Co Stimulatory Blockade in Clinical Kidney Transplantation

J. Harold Helderman

Vanderbilt University School of Medicine

OBJECTIVES

- 1. Learn the immunologic basis for co-stimulatory blockade
- 2 Understand the rationale for belatacept
- 3. Review the outcome of Benefit at 2 and 5 years
- 4. Understand the advantages and disadvantages for Bela in kidney transplant
- Learn new approaches to Co-S blockade

Patient One-The Good

- 28 yo Caucasian woman with Type 1 diabetes
- and severe gastroparesis with several recent admissions for nausea and vomiting was accepted for LRD employing bela as main immunosuppressant avoiding oral medications. Received her LRD 9/27/2014. Current creatinine 0.6 mg/dl with no rejections.

Patient Two-The Bad

- 43 yo diabetic man in study randomized to bela in BENEFIT trial received a DDKT with immediate function, nadir creatinine 1.4 mg/dl. Creatinine rose to 2.4 mg/dl at month two. Biopsy showed CCT type 1 cellular rejection treated with thymoglobulin and steroids. Creatinine returned to 1.8 mg/dl.

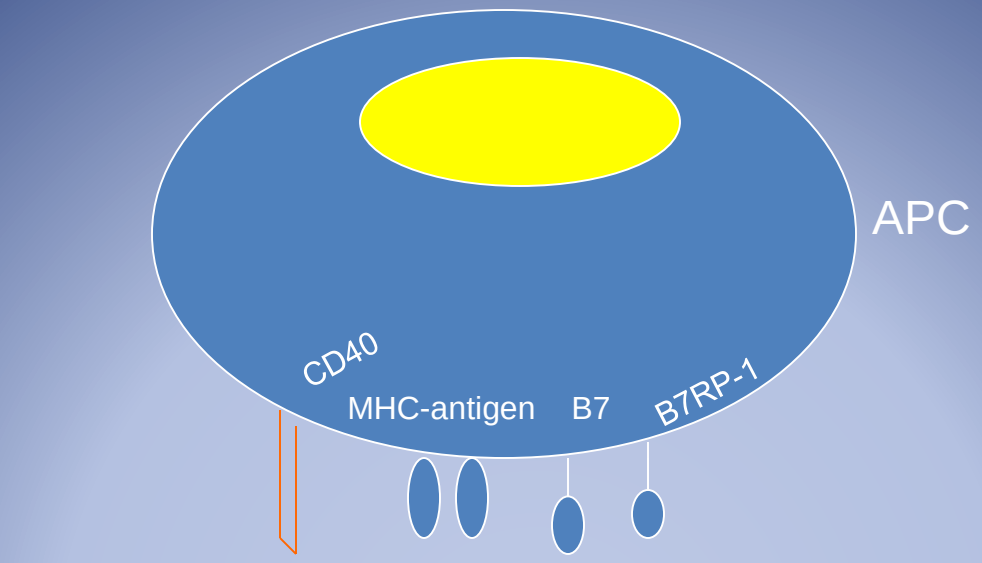
Patient 3-The Ugly

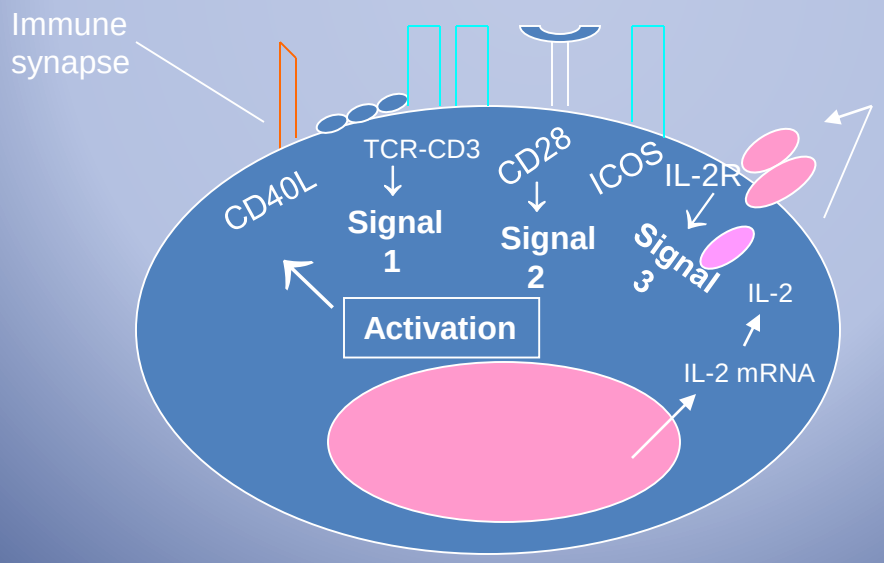
- 18 yo woman received an LRD from her mother as part of phase 3 trial with immediate function, creatinine 0.9 mg/dl. She had a gran mal seizure at year 2 with CT scan showing CNS mass the path of which was lymphoma. She was later found to be EBV negative. Despite adjustment in IS and chemotherapy, she succumbed 5 mos later.

- IMMUONOLOGIC RATIONALE

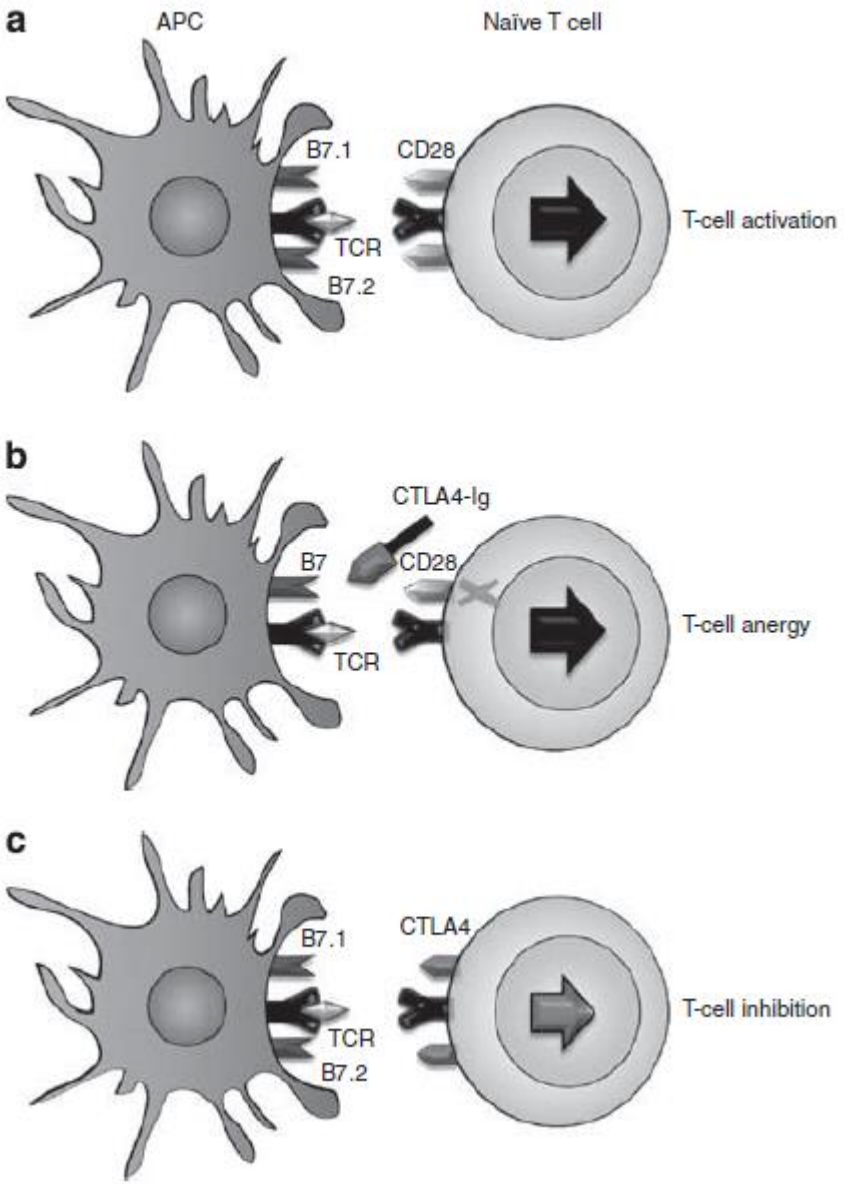
Three Signal Hypothesis

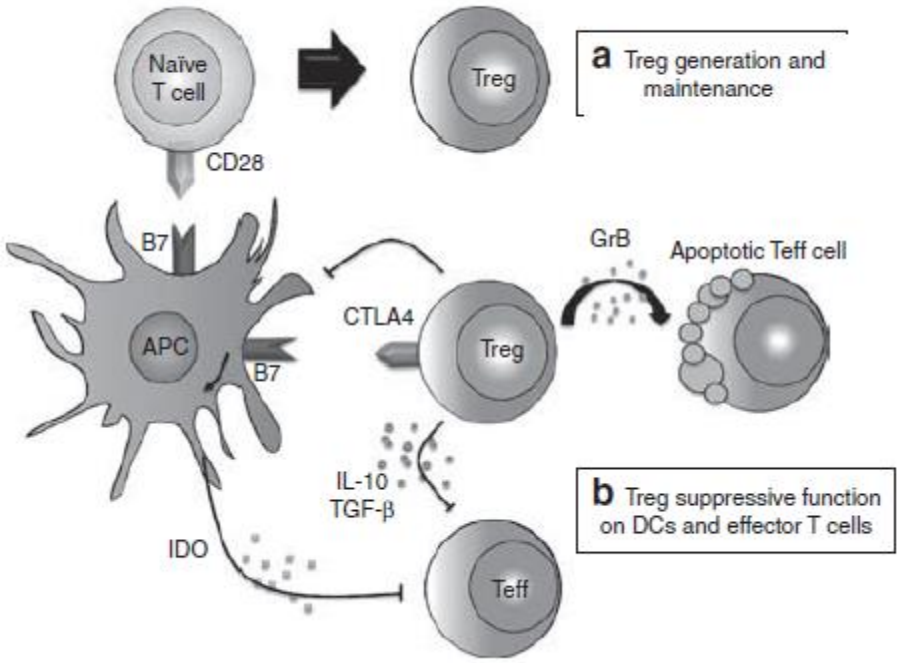
For Alloantigen Activation

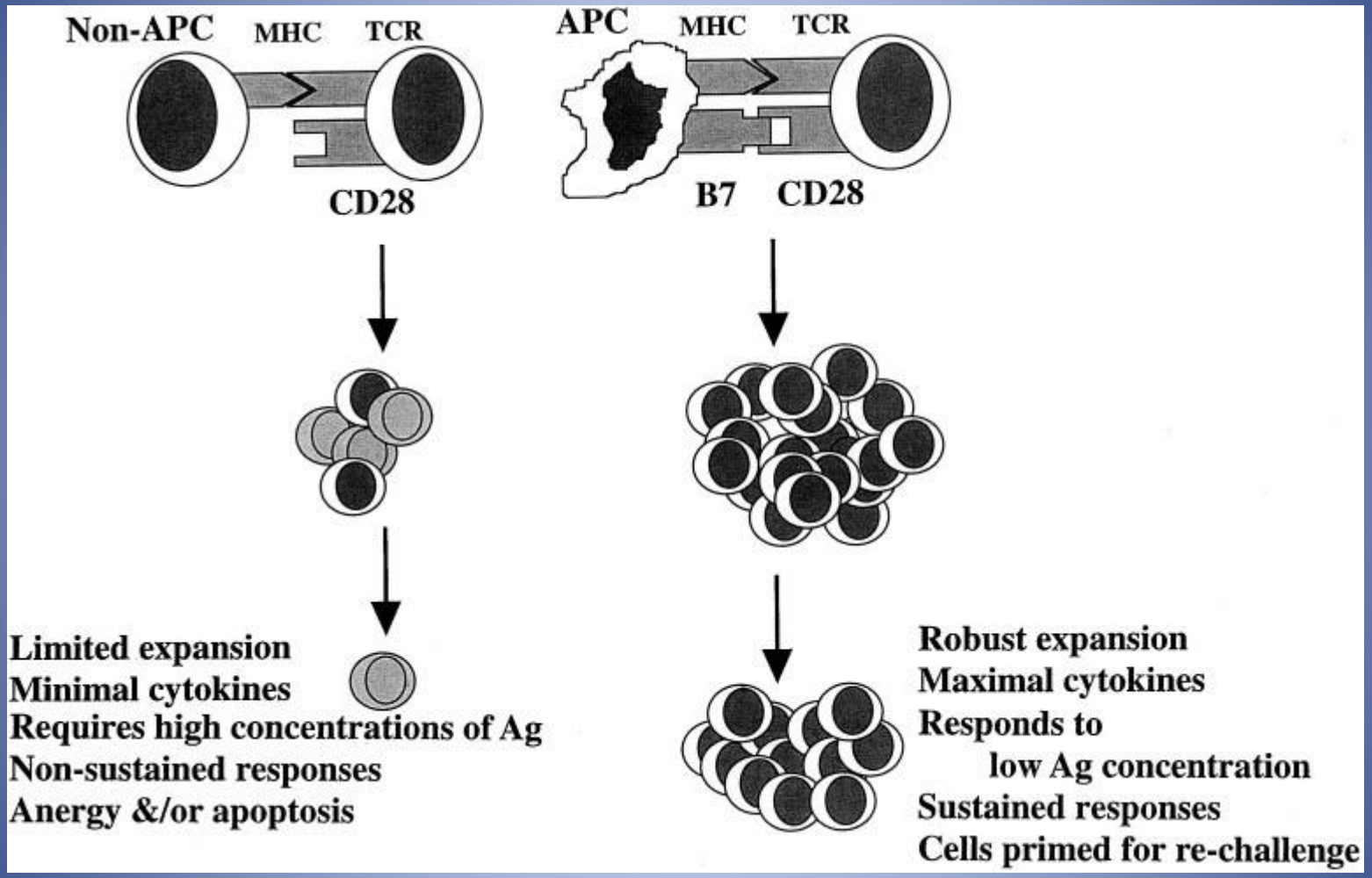

APC
CD40
MHC-antigen
B7
B7RP-1

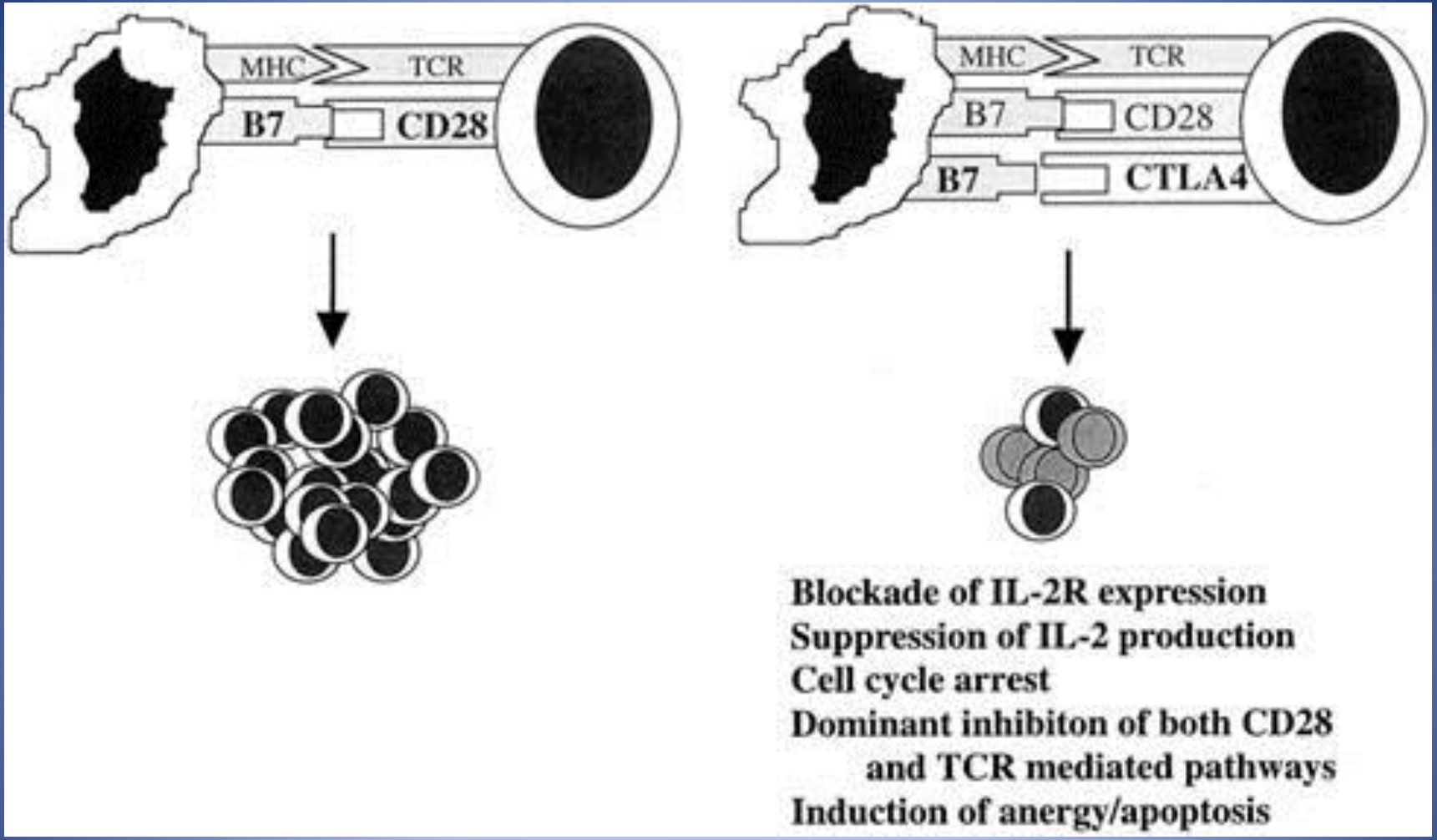

Immune synapse
CD40L
TCR-CD3
CD28
ICOS
IL-2R
Signal 1
Signal 2
Signal 3
Activation
IL-2
IL-2 mRNA

Naïve T cell

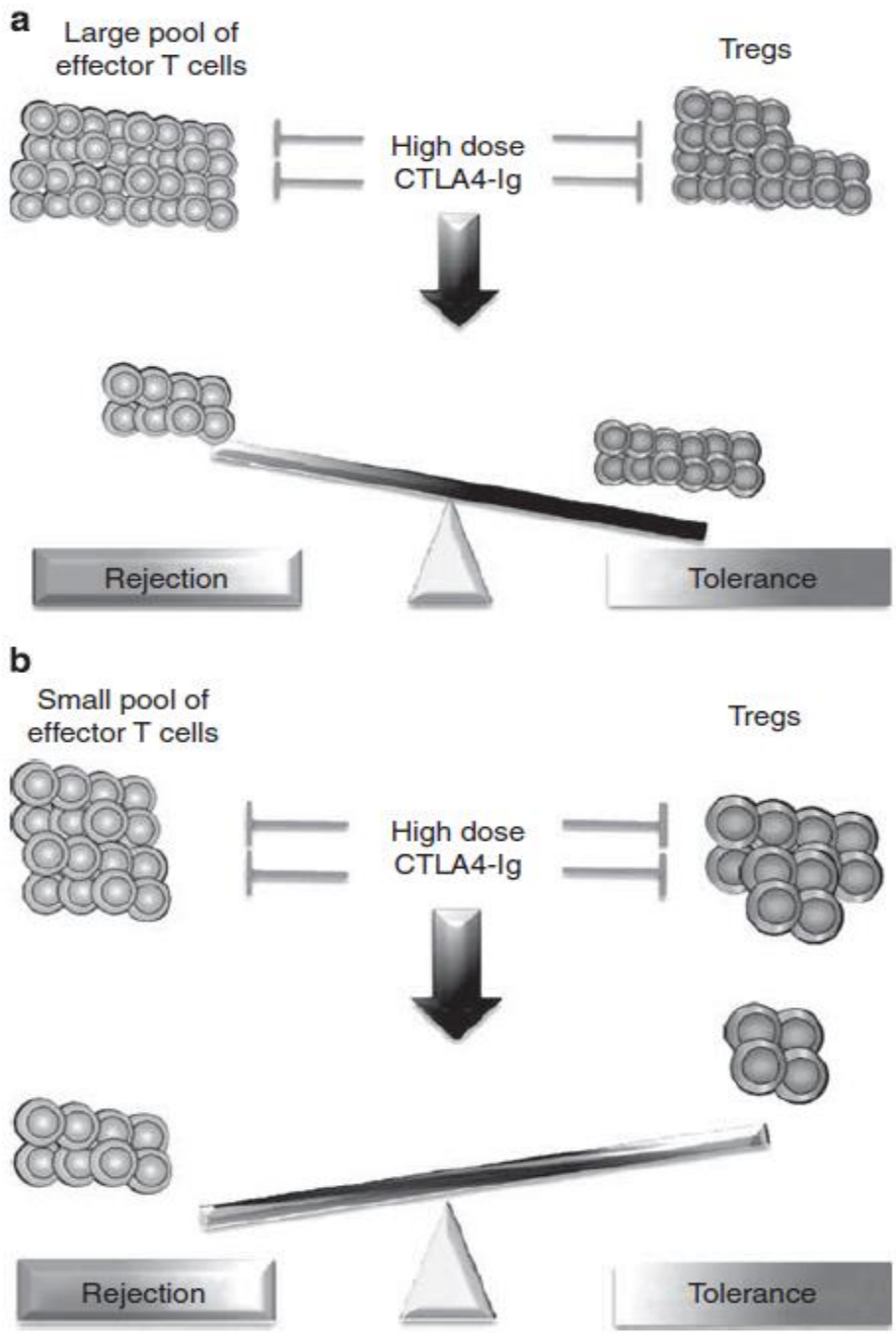

a
APC
Naïve T cell
B7.1
CD28
TCR
B7.2
T-cell activation
b
CTLA4-Ig
B7
CD28
TCR
T-cell anergy
c
B7.1
CTLA4
TCR
B7.2
T-cell inhibition


Naïve
T cell
Treg
a Treg generation and maintenance
CD28
B7
APC
B7
CTLA4
Treg
GrB
Apoptotic Teff cell
IL-10
TGF-β
IDO
Teff
b Treg suppressive function on DCs and effector T cells


Non-APC
MHC
TCR
CD28
APC
MHC
TCR
B7
CD28
Limited expansion
Minimal cytokines
Requires high concentrations of Ag
Non-sustained responses
Anergy &/or apoptosis
Robust expansion
Maximal cytokines
Responds to
low Ag concentration
Sustained responses
Cells primed for re-challenge



Hrefna Gudmundsdottir and Laurence A. Turka


a
Large pool of effector T cells
Tregs
High dose CTLA4-Ig
Rejection
Tolerance
b
Small pool of effector T cells
Tregs
High dose CTLA4-Ig
Rejection
Tolerance

RATIONALE FOR USE OF BELATACEPT

CD 28 – CD 80/86 Pathway

- 1st studied reagent CTLA4Ig -
  fusion protein -
  extra cellular domain of CTLA4 - Fc
  portion of human Ig
- Excellent pre clinical results but less spectacular non-human primate data

Sayegh and Turkha NEJM 338:1998

Co-Stimulatory Blockade in Primates

- 1. CTLA4-IG alone prolongs kidney transplant
- Kirk et al PNAS 94:1997

- 2. anti CD 154 induced tolerance in skin transplant model-
- Elstar Transplantation 72:2001

- 3.anti cd80 monoclonal delays rejection of kidney
- Kirk et al Transplantation 72:2001

CD28 – CD80/86

- LEA 29Y (Belatacept)
  - Leucine 104 → GlutamatE
  - Alanine 29 → Tyrosine
- 2nd generation CTLA4Ig
- Substitutions increase theoretic efficacy
  - 2 fold ↑ binding to CD 80
  - 4 fold ↑ binding to CD 86
  - 10 fold ↑ T cell function inhibition

Larsen et al AJT 5:2005

Co-Stimulatory Blockade in Humans

- Phase 3 Randomized Prospective
- Multicenter Registration Trial

- Benefit and Benefit Extended

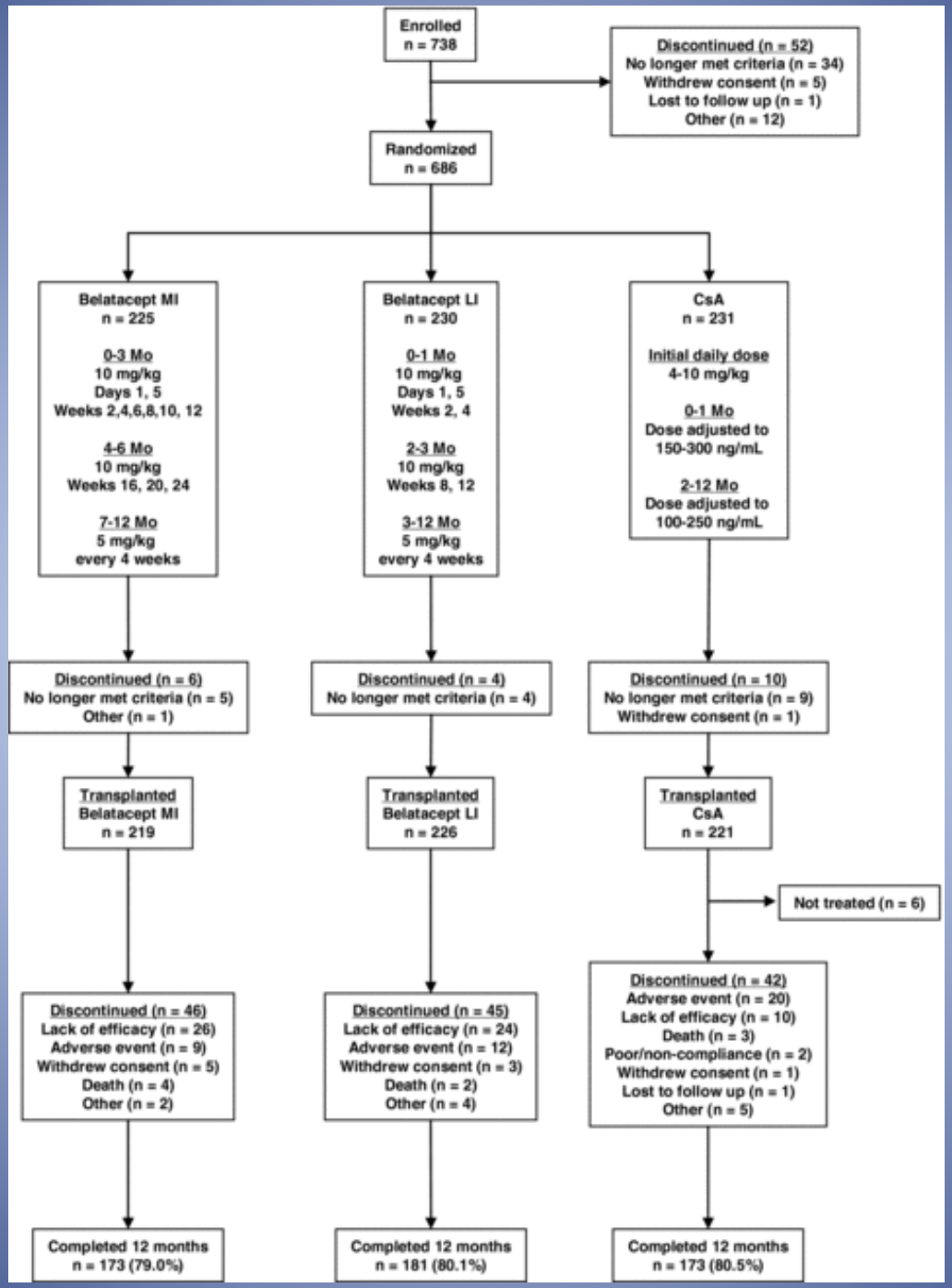
TWO AND FIVE YEAR RESULTS

OF BENEFIT TRIAL

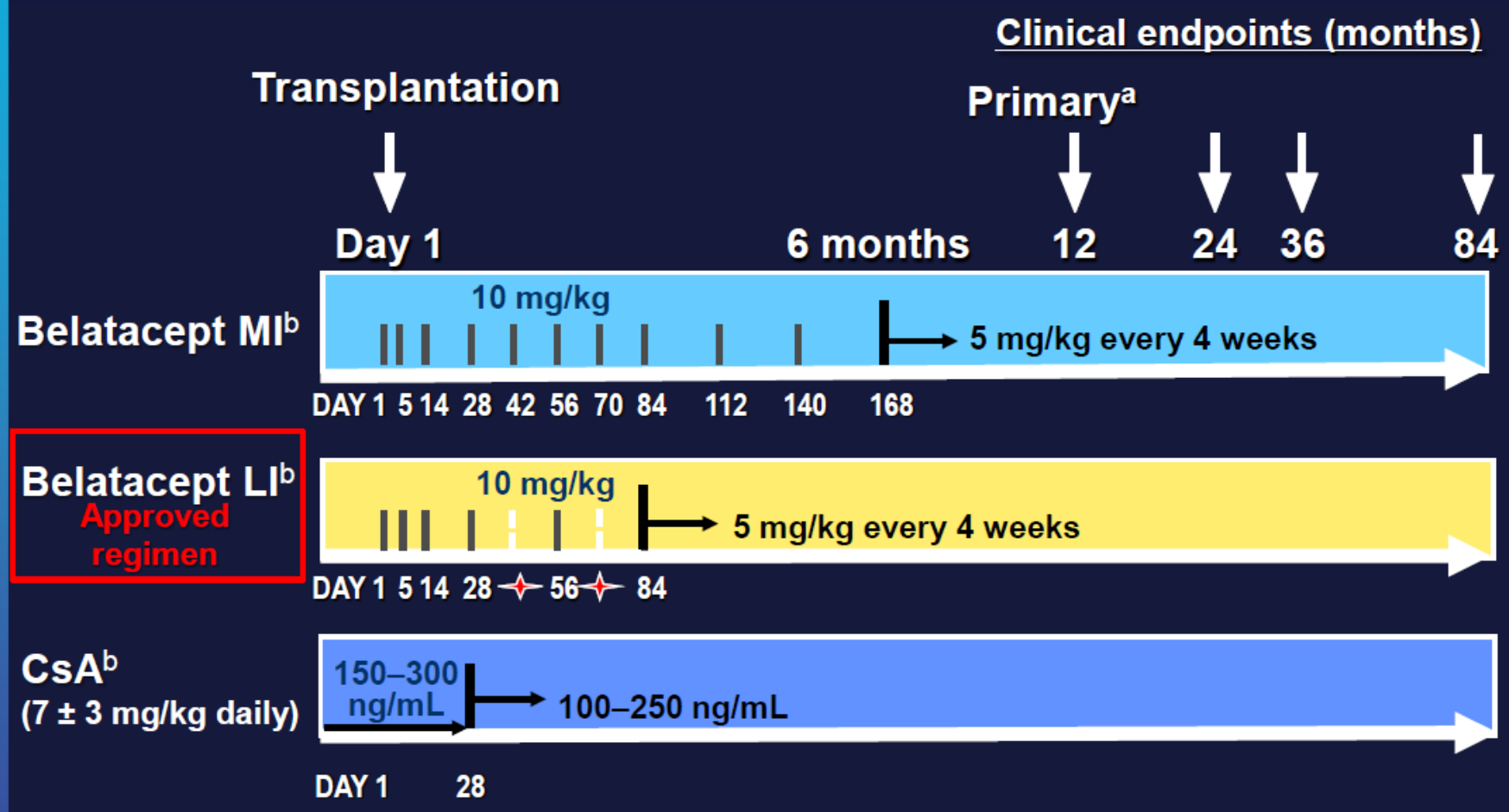
A Phase III Study of Belatacept-based Immunosuppression Regimens versus Cyclosporine in Renal Transplant Recipients (BENEFIT Study)

AJT 10:2010 Vincenti et al

Belatacept in Renal Transplantation (BENEFIT)



Study Design and Dosing



Placebo infusions

[a]Belatacept arms unblinded at 12 months.

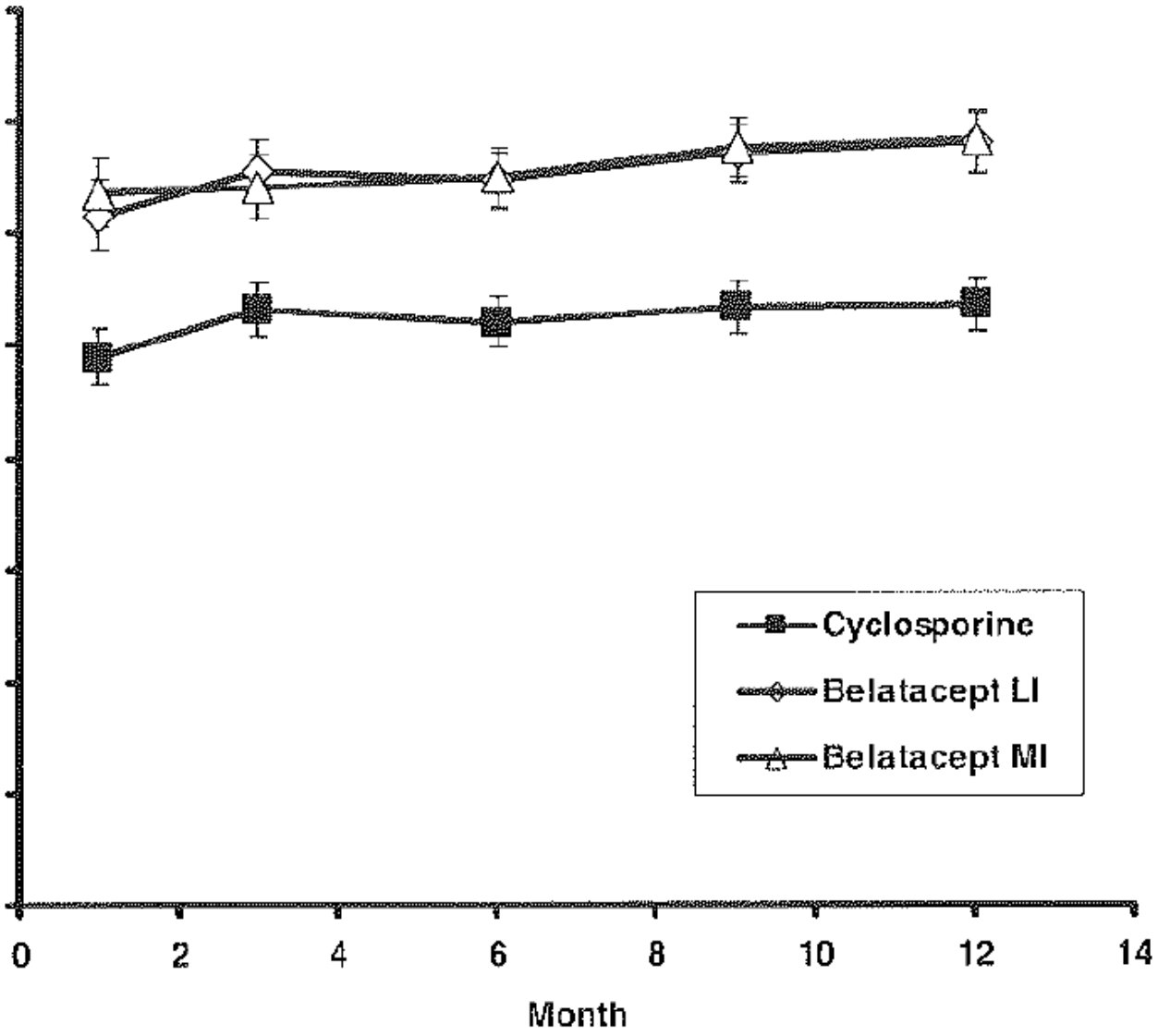
[b]All patients received basiliximab induction, mycophenolate mofetil, and corticosteroid taper.

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

Table 2: Outcomes: Patient/graft survival, renal function and structure and acute rejection

Month 12 endpoints	Belatacept MI (n = 219)	Belatacept LI (n = 226)	Cyclosporine (n = 221)
Patient/graft survival			
Patients surviving with functioning graft, n (%)	209 (95)	218 (97)	206 (93)
95% CI	92.7–98.2	94.1–98.9	89.9–96.5
Difference from CsA (97.3% CI)	2.2 (−2.9, 7.5)	3.2 (−1.5, 8.4)	–
Graft loss or death, n (%)	10 (5)	8 (4)	15 (7)
Graft loss	4 (2)	5 (2)	8 (4)
Death	6 (3)	4 (2)	7 (3)
Death with functioning graft	6 (3)	3 (1)	6 (3)
Imputed as graft loss or death, n (%)	0 (0)	0 (0)	1 (1)
Renal function and structure			
mGFR <60 mL/min/1.73 m^2 or decrease	115 (55)	116 (54)	166 (78)
Month 3–12 ≥10 mL/min/1.73 m^2, n (%)			
95% CI	48.3–61.8	47.5–60.9	72.4–83.5
Difference from CsA (97.3% CI)	−22.9 (−32.6, −12.9)	−23.7 (−33.3, −13.7)	–
p-Value	<0.0001	<0.0001	–
Mean mGFR, mL/min/1.73 m^2 (SD)	65.0 (30.0)	63.4 (27.7)	50.4 (18.7)
Estimated difference from CsA (97.3% CI)	14.6 (8.8, 20.3)	12.9 (7.2, 18.6)	–
p-Value	<0.0001	<0.0001	–
CAN, n (% [95% CI])	40 (18 [13.1–23.4])	54 (24 [18.3–29.5])	71 (32 [26.2–38.6])
Difference from CsA (97.3% CI)	−14.2 (−23.2, −5.0)	−8.5 (−17.9, 0.9)	–
Mild CAN (stage I), n (%)	21 (10)	29 (13)	41 (19)
Moderate CAN (stage II), n (%)	5 (2)	6 (3)	9 (4)
Severe CAN (stage III), n (%)	4 (2)	6 (3)	6 (3)
Acute rejection			
Acute rejection, n (%)	49 (22)	39 (17)	16 (7)
95% CI	16.9–27.9	12.3–22.2	3.8–10.7
Difference from CsA (97.3% CI)	15.1 (7.9, 22.7)	10.0 (3.3, 17.1)	–
Banff grade, n (%)			
Mild acute (IA)	7 (3)	4 (2)	3 (1)
Mild acute (IB)	3 (1)	8 (4)	5 (2)
Moderate acute (IIA)	17 (8)	16 (7)	6 (3)
Moderate acute (IIB)	20 (9)	10 (4)	2 (1)
Severe acute (III)	2 (1)	1 (<1)	0

Belatacept in Renal Transplantation (BENEFIT)



Patients without AR
Patients with AR

CONCLUSIONS BENEFIT TRIAL

1. BELA AFFORDS EQUAL GRAFT AND PATIENT SURVIVAL AS CNI

1. THERE ARE MORE ACUTE EARLY REJECTIONS THAN CNI EASILY REVERSED

3.RENAL FUNCTION SUPERIOR TO CNI

Belatacept-Treated Patients Had Better Graft Survival at 7-Years Post-Transplant Compared With Cyclosporine-Treated Patients: Final Results From BENEFIT

F Vincenti[1], JM Grinyó[2], L Rostaing[3], KM Rice[4], SM Steinberg[5], MC Moal[6], M Polinsky[7], U Meier- Kriesche[7], CP Larsen[8]

[1]University of California, San Francisco, CA, USA; [2]University Hospital Bellvitge, Barcelona, Spain; [3]University Hospital, and INSERM U563, IFR-BMT, Toulouse, France; [4]Baylor University Medical Center, Dallas, TX, USA; [5]Sharp Memorial Hospital, San Diego, CA, USA; [6]Hôpital de La Cavale Blanche, Brest, France; [7]BMS, Lawrenceville, NJ, USA; [8]Emory University Transplant Center, Atlanta, GA, USA

Background

- Long-term allograft survival has not improved appreciably in kidney transplant recipients
- No prospective phase III studies have examined patient outcomes beyond 5 years
- In no prospective, phase III study has an immunosuppressive regimen demonstrated a survival advantage over CsA-containing regimens
- Analyses of the phase III BENEFIT study at 3 and 5 years demonstrated that belatacept-based immunosuppression was associated with significantly better renal function vs. CsA in kidney transplant recipients

1. Meier-Kriesche U, et al. *Am J Transplant*. 2004;4:1289-12; 2. Lamb KE, et al. *Am J Transplant*. 2011;11:450-462; 3. The Canadian Multicentre Transplant Study Group. *N Engl J Med*. 1983;309:809-815; 4. Opelz G, et al. *Transplantation*. 2009;87:795-802; 5. Pirsch JD, et al. *Transplantation*. 1997;63:977-983; 6. Miller J, et al. *Transplant Proc*. 1997;29:304-305; 7. Ekberg H, et al. *N Engl J Med*. 2007;357:2562-2575; 8. Vincenti F, et al. *Transplantation*. 2002;5:2521-2530; 9. Vincenti F, et al. Am J Transplant. 2012;12:210-217; 10. Rostaing L, et al. *Am J Transplant*. 2013;13:2875-2883.

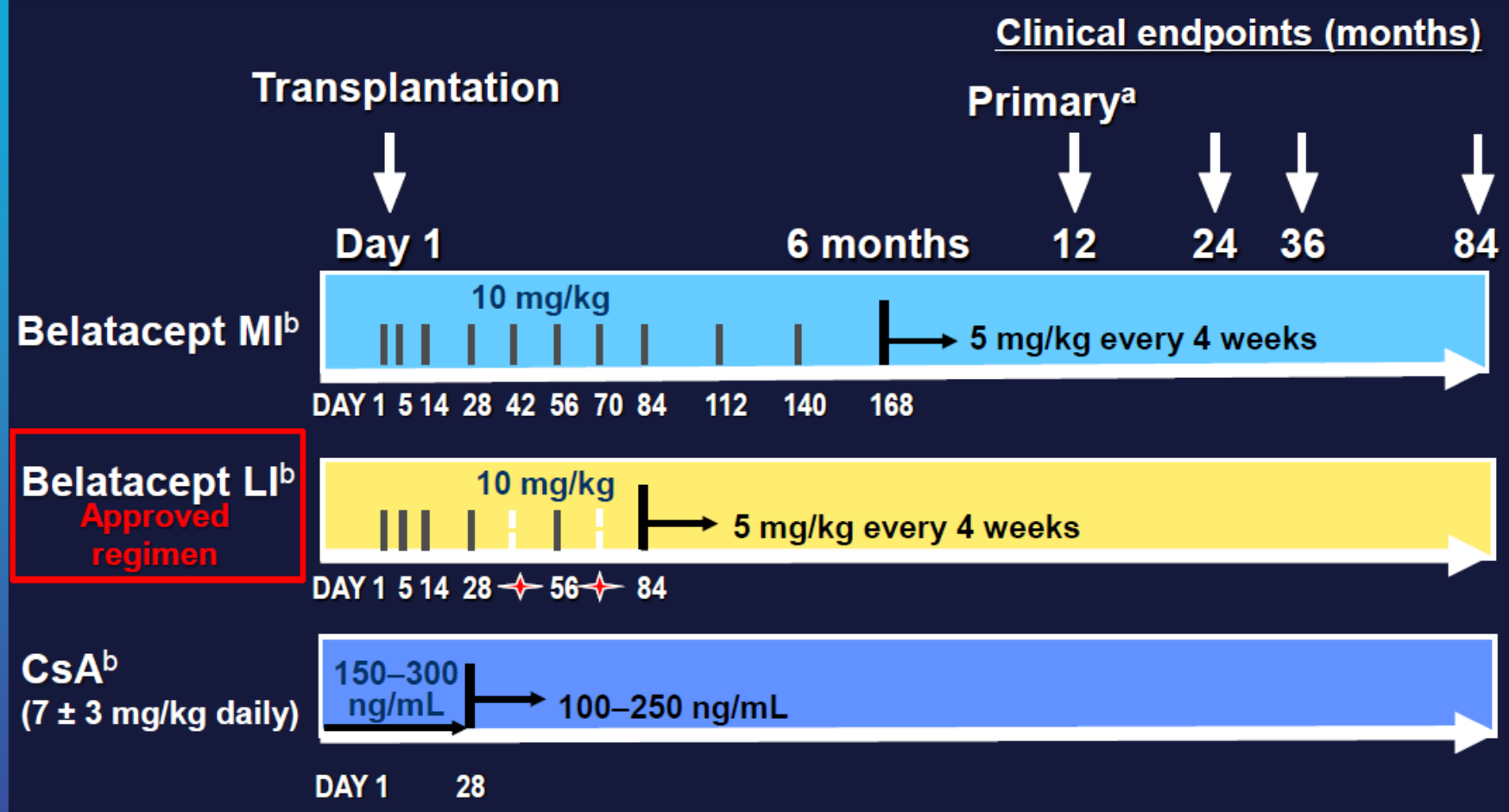
CsA=cyclosporine A.

Objective

- Report the long-term efficacy and safety outcomes up to Year 7 (Month 84) in the ITT population of BENEFIT

ITT=intent-to-treat.

Study Design and Dosing



Placebo infusions

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

Patient Disposition

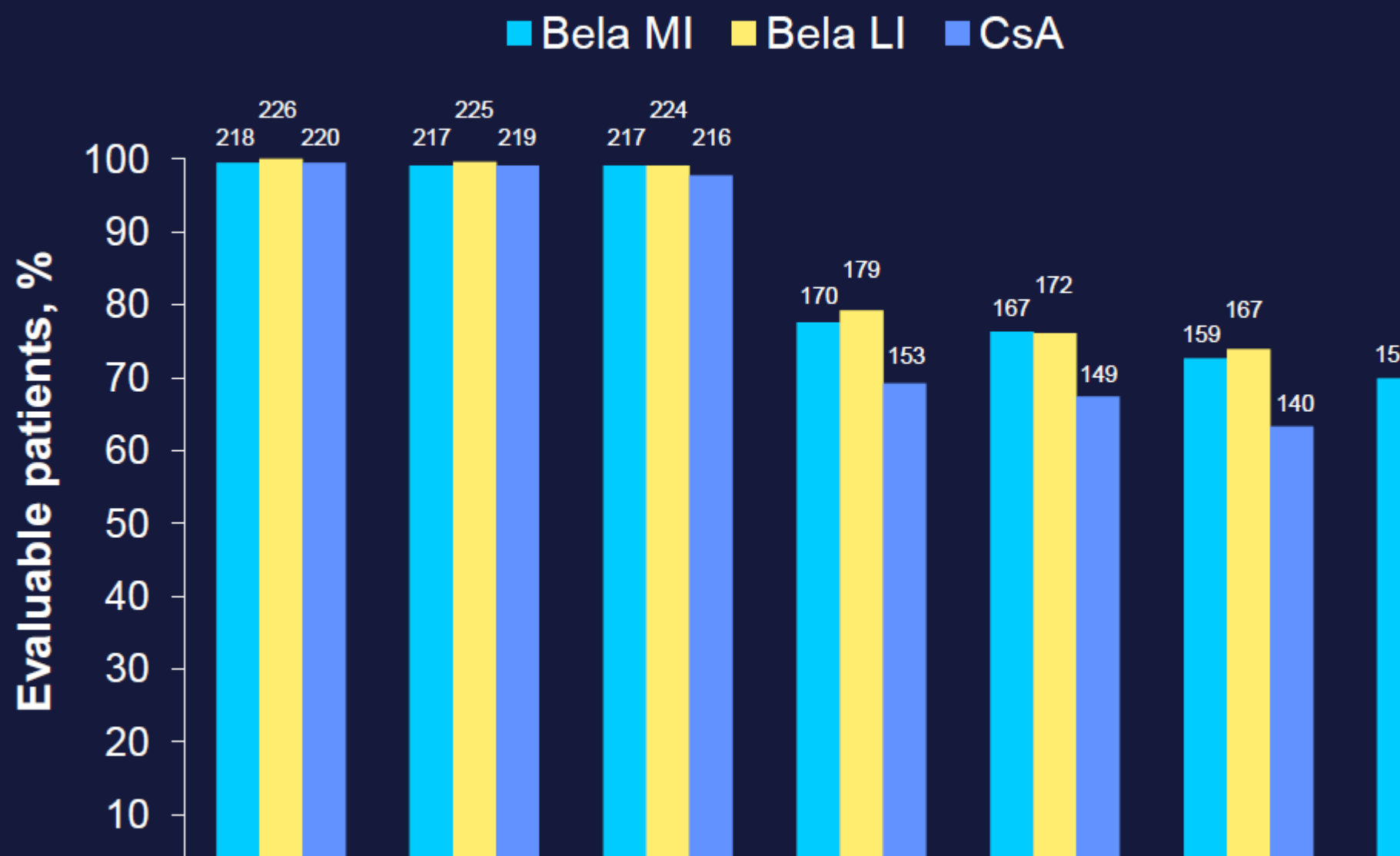
Mean follow-up: 70 mos (bela MI, 71.1 mos; bela LI, 72.0 mos; CsA, 66.3 mos)

Enrolled, n=738

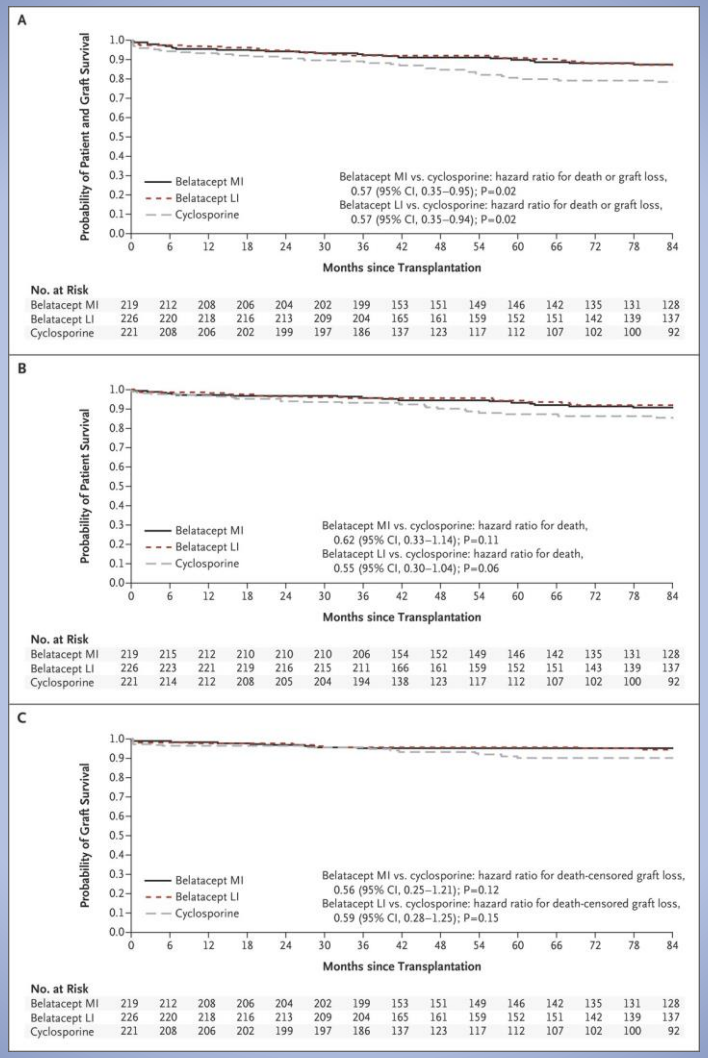
Randomized, n=666

Belatacept MI	Belatacept LI	CsA
Randomized and transplanted, n=219	Randomized and transplanted, n=226	Randomized and transplanted, n=221
Randomized, transplanted, and treated , n=219	Randomized, transplanted, and treated, n = 226	Randomized, transplanted, and treated, n=215
Discontinued, n=91 Ineligible for/refused entry to LTE, n=39 Withdrawal of consent, n=14 Adverse event, n=13 Death, n=13 Other, n=5 Lost to follow-up, n=4 Pregnancy, n=2 Poor/noncompliance, n=1 Lack of efficacy, n=0 Administrative reason, n=0	**Discontinued, n=90** Ineligible for/refused entry to LTE, n=34 Withdrawal of consent, n=20 Adverse event, n=11 Death, n=11 Lost to follow-up, n=4 Other, n=4 Lack of efficacy, n=3 Poor/noncompliance, n=1 Pregnancy, n=1 Administrative reason, n=1	**Discontinued, n=123** Ineligible for/refused entry to LTE, n=41 Death, n=23 Withdrawal of consent, n=22 Adverse event, n=12 Lost to follow-up, n=8 Lack of efficacy, n=6 Other, n=6 Poor/noncompliance, n=4 Administrative reason, n=1
Completed 84 months, n=128	**Completed 84 months, n=136**	**Completed 84 months, n=92**
Evaluable at 84 months, n=153	**Evaluable at 84 months, n=163**	**Evaluable at 84 months, n=131**

Proportion of Patients Assessed for Dea
or Graft Loss



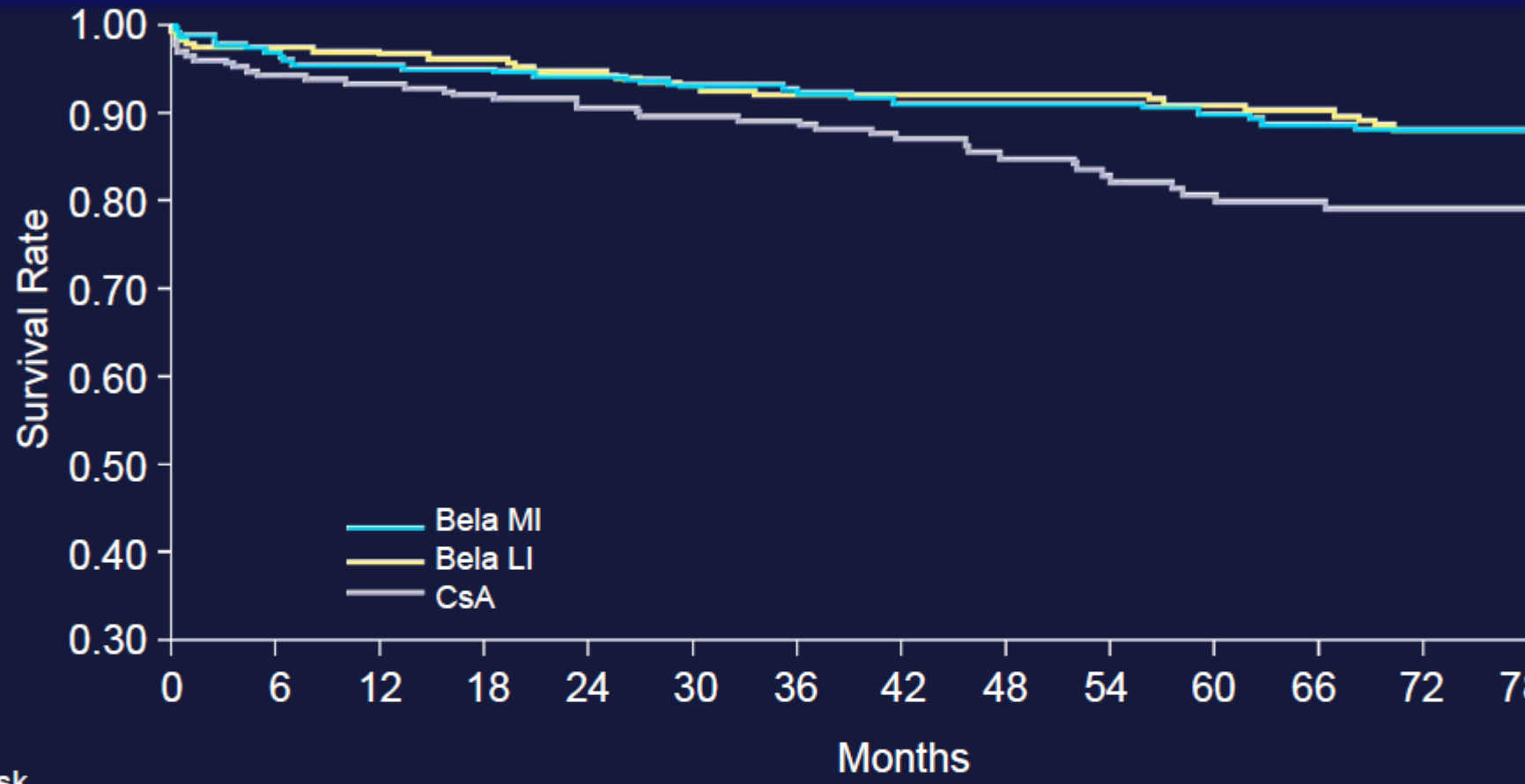
Kaplan–Meier Curves for Patient and Graft Survival.



Vincenti F et al. N Engl J Med 2016;374:333-343

The NEW ENGLAND JOURNAL of MEDICINE

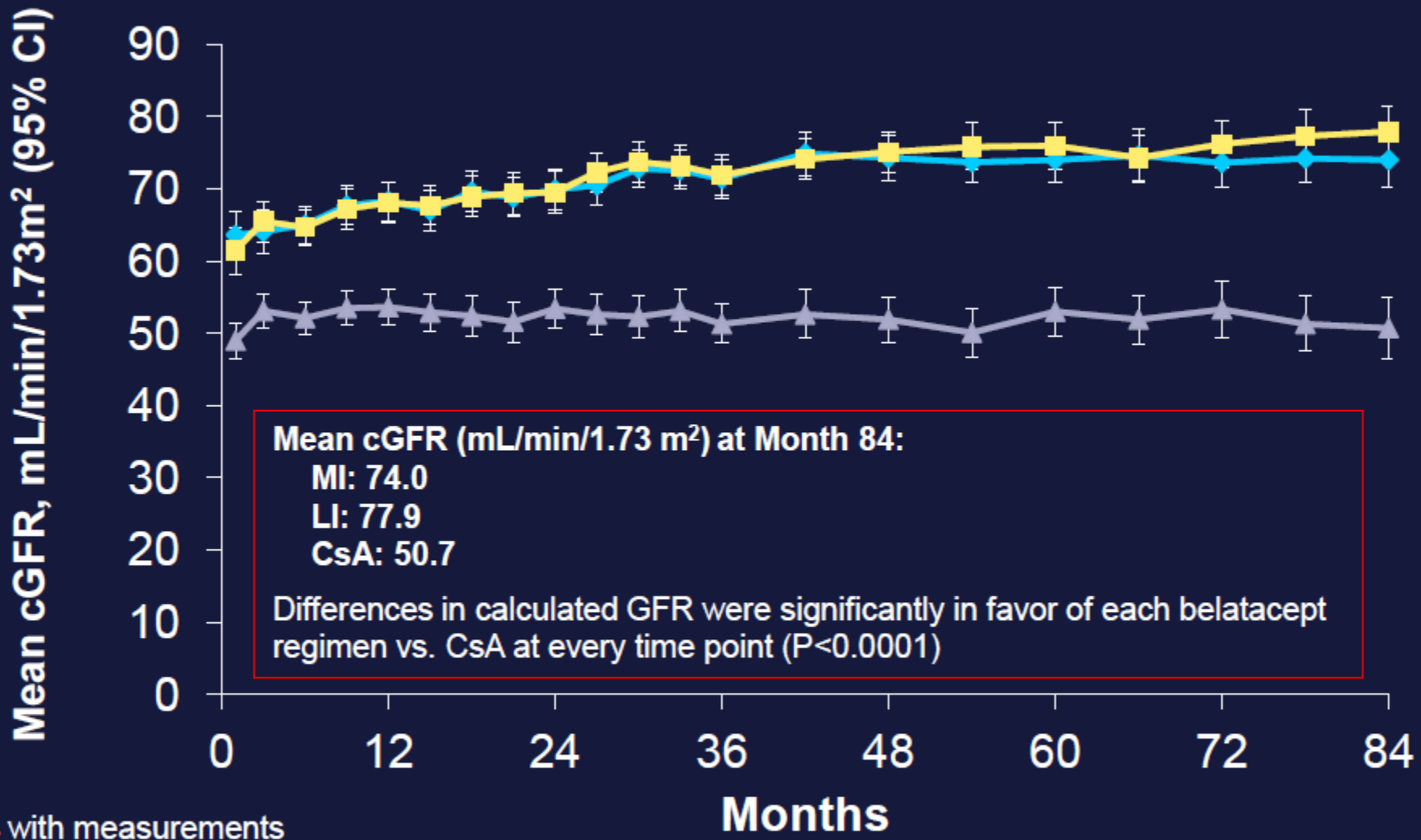
Time to Death or Graft Loss From Randomization to Month 84



N at risk														
Bela MI	219	212	208	206	204	202	199	153	151	149	146	142	135	13
Bela LI	226	220	218	216	213	209	204	165	161	159	152	151	142	13
CsA	221	208	206	202	199	197	186	137	123	117	112	107	102	10

Month 60 **Month 84**

Calculated GFR Over 84 Months*: Without Imputation

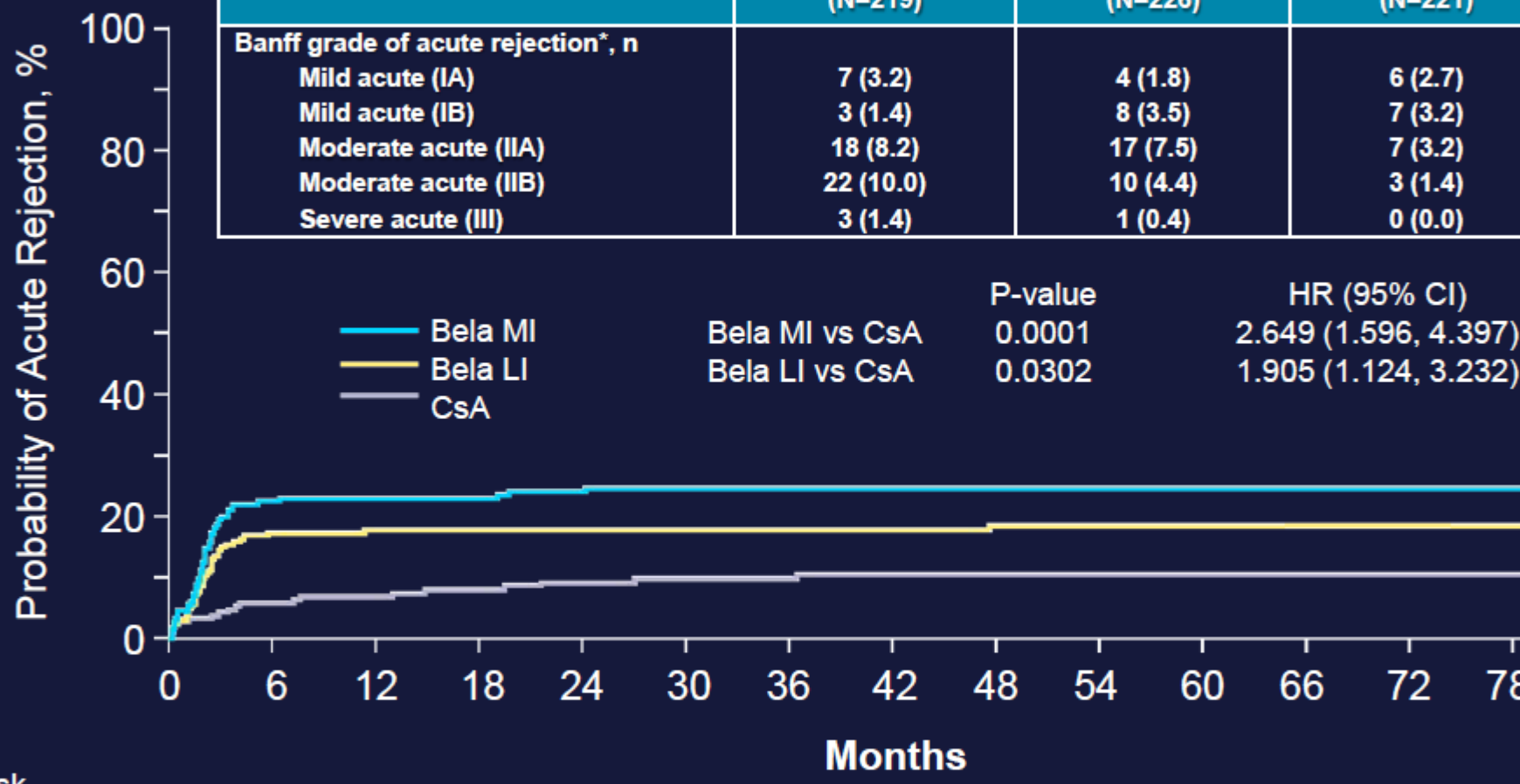


Patients with measurements

MI:	214	192	179	170	136	132	122	109

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

Bela MI	219	154	147	144	140	137	136	128	127	125	122	117	111	10
Bela LI	226	168	164	162	160	157	155	149	144	142	137	135	130	12
CsA	221	180	167	156	147	141	135	123	115	110	106	101	96	94

Safety Summary Up to Month 84

	Belatacept MI (N=219)	Belatacept LI (N=226)	(N
Serious adverse events, n (%)*	155 (70.8)	155 (68.6)	16
Incidence rate†			
Serious infections – total‡	10.6	10.7	
Incidence rate†			
Any fungal infection*	7.8	6.7	
Any viral infection– total*	16.2	14.2	
BK polyomavirus	1.2	0.7	
Cytomegalovirus	2.3	2.3	
Herpes zoster	1.9	1.6	
Any malignancy‡	2.1	1.8	

Patients With PTLD Up to Month 84 by E
Status

EBV-positive patients

	Belatacept MI	Belatacept LI	Cs
Time Interval, months		n (incidence rate)*	
0–12	0	2 (1.00)	0
12–24	1 (0.54)	0	0
24–60	0	0	0
60–72	0	0	1 (1.
72–84	0	0	0
Overall	1 (0.09)	2 (0.18)	1 (0.

EBV-negative patients

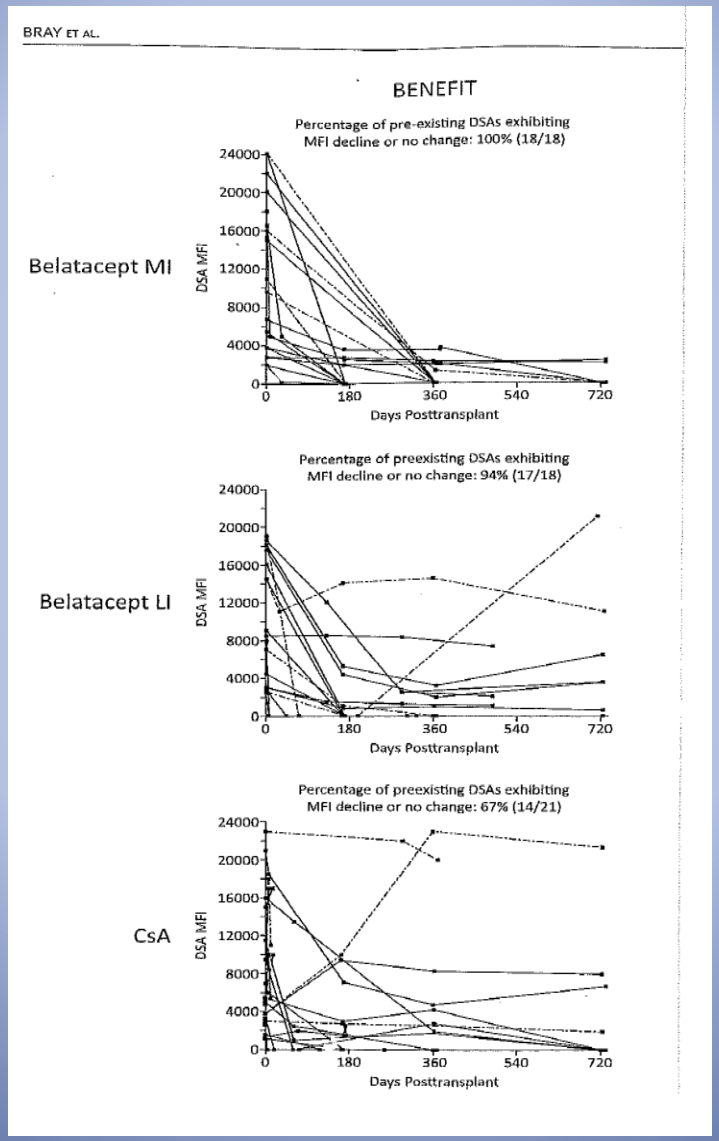
	Belatacept MI	Belatacept LI	Cs
Time Interval, months		n (incidence rate)*	
0–12	1 (4.29)	0	1 (2.
12–24	1 (4.49)	0	0

In the 7 year study de novo donor specific antibody formation was reduced

Vincenti et al N Eng J Med 374:2016

Bray et al.
American Journal of Transplantation

DOI: 10.1111/ajt/14738



Summary

- In this analysis of the final 7 year results from BENEFIT, belatacept-treated patients had better g survival and renal function than CsA-treated patie
- The belatacept safety profile was consistent with previous reports

ADVANTAGES

1. ADHERENCE
2. NO NEED FOR ORAL ABSORPTION
3. NO NEPHROTOXICITY
4. NO CONCERNS ABOUT GENETIC DIFFERENCES IN METABOLISM

DISADVANTAGES

1. CAN ONLY BE USED IN EBV POSITIVE
2. REQUIRES iv ADMININSTRATION
3. MORE EARLY CELLULAR REJECTION
4. MORE EXPENSIVE

Newer Strategies of Co Stimulatory Blockade

- 1. UCSF Bela
- 2. CD28 blockade
- 3. CD40- CD40 ligand (CD 154) blockade

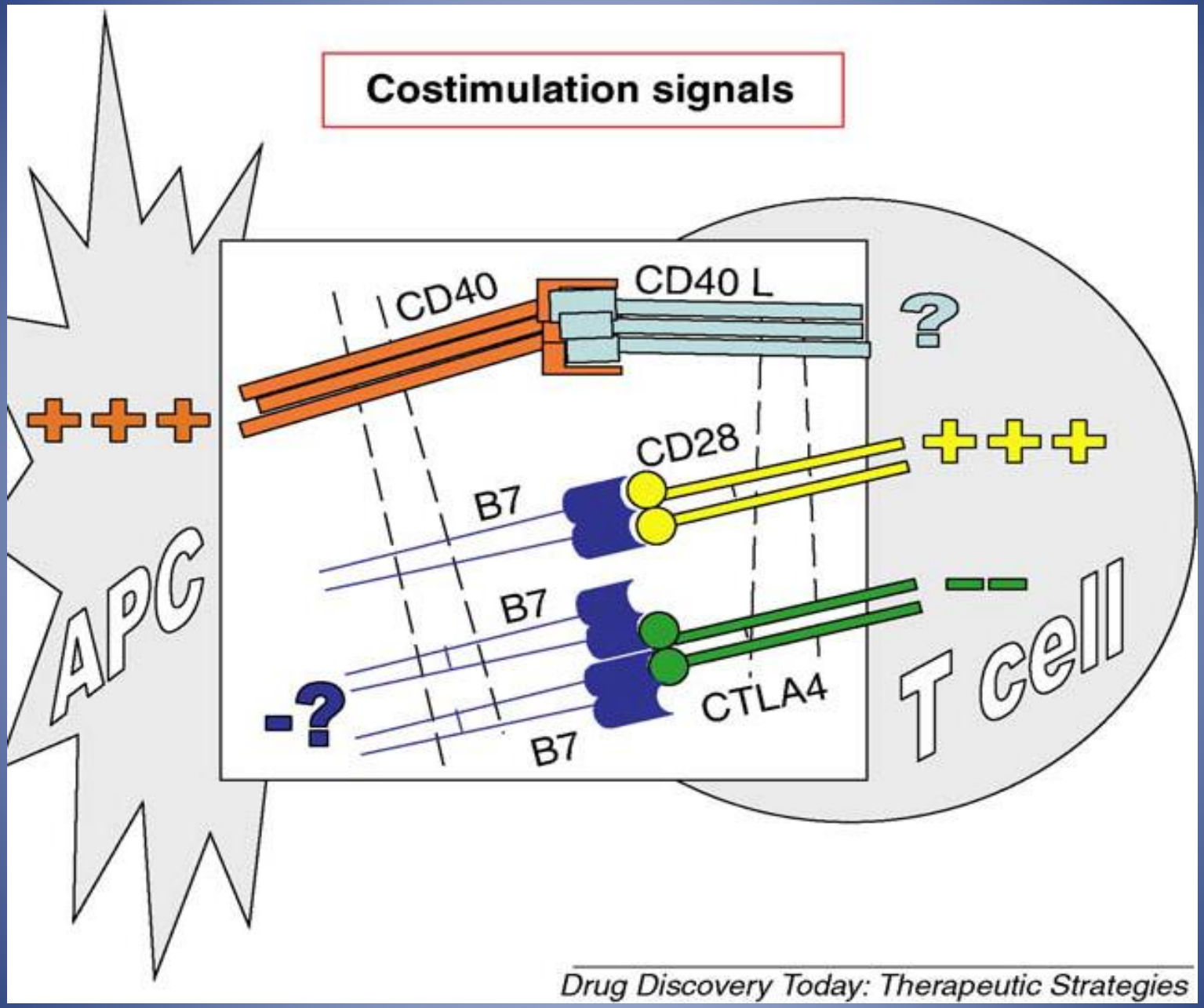
UCSF BELA

- 1. thymoglobulin induction
- 2. bela IV as per BENEFIT
- 3.MMF for PO day 0-30 then mTOR I
- 4. rapid prednisone taper to off

UCSF Bela

- 1. single center trial controlled by concomitant CNI based regimen
- 2. N=44
- 3. 1 year graft survival 98%
- 4. acute rejection rate 11%
- 5. equal AR to control with statistically better GFR and lipid panel

- With permission of F Vincenti


Costimulation signals
CD40
CD40 L
?
+++
CD28
+++
B7
APC
B7
--
T cell
-?
CTLA4
B7
Drug Discovery Today: Therapeutic Strategies

CD 28 Blockade

1.Blocks the co stimulatory signal but leaves B7 (CD80) available for negative signal of CTLA4

2. Very effective in vitro and animal studies

3. Phase 2 human studies performed

4. Proposed phase 3 controlled trial at UCSF and Duke about to begin

By permission F Vincente

CD40-CD40L (CD 154)

- 1. signaling through TNF receptor and NF-kB
- 2. the co stimulatory signal leads to B cell expansion and conversion to plasma cells
- 3. activation of CD8 killer T cells

CD40-CD154

- 1. CD154 blockade prevents rejection in non human primates- Kirk et al Nat Med 5:1999
- 2. utility limited because of thromboembolic events- Kawai et al Nat Med 6:2000

CD40-CD154

- 1. blockade of the complemenatry surface protein CD40 abrogates T and B cell activation
- 2. ASKP1240 fully humanized anti CD40 monoclonal effective in primate organ transplant models and has completed pahse 21 human trials
- 3. 2 competing anti CD 40 reagents are being tested as well