A phase II, non-randomized, multicenter, exploratory trial of single-agent BKM120 in patients with triple-negative metastatic breast cancer

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BACKGROUND

- Despite best available therapy, triple-negative breast cancer (TNBC) continues to be associated with poorer outcomes when compared to other breast cancer subtypes, and therefore poses a serious therapeutic challenge[1].
- It is widely accepted nowadays, that TNBC is not one disease, but comprised of a number of heterogeneous subpopulations very different in their genetic make-up, oncogene dependence, and response to treatment[2]. Therefore, therapeutic agents that specifically address those alterations may help improve clinical responses.
- Multiple core phosphatidylinositol-3-kinase (PI3K) pathway components are known to be altered in TNBC (Figure 1) [3,4], such as activating mutations in the *PI3KCA* gene or PTEN/INPP4B loss of protein expression. Although the relevance of these aberrations on the virulence of breast cancer and its response to PI3K inhibitors is yet to be elucidated, the consequential PI3K hyperactivity suggests that inhibitors of the PI3K pathway may be used to reverse resistance.
- BKM120 is a potent and highly specific oral pan-class I PI3K inhibitor currently in clinical development for multiple oncology indications in which PI3K pathway overactivation may play a role[5].
- This international, multi-institutional collaboration aims to identify which TNBC subpopulations regarding PI3K pathway status could benefit the most from this agent.

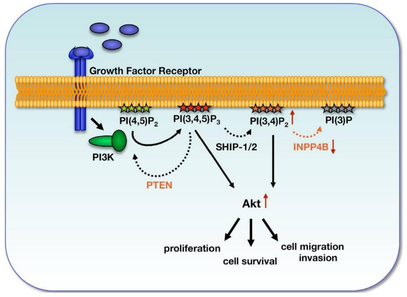

Figure 1 – The PI3K pathway indicating key molecular players[4].

STUDY DESIGN

This is a non-randomized, open-label, multicenter, investigator initiated single-arm exploratory phase II clinical trial.

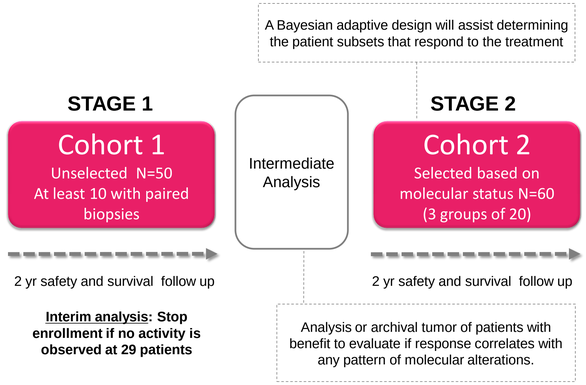

Figure 2 – Overall study flow chart.

OBJECTIVES

Primary

- To determine the clinical activity of BKM120, assessed by the clinical benefit rate at 4 months or more, in patients with metastatic TNBC who have developed disease progression after standard chemotherapy in the adjuvant or metastatic setting.

Secondary

- To identify biomarkers predictive of response to BKM120 (Table 1).
- To further evaluate clinical benefit assessed by progression-free survival and overall survival.
- To investigate the safety profile of this regimen.
- To evaluate the pharmacodynamic effects of BKM120 on components of the PI3K pathway and on glucose metabolism (Table 1).

METHODS

- Patients will first undergo screening, tumor measurement, and collection of available tumor block from the primary tumor and/or a metastatic site.
- Tumor block will be used for analysis of PI3K pathway alterations and their correlation with clinical response in order to define potential subpopulation that benefit most from BKM120 treatment.
- BKM120 will be administered orally as a once-daily 100-mg dose, in a continuous schedule until disease progression or unacceptable toxicity.
- Two clone investigator-initiated protocols (one for the US, one for Spain) will enroll in parallel.

Table 1 – Biomarkers to be assessed.

Biomarker category	Tumor Block (FFPE)	Paired fresh tumor biopsies	Whole blood, serum or plasma
Pharmacodynamic		pAkt, pS6, pERK, pMEK	glucose metabolism markers (e.g. glucose, insulin, c-peptide)
Generation of hypotheses toward the identification of responders	PTEN loss by IHC or FISH INPP4B loss by IHC or FISH PIK3CA mutation and p53 protein levels by IHC TP53 mutation RAS-like transcriptional profile Claudin-low transcriptional profile BRCA1/2 point mutations and major rearrangements; BRCA1 and BRCA2 protein levels by IHC LKB1 by IHC or FISH Other TBD		
Pre-screening of patients for enrollment into Stage 2	TBD based on results obtained in Stage 1		

KEY ELIGIBILITY CRITERIA

- Pathologically and radiologically confirmed metastatic triple-negative breast cancer (Stage IV disease)
- At least two prior chemotherapy regimens in the neoadjuvant, adjuvant, or metastatic setting
- Availability of a representative tumor specimen (primary or metastasis, archival or fresh) at baseline for retrospective analysis of relevant molecular alterations
- At least one measurable lesion defined by RECIST 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

ACCRUAL

A total of 110 patients are planned to be enrolled in this study in four sites in Spain and one site in the US. The first stage of the study will include a maximum 50 patients. The second stage will explore 60 patients with the predefined characteristics identified during Stage 1 as predictors of good response, based on their molecular profile (3 group maximum).

Enrollment began in Spain in June 2012, and is ongoing in all four sites, with 5 patients enrolled to date. Enrollment in the US has not started yet. For more information on the study please refer to ClinicalTrials.gov (NCT01629615) or contact Dr Cristina Saura at csaura@vhio.net.

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