Molecularly stratified parallel cohort, single-arm phase II trial of the phosphoinositide 3-kinase (PI3K) inhibitor Buparlisib (BKM120) in combination with tamoxifen in patients with hormone-receptor positive, HER2-negative inoperable (locally advanced or metastatic) breast cancer with prior exposure to antihormonal therapy

Clinical Study Report

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Sponsor	[redacted] University Hospital Essen Germany

1. Title page

Study Title	Molecularly stratified parallel cohort, single arm phase II trial of the phosphoinositide 3-kinase (PI3K) inhibitor Buparlisib (BKM120) in combination with tamoxifen in patients with hormone receptor-positive, HER2-negative inoperable (locally advanced or metastatic) breast cancer with prior exposure to antihormonal therapy
Study Title German	Biomarker-stratifizierte, einarmige Kohortenstudie der Phase II im Parallelgruppendesign mit dem Phosphoinositid 3-Kinase (PI3K)-Inhibitor Buparlisib (BKM120) in Kombination mit Tamoxifen bei Patientinnen mit Hormonrezeptor-positivem, HER2-negativem, inoperablen (lokal fortgeschrittenem oder metastatiertem) Mammakarzinom nach vorausgegangener antihormoneller Therapie
Short Title	PIKTAM
Sponsor	[redacted], University Hospital Essen, Germany
EudraCT No	2014-000599-24
Protocol No.	iOM-02282
AIO-No.	AIO-MAM-0114/ass
Novartis Study Code	CBKM120ZDE02T
Name of test drug/product	BKM120 (buparlisib)
Comparator	n/a
Dosage	Buparlisib at 100 mg / day, orally, in combination with tamoxifen, orally, at 20 mg / day, continuous dosing schedule without interruption starting on day 1 in 28 day cycle
Indication	Premenopausal and postmenopausal women with histologically confirmed, progressive, inoperable (locally advanced or metastatic) hormone receptor (HR)–positive, HER2-negative breast cancer with prior exposure to antihormonal therapy.
Design	Open-label, prospective, multicenter, molecularly stratified parallel cohort, single-arm single stage trial
Development phase	Phase II
Coordinating investigator	[redacted] University Hospital, Hufelandstr. 55, 45147 Essen, Germany
Clinical Research Organization	iOMEDICO AG, Hanferstr. 28, 79128 Freiburg, Germany
Author of report	[redacted]
Study initiation date	2014-12-29
Study completion date	2017-10-18
Version and date of report	V2.0, 2018-10-04

This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

2. Synopsis

Name of Sponsor/Company: [redacted] University Hospital Essen	Volume: V2.0 04-Oct-2018 Pages: 3-12	(For National Authority Use Only)
Name of Finished Product: Buparlisib (BKM120)		
Name of Active Ingredient: Pan-class I PI3K inhibitor		

Title of study:
Molecularly stratified parallel cohort, single arm phase II trial of the phosphoinositide 3-kinase (PI3K) inhibitor buparlisib (BKM120) in combination with tamoxifen in patients with hormone receptor-positive, HER2-negative inoperable (locally advanced or metastatic) breast cancer with prior exposure to antihormonal therapy

Coordinating investigator:
[redacted] University Hospital Essen, Germany

List of study center(s):
Twenty study centers in Germany participated in this study.

Publication (reference):
n/a

Studied period (years):	**Phase of development**:
29-Dec-2014 to 18-Oct-2017	II

Objectives:
Primary objective:
The primary objective of the study was to evaluate efficacy of BKM120 (Buparlisib) in combination with tamoxifen in patients with ER/PR-positive, HER2-negative breast cancer stratified to

- PIK3CA (phosphoinositide-4.5 bisphosphate 3-kinase catalytic subunit alpha isoform) mutation and preserved PTEN (phosphatase and tensin homologue) expression
- PIK3CA wildtype or mutation +/- loss of PTEN expression
- PIK3CA wild type and preserved PTEN expression

by determining Progression free survival (PFS)-rate in the full population, after 6 months of combination therapy.

Secondary objectives:

- To assess 6 month PFS rate in the subpopulations.
- To assess PFS in subpopulations and full population.
- To explore 1- and 2- year overall survival (OS) rate in subpopulations and full population.
- To assess overall response rate (ORR) in subpopulations and full population.
- To assess disease control rate (DCR) in subpopulations and full population.
- To assess safety and tolerability throughout the study according to CTCAE v4.03.
- To assess incidence and severity of depressive episodes during the course of treatment by PHQ-9 and GAD-7 questionnaires.

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Methodology:
This was an open-label, multi-centre, molecularly stratified parallel cohort, single-arm single-stage phase II trial.
After the identification of the biomarker status (pre-screening, n=48), patients were screened (n=35) and upon eligibility assigned to either molecular cohort. Assignment to either cohort did not influence treatment or any other study procedure. The following stratification groups were investigated:

- PIK3CA (phosphoinositide-4.5 bisphosphate 3-kinase catalytic subunit alpha isoform) mutation and preserved PTEN (phosphatase and tensin homologue) expression (A)
- PIK3CA wildtype or mutation +/- loss of PTEN expression (B)
- PIK3CA wild type and preserved PTEN expression (C)

Number of patients:	**planned**:	**randomized**:	**analyzed efficacy**:
	99 **Pre-Screened / Screened** 48 / 35 The study was prematurely closed due to a change in the risk benefit assessment of buparlisib (please refer to section 9.8)	N/A [1] **completed**: 13[2] [1]25 patients were assigned to molecular subgroups and received study treatment [2]13 patients discontinued treatment due to disease progression (regular treatment end)	21 Group A: n=8 Group B: n=2 Group C: n=11 **analyzed safety**: 25 Group A: n=9 Group B: n=3 Group C: n=13

Diagnosis and main criteria for inclusion:
Adult, pre- and postmenopausal women with histologically and/or cytologically confirmed, progressive, inoperable (locally advanced or metastatic) hormone receptor (HR)–positive, HER2-negative breast cancer with prior exposure to antihormonal therapy. Subject had a known PI3K pathway biomarker status.

1. Patient had provided a signed study Informed Consent Form (ICF) prior to any screening procedure
2. Patient was ≥ 18 years of age on the day of consenting to the study
3. Patient had histologically and/or cytologically confirmed diagnosis of breast cancer
4. Patient had radiologic or objective evidence of inoperable locally advanced, or metastatic breast cancer
5. Patient had a known hormone receptor status HR–positive (ER and/or PR positive) and HER2-negative status
6. Patient had a representative archival formalin-fixed tumor biopsy (metastasis or primary tumor)
7. Patient had a known PI3K pathway biomarker status (activated or non-activated, as determined by the PIK3CA and PTEN mutation status) prior to the start of treatment (based on results of the central study laboratory).
8. Patient had prior exposure to antihormonal therapy
9. Patient could have received up to one prior chemotherapy in the metastatic setting
10. Measurable or non-measurable lesions according to RECIST v1.1 criteria
11. Patient had an Eastern Cooperative Oncology Group (ECOG) performance status score

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≤ 2

12. Patient had adequate bone marrow and organ function Patient was able to swallow and retain oral medication

Main criteria for exclusion:

13. Patient had received previous treatment with a PI3K- or AKT-inhibitor or mTOR-inhibitors
14. Prior treatment with tamoxifen in the metastatic setting. Treatment with tamoxifen in the (neo-)adjuvant setting was allowed, but had to be discontinued for at least 1 year
15. Concurrent gonadotropin-releasing hormone (GnRH) analogon treatment. Prior treatment was allowed, if last application occurred ≥ 28 days before treatment start
16. Patient had received > 2 prior antihormonal treatments in the metastatic setting
17. Patient had received >1 prior chemotherapy in the metastatic setting
18. Patient had symptomatic central nervous system (CNS) metastases
19. Patient had other prior or concurrent malignancy (except for the following: adequately treated basal cell or squamous cell skin cancer, non melanomatous skin cancer, curatively resected cervical cancer or other adequately treated in situ cancer, early gastric or GI cancer resected completely by endoscopy procedures or any other cancer from which the patient had been disease free for ≥ 3 years)
20. Patient had been treated with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF) ≤ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated before enrolment, were allowed to be continued
21. Patient was currently receiving increasing or chronic treatment (> 5 days) with corticosteroids or another immunosuppressive agent
22. Patient was currently receiving warfarin or other coumarin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin, direct factor Xa inhibitors or fondaparinux was allowed
23. Patient had a known hypersensitivity to any of the excipients of buparlisib
24. Patient had a known hypersensitivity to tamoxifen
25. Patient who had received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who had not recovered to Grade 1 or better from related side effects of such therapy (except alopecia)
26. Patient had not recovered to Grade 1 or better (except alopecia) from related side effects of any prior antineoplastic therapy
27. Patient had had major surgery within 14 days prior to starting study drug or has not recovered from major side effects of any treatment
28. Patient had a score ≥ 12 on the PHQ-9 questionnaire
29. Patient selected a response of “1, 2 or 3” to question number 9 on the PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation (independent of the total score of the PHQ-9)
30. Patient had a GAD-7 mood scale score ≥ 15
31. Patient had a medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (e.g. risk of doing harm to self or others), or patients with active severe personality disorders (defined according to Diagnostic and Statistical Manual of Mental Disorders [DSM]-IV). For patients with psychotropic treatments ongoing at screening, the dose and the schedule were not to be

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modified within the previous 6 weeks prior to start of study drug

32. Patient had ≥ CTCAE grade 3 anxiety
33. Patient had clinically relevant cardiac abnormalities:
34. Gastrointestinal (GI) disease that could significantly alter the absorption of buparlisib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
35. Patient had active pneumonitis or previous pneumonitis
36. Patient had any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgement, contraindicate patient participation in the clinical study (e.g. chronic pancreatitis, chronic active hepatitis, uncontrolled hypertension, chronic pulmonary disease including dyspnea at rest or interstitial lung disease, etc.).
37. Patients with uncontrolled diabetes mellitus
38. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).

Test product, dose and mode of administration, batch number:
Buparlisib (BKM120), 100 mg / day orally, in combination with 20 mg tamoxifen / day, orally.

Duration of treatment:
Continuous dosing schedule: Buparlisib 100 mg per os daily per 28-day cycles starting on day 1 in combination with daily tamoxifen at a dose of 20 mg.
Patients received treatment with study drug until radiologically documented disease progression (as per RECIST v1.1), start of new cancer therapy, intolerable toxicity, withdrawal of consent or discontinuation due to any other reason.

Reference therapy, dose and mode of administration, batch number:
Not applicable

Criteria for evaluation:
Efficacy:
Primary endpoint
- 6 month PFS rate (6-months PFSR)

Secondary endpoints:
- 6-months PFSR in subpopulations
- Overall PFS
- 1- and 2- year overall survival rates
- Overall response rate
- Disease control rate based on tumor assessment as per RECIST 1.1

Safety:
- Adverse event (AE) assessment according to NCI-CTCAEs 4.03 criteria
- Withdrawal of treatment due to AEs
- Laboratory parameters
- Vital signs

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- ECOG Performance Status
- Physical examination
- Electrocardiogram (ECG)
- Patient-reported mood questionnaires (PHQ-9 and GAD-7[Generalized Anxiety Disorder Scale])

Statistical methods:

The Statistical Analysis Plan (SAP) dated 10-Apr-2017 defined the statistical analyses for all study evaluations.

Summary statistics included:

- Nominal variables: frequencies and percentages
- Ordinal variables: frequencies, percentages, mean, median, minimum and maximum.
- Continuous variables: number (N) of observations, mean, standard deviation (SD), 25th percentile, median, 75th percentile, minimum and maximum.

In general, summaries were presented for the total population and by biomarker stratification group.

Demographic and other baseline data (including disease characteristics) were summarized descriptively for all patients and by biomarker stratification group.

To ensure comparability of treatment for the biomarker stratification groups, dose intensity, number of dose modifications, and reason for modifications were summarized for the modified intent to treat (mITT) population and per biomarker stratification group.

The 12-week relative dose intensity, measured by the number of patients who received at least 75% of the planned study medication within the first 12 weeks of treatment were displayed for the mITT population and per biomarker stratification group and served as indirect measure of the treatment compliance.

Frequency tables for concomitant diseases were generated for the mITT and SAF populations.

Overall response assessment was performed by the local investigator assessment and, in addition, according to RECIST v1.1 as follows: Patients with non-measurable lesions only were assessed for CR, progressive disease (PD) and non-CR/non-PD. Patients presenting at least one measurable lesion at enrolment were assessed for CR, PR, SD, and PD. Those patients served for the analysis of ORR and DCR. Since ORR and DCR were secondary endpoints in this trial, a confirmation of response was not required. Tumor evaluation according to RECIST v1.1 had to be performed every 12 weeks (± 7 days) until disease progression or start of a new antineoplastic therapy.

Survival status was assessed throughout the study (treatment phase and follow-up phase) until study completion.

Safety was monitored by assessing routine laboratory parameters (hematology, chemistry, urinalysis, and coagulation), vital signs, ECG, ECOG performance status, PHQ-9 and GAD-7 questionnaires, and continuous collection of the (S)AEs graded according to CTCAE as well as documentation of withdrawal due to (S)AEs. Any patient who presented with suicide ideation

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had to interrupt study drug and to be referred for psychiatric consultation regardless of grade or response to question 9 in the PHQ-9 questionnaire. In addition, for any patient who did not answer question 9 or the whole PHQ-9 questionnaire, assessment of suicidal ideation was required.

Hypothesis

Null hypothesis: The 6-month PFS rate is less than or equal to p_0 = 0.400. Alternative hypothesis: The 6-month PFS rate is greater than or equal to p_1 = 0.540. The null hypothesis is accepted if the number of progression-free patients is equal to or less than a critical value r determined as follows: r is the smallest number of progression-free patients for which applies $\sum_{i=1}^{r} Bin(i|0.400, n) > 0.95$ (exact binomial test, n = number of patients in mITT population). If the number of progression-free patients is r+1 or greater the null hypothesis is rejected.

Sample size calculation

An exact single stage phase II design according to (A'Hern 2001) was used.

The study required 84 patients to decide whether the PFSR, P, was less than or equal to p_0=0.400 or greater than or equal to p_1=0.540. If the number of patients without tumor progression was 42 or more, the hypothesis that P ≤ 0.400 was rejected with a target error rate of 0.050 and an actual error rate of 0.040. If the number of patients without tumor progression was 41 or less, the hypothesis that P ≥ 0.540 was rejected with a target error rate of 0.200 and an actual error rate of 0.199.

Due to dropouts, an additional accrual of approximately 15 patients was expected. Therefore, the total expected sample size treated with tamoxifen and buparlisib should have been 99 patients.

PI3K pathway activation was defined as at least one alteration observed in one of the markers i.e. PIK3CA gene mutation (in at least one of the exons: 10 or 21) and/or loss of PTEN expression analyzed by immunochemistry (< 10% of tumor cells expressing PTEN at 1+ level) independent of availability of remaining test results.

Summary - Conclusions:

Baseline characteristics:

The median age at date of informed consent was 62.8 years, range 49.0 – 80.7 years in the mITT population and 62.9 years, range 49.0 – 80.7 years in the safety set (SAF). Most patients in both populations had an ECOG performance status of 0 (71.4% and 72.0%, respectively), the remaining patients had an ECOG status of 1. PHQ-9 and GAD-7 scores ranged from 0 to 9 (median 1.0) and from 0 to 6 (median 1.0), respectively, in the mITT population and from 0 to 9 (median 2.0) and from 0 to 6 (median 1.0), respectively, in the safety set, with higher scores indicating higher levels of depression and anxiety, respectively. Median time from primary diagnosis to date of first study treatment was 4.9 years (range 0.9 – 26.9 years) in the mITT and 7.8 years (range 0.9 – 26.9 years) in the SAF. The median disease-free interval defined as the time from the last R0 resection of the primary tumor to the date of first relapse, was 9.6 years (range 2.1 – 15.1 years) (mITT) and 10.6 years (range 2.1 – 16.1 years) (SAF), respectively. The vast majority of patients had tumor resections before entering the study (n=20, 95.2% and n=23, 92.0%, respectively).

The stratification groups comprised of n=9 patients in the group PIK3CA mut/PTEN preserved (group A), n=3 in the group PIK3CA wt or mut/PTEN loss (group B), and n=13 in the group

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PIK3CA wt/PTEN preserved (group C). Patients were further stratified by PI3K pathway activation (n=13 [non-activated = group C] vs n=12 [activated = group A +B]). Baseline characteristics in the stratified groups were similar to those of the total population.

Efficacy results:

Primary efficacy:

The primary objective of this study was to evaluate efficacy of buparlisib in combination with tamoxifen in patients with ER/PR-positive, HER2-negative breast cancer. The PFS-rate in the full population was determined after 6 months of combination therapy. Seven patients (33.3%) in the mITT population were progression-free at 6 months with a one-sided 95%-CI of 16.82 – 100 and a p-value of 0.800 (exact binominal test).

Secondary efficacy:

PFS-rate - Stratification by biomarker: Five out of 8 patients (62.5%) of the PIK3CA mut/PTEN wt group were progression-free at 6 months (95%-CI of 28.92 – 100, p-value of 0.174; exact binominal test). In the group PIK3CA wt or mut/PTEN loss 0 out of 2 patients were progression-free at 6 months with a one-sided 95%-CI of 0.0 – 100 and a p-value of 1.000 (exact binominal test). In PIK3CA wt/PTEN wt patients 2 out of 11 patients (18.18%) were progression-free at 6 months with a one-sided 95%-CI of 3.33 – 100 and a p-value of 0.970 (exact binominal test).

PFS rate - Stratification by PI3K pathway activation: Two out of 11 patients (18.18%) of the PI3K non-activated group were progression-free at 6 months with a one-sided 95%-CI of 3.33 – 100 and a p-value of 0.970 (exact binominal test). In the PI3K activated group 5 out of 10 patients (50.0%) were progression-free at 6 months with a one-sided CI of 22.24 – 100 and a p-value of 0.367 (exact binominal test).

PFS overall: The median PFS was 4.8 months (95% CI: 2.5 – 10.0) in the mITT population and 6.1 months (95% CI: 2.6 – 10.6) in the SAF population. It was longest in patients with the status PIK3CA mut/PTEN preserved (8.7 months, 95% CI: 1.4 – 16.7) and shortest in patients with PIK3CA wt or mut/PTEN loss (2.1 months, 95% CI: 1.7 – 2.5) (mITT population). Due to the small patient number in these subgroups (n=2 and 3 patients, respectively) these results, however, have to be interpreted with caution. The median PFS in patients with status PI3K non-activated vs activated was comparable with 4.8 months and 4.6 months (95% CI: 1.4 – 10.0 and 1.4 – 16.7), respectively (mITT).

OS: In all patients of the mITT population, the median OS was 23.8 months (95% CI: 12.6 – 25.5). The 1-year OS rate was 81.0% (95% CI: 56.9 – 92.4) and the 2-year OS rate was 46.6% (95% CI: 24.4 – 66.1). Overall survival data were in the same range in the biomarker-stratified groups as well as in the groups stratified according to PI3K pathway activation.

ORR and DCR according to RECIST criteria v1.1: In the total population no patient had a CR, 2 patients (12.5%, exact binomial 95%-CI: 1.6 – 38.3) showed a PR, SD was seen in 8 patients (50.0%, exact binomial 95%-CI: 24.7 – 75.3), and in 5 patients (31.3%, exact binomial 95%-CI: 11.0 – 58.7) PD was seen. The 2 patients with a PR were in the group with the status PIK3CA mut/PTEN preserved.

The ORR was 12.5% (2 out of 16 patients, exact 95%-CI: 1.6 – 38.3) in the total mITT population and the DCR was 43.8% (7 patients, exact 95%-CI: 19.8 – 70.1). These 2 patients

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showed PIK3CA mut/PTEN preserved status.

In 2 patients with status "PI3K activated" a PR was seen. There were 5 patients (55.6%, exact 95%_CI: 21.2 – 86.3) that had SD in the group with the status "PI3K non-activated", and 3 patients with SD (42.9%, exact 95% CI: 9.9 – 81.6) in the group with "PI3K-activated" status.

Best response as assessed by the investigators was very similar and there were 3 patients (14.3%, exact 95% CI: 3.0 – 36.3) showing a PR, 8 patients (38.1%, exact 95% CI: 18.1 – 61.6) showing SD and 9 patients (42.9%, exact 95% CI: 21.8 – 66.0) having PD out of the 21 patients of the total mITT population. Again, no patient showed a CR.

The clinically assessed ORR and DCR were an ORR of 14.3% (3 patients, exact 95% CI: 3.0 – 36.3) and a DCR of 47.6% (10 patients, exact 95% CI: 25.7 – 70.2) out of the 21 patients of the total mITT population.

In patients stratified according to the PI3K status there was 1 patient with a clinically assessed PR with a PI3K non-activated status and 2 patients with an activated status had a PR. .

Measurements of Treatment Compliance: The 12-week relative dose intensity was used as indirect measure of treatment compliance and treatment compliance was measured by the number of patients who received at least 75% of the planned 12-week dose. Nine patients (42.9%) received ≥75% of the planned buparlisib dose and in 12 patients (57.1%) the 12-week relative dose intensity was <75.0% (mITT population).

Safety results:
Exposure:

The overall median relative dose intensity was 76.4% (range 30.4% - 100.0%) for buparlisib and 96.4% (30.4% - 110.7%) for tamoxifen in the SAF population

Overall, 7 patients (28.0%) had buparlisib dose modifications, 14 patients (56.0%) had interruptions and 4 patients (16.0%) missed a whole cycle of buparlisib. Overall, one (4.0%) tamoxifen dose modification and 9 interruptions (36.0%) were observed.

Reasons for buparlisib dose modifications (overall) were as follows: Adverse events (in 14 patients, 56.0%), non-compliance (in 3 patients, 12.0%), and administrative reason (in 1 patient, 4.0%).

Reasons for tamoxifen dose modifications (overall) were as follows: Adverse events (in 7 patients, 28.0%), non-compliance (in 2 patients, 8.0%), administrative reason (in 1 patient, 4.0%) and patient wish (in 1 patient, 4.0%).

The main reason for end of treatment was PD (52.0%, n=13 patients) and AEs (44.0%, n=11 patients).

Adverse events and NCI-CTCAE toxicities:

In the SAF, 24 of 25 patients (96.0%) experienced at least one treatment-emergent adverse event (TEAE); 23 of 25 patients (92.0%) experienced at least one TEAE that was assessed as related to buparlisib (rTEAE).

In total, 208 TEAEs were reported. Of these, 123 TEAEs were assessed as related to buparlisib.

Nine patients (36.0%) experienced at least one treatment-emergent serious adverse event

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(TESAE) and in 5 patients (20.0%) TESAEs were considered as related to buparlisib. In total, 18 TESAEs were reported and 13 TESAEs were assessed as related to buparlisib.

Thirteen patients (52.0%) had at least one related TEAE grade 3/4 and 11 patients (44.0%) stopped treatment due to a related TEAE.

There was a total of 24 grade 3/4 TEAEs assessed as related to buparlisib and 19 related TEAEs that led to treatment discontinuation.

One patient (4.0%) died due to a TEAE but this event was not assessed as related to buparlisib.

The most common related AEs were in the following SOCs: Gastrointestinal disorders (52.0%, n=13), e.g. vomiting and nausea; skin and subcutaneous tissue disorders (40.0%, n=10), e.g. palmar-plantar erythrodysaesthesia syndrome, photosensitivity reaction and pruritus; psychiatric disorders (36.0%, n=9) e.g. depression and anxiety; investigations (32.0%, n=8), e.g. ALT and AST increased; general disorders and administration site conditions (28.0%, n=7), e.g. fatigue; metabolism and nutrition disorders (28.0%, n=7), e.g. decreased appetite, and nervous system disorders (28.0%, n=7), e.g. dizziness and dysgeusia.

From previous trials hyperglycemia, mood disorders, liver toxicity, skin rash and hypersensitivity, posterior reversible encephalopathy syndrome, gastrointestinal events, lung toxicity/pneumonitis, and cardiovascular events were identified as AEs of special interest (AESI). Therefore, specific safety event categories (SEC) were defined in this study that consisted of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment. Most events (n=34, 14 patients affected) were in the category gastrointestinal events, followed by skin rash / hypersensitivity (n=22, 11 patients affected) and psychiatric and mood disorders (n=21, 12 patients affected). There were 5 patients (20.0%) that had a buparlisib-related SAE and 4 patients with an SAE that was assessed as being not related. Most related SAEs occurred in the SOCs psychiatric disorders (12.0%) and skin and subcutaneous tissue disorders (8.0%).

Eleven patients (44.0%) experienced a TEAE that caused treatment discontinuation and was estimated as related to treatment with buparlisib. Most related TEAEs causing a stop of treatment were within the SOC psychiatric disorders (20.0%), gastrointestinal disorders and skin and subcutaneous tissue disorders (12.0% each), and investigations (8.0%).

Other observations related to safety:

There were only very few newly occurring on-treatment laboratory values of grade 3 or 4: ALT increased (n=6/23, 26.1%); AST increased (n=4/23, 17.4%) and glucose increased (n=2/22, 9.1% of patients (SAF)).

There was only 1 patient (PIK3CA mut/preserved PTEN expression status) with abnormal, clinically relevant changes in ECG parameters. No other patient showed abnormal ECG changes that were assessed as clinically relevant. In 19 patients, systolic and diastolic blood pressure was noted that was considered as hypertension.

There was 1 patient with a deterioration of ECOG performance status from 0 to 2 on cycle 2. At EOT visit, further 3 patients showed an ECOG performance status of 2; in 2 of these patients the ECOG status changed from 0 to 2 and in 1 patient from 1 to 2.

The total PHQ-9 scores can be categorized as follows: 0-4=none; 5-9=mild; 10-19=moderate; 20-27=severe. Overall, there was no obvious shift in PHQ-9 scores throughout the study. At

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baseline, the median score was 1.0, range 0.0-7.0. The highest median score was 2.5 in cycle 3, range 0.0-6.0, and was 2.0, range 0.0-20.0 at EOT. This means that the variability of the scores was high. Overall, there were 9 out of 25 patients (36.0%) that experienced a worsening of their health status (at least one category) from baseline to worst-on-treatment.

Conclusion:

The PIKTAM study was a phase II study designed to investigate the combination of the PI3K inhibitor buparlisib (BKM120) plus tamoxifen in patients with hormone receptor-positive, HER2-negative inoperable (locally advanced or metastatic) breast cancer with prior exposure to antihormonal therapy. Efficacy endpoints were investigated in the full population as well as in molecularly stratified subgroups.

An improved PFS-rate after 6 months of combination therapy could not be established in the full population since the null hypothesis of a 6-months PFS rate ≤ 0.4 could not be rejected, but there might be a trend that the subgroup with the status PIK3CA mut/PTEN wt and patients with the status PI3K activated benefitted more from study treatment. Yet, due to the small number of patients in the stratification groups conclusions regarding certain stratification groups have to be interpreted with caution. However, efficacy analyses were restricted by the fact that due to a re-evaluation of the risk benefit assessment of buparlisib patient recruitment was stopped prematurely.

The safety profile in the PIKTAM study was comparable to safety data in previous trials with buparlisib and the most common related AEs were within the SOC gastrointestinal disorders, psychiatric disorders, and skin and subcutaneous tissue disorders. No new or potentially critical safety issue was identified in this study.

However, due to a re-evaluation of the risk benefit assessment of buparlisib PIKTAM was prematurely closed during the recruitment period and thus calculated sample size could not be achieved.

Meanwhile, the further development of Pan-Pi3K-inhibitors was terminated, but the use of specific PI3K inhibitors plus endocrine therapy in patients with PIK3CA mutations could still be a therapeutic option and should be investigated further.

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