A PHASE I TRIAL OF IRINOTECAN (IRI) AND BKM120 IN PREVIOUSLY TREATED PATIENTS (PTS) WITH METASTIC COLORECTAL CANCER (MCRC)

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Abstract

Background BKM120 is an oral pan-class PI3K inhibitor. The published results of a phase I trial of single agent BKM120 showed that BKM120 was well-tolerated and safe with favorable PK profile and promising anti-tumor effect. Irinotecan is one of the most active agents in the treatment of advanced colorectal cancer.
Methods The primary objective of this phase I trial is to identify the maximum tolerated dose (MTD) for Irinotecan and BKM120 combination in previously treated mCRC. The secondary objectives are to characterize the PK of Iri with or without BKM120 as well as PK of BKM120 when administered with Iri, to determine clinical response to the combination, and to correlate the expression of biomarkers associated with PI3K signaling pathway with clinical response to the combination of Iri plus BKM120. A traditional 3 + 3 dosing scheme is used for dose escalation. Iri is given intravenously every 14 days and BKM daily. Iri starts on cycle 1 day 1 while BKM120 starts after 24 hours after the first dose of Iri to allow us to monitor the PK of Iri both in the absence and presence of BKM120. The patients are assessed for safety and toxicities every cycle (q14 days).
Results Thirteen pts have been enrolled: 8 were evaluable for toxicity: 3 in cohort 0 (Iri 120 mg/m2 + BKM120 50 mg/d) and 5 in cohort 1 (Iri 150 mg/m2 + BKM 120 50 mg/d). The most common drug related adverse events were nausea and vomiting, abdominal pain, fatigue, depression, dizziness, diarrhea, and anorexia. The most common laboratory abnormalities seen were hyperglycemia, hypokalemia, and elevations in transaminases. One dose limiting toxicity (DLT), genital mucositis, was observed in a male pt in Cohort 1. The MTD has not been reached. Five pts completed 4 cycles of therapy and had tumor assessment: 1 had progressive disease, 3 had stable disease, and 1 had minimal response. The cycle 1 vs cycle 2 PK for cohort 0 (Iri 120 mg/m^2 and BKM120 50 mg) showed no significant effects of BKM120 co-administration on the disposition of Iri. In Cohort 1 (Iri 150mg/m^2 and BKM120 50mg), 5 of the 6 pts showed no significant effects of BKM120 co-administration on the disposition of Iri. The BKM120 PKs as well as the molecular correlates will be presented in future meetings. The trial is actively accruing patients.
Conclusion This is the first human trial of the combination of Iri and BKM120. No significant toxicities have been observed and the PK of Iri does not seem to be affected by BKM120. These preliminary data support continuing the effort to find the MTD for the combination of Iri and BKM120 for use in phase II trials and to identify potential biomarkers of response and toxicities.

Introduction

MCRC, a definite area of need for novel therapy

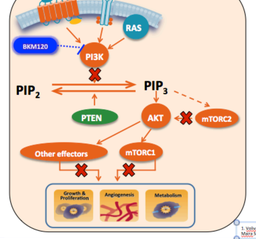
•ATP competitive, highly specific inhibition of class I PI3K

•Antiproliferative activity in tumor cell lines (GI_{50} 158–1010 nM)

•Pro-apoptotic activity in PIK3CA-mutated breast cancer cell lines

•Potent anti-tumor activity in tumor xenograft models with or without PI3K/PTEN mutations

BKM120 and the PI3K Pathway



BKM120
- Potent oral pan-class I PI3K inhibitor that selectively inhibits all four class I PI3K isoforms (α,β,γ,δ) [1,2]

1. Vallon C, et al. AACR 2010:4498 (abstract); 2. Maira M, et al. AACR 2010:4497 (abstract); 3. Maira SM, et al. Mol Cancer Ther 2008;7:1851–1863

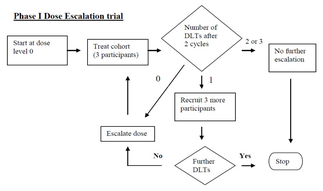
Objectives

- Primary:
  - To identify MTD for Irinotecan and BKM120 used in combination in the treatment of MCRC

Secondary:
- To characterize the PK of BKM120 when administered with Irinotecan.
- To characterize the PK of Irinotecan with and without BKM120.
- To determine the clinical response.
- To correlate the expression of biomarkers associated with the PI3K signaling pathway with clinical response.

Study schema

FIGURE 1: STUDY SCHEMA



Treatment Cohorts

Dose-Escalation Schedule
1 cycle = 14 days

	Cohort	Irinotecan (mg/m^2)IV q2wks	BKM120 (mg) Po daily
	-1	100	50
Starting Dose →	0	120	50
	+1	150	50
	+2	150	80
	+3	150	100
	+4	180	100

Eligibility

Inclusion:
- Histologically confirmed previously treated MCRC
- Previous exposure to Irinotecan allowed
- ECOG 0-2
- Adequate hematologic, hepatobiliary, renal function
- Measurable and non-measurable disease

Exclusion:
- Treatment with drugs known to be moderate and strong inhibitors or enhancers if CYP3A
- Pts with significant mood disorders
- Fasting plasma glucose of ≤120 mg/dl
- History of or active major mood or psych disorders or meets cut-off score for mood assessment questionnaire.

DLT definitions

Standard hematologic and non-hematologic AEs

Protocol-specific DLTs
- ≥Grade 2 pancreatitis
- ≥1 Grade level increase in neurotoxicity
- ≥Grade 2 phototoxicity or skin rash (associated with pain, desquamation, exfoliation) necessitating interruption of BKM120 for >21 consecutive days
- Grade 2 hyperglycemia (FPG 200–249 mg/dL [11.1–13.8 mmol/L]) that does not resolve to Grade 0 within 14 consecutive days of oral antidiabetics[a]
- ≥Grade 3 hyperglycemia
- Grade 2 mood alteration that does not resolve to ≤ Grade 1 within 14 days despite medical treatment (for anxiety only, if worsened from baseline)[b]
- ≥Grade 3 mood alterations

Patient characteristics

Pt#	Age	Sex	ECOG PS	# prev tx	Sites of disease
1	68	M	1	1	Liver, lung
2	60	M	1	2	Liver, lung, peritoneum
3	69	F	1	3	Liver, lung
4	58	M	1	3	Liver, lung, peritoneum, others
5	63	M	0	3	Liver, lung
6	58	M	1	3	Liver, lung, peritoneum, others
7	42	F	1	2	Lung
8	38	M	0	3	Liver, lung, peritoneum
9	47	M	1	3	Liver, lung, others
10	45	F	1	2	Liver, lung, others
11	80	M	1	5	Liver, lung, others
12	44	M	1	6	Liver, lung, others
13	56	F	1	3	Liver, lung

Irinotecan pharmacokinetics, SN-38 and SN-38 Glucuronide

Irinotecan

Dose		Cmax, ng/mL	AUC, hr*ng/mL	T ½, hr
120 mg/m^2	Cycle 1	1402 ± 149	7053 ± 431	6.7 ± 0.8
	Cycle 2	1423 ± 171	7252 ± 290	6.7 ± 1.3
(n=3)	Ratio (Cycle 2/Cycle 1)	1.03 ± 0.23	1.03 ± 0.08	0.99 ± 0.12
150 mg/m^2	Cycle 1	1861 ± 233	10100 ± 2234	6.7 ± 0.9
	Cycle 2	2018 ± 388	12789 ± 6097	6.1 ± 0.8
(n=6)	Ratio (Cycle 2/Cycle 1)	1.10 ± 0.21	1.15 ± 0.45	0.89 ± 0.12

SN-38

Dose		Cmax, ng/mL	AUC, hr*ng/mL	T ½, hr
120 mg/m^2	Cycle 1	29.9 ± 9.4	441 ± 71	13.0 ± 0.19
	Cycle 2	27.5 ± 7.5	604 ± 410	15.7 ± 4.4
(n=3)	Ratio (Cycle 2/Cycle 1)	0.93 ± 0.12	1.05 ± 0.15	1.26 ± 0.56
150 mg/m^2	Cycle 1	42.0 ± 12.2	7053 ± 431	20. ± 14.
	Cycle 2	54.8 ± 27.3	7252 ± 290	16 ± 7
(n=6)	Ratio (Cycle 2/Cycle 1)	1.30 ± 0.41	1.33 ± 0.66	0.95 ± 0.27

SN-38 Glucuronide

Dose		Cmax, ng/mL	AUC, hr*ng/mL	T ½, hr
120 mg/m^2	Cycle 1	101 ± 46	1105 ± 438	11.7 ± 2.7
	Cycle 2	90 ± 34	1017 ± 372	13.9 ± 6.1
(n=3)	Ratio (Cycle 2/Cycle 1)	0.92 ± 0.13	0.94 ± 0.10	1.16 ± 0.31
150 mg/m^2	Cycle 1	135 ± 66	1859 ± 624	13.9 ± 1.5
	Cycle 2	116 ± 46	2164 ± 1300	13.1 ± 2.8
(n=6)	Ratio (Cycle 2/Cycle 1)	0.93 ± 0.16	1.37 ± 0.90	0.94 ± 0.22

Individual plasma concentration versus time profiles for Irinotecan, SN-38, and SN-38 glucuronide for the 150 mg/m^2 cohort. The plots in red are for patient 8, who exhibited very high drug concentrations in Cycle 2. The green line represents the mean of plasma concentrations from all eight patients at each time point.

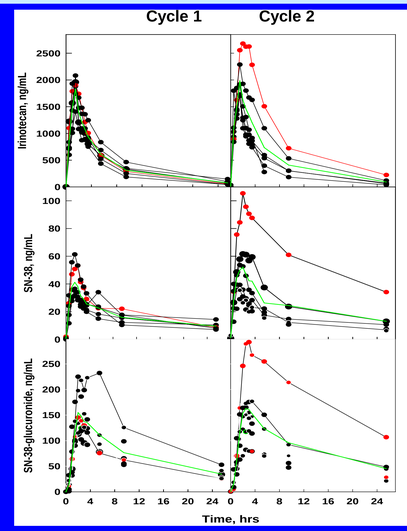
No significant effects of BKM120 co-administration (50 mg p.o.) on the disposition of Irinotecan (120 mg/m^2 infusion)

5 of 6 patients at the 150 mg/m^2 irinotecan dose showed no significant effects of BKM120 co- administration (50 mg p.o.) on the disposition of Irinotecan

One patient at the 150 mg/m^2 irinotecan dose showed markedly higher Cmax and AUC, but no change in t ½, when BKM120 was co-administered.

Overall conclusions— BKM120 had no consistent, significant effect on the disposition of irinotecan. The dramatically different results with one patient cannot be explained.

Cohort 1



Clinical response

Pts evaluable for response	5
Minimal response	1
Stable disease	3
Progressive disease	1

Toxicity evaluation

DLT in Cohort 1: Genital mucositis.

	All n= 13		Cohort 0 n= 4		Cohort 1 n=9	
Aes (Lab)	All	G3/4	All	G3/4	All	G3/4
Hyperglycemia	4	0	0	0	4	0
Hypokalemia	4	0	2	0	2	0
Elevated AST	4	1	0	0	3	1
Hyponatremia	4	0	0	0	4	0
Elevated ALT	3	0	0	0	3	0
Elevated bilirubin	2	0	0	0	2	0
Hypocalcemia	2	0	1	0	1	0
Decreased WBC	2	0	0	0	2	0
Elevated triglycerides	2	0	1	0	1	0
Decreased albumin	2	0	0	0	2	0
Elevated creatinine	2	0	2	0	0	0

	All n= 13		Cohort 0 n= 4		Cohort 1 n=9	
AEs	All	G3/4	All	G3/4	All	G3/4
Nausea	11	0	2	0	9	0
Vomiting	9	0	4	0	5	0
Abdominal pain	8	0	3	0	5	0
Fatigue	6	0	2	0	4	0
Depression	5	0	2	0	3	0
Dizziness	5	0	1	0	4	0
Diarrhea	4	0	1	0	3	0
Anorexia	4	0	1	0	3	0
Fever	3	0	0	0	3	0
Mucositis, oral	3	0	0	0	3	0

Summary

- The combination of BKM120 at 50 mg and Irinotecan at 120mg/m^2 and at 150 mg/m^2 appear to be tolerable.
  - The most common adverse effects observed are nausea and vomiting, abdominal pain, fatigue, depression and dizziness.
- The MTD has not been reached yet.
- One DLT was seen in cohort 1 in a pt who was off BKM120 for more than 7 days 2^0 to genital mucositis.
- BKM120 at 50 mg had no consistent, significant effect on the disposition of irinotecan given at both doses of 120mg/m^2 and 150 mg/m^2.
- Of the 5 patients whose disease were evaluable, 3 had stable disease nad 1 had minimal response.

Conclusions

- This is the first human trial of the combination of Irinotecan and BKM120.
- At the present dose levels, the combination of Irinotecan and BKM120 appears to be tolerable.
- The PK of Irinotecan does not seem to be affected by BKM120.
- It is early to discern activity of this combination in the treatment of MCRC.
- These preliminary data support continuing the effort to find the MTD for the combination of Irinotecan and BKM120 for use in phase II trials and to identify potential biomarkers of response and toxicities.

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