum tolerated dose are significantly lower than the experimentally determined unbound inhibition constants or IC50, the inhibition will not translate into clinical significance. A clinically relevant effect on P-gp substrates can be excluded.

Fulvestrant: Data from a clinical study in patients with breast cancer indicated no effect of fulvestrant on alpelisib exposure (and vice versa) following co-administration of the drugs.

Special populations

Effect of age, weight and gender

The population PK analysis showed that there are no clinically relevant effects of age, body weight, or gender on the systemic exposure of alpelisib that would require Piqray dose adjustment.

Pediatric patients (below 18 years)

The pharmacokinetics of Piqray in pediatric patients have not been established.

Geriatric patients (65 years or above)

Of 284 patients who received Piqray in the phase III study (in Piqray plus fulvestrant arm), 117 patients were ≥65 years of age and 34 patients were ≥75 years of age. In patients treated with Piqray plus fulvestrant, there was a higher incidence of Grade 3-4 hyperglycemia in patients ≥ 65 years of age (44%) compared to patients < 65 years of age (32%). No overall differences in the effectiveness of Piqray were observed between these patients and younger patients (see section 4 Dosage regimen and administration).

Race/Ethnicity

Population PK analyses and PK analysis from a single agent study in Japanese cancer patients showed that there are no clinically relevant effects of ethnicity on the systemic exposure of Piqray.

Non-compartmental PK parameters after single and multiple daily doses of Piqray for Japanese patients were very similar to those reported in the Caucasian population.

Renal impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment. Patients with severe renal impairment have not been studied and caution should be used. Based on a population pharmacokinetic analysis that included 117 patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2) / (CLcr ≥90 mL/min), 108 patients with mild renal impairment (eGFR 60 to <90 mL/min/1.73m^2)/ (CLcr 60 to <90 mL/min), and 45 patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2), mild and moderate renal impairment had no effect on the exposure of alpelisib (see section 4 Dosage regimen and administration).

Hepatic impairment

No dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (Child-Pugh A, B and C).

Based on a pharmacokinetic trial in patients with hepatic impairment, moderate and severe hepatic impairment had negligible effect on the exposure of alpelisib (see section 4 Dosage regimen and administration). The mean exposure for alpelisib was increased by 1.26-fold in patients with severe (GMR: 1.00 for C_{max}; 1.26 for AUC_{last} /AUC_{inf}) hepatic impairment.

Based on a population pharmacokinetic analysis that included 230 patients with normal hepatic function, 45 patients with mild hepatic impairment and no patients with moderate hepatic impairment, further supporting the findings from the dedicated hepatic impairment study, mild and moderate hepatic impairment had no effect on the exposure of alpelisib, (see section 4 Dosage regimen and administration).

12 Clinical studies

SOLAR-1

Piqray was evaluated in a pivotal phase III, randomized, double-blind, placebo controlled study of Piqray in combination with fulvestrant in men and postmenopausal women with HR+, HER2- locally advanced breast cancer whose disease had progressed or recurred on or after an aromatase inhibitor based treatment (with or without CDK4/6 combination).

A total of 572 patients were enrolled into two cohorts, cohort with PIK3CA mutation or cohort without PIK3CA mutation breast cancer. PIK3CA mutation status was determined by clinical trial assays. Patients were randomized to receive either Piqray 300 mg plus fulvestrant or

placebo plus fulvestrant in a 1:1 ratio. Randomization was stratified by presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor(s).

Within the cohort with a PIK3CA mutation, 169 patients were randomized to receive Piqray in combination with fulvestrant and 172 patients were randomized to placebo in combination with fulvestrant. Within this cohort, 170 (49.9%) patients had liver/lung metastases and 20 (5.9%) patients had received prior CDK4/6 inhibitor treatment.

Within the cohort without PIK3CA mutation, 115 patients were randomized to receive Piqray in combination with fulvestrant and 116 were randomized to receive placebo in combination with fulvestrant. 112 (48.5%) patients had liver/lung metastases and 15 (6.5%) patients had prior CDK4/6 inhibitor treatment.

In the cohort with PIK3CA mutation, 97.7% of patients received prior hormonal therapy and 47.8% of patients had the last setting as metastatic and 51.9% of patients whose last setting was adjuvant therapy. Overall, 85.6% of the patients were considered to have endocrine resistant disease; primary endocrine resistance was observed in 13.2% and secondary endocrine resistance in 72.4% of patients.

In both cohorts with or without PIK3CA mutation, demographics and baseline disease characteristics, ECOG (Eastern Cooperative Oncology Group) performance status, tumor burden, and prior antineoplastic therapy were well balanced between the study arms.

During the randomized treatment phase, Piqray 300 mg or Piqray matching placebo was administered orally once daily on a continuous basis. Fulvestrant 500 mg was administered intramuscularly on Cycle 1 Day 1 and 15 and then at Day 1 of a 28-day cycle during treatment phase (administration +/- 3 days).

Patients were not allowed to cross over from placebo to Piqray during the study or after disease progression.

The primary endpoint for the study was progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1), based on the investigator assessment in patients with a PIK3CA mutation. The key secondary endpoint was overall survival (OS) for patients with a PIK3CA mutation.

Other secondary endpoints included PFS for patients without a PIK3CA mutation, OS for patients without a PIK3CA mutation, as well as overall response rate (ORR) and clinical benefit rate (CBR) by PIK3CA mutation cohort.

Cohort with PIK3CA mutation

Patients enrolled with a PIK3CA mutation had a median age of 63 years (range 25 to 92). 44.9% patients were 65 years of age or older and <85 years. The patients included were White (66.3%), Asian (21.7%), Black or African American (1.2%).

Primary analysis

The study met its primary objective at the final PFS analysis (data cut-off date 12-Jun-2018) demonstratingstatistically significant improvement in PFS by investigator assessment in the PIK3CA mutant cohort for patients receiving Piqray plus fulvestrant, compared to patients receiving placebo plus fulvestrant (HR= 0.65 with 95% CI: 0.50, 0.85; one sided stratified log-rank test p= 0.00065), with an estimated 35% risk reduction of disease progression or death in favor of treatment with Piqray plus fulvestrant. The median PFS was prolonged by 5.3 months, from 5.7 months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm to 11 months (95% CI: 7.5, 14.5) in the Piqray plus fulvestrant arm.

Primary PFS results were supported by consistent results from a blinded independent review committee (BIRC) assessment in this cohort, which included a randomly selected subset of 50%

of randomized patients (HR= 0.48 with 95% CI: 0.32, 0.71).

PFS results are summarized in Table 12-1, Figure 12-1 and 12-2 for details.

Table 12-1 Study C2301- Primary efficacy analysis – Summary of results based on RECIST (FAS, cohort with PIK3CA mutation)

	Piqray + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Hazard ratio (HR)	p-value[a]
Median progression-free survival (PFS[a]) (months, 95% CI)				
Investigator radiological assessment				
PIK3CA mutant cohort (N=341)	11.0 (7.5 to 14.5)	5.7 (3.7 to 7.4)	0.65 (0.50 to 0.85)	0.00065
*Blinded independent review committee assessment**				
PIK3CA mutant cohort (N=173)	11.1 7.3 to 16.8	3.7 2.1 to 5.6	0.48 (0.32 to 0.71)	N/A

Data cut-off date: 12JUN2018
CI=confidence interval; N=number of patients; N/A = is not applicable
[a]p-value is obtained from the one-sided stratified log-rank test.
**Sample-based audit approach of 50% randomized patients*

Figure 12-1 Study C2301 primary efficacy analysis - Kaplan-Meier plot of PFS per investigator assessment (FAS, PIK3CA mutant cohort). Data cut-off date: 12-Jun-2018.

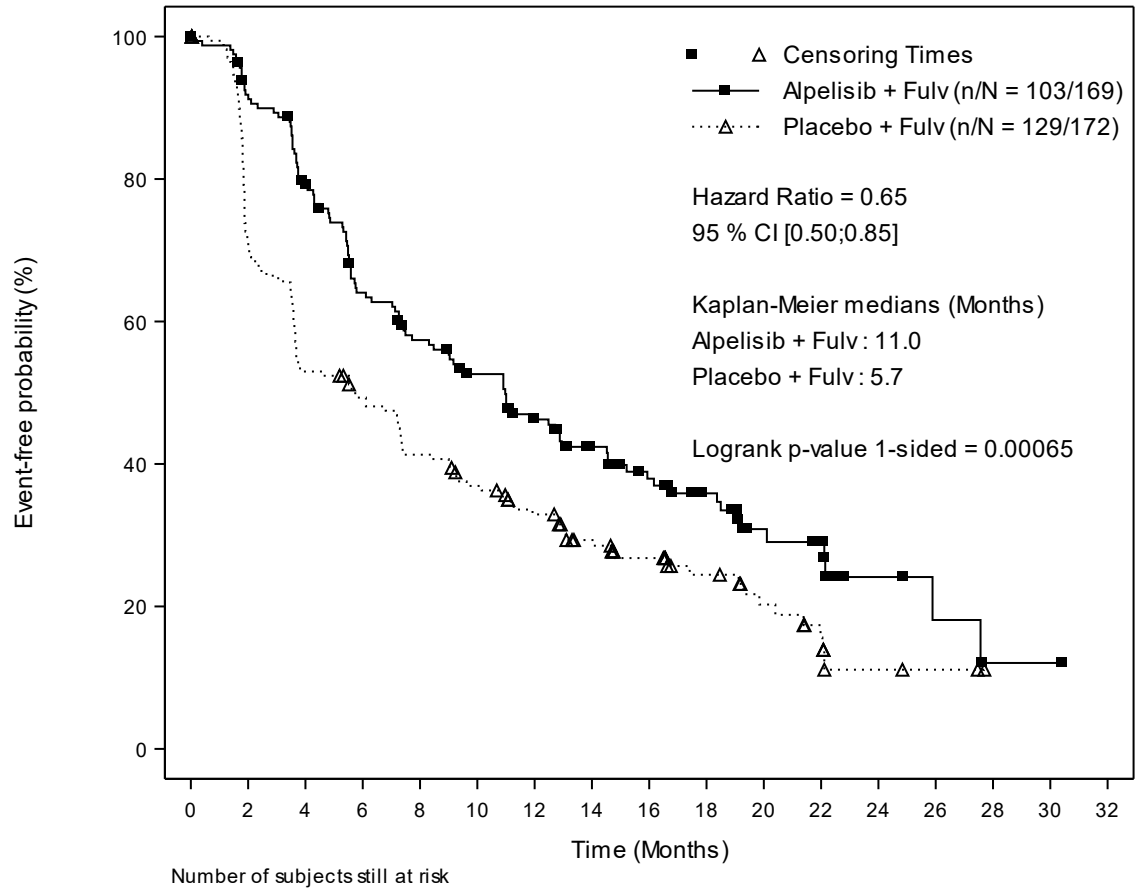
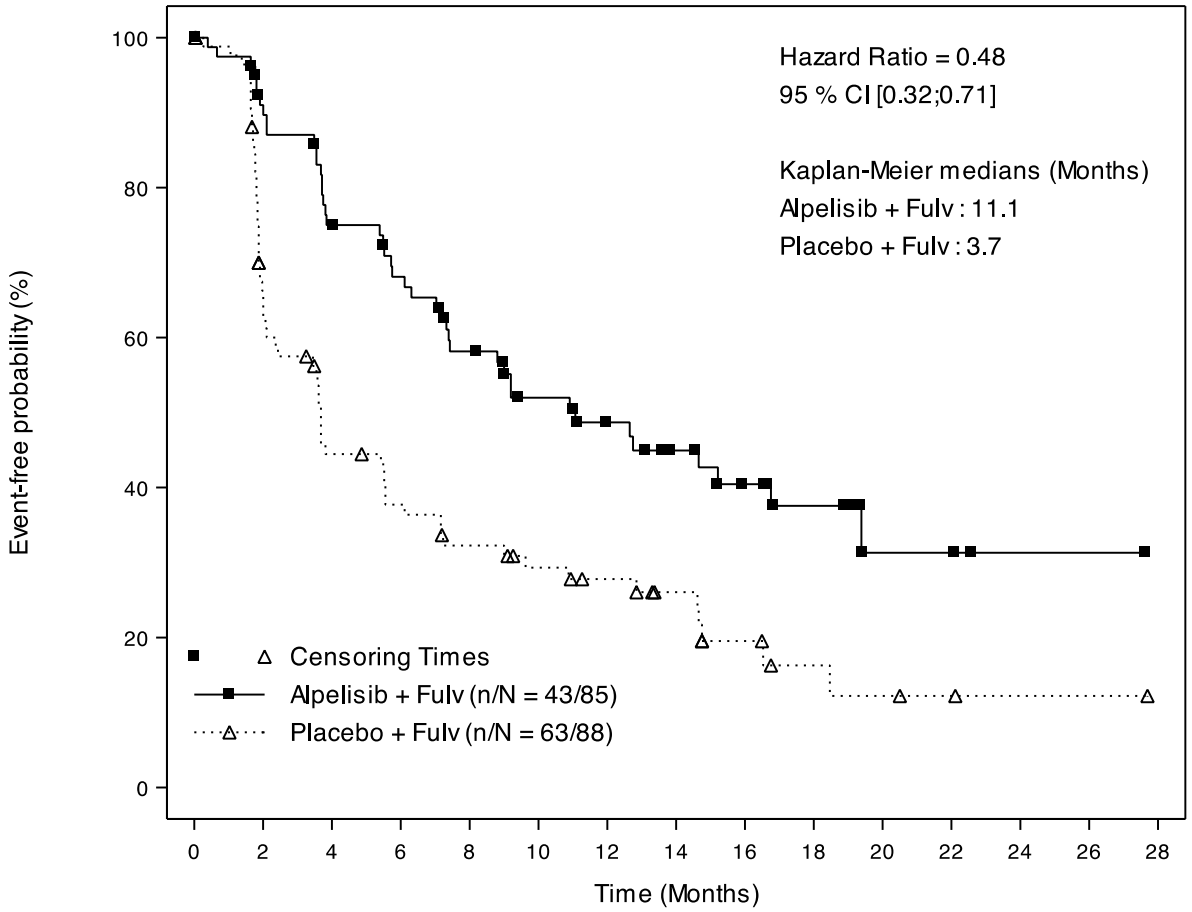


Figure 12-2 Study C2301 Kaplan-Meier plot of PFS per BIRC assessment (FAS, PIK3CA mutant cohort). Data cut-off date: 12-Jun-2018.



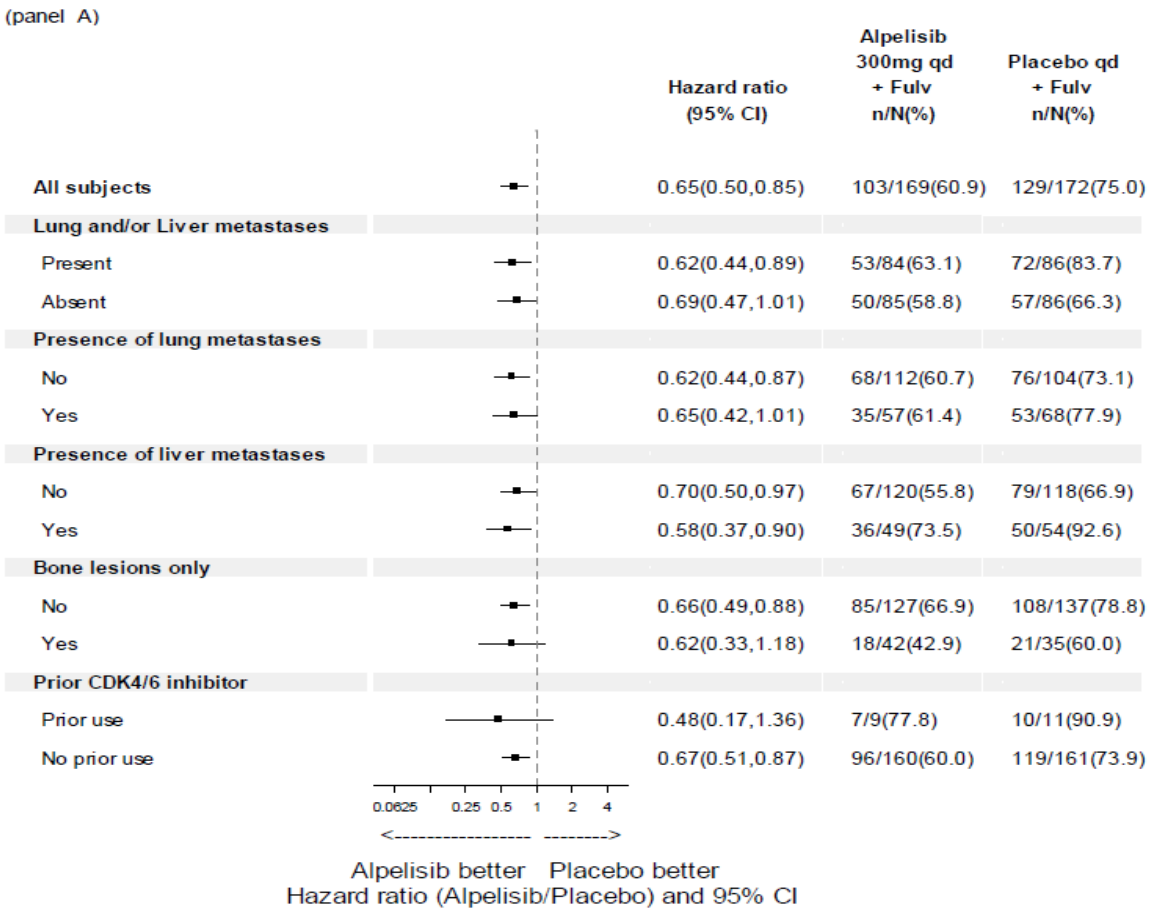
Number of subjects still at risk

Time (Months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Alpelisib + Fulv	85	77	69	66	56	55	49	47	40	37	32	31	26	24	21	19	16	12	12	11	3	3	3	1	1	1	1	1	0
Placebo + Fulv	88	83	53	46	34	33	28	27	23	23	19	17	16	14	12	7	7	4	4	3	3	2	2	1	1	1	1	1	0

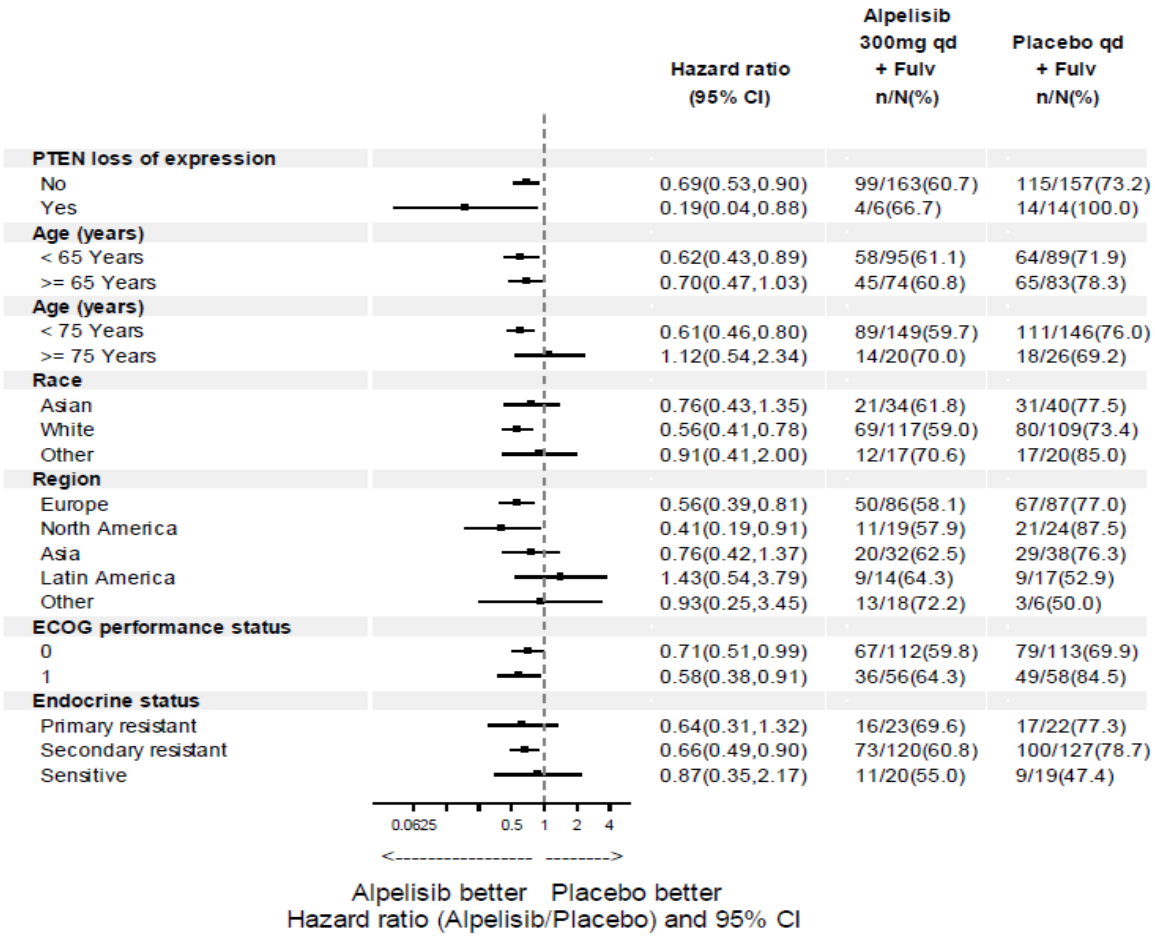
PFS subgroup analyses by randomization stratification factors demonstrated a homogeneous and generally consistent treatment effect per investigator assessment across major demographic and prognostic subgroups irrespective of CDK4/6 prior treatment and presence or absence of lung/liver metastases.

- Although limited in patient numbers, for the analysis of prior CDK4/6 treatment sub-group, the HR (95% CI) for PFS was 0.48 (0.17, 1.36).
- In the subgroup of patients with presence of lung/liver metastases, the HR (95% CI) was 0.62 (0.44, 0.89). See Figure 12-3 and 12-4 for details.

Figure 12-3 Study C2301 - PFS per investigator assessment in major demographic and prognostic subgroups (FAS, PIK3CA mutant cohort). Data cut-off date: 12-Jun-2018.



(panel B)


Alpelisib 300mg qd + Fulv n/N(%)
Placebo qd + Fulv n/N(%)
Hazard ratio (95% CI)
PTEN loss of expression
No 0.69(0.53,0.90) 99/163(60.7) 115/157(73.2)
Yes 0.19(0.04,0.88) 4/6(66.7) 14/14(100.0)
Age (years)
< 65 Years 0.62(0.43,0.89) 58/95(61.1) 64/89(71.9)
>= 65 Years 0.70(0.47,1.03) 45/74(60.8) 65/83(78.3)
Age (years)
< 75 Years 0.61(0.46,0.80) 89/149(59.7) 111/146(76.0)
>= 75 Years 1.12(0.54,2.34) 14/20(70.0) 18/26(69.2)
Race
Asian 0.76(0.43,1.35) 21/34(61.8) 31/40(77.5)
White 0.56(0.41,0.78) 69/117(59.0) 80/109(73.4)
Other 0.91(0.41,2.00) 12/17(70.6) 17/20(85.0)
Region
Europe 0.56(0.39,0.81) 50/86(58.1) 67/87(77.0)
North America 0.41(0.19,0.91) 11/19(57.9) 21/24(87.5)
Asia 0.76(0.42,1.37) 20/32(62.5) 29/38(76.3)
Latin America 1.43(0.54,3.79) 9/14(64.3) 9/17(52.9)
Other 0.93(0.25,3.45) 13/18(72.2) 3/6(50.0)
ECOG performance status
0 0.71(0.51,0.99) 67/112(59.8) 79/113(69.9)
1 0.58(0.38,0.91) 36/56(64.3) 49/58(84.5)
Endocrine status
Primary resistant 0.64(0.31,1.32) 16/23(69.6) 17/22(77.3)
Secondary resistant 0.66(0.49,0.90) 73/120(60.8) 100/127(78.7)
Sensitive 0.87(0.35,2.17) 11/20(55.0) 9/19(47.4)
0.0625
0.5
1
2
4
Alpelisib better
Placebo better
Hazard ratio (Alpelisib/Placebo) and 95% CI

(panel C)

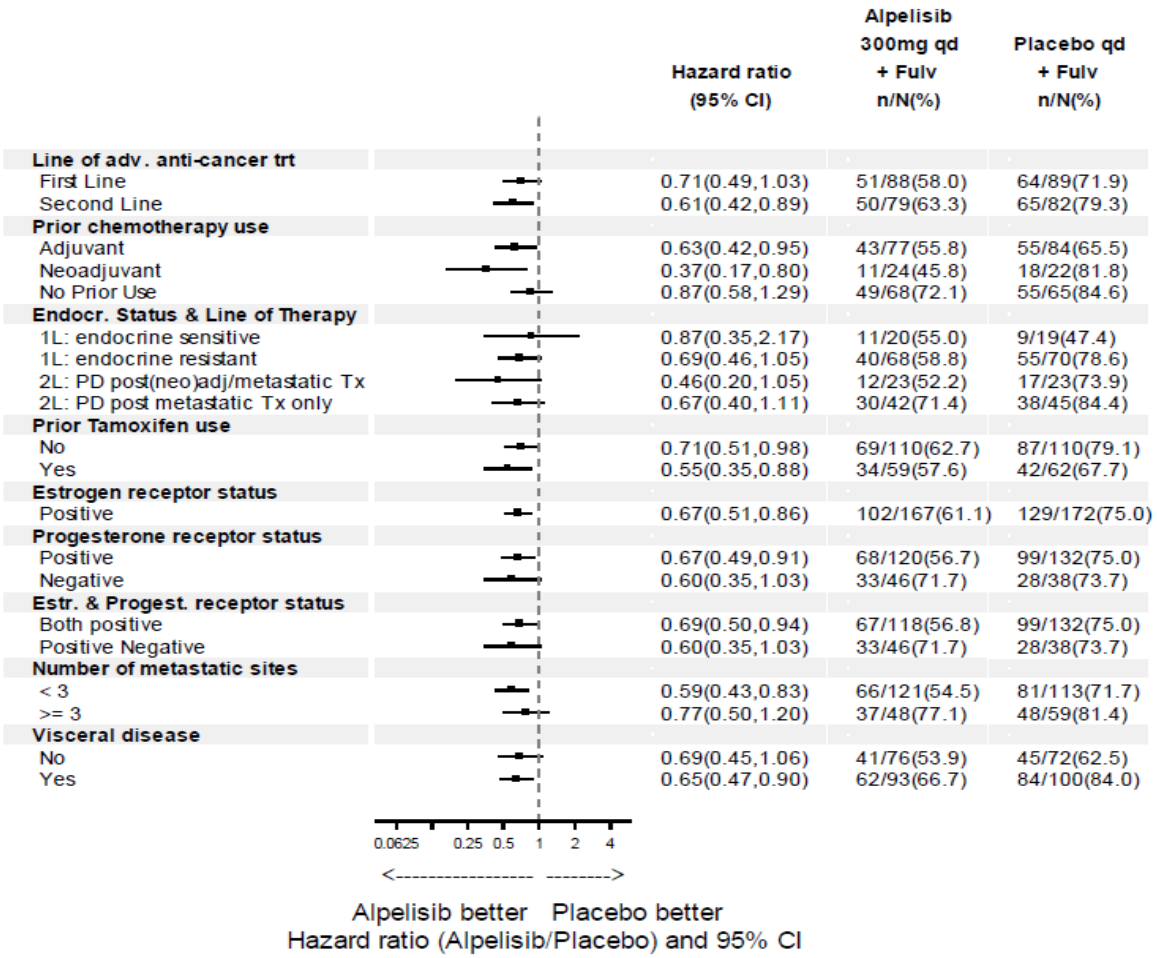
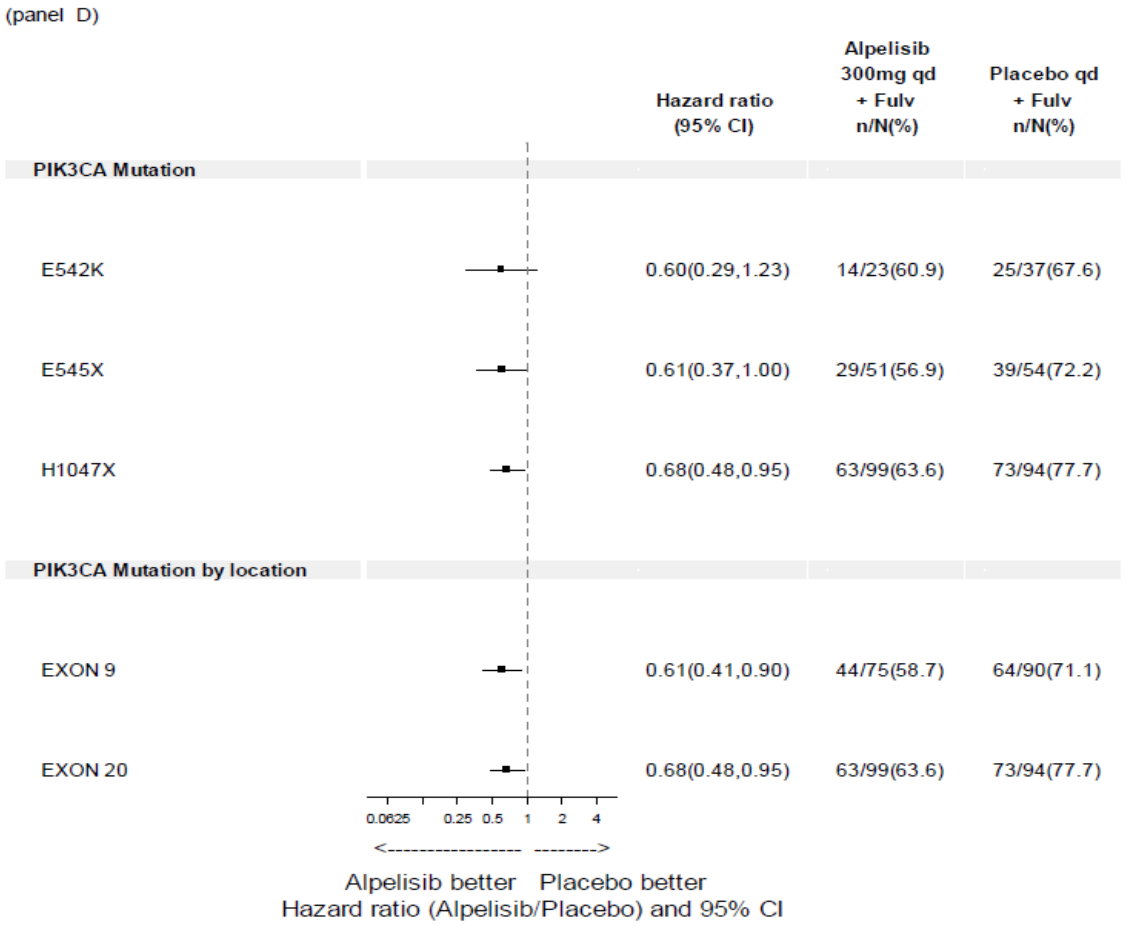

Alpelisib 300mg qd + Fulv n/N(%)
Placebo qd + Fulv n/N(%)
Hazard ratio (95% CI)
Line of adv. anti-cancer trt
First Line 0.71(0.49,1.03) 51/88(58.0) 64/89(71.9)
Second Line 0.61(0.42,0.89) 50/79(63.3) 65/82(79.3)
Prior chemotherapy use
Adjuvant 0.63(0.42,0.95) 43/77(55.8) 55/84(65.5)
Neoadjuvant 0.37(0.17,0.80) 11/24(45.8) 18/22(81.8)
No Prior Use 0.87(0.58,1.29) 49/68(72.1) 55/65(84.6)
Endocr. Status & Line of Therapy
1L: endocrine sensitive 0.87(0.35,2.17) 11/20(55.0) 9/19(47.4)
1L: endocrine resistant 0.69(0.46,1.05) 40/68(58.8) 55/70(78.6)
2L: PD post(neo)adj/metastatic Tx 0.46(0.20,1.05) 12/23(52.2) 17/23(73.9)
2L: PD post metastatic Tx only 0.67(0.40,1.11) 30/42(71.4) 38/45(84.4)
Prior Tamoxifen use
No 0.71(0.51,0.98) 69/110(62.7) 87/110(79.1)
Yes 0.55(0.35,0.88) 34/59(57.6) 42/62(67.7)
Estrogen receptor status
Positive 0.67(0.51,0.86) 102/167(61.1) 129/172(75.0)
Progesterone receptor status
Positive 0.67(0.49,0.91) 68/120(56.7) 99/132(75.0)
Negative 0.60(0.35,1.03) 33/46(71.7) 28/38(73.7)
Estr. & Progest. receptor status
Both positive 0.69(0.50,0.94) 67/118(56.8) 99/132(75.0)
Positive Negative 0.60(0.35,1.03) 33/46(71.7) 28/38(73.7)
Number of metastatic sites
< 3 0.59(0.43,0.83) 66/121(54.5) 81/113(71.7)
>= 3 0.77(0.50,1.20) 37/48(77.1) 48/59(81.4)
Visceral disease
No 0.69(0.45,1.06) 41/76(53.9) 45/72(62.5)
Yes 0.65(0.47,0.90) 62/93(66.7) 84/100(84.0)
0.0625 0.25 0.5 1 2 4
Alpelisib better Placebo better
Hazard ratio (Alpelisib/Placebo) and 95% CI

Figure 12-4 Study C2301 - PFS per investigator assessment by PIK3CA mutations (FAS, PIK3CA mutant cohort). Data cut-off date: 12-Jun-2018.



Treatment with the combination of Piqray plus fulvestrant was associated with marked improvements in ORR and CBR relative to placebo + fulvestrant. See Table 12-2 for details.

Table 12-2 Study C2301 - Overall response rate and clinical benefit rate per investigator assessment (FAS, PIK3CA mutant cohort). Data cut-off date: 12-Jun-2018.

Analysis	**Piqray plus fulvestrant (%, 95% CI)**	**Placebo plus fulvestrant (%, 95% CI)**	**p-value[c]**
Full analysis set	N=169	N=172	
Objective Response Rate[a]	26.6 (20.1 to 34.0)	12.8 (8.2 to 18.7)	0.0006
Clinical Benefit Rate[b]	61.5 (53.8 to 68.9)	45.3 (37.8 to 53.1)	0.002
Patients with measurable disease	**N=126**	**N=136**	
Objective Response Rate[a]	35.7 (27.4 to 44.7)	16.2 (10.4 to23.5)	0.0002
Clinical Benefit Rate[b]	57.1 (48.0 to 65.9)	44.1 (35.6 to 52.9)	0.02

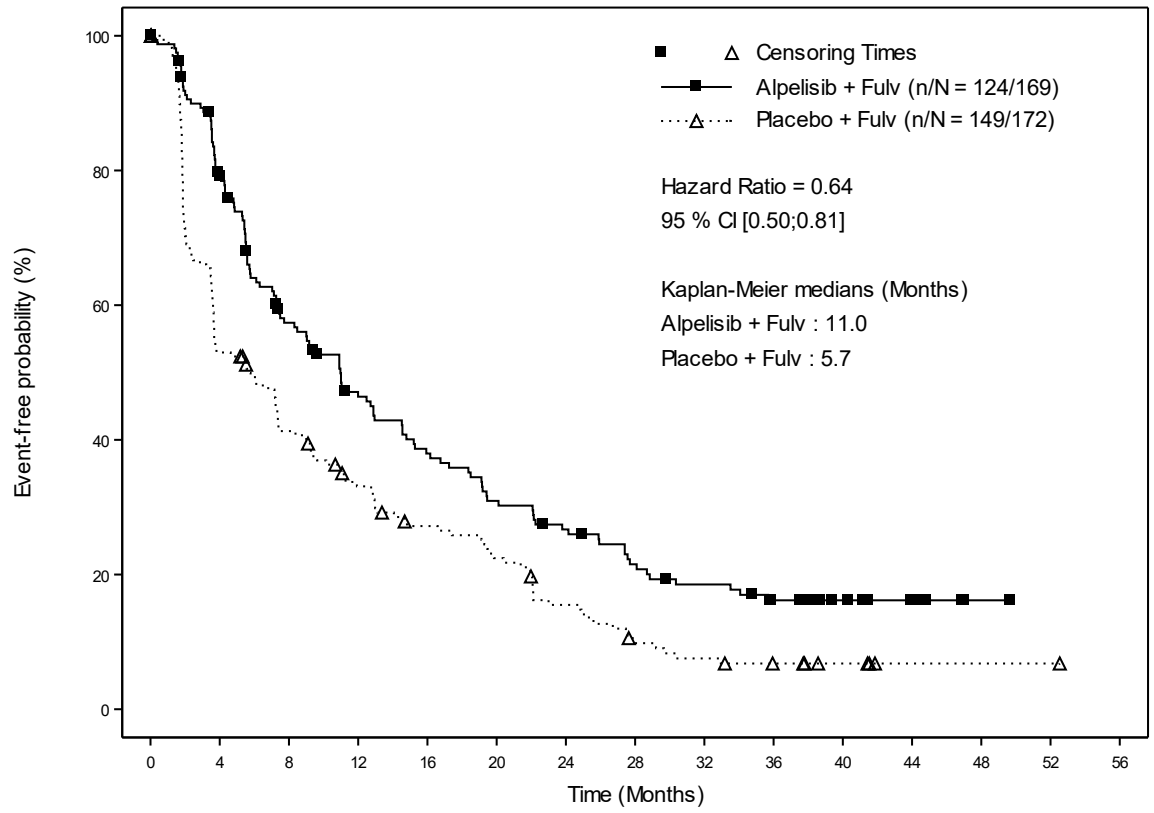
[a] ORR= proportion of patients with confirmed Complete Response or Partial Response
[b] CBR: proportion of patients with confirmed Complete Response or Partial Response, or (Stable Disease or Non-Complete Response/Non-Progression Disease >=24 weeks)
[c] p-value is obtained from the Cochran-Mantel Haenszel test.

The global health status/Quality of Life (QoL) outcomes were similar between the Piqray plus fulvestrant arm and the placebo plus fulvestrant arm. Time-to-Deterioration (TTD) in global health status EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30) was defined as time between baseline and first occurrence of ≥10 point worsening of global health status (EORTC QLQ-C30 global health scale score) compared to baseline with no later improvement above this threshold observed during the treatment period or death due to any cause. The addition of Piqray to fulvestrant showed no relevant difference in TTD in EORTC QLQ-C30 global health scale score compared with placebo plus fulvestrant,(HR=1.03; 95% CI: 0.72, 1.48).

Final OS Analysis

The final OS analysis was conducted using a data cut-off date of 23-Apr-2020 and PFS was re-run using this data cut. With a median duration from randomization to data cut-off of approximately 42 months, the PFS benefit was sustained and consistent with results from the final PFS analysis. There was an estimated 36% risk reduction of progression or death in favor of treatment with Piqray plus fulvestrant (HR = 0.64; 95% CI: 0.50, 0.81). See Figure 12-5 for details.

Figure 12-5 Study C2301 - Kaplan-Meier plot of PFS per investigator assessment (FAS, PIK3CA mutant cohort): descriptive update with data cut-off date of 23-Apr-2020

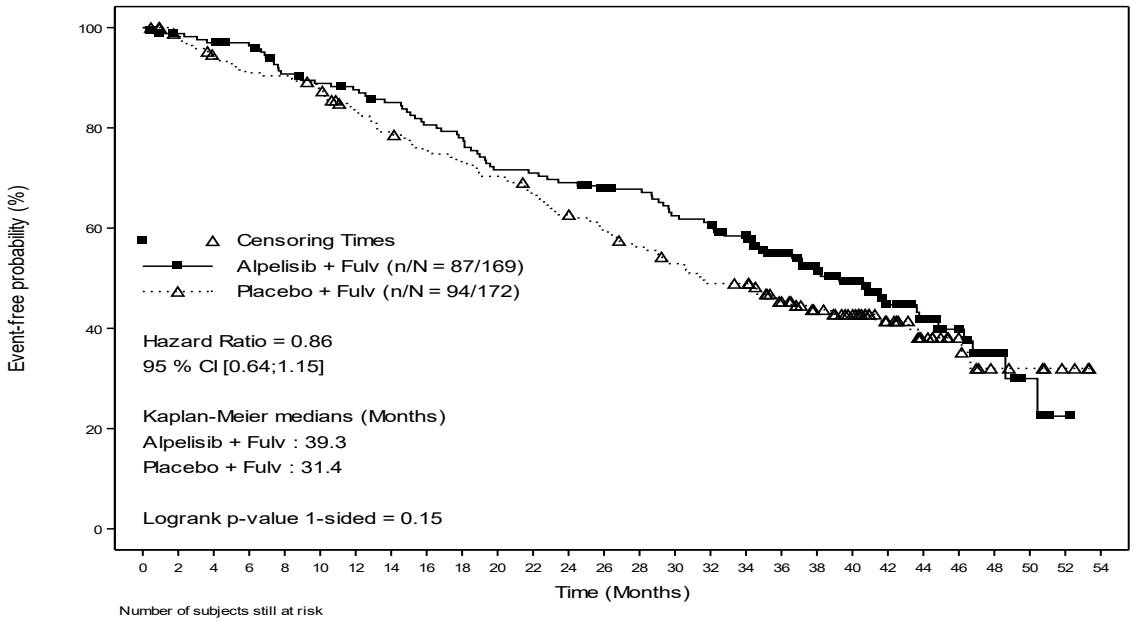


Number of subjects still at risk

Time (Months)	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56
Alpelisib + Fulv	169	123	85	66	54	44	37	29	24	18	12	6	1	0	0
Placebo + Fulv	172	89	67	51	40	33	22	13	10	7	4	1	1	1	0

At the final OS analysis, the study did not meet its key secondary objective. As of the data cut-off date of 23-Apr-2020, a total of 87 (51.5%) deaths were reported in the Piqray plus fulvestrant arm and 94 (54.7%) in the placebo plus fulvestrant arm. The HR was 0.86 (95% CI: 0.64, 1.15; p = 0.15, one-sided) and the pre-specified O'Brien-Fleming efficacy boundary of $p \leq 0.0161$ was not crossed. Median OS was prolonged by a clinically relevant 7.9 months, from 31.4 months (95% CI: 26.8, 41.3) in the placebo plus fulvestrant arm to 39.3 months (95% CI: 34.1, 44.9) in the Piqray plus fulvestrant arm. See Figure 12-6 for details.

Figure 12-6 Study C2301 key secondary analysis - Kaplan-Meier plot of OS (FAS, PIK3CA mutant cohort) with cut-off date of 23-Apr-2020.



Number of subjects still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54
Alpelisib + Fulv	169	162	159	156	145	141	138	133	126	122	112	111	108	103	102	94	91	85	68	56	47	35	26	19	9	4	1	0
Placebo + Fulv	172	164	155	150	149	143	133	126	119	115	111	104	98	92	86	80	74	73	60	49	42	29	20	13	7	6	3	0

OS subgroup analyses by randomization stratification factors demonstrated a homogeneous and generally consistent treatment effect per investigator assessment. Although limited in patient numbers, for the analysis of prior CDK4/6i treatment subgroup, median OS in the Piqray plus fulvestrant arm was 29.8 months (95% CI: 6.7, 38.2) compared to 12.9 months (95% CI: 2.5, 34.6) in the placebo plus fulvestrant arm. In the subgroup of patients with presence of lung/liver metastases, median OS in the Piqray plus fulvestrant arm was 37.2 months (95% CI: 28.7, 43.6) compared to 22.8 months (95% CI: 19, 26.8) in the placebo plus fulvestrant arm.

Cohort without PIK3CA mutation

The proof of concept criteria to conclude a treatment benefit with Piqray and fulvestrant with respect to PFS in subjects in the PIK3CA non-mutant cohort were not met (HR = 0.85; 95% CI: 0.58, 1.25) (see section 4 Dosage regimen and administration).

BYLieve

Piqray was evaluated in a Phase II, multicenter, open-label, three-cohort, non-comparative study of Piqray plus endocrine therapy (either fulvestrant or letrozole) in subjects (pre- and post-menopausal women and men), 18 years or older, with HR-positive, HER2-negative advanced (locoregionally recurrent or metastatic) breast cancer, not amenable to curative therapy harboring PIK3CA mutation(s) in the tumor tissue, whose disease has progressed on or after prior treatments.

A total of 380 patients, with HR-positive, HER2-negative advance breast cancer harboring a PIK3CA mutation in tumor tissue, were enrolled.

Patients were assigned to alpelisib 300 mg plus fulvestrant 500 mg; patients whose last prior treatment was a CDK4/6i plus any AI in cohort A. Patients were treated until disease progression, intolerable toxicity, or until 18 months after last subject first treatment.

The primary objective of the study was to assess the proportion of patients who were alive without disease progression at 6-months based on local Investigator assessment per RECIST v1.1 among patients with HR-positive, HER2- negative advance breast cancer harboring a PIK3CA mutation who have progressed on or after prior treatments.

In BYLieve, a total of 99 patients out of the 127 (78%) enrolled in cohort A were postmenopausal women. The 22 premenopausal women recruited in the study were treated with LHRH agonists, either goserelin or leuprolide, prior to receiving alpelisib treatment in order to achieve adequate hormonal suppression. There were also six sterile women recruited in cohort A.

The analysis of the primary endpoint was to be performed for each cohort 6 months after the last patient had started treatment or discontinued early.

In cohort A, with a median duration of follow-up of 11.7 months (calculated from the start of treatment to the data cut-off date of 17-Dec-2019)., 61/121 patients (50.4%, 95% CI: 41.2, 59.6) were alive without disease progression at 6-months. The study met the primary objective for cohort A (lower bound of 95% CI was >30%).

One of the secondary end point was progression free survival (PFS).

Based on Investigator assessment, 72 PFS events were observed and the median PFS was 7.3 months (95% CI: 5.6, 8.3). Of these 72 PFS events, 57 were observed in the 95 post-menopausal women of Cohort A and the median PFS in this subgroup was similar 7.3 months (95 CI: 5.5, 8.4).

13 Non-clinical safety data

Alpelisib was evaluated in safety pharmacology, single- and repeated dose toxicity, genotoxicity and photo-toxicity studies.

Safety pharmacology and repeat dose toxicity

The majority of the observed alpelisib effects were related to the pharmacological activity of alpelisib as a p110α specific inhibitor of the PI3K pathway, such as the influence on the glucose homeostasis resulting in hyperglycemia and the risk of increased blood pressure.

The bone marrow and lymphoid tissue, pancreas, and some reproductive organs of both genders were the main target organs for adverse effects, which were generally reversible upon cessation of treatment. Alpelisib showed no effect on neuronal or pulmonary function. No evidence of skin irritation or corrosion was observed with alpelisib.

Cardiovascular safety pharmacology: In an *in vitro* hERG test, (where functionality of the human cardiac hERG channel heterologously expressed in HEK293 cells *in vitro* is assessed), an IC_{50} of 9.4 µM (4.2 µg/ml) was found. No relevant electrophysiological effect was seen in dogs in several studies, up to single doses of 180 mg/kg *in-vivo*. An *in vivo* telemetry study in dogs showed an elevated blood pressure, starting at exposure lower than the exposure in humans, at the highest recommended dose of 300 mg/day.

Carcinogenicity and mutagenicity

No carcinogenicity studies have been conducted.

Alpelisib was not mutagenic in a *Salmonella* reverse mutation test in five strains, or aneugenic or clastogenic in human cell micronucleus and chromosome aberration tests *in vitro*. Also, an *in vivo* micronucleus test in peripheral blood reticulocytes obtained in week 4 of a 13-week rat repeated-dose toxicity study at dose levels of up to 20 mg/kg/day, at plasma exposure levels of about 1.7 times the exposure in humans at the highest recommended dose of 300 mg/day based on AUC, was negative.

Fertility and Reproductive toxicity

Please see section 9 Pregnancy, lactation, females and males of reproductive potential.

In repeated-dose toxicity studies up to 13 weeks duration, adverse effects were observed in reproductive organs of females and males, such as vaginal atrophy and oestrus cycle variations in rats (at or above 6 mg/kg/day, a dose that provides plasma exposure levels below the exposure in humans, at the highest recommended dose of 300 mg/day based on AUC), or prostate atrophy in dogs (at 15 mg/kg/day, at plasma exposure levels about 2.8 times the exposure in humans, at the highest recommended dose of 300 mg/day based on AUC) (see section 9 Pregnancy, lactation, females and males of reproductive potential). In general, the observed effects were reversible upon treatment discontinuation.

In fertility studies conducted in male and female rats, similar effects on fertility were observed. In females at doses of 20 mg/kg/day (approximately 1.7 times the estimated exposure (AUC) in humans at the recommended dose of 300 mg), increased pre- and post-implantation losses led to reduced numbers of implantation sites and live embryos. The NOAEL (No-observed-adverse-effect-level) for female fertility was determined at 10 mg/kg/day (at exposure levels (AUC) at or below the recommended human dose of 300 mg). In males, at doses of ≥ 10 mg/kg/day, accessory glands weights (seminal vesicles, prostate) were reduced and correlated microscopically with atrophy and/or reduced secretion in prostate and seminal vesicles, respectively. Male fertility parameters were unaffected at doses up to 20 mg/kg/day.

Toxicokinetic endpoints were not included in either of the two fertility studies since the toxicokinetic parameters of alpelisib in rats had been sufficiently established earlier.

Phototoxicity

An *in vitro* phototoxicity test on the on the mouse Balb/c 3T3 fibroblast cell line did not identify a relevant phototoxicity potential for alpelisib.

Juvenile animal studies

Juvenile animal studies are not available.

14 Pharmaceutical information

Incompatibilities

Not applicable.

Storage

See folding box.

Store at or below 30°C. Store in the original package (PVC/PCTFE/Alu blister) in order to protect from moisture.

Piqray must be kept out of the reach and sight of children.

Instructions for use and handling

Not applicable

Manufacturer

See folding box.

Presentation

PIQRAY 200MG DAILY DOSE PACK

- *14 tablets of 200 mg*
- *28 tablets of 200 mg*

PIQRAY 250MG DAILY DOSE PACK (200mg + 50mg)

- *14 tablets of 50 mg + 14 tablets of 200 mg*
- *28 tablets of 50 mg + 28 tablets of 200 mg*

PIQRAY 300MG DAILY DOSE PACK (150mg + 150mg)

- *28 film-coated tablets of 150 mg*
- *56 film-coated tablets of 150 mg*

Not all presentations may be available locally.

Information issued: Dec 2021. SIN

Novartis Pharma AG, Basel, Switzerland

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