Successful Phase II Trial Using Mesenchymal Stem Cells (MSC) in Combination with Steroids for the Primary Treatment of Acute Graft Versus Host Disease (aGVHD)

Partow Kebriaei, MD, BMT, MD Anderson Cancer Center, Houston, TX; Luis Isola, MD, Mount Sinai Hospital, NY, NY; Erkut Bahceci, MD, Yale Univ, New Haven, CT; H. Kent Holland, MD, Northside Hospital, Atlanta, GA; Scott Rowley, MD, Hackensack Univ, Hackensack, NJ; Joseph McGuirk, DO, Kansas City Cancer Center, Kansas City, MO; Marcel Devetten, MD, Univ of Nebraska Medical Center, Omaha, NE; Jan Jansen, MD, PhD, St Francis Hospital, Beech Grove, IN; Roger Herzig, MD, Univ of Louisville Hospital, Louisville, KY; Michael Schuster, MD, NY Presbyterian Hospital, NY, NY; Rod Monroy, PhD, Osiris Therapeutics, Inc., Baltimore, MD and Joseph Uberti, MD, PhD, Karmanos Cancer Institute, Detroit, MI.

Data was presented at the December 2006 American Society of Hematology meeting

Objective/Protocol

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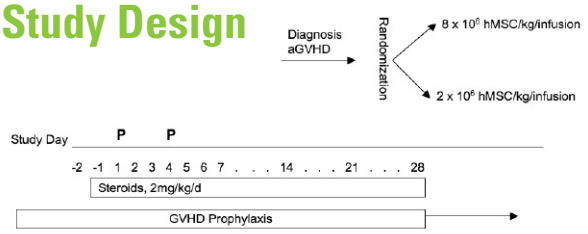
To evaluate the safety and efficacy of two dose levels of Prochymal™ as adjunctive therapy to steroids. Prochymal™ was administered on days 1 and 4 in subjects with newly diagnosed acute GVHD, grades II-IV, post hematopoietic stem cell transplantation (HSCT).

Endpoints

- **Primary:**
  - Response by day 28
- **Secondary:**
  - Improvement in GVHD:
    - one or more organs by day 28
  - Time to best response
  - Survival
  - Relapse

Study Design



- Prochymal (P) infused twice, days 1 and 4
- Dose: 2 x 10^6 or 8 x 10^6 hMSC/kg
- Prochymal added to steroid therapy
- GVHD prophylaxis continued
- Evaluated Prochymal from 4 different donors

Patient Characteristics

	High Dose	Low Dose
Sex (no.(%)		
Male	10	12
Female	5	5
Median Age, y, (range)	49 (34-67)	53 (42-67)
Disease, no.		
AML/MDS	8	6
NHL	2	3
CLL	1	3
ALL	3	1
MF	0	2
AA	0	1
MM	1	0
Hodgkins	0	1
Donor Matching		
MRD	9	10
MUD	6	7
Grade of GVHD		
II	9	12
III	5	3
IV	1	2

Patient Eligibility

Inclusion Criteria

- Age: 18 to 70 years
- Newly Diagnosed, Grade II-IV Acute GVHD
  - Biopsy: not required but recommended
- Subjects received HSCT (BM, PBSC, or CB) after myeloablative, reduced intensity, or nonmyeloablative conditioning. Subjects receiving a DLI were also eligible
- Adequate renal function: CrCl > 30mL/min

Exclusion Criteria

- Subject has been previously treated for grade II-IV aGVHD
- Subject has been treated with methylpredisolone (≥ 2 mg/kgld) for more than 72 hours before first Prochymal infusion.
- Subject has received a transplant for a solid tumor
- Subject has received an investigational agent within 30 days of randomization

Treatment Characteristics

	High Dose	Low Dose
Stem Cell Source		
BM	0	1
PBSC	15	16
Conditioning		
Myeloablative	8	7
Reduced Intensity	3	5
Nonmyeloablative	2	3
Chemo + PBSC	2	1
DLI	0	1
Onset GVHD median days (range)	37 (14-121)	31 (18-115)
GVHD Prophylaxis		
Cyclosporine	3	3
Cyclosporine+MTX	0	0
Cyclosporine+MMF	1	1
Tacrolimus	5	8
Tacrolimus+MMF	3	1
Tacrolimus+MTX	3	4

One patient withdrew consent from the study and was not evaluable. Only 31 patients are considered for the analysis.

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Results

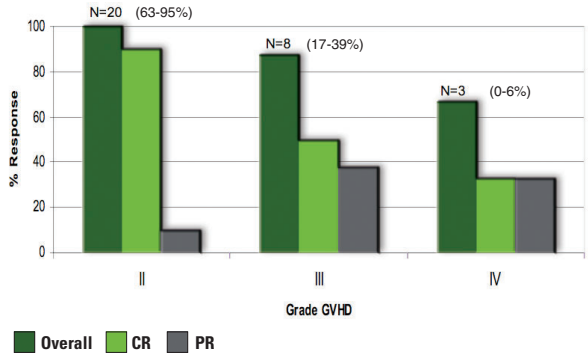
Response to Prochymal

Response Type	Number of Patients Responding (31 evaluable pts)	% Response
Overall Response	29	94
Complete Response	23	74
Partial Response	6	19
No Response	2	6

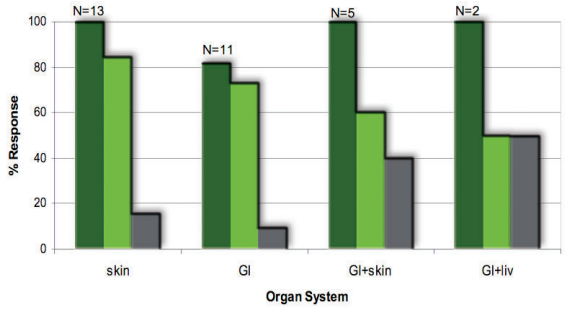
Comparison: High vs Low Dose and MRD vs MUD

	Overall Response %	Complete Response %	Partial Response %
High Dose N=16	100	66.7	33.3
MRD (9)	100	66.7	33.3
MUD (7)	100	66.7	33.3
Low Dose N=15	87.6	81.3	6.3
MRD (9)	88.9	77.8	11.1
MUD (6)	85.6	85.6	0

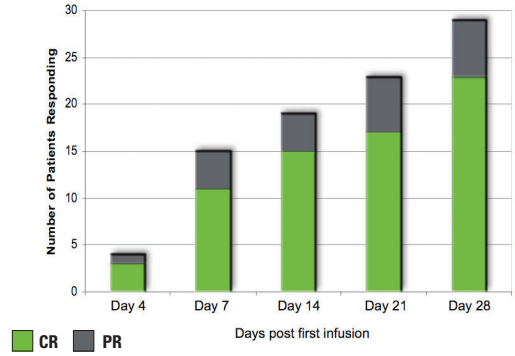
Response by Initial Grade



Response by Organ System



Cumulative Response by Time



Complete Response Improves Survival

- Patients were twice as likely to experience complete response with Prochymal and steroids (74%) vs steroids alone (35%)*
- Patients with complete response had significantly better survival

120 Day Survival by Treatment Response

Response	Survived	Deceased	% Survival*
Complete	21	2	91.3% (p < .001)
Not Complete	2	6	25%

**Biology of Blood and Marrow Transplantation Blood, MacMillan et al, 2002*

Sparing Second-line Therapy Improves Survival

120 Day Survival by Treatment Administered

Treatment	Survived	Deceased	% Survival
Prochymal Only	20	2	91% (p = .0011)*
2nd Line Administered	3	6	33%

**Proportion of patients not receiving second line therapy had significantly improved rates of survival (p = .0011, V²).*

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Summary/Conclusion

Favorable Safety Profile

- **No infusional toxicity**
  - – All infusions completed without stopping
  - – Patients tolerated repeated dosing
- **No ectopic tissue formation**
- **Two SAEs were deemed "possibly related"**
  - – Atrial flutter
  - – CMV antigenemia

Summary of Clinical Data

- **Prochymal with steroids for treatment of acute GVHD:**
  - – overall response rate of 94%
  - – complete response rate of 74%
  - – No differences in response between doses
- **Patients with skin GVHD:**
  - – 100% overall response rate and 85% complete response
- **Patients with difficult-to-treat GI-GVHD:**
  - – 82% overall response rate and 73% complete response

Summary of Clinical Data

- **Survival at 120 days post first infusion:**
  - – 91% (21/23) of complete responders
  - – 25% (2/8) of not complete responders
- **A total of 8 patient deaths were reported**
  - – No treatment related deaths
  - – Median of 44 days (range13-58 days) after infusion
  - – Causes
    - Complications associated with refractory GVHD (6)
    - Cancer relapse (1)
    - Intracranial bleed after a fall (1)

Conclusions

- **Prochymal appears to be well tolerated**
- **Prochymal + steroids leads to higher complete response rate than steroids alone**
- **Prochymal + steroids may have survival benefit in patients achieving complete response, and in patients spared second line therapy**
- **Patients with difficult-to-treat GI-GVHD responded well to Prochymal**
- **Re-treatment with additional infusions of Prochymal may be needed to treat or control subsequent flares of GVHD**
- **Efficacy of Prochymal is being evaluated in a double blind, placebo controlled trial**

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