An open-label, dose escalation, multi-center phase 1 study of PRLX 93936, an agent synthetically active against the activated Ras pathway, in the treatment of relapsed or relapsed and refractory multiple myeloma

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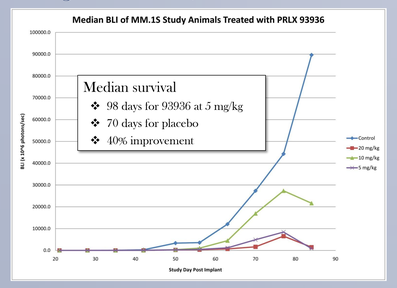
Introduction

Overall survival for patients with multiple myeloma (MM) has improved, but most patients relapse and eventually succumb to complications of the disease. The development of new therapeutic agents to treat relapsed and relapsed/refractory MM is therefore vital. Proteins of the Ras family are frequently mutated in MM and are associated with reduced responsiveness to therapy and inferior long-term outcomes.[1-4] However, direct, selective, potent inhibitors of mutant Ras proteins are not clinically available. Extensive efforts have been made to identify agents which are synthetically active against the activated Ras pathway that may not inhibit the Ras protein itself, but target other molecules selectively important for cells harboring Ras mutations. **PRLX 93936, 3-(2-ethoxyphenyl)-2-[(1-piperazinyl) methyl]-4(3H)-quinazolinone, is an analog of such a synthetically active compound against the activated Ras pathway.**

PRLX 93936 has demonstrated promising efficacy in preclinical laboratory studies and mouse models of MM with an improvement in survival and 30% suppression in tumor growth at the lowest tested dose. Notably, activity was observed at the 5 mg/kg dose (the equivalent of 15 mg/m^2 in humans).



Objectives & Methods

A phase 1, multi-center, open-label, dose escalation trial was conducted to determine the maximum tolerated dose (MTD), assess toxicities, and evaluate response to treatment with PRLX 93936 alone and in combination with dexamethasone for patients (Pts) with relapsed or relapsed/refractory MM. Pts with relapsed or relapsed/refractory MM previously treated with at least two prior anti-myeloma regimens (including a proteasome inhibitor and/or immunomodulatory drug) were eligible. Pts were allowed to participate regardless of Ras mutational status.

PRLX 93936 as a single agent was given intravenously on days 1, 3, 5, 8, 10, 12, 15, 17 and 19 of a 28-day treatment cycle (3 days/week for 3 weeks followed by a 9 day rest period). Sequential cohorts of at least three Pts were treated with escalating doses of PRLX 93936 beginning at 10 mg/m^2, and the dose was increased in increments of 5 mg/m^2 until the MTD was established. Pts received a minimum of 2 cycles of treatment at their assigned dose level for evaluation of anti-myeloma activity of PRLX 93936 and could receive up to 8 cycles followed by an option of maintenance therapy. Dexamethasone at a dose of 20 mg provided on each day of PRLX 93936 infusion could be added at the investigator's discretion after a minimum of 2 cycles or after cycle 1 for patients with progressive disease.

Patient Population & Treatment

Baseline Demographics

- 14 total patients enrolled (4 women, 10 men)
- 13 patients completed therapy
- Median age was 61 years (range, 48-81)
- Patients were 76.9% White, 15.2% Black/African American, and 7.7% Asian

Baseline Disease Characteristics

- Median time between diagnosis and first infusion of PRLX 93936 was 6.8 years (range, 1.9-13.1)
- ISS Stage of Disease at Baseline (n=10, unk 3 Pts):

	# Patients	% Patients
ISS Stage 1	4 Pts	40.0%
ISS Stage 2	4 Pts	40.0%
ISS Stage 3	2 Pts	20.0%

- Median lines of therapy prior to enrollment: 4 (range, 2-9)
- Prior Therapies (n=13):

	# Patients	% Patients
Stem Cell Transplant	6 Pts	46.2%
Dexamethasone	13 Pts	100.0%
Bortezomib	12 Pts	92.3%
Lenalidomide	11 Pts	84.6%
Carfilzomib	3 Pts	23.1%
Pomalidomide	3 Pts	23.1%
Alkylating Agents	10 Pts	76.9%

- Relapsed vs. Relapsed/Refractory Disease (n=13):

	# Patients	% Patients
Relapsed/Refractory	12 Pts	92.3%
Relapsed	1 Pt	7.7%

- High LDH vs. Normal LDH at study entry (n=13):

	# Patients	% Patients
High LDH	5 Pts	38.5%
Normal LDH	8 Pts	53.8%

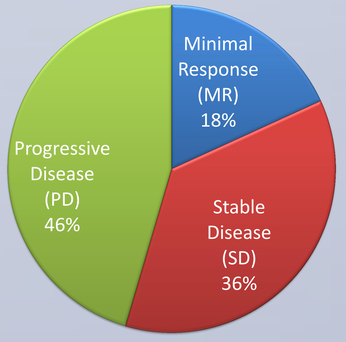
Treatment with PRLX 93936

- 11 of 13 patients who completed treatment completed at least one full 28-day cycle (range, 1-15)
  - 3 Pts at the 10 mg/m^2 dose
  - 3 Pts at the 15 mg/m^2 dose
  - 5 Pts at the 20 mg/m^2 dose
  - 2 Pts at the 25 mg/m^2 dose
- 2 of 13 patients did not complete a full cycle
- Treatment for one patient is still ongoing

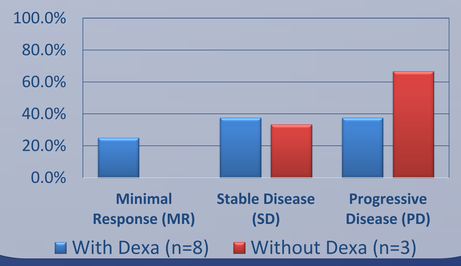
Results

Response Data

- Response was assessed per the International Myeloma Working Group uniform response criteria, incorporating the modified EBMT response criteria for MR
- Best Responses among 11 evaluable patients:
  - Minimal Response (MR) = 2 Pts
  - Stable Disease (SD) = 4 Pts
  - Progressive Disease (PD) = 5 Pts



- Analysis of the impact of dexamethasone addition is on-going. No significant additive toxicity has been seen and responses appeared improved as below.
- Prior to the study, all pts were exposed or refractory to dexamethasone. During this trial, use of dexamethasone given in conjunction with PRLX 93936 was at the investigator's discretion, and directed by absence of response to monotherapy alone.
- 61.5% of pts (8 of 13) received dexamethasone in conjunction with PRLX 93936 during the course of the study
- Among 11 evaluable pts, Best Response of pts who received dexamethasone with PRLX 93936 was compared to Best Response of those who did not receive dexamethasone with PRLX 93936:



Results (cont'd)

AE Profile

- Adverse events were assessed with each cycle according to version 4.0 of the CTCAE.
- 7 of 13 pts who completed therapy experienced at least one serious adverse event (SAE)
  - Most frequently reported SAEs (2 each) included sepsis and cellulitis
  - Four SAEs were considered related to PRLX 93936 by the investigator (thrombocytopenia, neutropenia, nausea, and vomiting)

Determination of MTD

- Dose limiting toxicities were seen in two Pts, both at 25mg/m^2 and included: nausea, vomiting, and neutropenia (both pts) and thrombocytopenia, weakness, elevated AST, & elevated creatinine (1 patient)
- The 20mg/m^2 dose was expanded with no additional dose limiting toxicities observed
- MTD was determined to be 20mg/m^2

Conclusions

PRLX 93936, a synthetically active compound against the activated Ras pathway, demonstrated activity in combination with low dose dexamethasone in Pts with heavily pre-treated, relapsed and refractory MM, with MRs seen in 18% of Pts to date. Toxicity has proven manageable and the MTD has been defined at 20 mg/m^2. Correlative studies evaluating the impact of PRLX 93936 on the Ras pathway are on-going.

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Disclosures

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