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ORIGINAL ARTICLE

An exposure–safety analysis to support the dosage of the novel AKT inhibitor capivasertib

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Abstract

Purpose This study aimed to evaluate capivasertib exposure–response relationships for clinical safety events to support dosage selection.

Methods Data from 277 patients with solid tumors participating in three phase 1 studies were analyzed. Capivasertib 80–800 mg was administered as monotherapy orally twice daily (BID) on continuous or intermittent (4 days on, 3 days off [4/3] or 2 days on, 5 days off [2/5]) schedules. Relationships between exposure related metrics (dose, weekly dose, AUC, AUC_{PWD}, C_{max}, and C_{min}) and probability of safety endpoints (adverse event [AE] leading to dose discontinuation, AE leading to dose modification, serious AE [SAE], AE grade ≥ 3, AE grade ≥ 1, diarrhea AE grade ≥ 2, rash AE grade ≥ 2, hyperglycemia AE grade ≥ 3 and increased blood glucose > 13.9 mmol/L) were evaluated by logistic regression.

Results Significant exposure–response relationships were identified for all safety endpoints evaluated, except for AE grade ≥ 1. The analysis suggested that most of the safety endpoints are driven by the total weekly exposure, whereas glucose elevations are driven by the exposure achieved within a dosing interval. The probability of experiencing an AE leading to dose discontinuation, AE leading to dose modification, SAE, AE grade ≥ 3, diarrhea or rash were lower with the 480 mg BID [4/3] schedule than with the 320 mg BID continuous schedule.

Conclusion Significant exposure–response relationships were identified for safety endpoints when capivasertib was administered to patients with solid tumors suggesting that the intermittent [4/3] schedule is better tolerated than the continuous schedule due to lower total weekly exposure.

Keywords AKT inhibitor · Capivasertib · Exposure–safety analysis · Exposure–response analysis · Modeling · Recommended dose

Introduction

The phosphatidylinositol 3-kinase (PI3K)/Akt serine/threonine kinase (AKT) signaling pathway is an important signaling pathway regulating cell proliferation and survival [1, 2]. Hyperactivation of the pathway due to PTEN deficiency or activating mutations in the catalytic subunit alpha of phosphatidylinositol-3-kinase (*PIK3CA*) and in *AKT1* is implicated in tumor growth across cancer indications [3]; hence, the PI3K/AKT pathway has been a target of oncology drug discovery [1, 2, 4].

Capivasertib, a potent, selective inhibitor of all AKT isoforms (AKT1/2/3) [5, 6], demonstrated efficacy in combination with fulvestrant for the treatment of hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer and with paclitaxel for the treatment of triple-negative breast cancer (TNBC) in clinical

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phase 2 trials with an intermittent capivasertib dose regimen of 400 mg twice daily (BID) given 4 days on, 3 days off [4/3] [7, 8]. The [4/3] schedule of capivasertib administration has been used in all subsequent phase 3 trials. The phase 3 CAPItello-291 trial in patients with aromatase inhibitor-resistant, HR-positive/HER2-negative advanced breast cancer showed statistically significant and clinically meaningful improvement in progression-free survival in the overall population and in the population of patients with *PIK3CA/AKT1/PTEN*-altered tumors [9]. These data led to approval of capivasertib–fulvestrant in several markets [10–15] and the inclusion of the combination as a treatment option in clinical guidelines [16, 17].

Earlier on during clinical development, the first-in-human study of capivasertib explored a range of oral doses (80–800 mg BID) and schedules (continuous, intermittent [4/3], and intermittent 2 days on, 5 days off [2/5]) for capivasertib given as monotherapy to patients with solid tumors [18, 19]. The recommended phase 2 doses were determined at 320 mg BID, 480 mg BID, and 640 mg BID for the continuous, [4/3], and [2/5] schedules, respectively, and were primarily based on empirical evaluation of dose-limiting toxicities (DLTs). The DLTs were diarrhea, rash, and hyperglycemia [18, 19], which were broadly consistent with observations from studies of other AKT inhibitors (ipatasertib and MK2206) [20, 21] and other drugs affecting the PI3K/AKT pathway [22]. Based on the combination of tolerability, pharmacokinetic (PK), and pharmacodynamic considerations, capivasertib 480 mg BID [4/3] was selected as the recommended phase 2 dose for capivasertib monotherapy [18]. There was also evidence of greater target engagement in tumor tissue with 480 mg BID on a [4/3] schedule than with 320 mg continuous dosing [18], further supporting dose and schedule selection. Findings from phase 1/2 trials reinforced selection of a slightly lower dose of 400 mg BID [4/3] when capivasertib is used in combination with fulvestrant or paclitaxel [7, 8, 23–25].

The PK of capivasertib have been characterized in studies of patients with solid tumors [18, 19, 23, 26, 27], in healthy volunteer studies [28–30] and in a population PK (PopPK) analysis of pooled studies [31]. Capivasertib plasma exposure was approximately dose proportional in the dose range of 80–480 mg, with a half-life of approximately 8 h [31]. Capivasertib PK showed moderate between-subject variability, and no patient covariate (including race, gender, body weight, renal or hepatic function) was predicted to impact exposure to capivasertib by >20% [31]. Therefore, no a priori dose adjustment is required for intrinsic patient factors [10].

Information collected from early phase clinical trials is used for initial assessment of drug safety profile over a wide dose range and estimation of a maximum tolerated dose. Uncertainty in safety evaluations, however, is a common problem in oncology drug development due to the small sample size and use of adaptive or complex study designs [32]. This may complicate the analysis of exposure–response for adverse events (AEs) and, therefore, the selection of the optimal therapeutic regimen for further clinical trials. In addition, interpretation of safety information generated in oncology trials is often confounded by differences in baseline patient characteristics, the between-subject variability of drug exposure, complex treatment schedules, toxicity-mediated dose reductions and extensive use of co-medications [32]. Multivariate exposure–safety analyses of individual patient data allow to delineate the impact of various factors on the observed safety profiles across clinical studies with different designs and various patient populations, guiding the selection of the therapeutic regimen for future trials. Such an approach was used for risk–benefit analyses of treatment with the AKT inhibitor ipatasertib in prostate cancer [33, 34], the programmed cell death ligand 1 antibody atezolizumab [35], the programmed cell death (PD-1) antibody nivolumab [36], and hypofractionated radiotherapy regimens [37], a model-based analysis was also applied to evaluate factors affecting the probability of immune-related AEs associated with the PD-1 antibody pembrolizumab [38].

The aim of the analysis reported here was to evaluate exposure–response relationships for the following safety endpoints of capivasertib when given as monotherapy to patients with solid tumors: AE leading to dose discontinuation, AE leading to dose modification (interruption and/or reduction), serious AE (SAE), AE grade≥3, AE grade≥1, diarrhea AE grade≥2, rash AE grade≥2, hyperglycemia AE grade≥3 and increased blood glucose>13.9 mmol/L, based on pooled data from three phase 1 clinical trials.

Methods

Experimental data

Safety data from 277 patients participating in three trials of capivasertib given as monotherapy were included in the analysis (Supplementary Table 1).

Study 1 (NCT01226316) was a phase 1 open-label multipart study. Parts A and B were dose-escalation and dose-expansion parts, respectively, to assess tolerability of capivasertib in patients with advanced solid malignancies; parts C and D were expansion cohorts of patients with *PIK3CA*-mutated breast or gynecologic cancers or *AKT1*-mutated breast or gynecologic cancers or other solid tumors to assess safety and efficacy of the selected dosing regimen [18, 25, 39]. The duration of the treatment cycles

was 21 days. For parts A and B, the treatment was started with a single capivasertib administration, followed by a 3- to 7-day washout (Cycle 0). Patients received capivasertib 80–800 mg BID on a continuous or intermittent schedule [4/3] and [2/5] [18]. For parts C and D, capivasertib monotherapy was given at 480 mg [4/3] [18, 25, 39]. Part D also included patients receiving capivasertib in combination with fulvestrant [25], but only patients receiving capivasertib as monotherapy have been included in the present analysis.

Study 4 (NCT01353781) was a phase 1 dose-escalation study in Japanese patients with advanced solid malignancies [19]. The treatment was started with single capivasertib administration, followed by a 3- to 7-day washout (Cycle 0); duration of subsequent cycles was 21 days. Patients received capivasertib 80–640 mg BID on a continuous or intermittent schedule [4/3] and [2/5].

The OAK study (NCT01895946) was a phase 1 open-label study aimed to compare tablet and capsule capivasertib formulations and to explore the impact of food intake on drug exposure [26]. Patients received 480 mg capivasertib BID on an intermittent schedule [4/3].

Dose and systemic exposure calculations

Blood samples for characterizing capivasertib PK were collected and analyzed using a PopPK approach [31], which was used to project the individual exposure metrics. The exposure–response analyses were conducted using a subset of patients from the PopPK analysis where capivasertib was used as monotherapy. The capivasertib dose, planned weekly dose (PWD), area under the curve (AUC) at steady-state (SS), AUC based on planned weekly dose (AUC_{PWD}) at SS, maximum concentration (C_{max}) at SS and minimum concentration (C_{min}) at SS were selected as the exposure metrics for the exposure–response analyses. As different schedules were assessed between and within studies, the exposure metrics were derived for the last dose of the last dosing day in the second week of treatment (i.e. on days 14, 11, and 9 for the continuous, [4/3] and [2/5] schedules, respectively), to ensure SS conditions, using the planned dose. C_{max} was the maximum concentration, C_{min} was the 12 h post-dose concentration and AUC was calculated from dose/apparent clearance (CL/F). The relative dose intensity (RDI) was calculated as the percentage of the average weekly dose relative to the PWD to examine the tolerability of capivasertib monotherapy at the given dosing schedules.

Safety endpoints

AEs were collected throughout the trials, graded using Common Terminology Criteria for Adverse Events v4. Treatment-emergent AEs (TEAEs), defined as any AE that started after the first dose of study treatment or that started prior to dosing and worsened during on treatment period (by investigator report of a change in intensity) following exposure to treatment, were included in the analysis.

The following safety endpoints were evaluated: AE leading to dose discontinuation, AE leading to dose modification (interruption and/or reduction), SAE, AE grade ≥ 3, AE grade ≥ 1, diarrhea AE grade ≥ 2, rash AE grade ≥ 2, hyperglycemia AE grade ≥ 3 and increased blood glucose > 13.9 mmol/L. An SAE was defined as any AE that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in a significant, persistent or permanent disability, or a congenital anomaly or birth defect in any subsequent children. Increased blood glucose was defined as > 13.9 mmol/L based on the Common Terminology Criteria for Adverse Events version 4 (CTCAE v4) criteria for grade 3 hyperglycemia used in the studies included in this analysis. These analyses were confined to hyperglycemia AE grade ≥ 3 and were not designed to assess the use of comedications during the treatment, such as hypoglycemic agents. The absolute value or percentage change to blood glucose were not included in the analyses. The rash AE endpoint pooled the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms: rash maculo-papular, rash macular, rash, rash generalized, rash papular and rash pruritic, while the diarrhea AE and hyperglycemia AE included the MedDRA preferred terms diarrhea and hyperglycemia, respectively.

The grade selection for diarrhea and rash was based on clinical relevance in terms of limiting quality of life; for hyperglycemia the grade was higher considering this is a pharmacodynamic effect of AKT inhibition and often seen as asymptomatic change of laboratory value only.

Exposure–response analysis

Logistic regression models were used to establish associations between the probability of the safety endpoints with the exposure metrics at a statistically significant level of 0.005.

Software

Dataset preparation was performed using Statistical Analysis Software (SAS®) version 9.4 (SAS Institute, NC, USA) and R Project for Statistical Computing, Version 4.0.2 (Comprehensive R Archive Network, http://cran.r-project.org) according to the data specifications. The analysis was performed using NONMEM Version 7.3.0 (ICON, Ellicot City, MD, USA), entimICE version 4.4 (Entimo AG, Berlin, Germany) and R Project for Statistical Computing.

Results

Patient characteristics and planned Capivasertib dose

Patient baseline characteristics are described in Table 1. Overall, the dataset comprised 277 subjects; 67.5% were females and 76.9% identified as White. The median (range) for weight was 70 (32–129) kg and 76.2% of the patients were <65 years of age. All patients had advanced solid tumors and were classified as either 0 or 1 for WHO performance status. Primary tumor sites included breast, lung, cervix, uterus, pleura, ovary, liver, colorectal, or colon [18, 19, 26].

Capivasertib was administered as monotherapy at 80–800 mg BID, where 480 mg BID was the most common dose level (61.0% of patients; Supplementary Table 2), as it was the selected recommended phase 2 dose (given [4/3]) in the expansion phases of the dose-escalation studies and for the formulation/food study. The recommended doses of 320 mg for the continuous and 640 mg BID for the [2/5] schedule were less frequently used (6.5% and 8.7% of patients, respectively; Supplementary Table 2).

Table 1 Baseline patient characteristics

Characteristic		Study 1 (*N*=206)	Study 4 (*N*=41)	OAK (*N*=30)	Total (*N*=277)
Age, years; n (%)	≥65	52 (25.2)	4 (9.8)	10 (33.3)	66 (23.8)
	<65	154 (74.8)	37 (90.2)	20 (66.7)	211 (76.2)
Sex; n (%)	Female	148 (71.8)	24 (58.5)	15 (50.0)	187 (67.5)
	Male	58 (28.2)	17 (41.5)	15 (50.0)	90 (32.5)
Race	White	185 (89.8)	0	28 (93.3)	213 (76.9)
	Asian	9 (4.4)	41 (100)	0	50 (18.1)
	Japanese	3 (1.5)	41 (100)	0	44 (15.9)
	Other Asian	6 (2.9)	0	0	6 (2.2)
	Black	5 (2.4)	0	1 (3.3)	6 (2.2)
	Other	5 (2.4)	0	1 (3.3)	6 (2.2)
	Missing	2 (1.0)	0	0	2 (0.7)
Body weight, kg; median (range)		72 (32–129)	57 (40–97)	78 (53–115)	70 (32–129)
Hepatic function	Normal	150 (72.8)	32 (78.0)	22 (73.3)	204 (73.6)
	Mild impairment	53 (25.7)	9 (22.0)	8 (26.7)	70 (25.3)
	Moderate impairment	3 (1.5)	0 (0.0)	0 (0.0)	3 (1.1)
Renal function	Normal	119 (57.8)	28 (68.3)	20 (66.7)	167 (60.3)
	Mild impairment	70 (34.0)	9 (22.0)	10 (33.3)	89 (32.1)
	Moderate impairment	17 (8.3)	4 (9.8)	0 (0.0)	21 (7.6)
Blood glucose, mmol/L; median (range)		5.3 (3.7–8.1)	5.2 (4.6–7.2)	5.4 (3.7–6.5)	5.3 (3.7–8.1)[a]
HbA1c, mmol/mol; median (range)		37.0 (25.0–49.0)	46.0 (35.0–56.0)	36.0 (24.0–49.0)	37.0 (24.0–56.0)[b]

HbA1c, glycated hemoglobin

[a]Missing: 9 patients (3.2%); [b]Missing: 49 patients (17.7%)

Summary of exposure metrics and safety endpoints

The summary of the exposure metrics and safety endpoints by schedule and dose level are given in Tables 2 and 3, respectively.

The RDI was predominantly decreased with increasing dose for the continuous schedule and was ≤80% for the 400 and 480 mg doses. On the other hand, the RDI was >90% for the [4/3] and [2/5] schedules at all dose levels, suggesting better tolerability with the intermittent schedules in patients enrolled in these early-phase studies (Table 2). In total, across all doses and schedules, 18.4% of patients had AEs leading to dose discontinuation, 50.2% AEs leading to dose modification, 38.6% SAEs, 65.7% AEs grade≥3, 98.9% AE grade≥1, 36.8% diarrhea AE grade≥2, 26.4% rash AE grade≥2, 26.0% hyperglycemia grade≥3, and 45.5% increased blood glucose>13.9 mmol/L (Table 3).

Exposure–response relationships

Detailed exposure–response analysis was carried out to identify statistically significant relationships between exposure metrics and safety endpoints (Supplementary Fig. 1). No significant relationships were observed for AE grade≥1. Significant relationships for the remaining safety endpoints are summarized below. The exposure metric that showed the most significant (lowest p-value) association with each safety endpoint (by univariate logistic regression) are highlighted below in bold:

- AE leading to dose discontinuation: **PWD**.
- AE leading to dose modification: PWD, AUC, **AUC_{PWD}**, C_{max}, and C_{min}.
- AE grade≥3: dose, PWD, AUC, **AUC_{PWD}**, C_{max}, and C_{min}.
- SAE: dose, PWD, AUC, **AUC_{PWD}**, C_{max}, and C_{min}.
- Hyperglycemia AE grade≥3: dose, **AUC**, AUC_{PWD}, C_{max}, and C_{min}.
- Increased blood glucose>13.9 mmol/L: dose, AUC, AUC_{PWD}, **C_{max}**, and C_{min}.
- Diarrhea AE grade≥2: PWD, **AUC_{PWD}**.
- Rash AE grade≥2: **PWD**.

Hence, the total weekly exposure constituted the main driver for most safety endpoints (Fig. 1A), whereas hyperglycemia and increased blood glucose were primarily driven by the exposure achieved within the 12 h dosing interval (Fig. 1B).

At a given dose, there was a statistically significant effect of schedule for AE leading to dose discontinuation, AE

Table 2 Summary of exposure metrics by study, schedule, and dose level

Study	Schedule	Dose (mg)	PWD (mg)	*N*	Exposure metrics; median (range)				
					RDI (%)	$AUC_{ss(0–12\ h)}$ (mg·h/L)	AUC_{PWD} (mg·h/L)	C_{max} (mg/L)	C_{min} (mg/L)
Study 1	Continuous	80	1120	5	100.0 (95.9–100.6)	0.87 (0.69–1.70)	12.16 (9.71–23.78)	0.15 (0.13–0.26)	0.03 (0.02–0.09)
		160	2240	5	97.6 (83.5–102.3)	2.99 (1.94–4.80)	41.79 (27.09–67.27)	0.42 (0.37–0.83)	0.11 (0.07–0.19)
		240	3360	6	100.3 (98.8–100.9)	3.19 (2.15–4.68)	44.70 (30.11–65.50)	0.53 (0.31–0.97)	0.11 (0.08–0.16)
		320	4480	12	98.1 (37.2–102.4)	5.86 (3.51–10.74)	82.01 (49.12–150.34)	0.87 (0.58–1.62)	0.20 (0.10–0.38)
		400	5600	11	80.3 (55.4–102.1)	5.79 (4.28–13.70)	81.04 (59.96–191.78)	0.90 (0.52–2.26)	0.19 (0.14–0.55)
		480	6720	6	50.2 (45.3–83.3)	9.98 (7.24–18.06)	139.62 (101.36–252.63)	1.62 (1.12–2.33)	0.37 (0.16–0.77)
		600	8400	2	103.1 (100–106.2)	14.27 (12.74–15.79)	199.70 (178.34–221.05)	2.52 (2.04–3.00)	0.46 (0.43–0.50)
	[4/3]	480	3840	127	97.9 (26.4–138.9)	9.69 (3.97–26.5)	77.42 (31.74–212.16)	1.59 (0.60–3.91)	0.33 (0.11–1.07)
		640	5120	10	100.0 (70.5–122.2)	15.92 (9.62–28.95)	127.41 (76.99–231.67)	2.43 (1.41–5.27)	0.55 (0.24–1.30)
	[2/5]	640	2560	8	94.0 (80.9–109.1)	14.96 (8.18–26.83)	59.82 (32.70–107.11)	2.08 (1.35–3.90)	0.57 (0.28–0.95)
		800	3200	14	101.1 (42.5–133.3)	26.44 (11.83–70.78)	105.81 (47.34–283.19)	3.93 (2.34–5.60)	1.08 (0.38–3.61)
Study 4	Continuous	80	1120	3	100.0 (88.7–102.3)	1.48 (1.17–2.40)	20.74 (16.33–33.63)	0.22 (0.14–0.49)	0.06 (0.05–0.08)
		240	3360	7	100.0 (41.9–106.7)	5.22 (2.71–10.71)	73.04 (37.97–150.00)	0.82 (0.56–1.67)	0.17 (0.08–0.46)
		320	4480	6	91.5 (59.3–101.1)	6.56 (4.15–28.42)	91.79 (58.03–396.46)	1.38 (0.74–3.99)	0.15 (0.12–1.40)
		400	5600	5	72.1 (51.4–85.7)	7.75 (6.91–13.91)	108.53 (96.72–194.44)	1.24 (1.06–2.35)	0.27 (0.21–0.55)
	[4/3]	360	2880	8	107.9 (91.4–112)	6.10 (3.95–11.18)	48.80 (31.58–89.44)	0.96 (0.53–1.84)	0.21 (0.10–0.47)
		480	3840	6	107.9 (79.1–108.6)	10.85 (7.97–12.05)	86.78 (63.79–96.48)	1.88 (1.55–2.78)	0.29 (0.19–0.42)
	[2/5]	640	2560	6	111.2 (100–119)	15.24 (13.39–34.02)	60.97 (53.56–136.17)	2.48 (1.61–3.40)	0.57 (0.40–1.65)
OAK	[4/3]	480	3840	30	100 (45.6–115.4)	9.75 (4.43–26.60)	77.97 (35.49–213.33)	1.58 (0.90–4.63)	0.33 (0.12–1.51)

$AUC_{ss(0–12\ h)}$, area under the curve during a dose interval (0–12 h) at steady-state; AUC_{PWD}, area under the curve based on planned weekly dose; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; PWD, planned weekly dose; RDI, relative dose intensity

Table 3 Summary of safety endpoints by dosing schedule and dose level

Schedule	Dose (mg)	*N*	Safety endpoint; *n* (%)								
			AEDD	AEDM	AE grade≥1	AE grade≥3	Diarrhea AE grade≥2	Increased BG > 13.9 mmol/L	Hyperglycemia AE grade≥3	Rash AE grade≥2	SAE
Continuous	80	8	0	2 (25.0)	8 (100)	2 (25.0)	0	0	0	1 (12.5)	2 (25.0)
	160	5	0	1 (20.0)	5 (100)	0	0	0	0	1 (20.0)	1 (20.0)
	240	13	1 (7.7)	2 (15.4)	12 (92.3)	4 (30.8)	4 (30.8)	4 (30.8)	2 (15.4)	3 (23.1)	0
	320	18	3 (16.7)	8 (44.4)	18 (100)	10 (55.6)	5 (27.8)	3 (16.7)	2 (11.1)	5 (27.8)	4 (22.2)
	400	16	7 (43.8)	15 (93.8)	16 (100)	15 (93.8)	10 (62.5)	7 (43.8)	4 (25.0)	8 (50.0)	6 (37.5)
	480	6	4 (66.7)	5 (83.3)	6 (100)	6 (100)	5 (83.3)	2 (33.3)	2 (33.3)	3 (50.0)	6 (100)
	600	2	2 (100)	1 (50.0)	2 (100)	2 (100)	1 (50.0)	1 (50.0)	0	2 (100)	2 (100)
[4/3]	360	8	0	3 (37.5)	6 (75.0)	3 (37.5)	4 (50.0)	3 (37.5)	1 (12.5)	1 (12.5)	0
	480	163	27 (16.6)	90 (55.2)	163 (100)	114 (69.9)	64 (39.3)	82 (50.3)	45 (27.6)	45 (27.6)	68 (41.7)
	640	10	4 (40)	2 (20.0)	10 (100)	7 (70.0)	3 (30.0)	7 (70.0)	4 (40.0)	0	6 (60.0)
[2/5]	640	14	2 (14.3)	2 (14.3)	14 (100)	11 (78.6)	3 (21.4)	8 (57.1)	7 (50.0)	2 (14.3)	7 (50.0)
	800	14	1 (7.1)	8 (57.1)	14 (100)	8 (57.1)	3 (21.4)	9 (64.3)	5 (35.7)	2 (14.3)	5 (35.7)
Total		277	51 (18.4)	139 (50.2)	274 (98.9)	182 (65.7)	102 (36.8)	126 (45.5)	72 (26.0)	73 (26.4)	107 (38.6)

AE, adverse event; AEDD, adverse event leading to dose discontinuation; AEDM, adverse event leading to dose modification (interruption and/or reduction); BG, blood glucose; SAE, serious AE

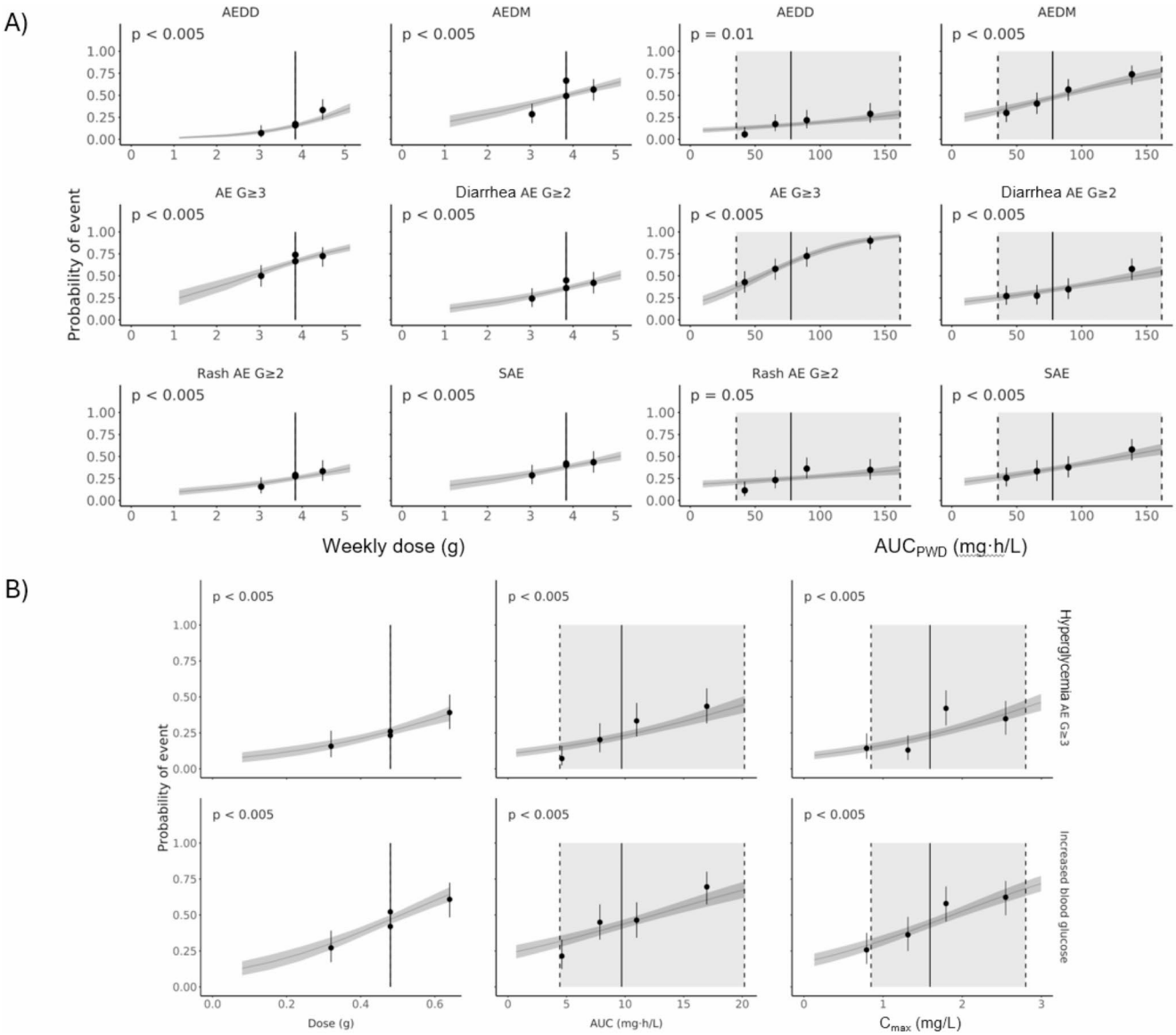

Fig. 1 Relationship between exposure metrics and probability of event by (**A**) weekly dose and AUC_{PWD} and (**B**) Dose, AUC, and C_{max}. Dots and solid black vertical lines: quartile of exposure metric with 95% CI; gray horizontal lines and dark gray areas: exposure–response relationship with 95% CI; solid and slashed gray vertical lines: 2.5th, 50th, and 97.5th percentiles of exposure metric at 480 mg [4/3]; light gray area: 95% prediction interval of exposure metric at 480 mg [4/3]; *p*-value represents the significance level of the exposure metric. AUC, area under the curve; AUC_{PWD}, area under the curve based on planned weekly dose; AE, adverse event; AEDD, adverse event leading to dose discontinuation; AEDM, adverse event leading to dose modification (interruption and/or reduction); CI, confidence interval; C_{max}, maximum plasma concentration; G, grade; SAE, serious adverse event

leading to dose modification, and diarrhea AE grade≥2 with intermittent schedules associated with lower probability of events compared with the continuous schedule, whereas the probabilities of hyperglycemia AE grade≥3 and increased blood glucose>13.9 mmol/L did not depend on the schedule (Fig. 2A). However, at a given weekly dose, the effect of schedule was statistically significant for hyperglycemia AE grade≥3 and increased blood glucose>13.9 mmol/L only, with intermittent schedules associated with higher probability of events compared with the continuous schedule; the [2/5] schedule was inferior, i.e. associated with higher probability of events, to the [4/3] schedule (Fig. 2B). Given the higher weekly dose on the 320 mg continuous schedule (4480 mg) compared with the intermittent schedule [4/3] at 480 mg (3840 mg), the probability of hyperglycemia AE grade≥3 and increased blood glucose>13.9 mmol/L is not expected to be significant between the continuous and intermittent 480 mg [4/3] schedules.

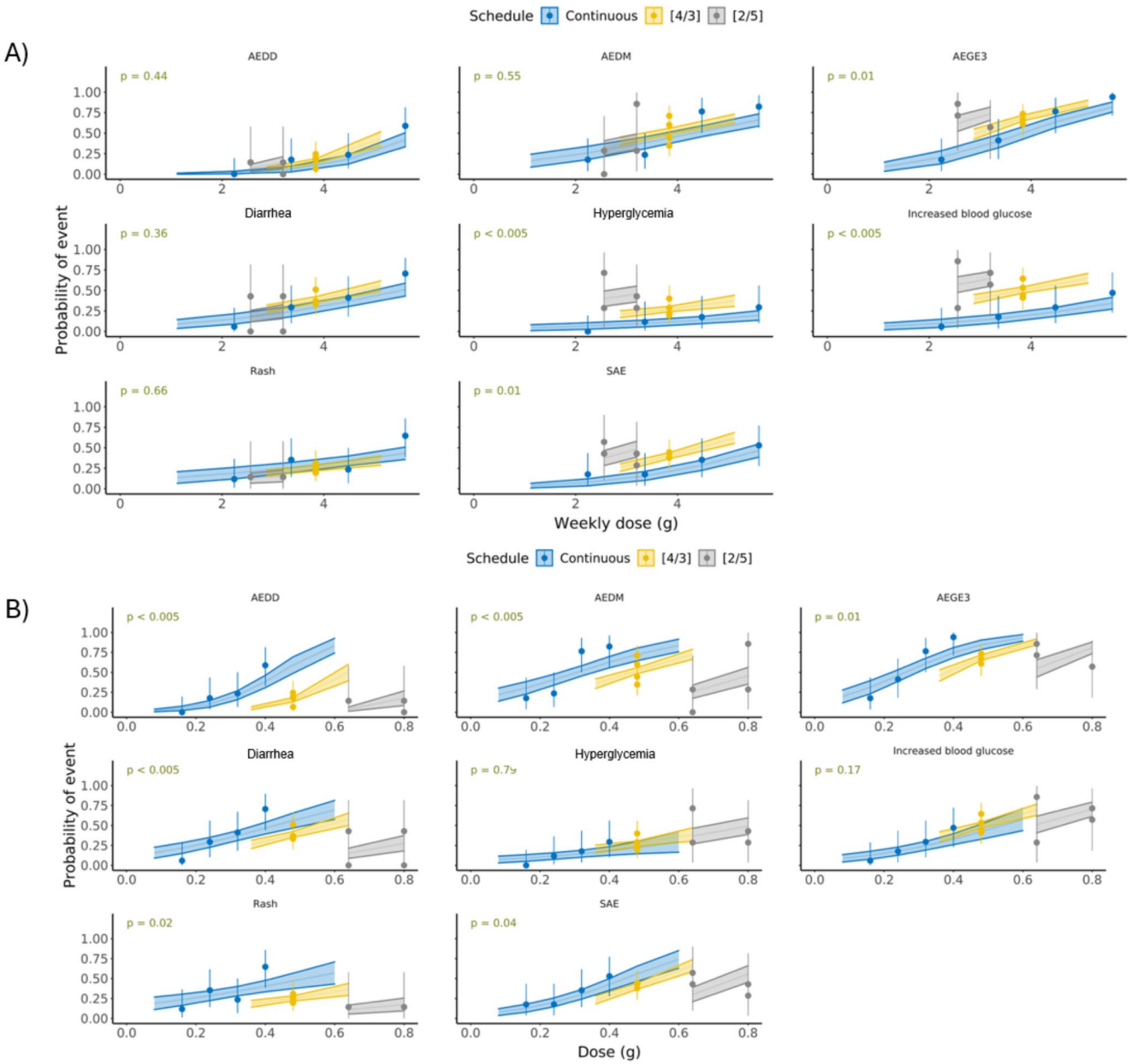

Fig. 2 Relationship, according to administration schedule, between dose and probability of event by (**A**) dose and (**B**) weekly dose. Dots and vertical lines: quartile of exposure metric with 95% CI; horizontal lines and colored areas: exposure–response relationship with 95% CI; *p*-value represents the significance level of the schedule. AE, adverse event; AEDD, adverse event leading to dose discontinuation; AEDM, adverse event leading to dose modification (interruption and/or reduction); AEGE3, adverse event grade≥3; CI, confidence interval; SAE, serious adverse event

Discussion

This safety analysis has characterized the exposure–response relationships for capivasertib monotherapy for AE leading to dose discontinuation, AE leading to dose modification, SAE, AE grade≥3, diarrhea AE grade≥2, rash AE grade≥2, hyperglycemia AE grade≥3, and increased blood glucose>13.9 mmol/L with several exposure metrics. We focused on diarrhea, rash, and hyperglycemia in terms of AEs of special interest, as all three were DLTs as well as the most common AEs grade≥3 in the first-in-human study of capivasertib (hyperglycemia was the most common, followed by diarrhea and then, maculopapular rash) [18]. The exposure–response models were able to establish relationships for all safety endpoints evaluated based on linear logistic regressions, except for AE grade≥1, which occurred in almost all patients.

The exposure metrics were projected using the planned starting dose and proved to be adequate predictors for

the incidence of the safety endpoints. Although other approaches, such as using the average exposure metric until the time of event, were considered, estimating different exposure metrics for each safety endpoint would complicate the subsequent interpretation as this may have led to biased analyses. Instead, the current analysis employed exposure metrics at SS, which are recommended as they do not depend on the outcome [40].

Hyperglycemia AE of grade≥3 and increased blood glucose (>13.9 mmol/L) were influenced by capivasertib exposure during a dosing interval, showing a stronger correlation with dose, AUC, and C_{max} than with the weekly exposure. Conversely, all other safety endpoints were predominantly associated with cumulative capivasertib exposure, demonstrating a stronger correlation with weekly dose and/or AUC_{PWD}. Consequently, the likelihood of AE leading to dose discontinuation, AE leading to dose modification, SAE, AE of grade≥3, diarrhea of grade≥2, and rash of grade≥2 is predicted to be lower with the [4/3] intermittent schedule compared with the continuous schedule at a given dose. However, the probability of hyperglycemia AE of grade≥3 and increased blood glucose>13.9 mmol/L is predicted to increase with the dose, regardless of the dosing schedule. While hyperglycemia is a known pharmacodynamic effect of AKT inhibition and often seen as asymptomatic change to blood glucose, oral hypoglycemic drugs are indicated in the clinical management of hyperglycemia AE grade≥2. Use of metformin was explored at baseline, but usage was too low in the study population to allow meaningful inferences about combination therapy of capivasertib with hypoglycemic agents.

The probability of rash AE grade≥2, AE leading to dose discontinuation, AE leading to dose modification, AE grade≥3, SAE and diarrhea AE grade≥2 was higher with the continuous schedule at 320 mg (4480 mg weekly) compared with the intermittent schedule [4/3] at 480 mg (3840 mg weekly) due to the lower total weekly exposure, while the [2/5] schedule at 640 mg presented higher probability of hyperglycemia AE grade≥3 and increased blood glucose>13.9 mmol/L than the [4/3] schedule at 480 mg. Therefore, our results further reinforce the selection of 480 mg BID on a [4/3] schedule as a recommended monotherapy dose based on safety outcomes.

Conclusion

In patients with solid tumors who were administered capivasertib as monotherapy, significant relationships were identified between the total weekly exposure (weekly dose and AUC_{PWD}) and the probability of experiencing AE leading to dose discontinuation, AE leading to dose modification (interruption and/or reduction), SAE, AE grade≥3, diarrhea AE grade≥2, and rash AE grade≥2. The probabilities of experiencing hyperglycemia AE grade≥3 and increased blood glucose>13.9 mmol/L were more closely related to the exposure during a dosing interval (dose, AUC, and C_{max}).

Overall, the analyses suggest that the 4/3 intermittent schedule was better tolerated, except for hyperglycemia AE grade≥3 and increased blood glucose>13.9 mmol/L events, compared with a continuous schedule due to the generally lower total weekly exposure.

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Data availability Data underlying the findings described in this manuscript may be obtained in accordance with the sponsor's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The sponsor's Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Declarations

Competing interests Carlos Fernandez Teruel and Ignacio González-García are former employees of AstraZeneca. Marie Cullberg, Gaia Schiavon, and Diansong Zhou are employees of AstraZeneca and have ownership, options, and/or interests in AstraZeneca stock.

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