Results of a Phase I/II Trial of Pixantrone (BBR 2778) in Combination with Fludarabine, Dexamethasone and Rituximab ('FPD-R') in the Treatment of Patients with Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma (NHL)

L. Fayad [1], J. Liebmann [2], M. Modiano [3], G. I. Cohen [4], B. Pro [1], J. Romaguera [1], S. Stromatt [5]

[1] MD Anderson Cancer Center, Houston, TX; [2] New Mexico Oncology, Albuquerque, NM; [3] Arizona Clinical Research Center, Tucson, AZ; [4] Greater Baltimore Medical Center, Baltimore, MD; [5] Cell Therapeutics, Inc., Seattle, WA, U.S.

INTRODUCTION

- The fludarabine-mitoxantrone-dexamethasone-rituximab (FND-R) regimen has significant activity in patients with untreated and relapsed indolent B cell lymphoma.
- Pixantrone (BBR 2778) is a novel aza-anthracenedione with substantially less delayed cardiotoxicity than doxorubicin or mitoxantrone in animal models.
- Pixantrone has superior activity against murine lymphoma and leukemia in in vivo models when compared with doxorubicin or mitoxantrone.
- The current study substituted pixantrone for mitoxantrone in the combination therapy FND-R (FPD-R).
- Patients with indolent NHL and patients with aggressive NHL have responded to treatment with pixantrone.
  - Indolent relapsed/refractory NHL: pixantrone + rituximab vs. rituximab[1]
    - Time to tumor progression (TTP) pixantrone + rituximab: 395 days
    - TTP, rituximab: 245 days (log rank p-value < 0.001)
    - Overall response rate (ORR), pixantrone + rituximab: 75%, CR 35%
    - ORR, rituximab: 33%, CR 11%
  - Aggressive NHL: CPOP - cyclophosphamide, pixantrone, vincristine, and prednisone (P. Borchmann et al. ASH Annual Meeting 2006, #529, Session: Follicular Lymphoma, Dec 11, 2006, 1:30 pm)
    - ORR 77%
    - Median duration of response: 10.2 mo., 95% confidence interval: 6.7-23 mo.

OBJECTIVES

- To determine the recommended dose (RD) of pixantrone when substituting for mitoxantrone in the FND-R regimen ('FPD-R')
- To evaluate the safety and efficacy of this regimen in patients with relapsed or refractory indolent NHL

STUDY DESIGN

- Multicenter, open-label study
- Up to 8 cycles, or until disease progression, toxicity or withdrawal of consent
- Cardiac scan (MUGA) every two cycles
- Responses evaluated using Cheson criteria
- Objective response assessed every two cycles

Study Treatment Schedule

Drug	Dose	Day(s)*	Infusion Time
Pixantrone	80** - 120 mg/m^2	2	1 hour
Fludarabine	25 mg/m^2	2 - 4	30 minutes
Dexamethasone	20 mg/day	1 - 5	Oral administration
Rituximab	375 mg/m^2/day	1	Slow infusion

* 28 day cycles; **First 3 pts enrolled.

PATIENT CHARACTERISTICS

Patients enrolled / safety / efficacy evaluable*	29 / 28 / 27
Age in years, median (range)	63 (32-78)
Male / Female	15 /14
WHO Performance Status 0 / 1	15 / 14
Prior Therapies	
Pts with prior therapy	29
Pts with prior rituximab	14
Pts with prior chemotherapy	26
Pts with prior fludarabine	4
Pts with prior anthracycline therapy	20
Median (range) cumulative dose anthracycline, mg	488 (243 – 837)
Pathology	
Follicular center cell grade 1/2	18
Small lymphocytic	6
Lymphoplasmacytoid	1
Marginal zone	3
Diffuse large B cell (protocol violation)	1

*1patient did not receive study drug
1patient had aggressive NHL (protocol violation)

Drug Administration

- Median number of cycles per patient (range) = 5 (1 – 8)
- At the 120 mg/m^2 dose level, a total of 108 cycles of study therapy were given.

Patient Eligibility

- Histologically confirmed relapsed or refractory indolent NHL, including:
  - Follicular center cell lymphoma grade I/II
  - Small lymphocytic lymphoma
  - Lymphoplasmacytoid lymphoma
  - Marginal zone (MALT, monocytoid B cell, splenic marginal zone)
- 1-3 prior treatment regimens
- WHO Performance Status of 0 or 1
- LVEF > 50% by MUGA scan
- Adequate bone marrow, renal and liver functions
- No prior fludarabine treatment within 12 months of treatment start
- No prior rituximab treatment unless there had been a CR or PR to treatment
- No radiotherapy or chemotherapy within 4 weeks of treatment start
- No radioimmunotherapy within 3 months of treatment start
- Cumulative dose of doxorubicin equivalent ≤ 450 mg/m^2
- No known Type I hypersensitivity or anaphylactic reactions to murine proteins

SAFETY

- No dose limiting toxicity reported in the 3 patients treated at 80 mg/m^2.
- Grade 4 neutropenia for 7+ days in 1 of the 6 initial patients at 120 mg/m^2. This dose level was assessed as the recommended dose in the FPD-R combination, without further escalation.

Treatment-related Grade 3 / 4 Adverse Events Occurring in ≥ 2 pts*

Event	Grade 3	Grade 4	Total (%)
Lymphopenia	25	0	25 (89%)
Leukopenia	14	8	22 (79%)
Neutropenia	12	11	23 (82%)
Thrombocytopenia	5	1	6 (21%)
Infection	6	0	6 (21%)
Febrile neutropenia	3	0	3 (11%)
Hypokalemia	3	0	3 (11%)
Abdominal pain	3	0	3 (11%)
Nausea	2	0	2 (7%)
Hyperglycemia	2	0	2 (7%)
Bronchitis	2	0	2 (7%)
Chest pain	2	0	2 (7%)
Back pain	2	0	2 (7%)

* Additional grade 3 events reported in 1 pt each were anemia, fatigue, dehydration, syncope, iritis, epistaxis, hyponatremia, night sweats, hypotension, sepsis, constipation, and small intestinal obstruction. No additional grade 4 events were reported.

Cardiac Safety

- A total of 7 of 28 (25%) patients evaluable for safety had a decline in LVEF ≥ 10% to ≤ 20%.
- In 4 patients the decline in LVEF was transient and returned toward baseline with continued follow-up.
- Five of the 7 patients with a decline in LVEF were asymptomatic.
- Two patients reported transient shortness of breath with spontaneous resolution without treatment. No episodes of CHF were reported.
- No pt had a decline in LVEF > 20 %.

TREATMENT RESPONSES

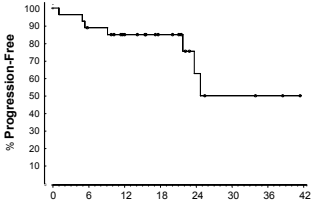
Overall Response Rate in Evaluable Population: 89%

Best Overall Tumor Response N = 27*		
Response**	**n**	**(%)**
Complete Response (CR)	17	63
CR Unconfirmed (CRu)	2	7
Partial Response (PR)	5	19
Overall Response (ORR)	24	89

*1 pt did not receive study drug; 1 pt had aggressive NHL (protocol violation)
**Response guidelines from an international workshop to standardize response criteria (Cheson criteria) for non-Hodgkin's lymphomas.

Time to Tumor Progression

Response Evaluable Population
N = 27



- Median duration of response: 25 months (Kaplan-Meier estimate)
- Range 2.4 to 43 months
- Five responders went on to BMT

- 1-year progression-free rate: 85%
- 2-year progression-free rate: 63%
- 3-year progression-free rate: 50.4%

SUMMARY and CONCLUSIONS

- The RD of pixantrone in the FPD-R regimen was 120 mg/m^2.
- The primary toxicity was hematologic; no serious cardiotoxicity was observed.
- This treatment is highly active and is associated with major, durable responses; the overall response rate was 89%.
- The regimen can be given on an outpatient basis and is generally well tolerated in relapsed and refractory indolent NHL patients.

Reference

1. A. Santoro, J. Voglova, N. Gabrail, T. Ciuleanu, M. Liberati, B. W. Hancock, S. Stromatt, and D. Caballero. Comparative trial of BBR 2778 (pixantrone) + rituximab vs single agent rituximab in the treatment of relapsed/refractory indolent non-Hodgkin's lymphoma (NHL). J Clin Oncol (Meeting Abstracts) 2006 24: 7578

Disclosure statement

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