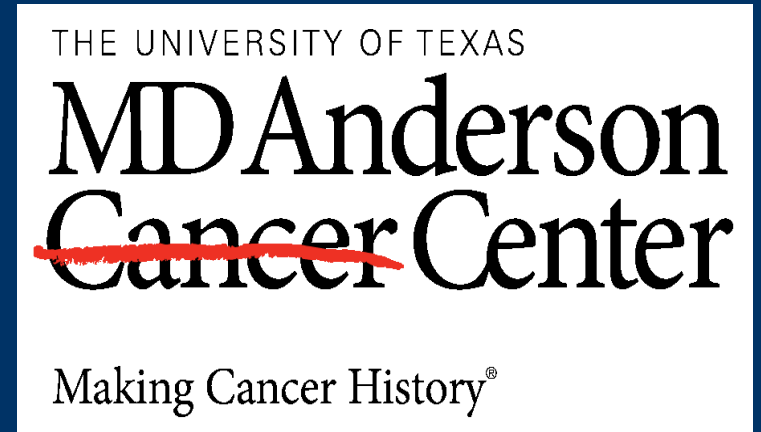


Safety, Pharmacokinetics, and Efficacy of BP-100.1.01 (Liposomal Grb-2 Antisense Oligonucleotide) in Patients with Refractory or Relapsed Acute Myeloid Leukemia (AML), Philadelphia Chromosome Positive Chronic Myelogenous Leukemia (CML), Acute Lymphoblastic Leukemia (ALL), and Myelodysplastic Syndrome (MDS)

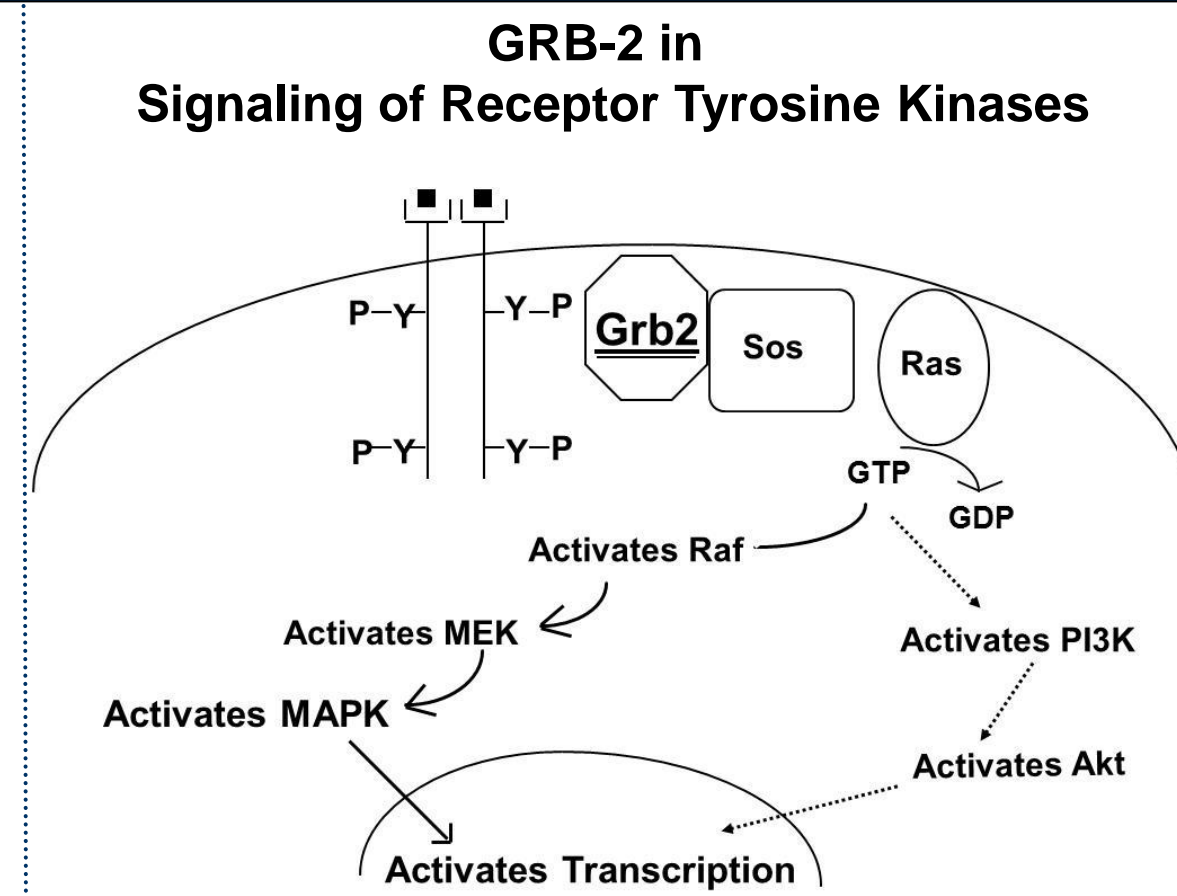
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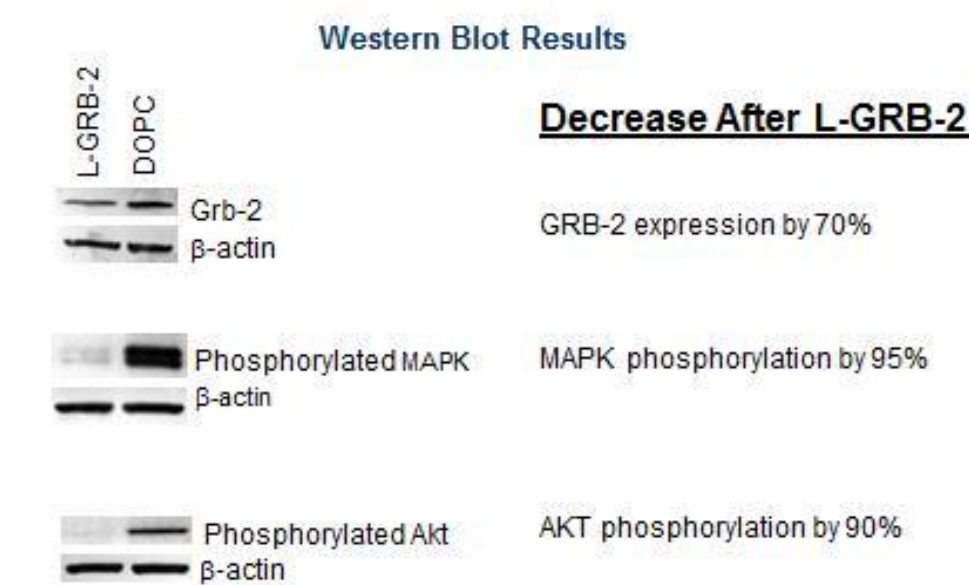


Abstract

The adaptor protein Growth Receptor Bound protein-2 (Grb-2) is essential to cancer cell signaling. Suppressing the function or expression of Grb2 should interrupt its vital signaling function and have a therapeutic application in cancer. BP-100.1.01 is a neutral-charge, liposome-incorporated antisense drug substance designed to inhibit Grb-2 expression. BP-100.1.01 is systemically delivered by I.V. injection. To define the safety, maximum tolerated dose, optimal biologically active dose, pharmacokinetics and anti-leukemia activity of BP-100.1.01 in patients with hematologic malignancies. This clinical trial is a standard 3+3 dose-finding study in patients with refractory or relapsed AML, CML, ALL and MDS. A total of 13 patients have been included, all of them in the first cohort. One patient (the first patient on study) experienced grade 3 mucositis and hand-foot syndrome. Two patients had transient improvement and/or stable disease. In addition, 2 patients had transient improvement in leukemia cutis lesions. Preliminary results suggest that BP-100.1.01, at a dose of 5mg/m² is well tolerated and there is suggestion of some possible anti-leukemia activity. The study continues accruing and Cohort 2 is open with dosing at 10 mg/m².



Liposomal GRB-2 Decreased Expression of Target Proteins *In Vivo*



Summary BP-100-1.01 *In Vivo* Toxicity Studies in Mice

Study	N*	Doses	Regimen	Results
Single Dose Toxicity	10	0, 15, 20, 30 or 40 mg/kg	Single dose	No hepatic or renal function toxicity No effect upon production of RBC, hemoglobin, hematocrit or platelets
Multiple Dose Toxicity	8	0, 15 or 25 mg/kg/day 0, 75 or 125 mg/kg total Dose	Daily dose x 5 days	No hepatic or renal function Toxicity No effect upon production of RBC, hemoglobin, hematocrit or platelets WBC reduced

* N= number of mice per group

Phase I Clinical Trial of BP-100-1.01

Objectives - Primary

- To determine the toxicity and tolerance of escalating doses of BP-100-1.01.
- To determine the maximum tolerated dose (MTD) of BP-100-1.01.

Objectives - Secondary

- To determine the optimal biologically active dose (OBAD), defined as a 50% reduction in Grb-2 expression in circulating leukemia cells (flow cytometry)
- To determine the in vivo pharmacokinetics of BP-100-1.01.
- To evaluate tumor response.
- To assess the pharmacokinetic data to correlate to the historical experience in order to demonstrate the liposomal delivery vehicle performs as expected.

Inclusion Criteria

- Age ≥ 18 years
- Refractory or relapsed acute myeloid leukemia, or Ph+ CML (chronic, accelerated or blast phase), or acute lymphoblastic leukemia, or myelodysplastic syndrome
- Patients with CML must have demonstrated resistance and/or intolerance to therapy with at least 2 tyrosine kinase inhibitors (TKI)
- AML and Ph+ ALL should have received at least one prior treatment regimen and either failed to achieve response or relapsed on treatment
- MDS patients should have failed prior therapy with a hypomethylating agent or lenalidomide if associated with a 5q-abnormality. Patients with 5q- unable to receive or intolerant to lenalidomide are also eligible
- patients must have clinically adequate hepatic and renal functions: ALT<2x ULN; Serum creatinine <2x ULN; Serum bilirubin <2x ULN
- Women of childbearing age must have a negative serum or urine pregnancy test prior to the initiation of study drug
- Patients must be off anti-cancer therapy for at least two weeks prior to study entry, with the exception of hydroxyurea or anagrelide (24 hours), TKI (5 days), and interferon (two weeks)
- ECOG Performance of 0-2

Exclusion Criteria

- Serious intercurrent medical illnesses, which would interfere with the ability of the patient to carry out the treatment program
- Pregnant or breastfeeding women
- Patients who have uncontrolled active infection
- Patients who have received another Investigational product within the longer of 14 days or 5 half-lives of the previous product

Treatment Schedule

BP-100-1.01, 5 mg/m², administered twice weekly for 28 days (first Cohort – 6 evaluable patients)

Study Design

- Phase I Dose Finding Study – traditional 3+3 design.
- Three patients to be dosed at initial dose (5 mg/m²).
- If no DLT observed, open Cohort 2.
- In the event of a DLT (defined as a treatment-related adverse event of Grade III or higher), the cohort is to be opened to three additional patients.
- If no additional DLT – Open Cohort 2 (10 mg/m²), potentially increasing in later cohorts to 20 mg/m², 40 mg/m² and 50 mg/m² in Cohort 5.

Patient Characteristics

Characteristic	Medium	Range
Total subjects treated	16	
Age	58	25 - 85
Gender - Male Female	11 5	
Number of prior regimens	5	1 - 9
Diagnosis at study entry AML CML (blast phase) MDS	9 5 2	
Performance status	2	0 - 2
WBC (1000/ml)	3.85	0.2 - 44.9
Blasts – PB (%)	54	19 - 97
HGB (g/ml)	9.0	7.5 - 10.3
Pt (Million/ml)	14.5	5 - 66
Screening Bone Marrow Cytogenetics (4 = ND) Philadelphia+ Other Cyto Abn	6 5*	

* 3 had no abnormal finding
Other - 9 of 16 treated patients failed to reach one full cycle of treatment due to disease progression and were deemed inevaluable per the protocol

Evaluable Patients to Date

Characteristic	Medium	Range
Evaluable patients to date Cohort 1 (completed) Cohort 2	6 1	
Age	55	38 - 85
Gender - Male Female	7 0	
Number of prior regimens	4	1 - 7
Diagnosis at study entry AML CML (blast phase) MDS	4 2 1	
Performance status	2	1 - 2
WBC (x10 ⁹ /L)	5.2	0.5 - 13.9
Blasts – PB (%)	48	7 - 93
HGB (g/dL)	9.0	7.5 - 9.6
Platelets (x10 ⁹ /L)	23	6 - 59
Screening Bone Marrow Cytogenetics (4 = ND) Philadelphia+ Other Cyto Abn	2 0*	

* 3 had no abnormal finding

Hematologic Experience in Evaluable Patients

Subject Number	Diagnosis	Peripheral Blood Blast Percentage*			Reason Discontinued	# Cycles Completed
		Baseline	Nadir	Off-Tx		
001	CML	93	82	97	DLT	0
006	AML	15	4	9	Disease Progression	5
007	MDS	8*	4*	6*	Disease Progression	5
010	AML	23*	10*	10*	Disease Progression	1
011	CML	24	7	50	Disease Progression	1
014	AML	33	14	21	Disease Progression	1
015	AML	54	31	71	Disease Progression	1

* For subjects 007 & 010: No circulating blasts. These numbers represent Bone Marrow Blast percentages.

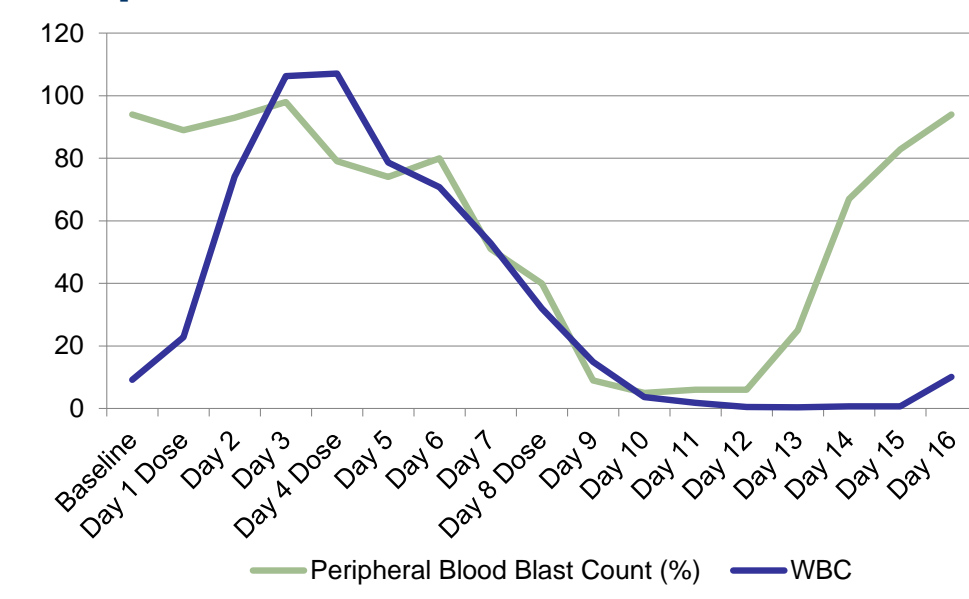
Adverse Events in Evaluable Patients

- Possibly Related to Study Drug.
- One patient (the first patient on study) experienced grade 3 mucositis and hand-foot syndrome. This patient had a history of mucositis on prior exposure to hydroxyurea. The Investigator was not able to rule out study medication as a contributing factor, and so this event was reported as Dose-Limiting Toxicity (DLT)
- The cohort was expanded to a total of 6 patients.
- No other drug related toxicities were noted in any of the patients treated.

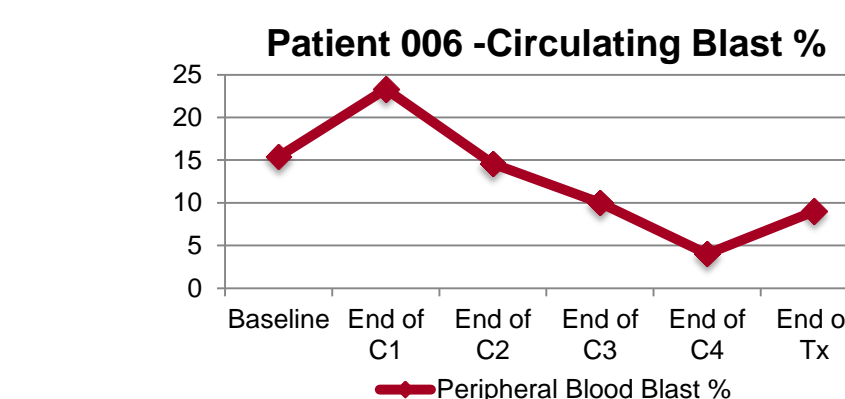
Experience in Patient 002

- 32 year-old, Hispanic male with myeloid blast crisis of CML with T315I when screened for this protocol.
- Prior therapies consist of:
 - Gleevec
 - Dasatinib
 - Nilotinib
 - DCC-2036
 - Cytarabine/Fludarabine/Dasatinib/Gemtuzumab PHA-739358
 - Clofarabine/Dasatinib
- Informed consent signed on July 22nd, 2010, dosed with BP-100-1.01 on July 27th, July 30th, and August 3rd, 2010.
- CNS disease was assumed (not confirmed) and intrathecal Ara-C was administered August 3rd, 2010.
- Began a 14 day washout from the Ara-C, after which he was to restart study medication.
- Prior to restart - patient succumbed to progressive disease on August 13th, 2010.
- Although this patient was not evaluable for DLT (discontinued therapy before end of cycle 1 without experiencing any toxicity), his peripheral blast percentage and lymphocyte counts did reveal an interesting temporal relationship to the limited dosing he received.

Experience in Patient 002 – cont.



Extended Treatment - Patient 006



Conclusions

- Preliminary results suggest that BP-100.1.01, at a dose of 5mg/m² is well tolerated and there is suggestion of some possible anti-leukemia activity.
- The study continues accruing and Cohort 2 is open with dosing at 10 mg/m².
- Of the evaluable patients, all showed a transient drop in circulating or bone marrow blast percentage. Patients 006 & 007 experienced transient improvement and/or stable disease and received a total of 5 cycles each. In addition, 2 patients have had transient improvement in leukemia cutis lesions.
- This has been a review of the first Cohort of patients treated in a Dose-Finding study. Note that the dose administered is expected to be below the Optimal Biological Dose (OBD).
- As the study progresses it is anticipated that clearer signs of activity will be noted. The study is currently recruiting into the second Cohort (10 mg/m²) with one patient evaluable, two others who were treated but progressed prior to a complete cycle, and one patient currently on study. No additional drug-related Adverse Events have been noted in these patients.

References

1. Tari AM et al. Liposome-incorporated Grb-2 antisense oligodeoxynucleotide increases the survival of mice bearing bcr-abl-positive leukemia xenografts.

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Disclosures

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