

ORIGINAL RESEARCH

# Capivasertib and fulvestrant for patients with hormone receptor-positive advanced breast cancer: characterization, time course, and management of frequent adverse events from the phase III CAPitello-291 study

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**Background:** Capivasertib is a potent, selective pan-AKT inhibitor. In CAPitello-291, the addition of capivasertib to fulvestrant resulted in a statistically significant ( $P < 0.001$ ) improvement in progression-free survival over fulvestrant monotherapy in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer and disease progression on or after aromatase inhibitor-based therapy. Characterization of the capivasertib-fulvestrant adverse event (AE) profile as managed in CAPitello-291 can inform future management guidance and optimize clinical benefit.

**Patients and methods:** Seven hundred and eight patients were randomized 1 : 1 to capivasertib (400 mg twice daily; 4 days on, 3 days off) or placebo, plus fulvestrant, on a 4-week cycle. Dose reductions/interruptions for capivasertib/placebo were permitted (up to two dose reductions). Safety analyses included exposure, AE, and clinical laboratory data and were conducted in patients who received at least one dose of capivasertib, fulvestrant, or placebo. Frequent AEs associated with phosphoinositide 3-kinase (PI3K)/protein kinase (AKT) pathway inhibition (diarrhea, rash, hyperglycemia) were characterized using group terms. AEs were summarized using descriptive statistics; time-to-event analyses were conducted.

**Results:** Safety analyses included 705 patients: capivasertib-fulvestrant ( $n = 355$ ) and placebo-fulvestrant ( $n = 350$ ). Frequent any-grade AEs with capivasertib-fulvestrant were diarrhea (72.4%), rash (38.0%), and nausea (34.6%); frequent grade  $\geq 3$  AEs were rash (12.1%), diarrhea (9.3%), and hyperglycemia (2.3%). Diarrhea, rash, and hyperglycemia occurred shortly after starting capivasertib-fulvestrant [median days to onset (interquartile range) of any grade: 8 (2–22), 12 (10–15), and 15 (1–51), respectively], and were managed with supportive medications, dose reductions, interruptions, and/or discontinuation. Discontinuation rates were 2.0%, 4.5%, and 0.3%, respectively. Overall, 13.0% discontinued capivasertib due to AEs.

**Conclusions:** Frequent AEs associated with PI3K/AKT pathway inhibition occurred early and were manageable. The low rate of treatment discontinuations suggests that, when appropriately managed, these AEs do not pose a challenge to clinical benefit.

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**Key words:** capivasertib, advanced breast cancer, diarrhea, hyperglycemia, rash, safety

## INTRODUCTION

Recent advances in the treatment of hormone receptor-positive (HR-positive)/human epidermal growth factor receptor 2-negative (HER2-negative) advanced breast cancer (ABC) have led to endocrine therapy in combination with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor becoming the preferred first-line treatment option for certain patients with metastatic disease.<sup>1,2</sup> Following disease progression on endocrine therapy and a CDK4/6 inhibitor,<sup>3</sup> the optimal sequencing of available treatments is less clear. Fulvestrant, a selective estrogen receptor degrader, is one recommended treatment option, either as monotherapy or as part of combination treatment.<sup>1,2</sup>

AKT is the key node of the phosphoinositide 3-kinase (PI3K)/protein kinase (AKT) pathway. PI3K/AKT pathway activation occurs frequently in HR-positive/HER2-negative ABC,<sup>4,5</sup> and PI3K/AKT/phosphatase and tensin homologue (PTEN) signaling is implicated in the development of resistance to endocrine therapy.<sup>5</sup> Inhibition of this pathway has been effective in pretreated HR-positive ABC. In the phase III SOLAR-1 study, alpelisib (a PI3K $\alpha$ -selective inhibitor) in combination with fulvestrant significantly improved progression-free survival (PFS) versus placebo plus fulvestrant in patients with HR-positive/HER2-negative *PIK3CA*-mutated ABC that had progressed on endocrine therapy.<sup>6</sup> Before this, everolimus (an inhibitor of the mammalian target of rapamycin) in combination with exemestane in the phase III BOLERO-2 study significantly improved PFS versus placebo plus exemestane in patients with HR-positive/HER2-negative ABC that had progressed on an aromatase inhibitor (AI).<sup>7</sup> Adverse events (AEs) observed with PI3K/AKT pathway inhibition include hyperglycemia, rash, stomatitis, diarrhea, nausea, and fatigue.<sup>8</sup> Hyperglycemia [Common Terminology Criteria for Adverse Events (CTCAE) v4.03] was the most frequently reported AE with alpelisib-fulvestrant in SOLAR-1 (any grade 64%; grade  $\geq 3$  37%); other AEs included diarrhea, nausea, rash, and decreased appetite.<sup>6</sup> Stomatitis (CTCAE v3) was the most frequently reported AE with everolimus-exemestane in BOLERO-2 (any grade 59%; grade  $\geq 3$  8%), although subsequent implementation of guidelines recommending the use of dexamethasone mouthwash reduced the rate of stomatitis<sup>9</sup>; other AEs included rash, fatigue, and diarrhea.<sup>7</sup>

Capivasertib is a potent, selective inhibitor of AKT1, AKT2, and AKT3,<sup>10</sup> and the first agent targeting AKT to have shown clinical benefit in combination with fulvestrant in a randomized clinical trial for patients with HR-positive ABC whose disease had progressed during or after previous AI therapy with or without a CDK4/6 inhibitor. In the CAPItello-291 phase III randomized, double-blind, multicenter, placebo-controlled study, the addition of capivasertib to fulvestrant resulted in statistically significant and clinically meaningful improvement in the dual primary endpoints of PFS in the overall population [hazard ratio (HR) 0.60, 95% confidence

interval (CI) 0.51-0.71,  $P < 0.001$ ] and in patients with *PIK3CA/AKT1/PTEN*-altered tumors (HR 0.50, 95% CI 0.38-0.65,  $P < 0.001$ ), compared with placebo plus fulvestrant.<sup>11</sup> These data led to the first regulatory approval of capivasertib plus fulvestrant in patients with HR-positive/HER2-negative advanced breast cancer with one or more tumor biomarker alterations (*PIK3CA*, *AKT1*, or *PTEN*) following progression on an endocrine-based regimen,<sup>12</sup> and also inclusion of this treatment option in guidelines in the United States.<sup>1</sup>

The safety profile of capivasertib in combination with fulvestrant in CAPItello-291 compared favorably with that of other PI3K/AKT pathway targeting agents that are used in this patient population. The most frequently reported AEs of grade 3 or higher were rash, diarrhea, and hyperglycemia,<sup>11</sup> as expected with the mechanism of action of capivasertib. Here, we report a detailed analysis of the most frequently reported AEs associated with PI3K/AKT pathway inhibition in CAPItello-291, including timing and management, both to inform appropriate patient monitoring and AE management and to optimize the clinical benefit of treatment.

## PATIENTS AND METHODS

### Study design

The design of CAPItello-291, including inclusion/exclusion criteria and randomization and stratification factors, has been previously published.<sup>11</sup> Briefly, adult women or men with HR-positive/HER2-negative locally advanced or metastatic breast cancer that had progressed on a prior AI, with or without a CDK4/6 inhibitor, in the metastatic setting or on or within 12 months of the end of treatment with a (neo)adjuvant AI, were eligible for inclusion in the study. Up to two prior lines of endocrine therapy and one prior line of chemotherapy in the advanced setting were permitted, and disease progression on prior therapy was required for randomization. Patients with type 2 diabetes mellitus were eligible for inclusion subject to a hemoglobin A1C (HbA1c) level  $<8.0\%$  at screening and insulin treatment not being required. Patients with type 1 diabetes mellitus were excluded.

Eligible patients were randomized 1 : 1 to receive oral capivasertib [400 mg twice daily (b.i.d.) for 4 days on followed by 3 days off] and fulvestrant (500 mg intramuscularly given per standard of care every 14 days for the first three injections, then every 28 days), or matching placebo and fulvestrant. One treatment cycle was defined as 4 weeks of capivasertib or placebo, and treatment continued until disease progression (Response Evaluation Criteria in Solid Tumours v1.1), unacceptable toxicity, withdrawal of consent, or death.

Additional details on AE management and safety assessments are provided in the Supplementary Methods, available at <https://doi.org/10.1016/j.esmoop.2024.103697>.

CAPitello-291 was conducted in accordance with the applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki. All patients provided written informed consent.

Statistical analysis

As the capivasertib-fulvestrant safety profile, in terms of incidence and severity of AEs reported in the *PIK3CA/ACT1/PTEN*-altered population was similar to the overall population in CAPitello-291 (Supplementary Table S1, available at <https://doi.org/10.1016/j.esmoop.2024.103697>),<sup>11</sup> the detailed analysis reported here is for the overall population only. The safety population included all patients who received at least one dose of capivasertib, fulvestrant, or placebo. Each patient was analyzed according to the treatment received: capivasertib or placebo. Pre-defined time windows were used for presentations of safety data that summarize values by visit/cycle (e.g. fasting glucose and HbA1c; see Supplementary Table S2, available at <https://doi.org/10.1016/j.esmoop.2024.103697>).

Safety and tolerability data were summarized using descriptive statistics comprising the number and percentage of patients reporting each AE. Prevalence of AEs over time was derived from patients remaining on treatment or in the 30-day safety follow-up, thereby correcting for patient withdrawals. AEs reported here focus on frequent AEs associated with PI3K/AKT pathway inhibition and other clinically relevant AEs. Characterization of frequent AEs associated with PI3K/AKT pathway inhibition was considered using group terms that were defined before database lock: diarrhea [Medical Dictionary for Regulatory Activities (MedDRA) preferred terms: diarrhea, frequent bowel movements, gastrointestinal hypermotility], rash (MedDRA preferred terms: rash, rash macular, rash maculopapular, rash papular, rash pruritic), hyperglycemia (MedDRA preferred terms: blood glucose increased, hyperglycemia). These group terms were selected to combine events of similar etiology. Details of additional skin-related AEs are also reported (MedDRA preferred terms: dermatitis exfoliative generalized, dermatitis, drug eruption, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, erythema, palmar-plantar erythrodysesthesia syndrome, rash erythematous, rash follicular, rash pustular and toxic skin eruption). In this paper, we use diarrhea, rash, and hyperglycemia to refer to the group term. Supporting medication use for the management of AEs was also documented for each AE.

RESULTS

Patient characteristics

The CAPitello-291 overall study population included 708 patients enrolled between 2 June 2020 and 13 October 2021 who were randomized to receive capivasertib-fulvestrant (355 patients) or placebo-fulvestrant (353

Table 1. Baseline characteristics of interest in the safety population

	Capivasertib-fulvestrant n = 355	Placebo-fulvestrant n = 350
Demographics		
Median age (range), years	59.0 (26-84)	58.0 (26-90)
Female sex, n (%)	352 (99.2)	346 (98.9)
ECOG PS, n (%)		
0	224 (63.1)	238 (68.0)
≥1	131 (36.9)	112 (32.0)
Anthropometric measurements		
Median weight (range), kg	65.0 (34-150)	66.0 (37-147)
Weight category, n (%)		
<50 kg	35 (9.9)	26 (7.4)
≥50-<70 kg	184 (51.8)	180 (51.4)
≥70-<90 kg	101 (28.5)	106 (30.3)
≥90 kg	31 (8.7)	36 (10.3)
Missing	4 (1.1)	2 (0.6)
Median BMI (range), kg/m <sup>2</sup>	25.5 (16-52)	25.4 (15-60)
BMI category, n (%)		
Underweight (<18.5 kg/m <sup>2</sup> )	15 (4.2)	14 (4.0)
Normal (18.5-<25.0 kg/m <sup>2</sup> )	146 (41.1)	148 (42.3)
Overweight (25.0-<30.0 kg/m <sup>2</sup> )	124 (34.9)	105 (30.0)
Obese (≥30 kg/m <sup>2</sup> )	66 (18.6)	79 (22.6)
Missing	4 (1.1)	4 (1.1)
Median HbA1c <sup>a</sup> (range)	5.4 (4.0-8.3)	5.4 (3.9-7.7)
HbA1c category, n (%)		
<6.5%	332 (93.5)	332 (94.9)
≥6.5%	21 (5.9)	18 (5.1)
Missing	2 (0.6)	0
Medical history of diabetes, n (%)	34 (9.6)	20 (5.7)

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; HbA1c, hemoglobin A1c.

<sup>a</sup>Patients with type 2 diabetes mellitus requiring insulin treatment or with HbA1c ≥8.0% at screening were excluded from CAPitello-291 (all patients with type 1 diabetes mellitus were excluded from CAPitello-291).

patients). The characteristics of the overall study population have been previously published in detail.<sup>11</sup>

The CAPitello-291 safety population included 705 patients who received at least one dose of capivasertib (355 patients; all patients in the overall capivasertib-fulvestrant arm) or at least one dose of placebo (350 patients; 3 patients who were randomized to the placebo-fulvestrant arm did not subsequently receive treatment). Demographics for the safety population at baseline were generally similar across treatment arms (see Table 1); however, some differences with potential to affect risk of hyperglycemia were noted. The proportion of patients with a medical history of type 2 diabetes mellitus was greater in the capivasertib-fulvestrant arm compared with the placebo-fulvestrant arm (9.6% versus 5.7%, respectively). Fewer patients in the capivasertib-fulvestrant arm had a body mass index (BMI) category of obese (BMI ≥30 kg/m<sup>2</sup>; 18.6% versus 22.6%, respectively), while more patients had a BMI category of overweight (BMI 25.0-<30.0 kg/m<sup>2</sup>; 34.9% versus 30.0%, respectively).

Exposure to treatment

At data cut-off for the primary analysis (15 August 2022), median total intended treatment duration of capivasertib or

placebo was 5.4 and 3.6 months, respectively, and similar to the median actual treatment duration, 5.3 and 3.5 months, respectively (Supplementary Table S3, available at <https://doi.org/10.1016/j.esmoop.2024.103697>), reflecting the short duration of interruptions. Changes to capivasertib dose level over time are shown in Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmoop.2024.103697>, with dose reductions occurring early in treatment in patients where this was necessary, and dosing remaining stable thereafter; among patients receiving capivasertib treatment, 80.4% of patients at the end of cycle 2 and 76.2% of patients at the end of cycle 11 were receiving the 400-mg b.i.d. dose of capivasertib.

AEs leading to dose reductions were reported in 19.7% (70/355) of patients receiving capivasertib, compared with 1.7% (6/350) of patients receiving placebo. Based on exposure data, patients with a recorded capivasertib dose reduction due to AEs ( $n = 73$ ) had a median time to first dose reduction of 35 days [interquartile range (IQR) 29-56 days, range 8-253 days], and 75% of all dose reductions occurred within the first 66 days of starting treatment. AEs leading to dose interruptions were reported in 38.9% (138/355) of patients receiving capivasertib [ $n = 124$  (34.9%) capivasertib only and  $n = 22$  (6.2%) capivasertib and fulvestrant], compared with 12.3% (43/350) of patients receiving placebo [ $n = 36$  (10.3%) placebo only and  $n = 9$  (2.6%) placebo and fulvestrant].<sup>11</sup> Based on exposure data, patients with a recorded capivasertib dose interruption due to AEs ( $n = 137$ ) had a median time to first dose interruption of 16 days (IQR 15-44 days, range 4-527 days). AEs leading to permanent discontinuation of capivasertib were reported in 13.0% (46/355) of patients [ $n = 33$  (9.3%) capivasertib only and  $n = 13$  (3.7%) capivasertib and fulvestrant] and 2.3% (8/350) of patients receiving placebo [ $n = 2$  (0.6%) placebo only and  $n = 6$  (1.7%) placebo and fulvestrant]. Median time to permanent discontinuation of capivasertib was 29.0 days (IQR 15-53 days, range 8-417 days).

Fifty-eight patients in the capivasertib-fulvestrant arm (16.3%) and 50 patients in the placebo-fulvestrant arm (14.3%) took additional doses of the oral agent, exceeding the intended dose and/or schedule (400 mg b.i.d., 4 days on, 3 days off). The frequency of additional doses was highest in cycle 1 (28 patients), and nearly all these patients (27/28) exceeded the specified dose by taking capivasertib/placebo on a non-dosing day, which may have been a consequence of patients taking time to adjust to the intermittent dosing schedule. Eight patients (8/58) had a total additional dose of >400 mg b.i.d. capivasertib during the additional dosing period. One of these patients experienced a serious diabetic metabolic decompensation event associated with exceeding the specified dose (see Supplementary Results, available at <https://doi.org/10.1016/j.esmoop.2024.103697> for additional details).

**Overall safety profile.** AEs of any grade occurred in 96.6% (343/355) of patients treated with capivasertib-fulvestrant

and 82.3% (288/350) of patients treated with placebo-fulvestrant. AEs of any grade occurring in  $\geq 10\%$  of patients treated with capivasertib-fulvestrant are shown in Table 2. The most frequent AEs with capivasertib-fulvestrant were diarrhea, rash, and nausea. Notably, weight loss was uncommon in both treatment arms; the incidence of any-grade decreased weight was 3.4% with capivasertib-fulvestrant and 2.3% with placebo-fulvestrant. There was only one case of pneumonitis in each treatment arm (0.3%; both grade 1), considered unrelated to treatment by investigators; both patients recovered in full. No patient had interstitial lung disease reported as an AE.

AEs of grade  $\geq 3$  occurred in 42.8% of patients treated with capivasertib-fulvestrant and 15.7% of patients treated with placebo-fulvestrant, most frequently rash (12.1% and 0.3%), diarrhea (9.3% and 0.3%), and hyperglycemia (2.3% and 0.3%) (Table 2). Grade  $\geq 3$  stomatitis occurred in 2.0% and 0%, respectively.

### Characterization of AEs associated with PI3K/AKT pathway inhibition

**Diarrhea.** Although any-grade diarrhea was the most frequent AE in the capivasertib-fulvestrant arm, the majority of events reported were low-grade in severity (grade 1, 46.2%; grade 2, 16.9%); 9.3% grade 3 and no grade 4 events were reported (Table 2). Furthermore, diarrhea AEs were rarely serious, and led to permanent discontinuation of treatment in only 2% of patients (Table 3).

The median time to onset of diarrhea was 8 days after starting capivasertib-fulvestrant treatment and was similar by grade; at least 75% of patients with diarrhea AEs had their first event of diarrhea onset within the first treatment cycle (Table 3; Supplementary Figure S2A, available at <https://doi.org/10.1016/j.esmoop.2024.103697>). Of all diarrhea AEs, 86.4% were categorized by the investigator as intermittent or short-term ( $\leq 4$  days).

Diarrhea AEs were managed with dose reductions/interruptions and supportive medication; diarrhea medication was required in 151/257 (58.8%) patients in the capivasertib-fulvestrant arm, with loperamide as the primary treatment (Table 4). Complications of diarrhea were uncommon for patients receiving capivasertib-fulvestrant, but included dehydration (1.6%; 4/257), hyponatremia (1.2%; 3/257), hypokalemia (3.1%; 8/257), creatinine increase (3.9%; 10/257) during or within 7 days after the event, and acute kidney injury (1.9%; 5/257) during or within 28 days after the event. Hypokalemia is a potential complication of persistent or severe diarrhea; marked hypokalemia of grade  $\geq 3$  ( $<3.0$ - $<2.5$  mmol/l and hospitalization indicated) was reported at a low rate (capivasertib-fulvestrant arm 2.3% versus 0% in the placebo-fulvestrant arm).

**Rash.** There were no AEs of grade 4 rash in the capivasertib-fulvestrant arm (Table 2). Rash AEs were rarely serious and rarely led to patients permanently discontinuing treatment



**Table 2. Most frequent AEs (≥10% incidence for any grade in the capivasertib-fulvestrant arm)**

AE, n (%)	Capivasertib-fulvestrant n = 355					Placebo-fulvestrant n = 350				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AE	343 (96.6)	52 (14.6)	139 (39.2)	139 (39.2)	9 (2.5)	288 (82.3)	115 (32.9)	118 (33.7)	44 (12.6)	10 (2.9)
Diarrhea (group term) <sup>a</sup>	257 (72.4)	164 (46.2)	60 (16.9)	33 (9.3)	0	71 (20.3)	61 (17.4)	9 (2.6)	1 (0.3)	0
Diarrhea	257 (72.4)	164 (46.2)	60 (16.9)	33 (9.3)	0	70 (20.0)	60 (17.1)	9 (2.6)	1 (0.3)	0
Frequent bowel movements	0	0	0	0	0	0	0	0	0	0
Gastrointestinal hypermotility	0	0	0	0	0	1 (0.3)	1 (0.3)	0	0	0
Rash (group term) <sup>a</sup>	135 (38.0)	57 (16.1)	35 (9.9)	43 (12.1)	0	25 (7.1)	19 (5.4)	5 (1.4)	1 (0.3)	0
Rash	78 (22.0)	41 (11.5)	18 (5.1)	19 (5.4)	0	15 (4.3)	10 (2.9)	4 (1.1)	1 (0.3)	0
Rash maculopapular	57 (16.1)	18 (5.1)	17 (4.8)	22 (6.2)	0	9 (2.6)	8 (2.3)	1 (0.3)	0	0
Rash papular	4 (1.1)	1 (0.3)	1 (0.3)	2 (0.6)	0	0	0	0	0	0
Rash pruritic	2 (0.6)	2 (0.6)	0	0	0	1 (0.3)	1 (0.3)	0	0	0
Rash macular	1 (0.3)	1 (0.3)	0	0	0	1 (0.3)	1 (0.3)	0	0	0
Nausea	123 (34.6)	85 (23.9)	35 (9.9)	3 (0.8)	0	54 (15.4)	42 (12.0)	10 (2.9)	2 (0.6)	0
Fatigue	74 (20.8)	49 (13.8)	23 (6.5)	2 (0.6)	0	45 (12.9)	35 (10.0)	8 (2.3)	2 (0.6)	0
Vomiting	73 (20.6)	54 (15.2)	13 (3.7)	6 (1.7)	0	17 (4.9)	10 (2.9)	5 (1.4)	2 (0.6)	0
Headache	60 (16.9)	47 (13.2)	12 (3.4)	1 (0.3)	0	43 (12.3)	33 (9.4)	8 (2.3)	2 (0.6)	0
Hyperglycemia (group term) <sup>a</sup>	60 (16.9)	26 (7.3)	26 (7.3)	7 (2.0)	1 (0.3)	14 (4.0)	8 (2.3)	5 (1.4)	1 (0.3)	0
Hyperglycemia	58 (16.3)	24 (6.8)	26 (7.3)	7 (2.0)	1 (0.3)	13 (3.7)	8 (2.3)	4 (1.1)	1 (0.3)	0
Blood glucose increased	2 (0.6)	2 (0.6)	0	0	0	1 (0.3)	0	1 (0.3)	0	0
Decreased appetite	59 (16.6)	37 (10.4)	21 (5.9)	1 (0.3)	0	22 (6.3)	11 (3.1)	9 (2.6)	2 (0.6)	0
Stomatitis	52 (14.6)	24 (6.8)	21 (5.9)	7 (2.0)	0	17 (4.9)	15 (4.3)	2 (0.6)	0	0
Asthenia	47 (13.2)	29 (8.2)	14 (3.9)	4 (1.1)	0	36 (10.3)	31 (8.9)	3 (0.9)	2 (0.6)	0
Pruritus	44 (12.4)	32 (9.0)	10 (2.8)	2 (0.6)	0	23 (6.6)	19 (5.4)	4 (1.1)	0	0
Anemia	37 (10.4)	15 (4.2)	15 (4.2)	7 (2.0)	0	17 (4.9)	4 (1.1)	9 (2.6)	4 (1.1)	0
Urinary tract infection	36 (10.1)	8 (2.3)	23 (6.5)	5 (1.4)	0	23 (6.6)	2 (0.6)	21 (6.0)	0	0

The listed events were reported in at least 10% of the patients for any grade in the capivasertib-fulvestrant arm. AEs are reported regardless of the relationship to the study drugs. AE, adverse event.

<sup>a</sup>Group terms (preferred terms): diarrhea (diarrhea, frequent bowel movements, gastrointestinal hypermotility); rash (rash, rash macular, rash maculopapular, rash papular, rash pruritic); hyperglycemia (blood glucose increased, hyperglycemia).

(Table 3). Seven patients (7/355; 2.0%) treated with capivasertib-fulvestrant had a serious AE of rash leading to hospitalization, compared with no patients treated with placebo-fulvestrant.

The median time to onset of the first rash event was 12 days after starting capivasertib-fulvestrant treatment, and was similar by grade (Table 3; Supplementary Figure S2B, available at <https://doi.org/10.1016/j.esmoop>).

**Table 3. Characterization of diarrhea, rash, and hyperglycemia**

	Diarrhea <sup>a</sup>		Rash <sup>a</sup>		Hyperglycemia <sup>a</sup>	
	Capivasertib-fulvestrant n = 355	Placebo-fulvestrant n = 350	Capivasertib-fulvestrant n = 355	Placebo-fulvestrant n = 350	Capivasertib-fulvestrant n = 355	Placebo-fulvestrant n = 350
Any grade	257 (72.4)	71 (20.3)	135 (38.0)	25 (7.1)	60 (16.9)	14 (4.0)
Grade 1	164 (46.2)	61 (17.4)	57 (16.1)	19 (5.4)	26 (7.3)	8 (2.3)
Grade 2	60 (16.9)	9 (2.6)	35 (9.9)	5 (1.4)	26 (7.3)	5 (1.4)
Grade 3	33 (9.3)	1 (0.3)	43 (12.1)	1 (0.3)	7 (2.0)	1 (0.3)
Grade 4	0	0	0	0	1 (0.3)	0
Serious AE, n (%)	6 (1.7)	1 (0.3)	7 (2.0)	0	3 (0.8)	0
AEs led to hospitalization, n (%)	6 (1.7)	1 (0.3)	7 (2.0)	0	3 (0.8)	0
Median (IQR) time to onset, days						
All grade	8 (2-22)	22 (10-57)	12 (10-15)	48 (22-108)	15 <sup>b</sup> (1-51)	48 (28-120)
Grade 1	9 (1-23.5)	22 (11-49)	15 (10-22)	48 (16-108)	15 (1-29)	62 (23-257)
Grade 2	6 (2-22.5)	39 (6-81)	12 (11-15)	41 (29-116)	16 (1-68)	29 (28-56)
Grade 3	9 (2-15)	25 (25-25)	11 (10-12)	73 (73-73)	18 (8-30) <sup>b</sup>	120 (120-120)
AE leading to capivasertib/placebo dose change, n (%)						
Reduction	28 (7.9)	0	16 (4.5)	0	2 (0.6)	0
Interruption	35 (9.9)	3 (0.9)	42 (11.8)	0	9 (2.5)	3 (0.9)
Discontinuation	7 (2.0)	0	16 (4.5)	0	1 (0.3)	1 (0.3)

AE, adverse event; IQR, interquartile range; NA, not applicable.

<sup>a</sup>Group terms (preferred terms): diarrhea (diarrhea, frequent bowel movements, gastrointestinal hypermotility); rash (rash, rash macular, rash maculopapular, rash papular, rash pruritic); hyperglycemia (blood glucose increased, hyperglycemia).

<sup>b</sup>Time to onset includes the one patient who had a grade 4 hyperglycemia event.

**Table 4. Supportive medications**

N		Capivasertib-fulvestrant <i>n</i> = 355				Placebo-fulvestrant <i>n</i> = 350			
		All grades	Grade 1	Grade 2	Grade 3	All grades	Grade 1	Grade 2	Grade 3
Diarrhea <sup>a,b</sup>	Patients with event, <i>n</i>	257	164	60	33	71	61	9	1
	Treatment required, <sup>c</sup> <i>n</i> (%)	151 (58.8)	75 (45.7)	47 (78.3)	29 (87.9)	28 (39.4)	20 (32.8)	7 (77.8)	1 (100.0)
	Loperamide	135	69	41	25	27	19	7	1
Rash <sup>a,d</sup>	Patients with event, <i>n</i>	135	57	35	43	25	19	5	1
	Treatment required, <sup>c</sup> <i>n</i> (%)	109 (80.7)	37 (64.9)	31 (88.6)	41 (95.3)	14 (56.0)	8 (42.1)	5 (100.0)	1 (100.0)
	Antihistamines	75	16	24	35	7	3	3	1
	Topical corticosteroids	64	21	18	25	5	2	3	0
	Systemic corticosteroids <sup>e</sup>	28	3	2	23	2	0	2	0
Hyperglycemia <sup>a</sup>	Patients with event, <i>n</i>	60	26	26	8 <sup>f</sup>	14	8	5	1
	Treatment required, <sup>c</sup> <i>n</i> (%)	28 (46.7)	1 (3.8)	19 (73.1)	8 (100.0)	4 (28.6)	2 (25.0)	1 (20.0)	1 (100.0)
	Metformin	18	1	13	4	3	1	1	1
	Insulin (and/or analogs)	10	0	4	6	2	0	1	1
	Other blood glucose-lowering drugs	10	0	7	3	1	0	0	1

<sup>a</sup>Group terms (preferred terms): diarrhea (diarrhea, frequent bowel movements, gastrointestinal hypermotility); rash (rash, rash macular, rash maculopapular, rash papular, rash pruritic); hyperglycemia (blood glucose increased, hyperglycemia).

<sup>b</sup>Includes patients receiving medication of loperamide based on the Anatomical Therapeutic Chemical code.

<sup>c</sup>Determined by completion of a yes/no tick box in the adverse event report form. Percentage values shown are calculated from the number of patients experiencing the event.

<sup>d</sup>Systemic corticosteroid use also required that the reason for use was defined as 'rash' (or a similar term) to avoid capturing corticosteroids for other indications.

<sup>e</sup>Includes patients receiving medication of systemic hormonal preparations, excluding sex hormones and insulins.

<sup>f</sup>Patients with event includes the one patient who had a grade 4 hyperglycemia event.

2024.103697); at least 75% of events started within the first treatment cycle. The prevalence of rash in the capivasertib-fulvestrant arm peaked within 1 month of treatment at ~30%, decreasing by the end of the second month to just above 10% (Supplementary Figure S3, available at <https://doi.org/10.1016/j.esmoop.2024.103697>). This decrease was unlikely to be driven by patients terminating capivasertib due to rash as only 16/355 (4.5%) patients discontinued capivasertib due to rash AE.

Rash AEs were managed with dose reductions/interruptions, and supportive medication was required in 109/135 (80.7%) patients in the capivasertib-fulvestrant arm (Table 4); rash was managed with oral antihistamines and/or topical corticosteroids in most patients. Twenty-eight patients (28/135; 20.7%) required supportive medication with systemic corticosteroids, and most of these patients (23/28) had a grade 3 rash event (Table 4). Almost half of patients with a grade 3 rash event (19/43) were able to remain on treatment until disease progression, with the rash event managed by dose reductions and/or supportive medication. Further details of other skin-related AEs are given in the Supplementary Results, available at <https://doi.org/10.1016/j.esmoop.2024.103697>.

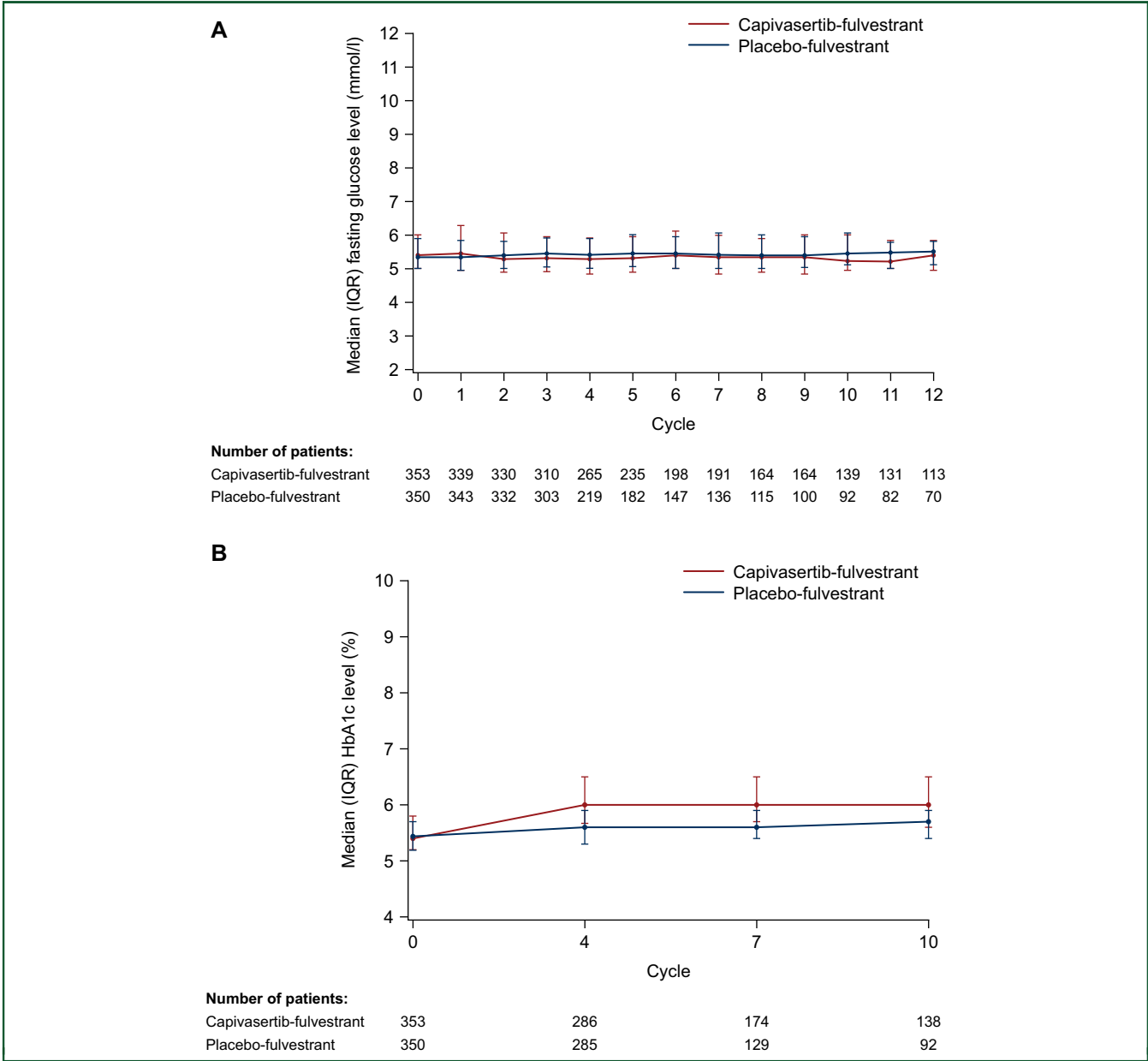
**Hyperglycemia.** The median time to onset of hyperglycemia with capivasertib-fulvestrant was 15 days, and was similar by grade (Table 3; Supplementary Figure S2C, available at <https://doi.org/10.1016/j.esmoop.2024.103697>). Grade ≥3 hyperglycemia occurred in 2.3% (8/355) of patients in the capivasertib-fulvestrant arm (only one patient had a grade 4 AE) and hyperglycemia AEs were rarely serious (Table 3). Rates of dose reduction or treatment interruption in the capivasertib-fulvestrant arm due to hyperglycemia AEs were low (Table 3); one patient permanently discontinued treatment in the capivasertib-fulvestrant arm due to a

hyperglycemia AE. This patient had a medical history of obesity, and developed grade 4 hyperglycemia on day 16 of cycle 1 (5 days after the most recent dose of capivasertib dose), resulting in a temporary interruption in capivasertib treatment. The patient was diagnosed with sepsis 2 days later and died the following day.

There was one report of grade 4 diabetic ketoacidosis in a patient with pre-existing type 2 diabetes and two patients experienced diabetic metabolic decompensation (one of whom also exceeded the specified capivasertib dose, as described above; see Supplementary Results, available at <https://doi.org/10.1016/j.esmoop.2024.103697>, for additional details).

Median fasting glucose in both treatment arms was within the normal range at baseline [5.39 mmol/l (IQR 5.00-5.99 mmol/l) in the capivasertib-fulvestrant arm; 5.33 mmol/l (IQR 5.00-5.88 mmol/l) in the placebo-fulvestrant arm] and remained within the normal range in both treatment arms (Figure 1A). Median HbA1c in both treatment arms was also within the normal range at baseline [5.4% (IQR 5.20%-5.80%) in the capivasertib-fulvestrant arm; 5.4% (IQR 5.2%-5.7%) in the placebo-fulvestrant arm], and remained within normal range throughout. HbA1c increased to 6.0% in the capivasertib-fulvestrant arm at cycle 4 (first time point assessed) and then remained consistent over time. In the placebo-fulvestrant arm, median HbA1c increased to 5.6% at cycle 4 and remained consistent over time (Figure 1B). Of the patients with normal HbA1c at baseline, 129/254 (50.8%) in the capivasertib-fulvestrant arm and 45/250 (18.0%) in the placebo-fulvestrant arm had a shift to values above the upper limit of normal during treatment.

Median fasting glucose and median HbA1c levels over time in patients with and without a medical history of diabetes, as well as by baseline glucose control, are shown in Supplementary Figure S4A and B, available at <https://doi.org/10.1016/j.esmoop.2024.103697>.



**Figure 1. Hyperglycemia markers over time for (A) fasting glucose and (B) HbA1c.** Fasting glucose was assessed pre-dose and 4 h post-dose (fasting or non-fasting) on cycle 1, week 1, day 1; on cycle 1, week 3, day 1; on cycle 2, week 1, day 1; and, from cycle 3 onwards, on week 1, day 1. Cycle 1 values shown here represent data from cycle 1, week 3, day 1. HbA1c was measured at baseline and on week 1, day 1 of cycles 4, 7, and 10. HbA1c, hemoglobin A1c; IQR, interquartile range.

[org/10.1016/j.esmoop.2024.103697](https://doi.org/10.1016/j.esmoop.2024.103697), respectively. In patients without a medical history of diabetes, or with normal baseline laboratory ranges for glucose control, median fasting glucose levels and median HbA1c levels were within the normal range over time in both treatment arms. Median fasting glucose and median HbA1c levels were also consistent over time in patients with baseline laboratory results within the pre-diabetic range. For patients with a medical history of diabetes, or baseline laboratory results within the diabetic range, median glucose and median HbA1c results were higher in the capivasertib group compared with the placebo group, with the change from baseline occurring early in therapy and remaining consistent over time thereafter.

Treatment for hyperglycemia AEs was required for 28 patients treated with capivasertib-fulvestrant (28/60 patients with event; 46.7%), most of whom (18/28, 64.3%) received metformin (Table 4). Use of any hypoglycemic medication for any reason (AE or other reason such as past medical history of diabetes) in the study was reported in 60 patients treated with capivasertib-fulvestrant; 32/60 (53.3%) were treated with an antidiabetic agent at baseline, before starting study therapy.

Eighteen patients in the capivasertib-fulvestrant arm who were treated with an oral antidiabetic medication during the study had no prior hypoglycemic medication use at baseline; the majority (15/18) received only one pharmacologic agent, suggesting that initial therapy was adequate for hyperglycemia management.

Seventeen patients in the capivasertib-fulvestrant arm had insulin administered for any reason during the study: nine patients with a medical history of diabetes (out of 34 in the study) and eight patients without diabetes (out of 321 in the study). Sixteen of the seventeen patients received insulin for hyperglycemia or related medical history; one patient was given insulin for an hepatoprotective indication, per local standard of care. For patients without diabetes at baseline, the median duration of insulin use was 1.5 days (range 1-19 days). For patients with a medical history of diabetes, the median duration of insulin use was 6 days (range 1-120 days).

**Risk factors for hyperglycemia.** Hyperglycemia AEs were slightly higher in patients with BMI  $\geq 30$  kg/m<sup>2</sup> versus patients whose BMI was  $< 30$  kg/m<sup>2</sup> irrespective of the study arm. In the capivasertib-fulvestrant arm, 21.2% (14/66) of patients with BMI  $\geq 30$  kg/m<sup>2</sup> had a hyperglycemia AE versus 16.1% (46/285) of patients with BMI  $< 30$  kg/m<sup>2</sup>. In the placebo-fulvestrant arm, 5.1% (4/79) of patients with BMI  $\geq 30$  kg/m<sup>2</sup> had a hyperglycemia AE versus 3.7% (10/267) of patients with BMI  $< 30$  kg/m<sup>2</sup>. The incidence of hyperglycemia AEs with capivasertib-fulvestrant was more frequent in patients with a medical history of diabetes mellitus (10/34, 29.4%) versus those without (50/321, 15.6%).

## DISCUSSION

Based on the findings reported here, capivasertib was well tolerated by patients in CAPItello-291 with HR-positive/HER2-negative ABC; the capivasertib safety profile compares favorably with that of other agents targeting the PI3K/AKT pathway in this patient population.<sup>11</sup> Diarrhea, rash, and hyperglycemia are frequent AEs associated with PI3K/AKT pathway inhibition, and their occurrence in CAPItello-291 was as expected, given that capivasertib is a potent, selective inhibitor of AKT1, AKT2, and AKT3.

Diarrhea was the most frequent any-grade AE with capivasertib-fulvestrant treatment, generally started within the first cycle of treatment, and was grade 1 in the majority of instances. Diarrhea duration within the study was frequently reported to span the entire duration of the study, due to the presence of intermittent diarrhea. As such, it is not possible to fully characterize the duration of diarrhea episodes and their relationship with the intermittent dosing of capivasertib; however, of all diarrhea AEs reported, most (86.4%) were categorized as intermittent by the investigator, or were short-term ( $\leq 4$  days). Fewer than 10% of patients in the capivasertib-fulvestrant arm had a dose reduction due to diarrhea, and the rate of permanent discontinuation of treatment was very low. It has previously been reported that there was a greater worsening of the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-C30) diarrhea symptom score with capivasertib-fulvestrant versus placebo-fulvestrant (least squares mean difference 18.5, 95% CI 15.0-22.0), although this did not negatively impact global health status/health-related quality of life,

which was maintained from baseline and maintained for longer versus placebo-fulvestrant.<sup>13</sup>

Rash was the most frequent grade  $\geq 3$  AE with capivasertib-fulvestrant treatment. Rash occurred early after commencement of treatment, with prevalence peaking around cycle 1, and could be managed in most patients with oral antihistamine and/or topical corticosteroids; the use of systemic corticosteroids for rash AEs was low. The rate of permanent discontinuation from capivasertib-fulvestrant treatment because of rash was also low, suggesting that rash was manageable in the CAPItello-291 population. To note, patients who had a grade 3 rash AE and continued on study treatment until disease progression were more likely to have had a dose reduction than those patients who discontinued the study due to grade 3 rash, suggesting that dose reductions may be helpful in managing cases of high-grade rash.

Hyperglycemia of any grade was reported as an AE in 16.9% of patients treated with capivasertib-fulvestrant, the majority being grade 1 (7.3%) or 2 (7.3%); 2.3% of patients had a grade  $\geq 3$  AE. Onset of hyperglycemia occurred early in treatment (median 15 days) highlighting the importance of frequent monitoring of fasting glucose, especially at the start of treatment and in patients at high risk of hyperglycemia.<sup>14</sup> Dose reductions/interruptions for patients with hyperglycemia AEs were rare. However, one patient who permanently discontinued capivasertib-fulvestrant treatment due to grade 4 hyperglycemia had an ongoing medical history of obesity (a predisposing factor for hyperglycemia) and later died of concomitant sepsis. The rate of insulin use was low in CAPItello-291; it was reported in around one-quarter of patients with a medical history of diabetes in the capivasertib-fulvestrant arm, and in  $< 3\%$  of patients without diabetes. The short duration of insulin use in the patients who required it suggests that insulin is rarely necessary for capivasertib-treated patients, and that when insulin is necessary it is not likely to be required for long-term treatment. The median duration of first insulin use in patients without diabetes (and with no hypoglycemic medication at baseline) was also short at 1.5 days, suggesting that insulin use is also effective in treating acute cases. Median fasting glucose and HbA1c over time were in the expected range, and were generally consistent over time. While patients with past medical history of diabetes had an increase in HbA1c in the capivasertib group, the median HbA1c remained below 8% over 12 months of therapy, suggesting no untoward effects of treatment and suggesting that any changes were effectively managed. Furthermore, less-stringent glycemic goals may be considered appropriate for patients with ABC.<sup>15</sup> Median fasting glucose and HbA1c over time in patients with baseline laboratory results, particularly for those within the pre-diabetic range, are indicative of good control. These results suggest that for diabetic patients, best practice would be for pretreatment checks for stability of the condition, alongside close monitoring, to allow for optimal management of diabetes that may require intensified diabetic treatment.



Diarrhea, rash, and hyperglycemia have been reported in studies of other PI3K/AKT pathway inhibitors,<sup>6,7</sup> and further characterization of these AEs has informed management guidance to optimize safety and clinical benefit.<sup>16,17</sup> The frequency and severity of rash was reduced successfully in the phase III SOLAR-1 study of alpelisib with the prophylactic use of anti-rash medication (oral antihistamines, in most cases)<sup>17</sup>; anti-rash prophylaxis was not incorporated into CAPItello-291, but rash was considered manageable, with low rates of treatment discontinuation. Hyperglycemia as an AE was managed with dose interruptions and oral hypoglycemic medication (metformin preferred) in CAPItello-291, and with insulin in few cases (10/355; 3%). Insulin (alone or in combination with other hypoglycemic medications) was also required to manage hyperglycemia observed in SOLAR-1 in 52/284 patients, including in patients with diabetes (5/12 patients) as well as in those without diabetes (13/113 patients and those with pre-diabetes (34/159 patients)).<sup>17</sup> Insulin use to manage hyperglycemia was also reported in 29 out of 74 patients with hyperglycemia in the phase II BYLieve study.<sup>16</sup> Other AEs have been reported in studies of other agents that work via the PI3K/AKT pathway, including stomatitis with use of everolimus. The implementation of management guidelines on the prophylactic use of dexamethasone mouthwash in patients with breast cancer reduced the rate and severity of everolimus-related stomatitis (versus BOLERO-2),<sup>9</sup> and a stepwise dose escalation of everolimus over the early weeks of treatment was an approach that proved necessary to reduce the incidence of grade  $\geq 2$  stomatitis.<sup>18</sup> However, stomatitis AEs were infrequent in CAPItello-291. Pneumonitis, which has been observed with the use of antibody–drug conjugates in treating solid tumors<sup>19</sup> and in patients with HR-positive/HER2-negative ABC treated with everolimus-exemestane,<sup>7</sup> occurred in only one patient in each treatment arm and was not deemed related to study drugs, with both patients recovering in full.

Use of different MedDRA versions to code AEs and CTCAE versions to grade severity, different group terms and analysis methods, as well as inherent differences among trial population and study designs makes comparing incidence rates across studies challenging. However, rates of dose reductions/interruptions for AEs in CAPItello-291 were generally lower than those reported in studies of PI3K pathway inhibitors. In SOLAR-1, dose reductions/interruptions for AEs within the alpelisib-fulvestrant arm occurred in 57.7% and 66.5% of patients, respectively<sup>17</sup> (compared with 19.7% and 38.9%, respectively, in the capivasertib-fulvestrant arm in CAPItello-291). The relatively low rate of dose modifications and permanent discontinuations of treatment indicates that exposure to capivasertib was not limited by AEs, and therefore did not compromise clinical benefit. Furthermore, the delivered dose of capivasertib was similar to the intended dosing, reflecting the short duration of capivasertib treatment interruptions and acceptable tolerability.

Capivasertib (400 mg) was administered on an intermittent dosing schedule (b.i.d.; 4 days on, 3 days off); this

schedule was selected early in clinical development (partially due to preclinical modeling), to strike the most appropriate balance between maximizing PI3K/AKT inhibition while limiting toxicity as much as possible. Additional doses exceeding the intended dose and/or schedule of capivasertib/placebo were reported in fewer than one in six patients in both treatment arms, and most occurred as result of a self-administration error on a designated non-dosing day of the intermittent dosing schedule. Additional dose events generally occurred early in the treatment period, suggesting that self-administration errors were corrected over time as patients became more accustomed to the intermittent dosing schedule.

In conclusion, this detailed analysis of frequent AEs associated with PI3K/AKT pathway inhibition demonstrates the early occurrence of diarrhea, rash, and hyperglycemia with capivasertib treatment. The tolerability of these frequent AEs is acceptable when they are managed as in CAPItello-291, as evidenced by a low rate of treatment discontinuations. Having a thorough understanding of the safety profile of new agents will enable appropriate patient monitoring and management, thereby optimizing the clinical benefit.

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