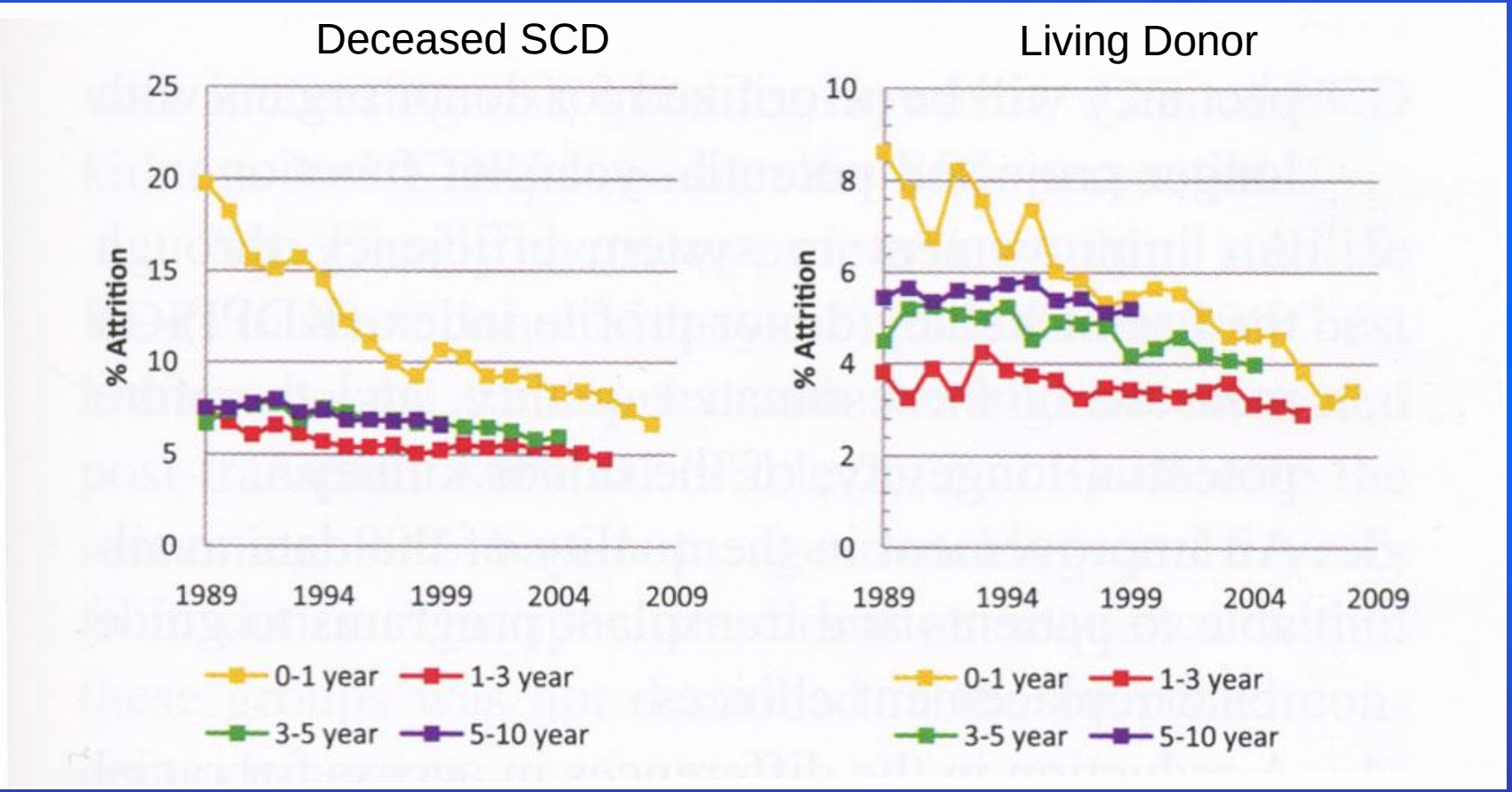
Novel Strategies to Improve Long-Term Outcome in Renal Transplanation

Flavio Vincenti

Cumulative graft failure yearly attrition rates of first kidney transplants



Lamb et al AJT 2011

Causes of Late Graft Dysfunction/Loss

Immunologic (Antigen Dependent)	Nonimmunologic (Antigen Independent
Cellular immunity TCMR Inflammation	Donor Factors donor age/reduced renal mass living *versus* deceased
Humoral immunity DSA, AMR, cAMR	Recipient factors adherence new onset diabetes recurrent disease cardiovascular risk factors
	Treatment CNI's nephrotoxicity
	Infection CMV BK (polyomavirus)

Why Kidneys Fail in the Long Term?

The balance is Tilting Towards Chronic Immunologic Injury (?humoral) As A Leading Cause of Late Graft Loss

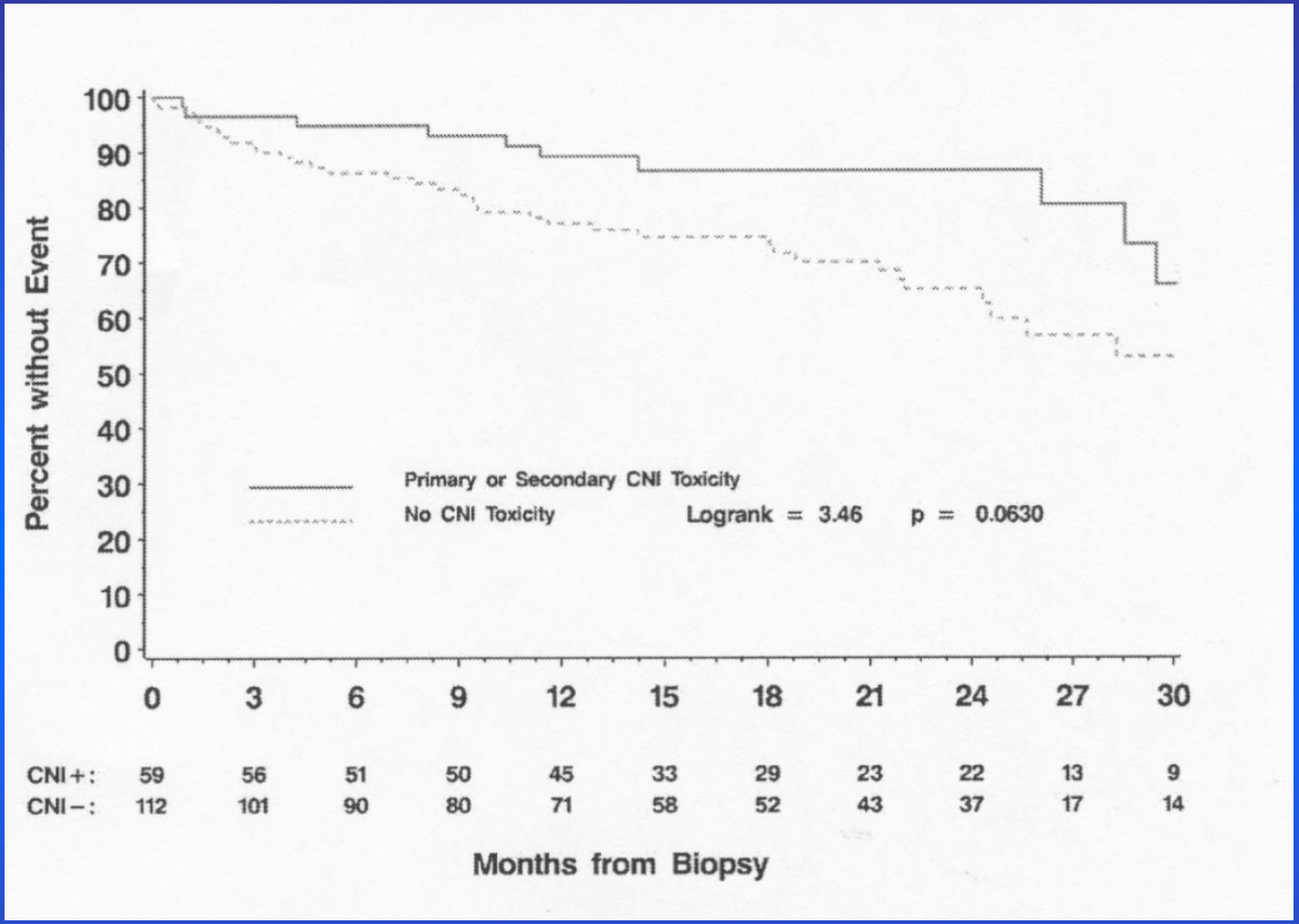
Evidence for Antibody-Mediated Injury as a Major Determinant of Late Kidney Allograft Failure

Robert S. Gaston, J. Michael Cecka, Bert L. Kasiske, Ann M. Fieberg, Robert Leduc, Fernando C. Cosio, Sita Gourishankar, Joseph Grande, Philip Halloran, Lawrence Hunsicker, Roslyn Mannon, David Rush, and Arthur J Matas

Transplantation Volume 90: 68-74

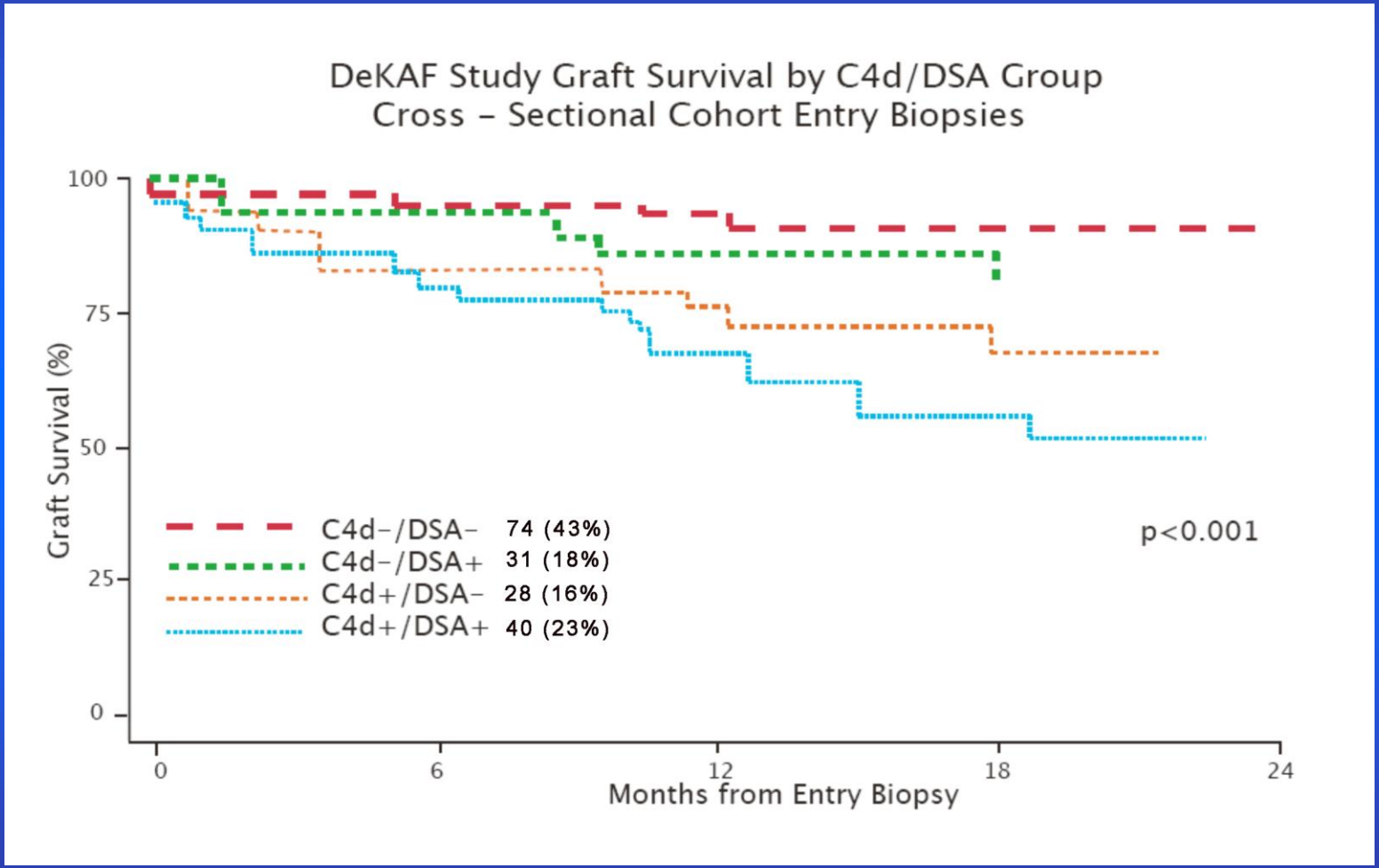
Methods

- One hundred seventy-three subjects transplanted before October 1, 2005 (mean time after transplant) 7.3±6.0 years) had a baseline serum creatinine level of 1.4±0.3 mg/dL before January 1, 2006 and underwent biopsy for new onset graft dysfunction after that date (mean creatinine at biopsy 2.7 ± 16 mg/dL).



Kaplan-Meier analysis of the impact of primary or secondary local diagnosis of calcineurin inhibitor (CNI) nephrotoxicity on kidney allograft survival after for-cause biopsy

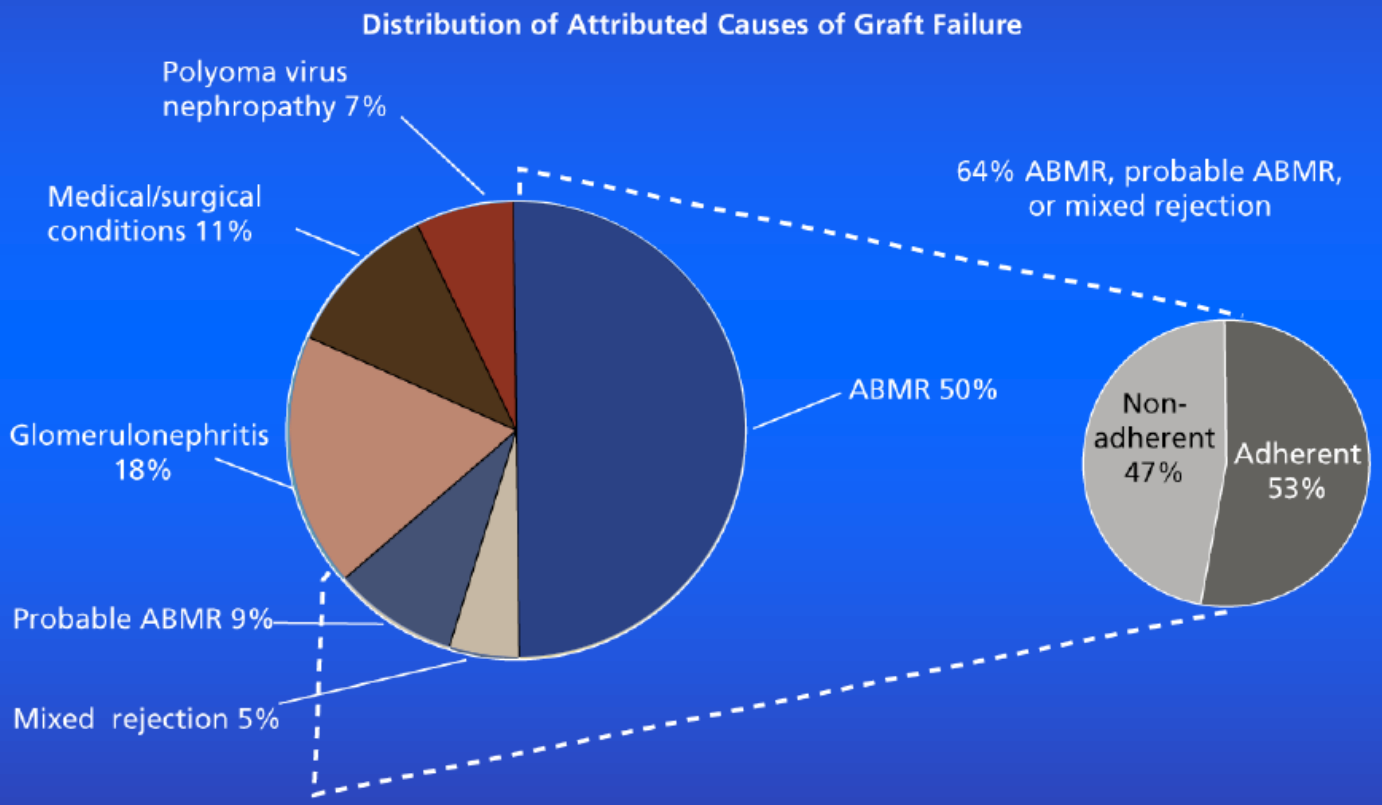
The DeKAF study also illustrates the impact of antibody-mediated injury on outcome



DeKAF = Long-term deterioration of kidney allograft function; DSA = Donor-specific antibody.

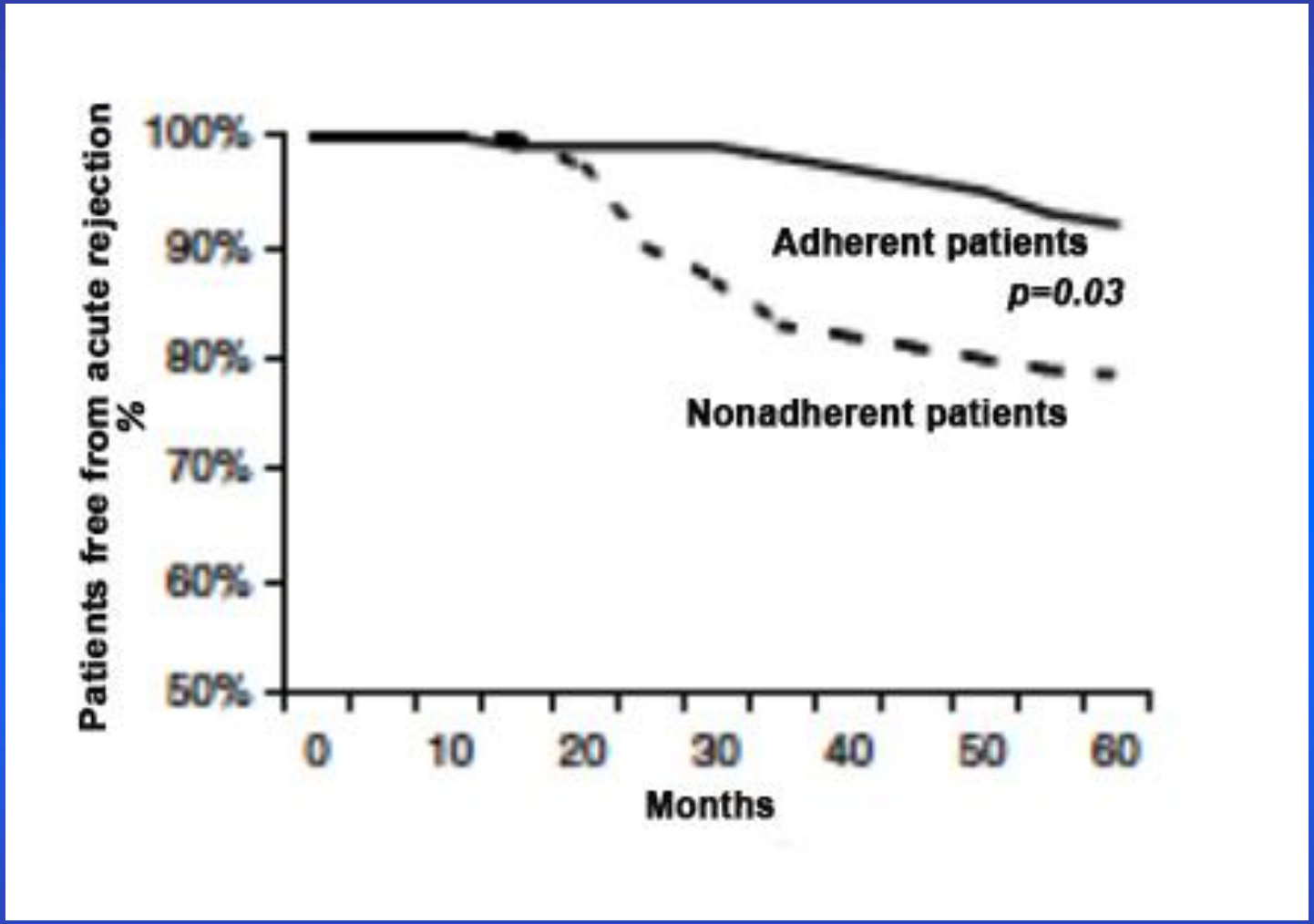
Gaston R et al. *Am J Transplant* 2009; Aug;9(8):1811-5.

The Role of Antibody-mediated Rejection and Non-adherence in Kidney Transplant Failure



- ABMR = antibody-mediated rejection
- Sellarés J et al. *Am J Transplant*. 2012;12:388-399.

Effect of Adherence on Outcome



Vlaminck H, et al. Am J Transplant. 2004;4(9):1509-1513 PMID: 15307839

American Journal of Transplantation 2008; 8: 324–331
Blackwell Munksgaard

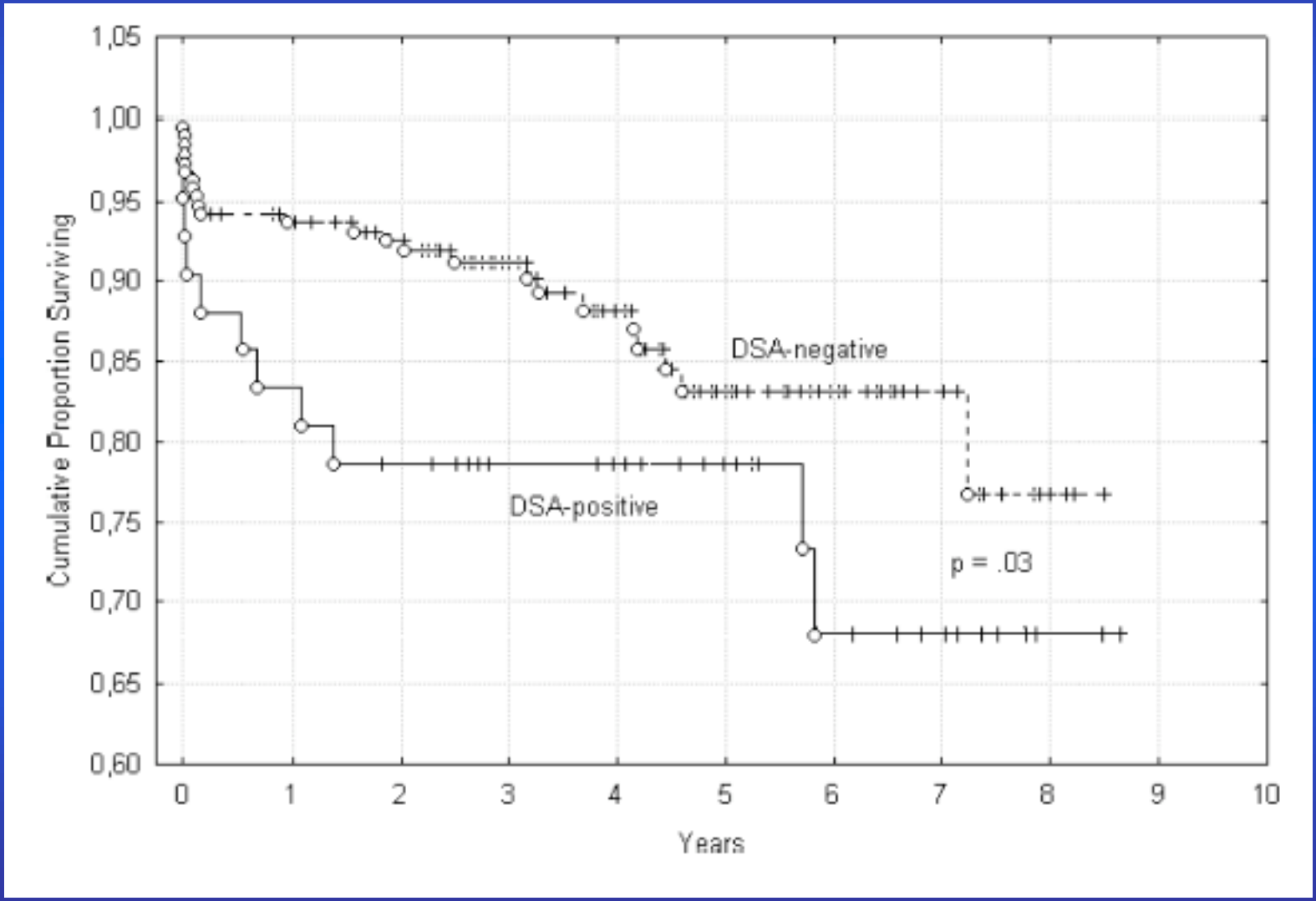
doi: 10.1111/j.1600-6143.2007.02072.x

Clinical Relevance of Preformed HLA Donor-Specific Antibodies in Kidney Transplantation

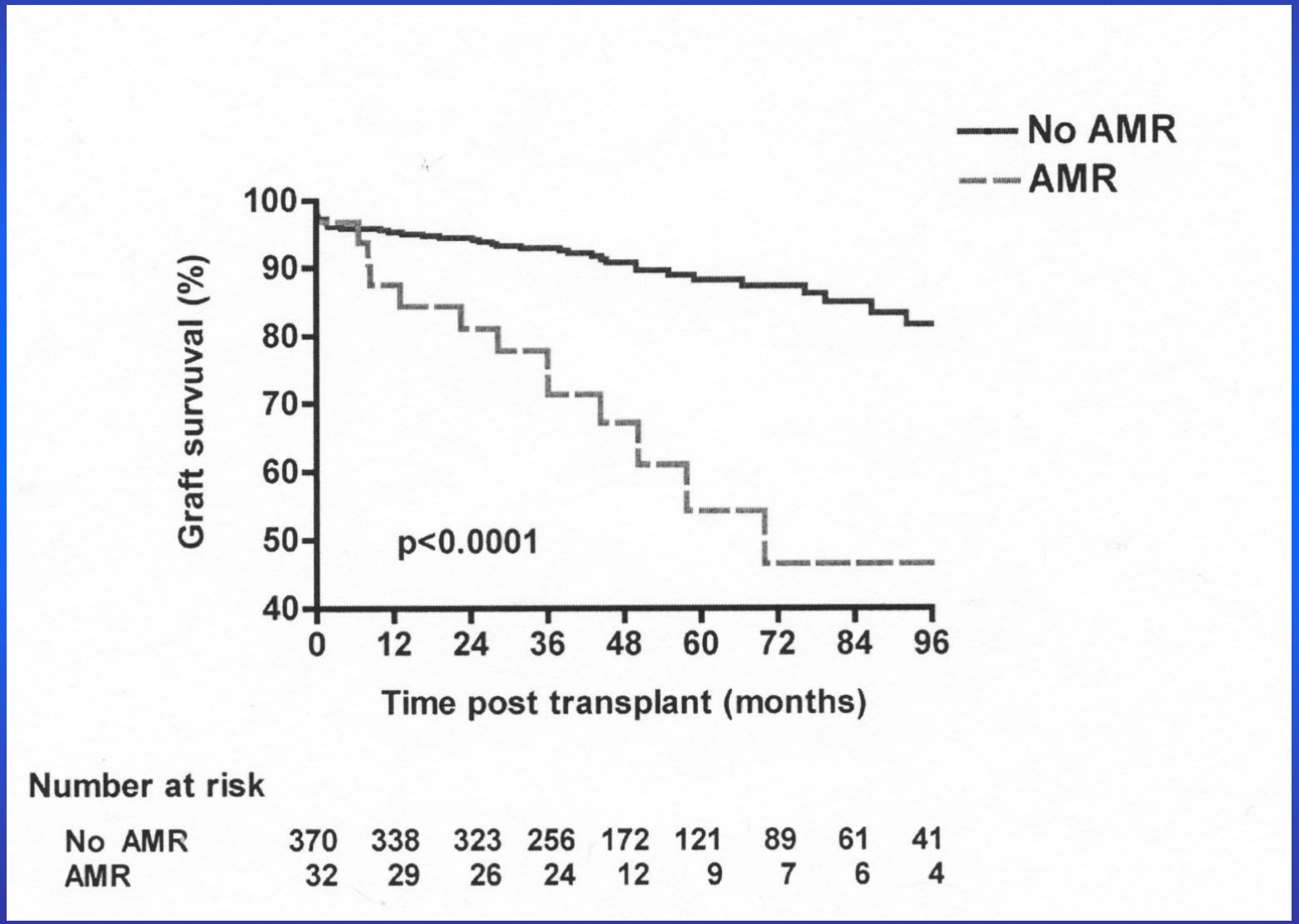
C. Lefaucheur[a,*], C. Suberbielle-Boissel[b], G. S. Hill[c], D. Nochy[c], J. Andrade[b], C. Antoine[a], C. Gautreau[b], D. Charron[b] and D. Glotz[a]

[a]*Departments of Nephrology and Kidney Transplantation and* [b]*Departments of Immunology and Histocompatibility, Saint-Louis Hospital, Paris, France*
[c]*Department of Histopathology, Georges Pompidou European Hospital, Paris, France*
**Corresponding author: Carmen Lefaucheur, carmen.lefaucheur@wanadoo.fr*

Eight-year grafts survival analysis of kidney transplants in relation to DSA status.



Graft survivals of those with and without episodes of acute antibody-mediated rejection

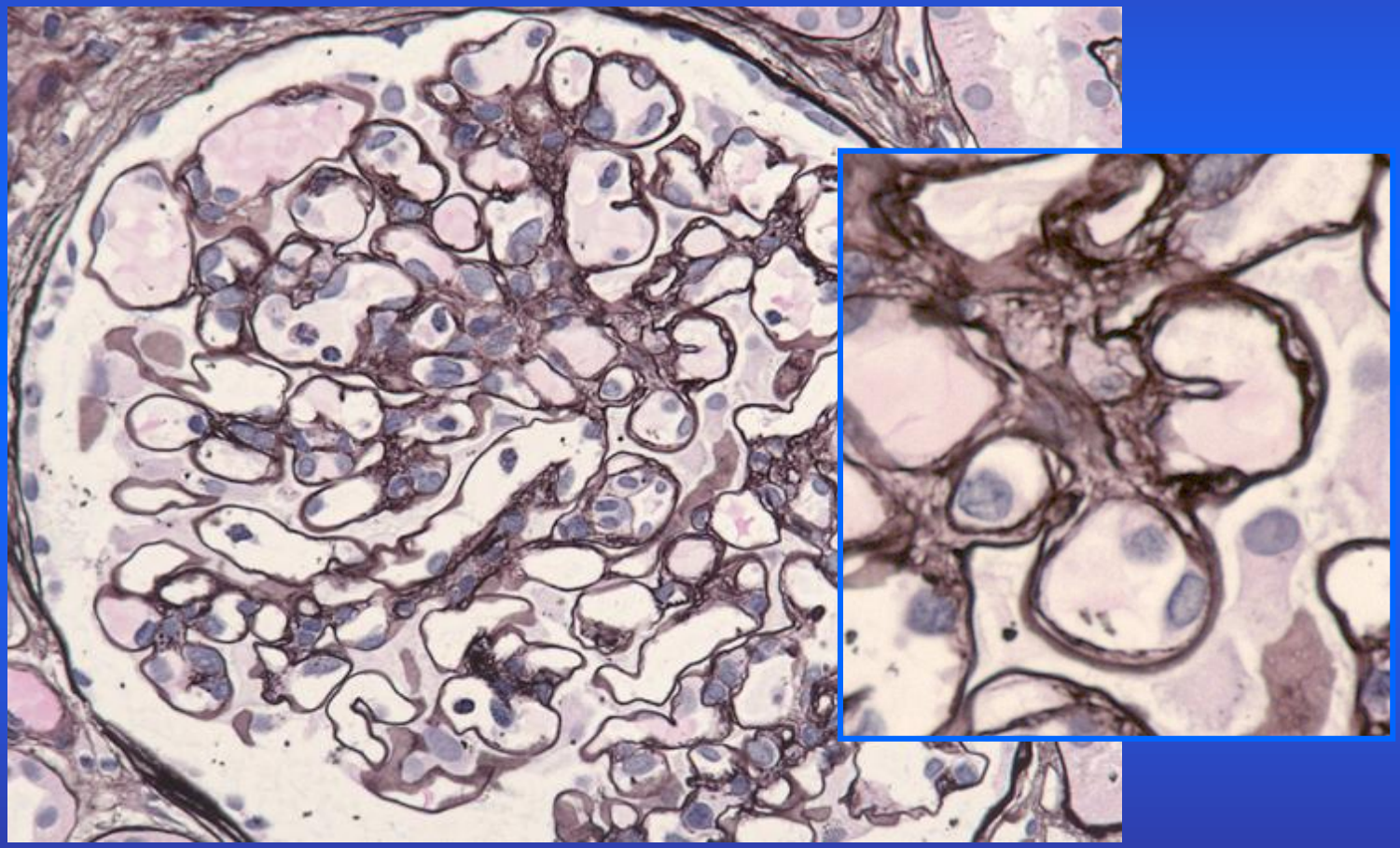


Number at risk

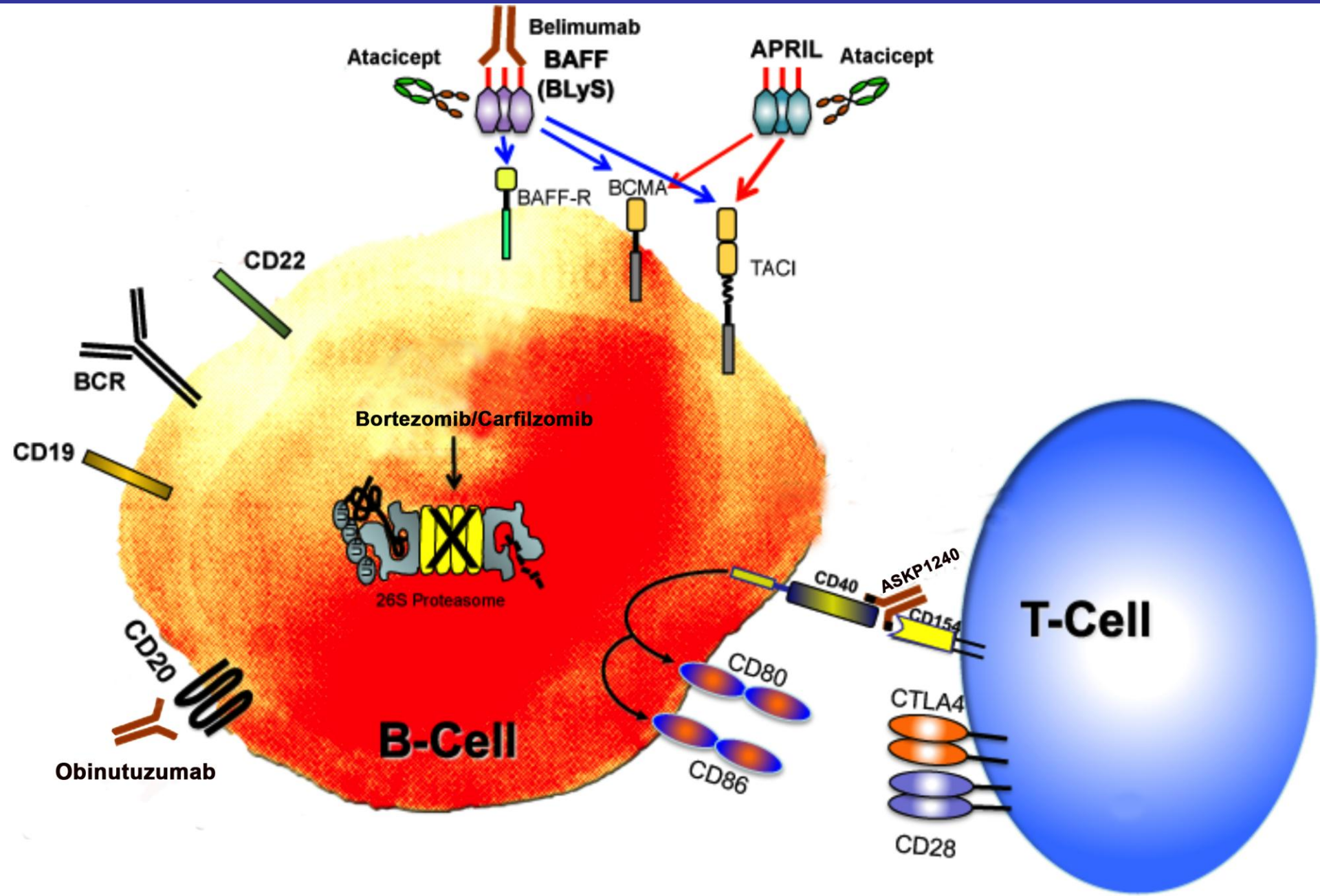
No AMR	370	338	323	256	172	121	89	61	41
AMR	32	29	26	24	12	9	7	6	4

Lefaucheur, et al. CJASN 2011

The Glomerular Injury to Avoid



Transplant glomerulopathy


Belimumab
Atacicept
BAFF
(BLyS)
APRIL
Atacicept
BAFF-R
BCMA
TACI
CD22
BCR
CD19
Bortezomib/Carfilzomib
26S Proteasome
CD20
Obinutuzumab
B-Cell
CD40
ASKP1240
CD154
T-Cell
CD80
CD86
CTLA4
CD28

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

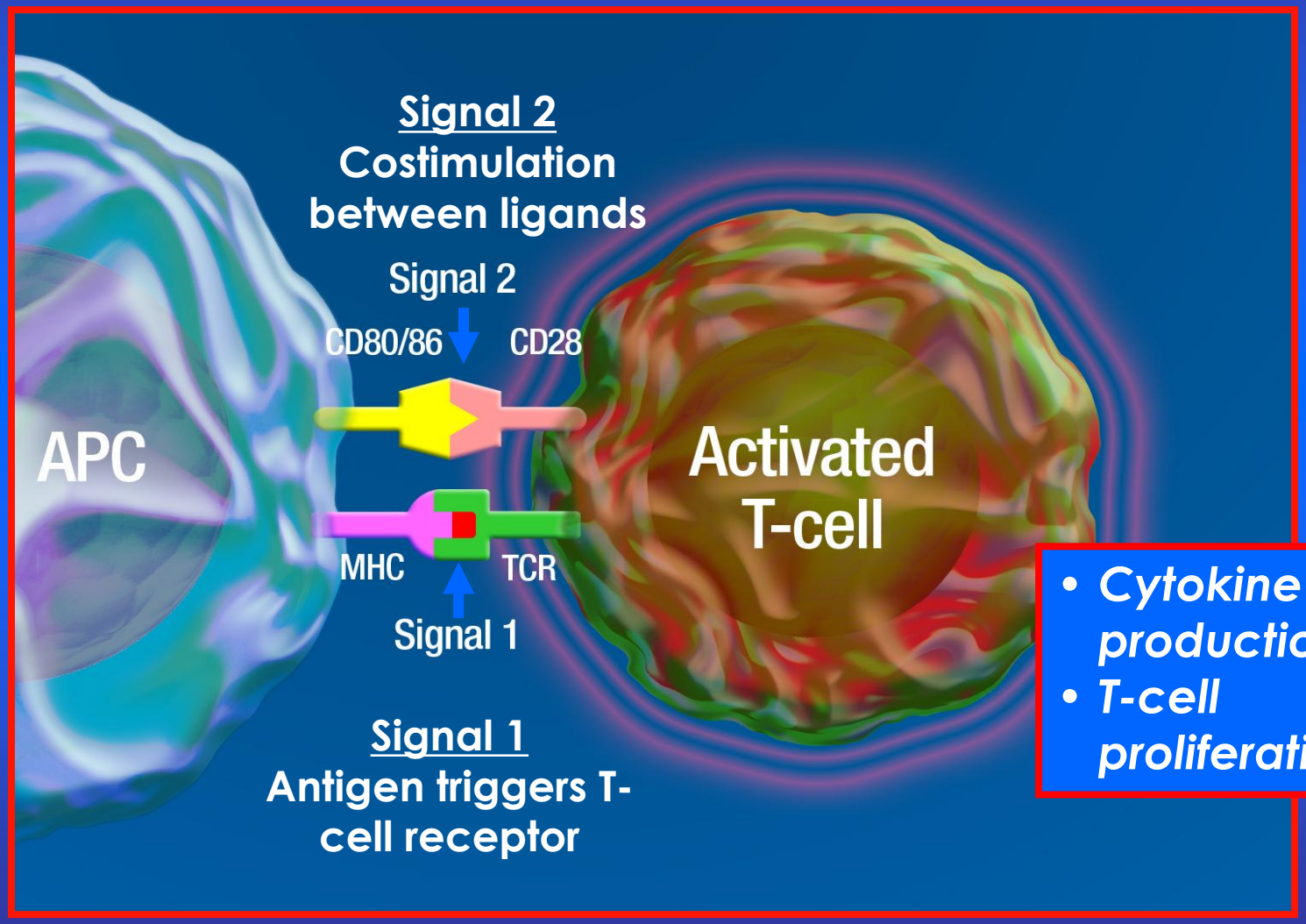
Belatacept and Long-Term Outcomes in Kidney Transplantation

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.

N ENGL J MED 374;4 NEJM.ORG JANUARY 28, 2016

T-Cells Require Costimulation for Full Activation

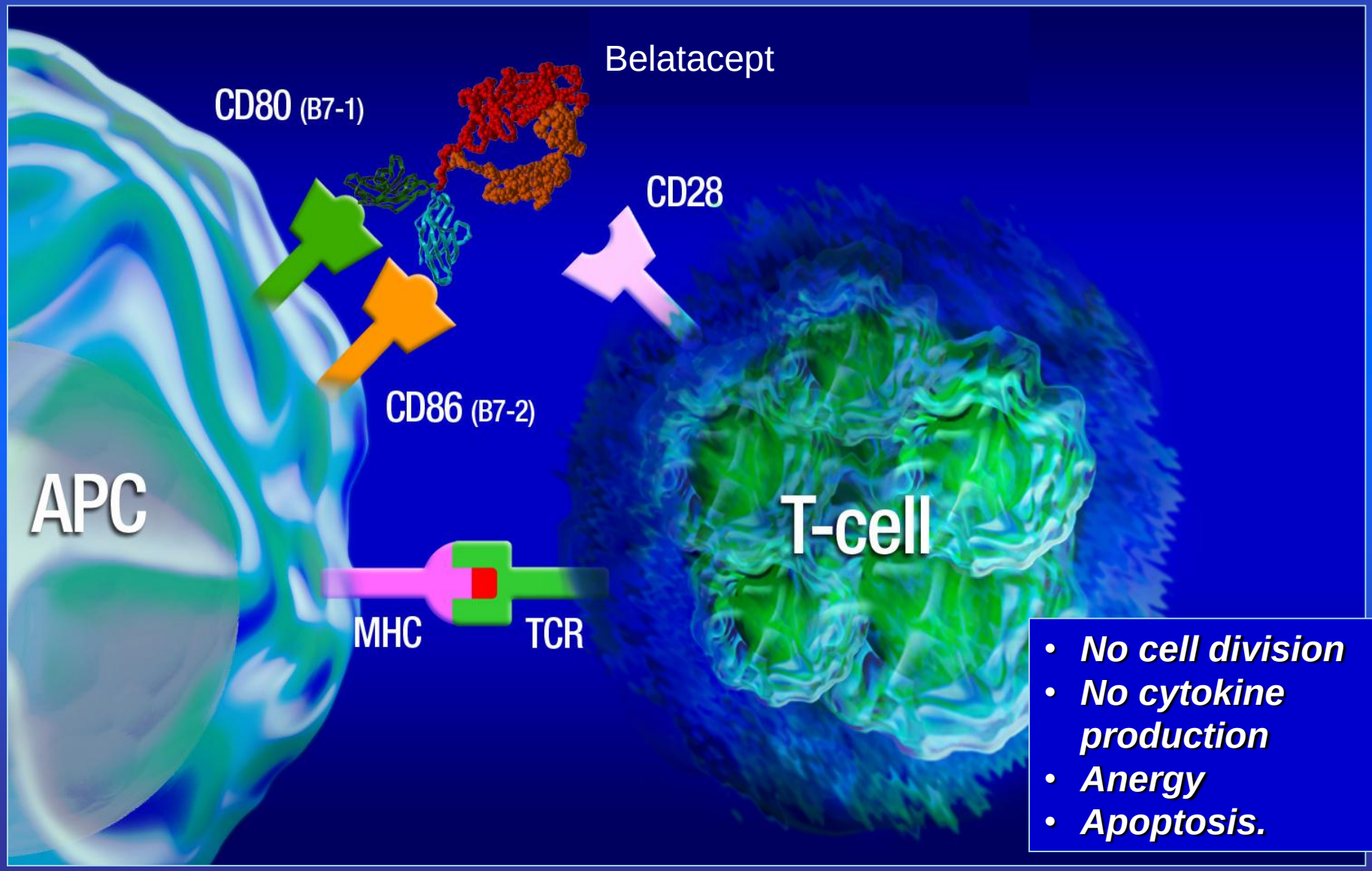
CD80/86-CD28 is the most important costimulatory pathway*



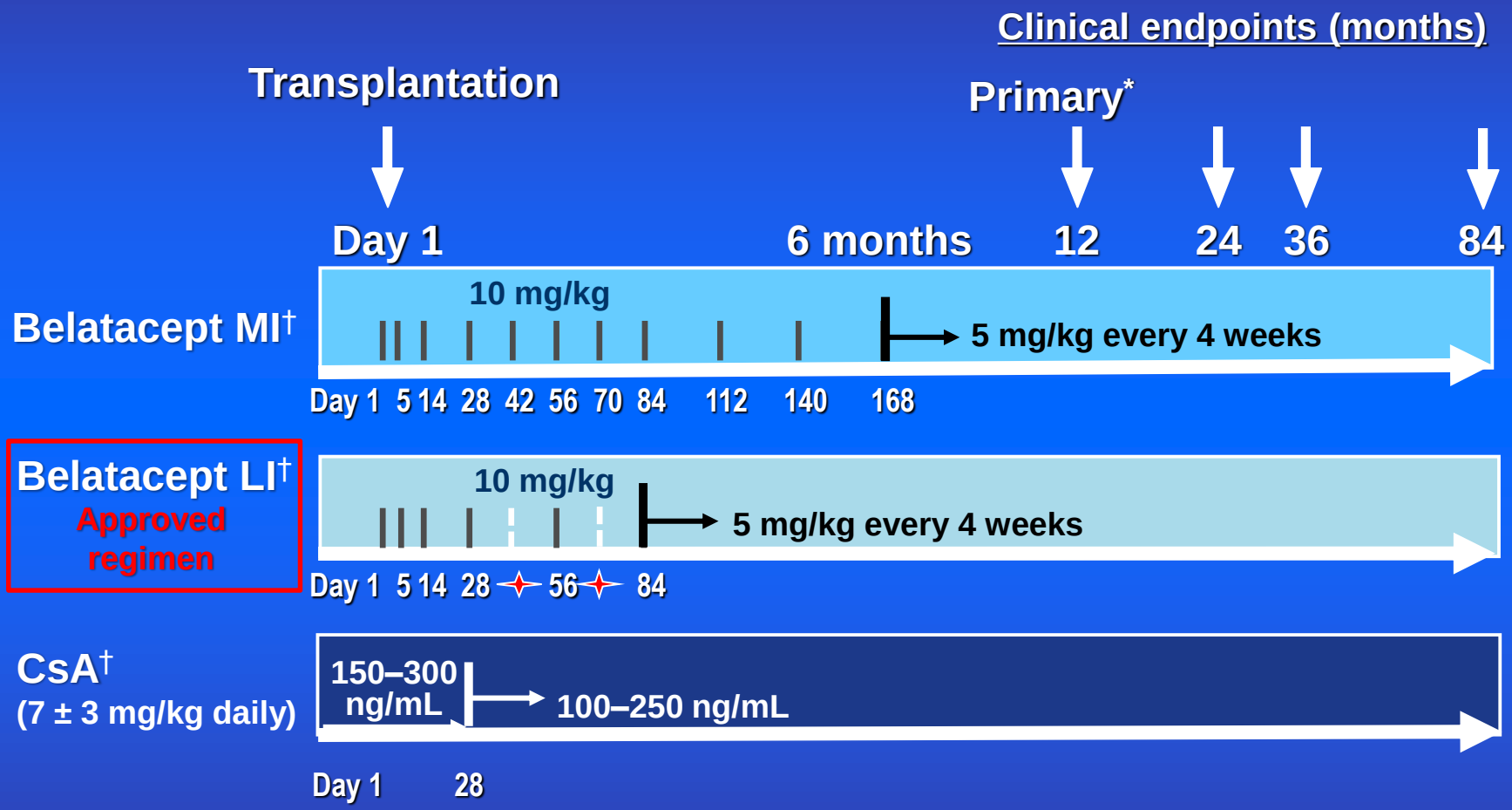
*Other costimulatory pathways exist that also serve this role

APC=antigen-presenting cells

Belatacept potently and selectively blocks T-cell activation



Study Design and Dosing

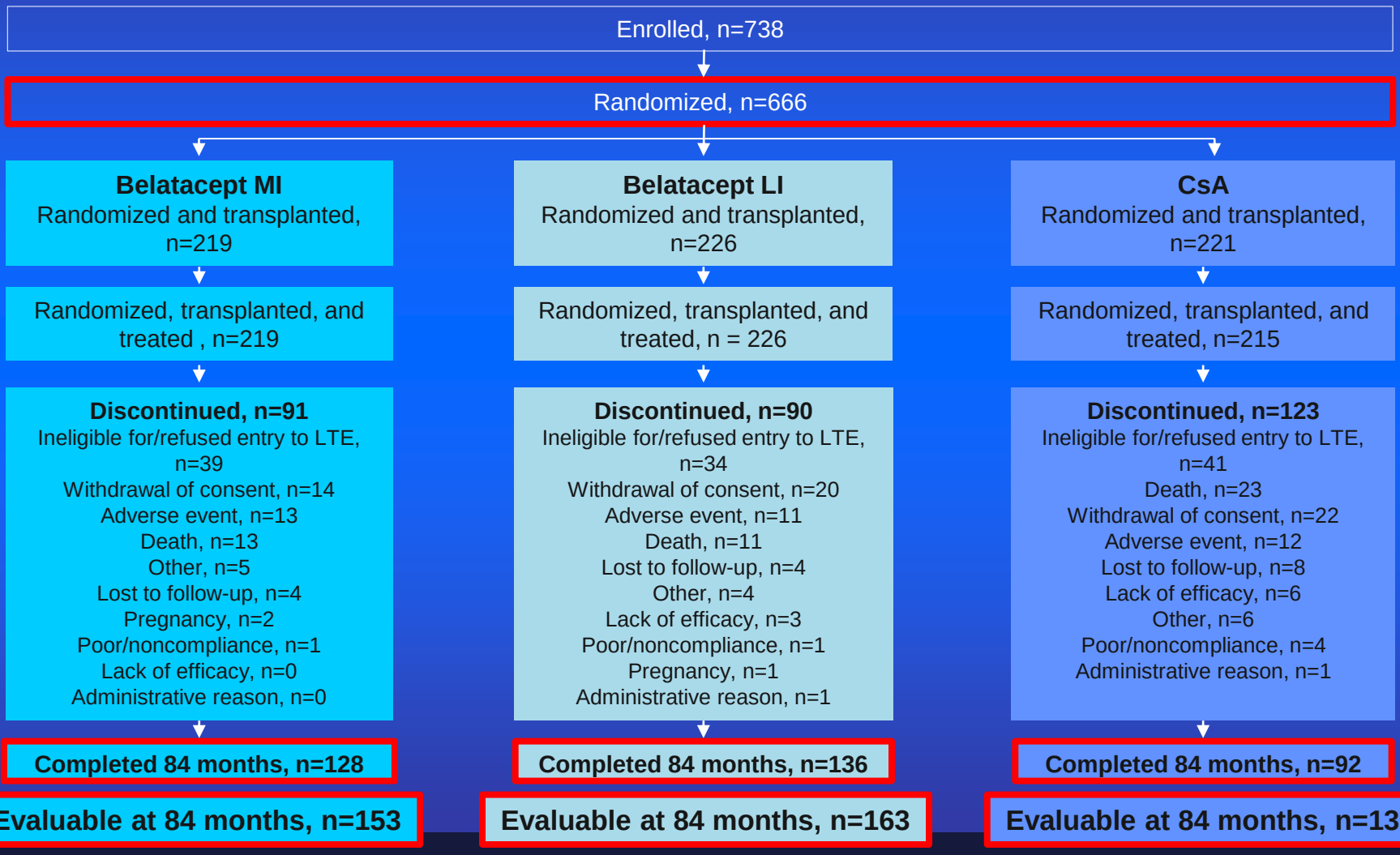


*Belatacept arms unblinded at 12 months.
†All patients received basiliximab induction, mycophenolate mofetil, and corticosteroid taper.

CsA=cyclosporine A; LI=less intensive; MI=more intensive.

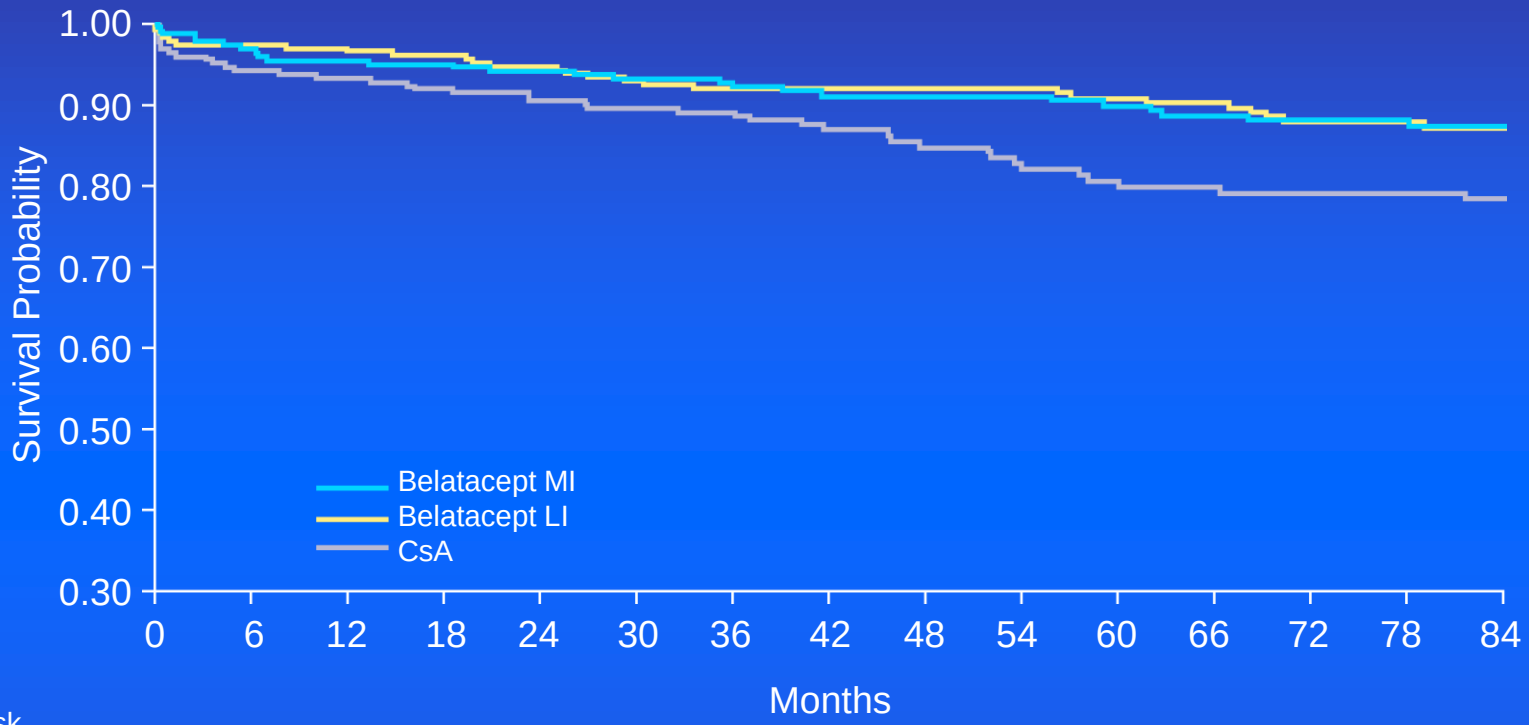
Patient Disposition

The median duration of follow-up for each treatment arm was 84.0 months



Evaluable patients were followed for more than 84 months or had died or experienced graft loss by Month 84.
CsA=cyclosporine A; LI=less intensive; LTE=long-term extension; MI=more intensive.

Time to Death or Graft Loss From Randomization to Month 84



N 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
CsA	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92

Month 60

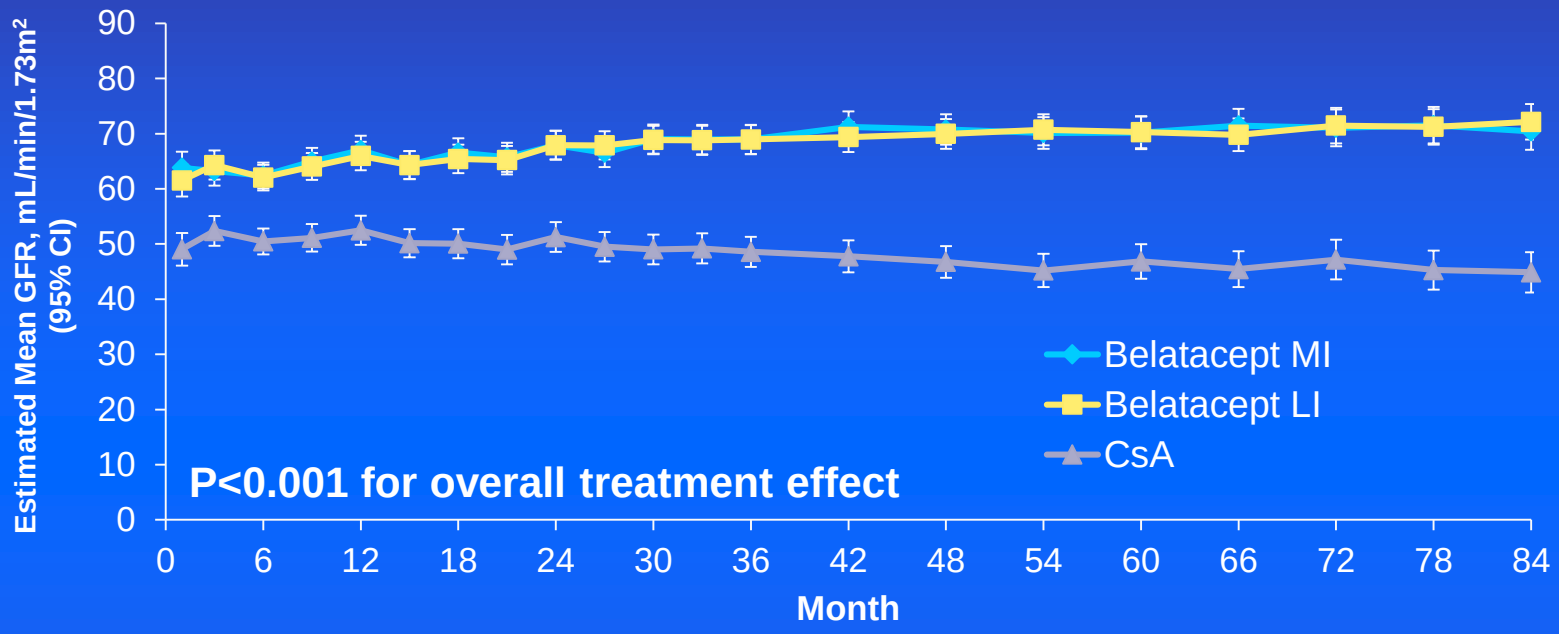
	P-value	HR (95% CI)
Bela MI vs. CsA	0.0100	0.521 (0.306, 0.889)
Bela LI vs. CsA	0.0045	0.477 (0.277, 0.819)

Month 84

	P-value	HR (95% CI)
Bela MI vs. CsA	0.0225	0.573 (0.348, 0.946)
Bela LI vs. CsA	0.0210	0.570 (0.348, 0.935)

Bela=belatacept; CI=confidence interval; CsA=cyclosporine A; HR=hazard ratio; LI=less intensive; MI=more intensive.

Estimated Mean GFR Over 84 Months: MEM Without Imputation

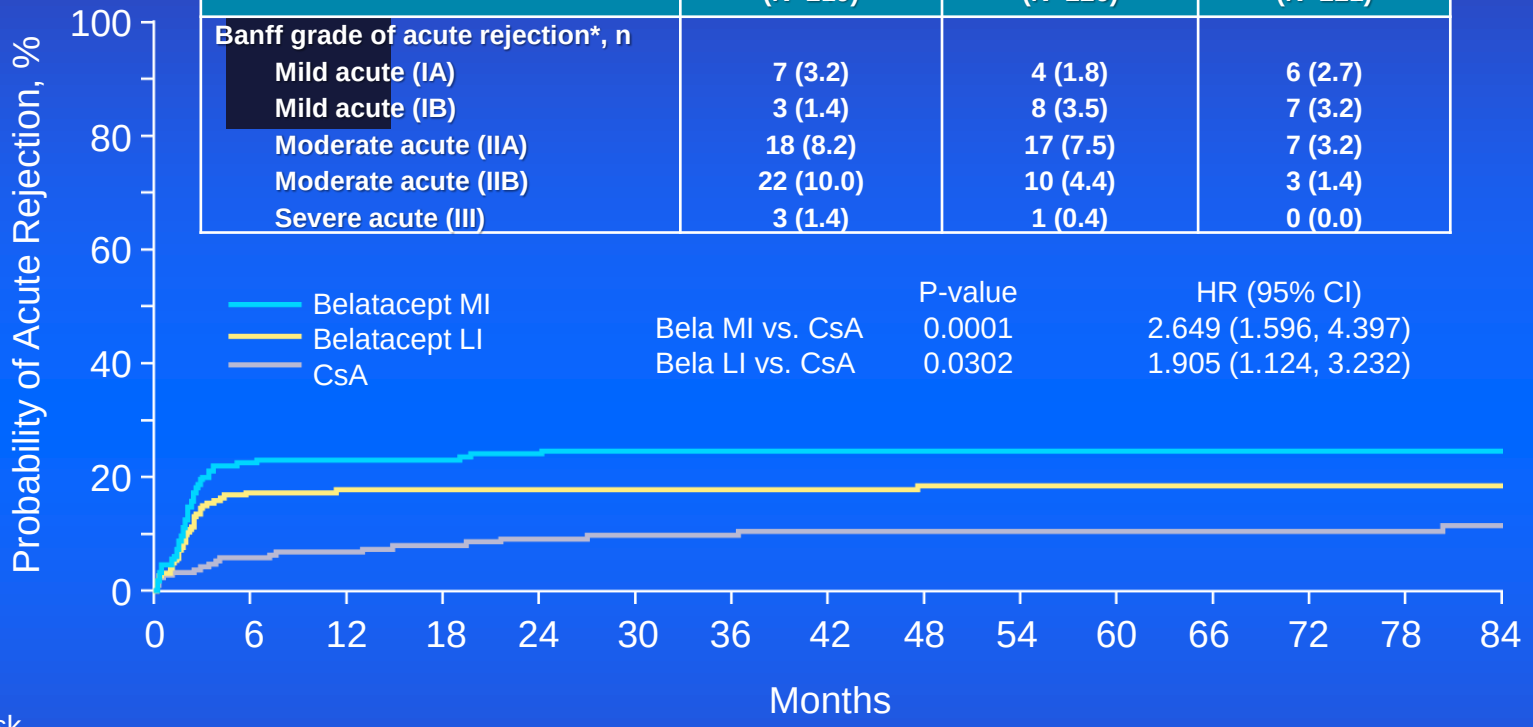


	Belatacept MI		Belatacept LI		CsA
	GFR	Difference vs. CsA	GFR	Difference vs. CsA	GFR
Month 12	67.0	14.5	66.0	13.5	52.5
Month 36	68.9	20.3	68.9	20.4	48.6
Month 60	70.2	23.3	70.3	23.4	46.8
Month 84	70.4	25.6	72.1	27.3	44.9

CsA=cyclosporine A; GFR=glomerular filtration rate; LI=less intensive; MEM=mixed effects modeling; MI=more intensive.

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)



N at risk

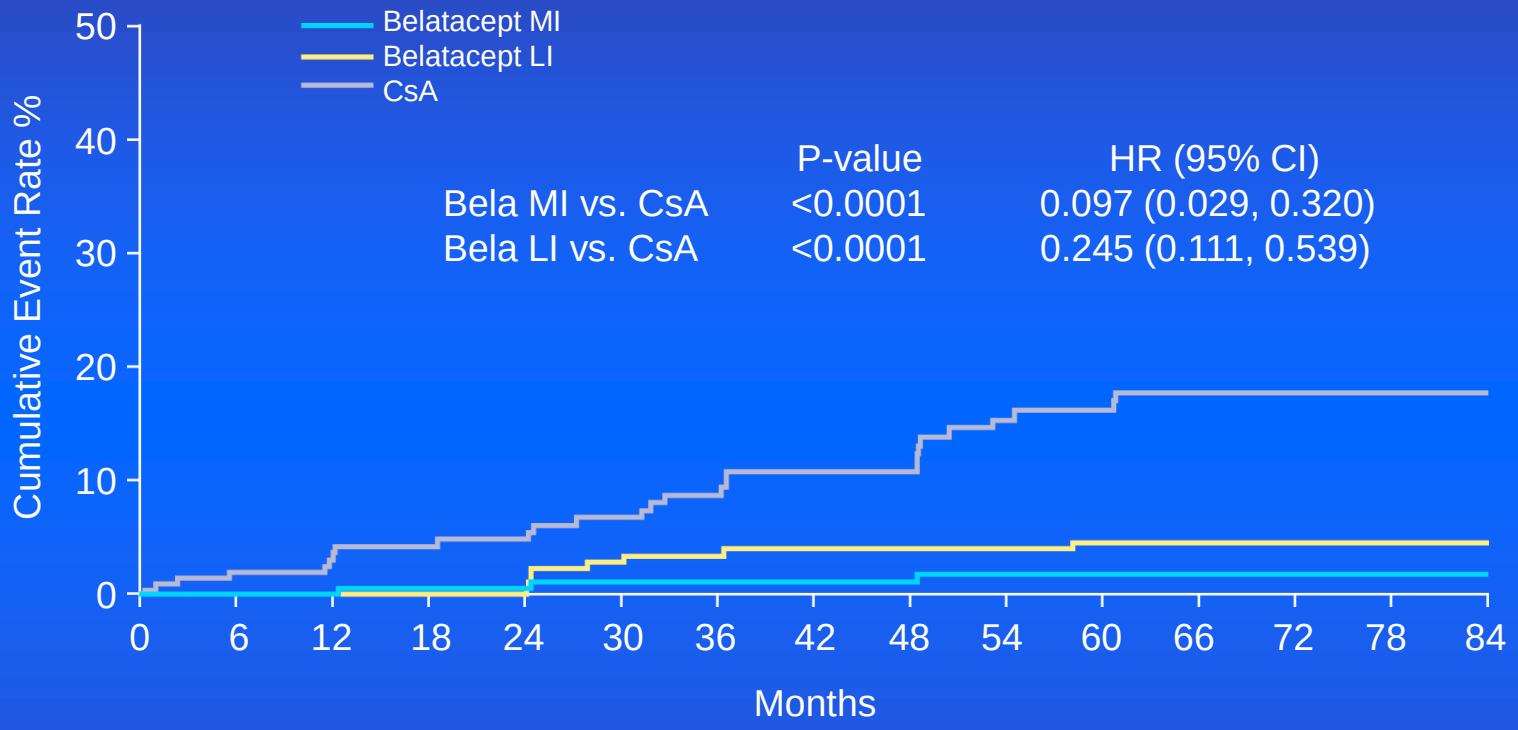
Belatacept MI	219	154	147	144	140	137	136	128	127	125	122	117	111	108	105
Belatacept LI	226	168	164	162	160	157	155	149	144	142	137	135	130	125	122
CsA	221	180	167	156	147	141	135	123	115	110	106	101	96	94	89

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.

Bela=belatacept; CI=confidence interval; CsA=cyclosporine A; HR=hazard ratio; LI=less intensive; MI=more intensive.

Kaplan-Meier Analysis of Cumulative De Novo DSA Over Time



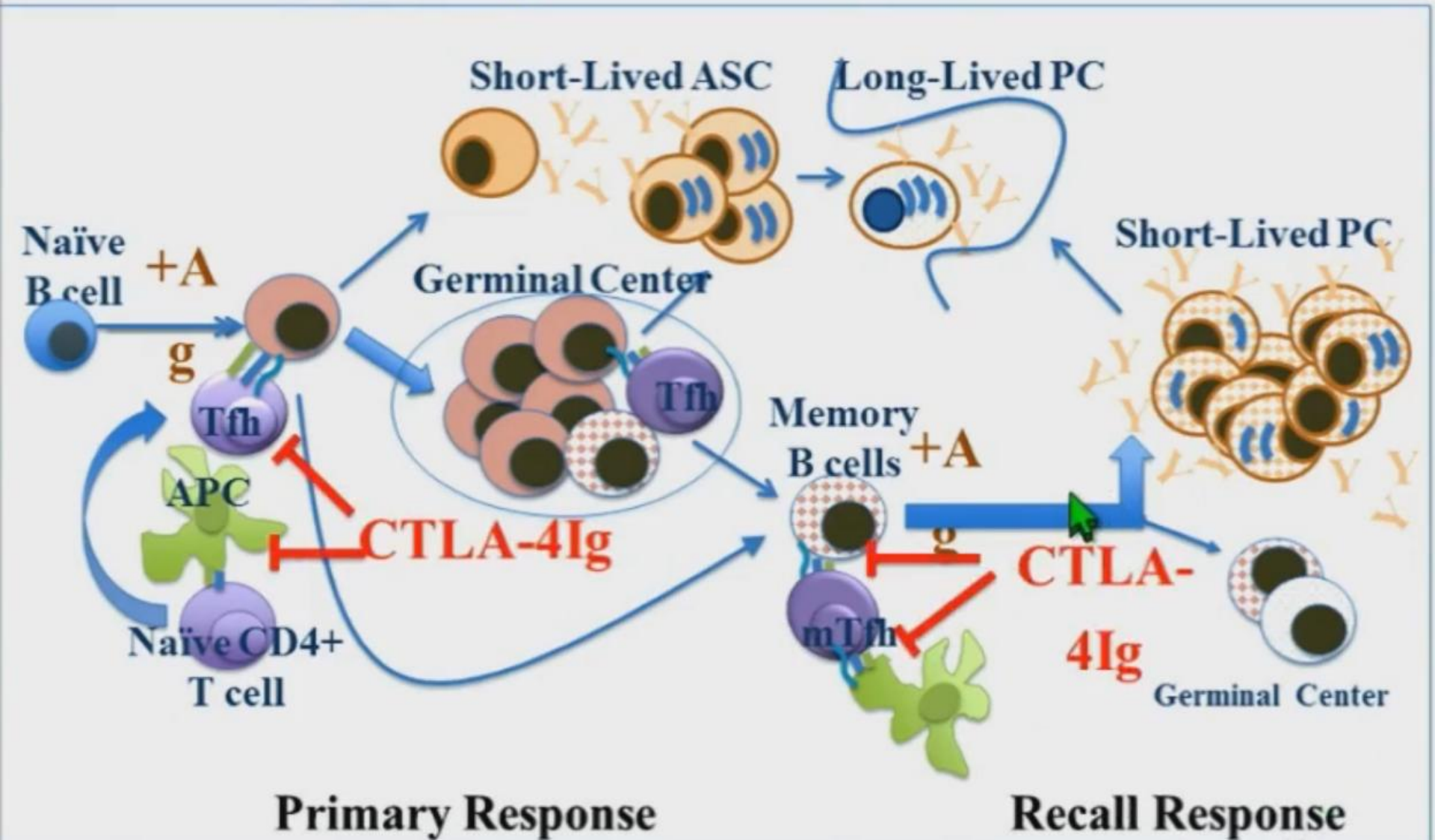
N at risk

Belatacept MI	219	182	174	168	163	158	156	148	147	144	141	136	130	127	124
Belatacept LI	226	187	183	180	178	169	165	158	154	152	145	143	138	133	130
CsA	215	186	171	159	150	143	136	124	115	108	103	97	92	90	85

Bela=belatacept; CI=confidence interval; CsA=cyclosporine A; DSA=donor-specific antibody; HR=hazard ratio; LI=less intensive; MI=more intensive.

1147: Controlling Alloreactive B Cell Responses in Sensitized Recipients With CTLA-4Ig

J Chen, V Vu, D Yin, Q Wang, R Sciammas[1] and A Chong
University of Chicago, [1]Houston Methodist Research Institute



Why Belatacept Has Not Fulfilled Its Potential As A Transformational Immunosuppression Agent

- Higher rejection rates and histologically more severe

→ better regimens

- PTLD

→ not an issue with EBV + recipients and lower acute rejection

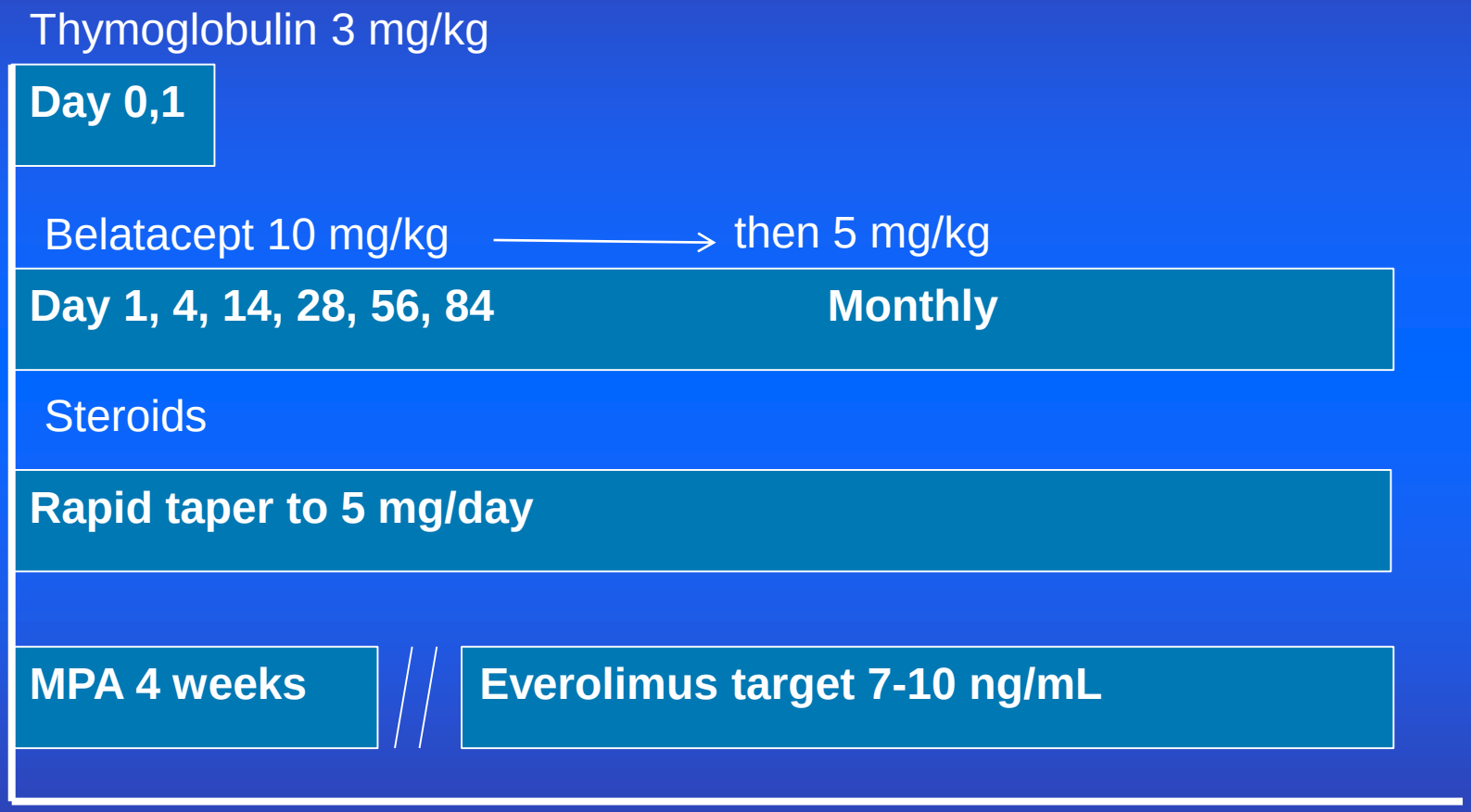
- IV administration

→ could be advantageous for compliance

- Cost

→ cost-effectiveness yet to be determined

Current UCSF De Novo Protocol



De novo Belatacept with mTORi UCSF Experience

- 44patients on *de novo* belatacept protocol
- 38% patients did not tolerate everolimus and switched back to MMF
- 11% incidence of acute rejection
  - All the rejections occurred in patient who did not tolerate everolimus

Applying precision medicine to transplantation to improve long term outcome

Precision Medicine

- 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/Individualized Medicine vs Precision Medicine

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

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 predictive biomarkers.

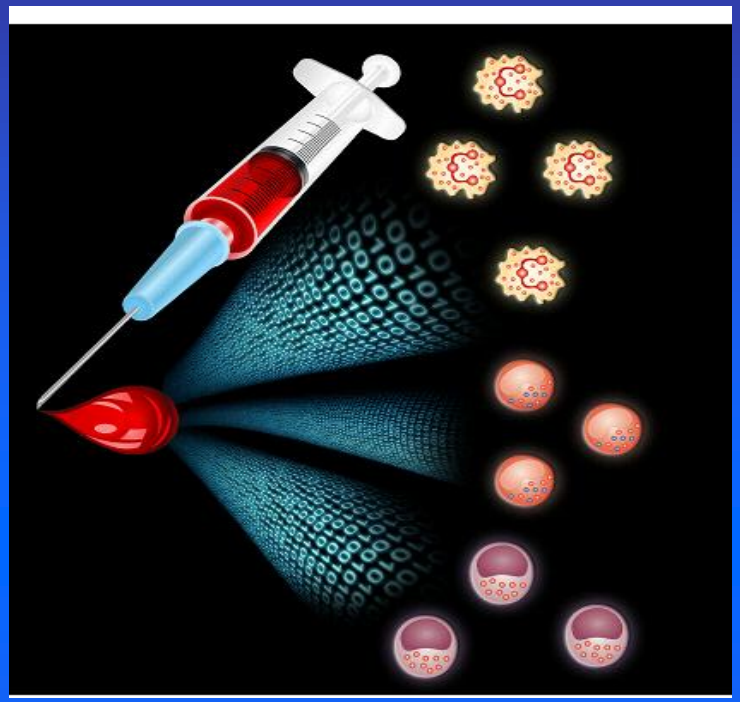
kSORT (Kidney Solid Organ Response Test)

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

Kidney- Solid Organ Rejection Test (kSORT)

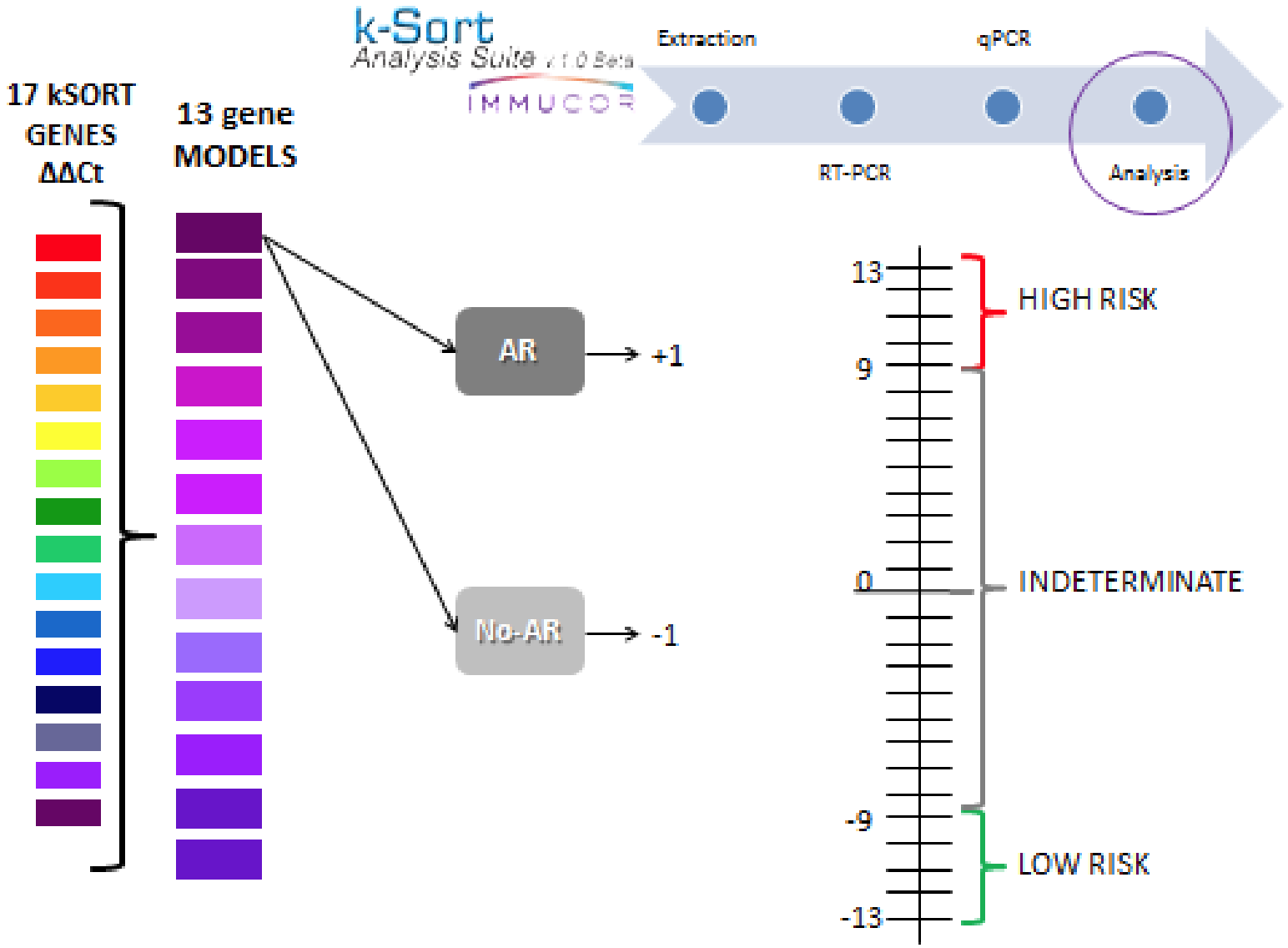
The answer in a drop of blood.....

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

QPCR Validation: SNSO1 NIH Trial

1B

PCR Validation Study: n=81

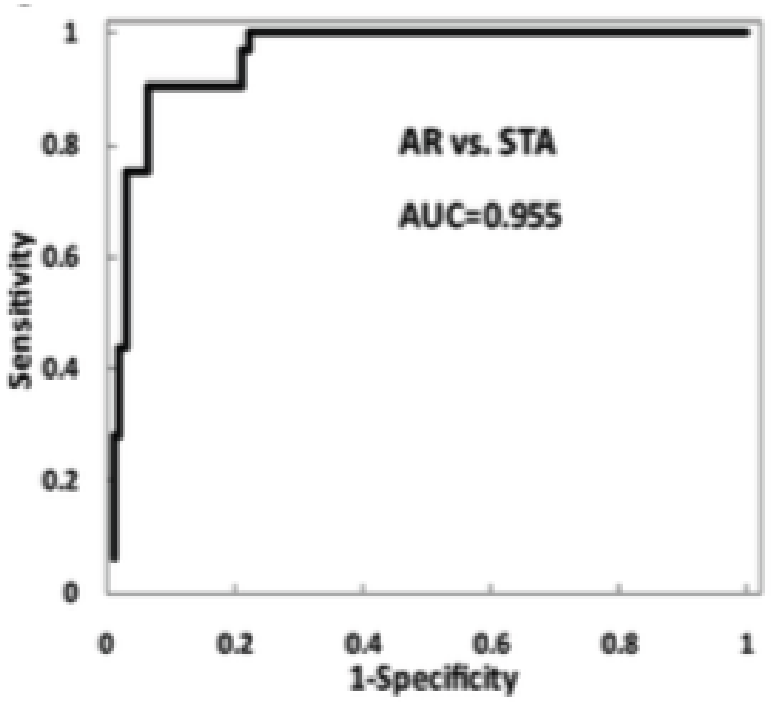
Single US center (Stanford University) for initial validation studies and gene selection (Li *et al*, AJT, 2013)

Test performance characteristics: Proof of Concept Single Study (10 genes; peds only; n=81)

- Sensitivity 91%
- Specificity 94%
- PPV 83%
- NPV 97%
- Area Under the Curve 0.955

N=367 blood samples matched with renal allograft biopsies, central read (R. Sibley, Stanford); NIH SNSO1 clinical trial

BLINDED ANALYSIS BY Rho/NIH



kSORT validated in pediatric and adult populations, LD and DD recipients; independent of Rx

OPEN ACCESS Freely available online

PLOS | MEDICINE

The kSORT Assay to Detect Renal Transplant Patients at High Risk for Acute Rejection: Results of the Multicenter AART Study

Silke Roedder[1¤], Tara Sigdel[1¤], Nathan Salomonis[2¤], Sue Hsieh[1], Hong Dai[3¤a], Oriol Bestard[4], Diana Metes[5], Andrea Zeevi[5], Albin Gritsch[6], Jennifer Cheeseman[7], Camila Macedo[5], Ram Peddy[3], Mara Medeiros[8], Flavio Vincenti[1], Nancy Asher[1], Oscar Salvatierra[9], Ron Shapiro[5], Allan Kirk[7¤b], Elaine Reed[6], Minnie M. Sarwal[1*]

N=558 biopsy matched blood samples profiled by QPCR

8 programs; US, EU, Mexico , ADULT and PEDS

doi: 10.1111/j.1600-6143.2012.04253.x

N=367 biopsy matched blood samples profiled by QPCR

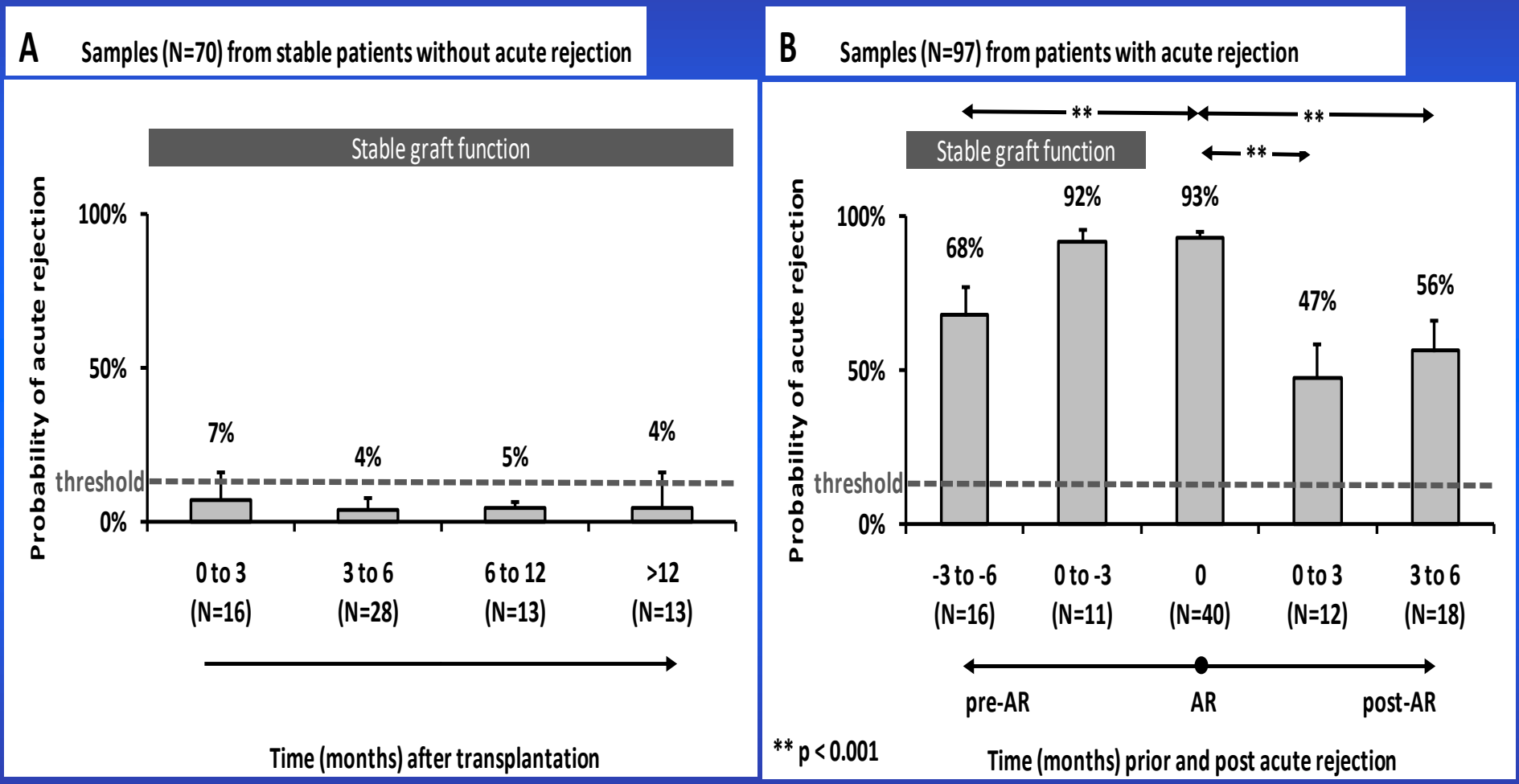
12 programs; US,, PEDS

A Peripheral Blood Diagnostic Test for Acute Rejection in Renal Transplantation

L. Li[a,b,†], P. Khatri[b,†], T. K. Sigdel[a,b,†], T. Tran[a,b], L. Ying[b], M. J. Vitalone[a,b], A. Chen[b], S. Hsieh[a,b], H. Dai[a,b], M. Zhang[b], M. Naesens[b], V. Zarkhin[b], P. Sansanwal[a], R. Chen[b], M. Mindrinos[d], W. Xiao[e], M. Benfield[f], R. B. Ettenger[g], V. Dharnidharka[h], R. Mathias[i], A. Portale[j], R. McDonald[k], W. Harmon[l], D. Kershaw[m], V. M. Vehaskari[n], E. Kamil[o], H. J. Baluarte[p], B. Warady[q], R. Davis[d], A. J. Butte[b], O. Salvatierra[b,c] and M. M. Sarwal[a,b,*]

study from 12 US pediatric transplant programs. A total of 367 unique human PB samples, each paired with a graft biopsy for centralized, blinded phenotype classification, were analyzed (115 acute rejection (AR), 180 stable and 72 other causes of graft injury). Of the differentially expressed genes by microarray, Q-PCR analysis of a five gene-set (*DUSP1, PBEF1, PSEN1, MAPKS* and *NKTR*) classified AR with high accuracy. A logistic regression model was built on independent training-set (n = 47) and validated on independent test-set (n = 198)samples, discriminating AR from STA with 91% sensitivity and 94% specificity and AR from all other non-AR phenotypes with 91% sensitivity and

kSORT for prediction of preAR



Applying precision medicine to belatacept therapy

Selection of patients responsive to belatacept

American Journal of Transplantation 2016; XX: 1–11
Wiley Periodicals Inc.

doi: 10.1111/ajt.13613

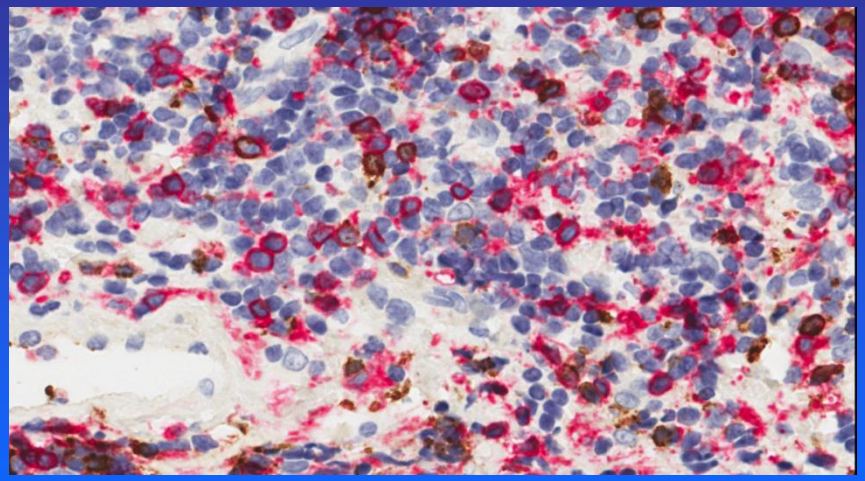
CD57+ CD4 T Cells Underlie Belatacept-Resistant Allograft Rejection

J. Espinosa[1,2], F. Herr[3], G. Tharp[4], S. Bosinger[4], M. Song[1], A. B. Farris III[5], R. George[1], J. Cheeseman[1,2], L. Stempora[1,2], R. Townsend[6], A. Durrbach[3,7] and A. D. Kirk[1,2,*]

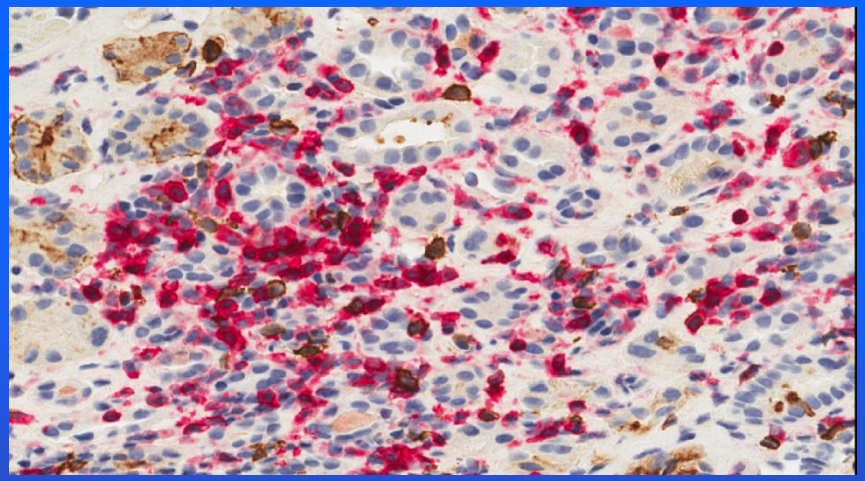
Received 24 July 2015, revised 16 October 2015 and accepted for publication 18 October 2015

UCSF Histology

a



b



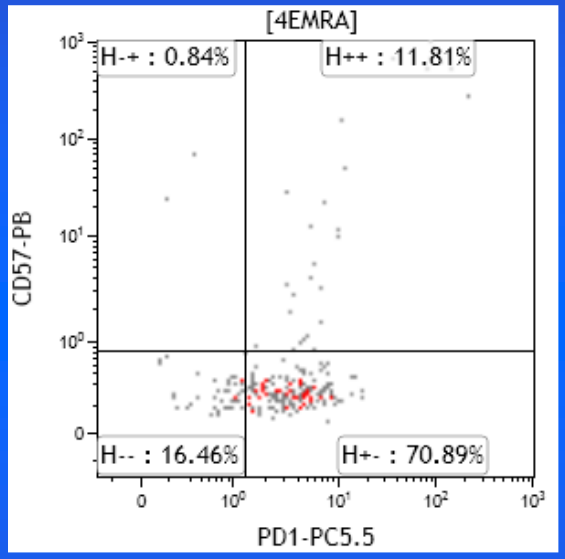
Representative images from a Belatacept (a) and CNI (b) patient with acute cellular rejection featuring CD57 (brown) and CD4 (red) positive cells in the cellular infiltrate. Semiquantitative analysis showed a higher density of CD57 positive cells in the Belatacept patients.

APPLYING PRECISION MEDICINE

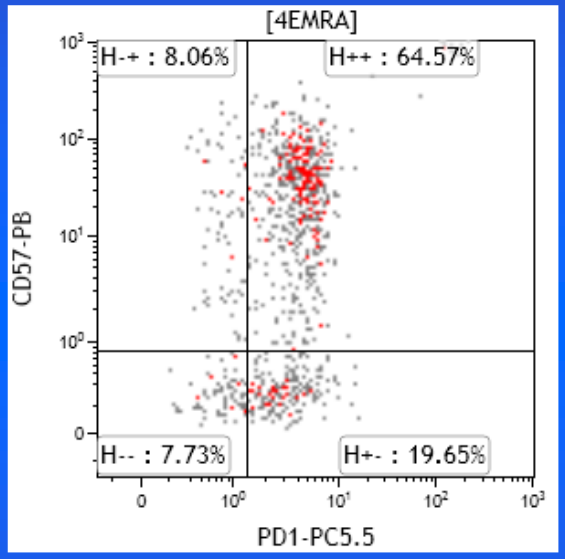
The PACER Trial

Select patients for belatacept who lack CD4+ CD57+ PD1- TEMRA+ cells unconstrained effectors) by flow and post transplant monitoring with kSORT

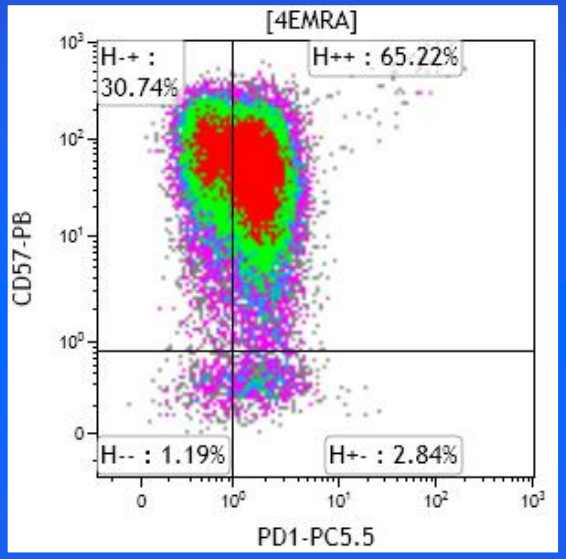
*low %CD57+PD1- in CD4 TEMRA



*moderate %CD57+PD1- in CD4 TEMRA



*very high %CD57+PD1- in CD4 TEMRA

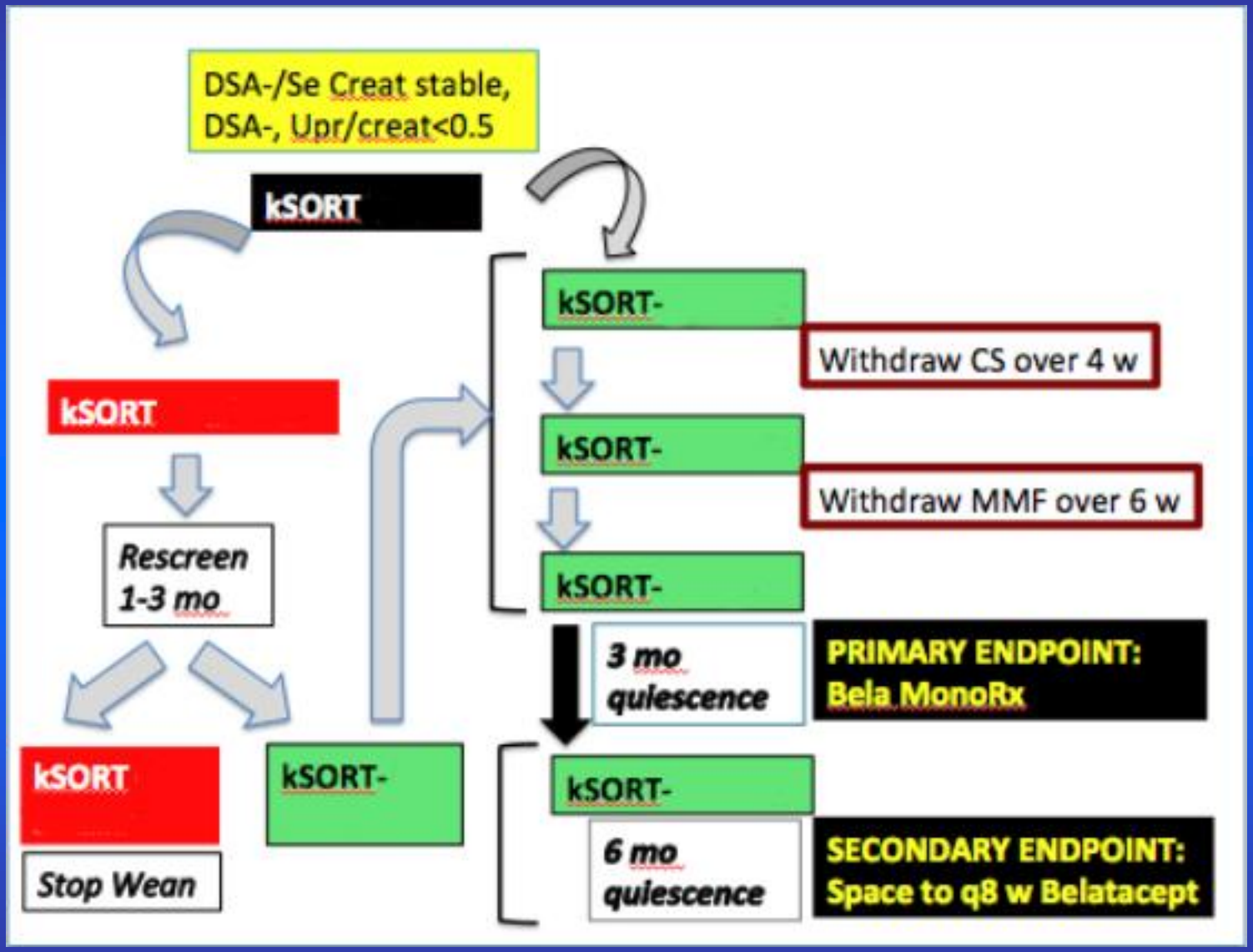


Example of 3 Patients with Different Risk Profiles for Belatacept

Precision Medicine Offers Belatacept Monotherapy (PROBE)

An initiative to both simplify and reduce costs of immunosuppression with belatacept

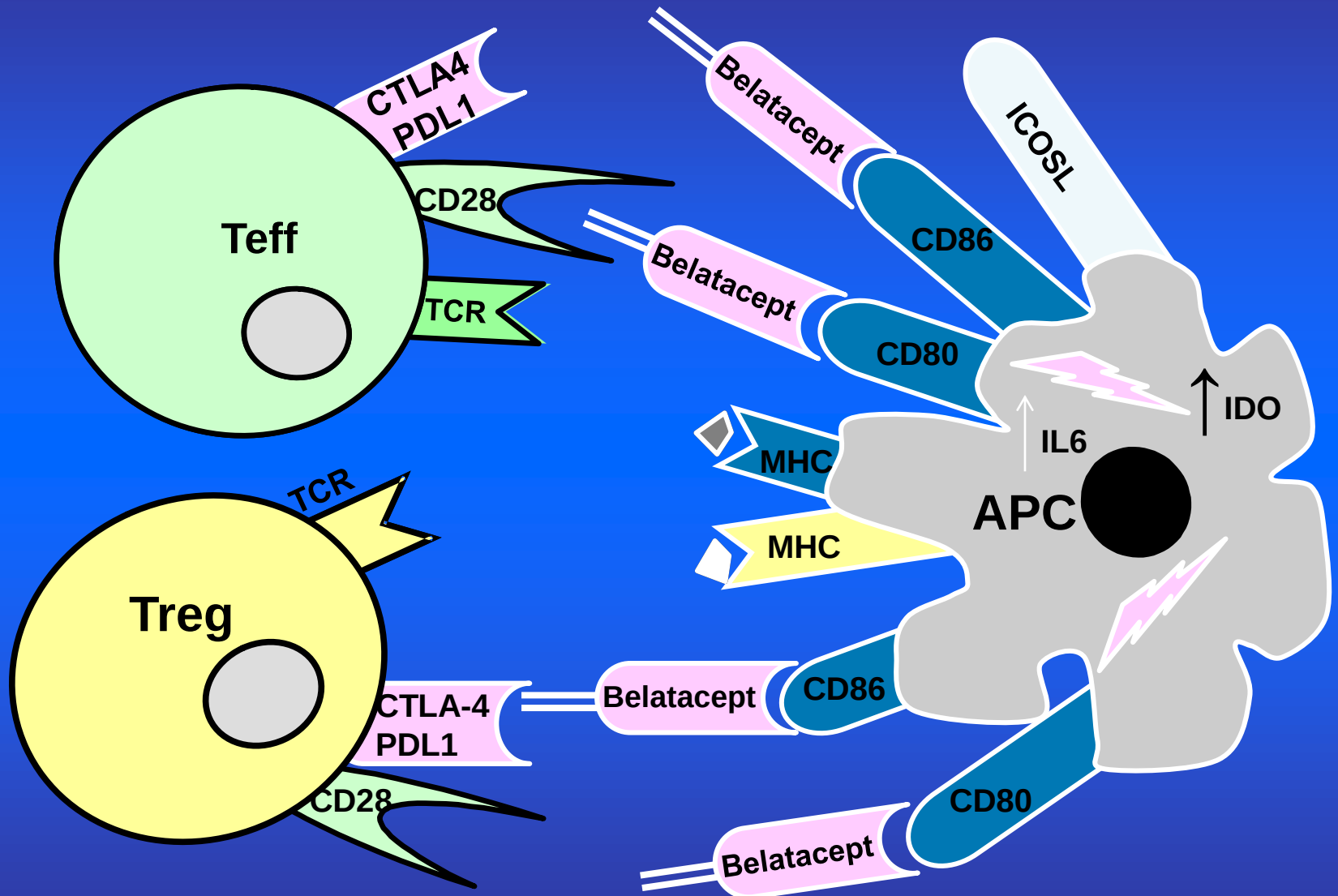
Precision Medicine Offers Belatacept Monotherapy (PROBE)



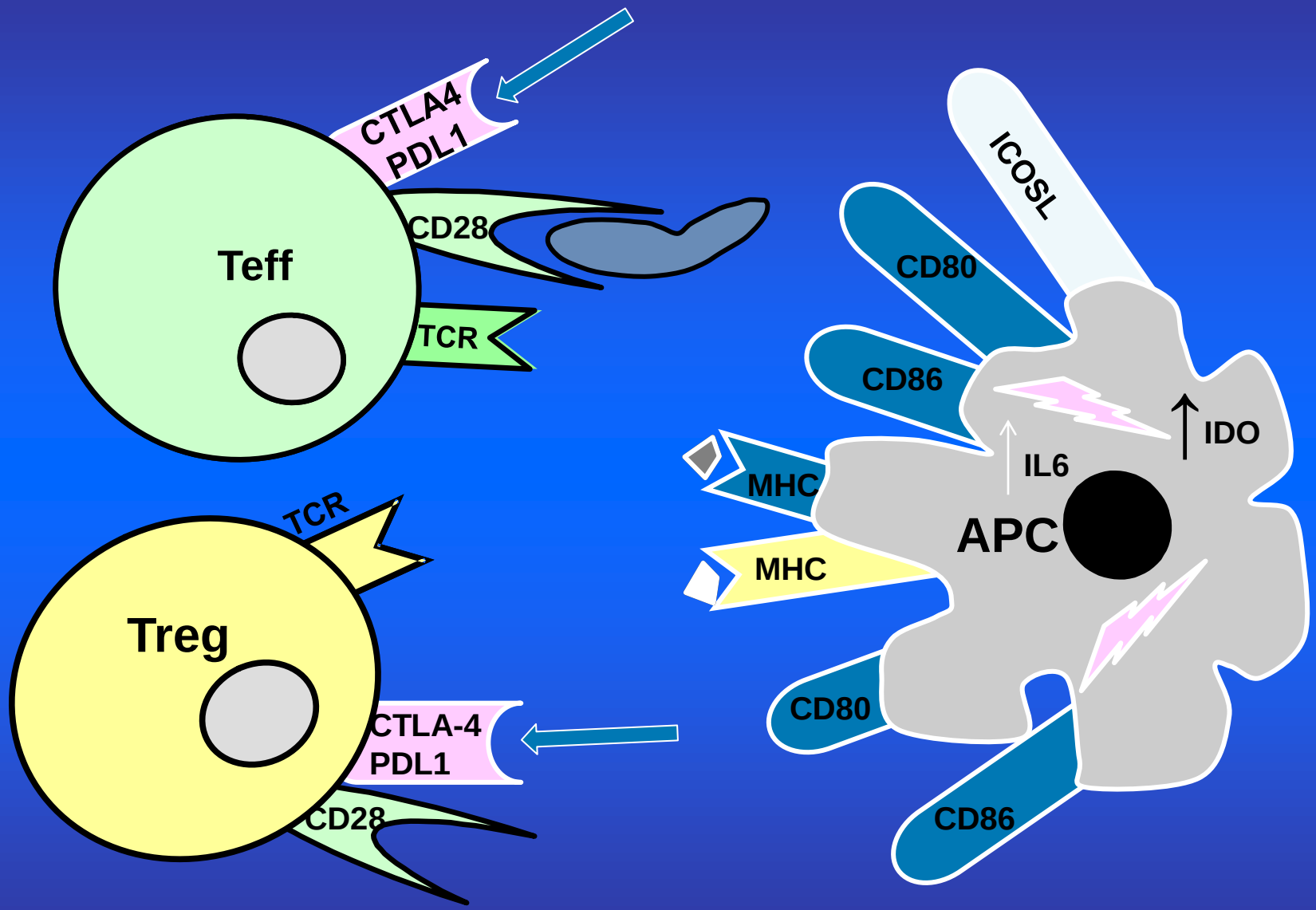
What Else Is New in The Therapeutic Landscape

- Non Agonistic Anti-CD28
- Anti-CD40 mAbs

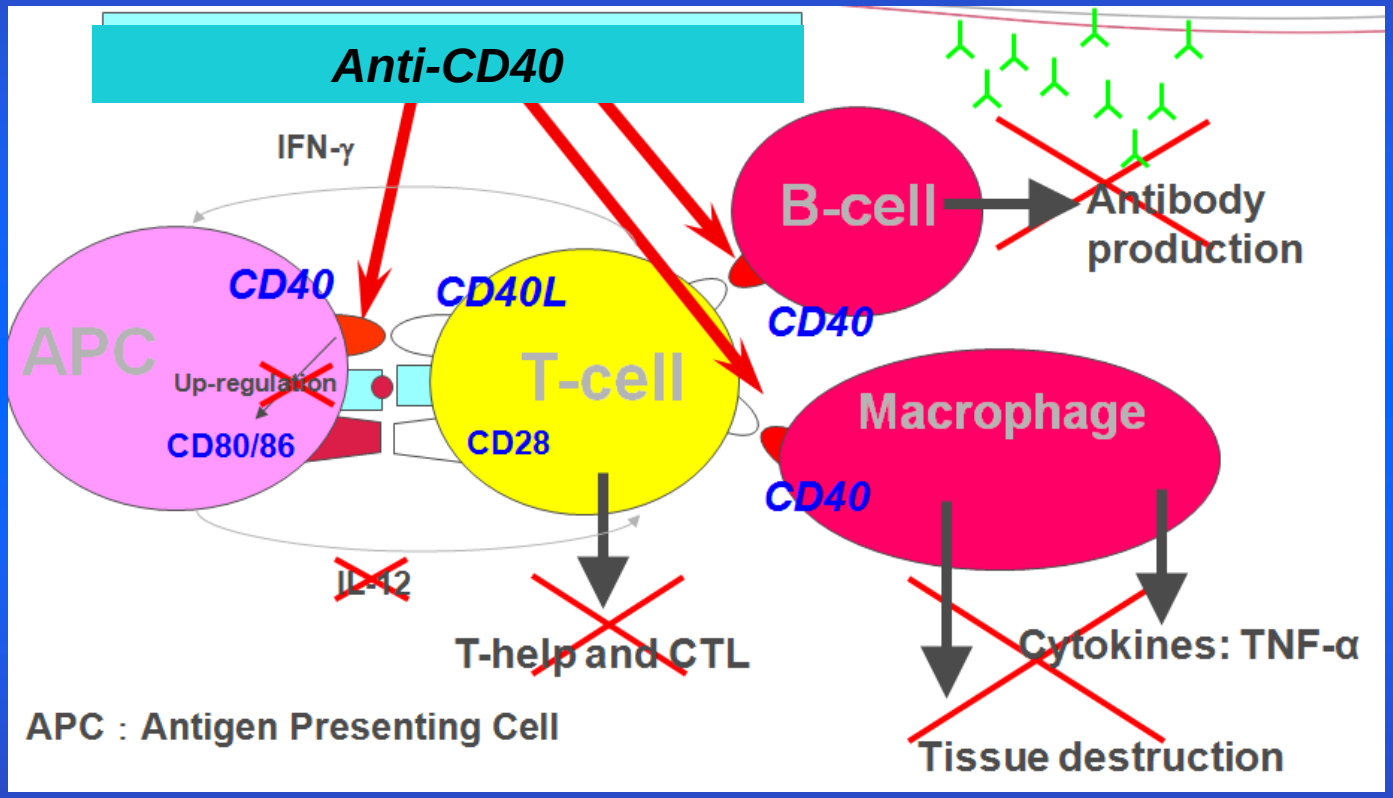
- Reduced Tconv activation (no CD28/B7) but no effect on CD28/ICOSL
- No inhibition of activation of CD28$^-$ T cells
- Reduced intrinsic negative regulation (no CTLA-4 signal and no PDL1/CD80andCD86 signal)



- Reduced fitness/survival (no CD28 signals)
- Reduced suppression (no CTLA-4 signals)


CTLA4
PDL1
CD28
Teff
TCR
TCR
Treg
CTLA-4
PDL1
CD28
ICOSL
CD80
CD86
IDO
IL6
MHC
APC
MHC
CD80
CD86

Mechanism of Action Anti-CD40



Repositioning Drugs

- Infliximab (CTOT19)
- IL6 Inhibition with Tocilizumab (UCSF /CEDARS)

Conclusion

- Regulations, endpoints, costs, and generics have stifled innovation in transplantation
- Unmet needs persist and require novel approaches and solutions
- The adoption of Precision Medicine and Biomarkers will facilitate the development of novel therapies with the promise of improving long term outcome