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Phase I Study of the PI3Kα Inhibitor Alpelisib (BYL719), as a Single Agent in Patients With Advanced Solid Tumors (aST)

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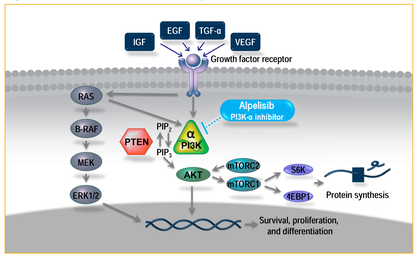
INTRODUCTION

- The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway is the most commonly activated signaling pathway in cancer.[1]
- Activation of the PI3K/AKT/mTOR pathway promotes tumor growth and progression, as well as resistance to anticancer therapies.[1-4]
- PI3K/AKT/mTOR pathway activation frequently occurs as a result of mutation or amplification of *PIK3CA*, the gene that encodes the catalytic subunit (p110α) of PI3K.[5-8]
- Alpelisib (BYL719) is an oral inhibitor that selectively targets the α-isoform of class I PI3K (**Figure 1**).[9]

Figure 1. Mechanism of Action for Alpelisib



4EBP1, 4E-binding protein 1; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; IGF, insulin-like growth factor; MEK, mitogen-activated protein kinase/ERK kinase; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog; S6K, ribosomal S6 kinase; TGF-α, transforming growth factor alpha; VEGF, vascular endothelial growth factor.

- Alpelisib has shown antitumor activity in a variety of cancer cell lines, especially in those harboring *PIK3CA* mutations,[9,10] and in tumor xenograft models with mutated or amplified *PIK3CA*.[9]
- Alpelisib has been investigated in a Phase IA study as a single agent in patients with *PIK3CA*-altered advanced solid tumors, or *PIK3CA*-altered or wild-type estrogen receptor-positive (ER+) advanced breast cancer, and in combination with fulvestrant in patients with *PIK3CA*-altered or wild-type ER+ breast cancer (CBYL719X2101/NCT01219699).
- Here we report the updated results from the single-agent part of this study.

STUDY OBJECTIVES

Primary

- To determine the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) of oral alpelisib as a single agent in patients with *PIK3CA*-altered advanced solid tumors, or *PIK3CA*-altered or wild-type ER+ breast cancer.

Secondary

- To assess the safety and tolerability of single-agent alpelisib.
- To characterize the pharmacokinetic profile of single-agent alpelisib.
- To assess the preliminary efficacy of single-agent alpelisib.

Exploratory

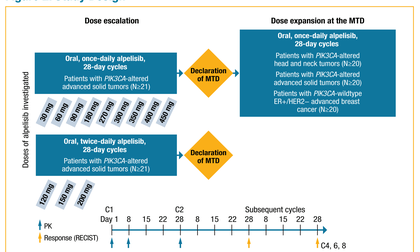
- To assess downstream effects of PI3K pathway inhibition, markers of response, and perform biomarker analysis.

METHODS

Study Design

- In the single-agent part of this first-in-man, multicenter, open-label, Phase I study, the safety and preliminary efficacy of alpelisib was investigated. The study comprised two stages (**Figure 2**):
  - Dose escalation stage which enrolled patients with *PIK3CA*-altered (mutation or amplification) advanced solid tumors.
  - Dose expansion stage which also enrolled a subset of patients with *PIK3CA* wild-type ER+/HER2– locally advanced or metastatic breast cancer.

Figure 2. Study Design



C, cycle; ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor 2-negative; MTD, maximum tolerated dose; PK, pharmacokinetics; RECIST, Response Evaluation Criteria In Solid Tumors.

- Patients received oral alpelisib once or twice daily on a continuous schedule of 28-day cycles.
  - Once-daily (QD) doses of alpelisib investigated were: 30 mg, 60 mg, 90 mg, 180 mg, 270 mg, 300 mg, 350 mg, 400 mg, and 450 mg.
  - Twice-daily (BID) doses of alpelisib investigated were: 120 mg, 150 mg, and 200 mg.
- Dose escalation was guided by an adaptive Bayesian logistic regression model with overdose control.[11]

Key Inclusion Criteria

- Adult (≥18 years) patients with histologically confirmed, advanced unresectable solid tumors with documented progression on standard therapy or for whom no standard anticancer therapy exists.
- Documented *PIK3CA* gene alteration status (i.e. mutated, amplified, or wild-type).
- Archival or fresh tumor tissue sample available for assessment of molecular alterations.
- At least one measurable or non–measurable lesion as per Response Evaluation Criteria In Solid Tumors (RECIST) v1.0.
- World Health Organization (WHO) performance status ≤2.
- Adequate organ function as assessed by laboratory tests.
- Fasting plasma glucose <140 mg/dL (7.8 mmol/L).

Key Exclusion Criteria

- Brain metastasis, unless treated and free of signs/symptoms attributable to metastasis in the absence of corticosteroid therapy.
- Failure to benefit from prior treatment with a PI3K, AKT, or mTOR inhibitor.
- Clinically manifest diabetes mellitus, history of gestational diabetes mellitus, or documented steroid-induced diabetes mellitus.

Assessments

- Radiologic response was assessed by computerized tomography or magnetic resonance imaging according to RECIST v1.0 on Day 28 of Cycle 2 and every 8 weeks thereafter.
- Adverse events (AEs) were assessed continuously according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0, unless otherwise specified.
- Routine laboratory assessments were conducted at baseline, weekly until Day 28 of Cycle 2, and then every 2 weeks.
- Pre- and post-treatment fresh and archival tumor biopsies were obtained where possible and were used to assess biomarkers that may be predictive of response (i.e. *PTEN* alteration, *KRAS*, and *BRAF* mutations).

RESULTS

Patient Demographics and Characteristics

- As of March 10, 2014, 132 patients with *PIK3CA*-altered advanced solid tumors, or *PIK3CA*-altered or wild-type ER+ advanced breast cancer received alpelisib in this Phase I study (**Table 1**): 106 patients on the once-daily schedule (30 mg–450 mg/QD) and 26 patients on the twice-daily schedule (120 mg–200 mg/BID).
- As of the data cut-off (March 10, 2014), study treatment had been discontinued in 122 (92%) patients. Primary reasons for treatment discontinuation were:
  - Disease progression (99 [75%] patients).
  - AE (18 [14%] patients).
  - Withdrawal of consent (3 [2%] patients).
  - Death (2 [2%] patients; not suspected to be study drug-related).

Table 1. Patient Characteristics at Baseline

Characteristic	Total (N=132)
Median age, years (range)	59 (21–82)
<65 years (%)	93 (71)
≥65 years (%)	39 (30)
Gender, male/female, n (%)	35/97 (27/74)
ECOG PS, 0/1/2, n (%)	51/74/6 (39/56/5)*
Primary cancer site, n (%)	
Breast	35 (27)
Head and neck	13 (10)
Colorectal	35 (27)
Ovarian	14 (11)
Other†	35 (27)
Time since initial diagnosis of primary site, n (%)	
<12 months	8 (6)
12–<36 months	56 (42)
≥36 months	68 (52)
Median no. of prior antineoplastic therapies, n (range)	4 (1–19)
PIK3CA molecular status, n (%)	
Mutant	123 (93)
Wild-type	5 (4)
Missing	4 (3)

ECOG PS, Eastern Cooperative Oncology Group performance status.
*One patient result was missing for ECOG PS.
†Primary cancer sites classed as 'other' include: lung, cervix, oral cavity, uterus, and endometrium.
Data cut-off: March 10, 2014.

Dose-limiting Toxicities

- Of 76 patients evaluable during dose escalation, DLTs were observed in: 4 patients treated with 450 mg/QD alpelisib; 1 patient treated with 150 mg/BID alpelisib; and 4 patients treated with 200 mg/BID alpelisib (**Table 2**).

Table 2. Dose-limiting Toxicities

	Dose	Patients experiencing DLTs	DLT
Once-daily doses	450 mg/QD (n=9)	4	Grade 3 hyperglycemia (2 patients)* Grade 3 nausea (2 patients)
Twice-daily doses	150 mg/BID (n=15)	1	Grade 3 hyperglycemia and hypophosphatemia
	200 mg/BID (n=6)	4	Grade 3 hyperglycemia (1 patient) Grade 4 hyperglycemia (3 patients)

BID, twice-daily; DLT, dose-limiting toxicity; QD, once-daily.
*One case of Grade 3 hyperglycemia was not suspected to be related to study drug.
Data cut-off: March 10, 2014.

- The MTD of alpelisib QD has previously been declared as 400 mg/QD;[12] here, the MTD of alpelisib BID was declared as 150 mg/BID.

Safety and Tolerability

- Overall, across all doses, the median duration of exposure to alpelisib was 11.9 weeks (range 0.4 to >98 weeks).
  - Sixty-three (48%) patients received the QD MTD of alpelisib, and 15 (11%) patients received the BID MTD of alpelisib.
  - Twenty-eight (21%) patients received study treatment for ≥24 weeks.
- The most frequent (≥10%) AEs suspected to be study drug-related are presented in **Table 3**.
  - In the overall study population (N=132), the most common suspected study drug-related AE was hyperglycemia which was reported in 62 (47%) patients, and was Grade 3/4 in 31 (24%) patients.
  - Grade 1/2 rash was observed in 17 (13%) patients receiving alpelisib. Grade 1/2 and Grade 3/4 maculopapular rash was observed in 11 (8%) and 3 (2%) patients receiving alpelisib respectively.
  - Other than hyperglycemia, Grade 3/4 AEs suspected to be study drug-related were rare (0–3%).
  - At the MTDs the most common (>30%; all grade) AEs suspected to be study drug-related were:
    - Alpelisib 400 mg/QD (n=63 including dose expansion): hyperglycemia (51%), nausea (48%), diarrhea (41%), decreased appetite (38%), fatigue (32%), and vomiting (30%).
    - Alpelisib 150 mg/BID (n=15): hyperglycemia and nausea (both 53%), diarrhea, decreased appetite, fatigue, and stomatitis (all 33%).
- AEs requiring dose interruption and/or reduction were reported in 79 (60%) patients.

Table 3. Treatment-emergent Adverse Events (≥10%; All Grade) Suspected to be Related to Study Treatment

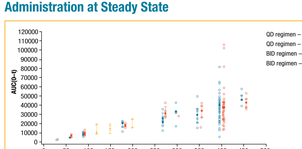
Drug-related Adverse Event, n (%)	Grade	Alpelisib MTDs		Total (N=132)
		400 mg/QD (n=63)	150 mg/BID (n=15)	
Hyperglycemia	All	32 (51)	8 (53)	62 (47)
	3/4	16 (25)	5 (33)	31 (24)
Nausea	All	30 (48)	8 (53)	61 (46)
	3/4	1 (2)	0	3 (2)
Diarrhea	All	26 (41)	5 (33)	50 (38)
	3/4	2 (3)	0	3 (2)
Decreased appetite	All	24 (38)	5 (33)	49 (37)
	3/4	1 (2)	0	2 (2)
Fatigue	All	20 (32)	5 (33)	38 (29)
	3/4	0	0	2 (2)
Vomiting	All	19 (30)	1 (7)	36 (27)
	3/4	3 (5)	0	3 (2)
Stomatitis	All	10 (16)	5 (33)	24 (18)
	3/4	0	0	0
Dysgeusia	All	7 (11)	2 (13)	18 (14)
	3/4	0	0	0
Dyspepsia	All	6 (10)	2 (13)	17 (13)
	3/4	0	0	0
Rash	All	5 (8)	3 (20)	17 (13)
	3/4	0	0	0
Weight decreased	All	4 (6)	2 (13)	15 (11)
	3/4	0	0	0
Dry skin	All	5 (8)	2 (13)	14 (11)
	3/4	0	0	0
Rash (maculopapular)	All	9 (14)	2 (13)	14 (11)
	3/4	3 (5)	0	3 (2)

BID, twice-daily; MTD, maximum tolerated dose; QD, once-daily.
Data cut-off: March 10, 2014.

Pharmacokinetics

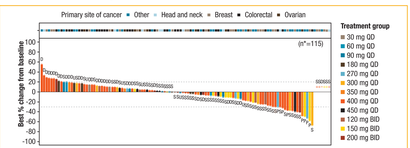
- Alpelisib was rapidly absorbed with a median T_{max} (Cycle 1, Day 1 [C1D1]) of 2 hours at both the MTDs (400 mg/QD; 150 mg/BID).
- The median half-life (C1D1) was 7.5 (range: 4.6–27.1) hours for alpelisib 400 mg/QD and 3.6 (range: 2.8–6.8) hours for alpelisib 150 mg/BID.
- Systemic exposure to the once- and twice-daily MTDs of alpelisib appeared to be dose proportional (**Figure 3**).
- The pharmacokinetic profiles of alpelisib were comparable across multiple time points (C1D1, C1D8, and C2D1), suggesting minimal drug accumulation.

Figure 3. Dose Proportionality of Once- and Twice-daily Alpelisib Administration at Steady State



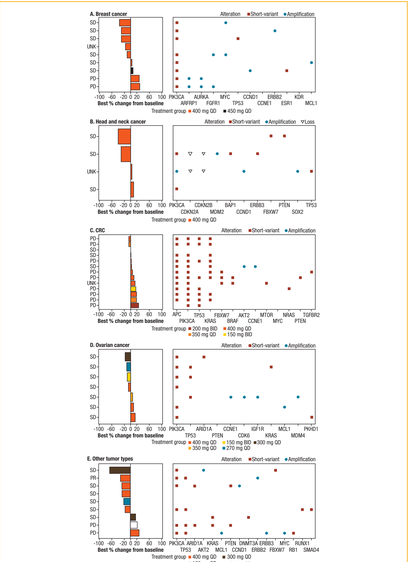
AUC, area under the curve; BID, twice-daily; C, cycle; D, day; QD, once-daily.
Data cut-off: March 10, 2014.

Figure 4. Best Percent Change from Baseline in Sum of Longest Diameters and Best Overall Response as Per Local Review



BID, twice-daily; D, progressive disease; P, partial response; QD, once-daily; S, stable disease; U, unknown.
*Patients with missing best percentage from baseline and unknown best overall response are not included.
Data cut-off: March 10, 2014.

Figure 5. Genetic Alterations Observed in Tumor Samples With Known/ Likely Functional Significance Using NGS Analysis and Best Percentage Change From Baseline in Sum of Longest Diameters as per Investigator by Treatment Group



BID, twice-daily; CRC, colorectal cancer; NGS, next-generation sequencing; PD, progressive disease; PR, partial response; QD, once-daily; SD, stable disease, UNK, unknown.
Only patients with both efficacy data and NGS data are reported.
Data cut-off: March 10, 2014.

Preliminary Clinical Activity

- As of March 10, 2014, 131 patients overall were evaluable for radiologic response (i.e. had undergone at least one post-baseline tumor assessment) (**Figure 4**):
  - Partial responses (PRs) were observed in 15 patients with *PIK3CA*-altered solid tumors; 7 (5%) of which were confirmed (2 at 270 mg/QD, 1 at 350 mg/QD, 2 at 400 mg/QD, 2 at 150 mg/BID).
  - Sixty-eight (52%) patients had stable disease (SD), including 31 (50%) patients receiving 400 mg/QD and 8 (53%) patients receiving 150 mg/BID.
- Disease control rates (defined as complete response + PR + SD) at the MTDs were 53% for patients receiving alpelisib 400 mg/QD and 67% in patients receiving alpelisib 150 mg/BID.
- Median progression-free survival at ≥270 mg in ER+/HER2– breast cancer was 166 days (95% CI: 77–219 days).

Biomarker Analysis

- Overall, 42 patients were evaluable for both efficacy data and next-generation sequencing (NGS) analysis (**Figure 5A–E**).
  - One patient with *PIK3CA* and TP53 mutations and ERBB2 (HER2) amplification treated with alpelisib 400 mg/QD had a PR.

CONCLUSIONS

- **Single-agent alpelisib has demonstrated a favorable safety profile in patients with *PIK3CA*-altered advanced solid tumors, or *PIK3CA*-altered or wild-type ER+ breast cancer.**
  - **The most common AEs were largely on-target effects (e.g. hyperglycemia and gastrointestinal AEs) typical of those experienced with PI3K inhibitors.**
- **The MTD of twice-daily alpelisib was declared as 150 mg/BID.**
- **Alpelisib showed encouraging preliminary clinical activity in patients with *PIK3CA*-altered advanced solid tumors including those with *PIK3CA*-altered ER+ breast cancer. Due to the small number of patients with wild-type ER+ breast cancer, it is not possible to draw any further conclusions about the action of alpelisib in these patients.**
- **Alpelisib is the first α-isoform-specific PI3K inhibitor to show single-agent responses in tumors with activating mutations.**

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ACKNOWLEDGMENTS

The authors thank the patients and their families who participated in this study.
They also thank Karl Schumacher of Novartis Pharma AG for his contribution to this poster.
Medical editorial assistance was provided by Alex Coulthard BSc (Hons) and was funded by Novartis Pharmaceuticals.

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Presented at the European Society for Medical Oncology Congress; 26–30 September, 2014; Madrid, Spain

This study was sponsored by Novartis Pharmaceuticals Corporation.