

Evaluating the Safety and Efficacy of TOL-101 Induction to Prevent Kidney Transplant Rejection, Part A Interim Analysis

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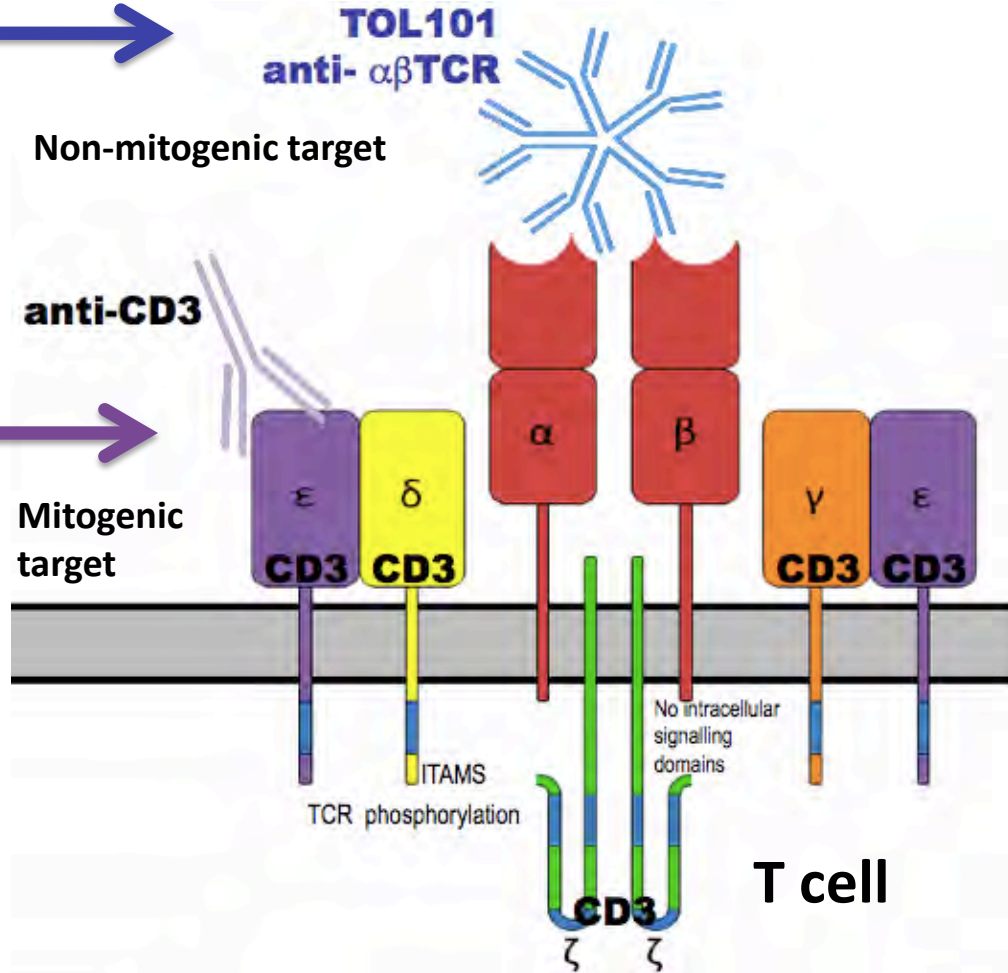
The Different Sites of T Cell Receptor Binding of anti-CD3 and TOL101 Antibodies Affect the Intensity of Activation, Proliferation, and Cytokine Production Resulting in Different Clinical Event Profiles.

TOL101

Functional inactivation
No depletion
Low cytokine production
Low proliferation
Reduced adverse events

Anti-CD3

Depletion
High cytokine production
High proliferation
Significant adverse events




The Role of Induction Therapy in Renal Transplantation

Both Immune and Non-Immune Strategies

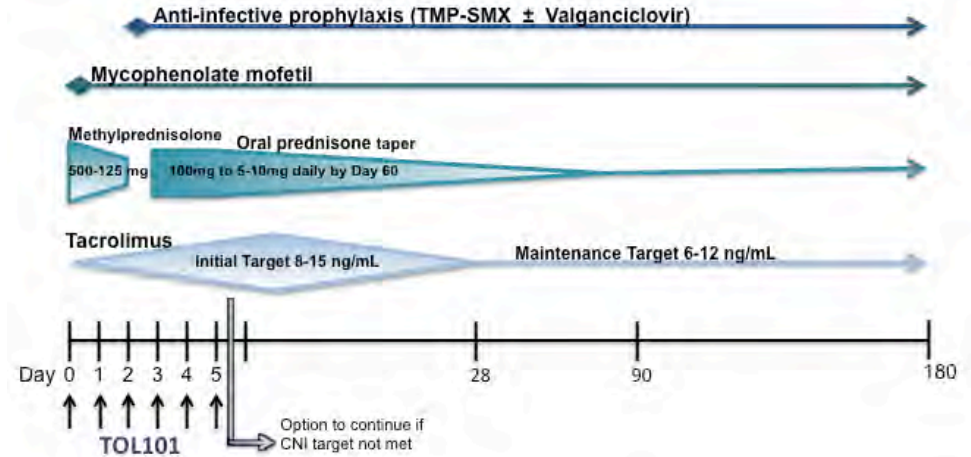
- Prevention of a Primary Immune Response to Donor HLA Antigens
- Remove and/or Defunctionalize Passenger Leukocytes
- Diminish the Intensity of Ischemia-Reperfusion Injury
- Provide an Immunosuppressive Umbrella to Minimize the Introduction of Calcineurin Inhibitor Drugs
- Permit the Emergence of Regulatory Lymphocyte Populations

TOL101 Phase IIa/b Development Objectives

Phase 2a	Open label ascending dose trial in renal transplant recipients to identify two potentially therapeutic doses (PTD-A and PTD-B) of TOL101 for Part B	
TOL101 Phase 2a escalating dose strategy	0.28mg (1/10 th MABEL) (N=2) 1.4mg (n=2) 7mg (n=2) 14mg (n=2) 28mg (n=3) 42mg (Currently enrolling) 56mg (TBD)	 <p>Data presented today are interim analysis from this data</p>
TOL101 clinical endpoints	<p><i>Primary- Safety & tolerability</i> including infusion reactions, adverse events, cytokine release, infections, malignancies & standard biochemistry and hematology.</p> <p><i>Secondary- Efficacy</i> including BPAR, graft survival, subject survival, renal function, DGF, DSA</p> <p><i>Secondary- Immune monitoring</i> including CD3 counts, leukocyte subsets, antibodies to TOL101 (neutralizing or non-neutralizing).</p>	
Phase 2b	Randomized parallel arm active control trial to compare safety, PD, and clinical efficacy of two PTDs of TOL101 vs Thymoglobulin (TMG)	

TOL101 Dosing & Demographic Profile

TOL101 dosing schedule & maintenance therapy



Subject demographics

Current Demographics				
Treatment Group (mg TOL101)	Age	Sex	Race	Ethnicity
0.28 mg	54	M	White	Not Hispanic or Latino
	52	M	White	Not Hispanic or Latino
1.4 mg	54	M	Mixed	Hispanic or Latino
	34	F	White	Hispanic or Latino
7.0 mg	45	M	White	Hispanic or Latino
	42	M	White	Hispanic or Latino
14.0 mg	38	M	White	Not Hispanic or Latino
	40	M	White	Hispanic or Latino
28.0 mg	36	M	Black	Not Hispanic or Latino
	42	M	Black	Not Hispanic or Latino
	21	M	White	Not Hispanic or Latino

Safety & Hematology Observations

Measurement	TOL101 Dose				
	0.28mg (n=2)	1.4mg (n=2)	7mg (n=2)	14mg (n=2)	28mg(n=3)
Infusion Reactions Symptoms	0	1 patient Dose 2 - 6 Moderate nausea & Moderate Pruritis	0	1 patient Dose 5 Infusion site rash	1 patient Dose 1, Hypertension; Dose 2 Diaphoresis & Dyspnea Dose 1-5 Pruritis
Drug Related SAE's	0	0	0	0	1*
Infections & Malignancies	BK Virus D90 114,000 copies	None Reported	UTI infection	None Reported	Nosocomial Pneumonia
Biopsy proven acute rejection	Grade 1 A acute T cell rejection D34 Post TX	0	0	0	0
Hematological Examinations in 28mg Cohort			Lymphocyte count reduction Neutrophil increase All other parameters similar to pre-op baseline		

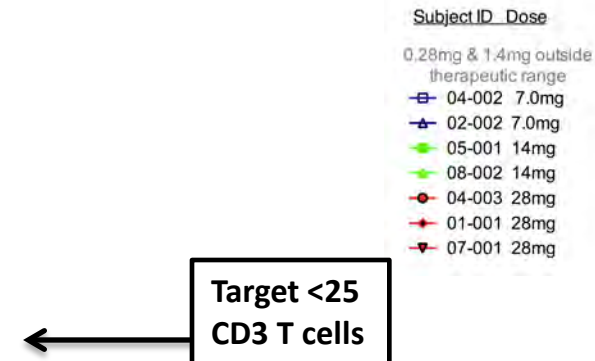
TOL101 Pharmacodynamics – Dose Dependent CD3 Modulation

CD3 counts

Dose dependent CD3 count reduction

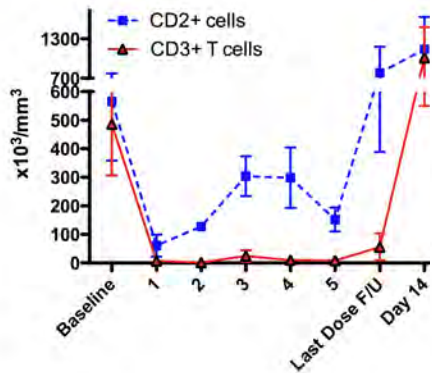
- Central flow cytometry laboratory- standardized method across all sites
- PD target CD3 count < 25 cells during dosing

CD3+ Counts (/mm³)



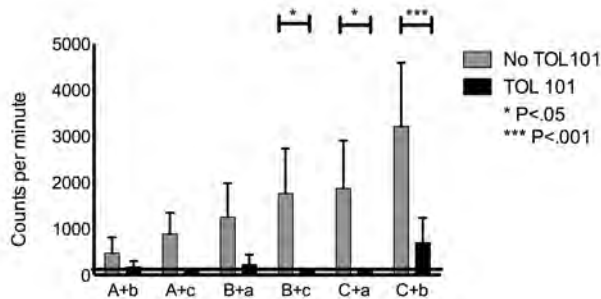
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T Cell Inactivation Without Cytokine Release



28mg cohort mean \pm SEM

TOL101 inhibits MLR



Non-depletional mechanism

CD3+ cells reduced to below 25

CD2+ T cells emerge with no $\alpha\beta$ TCR/CD3

Inactivates without depleting cells

Lack of TCR= Non-functional T cell

Functional Inactivation without inflammation

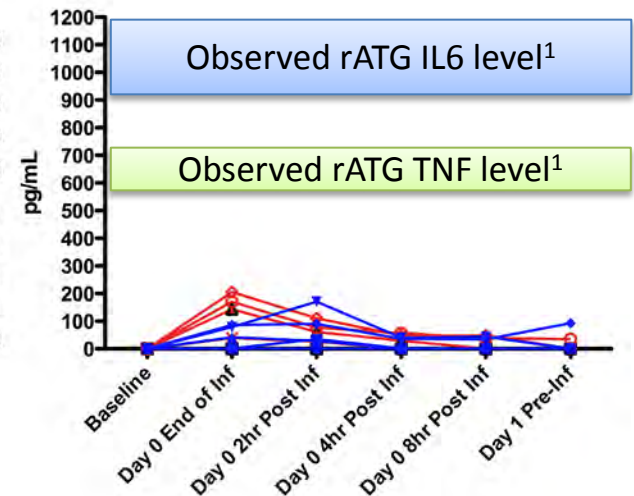
No cytokine release syndrome reported

Serum ELISA for IL2, IL10, IL6, TNF, IL1 β , IFN γ

TNF

IL6

- 05-001 14mg
- ▲ 08-002 14mg
- ◇ 01-001 28mg
- 04-003 28mg
- * 07-001 28mg
- 05-001 14mg
- ▲ 08-002 14mg
- ◇ 01-001 28mg
- 04-003 28mg
- * 07-001 28mg



Reference:

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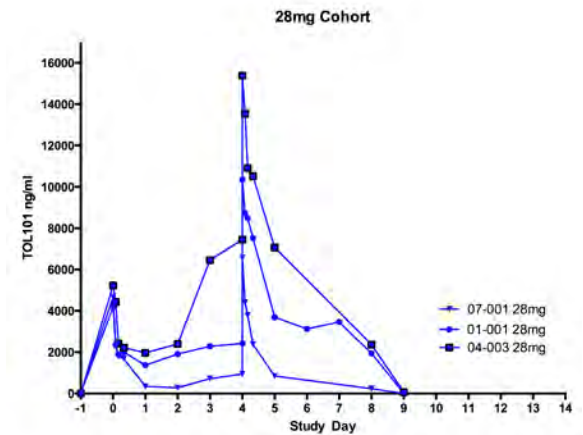
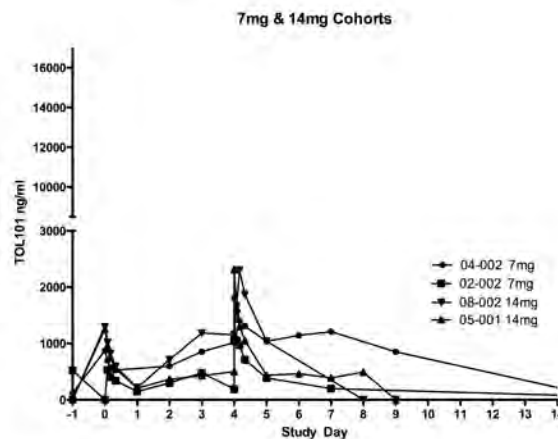
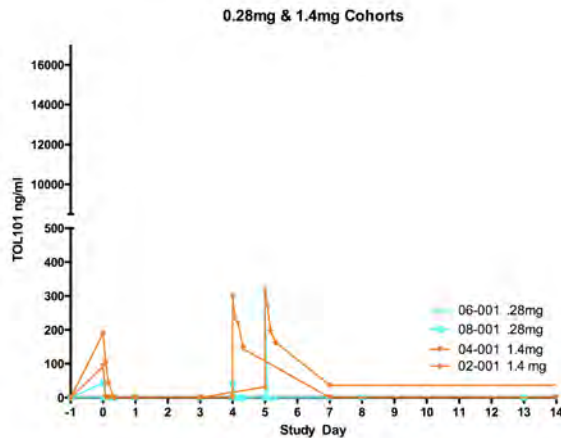
1. Guttman, et. al., Pharmacokinetics, Foreign Protein Immune Response, Cytokine Release, and Lymphocyte Subsets in Patients Receiving Thymoglobulin and Immunosuppression, Transplantation Proceedings, 29 (Suppl 7A), 24S-26S (1997).

Pharmacokinetics - TOL101 Clearance

Dose escalation showing increased bioavailability (\uparrow AUC)

Increased serum half life

No anti-mouse antibody detected in any treated subject



Conclusions

1. TOL101 dose escalation has occurred with promising safety profile
2. TOL101 induced dose dependent T cell modulation without inducing significant cytokine release or other SAE's
3. Immune monitoring shows specific targeting and mechanism of action to be functionally inactivating without depleting.
4. Potential to provide increased specificity and long-term safety index over currently used induction agents.
5. Dose escalation to be complete November 2011, with open label Phase 2b comparing directly with Thymoglobulin.

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