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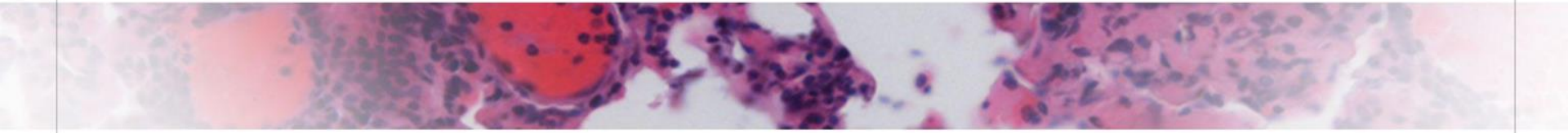

RGI-2001 Infusion for Prevention of Acute GVHD after Allogeneic Hematopoietic Cell Transplantation

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Background

- Acute graft-versus-host disease (aGVHD) is a major cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (alloHCT)
- aGVHD is primarily mediated by effector T-lymphocytes and prophylactic strategies have focused on T-cell suppression
- Calcineurin inhibitors inhibit the proliferation and activation of T-cells and have been used in combination with either methotrexate or mycophenolate mofetil as standard prophylaxis in HLA-matched alloHCT.
- Despite the use of prophylactic immunosuppressive therapy, Grades II-IV aGVHD occurs in 40% -60% of myeloablative matched related and unrelated alloHCT and severe cases contribute to non-relapse mortality

RGI-2001

- Studies in both humans and mice have confirmed the pivotal role $CD4^+Foxp3^+$ Treg cells play in controlling GVHD[1]
  - Development of Treg cell-based therapeutic modalities has been hampered, in part, by the small numbers of these cells

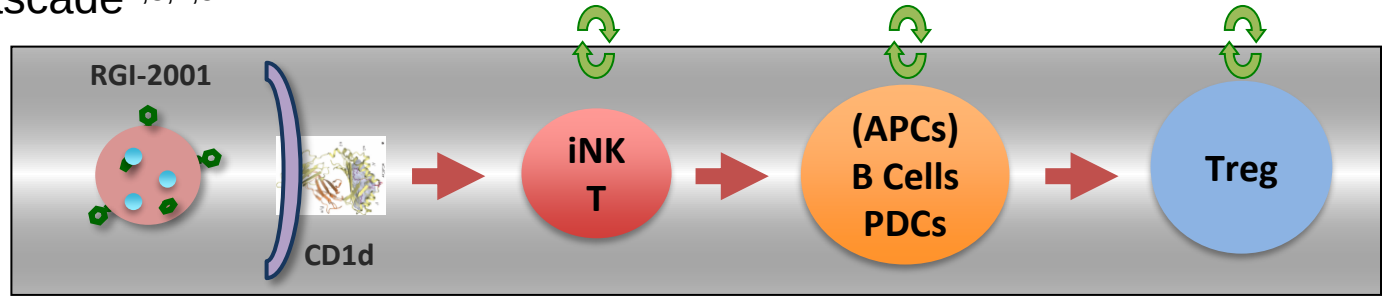
- RGI-2001 is being evaluated for the potential to reduce or prevent aGVHD after alloHCT through Treg expansion

- Earlier studies have shown that a single dose of RGI-2001 given on the day of alloHCT was safe and potentially contributed to aGVHD prevention[2]

1 Socié G, Blazar BR. Acute graft-versus-host disease: from the bench to the bedside. Blood 2009;114(20):4327–36. PMID 19713461
2 Chen, YB et al. Biology of Blood and Marrow Transplantation , Volume 23 , Issue 4 , 625 – 634 (April 2017)

RGI-2001 Induces Tregs

- RGI-2001 contains the active moiety α-GalCer encapsulated in a liposomal glycolipid
- α-GalCer, binds the CD1d receptor of antigen-presenting cells resulting in activation of invariant natural killer (iNKT) cells[1]
- This interaction results in a cytokine-dependent Treg proliferation in recipient bone marrow with subsequent modulation of the GVHD pathogenic cascade[2,3,4,5]



1 Luc Van Kaer. Nat Rev Immunol. 2005 Jan;5(1):31-42; 2 Julien et al. J Exp Med. 2011 Apr 11;208(4):729-45; 3. Biol Blood Marrow Transplant 2011 Aug 17 (8): 1154-68; 4. Nat Rev Immunol. 2012 Dec;12(12):845-57; 5.Eur J Immunol. 2014 May;44(5):1454-66.

Study Design

- RGI-2001-003 is an open-label, multi-center phase 2b study to evaluate the potential efficacy and safety of RGI-2001 when added to calcineurin inhibitor with methotrexate or mycophenolate mofetil (without T-cell depletion) for the prevention of aGVHD in subjects following myeloablative alloHCT

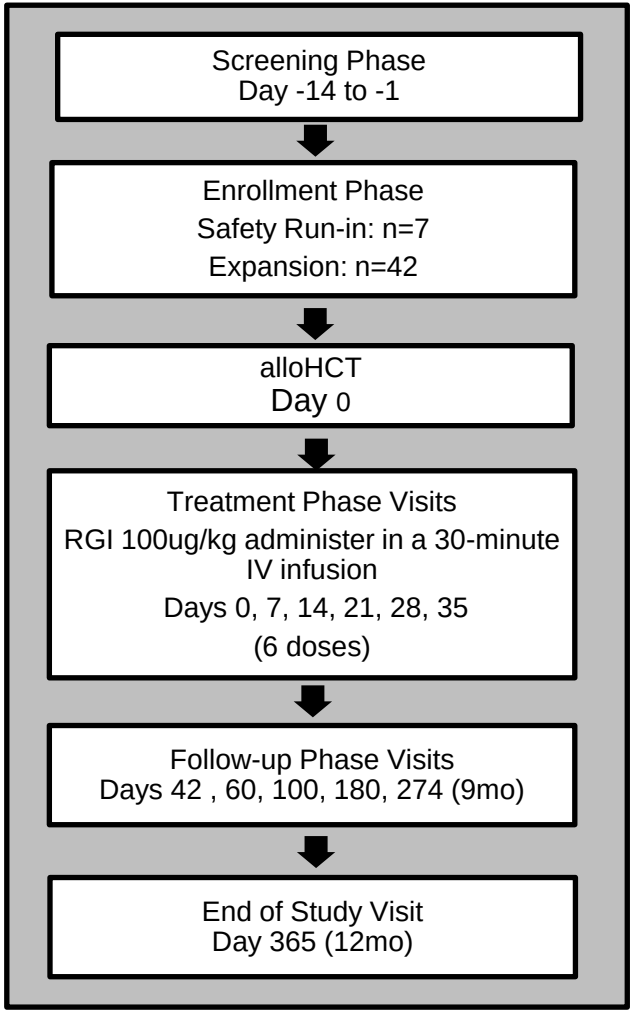
- The primary endpoint was the **incidence of Grade II-IV acute GVHD by Day 100** and incidence, nature, and severity of treatment-emergent AEs

Study Design

49 patients were enrolled across 7 US sites

Key eligibility criteria included:

- Ages 18-65
- Hematologic malignancy
  - AML, ALL, CMML, MPD, CML
- HLA-identical sibling, 8/8 URD, 7/8 URD
- Myeloablative conditioning
- BM or PBSC
- GVHD prophylaxis with CNI in combination with either MTX or MMF
- No planned use of any additional or alternative drug(s) for GVHD prophylaxis



Baseline Characteristics

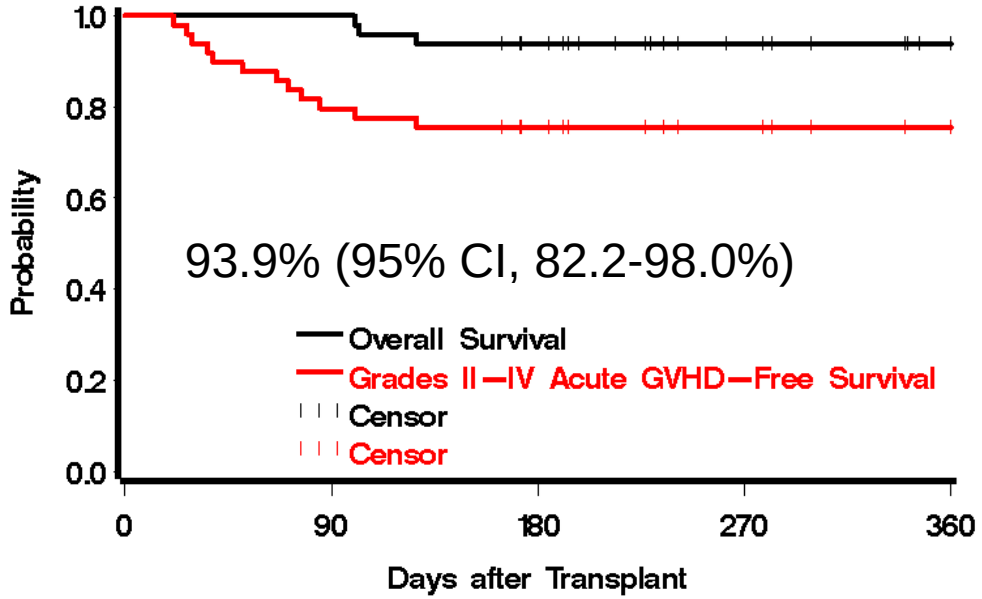
Characteristic	Number (%)
Age, median (range)	52 (21, 65)
Gender (male: female)	27:22 (55:45)
Race (white)	45 (92)
Disease	
AML	26 (53.1)
ALL	11 (22.4)
MDS	8 (16.3)
CML/Others	4 (8.3)
Donor type	
HLA-identical sibling	16 (32.7)
8/8 unrelated	32 (65.3)
7/8 unrelated	1 (2.0)
Conditioning Regimen	
Busulfan/Fludarabine	41 (83.6)
TBI/Cyclophosphamide	6 (12.2)
Others*	2 (4.1)
Graft source	
Peripheral blood	40 (81.6)
Bone marrow	9 (18.4)
GVHD Prophylaxis	
Tacrolimus+ MTX	49 (100)

Results/Outcomes

Outcome	N=49	95% CI
ANC engraftment	45 patients, median 13 days (range 5, 35)	
Platelet engraftment	41 patients, median 18 days (range 8, 35)	
Acute GVHD at Day 100, Day 180 Grade II-IV Grade III-IV	 20.4% 4.1%	 10.2-34.3% 0.5-14.0%
Overall Survival at Day 180 (3 deaths, d100, d102, d127)*	93.9%	82.2-98.0
aGVHD-Free Survival at Day 180 Grade II-IV Grade III-IV	 75.5 % 91.8%	 60.9-85.3% 80.0-96.9%
Relapse at Day 180 3 relapses by d180 (d63, d83, d97); 1 after d180 (d187)	6.1%	1.6-15.3%
NRM at Day 180 (2 NRM events, d100, d102)	4.1%	0.7-12.5%
PFS at Day 180	90.0%	77.2-95.6%

*GI GVHD, septic shock/COVID-19, disease relapse

RGI-2001 Kaplan-Meier estimates for overall survival and grades II-IV acute GVHD-free survival



Treatment Related Adverse Events (>4%)

Hematologic TEAE	TEAE N=49 n (%)	Grade 3/4 TEAE N=49 n (%)
Anemia	2 (4.1)	2 (4.1)
WBC decreased	2 (4.1)	2 (4.1)

Non-Hematologic TEAE		
Stomatitis	7 (14.3)	3 (6.1)
Diarrhea	6 (12.2)	0 (0)
Nausea	6 (12.2)	1 (2.0)
Abdominal pain	4 (8.2)	0 (0)
ALT increased	3 (6.1)	0 (0)
Alkaline phosphatase increased	3 (6.1)	0 (0)

- RGI-2001 IV infusion is given over 30 minutes
- No premedication is required
- No serious infusion reactions reported
- No study drug related SAEs
- Common AEs include gastrointestinal, rash and pruritis. Most of which were low grade

Conclusions

- RGI-2001 showed promising potential efficacy when added to standard GVHD prophylaxis of CNI plus methotrexate after MAC HCT
  - Grades II-IV aGVHD, 20.4% (95% CI, 10.2-34.3%)
  - Grades III-IV aGVHD, 4.1% (95% CI, 0.5-14.0%)
  - Grades II-IV aGVHD-free survival at d180, 75.5% (95% CI, 60.9-85.3%)

Conclusions

- RGI-2001 is safely given as a short IV infusion weekly for 6 doses
- RGI-2001 may be attractive to combine with other approaches which capitalize on Treg activity – i.e. post-transplant cyclophosphamide platforms
- A future randomized Phase III clinical trial is needed to confirm the efficacy and safety of RGI-2001 for prevention of aGVHD