Sponsor

Novartis

Generic Drug Name

buparlisib and trametinib

Trial Indication(s)

Adult patients with selected advanced solid tumors

Protocol Number

CBKM120B2101

Protocol Title

A phase Ib, open-label, multi-center, dose-escalation study of oral BKM120 in combination with oral GSK1120212 in adult patients with selected advanced solid tumors

Clinical Trial Phase

Ib

Phase of Drug Development

Phase I

Study Start/End Dates

26-Apr-2010 / 03-Nov-2014

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a multi-center, open-label, dose-finding, phase Ib study conducted in two stages; a dose escalation part to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of BKM120 given in combination with GSK1120212 treatment, followed by an expansion part to further assess safety and preliminary anti-tumor activity of the combination of BKM120 and GSK1120212 in selected patient populations.

Centers

The study was performed in eight centers in five countries: two each in the USA, Spain, and Belgium and one each in Canada and Switzerland.

Publication

None

Objectives:

Primary objectives

To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) and schedule of BKM120 and GSK1120212 in combination when administered orally to adult patients with selected advanced solid tumors.

Secondary objectives

- To characterize the safety and tolerability of the oral combination of BKM120 and GSK1120212;
- To determine the single and multiple- dose pharmacokinetic (PK) profile of the combination;
- To assess preliminary anti-tumor activity of the combination;
- To assess treatment-induced PI3K and MEK/ERK pathway signaling inhibition and evidence of biological activity in tumor (phospho-S6 and pERK).

Test Product (s), Dose(s), and Mode(s) of Administration

Novartis supplied BKM120 as 10 mg, and 50 mg hard gelatin capsules for oral use. GSK1120212 was provided as 0.25 mg, 0.5 mg 1.0 mg and 2.0 mg white or yellow film coated tablets for oral use.

BKM120 and GSK1120212 were provided together in escalating doses. The dose expansion part was started with a dose of BKM120 70 mg + GSK1120212 1.5 mg (MTD) daily. It was subsequently reduced to BKM120 60 mg + GSK1120212 1.5 mg (RP2D) daily upon discussion and agreement with the Study Investigators due to long-term tolerability.

Statistical Methods

The patient's background and demographic characteristics including age, gender, race, ethnicity, height, weight, body mass index, body surface area, WHO performance status, tumor type, medical conditions, etc. were listed and by patient, and summarized using descriptive statistics (mean, median, standard deviation, minimum and maximum for continuous data) or contingency tables (categorical data). For categorical variables, the number and percentage of patients with missing data was provided. Relevant medical history, current medical conditions, prior anti-neoplastic therapy, and diagnosis and extent of cancer were listed and summarized.

The full analysis set (FAS) included all patients who received at least one dose of BKM120 or GSK1120212. Patients were classified according to the intended treatment combination. The safety set included all patients who received at least one dose of BKM120 or GSK1120212, and had at least one valid post-baseline safety assessment. The dose-determining set consisted of all patients from the safety set who either met the following minimum exposure criterion and underwent scheduled safety evaluations, or discontinued earlier due to DLT.

Estimation of the MTD in the dose escalation part of the study was based upon the estimation of the probability of DLT in Cycle 1 in patients of the dose determining set. For each combination (BKM120 +GSK1120212) an adaptive Bayesian logistic regression model (BLRM) using the EWOC principle was used to guide the dose-escalation of the combination treatment. The BLRMs were fitted on the Cycle 1 DLT data accumulated throughout the dose-escalation to model the dose-toxicity relationship of BKM120 and GSK1120212 when given in combination.

The assessment of safety was based mainly on the frequency of adverse events and on the number of lab evaluation outside of pre-defined ranges common toxicity criteria (CTC) grading limits or normal ranges as appropriate).

The tolerability of the study drug treatment was also assessed by summarizing the number of drug interruptions, dose reduction and drug intensity.

The efficacy analysis was based on full analysis set (FAS). Best overall response (BOR) by RECIST v1.0 was summarized using objective response rate (ORR) and disease control rate (DCR). The DCR and ORR were presented by selected indications (NSCLC, Ovarian and Pancreatic) and overall by treatment group and summarized with counts and percentages. Progression free survival (PFS) and overall survival (OS) were summarized for selected indications (NSCLC, Ovarian and Pancreatic).

The analyses of DCR and ORR were performed using the overall lesion responses reported by the Investigator (local radiology).

The percentage changes from baseline of the sum of the longest diameters (SLD) across target lesions were listed and the best percentage change from baseline displayed graphically.

Basic PK parameters for GSK1120212 and BKM120 were calculated including but not limited to, AUC0-tlast, AUC0-inf, AUC0-24, Cmax, and Tmax.

All biomarker sample results were listed. For selected biomarkers with results pre- and post-baseline (p-S6 and p-ERK) individual values as well as change from baseline were summarized by means of descriptive statistics and graphs.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria

- Patients with the following histologically/cytologically confirmed, advanced non resectable solid tumors for whom no standard anticancer therapy exists.

For the dose escalation part

- Advanced pancreatic cancer irrespective of KRAS or BRAF mutation status
- Advanced CRC with documented KRAS, NRAS or BRAF mutations
- Advanced malignant melanoma with BRAF or NRAS mutations
- Advanced NSCLC with documented KRAS mutation
- Other advanced tumors with documented KRAS, NRAS or BRAF mutations upon agreement with the sponsor
- Triple negative breast cancer

For the expansion arms

- Advanced NSCLC patients with tumors with documented RAS or BRAF mutations.
- Advance ovarian cancer with tumors with documented RAS or BRAF mutations.
- Advanced pancreatic cancer with tumors with documented RAS or BRAF mutations.
- Availability of a representative tumor specimen (primary or metastasis, archival or fresh) was mandatory at baseline for retrospective analysis of relevant molecular alterations (e.g., PIK3CA). Measurable or non-measurable, but evaluable disease as determined by RECIST 1.0. For the dose expansion part of the study, disease must be measurable and evaluable.
- Patients of either sex, and ≥ 18 years of age.

Key exclusion criteria

- Patients with primary CNS tumor or CNS tumor involvement. However, patients with metastatic CNS tumors may participate in this trial, if the patient is >4 weeks from therapy completion (including radiation and/or surgery), is clinically stable with respect to the CNS tumor at the time of study entry, is not receiving steroid therapy or taper, and is not receiving anti-convulsive medications (that were started for the brain metastases).
- Patients who have received prior systemic anti-cancer treatment within the following time frames:
    - Patients who have received cyclical chemotherapy within a period of time that is shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C) prior to starting study drugs.
    - Patients who have received biologic therapy (e.g., antibodies) within a period of ≤ 4 weeks prior to starting study drugs.
    - Patients who have been treated with continuous or intermittent small molecule therapeutics within a period ≤ 4 weeks prior to starting study drugs.

  - Patients who have received any other investigational agents within a period of time that is less than the cycle length used for that treatment or ≤ 4 weeks (whichever is shorter) prior to starting study drugs.
  - Patients who have received extended field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drugs.
- Patients who have undergone major surgery ≤ 4 weeks prior to starting study drug or who have not recovered from side effects of such procedure.
- Unacceptable ocular/retinal conditions as defined by:
  - History or current evidence of retinal vein occlusion (RVO) or central serous retinopathy (CSR), or predisposing factors to RVO or CSR (e.g. uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease such as hypertension, diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes).
  - Visible retinal pathology as assessed by ophthalmic exam that is considered a risk factor for RVO or CSR such as:
  - Evidence of optic disc cupping
  - Evidence of visual field defects on automated perimetry
  - Intraocular pressure >21 mm Hg as measured by tonography

Participant Flow Table

Patient disposition by treatment (FAS)

Disposition Reason	BKM 30 mg + GSK 0.5 mg N=4 n (%)	BKM 60 mg + GSK 0.5 mg N=5 n (%)	BKM 60 mg + GSK 1 mg N=6 n (%)	BKM 60 mg + GSK 1.5 mg N=40 n (%)	BKM 60 mg + GSK 2 mg N=9 n (%)	BKM 70 mg + GSK 1.5 mg N=34 n (%)	BKM 80 mg + GSK 1 mg N=4 n (%)	BKM 80 mg + GSK 1.5 mg N=6 n (%)	BKM 90 mg + GSK 1 mg N=5 n (%)	All patients N=113 n (%)
Patients treated										
Treatment discontinued	4 (100.0)	5 (100.0)	6 (100.0)	40 (100.0)	9 (100.0)	34 (100.0)	4 (100.0)	6 (100.0)	5 (100.0)	113 (100.0)
Primary reason for end of treatment										
Disease progression	4 (100.0)	3 (60.0)	5 (83.3)	27 (67.5)	5 (55.6)	18 (52.9)	0	1 (16.7)	5 (100.0)	68 (60.2)
Adverse Event(s)	0	2 (40.0)	1 (16.7)	8 (20.0)	2 (22.2)	15 (44.1)	4 (100.0)	3 (50.0)	0	35 (31.0)
Patient withdrew consent	0	0	0	2 (5.0)	1 (11.1)	1 (2.9)	0	2 (33.3)	0	6 (5.3)
Death	0	0	0	2 (5.0)	1 (11.1)	0	0	0	0	3 (2.7)
Administrative problems	0	0	0	1 (2.5)	0	0	0	0	0	1 (0.9)
Study evaluation after completion of treatment										
Patients no longer being followed for study evaluation completion	4 (100.0)	5 (100.0)	6 (100.0)	31 (77.5)	9 (100.0)	27 (79.4)	4 (100.0)	6 (100.0)	5 (100.0)	97 (85.8)
Patients continuing to be followed* for study evaluation completion	0	0	0	6 (15.0)	0	7 (20.6)	0	0	0	13 (11.5)
Primary reason for study evaluation completion										
Follow-up phase completed as per protocol	3 (75.0)	4 (80.0)	6 (100.0)	10 (25.0)	3 (33.3)	9 (26.5)	4 (100.0)	1 (16.7)	5 (100.0)	45 (39.8)

Disposition Reason	BKM 30 mg + GSK 0.5 mg N=4 n (%)	BKM 60 mg + GSK 0.5 mg N=5 n (%)	BKM 60 mg + GSK 1 mg N=6 n (%)	BKM 60 mg + GSK 1.5 mg N=40 n (%)	BKM 60 mg + GSK 2 mg N=9 n (%)	BKM 70 mg + GSK 1.5 mg N=34 n (%)	BKM 80 mg + GSK 1 mg N=4 n (%)	BKM 80 mg + GSK 1.5 mg N=6 n (%)	BKM 90 mg + GSK 1 mg N=5 n (%)	All patients N=113 n (%)
Death	0	0	0	16 (40.0)	2 (22.2)	7 (20.6)	0	2 (33.3)	0	27 (23.9)
Patient withdrew consent	0	0	0	4 (10.0)	2 (22.2)	7 (20.6)	0	2 (33.3)	0	15 (13.3)
Lost to follow-up	0	0	0	1 (2.5)	2 (22.2)	2 (5.9)	0	0	0	5 (4.4)
Administrative problems	1 (25.0)	0	0	0	0	1 (2.9)	0	0	0	2 (1.8)
Disease progression	0	1 (20.0)	0	0	0	1 (2.9)	0	1 (16.7)	0	3 (2.7)

Baseline Characteristics

Demographic summary by treatment (FAS)

Demographic Variable	BKM 30 mg + GSK 0.5 mg N=4	BKM 60 mg + GSK 0.5 mg N=5	BKM 60 mg + GSK 1.0 mg N=6	BKM 60 mg + GSK 1.5 mg N=40	BKM 60 mg + GSK 2.0 mg N=9	BKM 70 mg + GSK 1.5 mg N=34	BKM 80 mg + GSK 1.0 mg N=4	BKM 80 mg + GSK 1.5 mg N=6	BKM 90 mg + GSK 1.0 mg N=5	All patients N=113
Age (years)										
n	4	5	6	40	9	34	4	6	5	113
Mean	61.8	51.0	56.3	58.1	55.1	54.2	66.3	54.7	47.6	56.1
SD	12.04	14.51	13.75	9.60	11.48	11.62	9.60	12.08	7.64	11.14
Median	64.5	45.0	61.0	58.0	56.0	53.5	70.5	57.0	48.0	56.0
Minimum	45.0	38.0	29.0	33.0	39.0	25.0	52.0	39.0	35.0	25.0
Maximum	73.0	69.0	66.0	76.0	73.0	84.0	72.0	72.0	55.0	84.0
Sex - n (%)										
Male	2 (50.0)	3 (60.0)	4 (66.7)	18 (45.0)	4 (44.4)	13 (38.2)	1 (25.0)	3 (50.0)	1 (20.0)	49 (43.4)
Female	2 (50.0)	2 (40.0)	2 (33.3)	22 (55.0)	5 (55.6)	21 (61.8)	3 (75.0)	3 (50.0)	4 (80.0)	64 (56.6)
Predominant race - n (%)										
Caucasian	4 (100.0)	5 (100.0)	6 (100.0)	35 (87.5)	9 (100.0)	31 (91.2)	3 (75.0)	5 (83.3)	5 (100.0)	103 (91.2)
Black	0	0	0	2 (5.0)	0	1 (2.9)	0	1 (16.7)	0	4 (3.5)
Asian	0	0	0	1 (2.5)	0	2 (5.9)	1 (25.0)	0	0	4 (3.5)
Other	0	0	0	2 (5.0)	0	0	0	0	0	2 (1.8)
Ethnicity - n (%)										
Hispanic/Latino	1 (25.0)	2 (40.0)	3 (50.0)	9 (22.5)	2 (22.2)	7 (20.6)	0	2 (33.3)	1 (20.0)	27 (23.9)
Chinese	0	0	0	0	0	1 (2.9)	0	0	0	1 (0.9)
Mixed Ethnicity	0	0	0	0	0	0	0	1 (16.7)	0	1 (0.9)
Other	3 (75.0)	3 (60.0)	3 (50.0)	31 (77.5)	7 (77.8)	26 (76.5)	4 (100.0)	3 (50.0)	4 (80.0)	84 (74.3)
Body mass index (kg/m²)										
n	4	4	6	39	9	34	4	6	5	111
Mean	23.3	28.7	24.2	25.6	26.4	26.3	25.4	25.9	26.6	25.9
SD	7.03	1.28	5.07	5.25	6.33	6.68	5.17	6.54	9.27	5.92
Median	22.5	29.2	24.3	25.0	27.2	25.4	24.6	26.2	27.4	25.4
Minimum	15.7	26.8	18.4	16.7	18.2	19.2	20.3	18.0	17.2	15.7
Maximum	32.6	29.6	30.4	42.0	36.3	54.4	32.1	37.1	41.0	54.4
WHO Performance Status - n (%)										
0	1 (25.0)	2 (40.0)	3 (50.0)	16 (40.0)	3 (33.3)	14 (41.2)	2 (50.0)	1 (16.7)	3 (60.0)	45 (39.8)
1	3 (75.0)	3 (60.0)	3 (50.0)	23 (57.5)	6 (66.7)	20 (58.8)	2 (50.0)	5 (83.3)	2 (40.0)	67 (59.3)

2	0	0	0	1 (2.5)	0	0	0	0	0	1 (0.9)

FAS: full analysis set; SD: standard deviation; WHO: world health organization
Body Mass Index (kg/m²) = weight[kg] / (height[m]^2)

Summary of Efficacy

Primary Outcome Result(s)

Dose limiting toxicities occurring during the first cycle, by primary system organ class, preferred term and treatment (DDS)

Primary system organ class Preferred term	BKM 60 mg + GSK 1.0 mg N=6 n (%)	BKM 60 mg + GSK 1.5 mg N=35 n (%)	BKM 60 mg + GSK 2.0 mg N=8 n (%)	BKM 70 mg + GSK 1.5 mg N=31 n (%)	BKM 80 mg + GSK 1.5 mg N=5 n (%)	BKM 90 mg + GSK 1.0 mg N=5 n (%)	All patients N=103 n (%)
Any primary system organ class							
Total	1 (16.7)	3 (8.6)	1 (12.5)	9 (29.0)	3 (60.0)	1 (20.0)	18 (17.5)
Gastrointestinal disorders							
Total	1 (16.7)	1 (2.9)	1 (12.5)	7 (22.6)	1 (20.0)	1 (20.0)	12 (11.7)
Diarrhea	0	0	0	2 (6.5)	0	0	2 (1.9)
Dysphagia	0	0	0	2 (6.5)	0	0	2 (1.9)
Nausea	0	0	0	0	1 (20.0)	0	1 (1.0)
Stomatitis	1 (16.7)	1 (2.9)	1 (12.5)	4 (12.9)	0	1 (20.0)	8 (7.8)
Investigations							
Total	0	1 (2.9)	0	1 (3.2)	2 (40.0)	0	4 (3.9)
Blood CPK increased	0	0	0	1 (3.2)	1 (20.0)	0	2 (1.9)
Ejection fraction decreased	0	0	0	0	1 (20.0)	0	1 (1.0)
Lipase increased	0	1 (2.9)	0	0	0	0	1 (1.0)
Metabolism and nutrition disorders							
Total	0	1 (2.9)	0	0	1 (20.0)	0	2 (1.9)
Decreased appetite	0	0	0	0	1 (20.0)	0	1 (1.0)
Hypophagia	0	0	0	0	1 (20.0)	0	1 (1.0)
Type 2 diabetes mellitus	0	1 (2.9)	0	0	0	0	1 (1.0)
Respiratory, thoracic and mediastinal disorders							
Total	0	1 (2.9)	0	0	0	0	1 (1.0)
Pneumonitis	0	1 (2.9)	0	0	0	0	1 (1.0)

Primary system organ class Preferred term	BKM 60 mg + GSK 1.0 mg N=6 n (%)	BKM 60 mg + GSK 1.5 mg N=35 n (%)	BKM 60 mg + GSK 2.0 mg N=8 n (%)	BKM 70 mg + GSK 1.5 mg N=31 n (%)	BKM 80 mg + GSK 1.5 mg N=5 n (%)	BKM 90 mg + GSK 1.0 mg N=5 n (%)	All patients N=103 n (%)
Skin and subcutaneous tissue disorders							
Total	0	0	0	1 (3.2)	0	0	1 (1.0)
Rash macular	0	0	0	1 (3.2)	0	0	1 (1.0)

AE: adverse event; CPK: creatine phosphokinase; DDS: dose determining set; DLT: dose limiting toxicity
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically.
A patient with multiple occurrences of a DLTs under one treatment is counted only once in the AE category for that treatment.
A patient with multiple DLTs within a primary system organ class is counted only once in the total row.

Summary of posterior distribution of DLT rates at time of MTD declaration (DDS)

GSK1120212 dose (mg)	BKM120 dose (mg)	Posterior probabilities that Pr(DLT) is in interval: 0-0.16	0.16-0.33	0.33-1	Mean	SD	Quantiles 2.5%	50%	97.5%
0.5	20.0	0.999	0.001	0.000	0.029	0.025	0.002	0.023	0.095
	30.0	0.998	0.002	0.000	0.040	0.028	0.005	0.034	0.110
	50.0	0.983	0.017	0.000	0.072	0.033	0.022	0.067	0.150
	60.0	0.942	0.058	0.000	0.095	0.037	0.035	0.091	0.179
	70.0	0.784	0.216	0.000	0.125	0.047	0.046	0.121	0.230
	80.0	0.546	0.437	0.016	0.161	0.065	0.057	0.153	0.311
	90.0	0.374	0.528	0.099	0.202	0.093	0.067	0.186	0.426
	100.0	0.268	0.524	0.209	0.245	0.123	0.076	0.218	0.555
1.0	20.0	0.996	0.004	0.000	0.045	0.031	0.006	0.038	0.124
	30.0	0.990	0.010	0.000	0.059	0.034	0.011	0.052	0.141
	50.0	0.930	0.070	0.000	0.100	0.038	0.039	0.095	0.186
	60.0	0.780	0.220	0.000	0.131	0.040	0.064	0.127	0.220
	70.0	0.440	0.558	0.002	0.170	0.048	0.088	0.167	0.274
	80.0	0.199	0.738	0.063	0.218	0.067	0.106	0.211	0.368

GSK1120212 dose (mg)	BKM120 dose (mg)	Posterior probabilities that Pr(DLT) is in interval: 0-0.16	0.16-0.33	0.33-1	Mean	SD	Quantiles 2.5%	50%	97.5%
	90.0	0.095	0.666	0.238	0.271	0.096	0.124	0.257	0.497
	100.0	0.050	0.533	0.418	0.327	0.127	0.139	0.303	0.630
1.5	20.0	0.965	0.035	0.000	0.069	0.042	0.012	0.060	0.169
	30.0	0.930	0.070	0.000	0.086	0.044	0.020	0.080	0.189
	50.0	0.674	0.326	0.000	0.142	0.047	0.061	0.138	0.245
	60.0	0.339	0.658	0.003	0.183	0.048	0.099	0.179	0.287
	70.0	0.077	0.868	0.054	0.235	0.056	0.137	0.232	0.353
	80.0	0.019	0.673	0.308	0.297	0.076	0.165	0.291	0.462
	90.0	0.006	0.410	0.584	0.363	0.105	0.191	0.352	0.599
	100.0	0.002	0.244	0.754	0.430	0.133	0.214	0.414	0.724
2.0	20.0	0.832	0.160	0.008	0.103	0.066	0.018	0.089	0.268
	30.0	0.732	0.254	0.014	0.127	0.070	0.029	0.116	0.297
	50.0	0.313	0.625	0.062	0.202	0.076	0.081	0.193	0.377
	60.0	0.091	0.740	0.169	0.257	0.079	0.130	0.247	0.437
	70.0	0.012	0.562	0.426	0.322	0.088	0.176	0.313	0.518
	80.0	0.002	0.281	0.717	0.396	0.105	0.214	0.389	0.619
	90.0	0.000	0.136	0.863	0.472	0.127	0.250	0.465	0.734
	100.0	0.000	0.070	0.930	0.543	0.146	0.281	0.539	0.829

DDS: dose determining set; DLT: dose limiting toxicity; MTD: maximum tolerated dose; PrDLT: probability dose limiting toxicity

Summary of posterior distribution of DLT rates at end of study (DDS)

GSK1120212 dose (mg)	BKM120 dose (mg)	Posterior probabilities that Pr(DLT) is in interval: 0-0.16	0.16-0.33	0.33-1	Mean	SD	Quantiles 2.5%	50%	97.5%
0.5	20.0	1.000	0.000	0.000	0.019	0.018	0.001	0.014	0.065
	30.0	1.000	0.000	0.000	0.027	0.020	0.003	0.022	0.078
	50.0	0.999	0.001	0.000	0.053	0.025	0.016	0.048	0.111
	60.0	0.994	0.006	0.000	0.073	0.029	0.027	0.069	0.137
	70.0	0.929	0.071	0.000	0.100	0.039	0.036	0.095	0.186
	80.0	0.715	0.279	0.006	0.134	0.059	0.045	0.125	0.274
	90.0	0.526	0.409	0.065	0.174	0.090	0.053	0.155	0.398
	100.0	0.393	0.440	0.167	0.218	0.124	0.060	0.187	0.537
1.0	20.0	1.000	0.000	0.000	0.029	0.021	0.004	0.024	0.083

	30.0	0.999	0.001	0.000	0.039	0.024	0.007	0.034	0.098
	50.0	0.995	0.005	0.000	0.070	0.028	0.026	0.067	0.134
	60.0	0.973	0.027	0.000	0.096	0.030	0.045	0.093	0.161
	70.0	0.780	0.220	0.000	0.130	0.039	0.062	0.127	0.215
	80.0	0.461	0.520	0.019	0.174	0.062	0.077	0.165	0.318
	90.0	0.266	0.600	0.134	0.225	0.095	0.091	0.206	0.458
	100.0	0.157	0.555	0.289	0.280	0.130	0.104	0.250	0.603
1.5	20.0	0.998	0.002	0.000	0.043	0.026	0.008	0.038	0.107
	30.0	0.997	0.003	0.000	0.055	0.029	0.013	0.051	0.123
	50.0	0.969	0.031	0.000	0.095	0.031	0.043	0.093	0.164
	60.0	0.844	0.156	0.000	0.128	0.031	0.073	0.126	0.196
	70.0	0.396	0.603	0.000	0.173	0.039	0.102	0.170	0.257
	80.0	0.130	0.801	0.069	0.228	0.064	0.125	0.220	0.376
	90.0	0.048	0.656	0.297	0.292	0.099	0.145	0.274	0.531
	100.0	0.020	0.474	0.506	0.358	0.133	0.165	0.332	0.675
2.0	20.0	0.984	0.016	0.000	0.063	0.036	0.013	0.057	0.149
	30.0	0.966	0.034	0.000	0.079	0.039	0.020	0.074	0.167
	50.0	0.767	0.233	0.000	0.132	0.040	0.063	0.130	0.218
	60.0	0.379	0.620	0.001	0.175	0.039	0.106	0.172	0.257
	70.0	0.053	0.925	0.022	0.231	0.046	0.148	0.228	0.327
	80.0	0.008	0.684	0.308	0.299	0.072	0.178	0.293	0.459
	90.0	0.002	0.378	0.620	0.375	0.106	0.207	0.361	0.619
	100.0	0.001	0.205	0.795	0.450	0.137	0.233	0.433	0.754

DDS: dose determining set; DLT: dose limiting toxicity; MTD: maximum tolerated dose; PrDLT: probability dose limiting toxicity

Secondary Outcome Result(s)

Summary of best overall response per RECIST as per Investigator assessment by treatment (FAS)

	BKM 30 mg + GSK 0.5 mg (N=4) n (%)	BKM 60 mg + GSK 0.5 mg (N=5) n (%)	BKM 60 mg + GSK 1.0 mg (N=6) n (%)	BKM 60 mg + GSK 1.5 mg (N=40) n (%)	BKM 60 mg + GSK 2.0 mg (N=9) n (%)	BKM 70 mg + GSK 1.5 mg (N=34) n (%)	BKM 80 mg + GSK 1.0 mg (N=4) n (%)	BKM 80 mg + GSK 1.5 mg (N=6) n (%)	BKM 90 mg + GSK 1.0 mg (N=5) n (%)	All patients (N=113) n (%)
Best overall response										
Complete Response (CR)	0	0	0	1 (2.5)	0	0	0	0	0	1 (0.9)
Partial Response (PR)	0	0	0	4 (10.0)	0	2 (5.9)	0	0	0	6 (5.3)
Stable Disease (SD)	1 (25.0)	2 (40.0)	2 (33.3)	18 (45.0)	1 (11.1)	21 (61.8)	4 (100.0)	1 (16.7)	2 (40.0)	52 (46.0)

	BKM 30 mg + GSK 0.5 mg (N=4) n (%)	BKM 60 mg + GSK 0.5 mg (N=5) n (%)	BKM 60 mg + GSK 1.0 mg (N=6) n (%)	BKM 60 mg + GSK 1.5 mg (N=40) n (%)	BKM 60 mg + GSK 2.0 mg (N=9) n (%)	BKM 70 mg + GSK 1.5 mg (N=34) n (%)	BKM 80 mg + GSK 1.0 mg (N=4) n (%)	BKM 80 mg + GSK 1.5 mg (N=6) n (%)	BKM 90 mg + GSK 1.0 mg (N=5) n (%)	All patients (N=113) n (%)
Progressive Disease (PD)	3 (75.0)	3 (60.0)	2 (33.3)	10 (25.0)	6 (66.7)	8 (23.5)	0	2 (33.3)	3 (60.0)	37 (32.7)
Unknown	0	0	2 (33.3)	7 (17.5)	2 (22.2)	3 (8.8)	0	3 (50.0)	0	17 (15.0)
Overall response rate (CR or PR)	0	0	0	5 (12.5)	0	2 (5.9)	0	0	0	7 (6.2)
90% CI for ORR	[0.0; 52.7]	[0.0; 45.1]	[0.0; 39.3]	[5.1; 24.5]	[0.0; 28.3]	[1.1; 17.4]	[0.0; 52.7]	[0.0; 39.3]	[0.0; 45.1]	[2.9;11.3]
Disease control rate (CR or PR or SD)	1 (25.0)	2 (40.0)	2 (33.3)	23 (57.5)	1 (11.1)	23 (67.6)	4 (100.0)	1 (16.7)	2 (40.0)	59 (52.2)
90% CI for DCR	[1.3; 75.1]	[7.6; 81.1]	[6.3; 72.9]	[43.3; 70.8]	[0.6; 42.9]	[52.2; 80.7]	[47.3; 100.0]	[0.9; 58.2]	[7.6; 81.1]	[44.1; 60.3]

DCR: disease control rate; FAS: full analysis set; ORR: overall response rate

Estimate (90% CI) for ORR and DCR were obtained using exact binomial 90% confidence interval test.

Summary of best overall response per RECIST as per Investigator assessment – Ovarian cancer (FAS)

	BKM 60 mg + GSK 1 mg (N=1) n (%)	BKM 60 mg + GSK 1.5 mg (N=8) n (%)	BKM 70 mg + GSK 1.5 mg (N=12) n (%)	All patients (N=21) n (%)
Best overall response				
Complete Response (CR)	0	1 (12.5)	0	1 (4.8)
Partial Response (PR)	0	3 (37.5)	2 (16.7)	5 (23.8)
Stable Disease (SD)	0	2 (25.0)	8 (66.7)	10 (47.6)
Progressive Disease (PD)	0	1 (12.5)	1 (8.3)	2 (9.5)
Unknown	1 (100.0)	1 (12.5)	1 (8.3)	3 (14.3)
Overall response rate (CR or PR)	0	4 (50.0)	2 (16.7)	6 (28.6)
Disease control rate (CR or PR or SD)	0	6 (75.0)	10 (83.3)	16 (76.2)

Summary of best overall response per RECIST as per Investigator assessment - NSCLC (FAS)

	BKM 60 mg + GSK 1.5 mg (N=14) n (%)	BKM 70 mg + GSK 1.5 mg (N=2) n (%)	BKM 80 mg + GSK 1 mg (N=1) n (%)	All patients (N=17) n (%)
Best overall response				
Complete Response (CR)	0	0	0	0
Partial Response (PR)	1 (7.1)	0	0	1 (5.9)
Stable Disease (SD)	6 (42.9)	2 (100.0)	1 (100.0)	9 (52.9)
Progressive Disease (PD)	4 (28.6)	0	0	4 (23.5)
Unknown	3 (21.4)	0	0	3 (17.6)
Overall response rate (CR or PR)	1 (7.1)	0	0	1 (5.9)
Disease control rate (CR or PR or SD)	7 (50.0)	2 (100.0)	1 (100.0)	10 (58.8)

Summary of best overall response per RECIST as per Investigator assessment - Pancreatic cancer (FAS)

	BKM 30 mg + GSK 0.5 mg (N=2) n (%)	BKM 60 mg + GSK 1.5 mg (N=11) n (%)	BKM 60 mg + GSK 2 mg (N=3) n (%)	BKM 70 mg + GSK 1.5 mg (N=8) n (%)	All patients (N=24) n (%)
Best overall response					
Complete Response (CR)	0	0	0	0	0
Partial Response (PR)	0	0	0	0	0
Stable Disease (SD)	1 (50.0)	6 (54.5)	1 (33.3)	4 (50.0)	12 (50.0)
Progressive Disease (PD)	1 (50.0)	3 (27.3)	2 (66.7)	2 (25.0)	8 (33.3)
Unknown	0	2 (18.2)	0	2 (25.0)	4 (16.7)
Overall response rate (CR or PR)	0	0	0	0	0
Disease control rate (CR or PR or SD)	1 (50.0)	6 (54.5)	1 (33.3)	4 (50.0)	12 (50.0)

95 percent posterior credible interval of overall response rate for selected indications - patients at MTD/RP2D (FAS)

Efficacy intervals Posterior probabilities that ORR is in interval				Quantiles				
No/Weak (0, 15%)	Limited (15%, 30%)	Clinically relevant (30%, 50%)	Superior (50%, 100%)	Mean	SD	2.5%	50%	97.5%
Ovarian Cancer								
0.058	0.501	0.417	0.023	0.292	0.097	0.124	0.285	0.497
NSCLC								
0.901	0.094	0.005	0.000	0.068	0.059	0.003	0.052	0.223
Pancreatic cancer								
0.997	0.003	0.000	0.000	0.009	0.021	0.000	0.001	0.073

FAS: full analysis set; NSCLC: non-small cell lung cancer; ORR: overall response rate

Analysis of progression-free survival as per investigator assessment using Kaplan-Meier method – Ovarian cancer (FAS)

	MTD/RP2D (N=20)	All patients (N=21)
No. of events	12 (60.0)	12 (57.1)
Progression	12 (60.0)	12 (57.1)
Deaths	0	0
No. of censored	8 (40.0)	9 (42.9)
KM estimate (%) PFS rate [95% confidence interval] at		
2 months	88.2 [72.9, 100]	88.2 [72.9, 100]
4 months	75.6 [54.8,96.5]	75.6 [54.8,96.5]
6 months	63.0 [39.5,86.6]	63.0 [39.5,86.6]
25th percentile for PFS [95% confidence interval] (days)	127 [57.0, 218]	127 [57.0, 218]
Median PFS [95% confidence interval] (days)	218 [127, 393]	218 [127, 393]
75th percentile for PFS [95% confidence interval] (days)	377 [218, 421]	377 [218, 421]

FAS: full analysis set; KM: Kaplan-Meier; PFS: progression-free survival

Analysis of progression-free survival as per investigator assessment using Kaplan-Meier method - NSCLC (FAS)

	MTD/RP2D (N=16)	All patients (N=17)
No. of events	8 (50.0)	8 (47.1)
Progression	6 (37.5)	6 (35.3)
Deaths	2 (12.5)	2 (11.8)
No. of censored	8 (50.0)	9 (52.9)
KM estimate (%) PFS rate [95% confidence interval] at		
2 months	61.9 [35.6, 88.3]	63.2 [37.3, 89.1]
4 months	46.4 [13.6,79.3]	47.4 [14.3,80.5]
6 months	NA	NA
25th percentile for PFS [95% confidence interval] (days)	56.0 [53.0,137]	56.0 [53.0,137]
Median PFS [95% confidence interval] (days)	118 [56.0,161]	118 [56.0,161]
75th percentile for PFS [95% confidence interval] (days)	161 [118, NA]	161 [118, NA]

FAS: full analysis set; MTD: maximum tolerated dose ; KM: Kaplan-Meier; NA: Not applicable; NSCLC: non-small cell lung cancer; PFS: progression-free survival; RP2D: recommended Phase 2 dose

Analysis of progression-free survival as per investigator assessment using Kaplan-Meier method – Pancreatic cancer (FAS)

	MTD/RP2D (N=19)	All patients (N=24)
No. of events	13 (68.4)	17 (70.8)
Progression	10 (52.6)	14 (58.3)
Deaths	3 (15.8)	3 (12.5)
No. of censored	6 (31.6)	7 (29.2)
KM estimate (%) PFS rate [95% confidence interval] at		
2 months	61.1 [36.5, 85.7]	60.8 [39.4, 82.2]
4 months	8.9 [0.0, 25.4]	7.6 [0.0, 21.6]
6 months	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]
25th percentile for PFS [95% confidence interval] (days)	51.5 [38.0, 85.0]	53.0 [45.0, 71.0]
Median PFS [95% confidence interval] (days)	85.0 [53.0,110]	71.0 [55.0,102]
75th percentile for PFS [95% confidence interval] (days)	110 [85.0,144]	102 [72.0,114]

FAS: full analysis set; MTD: maximum tolerated dose ; KM: Kaplan-Meier; NA: Not applicable; PFS: progression-free survival; RP2D: recommended Phase 2 dose

Analysis of Overall Survival (OS) using Kaplan-Meier method - Ovarian cancer (FAS)

	MTD/RP2D (N=20)	All patients (N=21)
No. of Deaths	6 (30.0%)	6 (28.6%)
No. of censored	14 (70.0%)	15 (71.4%)
KM estimate (%) OS rate [95%CI] at		
2 months	100 [100,100]	100 [100,100]
4 months	100 [100,100]	100 [100,100]
6 months	86.7 [69.5,100]	87.5 [71.3,100]
25th percentile for OS [95% CI] (days)	410 [178, 796]	559 [178, 796]
Median OS [95% CI] (days)	796 [708, NA]	796 [708, NA]
75th percentile for OS [95% CI] (days)	NE	NE

CI: confidence interval; FAS: full analysis set; NE: not estimable

Analysis of Overall Survival (OS) using Kaplan-Meier method - NSCLC (FAS)

	MTD/RP2D (N=16)	All patients (N=17)
No. of Deaths	11 (68.8%)	11 (64.7%)
No. of censored	5 (31.3%)	6 (35.3%)
KM estimate (%) OS rate [95%CI] at		
2 months	87.5 [71.3, 100]	88.2 [72.9,100]
4 months	67.3 [43.7, 90.9]	68.3 [45.1, 91.5]
6 months	38.5 [13.0, 63.9]	39.0 [13.4, 64.6]
25th percentile for OS [95% CI] (days)	111 [57.0, 154]	111 [57.0,154]
Median OS [95% CI] (days)	154 [118, NA]	154 [118, NA]
75th percentile for OS [95% CI] (days)	422 [154, NE]	422 [154, NE]

FAS: full analysis set; MTD: maximum tolerated dose; NE: not estimable; RP2D: recommended Phase 2 dose

Analysis of Overall Survival (OS) using Kaplan-Meier method - Pancreatic cancer (FAS)

	MTD/RP2D (N=19)	All patients (N=24)
No. of Deaths	9 (47.4)	10 (41.7)
No. of censored	10 (52.6)	14 (58.3)
KM estimate (%) OS rate [95%CI] at		
2 months	94.1 [82.9, 100]	95.5 [86.8, 100]
4 months	68.0 [41.0, 94.9]	67.8 [43.2, 92.4]
6 months	17.0 [0.0, 45.0]	17.0 [0.0, 44.8]
25th percentile for OS [95% CI] (days)	117 [65.0, 146]	117 [77.0, 146]
Median OS [95% CI] (days)	142 [117, 178]	142 [117, 178]
75th percentile for OS [95% CI] (days)	178 [142, 210]	178 [142, 210]

FAS: full analysis set; MTD: maximum tolerated dose; RP2D: recommended Phase 2 dose

Summary of primary plasma PK parameters for BKM120 by RP2D and MTD treatment (FAS)

Cycle and day of sampling	Treatment	Tmax (h)	Cmax (ng/mL)	AUC0-24 (h*ng/mL)	AUC0-tlast (h*ng/mL)

Cycle and day of sampling	Treatment	Tmax (h)	Cmax (ng/mL)	AUC0-24 (h*ng/mL)	AUC0-tlast (h*ng/mL)
Cycle 1 Day 1	BKM 60 mg +GSK 1.5 mg (N=40)	1.25 [0.6; 8.0] (11)	342.00 [145.0;815.0] (11)	3346.74 [1586.7;4622.3] (11)	3346.74 [1561.2;4398.0] (11)
	BKM 70 mg +GSK 1.5 mg (N=34)	1.82 [0.5;23.8] (16)	432.00 [187.0; 990.0] (16)	4437.27 [1715.2; 8990.9] (16)	4339.57 [1675.2;9015.7] (16)
Cycle 1 Day 15	BKM 60 mg +GSK 1.5 mg (N=40)	2.17 [1.0; 12.3] (13)	558.00 [236.0; 1180.0] (13)	5488.80 [2482.9;13148.1] (7)	5500.52 [2418.6;13586.5] (13)
	BKM 70 mg +GSK 1.5 mg (N=34)	2.00 [0.0; 9.0] (14)	792.50 [209.0;1460.0] (14)	12619.25 [2510.2;19176.6] (12)	12814.84 [2043.0;18897.5] (14)
Cycle 1 Day 28	BKM 60 mg +GSK 1.5 mg (N=40)	1.52 [0.0; 6.0] (24)	516.50 [211.0;1260.0] (24)	8518.33 [3772.9;11059.0] (6)	2190.00 [780.0;11636.7] (24)
	BKM 70 mg +GSK 1.5 mg (N=34)	2.32 [0.0; 6.0] (14)	810.00 [300.0;2300.0] (14)	11984.08 [3511.7;16713.2] (7)	9699.09 [1220.6;17480.0] (14)

Median [Min; Max] (n)

Patients with at least 7 days of daily dosing prior to the pharmacokinetic assessments were included in the summary statistics of C1D15 and C1D28.

Number in round parenthesis is the number of the patients for whom the parameter is reported.

Summary of primary plasma PK parameters for GSK1120212 by RP2D and MTD treatment (FAS)

Cycle and day of sampling	Treatment	Tmax (h)	Cmax (ng/mL)	AUC0-24 (h*ng/mL)	AUC0-tlast (h*ng/mL)
Cycle 1 Day 1	BKM 60 mg +GSK 1.5 mg (N=40)	1.50 [1.0; 8.0] (11)	3.43 [0.9; 7.9] (11)	30.30 [19.0;45.9] (10)	27.25 [14.2;43.8] (11)
	BKM 70 mg +GSK 1.5 mg (N=34)	2.00 [0.5; 4.2] (16)	3.85 [1.4;14.5] (16)	38.69 [13.8;95.6] (16)	37.37 [13.5;97.7] (16)
Cycle 1 Day 15	BKM 60 mg +GSK 1.5 mg (N=40)	2.95 [1.5; 12.3] (13)	20.00 [11.5; 30.4] (13)	316.54 [205.9; 555.9] (8)	254.33 [115.7; 532.3] (13)
	BKM 70 mg +GSK 1.5 mg (N=34)	2.00 [1.0;14.6] (15)	19.30 [0.7; 52.5] (15)	475.49 [189.8; 650.2] (11)	348.79 [9.8; 650.2] (15)

Cycle and day of sampling	Treatment	Tmax (h)	Cmax (ng/mL)	AUC0-24 (h*ng/mL)	AUC0-tlast (h*ng/mL)
Cycle 1 Day 28	BKM 60 mg +GSK 1.5 mg (N=40)	2.48 [1.1; 7.6] (22)	16.95 [6.7; 43.5] (22)	326.53 [237.6; 523.2] (6)	91.80 [29.7; 515.1] (22)
	BKM 70 mg +GSK 1.5 mg (N=34)	3.62 [1.5; 8.0] (12)	15.60 [11.1;51.0] (12)	528.18 [215.5; 677.3] (5)	251.74 [48.8; 701.3] (12)

Median [Min; Max] (n)

Patients with at least 7 days of daily dosing prior to the pharmacokinetic assessments were included in the summary statistics of C1D15 and C1D28.

Summary of Safety

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class and treatment (Safety set)

Primary System Organ Class	BKM 30 mg + GSK 0.5 mg N=4 n (%)	BKM 60 mg + GSK 0.5 mg N=5 n (%)	BKM 60 mg + GSK1 mg N=6 n (%)	BKM 60 mg + GSK 1.5 mg N=40 n (%)	BKM 60 mg + GSK 2 mg N=9 n (%)
Total	4 (100.0)	5 (100.0)	6 (100.0)	40 (100.0)	9 (100.0)
Blood and lymphatic system disorders	2 (50.0)	1 (20.0)	0	8 (20.0)	3 (33.3)
Cardiac disorders	1 (25.0)	0	2 (33.3)	2 (5.0)	2 (22.2)
Ear and labyrinth disorders	0	0	1 (16.7)	0	0
Endocrine disorders	0	0	0	1 (2.5)	0
Eye disorders	1 (25.0)	0	2 (33.3)	10 (25.0)	2 (22.2)
Gastrointestinal disorders	4 (100.0)	4 (80.0)	5 (83.3)	36 (90.0)	8 (88.9)
General disorders and administration site conditions	3 (75.0)	2 (40.0)	3 (50.0)	32 (80.0)	7 (77.8)
Hepatobiliary disorders	1 (25.0)	0	1 (16.7)	3 (7.5)	1 (11.1)
Immune system disorders	0	0	1 (16.7)	0	0
Infections and infestations	0	1 (20.0)	2 (33.3)	14 (35.0)	5 (55.6)
Injury, poisoning and procedural complications	1 (25.0)	0	0	2 (5.0)	0
Investigations	1 (25.0)	1 (20.0)	5 (83.3)	29 (72.5)	7 (77.8)
Metabolism and nutrition disorders	2 (50.0)	3 (60.0)	3 (50.0)	24 (60.0)	8 (88.9)
Musculoskeletal and connective tissue disorders	2 (50.0)	2 (40.0)	4 (66.7)	8 (20.0)	2 (22.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	2 (5.0)	1 (11.1)
Nervous system disorders	0	3 (60.0)	2 (33.3)	17 (42.5)	4 (44.4)
Psychiatric disorders	1 (25.0)	1 (20.0)	1 (16.7)	6 (15.0)	3 (33.3)
Renal and urinary disorders	0	0	1 (16.7)	12 (30.0)	3 (33.3)
Reproductive system and breast disorders	0	0	0	0	1 (11.1)
Respiratory, thoracic and mediastinal disorders	0	3 (60.0)	2 (33.3)	23 (57.5)	1 (11.1)
Skin and subcutaneous tissue disorders	3 (75.0)	5 (100.0)	6 (100.0)	33 (82.5)	7 (77.8)
Vascular disorders	0	1 (20.0)	2 (33.3)	13 (32.5)	0

Table continued **Adverse events, regardless of study drug relationship, by primary system organ class and treatment (Safety set)**

Primary System Organ Class	BKM 70 mg + GSK 1.5 mg N=34 n (%)	BKM 80 mg + GSK1 mg N=4 n (%)	BKM 80 mg + GSK 1.5 mg N=6 n (%)	BKM 90 mg + GSK 1 mg N=5 n (%)	All patients N=113 n (%)
Total	34 (100.0)	4 (100.0)	6 (100.0)	5 (100.0)	113 (100.0)
Blood and lymphatic system disorders	12 (35.3)	1 (25.0)	2 (33.3)	1 (20.0)	30 (26.5)
Cardiac disorders	2 (5.9)	0	1 (16.7)	1 (20.0)	11 (9.7)
Ear and labyrinth disorders	1 (2.9)	1 (25.0)	0	0	3 (2.7)
Endocrine disorders	0	0	0	0	1 (0.9)
Eye disorders	7 (20.6)	1 (25.0)	0	2 (40.0)	25 (22.1)
Gastrointestinal disorders	33 (97.1)	3 (75.0)	5 (83.3)	5 (100.0)	103 (91.2)
General disorders and administration site conditions	26 (76.5)	3 (75.0)	5 (83.3)	4 (80.0)	85 (75.2)
Hepatobiliary disorders	0	0	0	0	6 (5.3)
Immune system disorders	0	0	0	0	1 (0.9)
Infections and infestations	16 (47.1)	1 (25.0)	3 (50.0)	2 (40.0)	44 (38.9)
Injury, poisoning and procedural complications	3 (8.8)	1 (25.0)	0	0	7 (6.2)
Investigations	30 (88.2)	4 (100.0)	6 (100.0)	2 (40.0)	85 (75.2)
Metabolism and nutrition disorders	20 (58.8)	3 (75.0)	4 (66.7)	3 (60.0)	70 (61.9)
Musculoskeletal and connective tissue disorders	11 (32.4)	0	2 (33.3)	0	31 (27.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (5.9)	0	0	1 (20.0)	6 (5.3)
Nervous system disorders	16 (47.1)	1 (25.0)	3 (50.0)	1 (20.0)	47 (41.6)
Psychiatric disorders	6 (17.6)	1 (25.0)	3 (50.0)	1 (20.0)	23 (20.4)
Renal and urinary disorders	10 (29.4)	0	1 (16.7)	3 (60.0)	30 (26.5)
Reproductive system and breast disorders	2 (5.9)	0	0	1 (20.0)	4 (3.5)
Respiratory, thoracic and mediastinal disorders	14 (41.2)	2 (50.0)	1 (16.7)	2 (40.0)	48 (42.5)
Skin and subcutaneous tissue disorders	30 (88.2)	4 (100.0)	4 (66.7)	5 (100.0)	97 (85.8)
Vascular disorders	11 (32.4)	2 (50.0)	3 (50.0)	0	32 (28.3)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Adverse events regardless of study drug relationship, by preferred term and treatment (at least 10 percent in all patients) (Safety set)

Preferred term	BKM 30 mg + GSK 0.5 mg N=4		BKM 60 mg + GSK 0.5 mg N=5		BKM 60 mg + GSK 1 mg N=6		BKM 60 mg + GSK 1.5 mg N=40		BKM 60 mg + GSK 2 mg N=9	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	4 (100.0)	1 (25.0)	5 (100.0)	4 (80.0)	6 (100.0)	6 (100.0)	40 (100.0)	29 (72.5)	9 (100.0)	8 (88.9)
Diarrhoea	1 (25.0)	0	2 (40.0)	0	3 (50.0)	0	24 (60.0)	0	6 (66.7)	1 (11.1)
Dermatitis acneiform	1 (25.0)	0	3 (60.0)	0	4 (66.7)	0	16 (40.0)	1 (2.5)	5 (55.6)	1 (11.1)
Blood creatine phosphokinase increased	0	0	0	0	4 (66.7)	2 (33.3)	20 (50.0)	6 (15.0)	3 (33.3)	0
Nausea	1 (25.0)	0	2 (40.0)	0	4 (66.7)	1 (16.7)	16 (40.0)	0	5 (55.6)	0
Stomatitis	1 (25.0)	0	1 (20.0)	0	2 (33.3)	1 (16.7)	17 (42.5)	2 (5.0)	4 (44.4)	2 (22.2)
Vomiting	0	0	1 (20.0)	0	3 (50.0)	0	16 (40.0)		3 (33.3)	0
Decreased appetite	1 (25.0)	0	1 (20.0)	0	2 (33.3)	1 (16.7)	13 (32.5)	0	4 (44.4)	0
Fatigue	2 (50.0)	0	1 (20.0)	0	1 (16.7)	0	17 (42.5)	4 (10.0)	1 (11.1)	0
Asthenia	1 (25.0)	0	1 (20.0)	0	3 (50.0)	1 (16.7)	7 (17.5)	1 (2.5)	4 (44.4)	0
Pyrexia	0	0	0	0	2 (33.3)	0	9 (22.5)	2 (5.0)	4 (44.4)	1 (11.1)
Rash maculo-papular	1 (25.0)	0	1 (20.0)	1 (20.0)	1 (16.7)	1 (16.7)	11 (27.5)	2 (5.0)	1 (11.1)	1 (11.1)
Aspartate aminotransferase increased	1 (25.0)	1 (25.0)	1 (20.0)	1 (20.0)	2 (33.3)	1 (16.7)	11 (27.5)	5 (12.5)	3 (33.3)	0
Rash macular	0	0	2 (40.0)	0	0	0	10 (25.0)	1 (2.5)	3 (33.3)	0
Alanine aminotransferase increased	1 (25.0)	1 (25.0)	1 (20.0)	1 (20.0)	1 (16.70	0	10 (25.0)	4 (10.0)	2 (22.2)	0
Constipation	2 (50.0)	0	1 (20.0)	0	2 (33.3)	0	7 (17.5)	0	0	0
Hyperglycaemia	2 (50.0)	0	3 (60.0)	0	0	0	6 (15.0)	3 (7.5)	4 (44.4)	0
Anaemia	2 (50.0)	0	1 (20.0)	0	0	0	6 (15.0)	1 (2.5)	2 (22.2)	0
Dry skin	0	0	0	0	2 (33.3)	0	7 (17.5)	0	0	0
Abdominal pain	1 (25.0)	0	1 (20.0)	0	2 (33.3)	1 (16.7)	4 (10.0)	1 (2.5)	2 (22.2)	0
Hypertension	0	0	0	0	1 (16.7)	0	8 (20.0)	3 (7.5)	0	0
Oedema peripheral	1 (25.0)	0	0	0	2 (33.3)	0	8 (20.0)	0	2 (22.2)	0

	BKM 30 mg + GSK 0.5 mg N=4		BKM 60 mg + GSK 0.5 mg N=5		BKM 60 mg + GSK 1 mg N=6		BKM 60 mg + GSK 1.5 mg N=40		BKM 60 mg + GSK 2 mg N=9	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Dyspnoea	0	0	1 (20.0)	0	1 (16.7)	0	11 (27.5)	4 (10.0)	0	0
Dehydration	0	0	0	0	1 (16.7)	0	2 (5.0)	0	5 (55.6)	2 (22.2)
Hypokalaemia	0	0	1 (20.0)	1 (20.0)	1 (16.7)	0	6 (15.0)	2 (5.0)	3 (33.3)	1 (11.1)
Weight decreased	0	0	0	0	2 (33.3)	1 (16.7)	4 (10.0)	0	2 (22.2)	0
Pruritus	0	0	0	0	0	0	0	0	0	0
Hypomagnesaemia	0	0	0	0	0	0	7 (17.5)	0	2 (22.2)	0
Skin fissures	0	0	0	0	1 (16.7)	0	7 (17.5)	0	0	0
Dysphagia	0	0	0	0	1 (16.7)	0	3 (7.5)	0	0	0
Thrombocytopenia	0	0	0	0	0	0	3 (7.5)	1 (2.5)	2 (22.2)	0
Urinary tract infection	0	0	0	0	0	0	4 (10.0)	0	1 (11.1)	0

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Table continued **Adverse events regardless of study drug relationship, by preferred term and treatment (at least 10 percent in all patients) (Safety set)**

	BKM 70 mg + GSK 1.5 mg N=34		BKM 80 mg + GSK 1 mg N=4		BKM 80 mg + GSK 1.5 mg N=6		BKM 90 mg + GSK 1 mg N=5		All patients N=113	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	34 (100.0)	30 (88.2)	4 (100.0)	4 (100.0)	6 (100.0)	5 (83.3)	5 (100.0)	3 (60.0)	113 (100.0)	90 (79.6)
Diarrhoea	27 (79.4)	5 (14.7)	2 (50.0)	0	2 (33.3)	0	4 (80.0)	0	71 (62.8)	6 (5.3)
Dermatitis acneiform	22 (64.7)	4 (11.8)	2 (50.0)	0	3 (50.0)	0	4 (80.0)	0	60 (53.1)	6 (5.3)
Blood creatine phosphokinase increased	17 (50.0)	6 (17.6)	2 (50.0)	0	3 (50.0)	2 (33.3)	2 (40.0)	0	51 (45.1)	16 (14.2)
Nausea	14 (41.2)	2 (5.9)	1 (25.0)	0	3 (50.0)	2 (33.3)	2 (40.0)	0	48 (42.5)	5 (4.4)
Stomatitis	17 (50.0)	5 (14.7)	1 (25.0)	0	1 (16.7)	0	2 (40.0)	0	46 (40.7)	10 (8.8)
Vomiting	15 (44.1)	2 (5.9)	1 (25.0)	0	4 (66.7)	1 (16.7)	1 (20.0)	0	44 (38.9)	3 (2.7)
Decreased appetite	10 (29.4)	0	1 (25.0)	0	3 (50.0)	1 (16.7)	1 20.0)	0	36 (31.9)	2 (1.8)
Fatigue	8 23.5)	0	1 (25.0)	0	1 (16.7)	0	1 (20.0)	0	33 (29.2)	4 (3.5)
Asthenia	11 (32.4)	1 (2.9)	1 (25.0)	0	3 (50.0)	0	1 (20.0)	0	32 (28.3)	3 (2.7)
Pyrexia	13 (38.2)	1 (2.9)	1 (25.0)	0	3 (50.0)	0	0	0	32 (28.3)	4 (3.5)
Rash maculo-papular	11 (32.4)	2 (5.9)	2 (50.0)	1 (25.0)	1 (16.7)	0	3 (60.0)	1 (20.0)	32 (28.3)	9 (8.0)
Aspartate aminotransferase increased	9 (26.5)	1 (2.9)	3 (75.0)	2 (50.0)	1 (16.7)	0	0	0	31 (27.4)	11 (9.7)
Rash macular	11 (32.4)	7 (20.6)	1 (25.0)	1 (25.0)	1 (16.7)	0	2 (40.0)	0	30 (26.5)	9 (8.0)
Alanine aminotransferase increased	9 (26.5)	3 (8.8)	3 (75.0)	3 (75.0)	0	0	2 (40.0)0	1 (20.0)	29 (25.7)	13 (11.5)
Constipation	13 (38.2)	0	0	0	1 (16.7)	1 (16.7)	0	0	26 (23.0)	1 (0.9)
Hyperglycaemia	6 (17.6)	1 (2.9)	2 (50.0)	1 (25.0)	1 (16.7)	0	1 (20.0)	0	25 (22.1)	5 (4.4)
Anaemia	9 (26.5)	2 (5.9)	1 (25.0)	1 (25.0)	2 (33.3)	0	0	0	23 (20.4)	4 (3.5)
Dry skin	11 (32.4)	0	1 (25.0)	0	1 (16.7)	0	0	0	22 (19.5)	0
Abdominal pain	8 (23.5)	1 (2.9)	1 (25.0)	0	1 (16.7)	0	1 (20.0)	0	21 (18.6)	3 (2.7)

	BKM 70 mg + GSK 1.5 mg N=34		BKM 80 mg + GSK 1 mg N=4		BKM 80 mg + GSK 1.5 mg N=6		BKM 90 mg + GSK 1 mg N=5		All patients N=113	
	All grades	Grade 3/4	All grades	Grade 3/4	All grade	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Hypertension	9 (26.5)	3 (8.8)	2 (50.0)	0	0	0	0	0	20 (17.7)	6 (5.3)
Oedema peripheral	5 (14.7)	0	0	0	1 (16.7)	0	1 (20.0)	0	20 (17.7)	0
Dyspnoea	5 (14.7)	3 (8.8)	0	0	0	0	1 (20.0)	0	19 (16.8)	7 (6.2)
Dehydration	5 (14.7)	0	1 (25.0)	0	2 (33.3)	1 (16.7)	0	0	16 (14.2)	3 (2.7)
Hypokalaemia	5 (14.7)	3 (8.8)	0	0	0	0	0	0	16 (14.2)	7 (6.2)
Weight decreased	7 (20.6)	0	0	0	0	0	0	0	15 (13.3)	1 (0.9)
Pruritus	12 (35.3)	2 (5.9)	0	0	0	0	2 (40.0)	1 (20.0)	14 (12.4)	3 (2.7)
Hypomagnesaemia	3 (8.8)	0	0	0	0	0	1 (20.0)	0	13 (11.5)	0
Skin fissures	4 (11.8)	0	1 (25.0)	0	0	0	0	0	13 (11.5)	0
Dysphagia	6 (17.6)	1 (2.9)	1 (25.0)	0	1 (16.7)	0	0	0	12 (10.6)	1 (0.9)
Thrombocytopenia	6 (17.6)	4 (11.8)	1 (25.0)	1 (25.0)	0	0	0	0	12 (10.6)	6 (5.3)
Urinary tract infection	6 (17.6)	2 (5.9)	0	0	0	0	1 (20.0)	0	12 (10.6)	2 (1.8)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Summary of deaths and adverse events by treatment (Safety set)

Category	BKM 30mg + GSK 0.5mg N=4 n (%)	BKM 60mg + GSK 0.5mg N=5 n (%)	BKM 60mg + GSK 1mg N=6 n (%)	BKM 60mg + GSK 1.5mg N=40 n (%)	BKM 60mg + GSK 2mg N=9 n (%)
All deaths	0	0	1 (16.7)	16 (40.0)	3 (33.3)
On-treatment deaths [1]	0	0	0	6 (15.0)	3 (33.3)
Adverse Events (AEs)	4 (100.0)	5 (100.0)	6 (100.0)	40 (100.0)	9 (100.0)
AEs suspected to be treatment-related	4 (100.0)	5 (100.0)	6 (100.0)	39 (97.5)	8 (88.9)
Grade 3-4 AEs	1 (25.0)	4 (80.0)	6 (100.0)	29 (72.5)	8 (88.9)
Suspected treatment-related grade 3-4 AEs	0	2 (40.0)	5 (83.3)	23 (57.5)	4 (44.4)
Serious adverse events (SAEs)	1 (25.0)	4 (80.0)	4 (66.7)	20 (50.0)	6 (66.7)
Suspected treatment-related SAEs	0	1 (20.0)	2 (33.3)	5 (12.5)	2 (22.2)
AEs leading to discontinuation	0	2 (40.0)	1 (16.7)	8 (20.0)	2 (22.2)
Suspected AEs leading to discontinuation	0	1 (20.0)	1 (16.7)	4 (10.0)	2 (22.2)
Other significant AEs	4 (100.0)	5 (100.0)	6 (100.0)	40 (100.0)	9 (100.0)
AEs requiring dose interruption and / or reduction	1 (25.0)	2 (40.0)	3 (50.0)	29 (72.5)	7 (77.8)
AEs requiring additional therapy	4 (100.0)	5 (100.0)	6 (100.0)	39 (97.5)	9 (100.0)

[1] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized
Additional therapy includes all non-drug therapy and concomitant medications

Table continued **Summary of deaths and adverse events by treatment (Safety set)**

Category	BKM 70mg + GSK 1.5mg N=34 n (%)	BKM 80mg + GSK 1mg N=4 n (%)	BKM 80mg + GSK 1.5mg N=6 n (%)	BKM 90mg + GSK 1mg N=5 n (%)	All patients N=113 n (%)
All deaths	7 (20.6)	0	2 (33.3)	0	29 (25.7)
On-treatment deaths [1]	3 (8.8)	0	2 (33.3)	0	14 (12.4)
Adverse Events (AEs)	34 (100.0)	4 (100.0)	6 (100.0)	5 (100.0)	113 (100.0)
AEs suspected to be treatment-related	33 (97.1)	4 (100.0)	6 (100.0)	5 (100.0)	110 (97.3)
Grade 3-4 AEs	30 (88.2)	4 (100.0)	5 (83.3)	3 (60.0)	90 (79.6)
Suspected treatment-related G3-4 AEs	28 (82.4)	4 (100.0)	4 (66.7)	3 (60.0)	73 (64.6)
Serious adverse events (SAEs)	15 (44.1)	1 (25.0)	3 (50.0)	1 (20.0)	55 (48.7)
Suspected treatment-related SAEs	9 (26.5)	0	2 (33.3)	0	21 (18.6)
AEs leading to discontinuation	15 (44.1)	4 (100.0)	3 (50.0)	0	35 (31.0)
Suspected AEs leading to discontinuation	14 (41.2)	3 (75.0)	2 (33.3)	0	27 (23.9)
Other significant AEs	34 (100.0)	4 (100.0)	6 (100.0)	5 (100.0)	113 (100.0)
AEs requiring dose interruption and / or reduction	29 (85.3)	3 (75.0)	2 (33.3)	3 (60.0)	79 (69.9)
AEs requiring additional therapy	34 (100.0)	4 (100.0)	6 (100.0)	5 (100.0)	112 (99.1)

[1] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized
Additional therapy includes all non-drug therapy and concomitant medications

Conclusion:

- The most frequent dose-limiting toxicities of BKM120 in combination with GSK11201212 were stomatitis, diarrhea, dysphagia and increased blood creatine phosphokinase levels.
- The MTD of BKM120 in combination with GSK1120212 was defined at 70 mg + 1.5mg daily and 60 mg BKM120 + 1.5 mg GSK1120212 daily was later declared during the expansion part as the RP2D.
- A secondary objective of the study was to obtain preliminary evidence of efficacy of BKM120 combined with GSK1120212. A number of patients received clinical benefit for a prolonged duration mainly in ovarian cancer patients with one complete response and five partial responses.
- The ORR for ovarian patients was 28.6%. The DCR in the ovarian cancer group was 76.2%. The ORR in NSCLC patient population was 5.9%. The DCR was 58.8%. No responders were observed among the pancreatic cancer patients. The DCR was 50%.
- PFS was much longer in ovarian cancer patients (218 days) than the NSCLC patients (118 days) and the pancreatic cancer patients (71 days) with an estimated PFS rate of 63% at 6 months for the ovarian cancer patients. The same pattern was seen for overall survival. The combination of BKM120 + GSK1120212 showed preliminary evidence of activity in patients with ovarian cancer in particular, most of whom were heavily pretreated.
- Pharmacokinetic analysis showed that the exposure of BKM120 was lower than in the FIM study [CBKM120X2101] (approximately 43% decrease at RP2D and 25% decrease at MTD), however the underlying phenomenon for this lower exposure is unknown. Exposure of GSK1120212 appeared to be increased (approximately 17% increase at RP2D and 40% increase at MTD) in the combination compared with the 2 mg dose in the FIM study, while no major change in its maximum concentration was observed. (GSK1120212 IB Version 6). Accumulation factors did not appear to have changed significantly from known values. Accumulation of trametinib is highly variable making it difficult to establish if this increased exposure is due to a potential interaction with buparlisib.
- After the final database lock, six deaths (28.6%) were reported in the 21 ovarian cancer patients and the median OS was 796 days (95% CI: 708, NA) with an OS rate at of 87.5% (95% CI: 71.3, 100.0) at 6 months.
- Of the biomarkers investigated, p-S6 and p-ERK provided a preliminary indication of the impact of MAPK and PI3K pathways in the patients.
- Overall, the safety profile of the combination of BKM120 and GSK1120212 observed in this study is acceptable and manageable.

Date of Clinical Trial Report

29-Jun-2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

12-Jul-2015

Date of Latest Update

Reason for Update