ProTmune™, the Next-Generation Graft for Allogeneic Hematopoietic Cell Transplantation: Phase 1 Safety and Efficacy Data

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BACKGROUND

Therapeutic solutions that advance the curative potential of allogeneic hematopoietic cell transplantation (HCT) for patients with hematologic malignancies must reduce the potential of donor T cells to cause GvHD and maintain the capacity of donor T cells to prevent cancer relapse.

ProTmune™ is a next-generation hematopoietic cell graft for patients with hematologic malignancies undergoing matched unrelated donor allogeneic HCT. ProTmune is being clinically investigated for reduction in the incidence and severity of acute graft vs. host disease (GvHD) and maintenance of graft-versus-leukemia (GvL) activity.

PROTECT Phase 1/2 Clinical Trial

PROTECT is a Phase 1, non-randomized, open-label / Phase 2 randomized, double blinded study of ProTmune versus a conventional matched unrelated donor mobilized peripheral blood (mPB) cell graft (NCT02743351).

Key Inclusion Criteria

- 18 to 70 years old
- AML, ALL, MDS and CML
- Molecular Matched Unrelated Donor mPB HCT
  - 8/8 HLA-A, -B, -C, and -DRB1
- Myeloablative Conditioning Regimen
  - CyTBI, BuCy, FluBu, TBI/VP or FluMel 140
- GvHD Prophylaxis Regimen
  - Methotrexate (15-10-10-10 mg/m^2), Tacrolimus
- mPB Unit Requirement (pre-manufacture)
  - Phase 1: ≥ 5 × 10^6 CD34+ cells/kg (included a reserve dose of 2 × 10^6 CD34+ cells/kg)
  - Phase 2: ≥ 3 × 10^6 CD34+ cells/kg (no reserve dose)

PROTECT Phase 1 Stage

- Open label, single arm study
- 1º Endpoint: Day 28 safety assessment for neutrophil engraftment and survival

PROTECT Phase 2 Stage

- Double-blinded, randomized, controlled study
- 1º Endpoint: Day 100 efficacy assessment for cumulative incidence of acute GvHD (Grade 2-4)
- Opened to enrollment September 2017

ACUTE GVHD

- Acute GvHD is a severe immunological disease that commonly arises in patients during the first weeks following allogeneic HCT when adoptively transferred donor immune cells attack the patient's tissues and organs, resulting in a potentially fatal immune system reaction
- Up to 60% of patients undergoing unrelated mPB transplant experience acute GvHD (Grade 2-4) (Jagasia et al, *Blood,* 2011)
- Acute GvHD is the leading cause of early morbidity and mortality in matched unrelated donor HCT, where death directly attributable to acute GvHD or its treatment occurs in 10% to 20% of patients
- Investigational methods to address acute GvHD, including the use of T-cell depleted grafts, have resulted in high rates of cancer relapse and mortality (Soiffer et al, *JCO,* 2017)
- There are currently no FDA-approved preventive therapies and very few treatment options for acute GvHD

PRODUCT DESCRIPTION

ProTmune is a next-generation hematopoietic cell graft designed to reduce acute GvHD while maintaining graft-versus-leukemia (GvL) activity. ProTmune has been granted Orphan Drug and Fast Track Designations by the U.S. FDA and Orphan Medicinal Product Designation by the EMA.

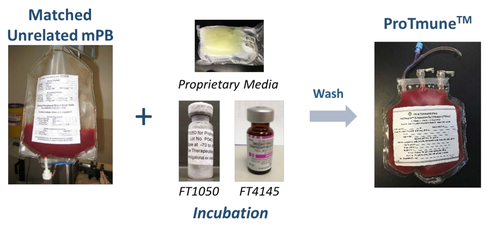


Figure 1. ProTmune is manufactured by pharmacologically modulating a mobilized peripheral blood graft ex vivo with two small molecules to transiently attenuate the alloreactivity of donor T cells while maintaining long term immunological GvL activity.

MECHANISM OF ACTION

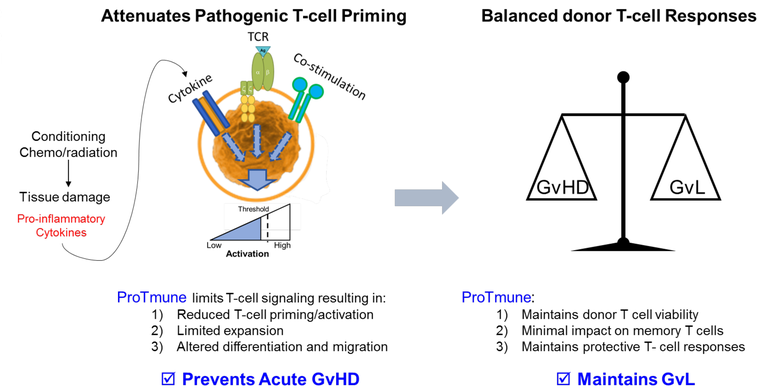


Figure 2. ProTmune attenuates pathogenic T-cell priming, activation and expansion, leading to reduced GvHD while maintaining GvL.

PRECLINICAL DATA

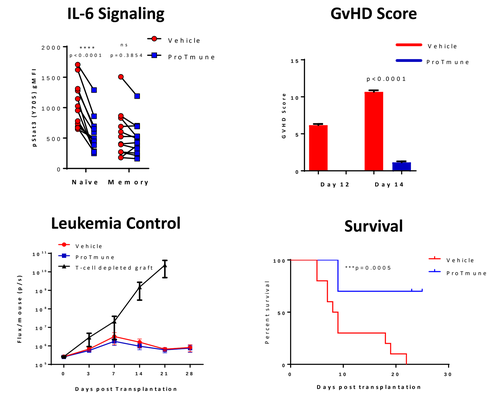
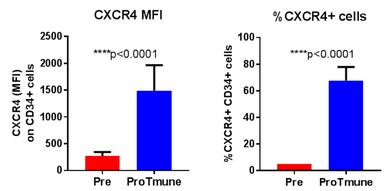


Figure 3. ProTmune demonstrates reduced pro-inflammatory cytokine signaling in human naïve T cells, reduced GvHD, maintained GvL and enhanced survival in murine HCT models.

PROTECT PHASE 1 CLINICAL DATA*

ProTmune Manufacturing

Parameter	Mean (range)
CD34+ Dose (10^6/kg)	6.6 (3.0 - 10.9)
CD34+ Recovery	*88% (74-100)*
CD3+ Dose (10^8/kg)	2.3 (1.2 - 3.1)
CD3+ Recovery	*86% (68-100)*
TNC Viability	88% (77 - 98)



Successful on-site manufacture of ProTmune confirmed by the pharmacologic increase in the potency marker CXCR4.

Day 28 Assessment

Subject	Disease	Age / Sex	MAC Regimen	Neutrophil Engraftment (d)	Graft Failure	ProTmune Related AEs	ProTmune Related SAEs	Overall Survival
1	MDS	66 / F	FluBu	14	No	Vomiting (G1)	None	Yes
2	AML	56 / F	BuCy	18	No	None	None	Yes
3	AML	66 / F	FluMel	22	No	None	None	Yes
4	ALL	34 / F	CyTBI	15	No	None	None	Yes
5	ALL	48 / M	CyTBI	16	No	Nausea (G2) Vomiting (G1)	None	Yes
6	ALL	56 / M	FluMel	18	No	None	None	Yes
7	AML	69 / F	FluMel	19	No	Nausea (G2) Chest Pain (G2)	None	Yes

Day 100 Assessment

Acute GvHD (CIBMTR) #	Organs Involved	Duration (d) Max Grade	Steroid Responsive	Leukemia Free	Overall Survival
None	---	---	---	Yes	Yes
None	---	---	---	Yes	Yes
Grade 2	Skin	7	Yes	Yes	Yes
None	---	---	---	Yes	Yes
Grade 2	Skin	8	Yes	Yes	Yes
Grade 3	Skin / Gut	5	Yes	Yes	Yes
None	---	---	---	Yes	Yes

* Data reflective of November 29, 2017. Database is not locked and final data are subject to change

maximum grade GvHD

ON-GOING STUDY ASSESSMENT

As of a November 29, 2017:

- There have been no events of graft failure
- All subjects remain leukemia-free
- Median time on study is 154 days [range 106- 254]; 5 of 7 subjects remain on study
- Non-relapse mortality was reported in two subjects:
  - Subject 1 on Day 228 from pulmonary edema
  - Subject 3 on Day 151 from atrial fibrillation
- No ProTmune-related SAEs have been reported by investigators
- Transplant-related SAEs include the following: Acute cholecystitis; atrial fibrillation; acute kidney injury; CMV colitis; enterococcal infection; failure to thrive; GvHD; lower GI hemorrhage; PRES-post reversible encephalopathy syndrome; pulmonary edema; and steroid myopathy

CONCLUSIONS

- **ProTmune can be reproducibly manufactured on-site and seamlessly delivered as part of standard-of-care HCT**
- **PROTECT Phase 1 Day 28 safety assessment demonstrated that ProTmune was well tolerated. All subjects engrafted with no events of graft failure**
- **PROTECT Phase 1 Day 100 efficacy assessment demonstrated three events of acute GvHD, all responsive to steroids. All seven subjects were alive and leukemia-free at Day 100 post-HCT**
- **A randomized, double-blind, Phase 2 study is open for enrollment. Key endpoints include the cumulative incidence of Day 100 Grade 2-4 acute GvHD, leukemia relapse and leukemia-free and overall survival**