
Precision Medicine and not Individualized Therapy is Required for Successful Novel Drug Development
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Disclosures

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- I have received grants and/or research support from:
  - Astellas
  - Angion
  - Bristol-Myers Squibb
  - Genentech
  - Novartis
  - Pfizer
  - Merck

Personalized/Individualized Medicine vs Precision Medicine

- Personalized medicine has been practiced in transplantation (i.e. low risk vs high risk)
- Precision medicine requires new diagnostics or biomarkers to select or modify immunosuppression regimens essentisl with novel therapies

- Can we apply genomic and biomarker information in selecting therapy that improves clinical care and outcomes in transplantation?
- The need: biomarkers that are accurate, reliable and are associated with events and endpoints that may lead to better patient outcome

Personalized Medicine in Transplantation

- Choice of induction agent (PRA, DSA, DGF)
- Choice of CNI
- Maintaining or D/C steroids
- Choice of anti-proliferatives

Precision Medicine

- Precision medicine is defined as treatments targeted to the particular patient on the basis of genetics, biomarkers or phenotypic characteristics that maximize efficacy and minimizes toxicities.

Without New Biomarkers it will be Difficult to Develop Novel Therapies for Precision Medicine in Transplantation or Improve Long Term Outcome

Rear View Mirror Strategies Do Not Work

CLINICAL RESEARCH www.jasn.org

Adverse Outcomes of Tacrolimus Withdrawal in Immune–Quiescent Kidney Transplant Recipients

Donald E. Hricik,* Richard N. Formica,† Peter Nickerson,‡ David Rush,‡ Robert L. Fairchild,§ Emilio D. Poggio,§ Ian W. Gibson,‡ Chris Wiebe,‡ Kathryn Tinckam,‖ Suphamai Bunnapradist,¶ Milagros Samaniego-Picota,** Daniel C. Brennan,†† Bernd Schröppel,‡‡ Osama Gaber,§§‖‖ Brian Armstrong,¶¶ David Ikle,¶¶ Helena Diop,*** Nancy D. Bridges,*** and Peter S. Heeger,‡‡ for the Clinical Trials in Organ Transplantation-09 Consortium

Methods

- The Clinical Trials in Organ Transplantation-09 CTOT Trial was a randomized, prospective study of non sensitized primary recipients of living donor kidney transplants. Subjects received rabbit anti-lymphocyte globulin, tacrolimus, mycophenolate mofetil, and prednisone.
- Six months post-transplantation, subjects without de novo donor-specific antibodies (DSAs), AR, or inflammation at protocol biopsy were randomized to wean off or remain on tacrolimus.

Results

- The study was terminated prematurely because of unacceptable rates of AR (4 of 14) and/or de novo DSAs (5 of 14) in the tacrolimus withdrawal arm.

Conclusions

….past performance does not predict future results in manupulating immunosuppresion regimens.Safe and effective application of novel regimens or drug elimination require reliable biomarkers.

Lack of Biomarkers Has Halted Development of Several Promising Drugs

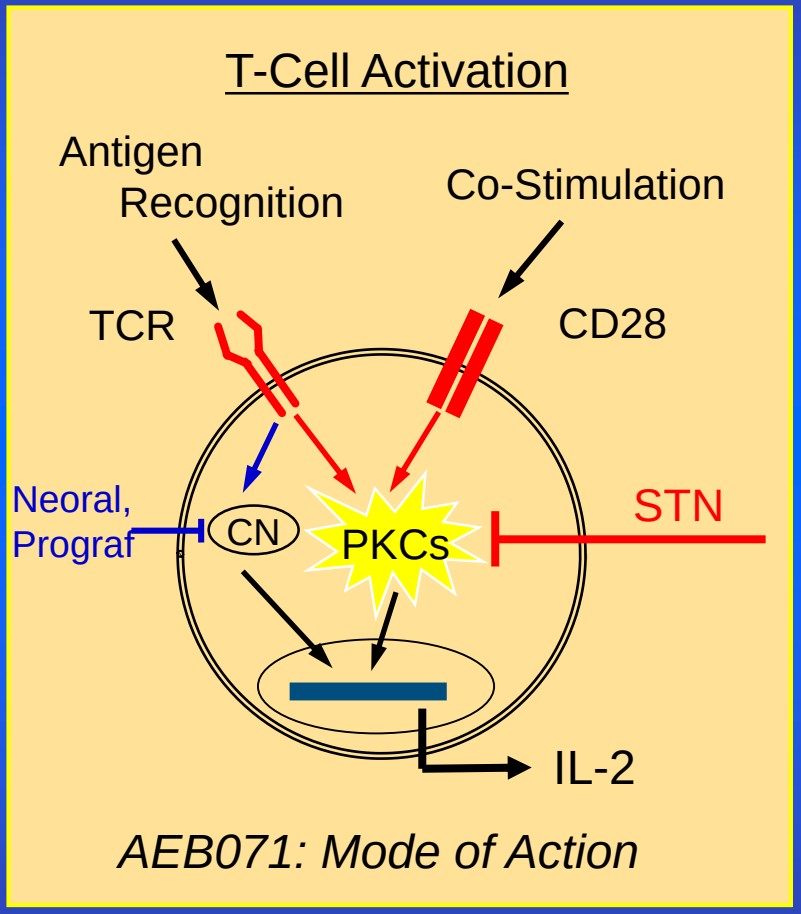
- Sotrastaurin – a CNI alternative targeting PKC
- Alefacept – targeting memory cells
- ASKP1240 – inhibits the CD40-CD154 pathway

Sotrastaurin (STN): Mechanism of action

Protein kinase C (PKC): A novel target in transplantation

STN is a small molecular weight immuno-suppressant with a novel mode of action:

- PKCs are known to integrate signals which emanate from the T cell antigen receptor (TCR) and the CD28 co-receptor and which together lead to T cell activation
- STN potently and selectively inhibits all classical & novel PKC isozymes
- Like CNIs, STN inhibits T cell activation but through inhibition of a different target, i.e., PKCs
- Mode of action different from CNIs, and complementary to CNIs

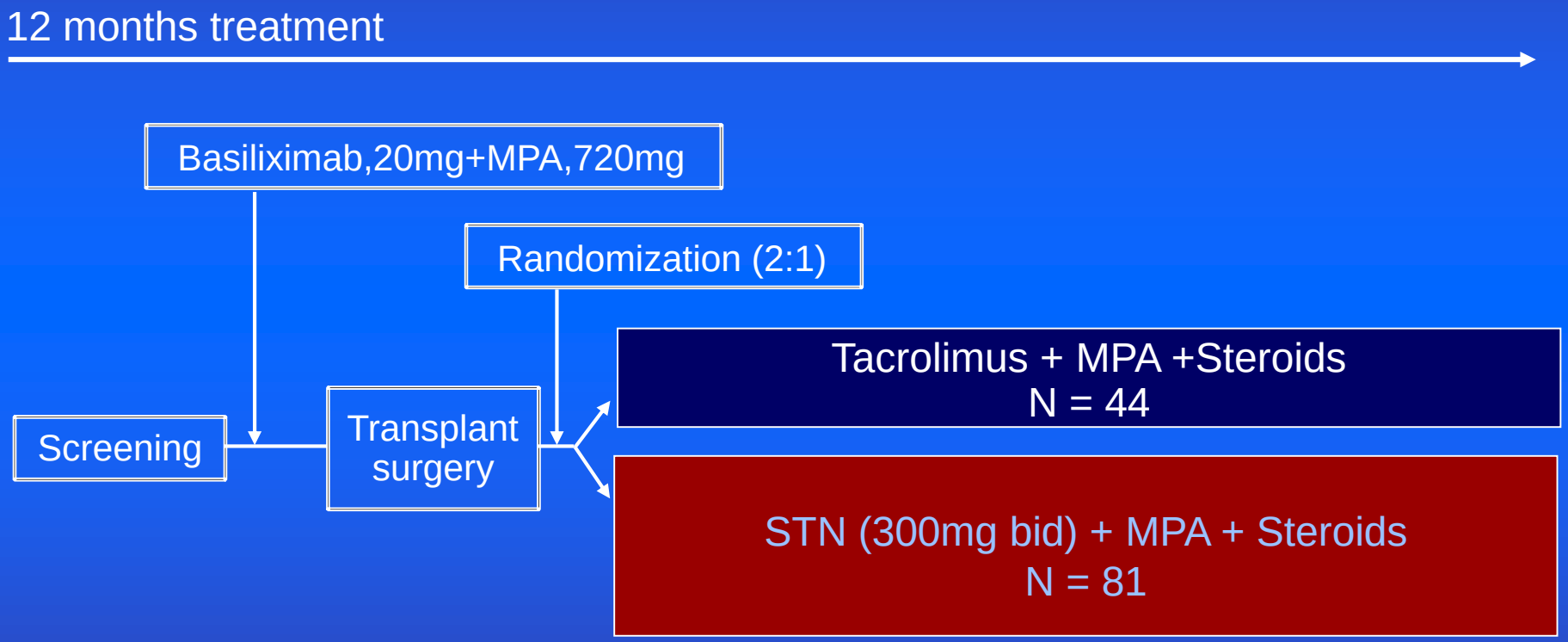


AEB071: Mode of Action

➥ Potential for CNI replacement, or for allowing CNI-minimization when combined with CNI.

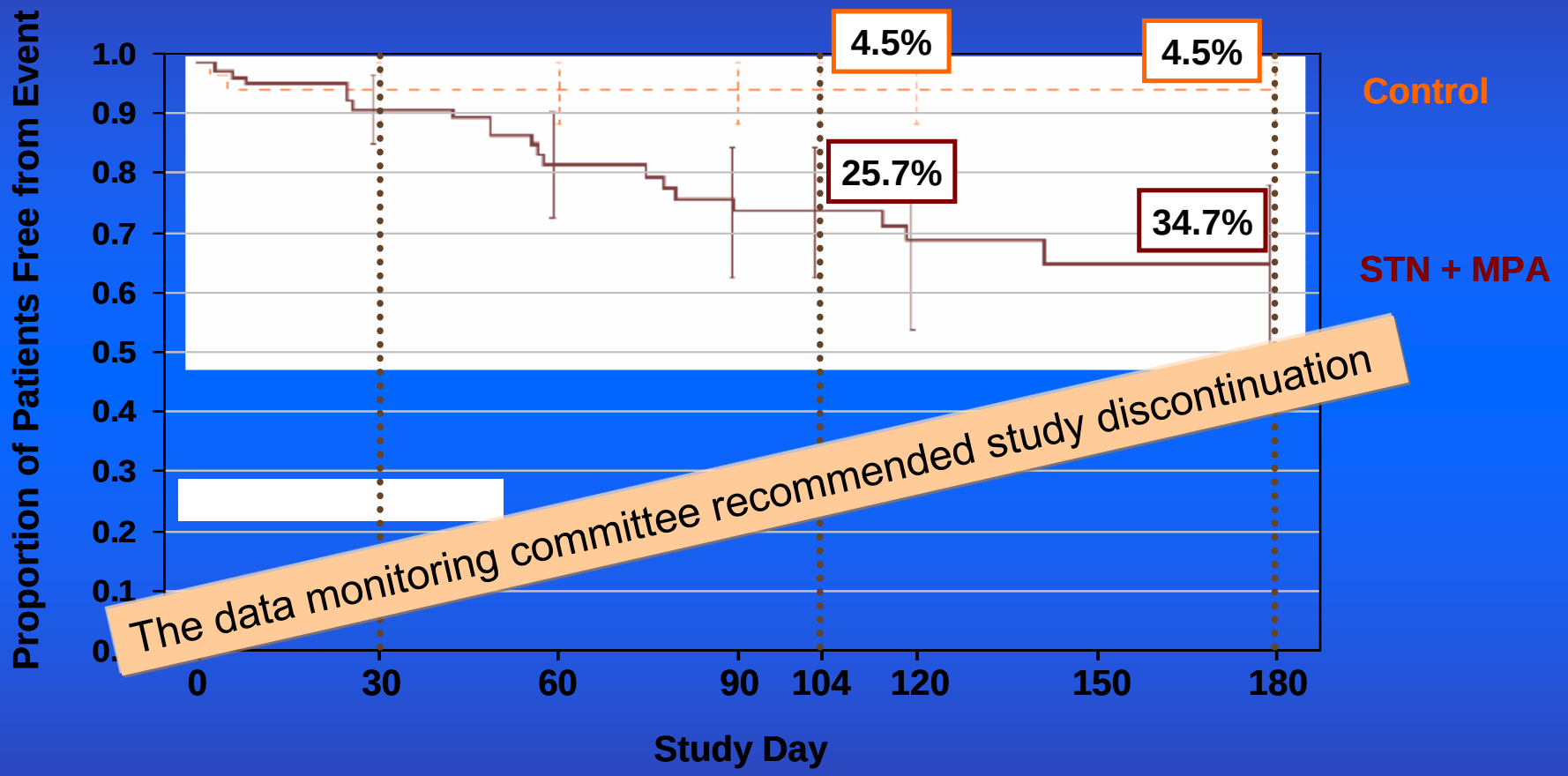
A2207 study design

CNI-free STN + myfortic regimen from transplantation



Efficacy results

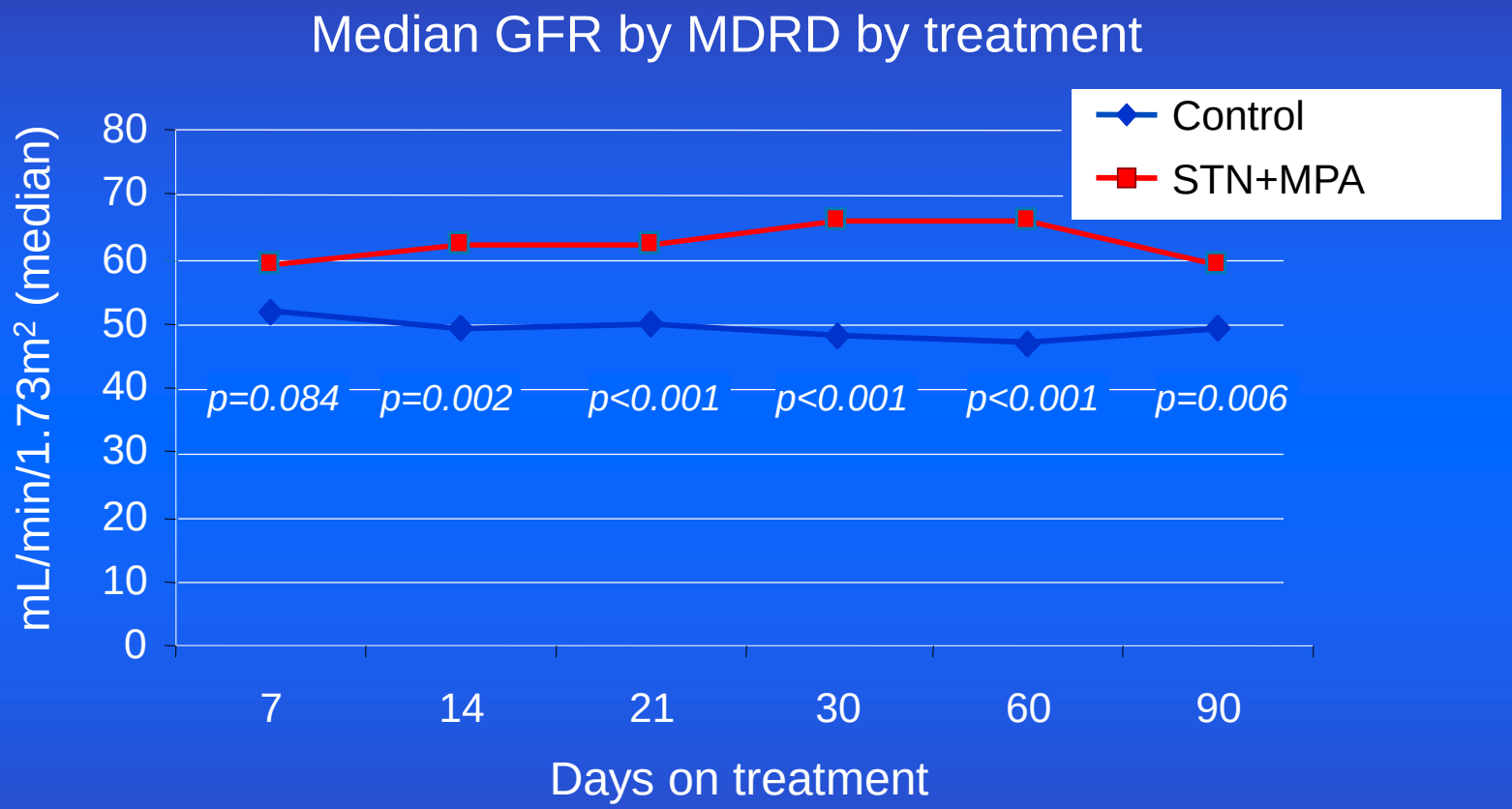
Kaplan–Meier plot of time to first on-treatment composite efficacy failure



STN+MPA	81	65	47	34	32	27	14	7
Control	44	40	32	27	25	19	15	7

Estimated GFR higher on the STN-myfortic regimen

All patients, including also those who didn't remain on study therapy

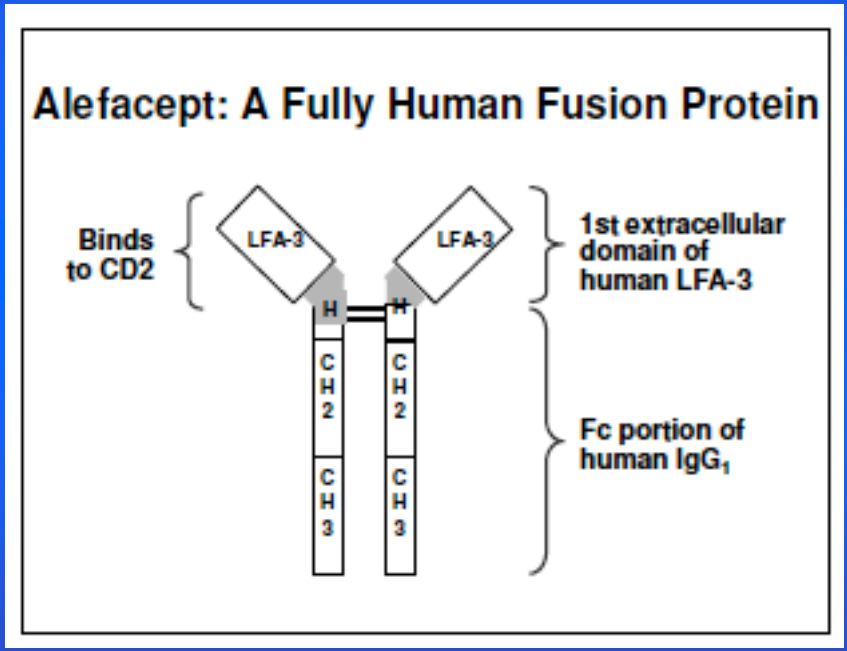


N providing data:

STN+MPA	77	69	69	67	61	60
Control	41	39	39	42	37	36

Alefacept

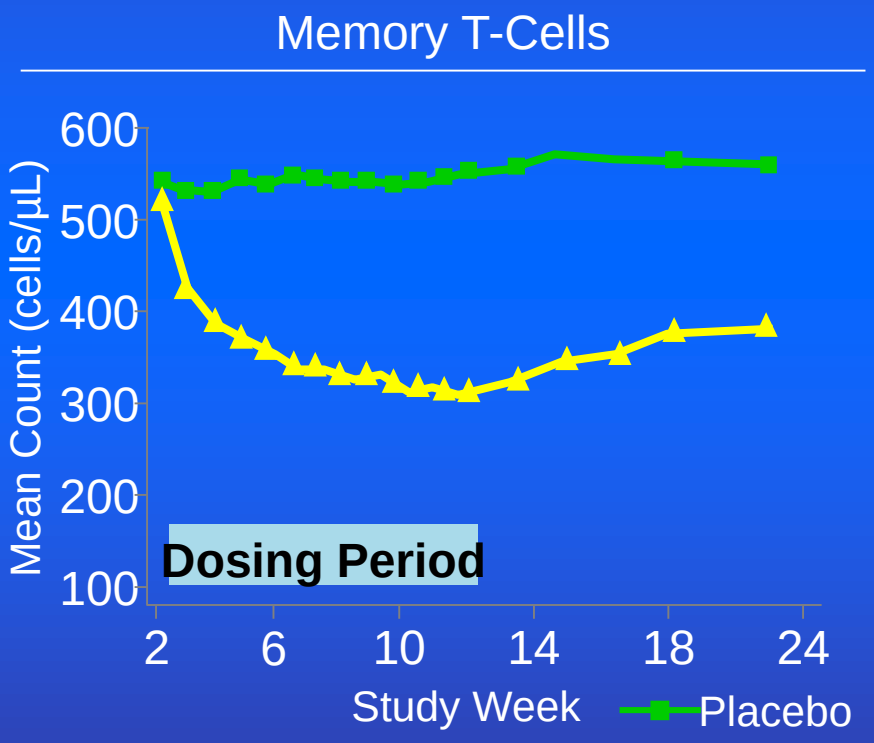
- Alefacept is a human dimeric fusion receptor protein LFA3 linked to the Fc portion of human IgG1
- LFA-3 portion binds to CD2 on T lymphocytes, blocking the interaction between LFA-3 and CD2, and interfering with T-cell activation
- Available in an IV and IM formulation
- Approved for use for psoriasis

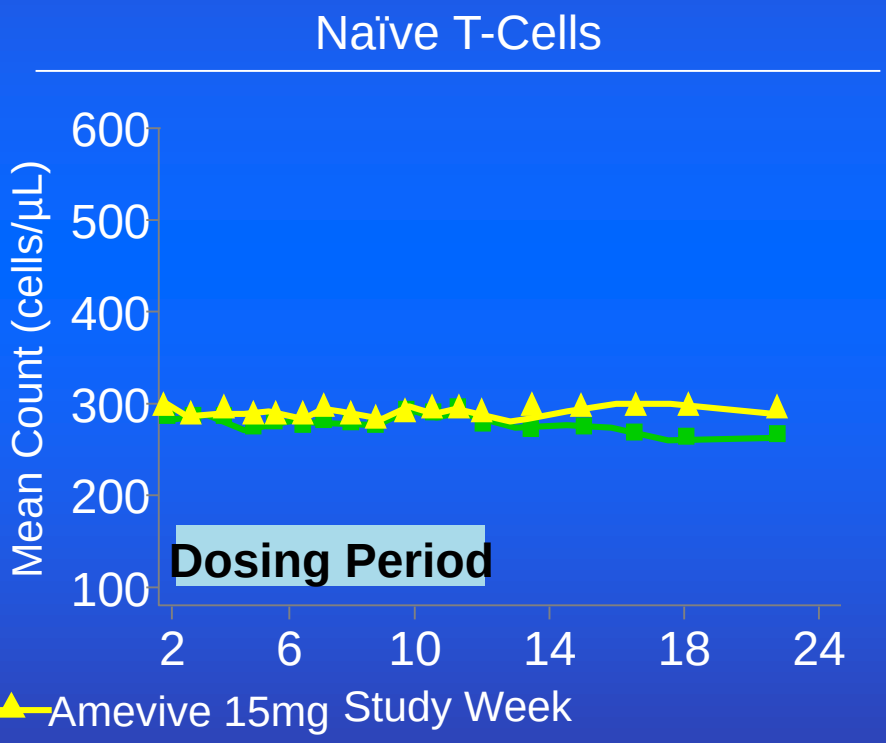


Alefacept: Mechanism of Action

Lebwohl M et al. Arch Dermatol 2003; 139: 719-772

Alefacept selectively targets memory T-cells in phase III psoriasis study





Alefacept Significantly Reduces T-Cell Memory Subsets in Kidney Transplant

- Alefacept significantly reduced T-cell memory subsets; nadirs observed after 8-12 weeks
- NO ALEFACEPT ARM MET NONINFERIORITY CRITERIA FOR ACUTE T-CELL-MEDIATED REJECTION AT MONTH 6

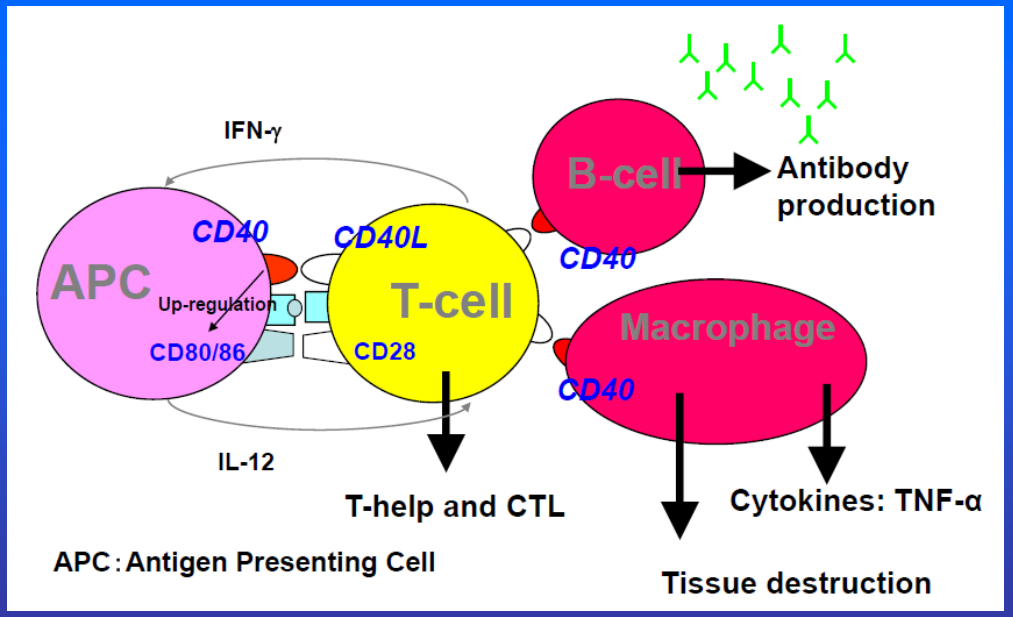
Outcome at Month 6	Alefacept/Low Tacrolimus/MMF (n=77)	Alefacept/Full Tacrolimus/No MMF (n=75)	Q2W/Alefacept/Low Tacrolimus/MMF (n=78)	Control (N=79)
Kaplan-Meier rate of BPAR, %	26.3	18.8	16.7	12.7
• P value for noninferiority to control	.06	.45	.59	--
Efficacy failure, %*	28.6	21.3	21.6	15.2
Renal function				
• GFR, mL/min/1.73m^2	62.0	59.5	60.8	61.0
Kaplan-Meier estimate of graft survival, %	96.1	97.3	93.6	96.2
Kaplan-Meier estimate of patient survival, %	96.1	98.7	94.9	96.2

*BPAR, graft loss, death, or lost to follow-up

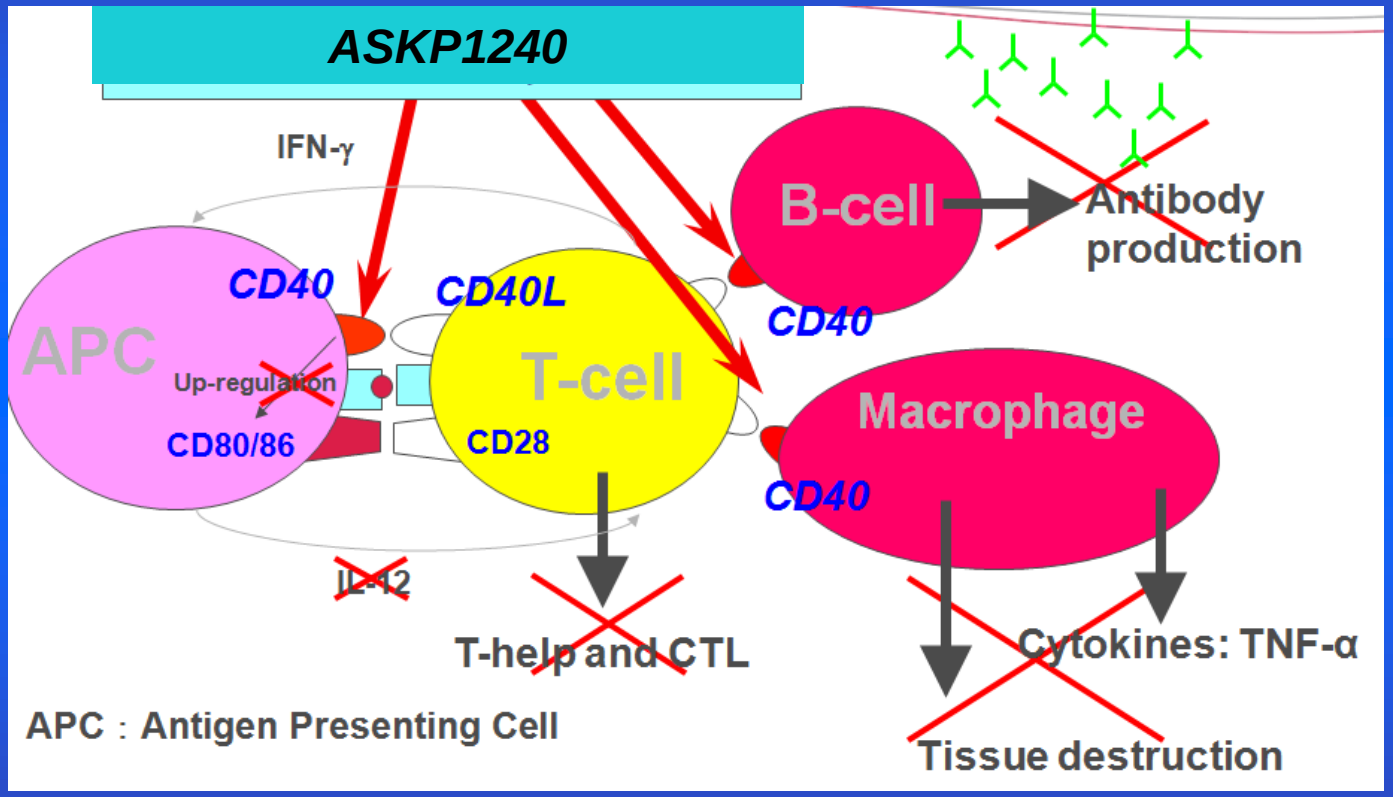
Bromberg J, et al. ATC 2011. Abstract 533.

TARGETING THE CD40-CD154 PATHWAY

- The mechanisms involved in alloresponse in transplant recipients have been widely investigated.
- Targeting co-stimulatory molecules is a promising area of investigation.
- CD40-CD154 interactions are key co-stimulatory molecules in the alloresponse.



The Mechanism of Action of ASKP1240



ASKP1240 in De Novo Kidney Transplant Recipients

R. Harland,[1] G. Klintmalm,[2] H. Yang,[3] S. Jensik,[4] T. Shah,[5] P West-Thielke,[6] F Shihab,[7] W. Zhang,[8] V Santos,[8] R. Tainaka,[8] X. Wang,[8] R. First,[8] J. Holman.[8]

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[5]Transplant Research Institute, Los Angeles, CA
[6]University of Illinois Chicago, Chicago, IL
[7]University of Utah Health Science Center Salt Lake City, UT
[8]Astellas Pharma Global Development, Northbrook, IL.

Meeting: 2015 American Transplant Congress

Abstract number: 3012

Keywords: Immunosuppression, Kidney transplantation

A Phase 2b, Randomized, Open-Label, Active Control, Multi-Center Study to Assess the Efficacy and Safety of ASKP1240 in de novo Kidney Transplant Recipients [ISN 7163-CL-0108]

Arm 1: Standard of Care

- Basiliximab Induction
- Tac Trough 4-11 ng/dL
- MMF 1g BID
- Steroids

Arm #2: CNI Avoidance*

- Basiliximab Induction
- ASKP1240
- MMF 1g BID
- Steroids

Arm #3: CNI Minimization/ MMF Avoidance

- ASKP1240
- Tac Trough 4-11 ng/dL (Day 0-30)
- Tac Trough 2-5 ng/dL (Day 31 onward)
- Steroids

* Arm #2 had excessive rejection rate by month 3. Subjects in Arm #2 were converted to SOC regimen.

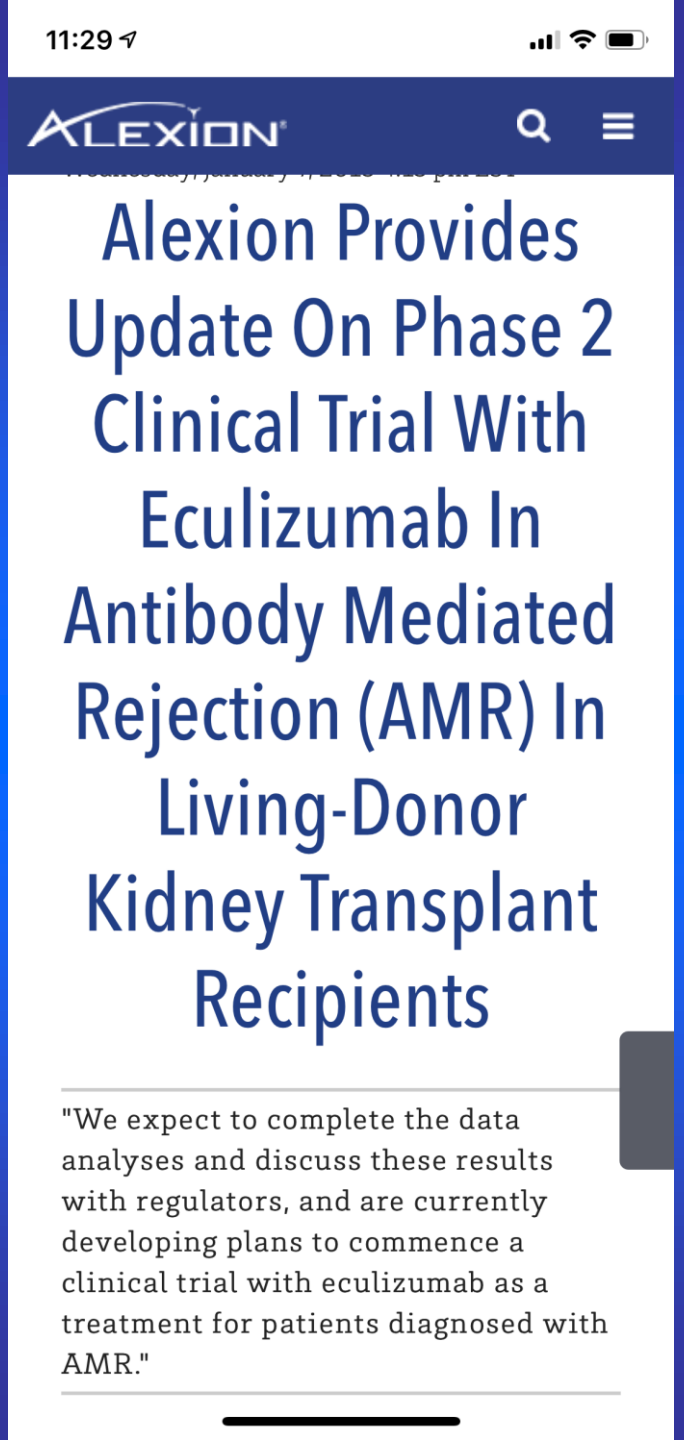
Results

138 subjects were transplanted and received at least one dose of study drug. Treatment groups were similar with regards to baseline donor and recipient characteristics. Key outcomes at Day 180 are shown below.

Parameter	SOC (n=48)	ASKP1240+MMF (n=46)	ASKP+Tac Minimization (n=44)
BPAR	3 (6.3%)	17 (37.0%)	4 (9.1%)
BK Infection	6 (12.2%)	7 (15.2%)	12 (27.3%)
CMV Infection	2 (4.1%)	4 (8.7%)	3 (6.8%)
GFR MDRD (mean mL/min)	63.5	63.9	62.6
Patient Survival	48 (100%)	45 (97.8%)	43 (97.7%)
Death Censored Graft Survival	47 (97.9%)	46 (100%)	43 (97.7%)

No subjects experienced thromboembolic events. There were 3 malignancies in ASKP1240 groups (1 renal cell carcinoma and 2 squamous cell carcinoma). No PTLD reported. No graft loss from BK infection/nephropathy. Anti-ASKP1240 antibodies were infrequent (3.3%).

The Failure of Eculizumab in Preventing AMR in Patients with DSA Compared to SOC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ALEXION
Alexion Provides Update On Phase 2 Clinical Trial With Eculizumab In Antibody Mediated Rejection (AMR) In Living-Donor Kidney Transplant Recipients
"We expect to complete the data analyses and discuss these results with regulators, and are currently developing plans to commence a clinical trial with eculizumab as a treatment for patients diagnosed with AMR."

CLINICAL RESEARCH www.jasn.org

Complement-Activating Anti-HLA Antibodies in Kidney Transplantation: Allograft Gene Expression Profiling and Response to Treatment

Carmen Lefaucheur,[1,2] Denis Viglietti,[1,2] Luis G. Hidalgo,[3] Lloyd E. Ratner,[4] Serena M. Bagnasco,[5] Ibrahim Batal,[6] Olivier Aubert,[1] Babak J. Orandi,[7] Federico Oppenheimer,[8] Oriol Bestard,[9] Paolo Rigotti,[10] Anna V. Reisaeter,[11] Nassim Kamar,[12] Yvon Lebranchu,[13] Jean-Paul Duong Van Huyen,[1,14] Patrick Bruneval,[1,15] Denis Glotz,[1,2] Christophe Legendre,[1,16] Jean-Philippe Empana,[1] Xavier Jouven,[1] Dorry L. Segev,[17] Robert A. Montgomery,[18] Adriana Zeevi,[19] Philip F. Halloran,[3] and Alexandre Loupy[1,16]

JASN February 2018, 29:620-635

- The histomolecular rejection phenotype included increased expression of five biologically relevant genes (CXCL11, CCL4, MS4A7, MS4A6A, and FCGR3A) indicative of endothelial activation.

- Compared with standard of care, eculizumab specifically abrogated this histomolecular rejection phenotype and was associated with a decreased 3-month rejection incidence rate in patients with complement-activating DSAs (56% vs 19%; P=0.001) but not in those with noncomplement-activating DSAs (9% vs 13%; P=0.65).

How Should AMR Clinical Trials be Designed

- All comers with Banff dx of AMR ?
- Strict C4d+ and DSA ?
- C1q binding DSAs and histomolecular confirmation?

Still More Complement Inhibition Trials in AMR

- C1 esterase inhibitor added to PE and IVIg (NCT02547220)
- C1 esterase inhibitor for AMR resistant to PE and IVIg (NCT03221842)

The Next Challenge: CABMR

- Variable causation
- No biomarkers
- All comers trials will be risky
- End point: GFR, Proteinuria, Progression of TG and Graft Loss

Can We Use Non Invasive Biomarkers That Predict Risk of Rejection to Modify Immunosuppression Burden

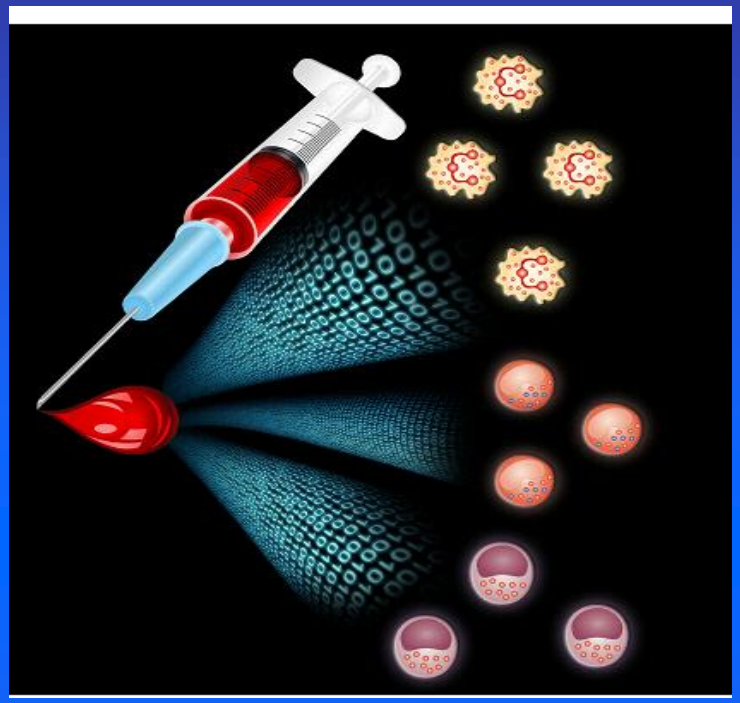
kSORT (Kidney Solid Organ Response Test)

Application of the kSORT blood assay for the non-invasive prediction of histological rejection

Kidney- Solid Organ Rejection Test (kSORT)

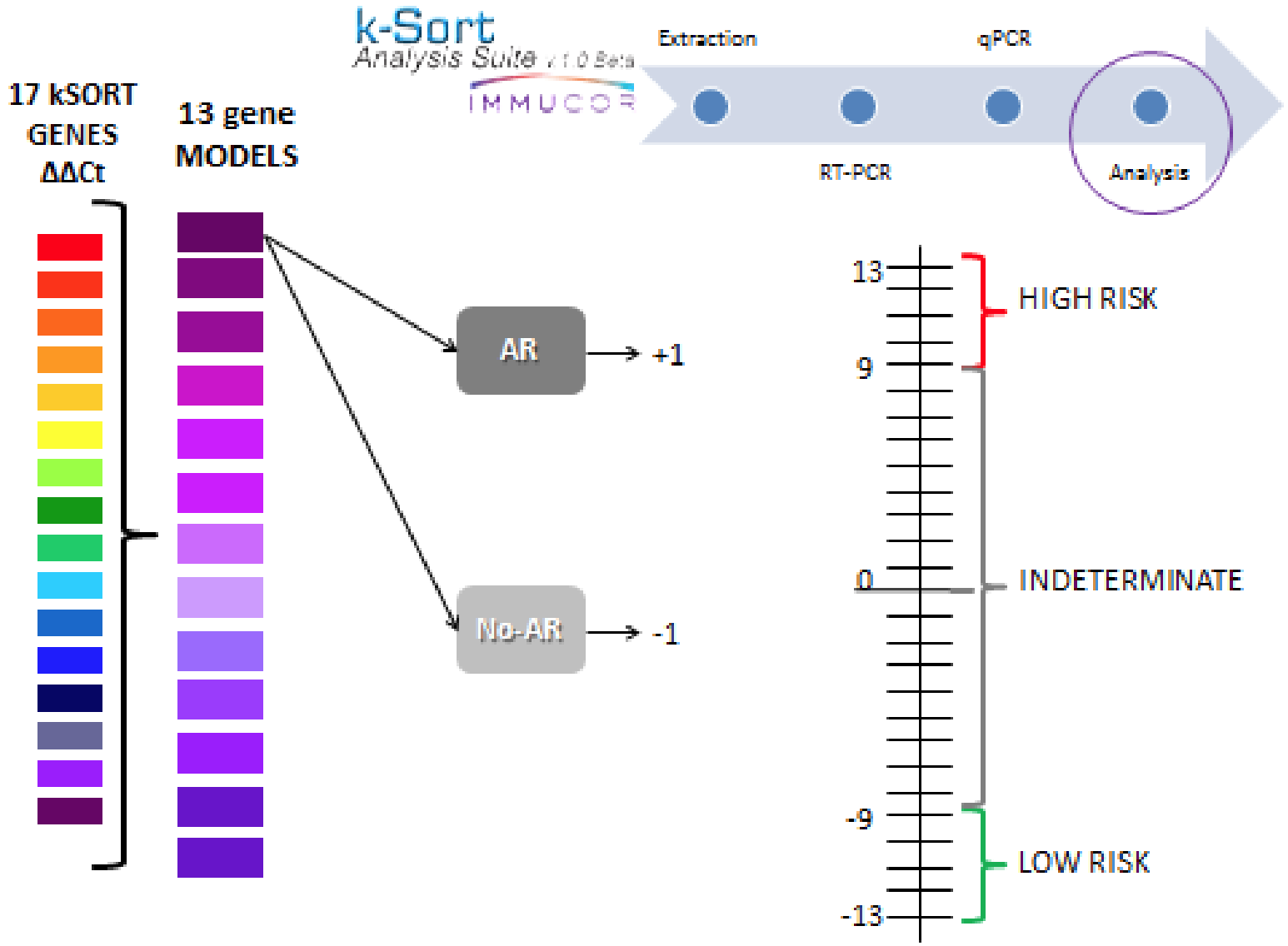
The answer in a drop of blood…..

17 gene PCR test measuring graft immune activation by RNA isolated from whole blood



CFLAR, DUSP1, IFNGR1, ITGAX, MAPK9, NAMPT, NKTR, PSEN1,CEACAM4, EPOR, GZMK, RARA, RHEB, RXRA, SLC25A37, RNF130, RYBP

Roedder et al, Plos Medicine, 2014; Li et al, AJT, 2012


k-Sort
Analysis Suite
IMMUCOR
Extraction
qPCR
RT-PCR
Analysis
17 kSORT GENES ΔΔCt
13 gene MODELS
AR
+1
No-AR
-1
13
HIGH RISK
9
0
INDETERMINATE
-9
LOW RISK
-13

kSORT Performance in Three Independent Clinical Trials

AART100	BIOPSY		
	AR	No-AR	*Total*
HIGH	36	3	*39*
IND	3	12	*15*
Low	3	43	*46*
Total	*42*	*58*	***100***

SAILOR	BIOPSY		
	AR	No-AR	*Total*
HIGH	14	6	*20*
IND	3	7	*10*
Low	1	67	*68*
Total	*18*	*80*	***98***

ESCAPE	BIOPSY		
	sc-AR*	No-AR	*Total*
HIGH	14	1	*15*
IND	2	8	*10*
Low	6	44	*50*
Total	22	53	**75**

PERFORMANCE	AART 100	SAILOR	ESCAPE
Sensitivity	92.3%	93.3%	70.0%*
Specificity	93.5%	91.8%	97.78%
Bx Correlation	92.9%	92.1%	89.23%
Indeterminate	15%	10%	13.3%

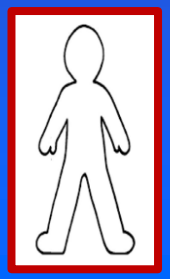
Outcomes and Clinical Utility of the kSORT assay in the PRISM (Prediction of Rejection In Sensitized Patient Blood SaMples) Prospective Clinical Trial of Highly Sensitized Kidney Transplant Recipients

Andrew Schroeder, Parhom Towfighi, Crystal Koh, Szu-Chuan Hseish, Juliane Liberto, Izabella Damm, Ruby, Tara Sigdel, Peggy Millar, Zoltan Laszik, Minnie M. Sarwal and Flavio Vincenti

University of California San Francisco, USA

PRISM: Study Design

95 patients, 6 mo follow-up, cPRA ≥ 50%



cPRA: 86. 4 ± 20%
kDPI: 42 ± 75%

	Pre -tx	2 wks	1 Mo	2 Mo	3 Mo	4 Mo	6 Mo	Cause bx
kSORT	X	X	X	X	X	X	X	X
DSA	X						X	X
Biopsy							X	X

PRISM Trial

- 54 patients had pre and post transplant samples for kSORT
- 47 had LR score
- 7 had intermediate score
- 10 had HR score
- **The overall predictive accuracy of the pre tx kSORT was 90% for no rejection**

PRECISION MEDICINE:
OPTIMIZING BELATACEPT USE IN KIDNEY TRANSPLANTATION

7 year follow-up analysis of BENEFIT Trial

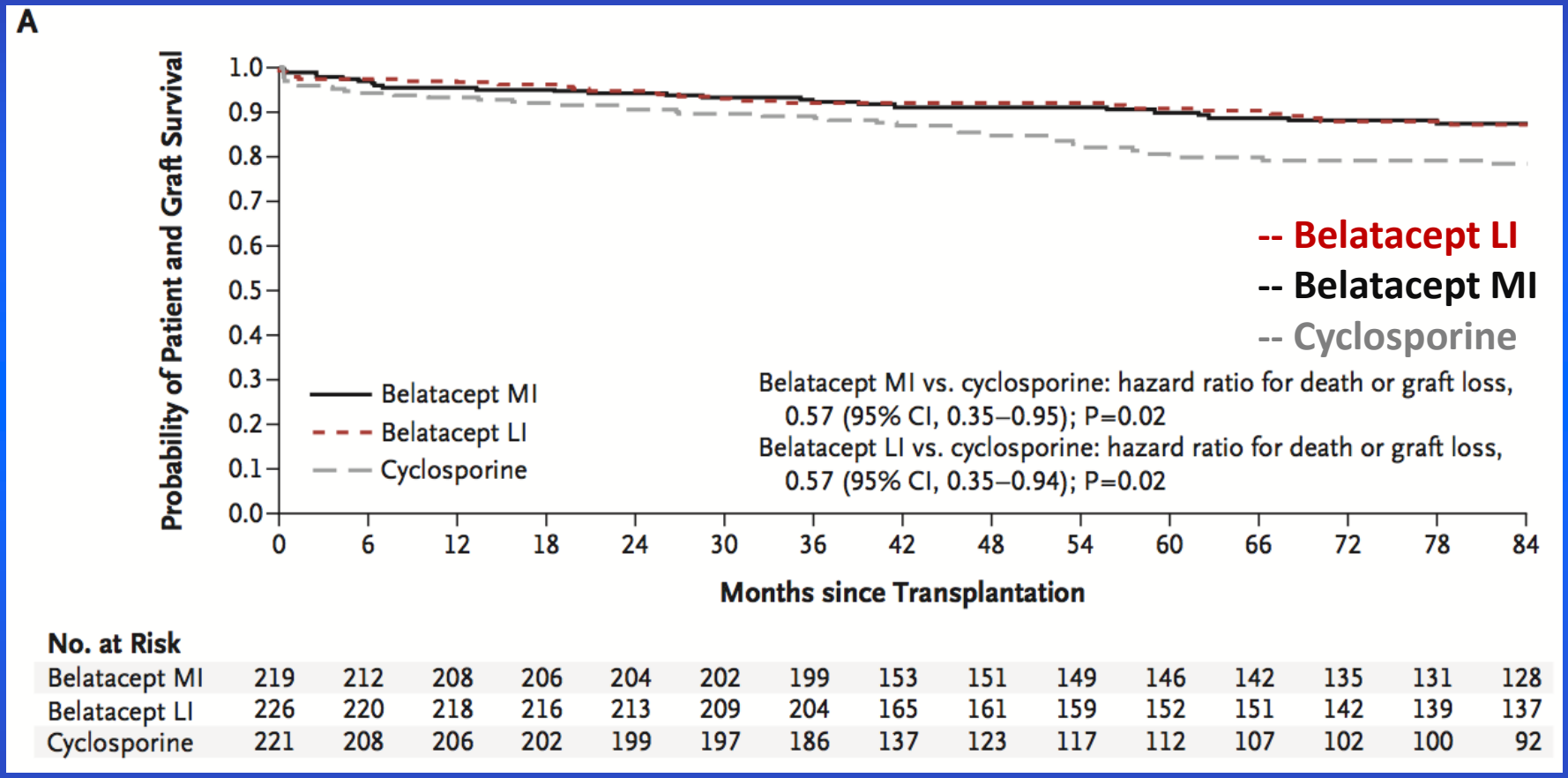
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belatacept and Long-Term Outcomes in Kidney Transplantation

Flavio Vincenti, M.D., Lionel Rostaing, M.D., Ph.D., Joseph Grinyo, M.D., Ph.D., Kim Rice, M.D., Steven Steinberg, M.D., Luis Gaite, M.D., Marie-Christine Moal, M.D., Guillermo A. Mondragon-Ramirez, M.D., Jatin Kothari, M.D., Martin S. Polinsky, M.D., Herwig-Ulf Meier-Kriesche, M.D., Stephane Munier, M.Sc., and Christian P. Larsen, M.D., Ph.D.

BENEFIT 7 year follow-up: *Patient & Graft Survival*

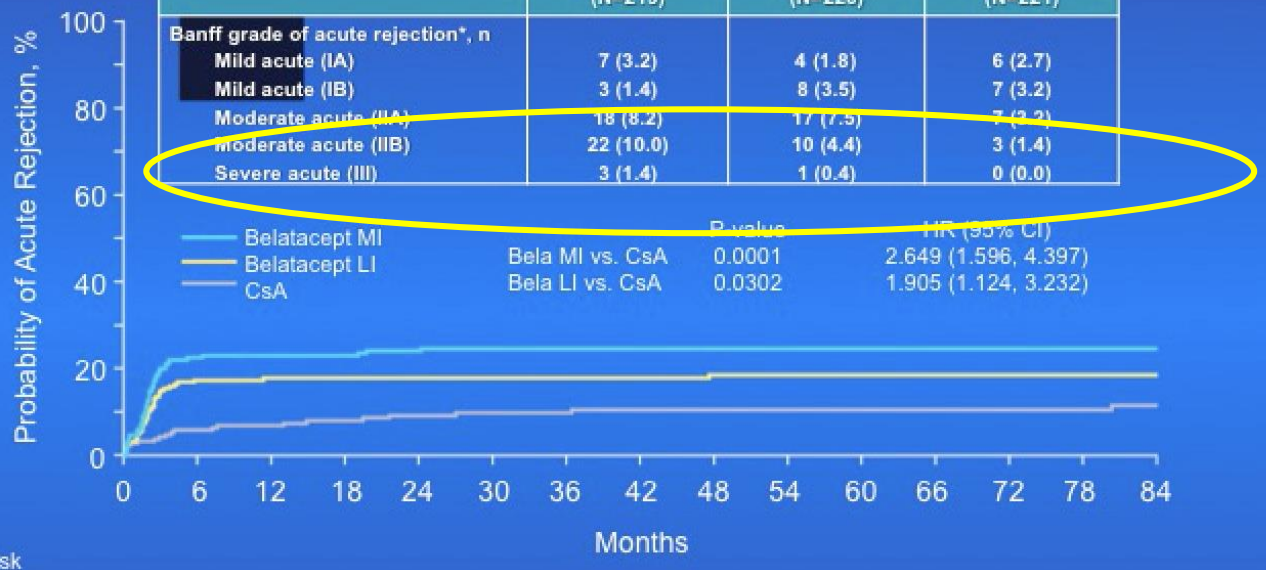


No. at Risk															
Belatacept MI	219	212	208	206	204	202	199	153	151	149	146	142	135	131	128
Belatacept LI	226	220	218	216	213	209	204	165	161	159	152	151	142	139	137
Cyclosporine	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92

43% reduction in risk of death or graft loss was observed in both **belatacept** arms compared to cyclosporine regimen

BENEFIT 7 year follow-up: *Acute Rejection*

	Belatacept MI (N=219)	Belatacept LI (N=226)	CsA (N=221)
Banff grade of acute rejection*, n			
Mild acute (IA)	7 (3.2)	4 (1.8)	6 (2.7)
Mild acute (IB)	3 (1.4)	8 (3.5)	7 (3.2)
Moderate acute (IIA)	18 (8.2)	17 (7.5)	7 (3.2)
Moderate acute (IIB)	22 (10.0)	10 (4.4)	3 (1.4)
Severe acute (III)	3 (1.4)	1 (0.4)	0 (0.0)



For patients with an event, the time to event was defined as minimum of event date and date of last dose (transplant date for non-treated patients) plus 56 days. For patients without an event, the time to event was defined as last follow-up date for on-treatment patients, date of last dose plus 56 days for off-treatment patients, and transplant date plus 56 days for non-treated patients. Between Month 36 and Month 84, 0 belatacept MI-treated, 1 (grade IIA) belatacept LI-treated, and 2 (grade IA [n=1], grade IIA [n=1]) CsA-treated patients experienced acute rejection.
*Three patients (n=1 [grade IIA], belatacept MI; n=2, CsA [n=1, grade IA; n=1, grade IIA]) experienced acute rejection more than 56 days after treatment discontinuation.

- Rates of acute rejection similar to previous reports
- Few cases occurring after 36 months (no causes in belatacept MI; 1 case in belatacept LI; 2 cases in cyclosporine)

Can we determine who will be potentially good candidates for belatacept?

Precision Medicine for Determining the Efficacy of a Novel Belatacept Regimen

Background

We investigated pretransplant recipient immune profiles to determine which lymphocyte populations would be the best predictor in identifying patients who will be at lowest risk for costimulation blockade-resistant rejection.

Methods

- 20 kidney transplant recipients were prospectively enrolled at our center to receive de novo belatacept from May 2016-March 2017.
  - 8 deceased donor recipients
  - 12 living donor recipients

- PMBCs collected prior to transplantation and at the time of cause and protocol biopsies

- Immunosuppression:
  - Induction: Thymoglobulin 3mg/ kg
  - Belatacept 10mg/kg administered (POD 1, 4, 14, 28, 56, and 84) followed by 5mg/kg monthly maintenance dose starting week 16.
  - MMF → converted to everolimus at 1 month
  - Corticosteroid maintenance

Pre-Transplant Flow Cytometry in Patients to be Treated with Belatacept

% CD4 TEMRA	2.29
% CD8 TEMRA	44.77
%CD57+PD1- in CD4	0.35
in CD4 CD45RO+	0.32
in CD4 Naïve	0.07
in CD4 CM	0.16
in CD4 TEM	0.56
in CD4 TEMRA	**10.22**
%CD57+PD1-in CD8	34.58
in CD8 CD45RO+	11.47
in CD8 Naïve	0.35
in CD8 CM	0.82
in CD8 TEM	15.09
in CD8 TEMRA	71.90
%CD28-in CD4	1.18
%CD28-in CD8	44.46
%CD28-PD1- in CD4	0.29
%CD28-PD1- in CD8	36.92
%CD28hiCD2+ in CD4	19.89
%CD28hiCD2+ in CD8	16.37
%CD28hiCD2+ in CD4 CD45RO+	66.74
%CD28hiCD2+ in CD8 CD45RO+	70.67

20 patients enrolled in the Belatacept Precision Medicine Project

Results

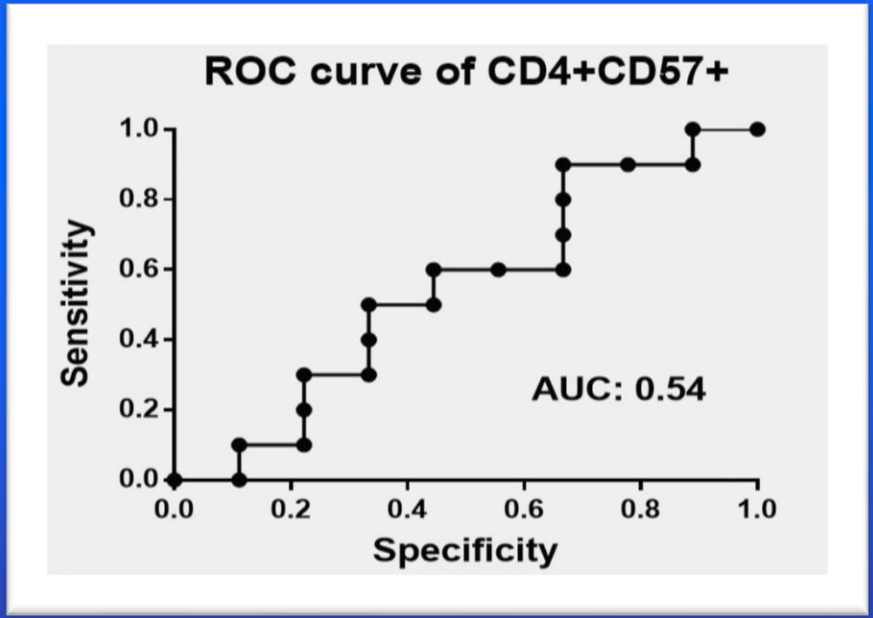
- **At end of 6 month follow-up:**
  - 18 patients remained on belatacept
  - 2 patients were converted to tacrolimus (due to rejection)

At 6 months (median):

	Total (N=20)	Acute rejection (N=4)
Serum creatinine (mg/dL)	1.06	1.04
eGFR (mL/min)	70	65
Urine protein/creatinine (g/g)	0.22	0.21

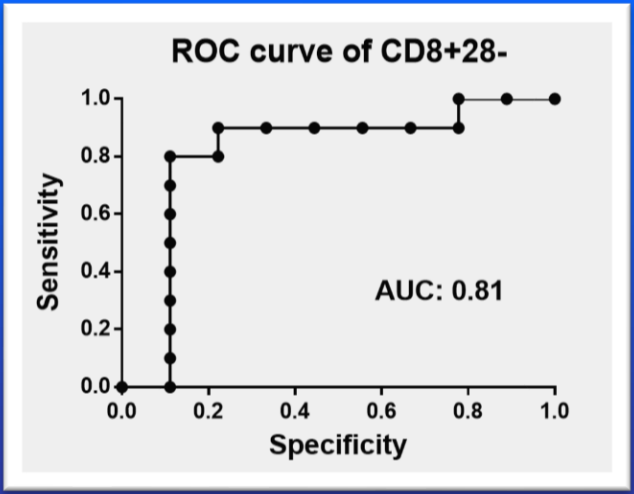
Results: *Immune profile*

- **No correlation** was found between rejection and percentage of **$CD4^+CD57^+$ T cells** in pre-transplant PBMCs, marker previously reported to be associated with rejection on belatacept-based regimen.

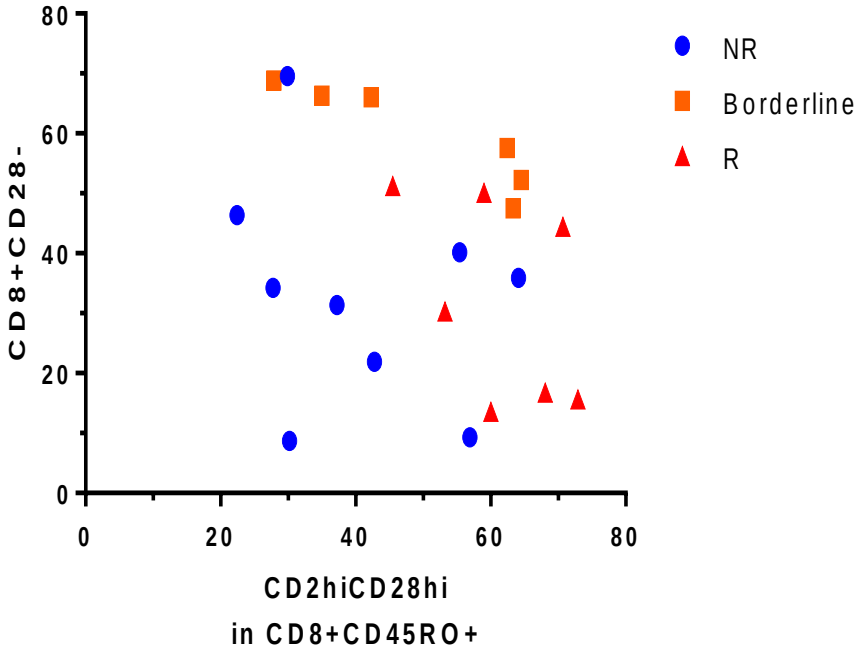


Results: *Immune profile*

- Patients who had **biopsy-proven rejection or borderline changes** had **significantly higher percentages of $CD8^+CD28^-$ T cells** in pre-transplant PBMC when compared to those who had normal biopsy.
- Patients with **greater than 50% of $CD8^+CD28^-$ T cells pre-transplant** were more likely to experience rejection (odds ratio was 18.7, sensitivity 87.5% with false positive of 12.5%, p= 0.02).

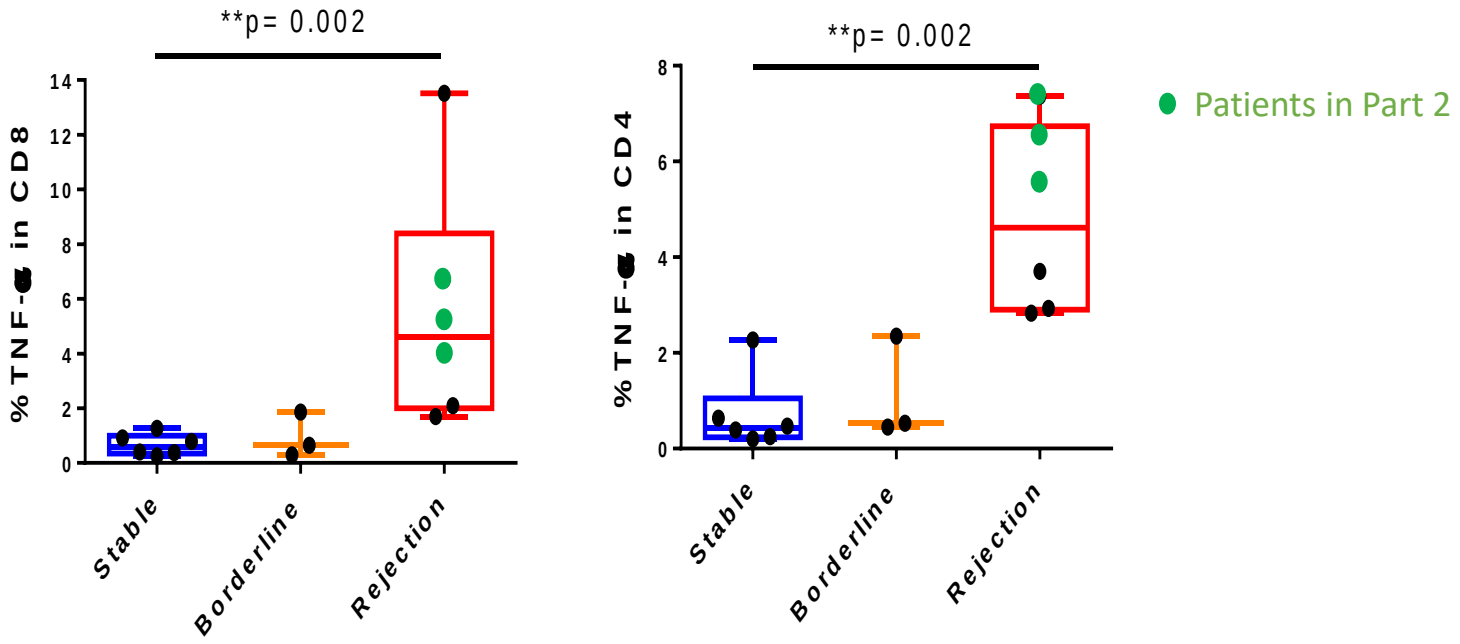


Patients who have rejection with low CD28- were found to have high CD2hiCD28hi in CD8+CD45RO+ T cells

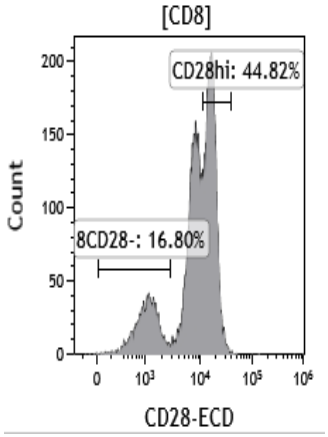


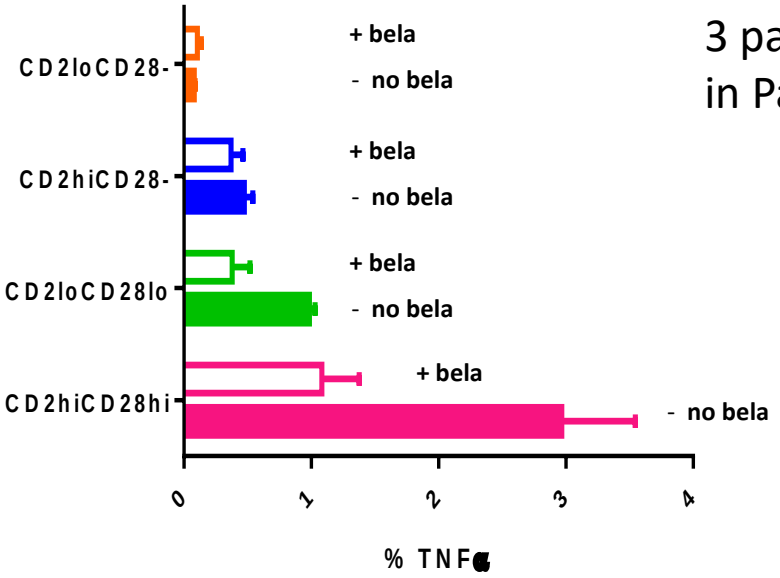
Short-term memory assay

3 patients who have rejection in Part 2 Bela Study are functionally able produce high level TNF in CD4/CD8 T cells in response to allo-stimulation



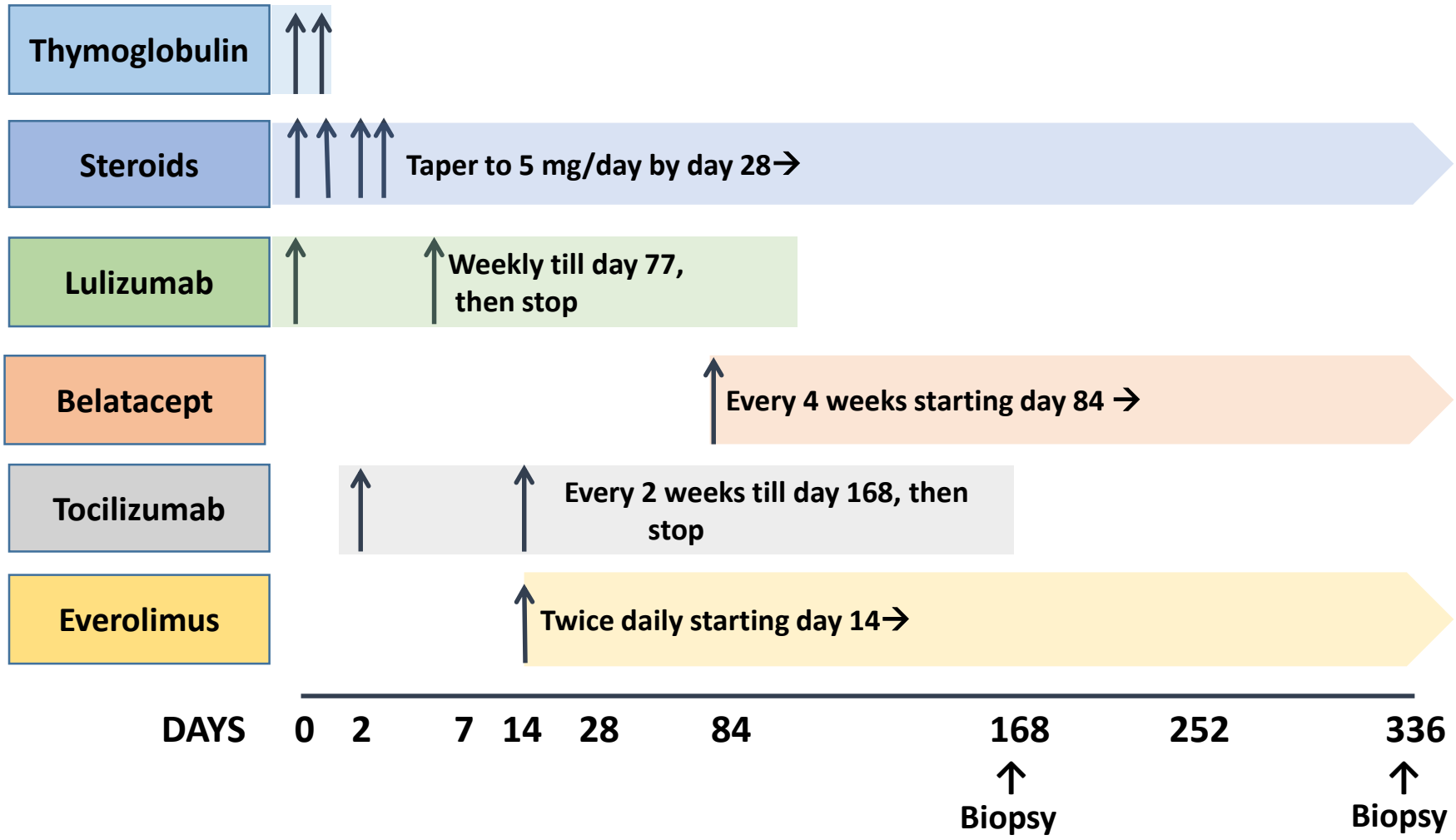
TNF-α production in CD8+CD28- is resistant to belatacept; However, patients who have high level of CD2hiCD28hi, cytokine production is not completely blocked in CD8+CD2hiCD28hi in response to allo- stimulation





3 patients who have rejection in Part 2 study

Study Diagram-CTOT 24



Conclusion

- Precision Medicine has greatly improved the use of novel agents in oncology and may have similar impact in organ transplantation
- Novel Therapies will require the application of Precision Medicine with the use of novel biomarkers for successful development in transplantation and demonstrate better safety and efficacy profiles to justify their costs


Precision Medicine : Riding
The Wave