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ORIGINAL ARTICLE

# Phase I study of BGT226, a pan-PI3K and mTOR inhibitor, in Japanese patients with advanced solid cancers

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## Abstract

The phosphatidylinositol 3-kinase (PI3K) pathway is a promising therapeutic target for various cancers. BGT226 is a pan-PI3K and mammalian target of rapamycin (mTOR) inhibitor. The tolerability and pharmacokinetics/pharmacodynamics of BGT226 were investigated in a phase I study in Japanese patients with advanced solid cancers. BGT226 was orally administered on days 1, 3, and 5 of each week. The initial dose of 10 mg was subsequently escalated to 20, 40, 80, and 100 mg in a cohort of three patients. Pharmacokinetics and pharmacodynamics were investigated using plasma, normal skin, and tumor samples. A total of 18 patients were enrolled and evaluated. The most frequently reported toxicities were diarrhea, nausea, decreased appetite, vomiting, and fatigue. They were all grade 1 or 2, and no dose-limiting toxicity was observed. However, all six patients treated at 100 mg experienced diarrhea and nausea, while two experienced a dose reduction and/or interruptions during the study. Two of five patients who exhibited stable disease continued the study treatment for ≥ 16 weeks. The absorption of BGT226 was rapid, and systemic exposure increased in a dose-dependent manner. Treatment with BGT226 did not change any of the biomarkers in neither normal skin nor tumor tissues. BGT226 was tolerated up to 100 mg three times a week in Japanese patients with solid cancers, without difference in toxicity profiles and pharmacokinetics compared to Western patients.

**Keywords** PI3K · mTOR · Pharmacokinetics · Pharmacodynamics · BGT226

## Introduction

The phosphatidylinositol 3-kinase (PI3K) pathway is one of the most characterized signaling pathways and plays an important role in regulating physiologic functions such as cellular proliferation, differentiation, metabolism, and survival [1, 2]. In a variety of cancers including breast, prostate, colorectal, and lung cancers as well as glioblastoma multiform, however, it isconstitutively activated via molecular abnormalities and is associated with tumorigenesis [3–6]. The mechanisms for activation of the PI3K pathway include mutations or amplification of *PIK3CA* (the gene encoding the catalytic subunit of PI3K), the dysfunction of phosphate and tensin homolog (PTEN, a negative regulator of PI3K), and aberrant signaling from membrane receptor tyrosine kinases [5–7].

Many cancers exhibit a genetic dependency on aberrant PI3K pathway signaling. Preliminary data suggest that activation of various components of the PI3K pathway may be a predictor of a poor prognostic outcome in some cancers [7, 8]. Furthermore, pathway activation contributes to therapeutic resistance of cancers such as that observed against anti-HER2 therapy in breast cancer [9]. Therefore, the PI3K pathway has been a therapeutic target in the development of anti-cancer drugs [5].

BGT226, which belongs to a class of imidazoquinolines, is a dual inhibitor of pan-class I PI3Ks and the mammalian target of rapamycin (mTOR). BGT226 demonstrated strong and reversible inhibition of PI3K through binding to the

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p110 subunit. This resulted in potent antiproliferative activity in a wide range of cancer cell lines with mutated or wild-type PI3K pathway, including glioblastoma, breast, prostate, non-small cell lung, head and neck, colorectal cancers, and multiple myeloma [10, 11].

BGT226 has been tested in various tumor xenograft models that harbored either a loss of PTEN or a *PIK3CA* mutation. It showed strong anti-tumor activity in an in vivo orthotopic model of HER2-positive breast cancer as well as models of glioblastoma, prostate, and non-small cell lung cancer in mice. The anti-tumor activity of BGT226 was associated with strong inhibition of activated downstream effector molecules, especially Akt/PKB, in tumor tissue [12].

Based on these preclinical observations, BGT226 was investigated in clinical studies. The purpose of this phase I study was to determine the maximum tolerated dose (MTD), as well as assess the safety, pharmacokinetics, and pharmacodynamics of BGT226 in Japanese patients. A parallel phase I study in Western countries has been reported [12].

## Patients and methods

### Patients

The main inclusion criteria were the presence of histologically confirmed advanced solid tumors that had progressed despite standard therapy, age ≥ 20 years, Eastern Cooperative Oncology Group performance status ≤ 2, life expectancy ≥ 12 weeks, and adequate hematological, renal and liver functions.

The main exclusion criteria were the presence of primary central nervous system tumors or brain metastases, peripheral neuropathy ≥ grade 2 in National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE v3.0), diarrhea ≥ grade 2, impaired cardiac function or clinically significant cardiac disease, uncontrolled concomitant medical conditions (e.g., hypertension, diabetes mellitus or infection), and gastrointestinal diseases that might alter the absorption of BGT226 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).

Anti-tumor drugs within 4 weeks prior to starting BGT226 (6 weeks for nitrosourea, mitomycin-C, or monoclonal antibodies) were prohibited, and patients treated with wide field radiotherapy within 4 weeks (2 weeks for limited field radiation for palliation) or major surgery within 2 weeks were also excluded.

The study was approved by the ethics committees of each participating institution and conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines as well as the Declaration of Helsinki. All patients provided written informed consent.

### Treatment and dose escalation

BGT226 was administered orally 2 h after a light breakfast with fasting for another 2 h on days 1, 3, and 5 of each week. A treatment cycle consisted of 28 days and continued until unacceptable toxicity, disease progression, or patient withdrawal. The initial dose was 10 mg once a day three times a week, and this was subsequently escalated to 20, 40, 80, and 100 mg. Dose escalation was supported by a Bayesian logistic regression model (BLRM). Because this was the first trial of BGT226 in Japanese patients, the pre-study probability of dose-limiting toxicities (DLTs) at each dose level was based on the safety profile of the preceding first clinical study of BGT226 in Western patients. The initial dose of 10 mg corresponded to 50% of the highest dose (20 mg) investigated at that time without the occurrence of DLT in the preceding study.

The dose was to be escalated until the maximum tolerated dose (MTD), which was defined as the highest dose not causing DLT in more than 33% of treated patients, during the first cycle. A minimum of three patients were assigned sequentially to a cohort that could be expanded for further elaboration of safety and pharmacokinetics profiles. At least 15 patients were required to be enrolled, so that the Bayesian model could have reasonable operating characteristics for an MTD recommendation. Patients were evaluated for DLT if they were treated with BGT226 for at least 9 out of 12 scheduled doses in cycle 1. Patients who withdrew from the study during cycle 1 for any reason other than DLT without meeting this requirement were excluded from the decision of dose escalation.

### Assessments

Toxicities were graded according to NCI-CTCAE. DLTs were defined as grade 3 neutropenia or thrombocytopenia for > 7 consecutive days, grade 4 thrombocytopenia, febrile neutropenia, grade 3 anemia with a hemolytic process, total bilirubin or creatinine 2.0–3.0 × upper limits of normal (ULN) for > 7 days, ≥ grade 3 increase in total bilirubin or creatinine, grade 3 elevation of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) for > 7 days, grade 4 AST/ALT elevation, ≥ grade 3 asymptomatic amylase/lipase elevation for > 7 days, grade 2 hyperglycemia not resolving for > 14 days, ≥ grade 3 hyperglycemia, ≥ grade 2 adrenal insufficiency not improving to grade 1 despite the use of optimal treatments, ≥ grade 2 thyroid dysfunction not improving to grade 1 for > 7 days, ≥ grade 3 cardiac toxicity or troponin elevation, ≥ grade 2 pancreatitis, skin toxicities resulting in an interruption of BGT 226 for > 7 days, ≥ grade

3 nausea or diarrhea despite the use of optimal treatment, ≥ grade 3 for other non-hematological toxicities, and a dose interruption due to lower grade toxicities for four or more consecutive doses.

The anti-tumor effect of BGT-226 was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST v1.0) every 8 weeks.

### Pharmacokinetics

Blood sampling for pharmacokinetic analysis was performed before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, 32, and 48 h after the administration of BGT226 on days 1 and 8 of cycle 1 as well as on day 1 of cycle 2, and before dosing on day 1 of cycle 3–5. Pharmacokinetic parameters were calculated by a non-compartmental analysis using WinNonlin® (Pharsight, Mountain View, CA).

### Biomarkers

Punch biopsies of normal skin were performed for pharmacodynamic investigation. Full thickness skin with a 3-mm diameter was obtained from the back at baseline and between 4 and 6 h after the administration of BGT226 on day 1 of cycle 2. Ki67 and p-S6 (Ser240/244) were evaluated immunohistochemically and compared between baseline and posttreatment. Mutation profiles of molecules in the PI3K signaling pathway were investigated using archival tumor tissue. When possible, fresh tumor samples were obtained by biopsy at baseline as well as between 4 and 6 h after the administration of BGT226 on day 1 of cycle 2. The effect of BGT226 on proteins of the PI3K signaling pathway, including p-Akt, p-eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1), and p-S6 (Ser240/244), as well as Ki67 and cyclin D1 was investigated by comparing baseline and posttreatment values.

Blood samples were collected at baseline and before BGT226 administration on days 1, 8 and 15 of cycle 1, day 1 of cycles 2 and 3, and in every other subsequent cycle to investigate treatment-related changes in markers relevant to PI3K signaling as well as circulating angiogenic markers [vascular endothelial growth factor (VEGF), soluble VEGF receptor (sVEGFR1), sVEGFR2, basic fibroblast growth factor, and placental growth factor]. Blood samples for circulating cellular death markers (M30/M65) were collected at baseline and before dosing on day 1 of cycle 1, and 6 h after BGT226 administration on day 8 of cycle 1, day 1 of cycles 2 and 3, and every other subsequent cycle.

## Results

A total of 18 patients were enrolled and evaluated (three patients each for the 10, 20, 40, and 80-mg cohorts, and six patients for the 100-mg cohort) from November 2008 to December 2009. All patients showed a good performance status of 0 or 1. Twelve patients had been treated with three or more regimens of chemotherapy before they were enrolled in this study (Table 1).

Most patients (89%) experienced toxicities related to BGT226. The most frequently reported toxicities were diarrhea (72%), nausea (61%), decreased appetite (50%), vomiting (39%), and fatigue (28%), with all patients either grade 1 or 2 (Table 2). The frequency of diarrhea and nausea in the 100-mg cohort was 100%, while lower incidences were observed in lower dose cohorts. Two patients experienced dose modifications due to adverse events at 100 mg during the study. One patient experienced a dose reduction to 80 mg and underwent three dose interruptions (Table 3). Another patient experienced a dose interruption.

BGT226 was rapidly absorbed after oral administration and its concentration was measurable in plasma as early as 0.5 h after dosing (first sampling time). Median peak plasma concentrations of BGT226 were observed between 1 and 4 h after dosing followed by a mono-exponential decline in the most patients. $C_{max}$ and $AUC_{last}$ values increased in a

**Table 1** Patient characteristics ($n = 18$)

| | |
|---|---|
| Age, years | |
| Median (range) | 58.5 (26–70) |
| Sex | |
| Female/male | 4/14 |
| Performance status | |
| 0/1 | 6/12 |
| Weight | |
| Median (range) | 58.4 (42–102) |
| Primary tumor | |
| Stomach | 4 |
| Rectum | 4 |
| Soft tissue sarcoma | 4 |
| Gallbladder | 2 |
| Others | 4 |
| Prior anti-cancer therapy | |
| Chemotherapy | 18 |
| Radiotherapy | 5 |
| Surgery | 14 |
| Number of chemotherapy regimens | |
| 1–2 | 6 |
| 3–4 | 9 |
| 5– | 3 |

**Table 2** Toxicities observed in > 20% of patients

| Dose | 10 mg | 20 mg | 40 mg | 80 mg | 100 mg | Total |
|---|---|---|---|---|---|---|
| Number of patients | 3 | 3 | 3 | 3 | 6 | 18 |
| Toxicities (number of patients, Grade 1/2) | | | | | | |
| Diarrhea | 0/0 | 1/0 | 3/0 | 3/0 | 2/4 | 9/4 |
| Nausea | 0/0 | 1/0 | 2/0 | 1/1 | 3/3 | 7/4 |
| Vomiting | 0/0 | 1/0 | 1/0 | 0/1 | 1/3 | 3/4 |
| Decreased appetite | 1/0 | 0/0 | 0/0 | 2/1 | 2/3 | 5/4 |
| Fatigue | 1/0 | 0/0 | 0/0 | 0/1 | 3/0 | 4/1 |

**Table 3** Patients with dose modifications

| Dose | 10 mg | 20 mg | 40 mg | 80 mg | 100 mg | Total |
|---|---|---|---|---|---|---|
| Number of patients | 3 | 3 | 3 | 3 | 6 | 18 |
| Dose modification | 1 | 0 | 0 | 0 | 2 | 3 |
| Reduction | 0 | 0 | 0 | 0 | 1 | 1 |
| Interruption | 1 | 0 | 0 | 0 | 2 | 3 |

**Table 4** Summary of plasma pharmacokinetics of BGT226

| Cycle/day | Dose (mg) | *N* | $T_{max}$ (h) Median (range) | $C_{max}$ (ng/mL) Mean (SD) | $AUC_{last}$ (ng h/mL) Mean (SD) | T1/2(h) Mean (SD) | $R_{acc}$ ($AUC_{last}$) Mean (SD) |
|---|---|---|---|---|---|---|---|
| C1D1 | 10 | 3 | 3 (2.87–3) | 0.675 (0.413) | 5.75 (3.47) | 15.9 (7.09) | |
| | 20 | 3 | 3 (2.98–3) | 1.16 (0.228) | 6.99 (2.7) | 8.3 (0.649) | |
| | 40 | 3 | 1.48 (1–3) | 2.12 (1) | 15.8 (8.49) | 7.33 (1.88) | |
| | 80 | 3 | 3.02 (3–3.98) | 2.58 (0.865) | 22.3 (15) | 11.8 (2.1) | |
| | 100 | 6 | 3.5 (1.5–6) | 3.37 (2.1) | 34.8 (16) | 9.22 (3.42) | |
| C1D8 | 10 | 3 | 3 (3–3) | 1.15 (0.757) | 7.12 (4.11) | 10.8 (2.2) | 1.3 (0.222) |
| | 20 | 3 | 3 (1–6.1) | 1.48 (0.812) | 8.29 (3.23) | 10.1 (2.27) | 1.19 (0.129) |
| | 40 | 3 | 3 (2–3.05) | 2.11 (0.783) | 18.1 (7.72) | 7.32 (0.642) | 1.19 (0.173) |
| | 80 | 3 | 4 (4–8.22) | 1.48 (0.474) | 17.5 (7.65) | 11.6 (3.23) | 0.881 (0.242) |
| | 100 | 6 | 3 (3–6) | 4.76 (2.92) | 62.5 (44.6) | 9.94 (4.01) | 1.77 (0.917) |
| C2D1 | 10 | 3 | 2 (1.5–3) | 0.835 (0.422) | 5.97 (3.57) | 13.8* (6.15) | 1.11 (0.268) |
| | 20 | 2 | 3.05 (3–3.1) | 1.26 (0.839) | 10.2 (6.15) | 11.8 (4.58) | 1.2 (0.367) |
| | 40 | 1 | 0.983 | 0.971 | 8.64 | 7.69 | 1.06 |
| | 80 | 3 | 3 (0.5–8.25) | 1.74 (0.715) | 22.8 (11) | 8.23 (1.78) | 1.11 (0.204) |
| | 100 | 4 | 3.03 (3–7.78) | 4.1 (1.63) | 53 (33.2) | 10.7 (2.77) | 2 (1.24) |

$T_{max}$ time to reach, $C_{max}$ maximum observed concentration, $AUC_{last}$ area under the curve up to the last measurement, *T1/2* half life, $R_{acc}$ accumulation ratio, *SD* standard deviation

*$n = 2$

dose-dependent manner, with no significant drug accumulation after multiple doses (Table 4). Intersubject variability in drug exposure ($AUC_{last}$ and $C_{max}$) was relatively high and ranged between 40 and 70% for most cohorts.

No objective responses were observed in this study. Five patients exhibited stable disease, and two patients continued the study treatment for 16 weeks.

Paired skin biopsies were obtained from 13 of 18 patients at baseline and on day 1 of cycle 2. The immunohistochemical evaluation of Ki67 and p-S6 showed no significant changes. Paired fresh tumor samples were obtained in a patient with colon cancer treated with 80 mg, but no obvious changes were observed in any of the biomarker parameters.

## Discussion

BGT226 was tolerated up to 100 mg three times a week in Japanese patients with solid cancers. Most patients experienced toxicities, with the most frequently reported toxicities

being diarrhea (72%), nausea (61%), decreased appetite (50%), vomiting (39%), and fatigue (28%). These findings substantially corresponded to the toxicity profile and frequency observed in a phase I study of BGT226 in Western countries, where diarrhea (65%), nausea (76%), decreased appetite (24%), vomiting (54%), and fatigue (27%) were the most frequently observed toxicities at the same dose range (10–100 mg) as the current study [12].

Although DLTs were not observed in six patients treated with 100 mg BGT226, no further dose escalation was performed in this study because 3 of 11 patients developed DLTs at 125 mg in the preceding phase I study in Western counties, which recommended a dose of 100 mg [12] that our study also support. Furthermore, two of six patients treated at 100 mg in the current study needed a dose reduction or interruption due to adverse events during the study treatment.

The pharmacokinetics of BGT226 had a relatively high interpatient variability, with exposure to BGT226 increasing dose dependently. Significant drug accumulation after thrice-a-week administration was not observed. Although the dose of BGT226 was not adjusted according to body size (e.g., body surface area), an apparent difference in AUC between Japanese and Western patients at 10–100 mg was not noted (Fig. 1) [12]. Together with the absence of a difference in the profile and frequency of toxicity between Japanese and Western patients, ethnic differences in the pharmacokinetics and toxicities of BGT226 were not apparent.

As one of the early PI3K inhibitors, we observed no responses to BGT226 in the 18 patients of the current study. Similarly, no responses were documented while tumor shrinkage that did not qualify for a partial response was observed in only 3 of 57 patients in the Western phase I study of BGT226. Pharmacokinetic and pharmacodynamic modeling based on clinical and preclinical data predicted that BGT226 doses > 4000 mg/day would be required to achieve effective systemic exposure [12]. This dose obviously exceeded the safety range of BGT226 for humans.

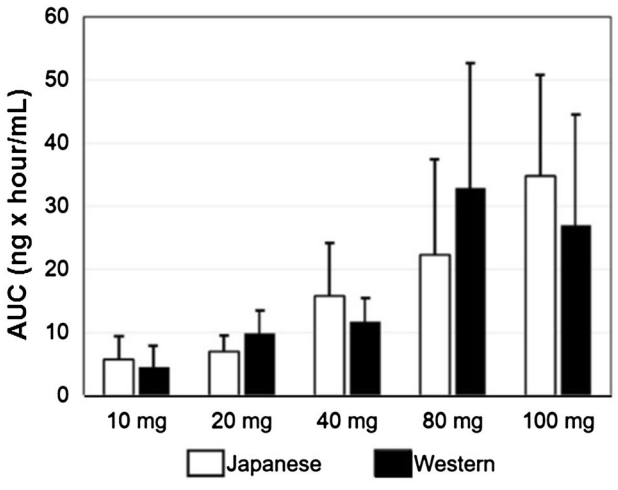


**Fig. 1** AUC of BGT226 in Japanese and Western cancer patients treated with 10–100 mg on Cycle 1 Day 1 in phase I studies [12]. Japanese and Western patients did not show a difference in AUC

Paired normal skin samples were obtained for pharmacodynamic evaluation in 13 of 18 patients by punch biopsy, and paired tumor samples were obtained in one patient with colon cancer treated with 80 mg. For both normal skin and tumor tissue, posttreatment samples were obtained 4–6 h after dosing on day 1 of cycle 2. However, treatment with BGT226 did not change any of the biomarkers in either normal skin or tumors. These biomarkers included Ki67 and p-S6 status in normal skin, and p-AKT, p-4EBP1, Ki67, and cyclin D1 in tumors. Such observations corresponded to the lack of responses observed in this study, which precluded investigation of the association between anti-tumor efficacy and mutations of genes in the PI3K pathway in archival tumor tissues. Similar to our observations, a consistent reduction in p-S6 was observed in few patients in a Western phase I study of BGT226 [12].

Many PI3K inhibitors are now under clinical development, with some showing clinical activity in hematological malignancies [6, 13, 14]. For example, copanlisib showed activity in follicular lymphoma in early clinical studies and was approved by the US Food and Drug Administration [13] while inhibitors of PI3Kδ including idelalisib and duvelisib, showed activity against lymphoid malignancies [14].

Although several clinical activities, including partial responses and long-term stable disease, were observed with several PI3K inhibitors used as a single agent [6, 15, 16], early clinical studies did not identify a consistent clinical activity in solid tumors [9, 17]. However, several reports have described improved efficacy when PI3K inhibitors were combined with other molecular-targeted drugs [6]. A pooled analysis of 136 patients with advanced cancers harboring *PIK3CA* and *PTEN* alterations who were treated with PI3K inhibitors in early clinical trials demonstrated that patients treated with combination therapies had a higher response than those treated with a single agent [18].

By being limited to *PIK3CA*-mutated tumors, alpelisib (BYL-719), an alpha-specific PI3K inhibitor, plus fulvestrant doubled progression-free survival compared to fulvestrant alone with a hazard ratio (HR) of 0.65 in postmenopausal patients with hormone receptor-positive, and HER2-negative advanced breast cancer in a recently reported randomized phase 3 study [19]. Taselisib, another PI3K inhibitor, also reduced the risk of death or progression by 30% in similar patients with a *PIK3CA* mutation [20]. Furthermore, the addition of buparlisib (BKM120) to fulvestrant prolonged progression-free survival in postmenopausal patients with hormone receptor-positive/HER2-negative breast cancer in a phase 3 study, with a HR of 0.78 in a total population. The

effect of adding bupalisib was greater (HR, 0.58) in patients with *PIK3CA*-mutated circulating tumor DNA than those without (HR, 1.02) [21]. These observations suggest that biomarkers such as *PIK3CA* mutations and/or combination with other drugs are important in the clinical development of PI3K inhibitors.

In conclusion, BGT226 up to 100 mg thrice a week was tolerated as a starting dose in Japanese patients with solid cancers, and a difference in toxicity profiles and pharmacokinetics was not observed between Japanese and Western patients. Exposures achieved with BGT226 were likely insufficient for clinically meaningful PI3K pathway inhibition.

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## Compliance with ethical standards

**Conflict of interest** Hironobu Minami has received research funding from Asahi-Kasei, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eizai, Exelixis, Fuji, Kowa, Kyowa-Kirin, Lilly, Nihon Shinyaku, Novartis, Ono, Otsuka, Pfizer, Sanofi, Shire Japan, Taiho, and Takeda, and speaker honoraria from Bayer, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eizai, Exelixis, Kowa, Kyowa-Kirin, Lilly, Novartis, Ono, Otsuka, Pfizer, Sanofi, Shire Japan, Taiho, and Takeda. Yutaka Fujiwara has received research funding from AbbVie, AstraZeneca, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Incyte, Merck Serono, MSD, and Novartis, and speaker honoraria from Bristol-Myers Squibb, MSD, ONO, and Taiho.

## References


1. Wickenden JA, Watson CJ (2010) Key signalling nodes in mammary gland development and cancer. Signalling downstream of PI3Kinase in mammary epithelium: a play in 3 Akts. Breast Cancer Res 12(2):202. https://doi.org/10.1186/bcr2558
2. Katso R, Okkenhaug K, Ahmadi K, White S, Timms J, Waterfield MD (2001) Cellular function of phosphoinositide 3-kinases: implications for development, homeostasis, and cancer. Annu Rev Cell Dev Biol 17:615–675. https://doi.org/10.1146/annurev.cellbio.17.1.615
3. Fry MJ (2001) Phosphoinositide 3-kinase signalling in breast cancer: how big a role might it play? Breast Cancer Res 3(5):304–312
4. Liu P, Cheng H, Roberts TM, Zhao JJ (2009) Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov 8(8):627–644. https://doi.org/10.1038/nrd2926
5. Engelman JA (2009) Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer 9(8):550–562. https://doi.org/10.1038/nrc2664
6. Courtney KD, Corcoran RB, Engelman JA (2010) The PI3K pathway as drug target in human cancer. J Clin Oncol 28(6):1075–1083. https://doi.org/10.1200/JCO.2009.25.3641
7. Bellmunt J, Werner L, Leow JJ, Mullane SA, Fay AP, Riester M, Van Hummelen P, Taplin ME, Choueiri TK, Van Allen E, Rosenberg J (2015) Somatic copy number abnormalities and mutations in PI3K/AKT/mTOR pathway have prognostic significance for overall survival in platinum treated locally advanced or metastatic urothelial tumors. PLoS One 10(6):e0124711. https://doi.org/10.1371/journal.pone.0124711
8. Valkov A, Kilvaer TK, Sorbye SW, Donnem T, Smeland E, Bremnes RM, Busund LT (2011) The prognostic impact of Akt isoforms, PI3K and PTEN related to female steroid hormone receptors in soft tissue sarcomas. J Transl Med 9:200. https://doi.org/10.1186/1479-5876-9-200
9. Mukohara T (2015) PI3K mutations in breast cancer: prognostic and therapeutic implications. Breast Cancer (Dove Medical Press) 7:111–123. https://doi.org/10.2147/bctt.S60696
10. Chang KY, Tsai SY, Wu CM, Yen CJ, Chuang BF, Chang JY (2011) Novel phosphoinositide 3-kinase/mTOR dual inhibitor, NVP-BGT226, displays potent growth-inhibitory activity against human head and neck cancer cells in vitro and in vivo. Clin Cancer Res 17(22):7116–7126. https://doi.org/10.1158/1078-0432.Ccr-11-0796
11. Baumann P, Schneider L, Mandl-Weber S, Oduncu F, Schmidmaier R (2012) Simultaneous targeting of PI3K and mTOR with NVP-BGT226 is highly effective in multiple myeloma. Anticancer Drugs 23(1):131–138. https://doi.org/10.1097/CAD.0b013e32834c8683
12. Markman B, Tabernero J, Krop I, Shapiro GI, Siu L, Chen LC, Mita M, Melendez Cuero M, Stutvoet S, Birle D, Anak O, Hackl W, Baselga J (2012) Phase I safety, pharmacokinetic, and pharmacodynamic study of the oral phosphatidylinositol-3-kinase and mTOR inhibitor BGT226 in patients with advanced solid tumors. Ann Oncol 23(9):2399–2408. https://doi.org/10.1093/annonc/mds011
13. Markham A (2017) Copanlisib: first global approval. Drugs 77(18):2057–2062. https://doi.org/10.1007/s40265-017-0838-6
14. Flinn IW, O'Brien S, Kahl B, Patel M, Oki Y, Foss FF, Porcu P, Jones J, Burger JA, Jain N, Kelly VM, Allen K, Douglas M, Sweeney J, Kelly P, Horwitz S (2018) Duvelisib, a novel oral dual inhibitor of PI3K-delta, gamma, is clinically active in advanced hematologic malignancies. Blood 131(8):877–887. https://doi.org/10.1182/blood-2017-05-786566
15. Bendell JC, Kurkjian C, Infante JR, Bauer TM, Burris HA 3rd, Greco FA, Shih KC, Thompson DS, Lane CM, Finney LH, Jones SF (2015) A phase 1 study of the sachet formulation of the oral dual PI3K/mTOR inhibitor BEZ235 given twice daily (BID) in patients with advanced solid tumors. Invest New Drugs 33(2):463–471. https://doi.org/10.1007/s10637-015-0218-6
16. Toyoda M, Watanabe K, Amagasaki T, Natsume K, Takeuchi H, Quadt C, Shirao K, Minami H (2018) A phase I study of single-agent BEZ235 special delivery system sachet in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol. https://doi.org/10.1007/s00280-018-3725-2
17. Miller TW, Rexer BN, Garrett JT, Arteaga CL (2011) Mutations in the phosphatidylinositol 3-kinase pathway: role in tumor progression and therapeutic implications in breast cancer. Breast Cancer Res 13(6):224. https://doi.org/10.1186/bcr3039
18. Janku F, Hong DS, Fu S, Piha-Paul SA, Naing A, Falchook GS, Tsimberidou AM, Stepanek VM, Moulder SL, Lee JJ, Luthra R, Zinner RG, Broaddus RR, Wheler JJ, Kurzrock R (2014) Assessing PIK3CA and PTEN in early-phase trials with PI3K/AKT/mTOR inhibitors. Cell Rep 6(2):377–387. https://doi.org/10.1016/j.celrep.2013.12.035
19. F André, E M Ciruelos, G Rubovszky, M Campone, S Loibl, H S Rugo, H Iwata, P Conte, I A Mayer, B Kaufman, T Yamashita, Y -S Lu, K Inoue, M Takahashi, Z Pápai, A-S Longin, D Mills, C Wilke, S Hirawat, Juric D (2018) Alpelisib (ALP) + fulvestrant (FUL) for advanced breast cancer (ABC): results of the phase III SOLAR-1 trial. Ann Oncol 29(suppl 8). Abstract Number LBA3
20. Jose Baselga SFD, Javier Cortés, Young-Hyuck Im, Véronique Diéras, Nadia Harbeck, Ian E. Krop, Sunil Verma, Timothy R. Wilson, Huan Jin, Lijia Wang, Frauke Schimmoller, Jerry Y. Hsu,

Jing He, Michelino DeLaurentiis, Pamela Drullinsky, William Jacot (2018) Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) v FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): primary analysis from SANDPIPER. Am Soc Clin Oncol LBA1006

21. Baselga J, Im SA, Iwata H, Cortes J, De Laurentiis M, Jiang Z, Arteaga CL, Jonat W, Clemons M, Ito Y, Awada A, Chia S, Jagiello-Gruszfeld A, Pistilli B, Tseng LM, Hurvitz S, Masuda N, Takahashi M, Vuylsteke P, Hachemi S, Dharan B, Di Tomaso E, Urban P, Massacesi C, Campone M (2017) Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 18(7):904–916. https://doi.org/10.1016/S1470-2045(17)30376-5