Cardiovascular and Renal Drugs Advisory Committee Meeting

Belatacept

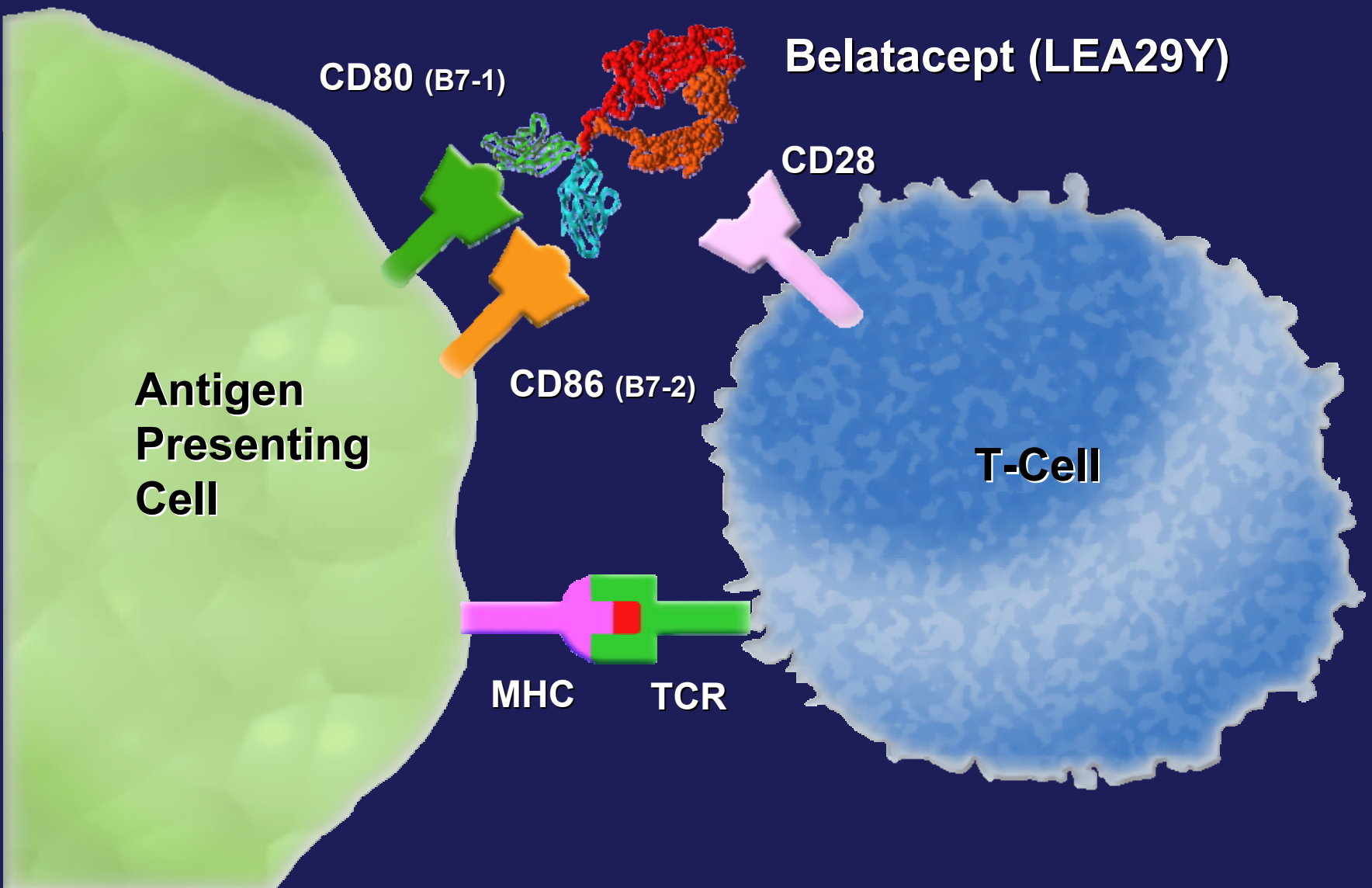
1 March 2010

Bristol-Myers Squibb

Belatacept: Introduction

Anthony Waclawski, PhD
Vice President, Global Regulatory Sciences
Bristol-Myers Squibb

Belatacept: Selective and Potent Immunosuppression



Regulatory Background

Fast Track Program	January 2005
Special Protocol Assessment	August 2005
Orphan Designation	February 2008
Pre-BLA meetings	Apr 2008–May 2009
Biologics Licensing Application	June 2009

Core Clinical Development Program

N = 1427

Phase II

- **IM103100**
  (N=218)
  Proof of concept

Phase III

- **IM103008**
  (N=666)
  Standard criteria donors
- **IM103027**
  (N=543)
  Extended criteria donors

Belatacept Clinical Program Results

- Improved renal function
- Improved cardiovascular and metabolic profile
- Preserved short-term patient and graft survival
- Characterized frequency and impact of rejection episodes
  - provided evidence of immunosuppressive efficacy
  - allowed full evaluation of clinical implications
- Identified two important risks and approach to minimization
  - PTLD
  - PML

Proposed Indication

- **Belatacept is indicated for the prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants.**
- **Belatacept has been used in combination with an interleukin-2 (IL-2) receptor antagonist, a mycophenolic acid (MPA) and corticosteroids.**

Experts Available to the Committee

Elizabeth Andrews, PhD, MPH
Vice President of Pharmacoepidemiology and Risk Management, RTI Health Solutions
RTI International, Research Triangle Park, NC

Vikas Dharnidarka, MD, MPH
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Assoc. Professor & Chief, Div. of Pediatric Nephrology
University of Florida, Gainesville, FL

Lawrence G. Hunsicker, MD
Professor of Medicine, University of Iowa School of Medicine
Medical Director of Organ Transplantation
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Christian P. Larsen, MD, DPhil
Professor and Chairman, Department of Surgery
Surgeon-in-Chief
Associate Vice President and Executive Director, Emory Transplant Center
Emory University School of Medicine, Atlanta, GA

Jutta Preiksaitis, MD, FRCP(C)
Professor, Division of Infectious Diseases
Medical Director, Provincial Laboratory for Public Health
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Associate Professor of Medicine
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Flavio Vincenti, MD
Professor, Division of Nephrology
UCSF Department of Medicine
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E. Steve Woodle, M.D., F.A.C.S.
Professor of Surgery;
Chief, Division of Transplantation
University of Cincinnati College of Medicine, Cincinnati, OH
Director, Israel Penn International Transplant Tumor Registry

Presentation Outline

Unmet Need in Transplantation ..... Dr. Christian Larsen

Discussion of Belatacept Registrational Program

- Design and Efficacy ..... Dr. Pushkal Garg
- Safety Results ..... Dr. Sheila Gujrathi

Risk Management & Benefit/Risk ..... Dr. Brian Daniels

Belatacept in Clinical Context ..... Dr. Lawrence Hunsicker

Unmet Need in Transplantation

Christian P. Larsen, MD, DPhil

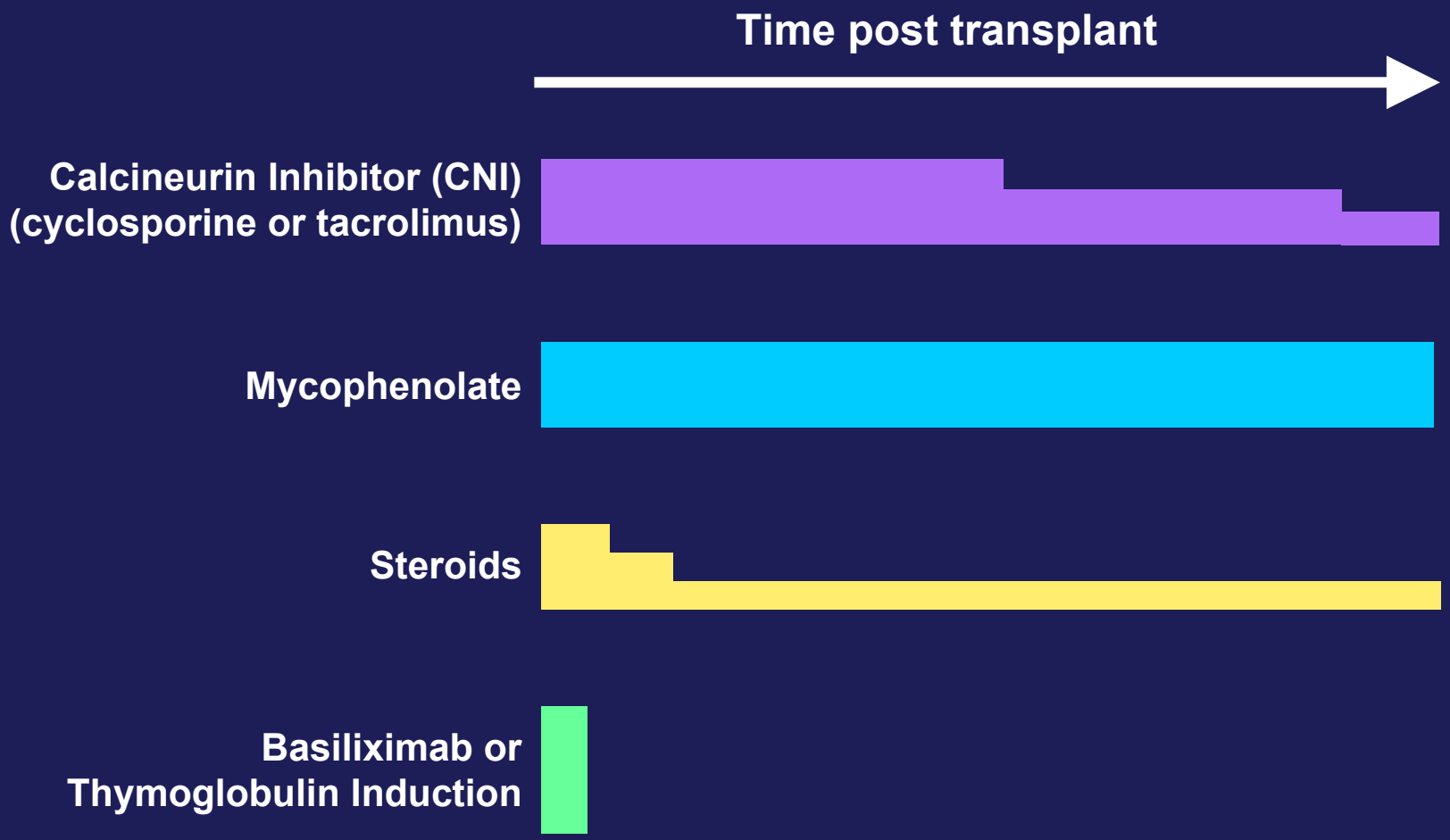
Professor and Chairman, Department of Surgery

Surgeon-in-Chief

Associate Vice President and Executive Director, Emory Transplant Center

Emory University School of Medicine, Atlanta, GA

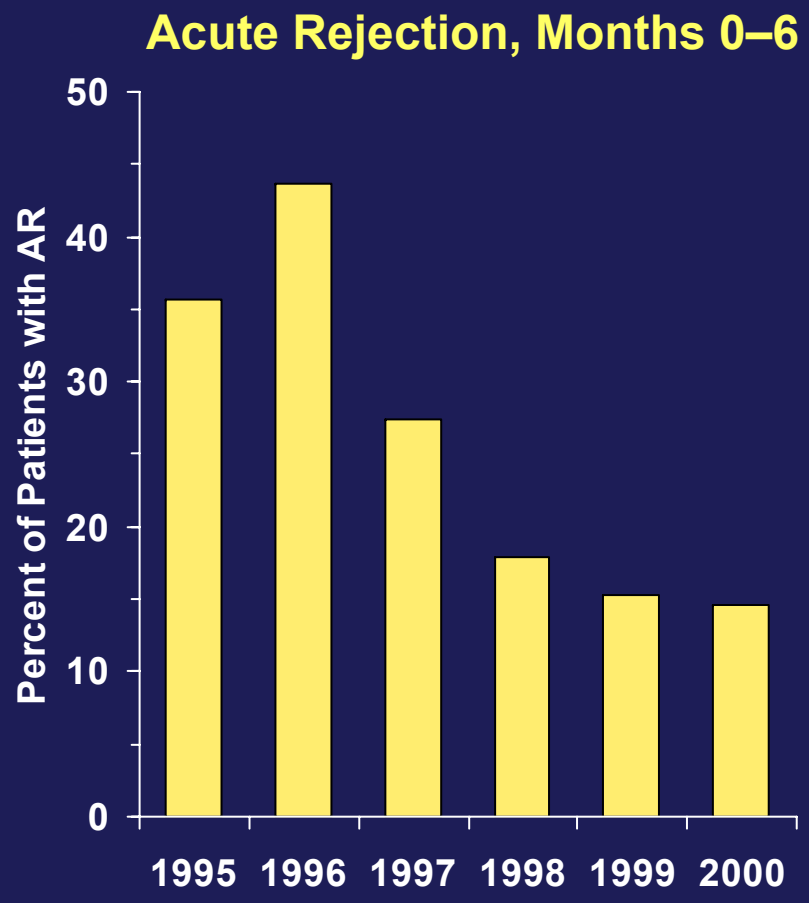
Immunosuppression Regimens for Renal Transplant



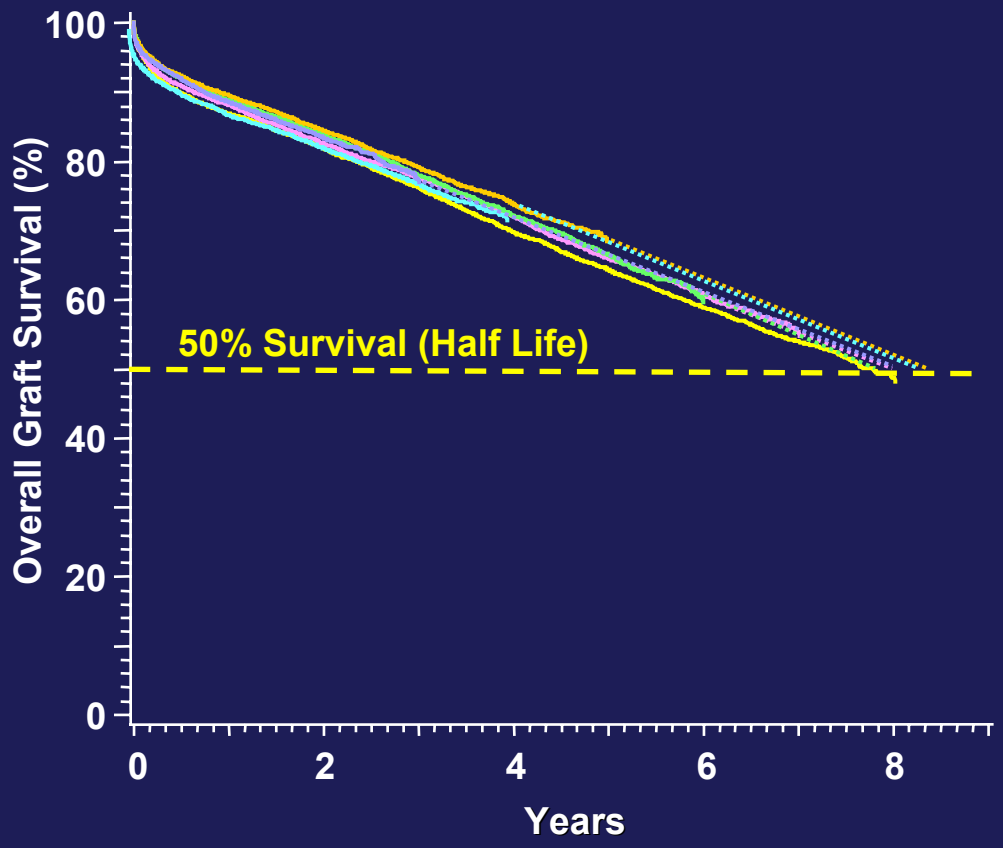
Transplantation History and CNIs

- Before 1980s, AR rates were high and short-term graft survival was poor
- Improving short-term outcomes was the important unmet medical need
- CNI therapy was a major advance in transplantation
  - Excellent 1-year patient and graft survival
  - AR rates: 10–20%
  - AR is treatable and its effects are largely reversible

Acute Rejection and Graft Survival

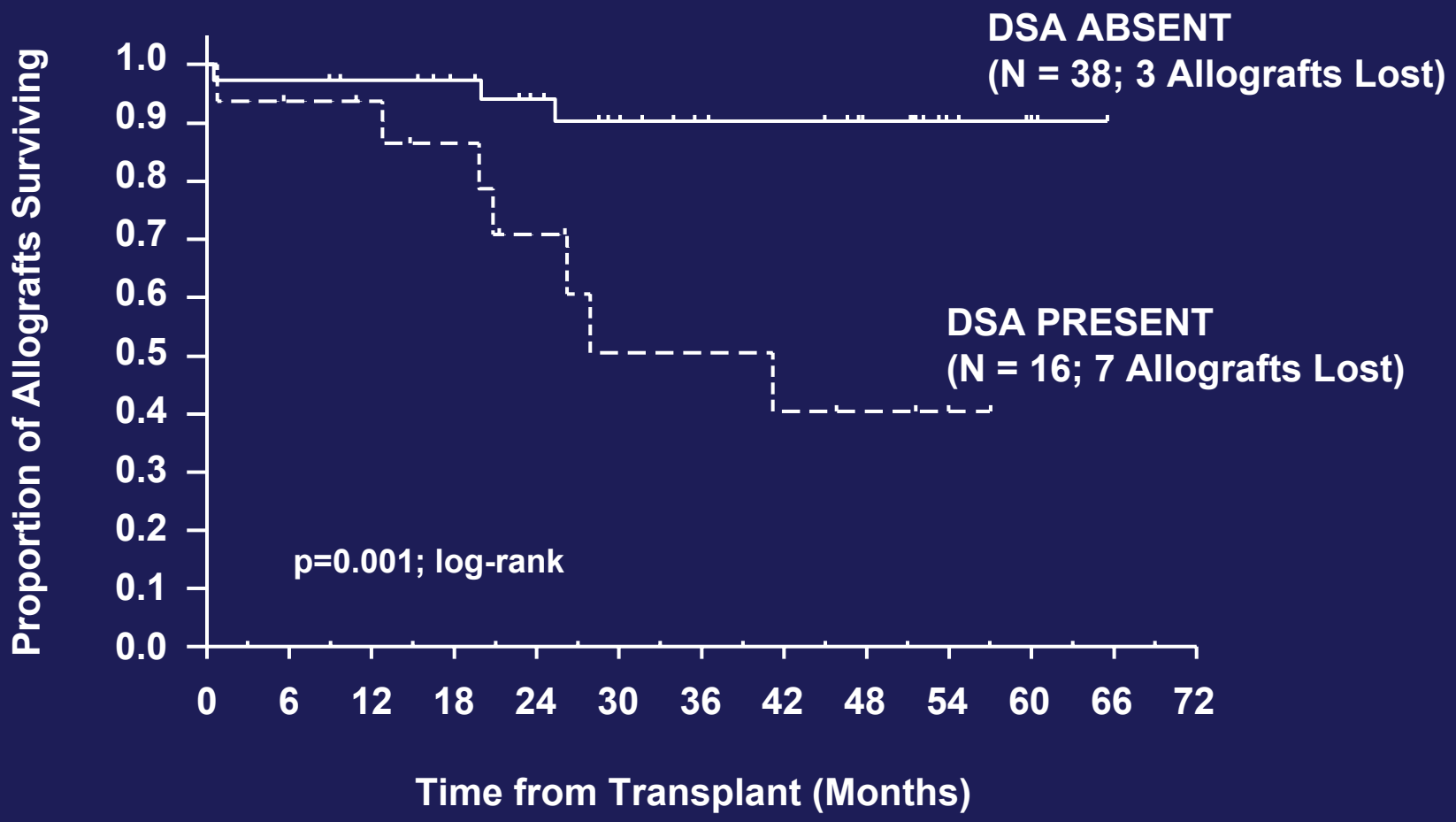


Meier-Kriesche et al., *Am J Transplant.* 2004; 4: 378–383



Meier-Kriesche et al. *Am J Transplant.* 2004; 4: 1289–1295

Donor Specific Antibodies (DSA) at Rejection Diagnosis are Associated with Reduced Allograft Survival

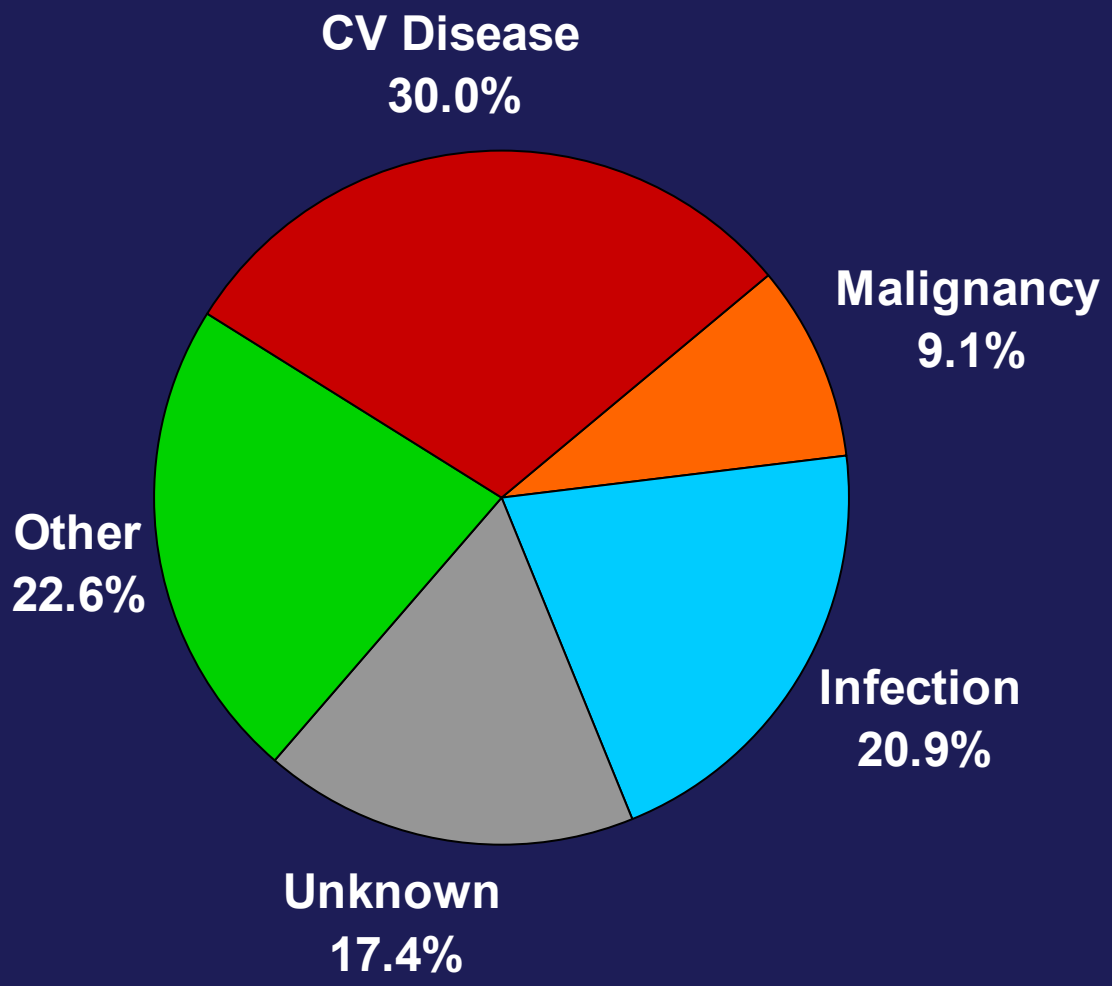


Everly, et al., "Reducing De Novo Donor-Specific Antibody Levels during Acute Rejection Diminishes Renal Allograft Loss"; *Am J Transplant* 2009; 9: 1063–1071

The CNI Paradox

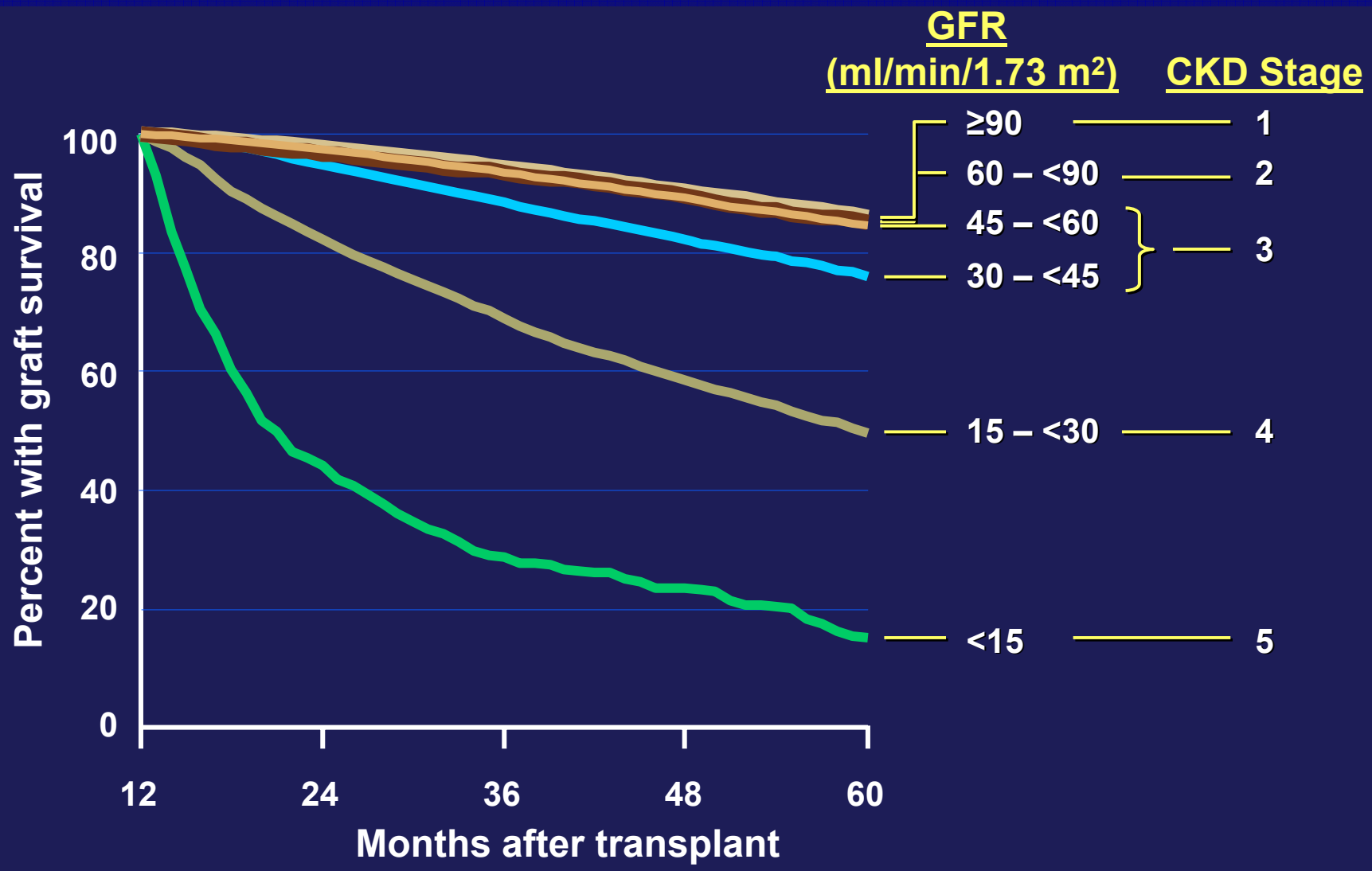
- CNIs are potent immunosuppressants, but are nephrotoxic which leads to:
  - Declining renal function
  - Graft fibrosis and scarring (CAN / IFTA)
- CNIs increase cardiovascular risk by contributing to:
  - Declining renal function
  - Diabetes
  - Hypertension
  - Hyperlipidemia
- These factors contribute to graft loss and patient death

Causes of Death with Functioning Graft



Patients age 18 & older, 2003–2007; USRDS 2009 ADR

Five-year Patient and Graft Survival According to One-year Renal Function



USRDS 2009 ADR.
Patients 18 and older receiving a kidney 2000-2005.

Unmet Need

- Avoid the CNI toxicities
  - Nephrotoxicity
  - Metabolic and cardiovascular effects
- Maintain the already good short-term outcomes
  - Patient and graft survival
  - Control of the alloimmune response
- These benefits should lead to improved long-term patient and graft survival

Development Program Overview

Pushkal Garg, MD

Executive Director, Global Clinical Research
Bristol-Myers Squibb

Phase 3 Development Objectives

- Demonstrate that belatacept:
  - Offers short-term survival comparable to CNIs
  - Improves:
    - Post-transplant renal function
    - Diabetes, blood pressure, and lipids
  - Results in acceptable rates of rejection
- Identify an efficacious and safe dose
- Show consistency of effect across a broad range of recipients
- Demonstrate durable efficacy and safety

Core Clinical Studies in Renal Transplantation

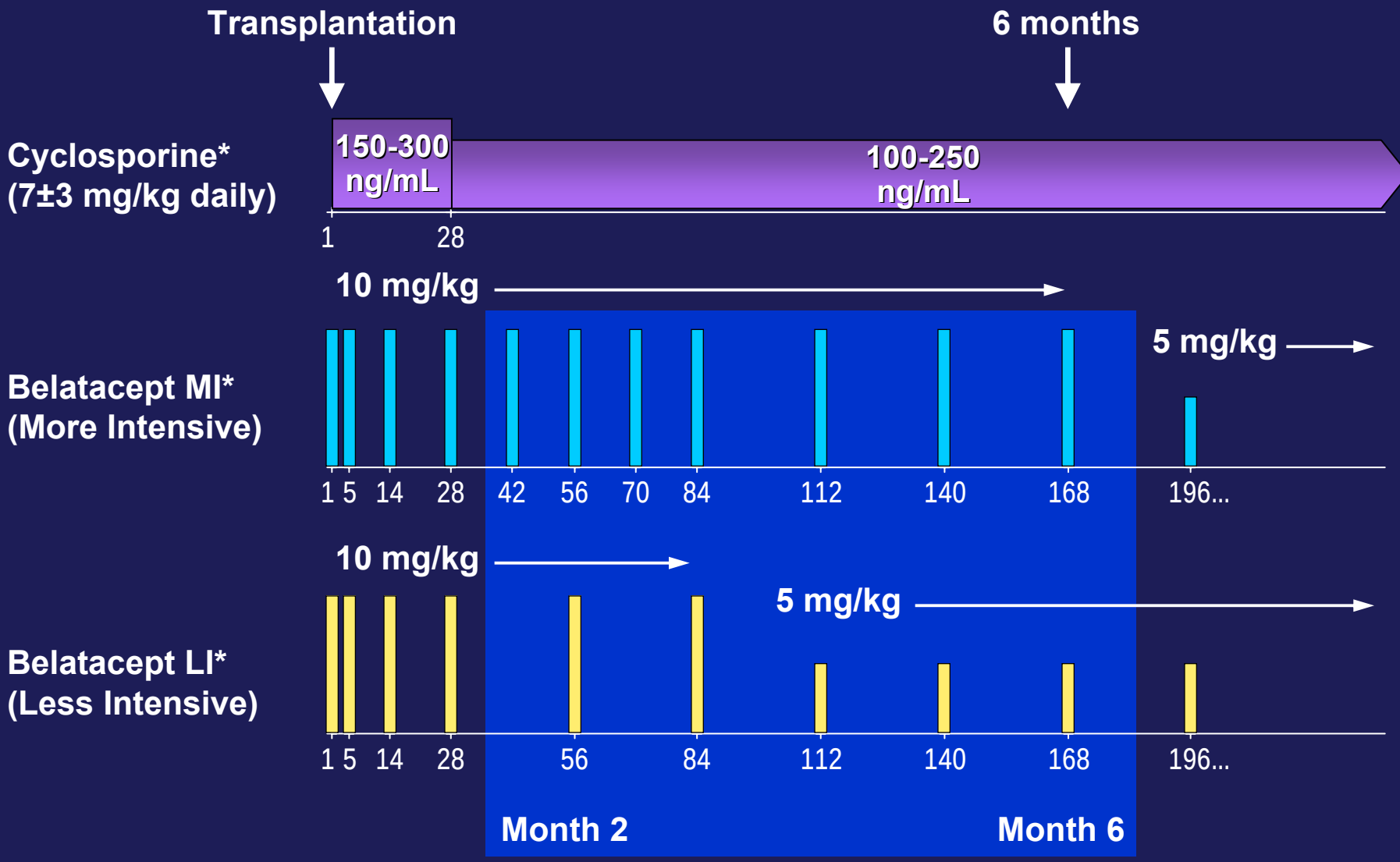
Phase II

- IM103100
  Proof of concept

Phase III

- IM103008
  Standard criteria donors
- IM103027
  Extended criteria donors

Treatment Regimen
Study -008 and Study -027



*All patients received basiliximab induction, mycophenolate mofetil, and corticosteroid-taper

Co-primary Endpoints — 12 Months

- **Composite patient and graft survival (non-inferiority; 10% margin)**
- **Composite renal impairment (superiority)**
- **Acute rejection (Study -008: non-inferiority, 20% margin)**

Secondary Endpoints — 12 Months

- Chronic allograft nephropathy (CAN) or interstitial fibrosis and tubular atrophy (IF/TA)
- New-onset diabetes after transplantation
- Hypertension
- Dyslipidemia

Patient Characteristics and Disposition

Recipient Demographics

Characteristic	Study -008 (N=666)	Study -027 (N=543)
Mean age, years	43	56
Gender, %		
Male	69	67
Race, %		
White	61	75
Black or African American	8	13
Geographic region, %		
North America	42	25
South America	16	26
Europe	27	49
Asia/Pacific	15	<1
Africa	<1	<1

Donor Characteristics

Study -008 (N=666)

- 42% deceased donor
- 58% living donor

Study -027 (N=543)

- Deceased donors
  - 49% age ≥60
  - 22% age 50–59 with complications
  - 29% anticipated CIT>24 hours or non-heart beating donor

Patient Disposition at Month 12

	Study -008 (N=666)			Study -027 (N=543)		
	Bela MI	Bela LI	CsA	Bela MI	Bela LI	CsA
Randomized, receiving transplant*	219	226	221	184	175	184
Randomized, receiving transplant and treatment	219	226	215	183	174	179
Discontinued treatment, n (%)	46 (21)	45 (20)	42 (20)	50 (27)	45 (26)	54 (30)
Adverse event	9 (4)	12 (5)	20 (9)	22 (12)	27 (16)	31 (17)
Lack of efficacy	26 (12)	24 (11)	10 (5)	16 (9)	15 (9)	14 (8)
Other	11 (5)	9 (4)	12 (5)	12 (7)	3 (2)	9 (5)

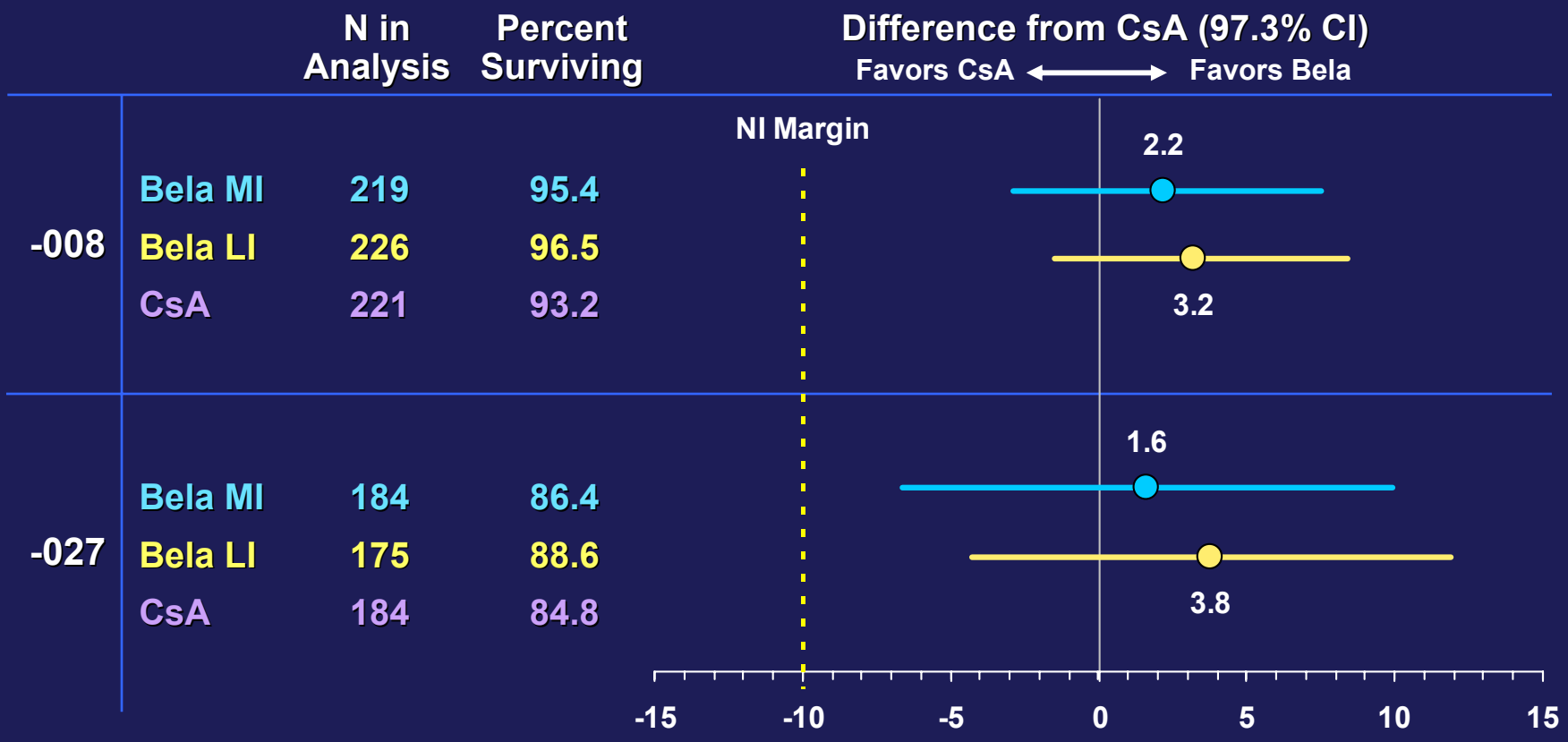
* Intent-to-treat population

Critical Data Collection Rates

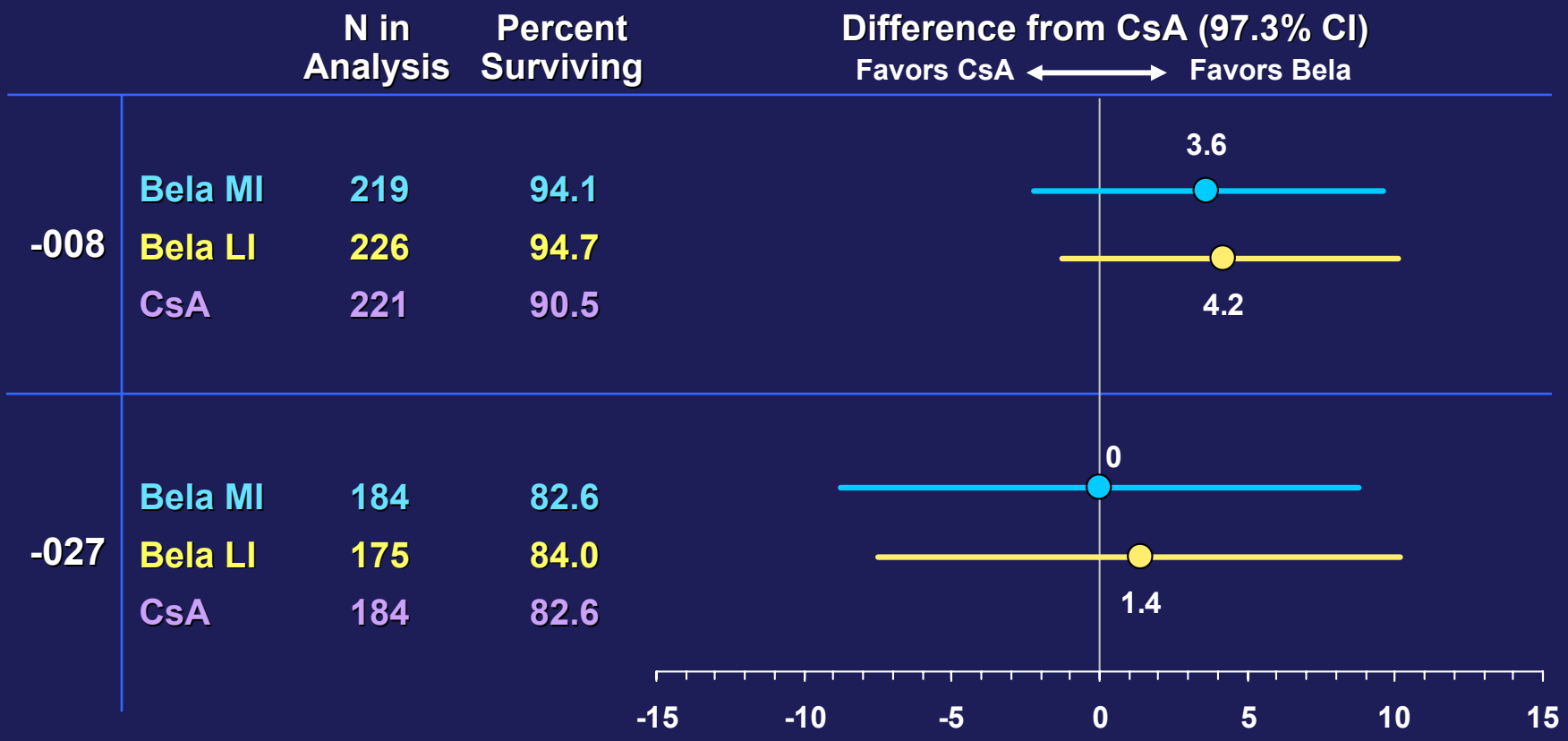
	Study -008 (N=666)	Study -027 (N=543)
Patient and graft status (%)	99.7	98.7
Renal function at Month 12		
Measured Iothalamate GFRs (%)	89	84
Calculated MDRD GFR (%)	90	87
Centrally-read biopsies		
Suspected rejection (%)	96	93
Month 12 for CAN / IFTA (%)	80	76

Patient and Graft Survival

Patients Surviving with a Functional Graft at Month 12



Patients Surviving with a Functional Graft at Month 24



Renal Function

Assessment of Glomerular Filtration Rate (GFR)

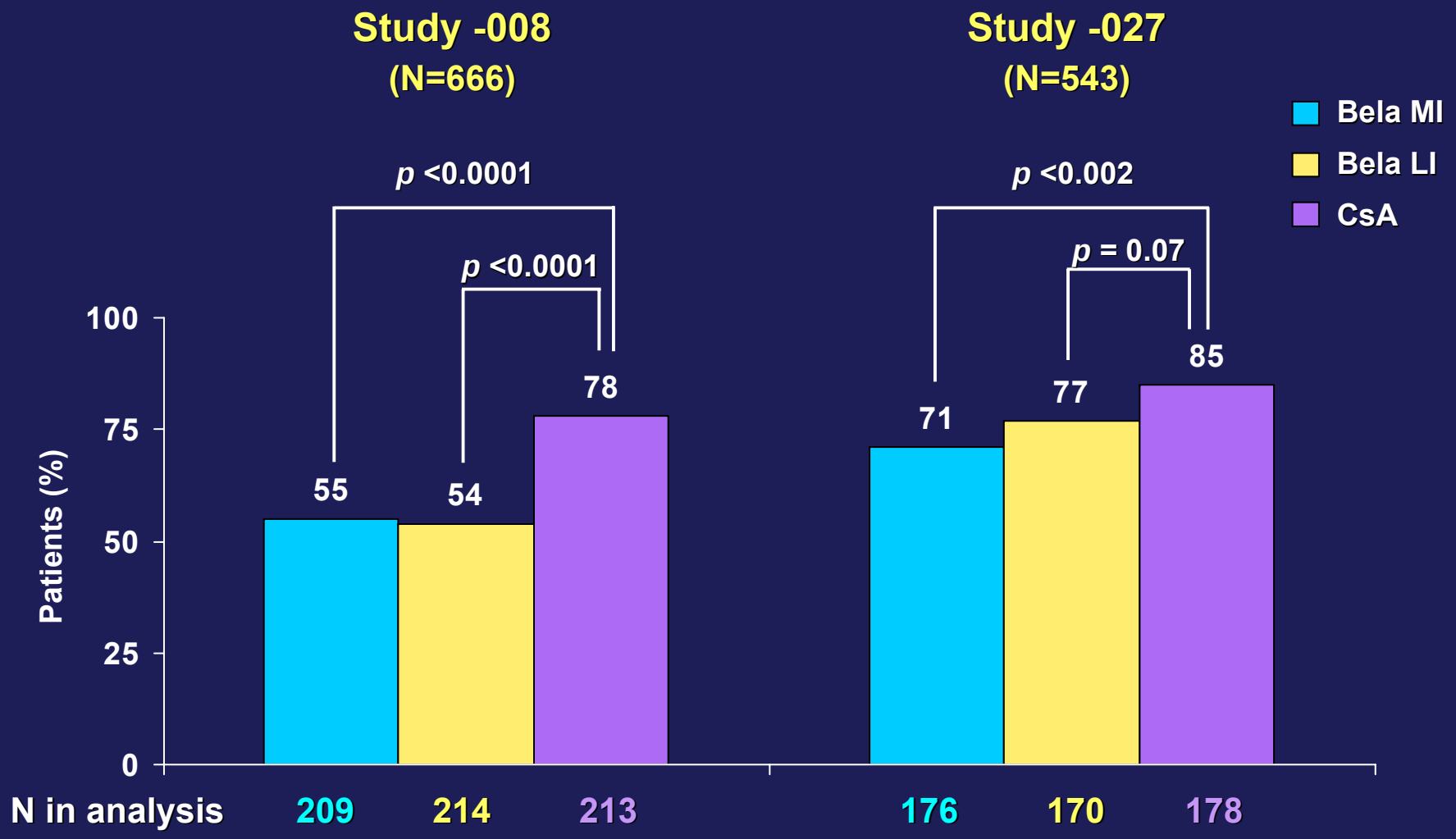
Methods

- Primary: measurement of cold iothalamate at Months 3 and 12
- Secondary: calculated using MDRD formula; performed serially

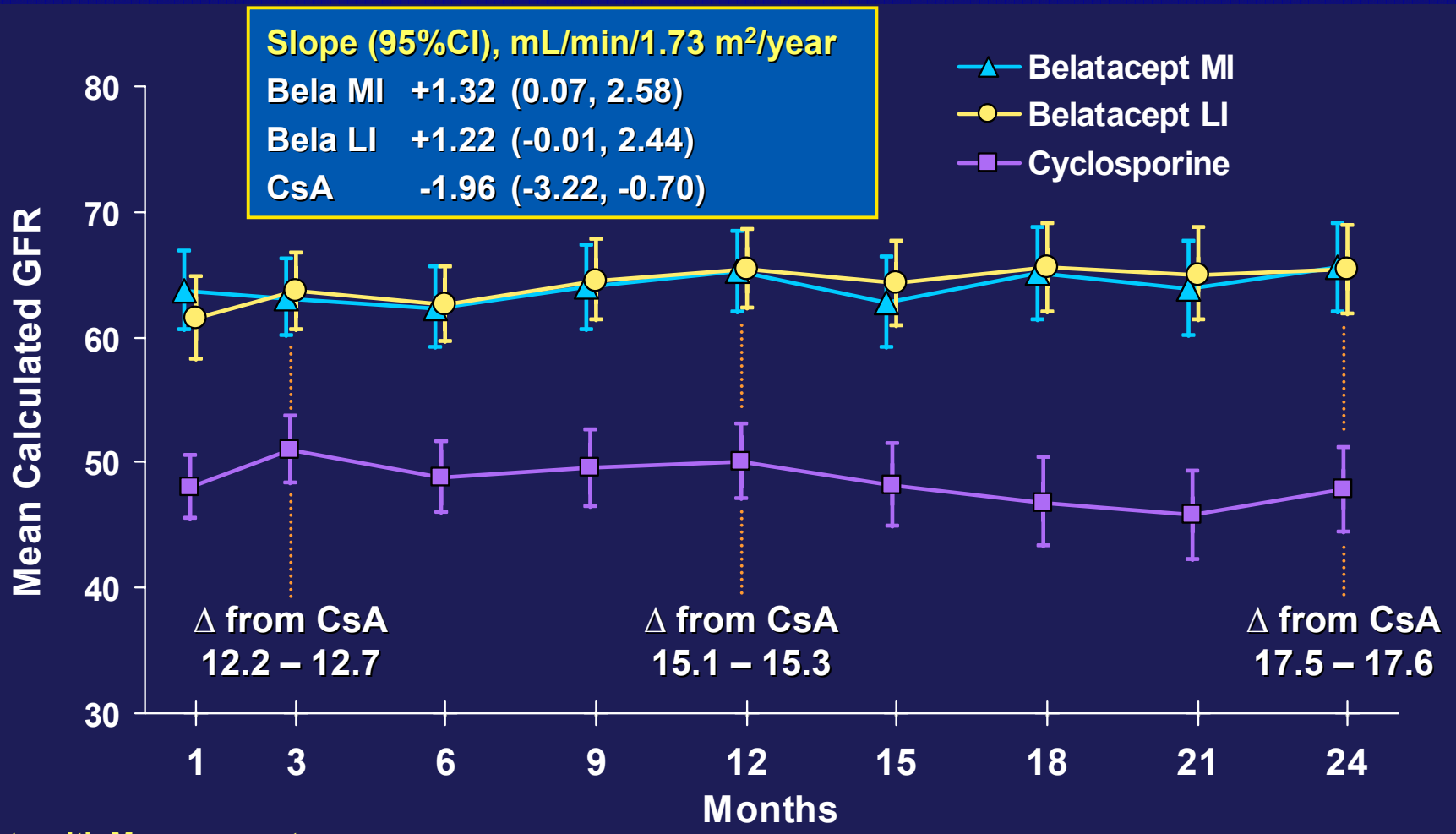
Endpoints

- Composite renal impairment endpoint
  - Proportion of patients with mGFR <60 or with decline of ≥10 from Months 3 to 12
- Mean values, rates of change, and CKD stages

Patients with Renal Impairment at Month 12



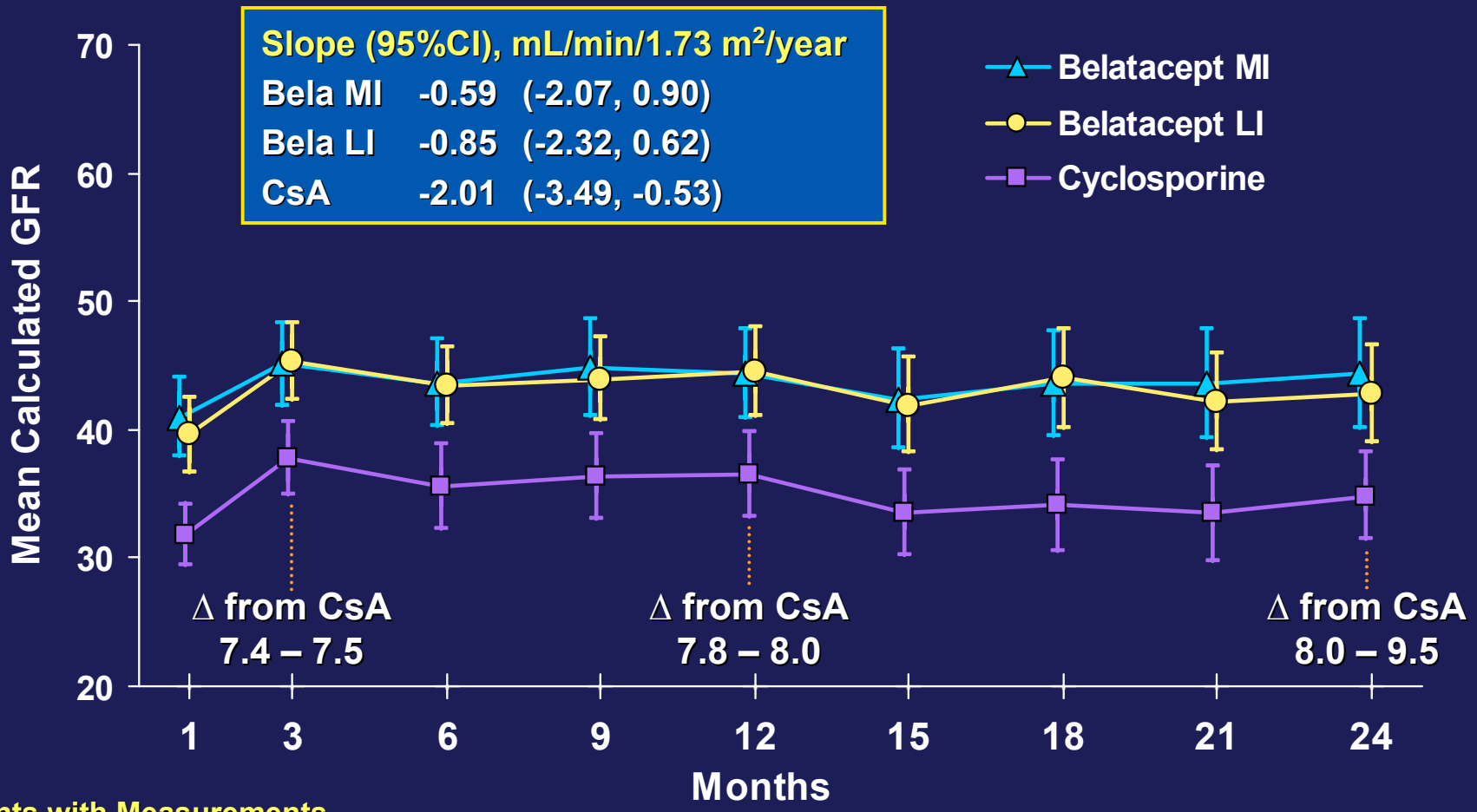
Calculated GFR Over Time: Study -008



Patients with Measurements

Bela MI	214	207	170	180	201	174	167	167	191
Bela LI	220	211	185	176	200	178	181	174	201
CsA	214	201	189	174	199	171	160	160	182

Calculated GFR Over Time: Study -027



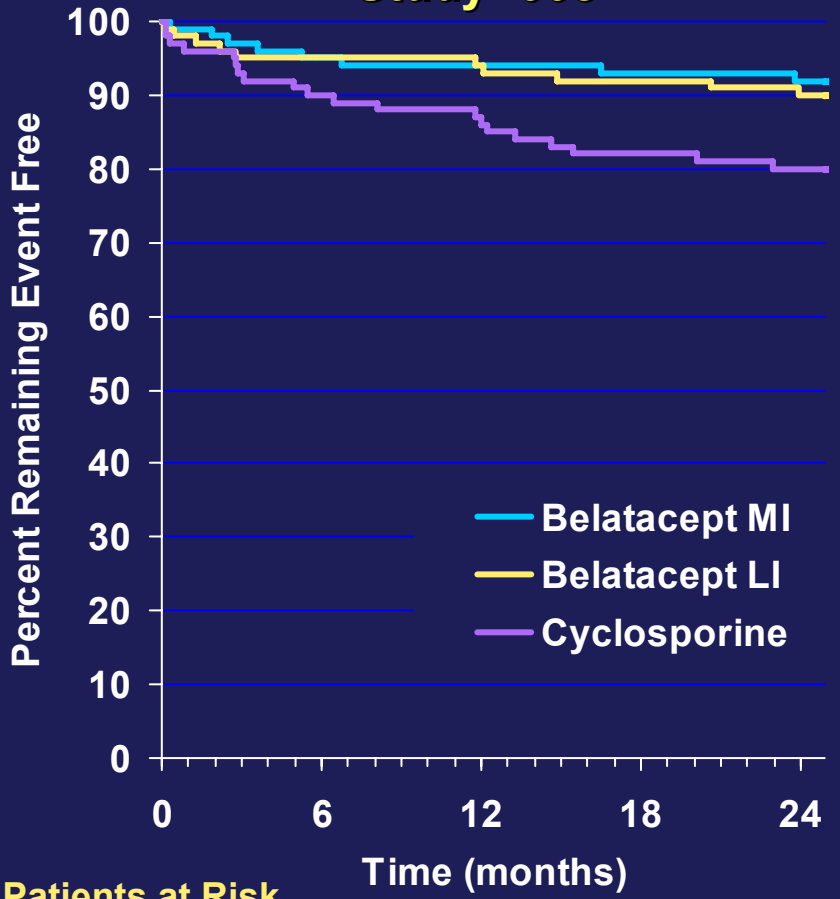
Patients with Measurements

Bela MI	182	177	161	153	165	145	143	140	152
Bela LI	173	168	152	149	158	141	143	145	158
CsA	184	172	153	147	159	139	140	137	154

Preservation of Renal Function and Structure

Time to Progression to Stage 4/5 CKD

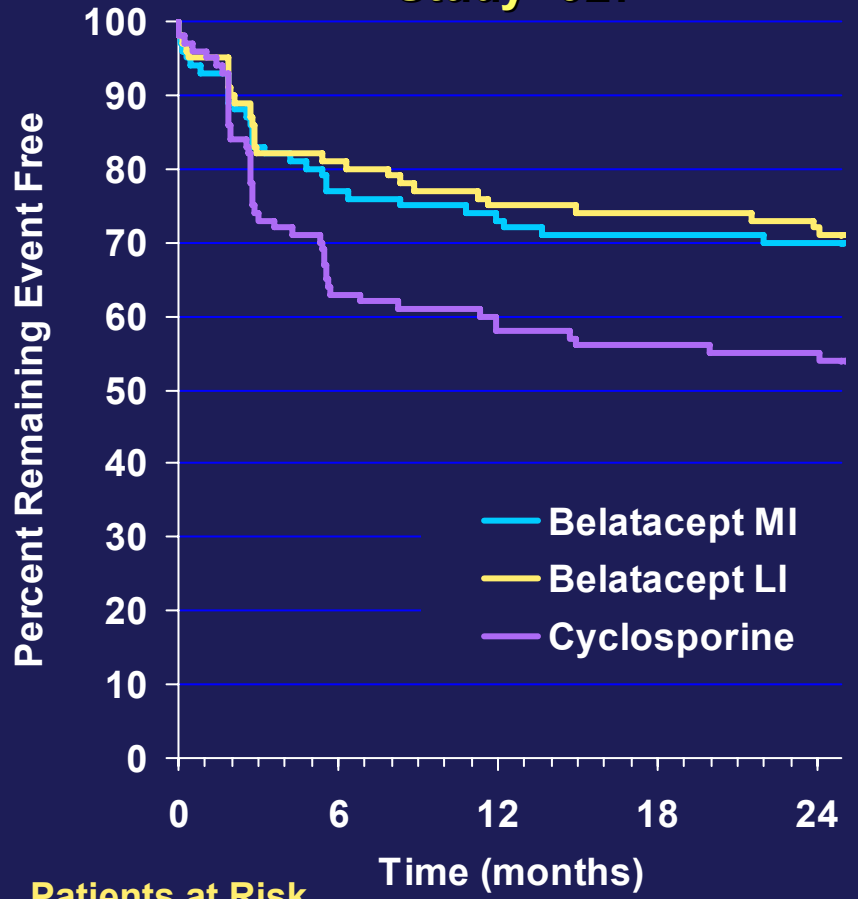
Study -008



Patients at Risk

MI	219	208	205	202	192
LI	226	215	212	208	192
CsA	221	197	191	178	159

Study -027

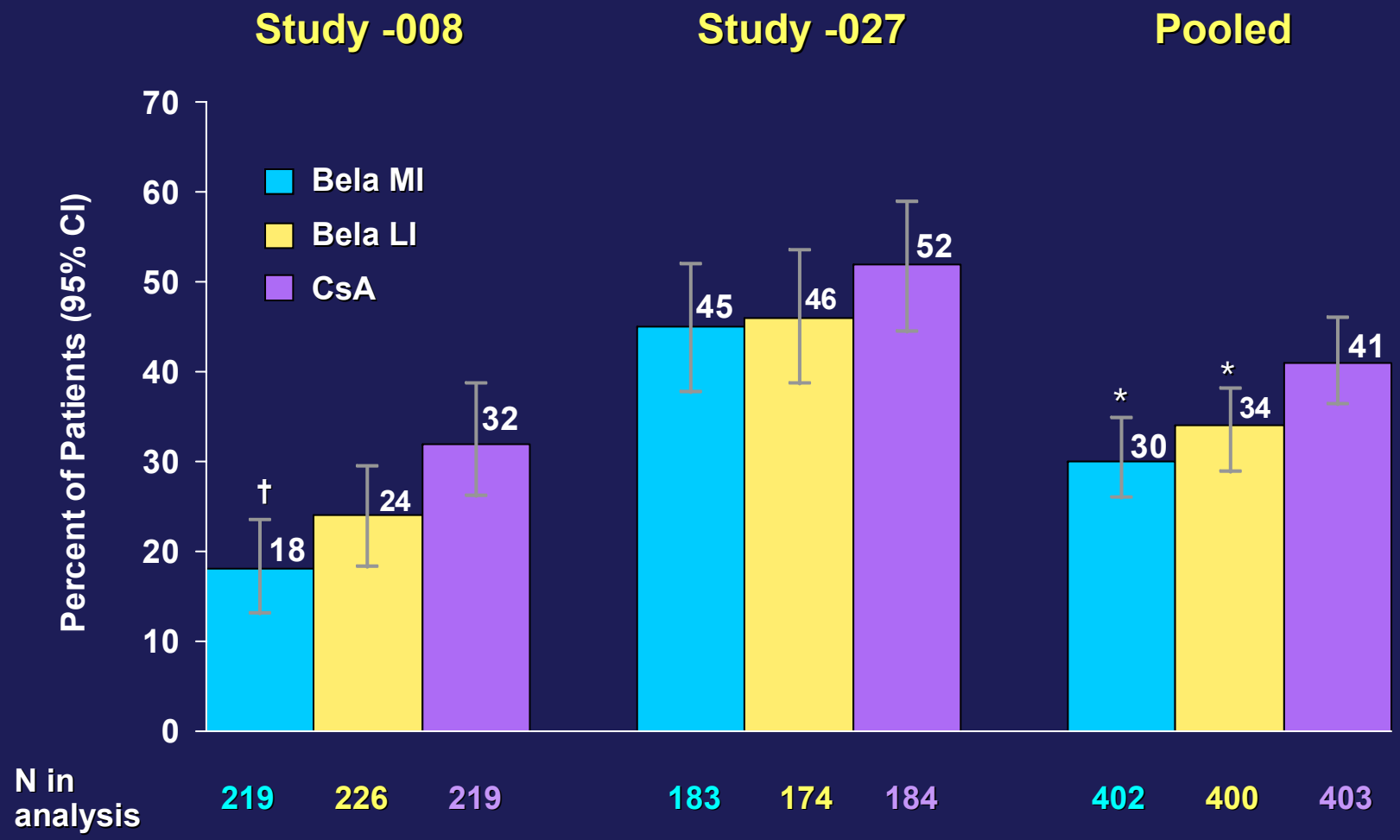


Patients at Risk

MI	184	139	131	127	122
LI	175	141	132	130	116
CsA	184	116	107	101	95

(Time to first of two GFR measures <30, death or graft loss)

Prevalence of CAN / IFTA at Month 12



CAN=chronic allograft nephropathy; †*P*<0.002 vs cyclosporine **P*<0.027 vs cyclosporine

Allograft Rejection

Assessment of Rejection Episodes

Identification

- Renal biopsy required for suspicion of rejection
- Diagnosis confirmed by blinded central pathologist

Classification

- Banff criteria
- Association with anti-donor HLA antibodies

Assessed graft survival and function after rejection

Rejection Episodes by Month 12

	Percent of Patients					
	Study -008			Study -027		
	Bela MI N=219	Bela LI N=226	CsA N=221	Bela MI N=184	Bela LI N=175	CsA N=184
Rejection	22.4*	17.3	7.2	17.9	17.7	14.1
Difference from CsA (97.3% CI)	15.1 (7.9, 22.7)	10.0 (3.3, 17.1)	–	3.8 (-4.7, 12.4)	3.6 (-5.0, 12.3)	–
Banff Grade						
IA	3.2	1.8	1.4	0	2.3	1.1
IB	1.4	3.5	2.3	3.8	1.1	1.1
IIA	7.8	7.1	2.7	5.4	9.7	9.2
IIB	9.1	4.4	0.9	8.7	4.6	2.7
III	0.9	0.4	0	0	0	0

*Did not meet 20% non-inferiority margin vs cyclosporine

Anti-Donor HLA Antibodies by Month 12 in Patients with Rejection and Overall

Number with Rejection	Study -008			Study -027		
	Bela MI N=49	Bela LI N=39	CsA N=16	Bela MI N=33	Bela LI N=31	CsA N=26
Number in the Analysis	44	37	14	32	31	25
Number with Anti-Donor HLA ABs	2	0	1	2	1	5

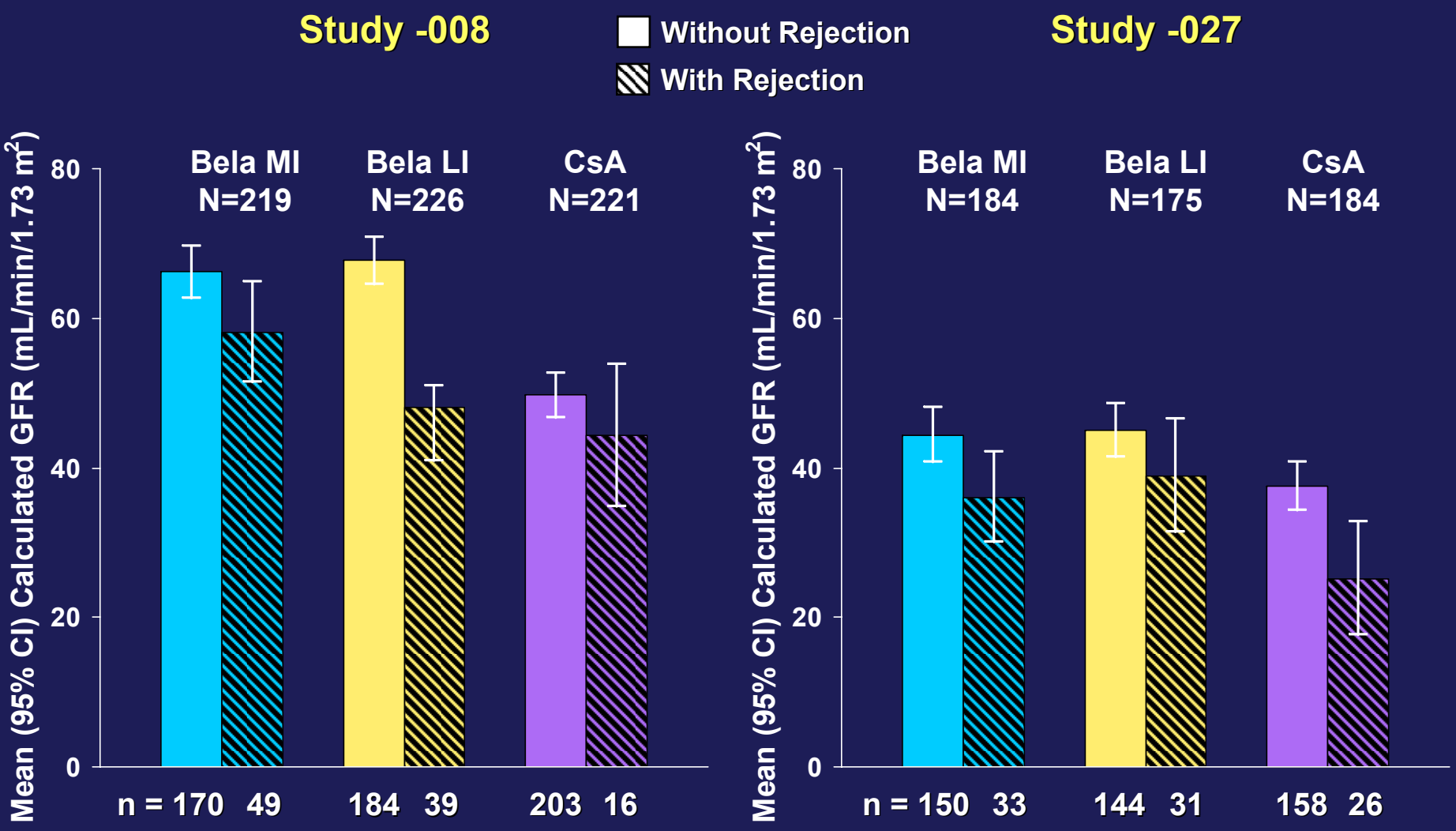
Number Overall	Bela MI N=219	Bela LI N=226	CsA N=221	Bela MI N=184	Bela LI N=175	CsA N=184
Number in the Analysis	208	216	198	179	168	173
Number with Anti-Donor HLA ABs	6	3	14	9	7	15

Graft Loss Overall and Due to Rejection by Month 12

	Study -008			Study -027		
	Bela MI N=219	Bela LI N=226	CsA N=221	Bela MI N=184	Bela LI N=175	CsA N=184
All Cause Graft Loss, N (%)	4 (1.8)	5 (2.2)	8 (3.6)	17 (9.2)	16 (9.1)	20 (10.9)
Graft Loss Caused by Rejection*, N (%)	1 (0.4)	2 (0.8)	2 (0.9)	3 (1.6)	2 (1.1)	6 (3.2)

*Adjudicated cause.

Renal Function at Month 12 by Rejection Status (With Imputation)



Prognostic Features of Rejection Episodes

Worse Graft Outcomes

- High Banff grade
- Associated with anti-HLA antibodies
- Late
- Recurrent
- Poor renal function after rejection

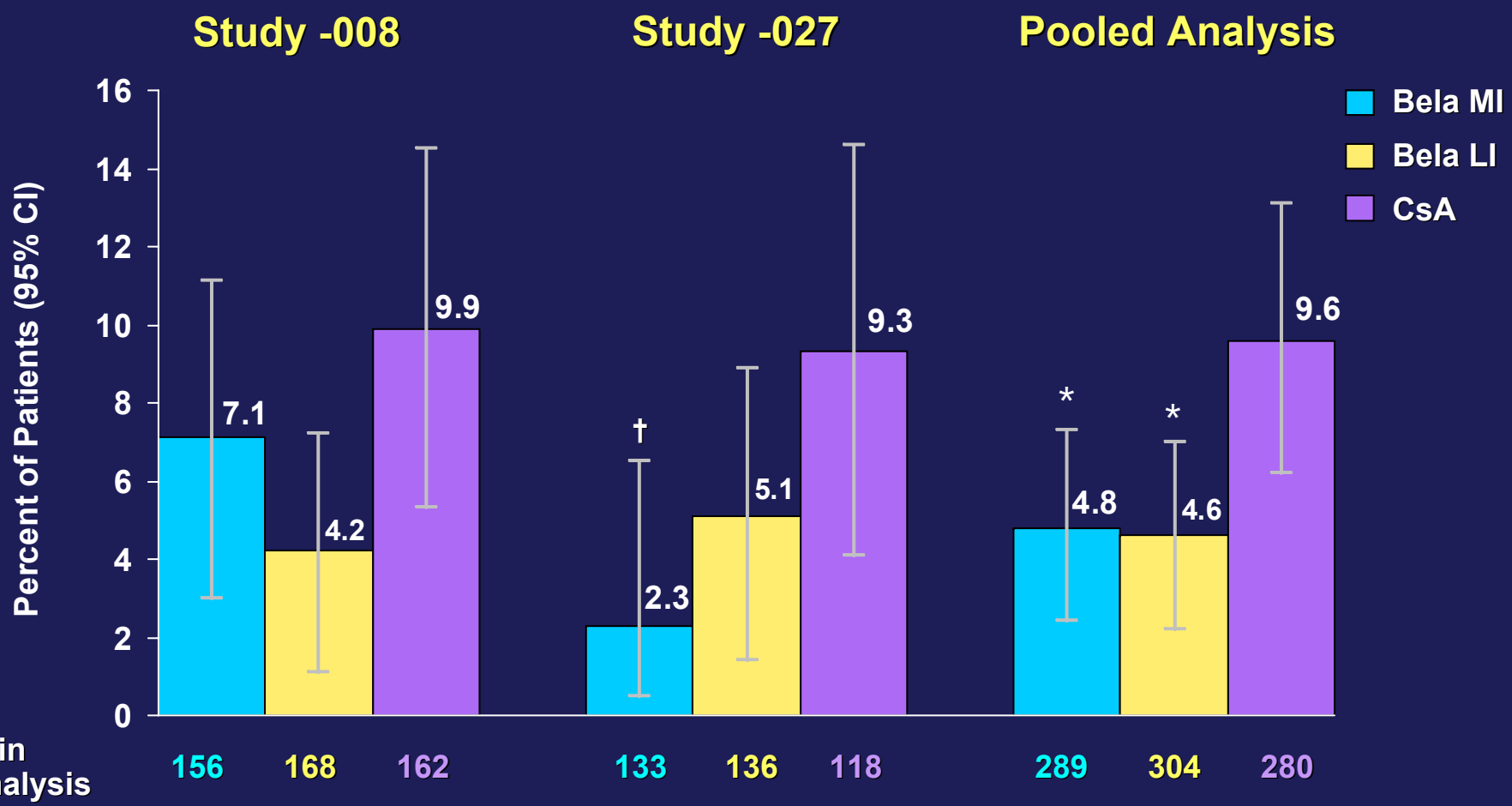
Better Graft Outcomes

- Low Banff grade
- Not associated with anti-HLA antibodies
- Early
- Single
- Good renal function after rejection

Tanaka et a.l; *Transplant Intl* 2004; 17:59-64
Vereerstraeten et al.; *Transplantation* 1997;63:1739-43
Opelz; *Transplantation* 2008; 85:661-6
Racusen et al.; *Amer J Transplantation* 2003; 3:708-14
Everly et al; *Amer J Transplantation* 2009;9:1063-71

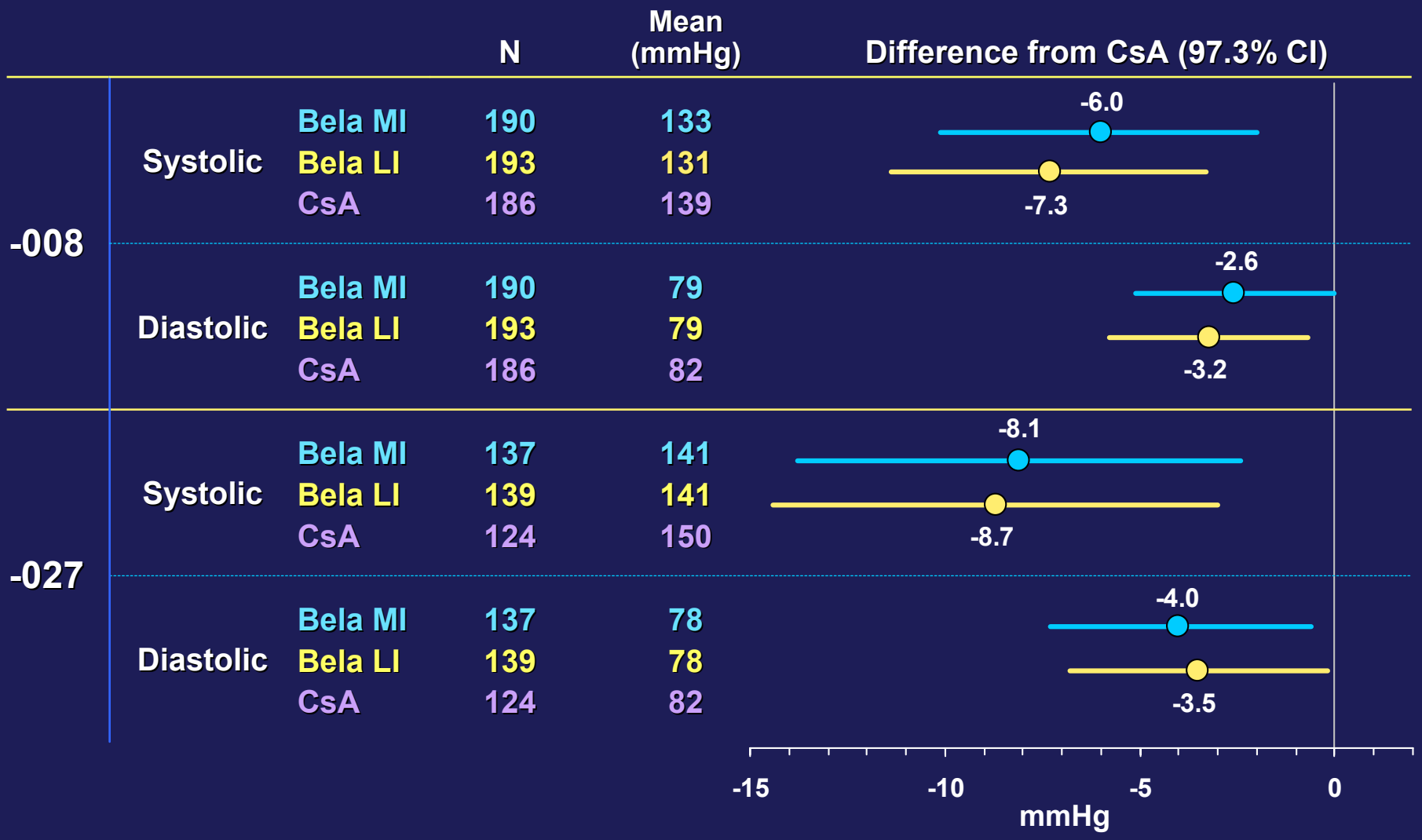
Cardiovascular & Metabolic Endpoints

New-Onset Diabetes at Month 12

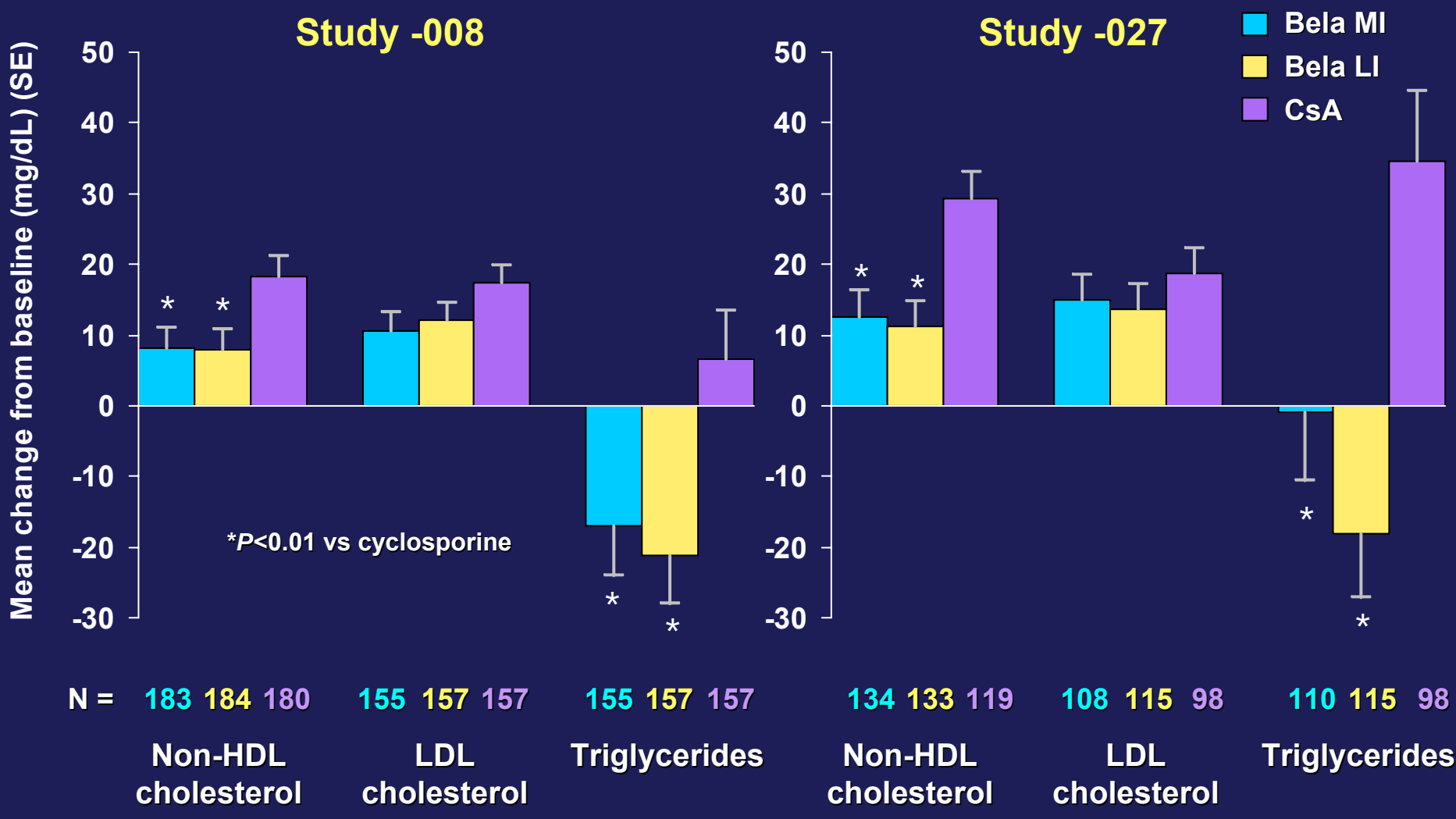


NODAT was defined as treatment with anti-diabetic medication for a duration of ≥30 days or at least two fasting plasma glucose (FPG) tests indicating FPG ≥126 mg/dL (7.0 mmol/L); NODAT was assessed only after Week 4; †*P*=0.03 vs cyclosporine; **P*<0.02 vs cyclosporine

Blood Pressure at Month 12



Changes in Serum Lipids at Month 12



Key Efficacy Results
Study -008 and Study -027

- Short-term patient and graft survival comparable to CsA
- Avoidance of CNI toxicities:
  - Better renal function with less CAN
  - Improved cardiovascular & metabolic profile
- Early treatable rejection episodes with limited impact on graft survival
- LI and MI doses provide similar efficacy
- Consistent efficacy across a range of recipient types
- Benefits persist over extended follow-up

Safety Results

Sheila Gujrathi, MD

Vice President, Global Clinical Research
Immunology
Bristol-Myers Squibb

Outline of Safety Presentation

- Safety Methods
- Exposure
- General Safety (AEs, SAEs, Deaths)
- Events of clinical interest
  - Infections
  - Malignancies
  - Post-Transplant Lymphoproliferative Disorder (PTLD)
  - Progressive Multifocal Leukoencephalopathy (PML)

Pooled Core Studies for Safety Analysis

Phase II

- IM103100
  Proof of concept study

Phase III

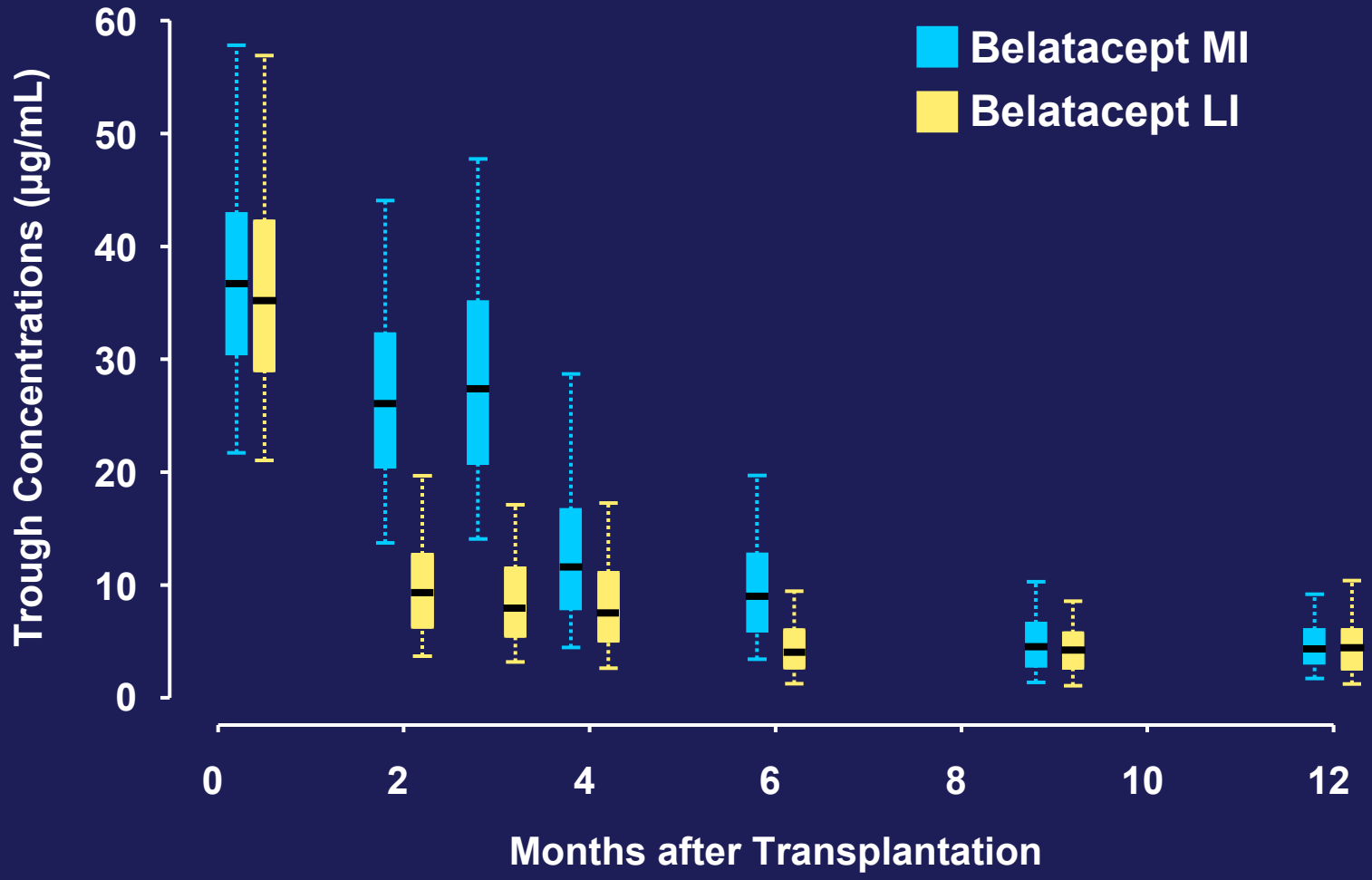
- IM103008
  Standard criteria donors
- IM103027
  Extended criteria donors

Exposure up to BLA Database Lock

	Number (%) of Patients		
	Belatacept MI N=476	Belatacept LI N=471	Cyclosporine N=465
Median, days (range)	751 (28–2829)	754 (28–2883)	724 (10–2703)
≥ 12 Months	366 (77)	369 (78)	350 (75)
≥ 24 Months	256 (54)	256 (54)	229 (49)
≥ 36 Months	67 (14)	69 (15)	42 (9)
≥ 60 Months	38 (8)	39 (8)	16 (3)

Extent of exposure to Belatacept is defined as last infusion date - first infusion date + 28 days.
Extent of exposure to Cyclosporine is defined as last dose date - first dose date + 10 days for Patients who discontinued treatment, and last dose date - first dose date + 1 day for ongoing Patients.
Interruptions in therapy were not deducted from calculation of days of exposure.

Exposure Differences between Belatacept MI and LI Regimens



Black lines indicate median
Boxes indicate 25th and 75th percentiles
Whiskers indicate 5th and 95th percentiles

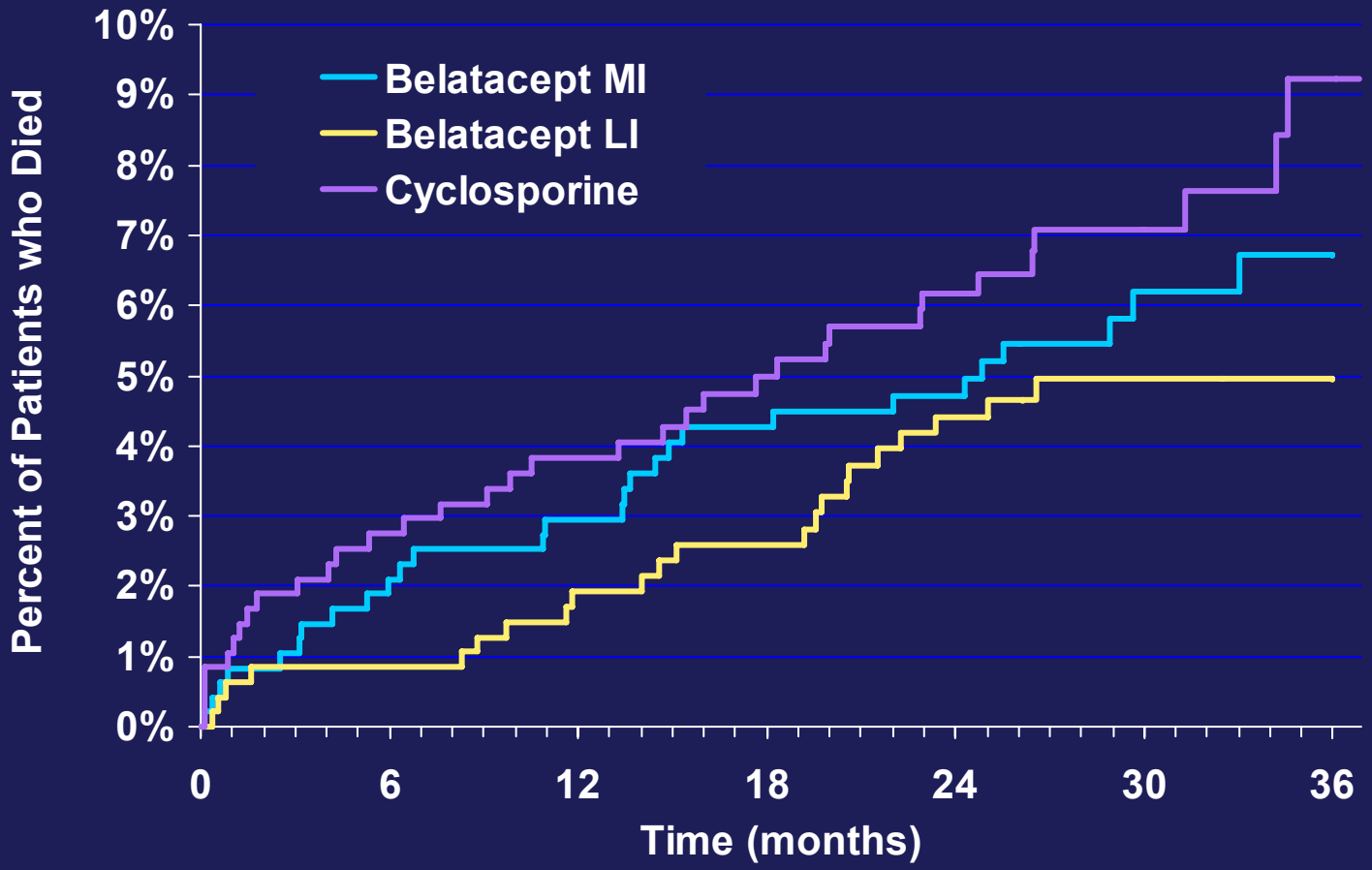
Overview of Adverse Events

	Number (%) of Patients		
	Belatacept MI N=477	Belatacept LI N=472	Cyclosporine N=476
AEs	474 (99)	470 (100)	472 (99)
SAEs	331 (69)	311 (66)	324 (68)
Discontinuation due to AEs	67 (14)	67 (14)	82 (17)

Total Deaths up to Safety Update Database Lock

	Number (%) of Patients		
	Belatacept MI N=477	Belatacept LI N=472	Cyclosporine N=476
Deaths to Month 12	14 (2.9)	9 (1.9)	18 (3.8)
Deaths to Safety Update Database Lock	31 (6.5)	23 (4.9)	35 (7.4)

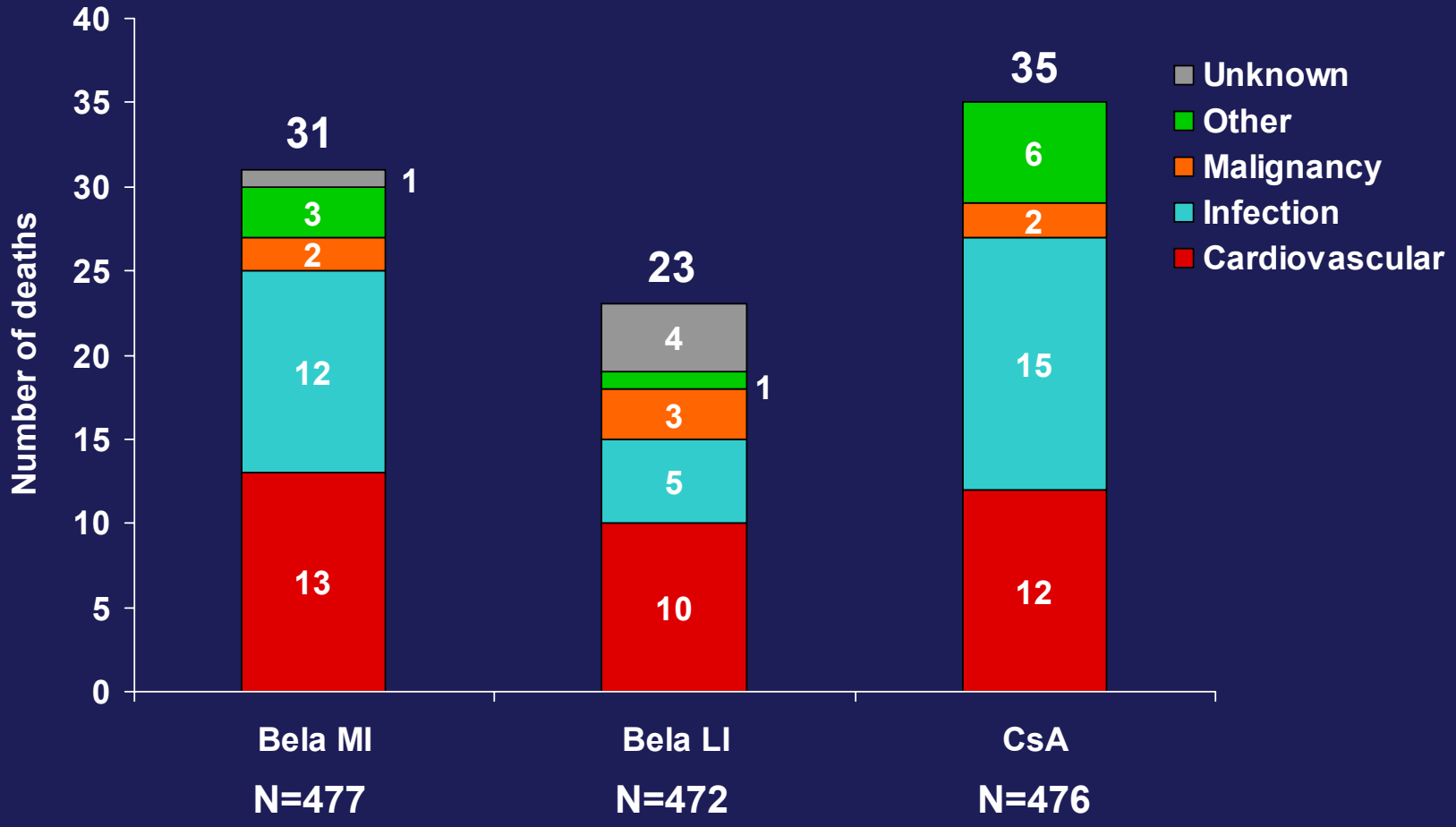
Time to Death



Patients at Risk

Belatacept MI	477	463	453	429	409	240	127
Belatacept LI	472	465	451	430	403	230	123
Cyclosporine	476	454	439	402	376	195	86

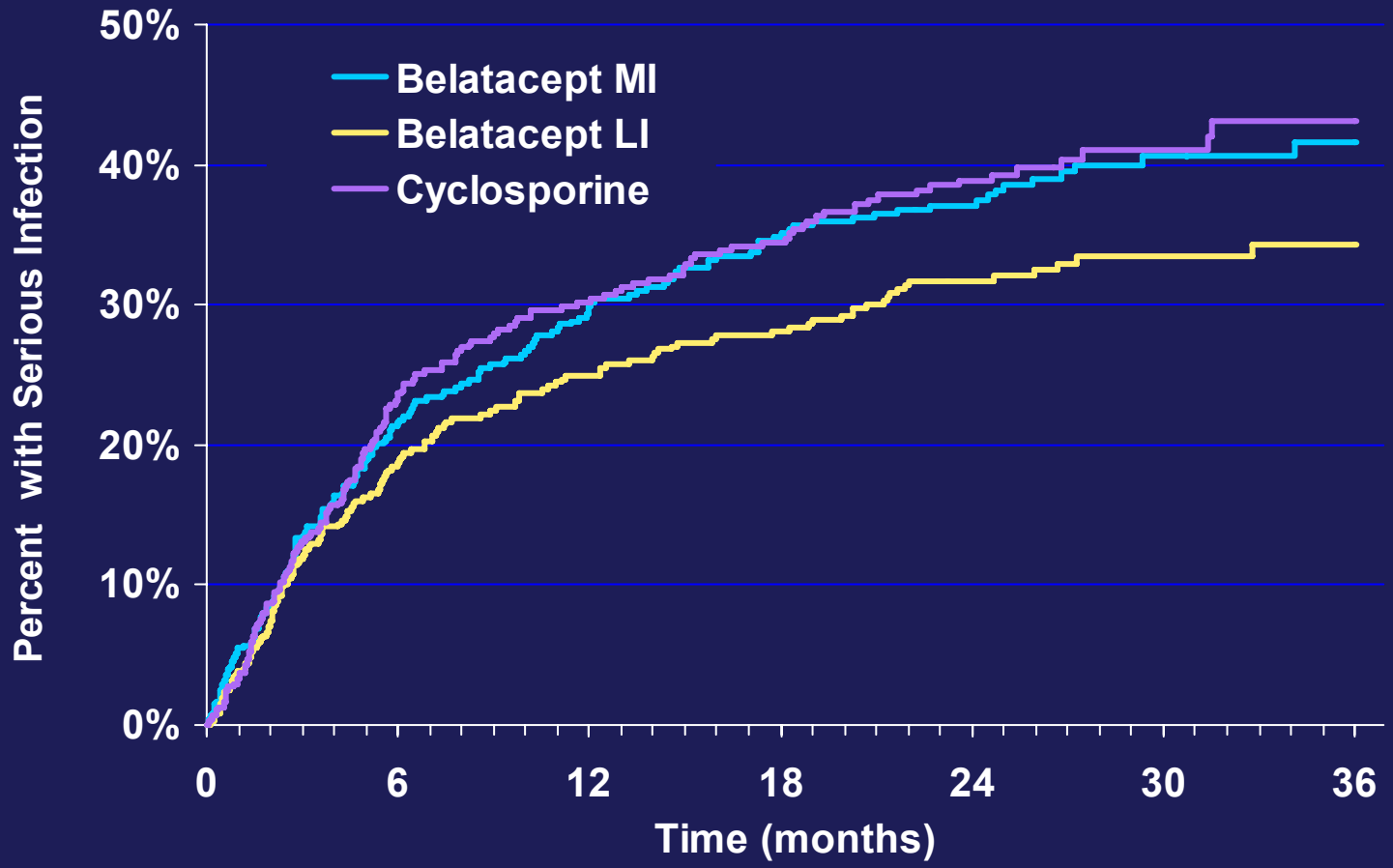
Adjudicated Causes of Death



Infections

	Number (%) of Patients		
	Bela MI N=477	Bela LI N=472	CsA N=476
Infections and Infestations	378 (79)	376 (80)	381 (80)
Serious Infections	169 (35)	142 (30)	166 (35)

Time to First Serious Infection



Patients at Risk

Belatacept MI	477	311	267	233	180	91	45
Belatacept LI	472	330	293	266	197	107	50
Cyclosporine	476	311	257	215	151	69	25

Infections Seen in Transplant Patients

	Number (%) of Patients		
	Bela MI N=477	Bela LI N=472	CsA N=476
Viral infections	183 (38)	168 (36)	160 (34)
CMV	65 (14)	62 (13)	69 (14)
Polyoma Virus*	30 (6)	16 (3)	26 (5)
Herpes	67 (14)	57 (12)	41 (9)
Fungal infections	99 (21)	78 (17)	95 (20)
Tuberculosis	5 (1)	3 (1)	1 (<1)

*Includes one case of PML in belatacept MI

Overview of PML Cases

Renal Transplant Patient from IM103-027

- 65-year old white female
- Received belatacept MI, basiliximab, MMF, and corticosteroids
- Dx ~23 months post transplant by MRI and positive CSF for JC virus
- Died on Day 754

Liver Transplant Patient from IM103-045

- 52-year-old white male
- Received belatacept MI (two additional doses over renal regimen), augmented MMF (3-4 g/day for first 3 months), and corticosteroids
- Dx ~6 months post transplant by MRI and positive CSF for JC virus
- Patient is alive with neurological deficits and continues to have worsening of symptoms in a skilled nursing facility

All Malignant Neoplasms

	Number (%) of Patients		
	Belatacept MI N=477	Belatacept LI N=472	CsA N=476
All Malignant Neoplasm†	43 (9.0)	26 (5.5)	31 (6.5)
Malignant neoplasms excluding non-melanoma skin cancers	32 (6.7)	23 (4.9)	23 (4.8)
PTLD*	8 (1.7)	6* (1.3)	2 (0.4)
Non-melanoma skin cancer	15 (3.1)	6 (1.3)	11 (2.3)
Fatal malignant neoplasms	5 (1.0)	4 (0.8)	5 (1.1)
Malignant neoplasms excluding non-melanoma skin cancers and PTLD	24 (5.0)	18 (3.8)	21 (4.4)

* Includes one case reported after DBL

† Patients counted once in the All malignant neoplasm row could be counted in more than 1 row appearing below it

PTLD in Renal Transplant Recipients

- Spectrum of diseases ranging from benign plasma cell hyperplasia to frank malignant lymphoma
- The highest incidence of PTLD is usually observed within the first 18 months after transplantation
- Localization patterns of NHL and 5-year survival in kidney transplant recipients (N=1094):

Location	Frequency	5-year Survival (%)
Kidney	10.3	65
Lymph Node	9.5	60
GI Tract	15.3	43
Liver	4.9	39
CNS	11.7	38
Lung	4.4	29
Disseminated	14	22

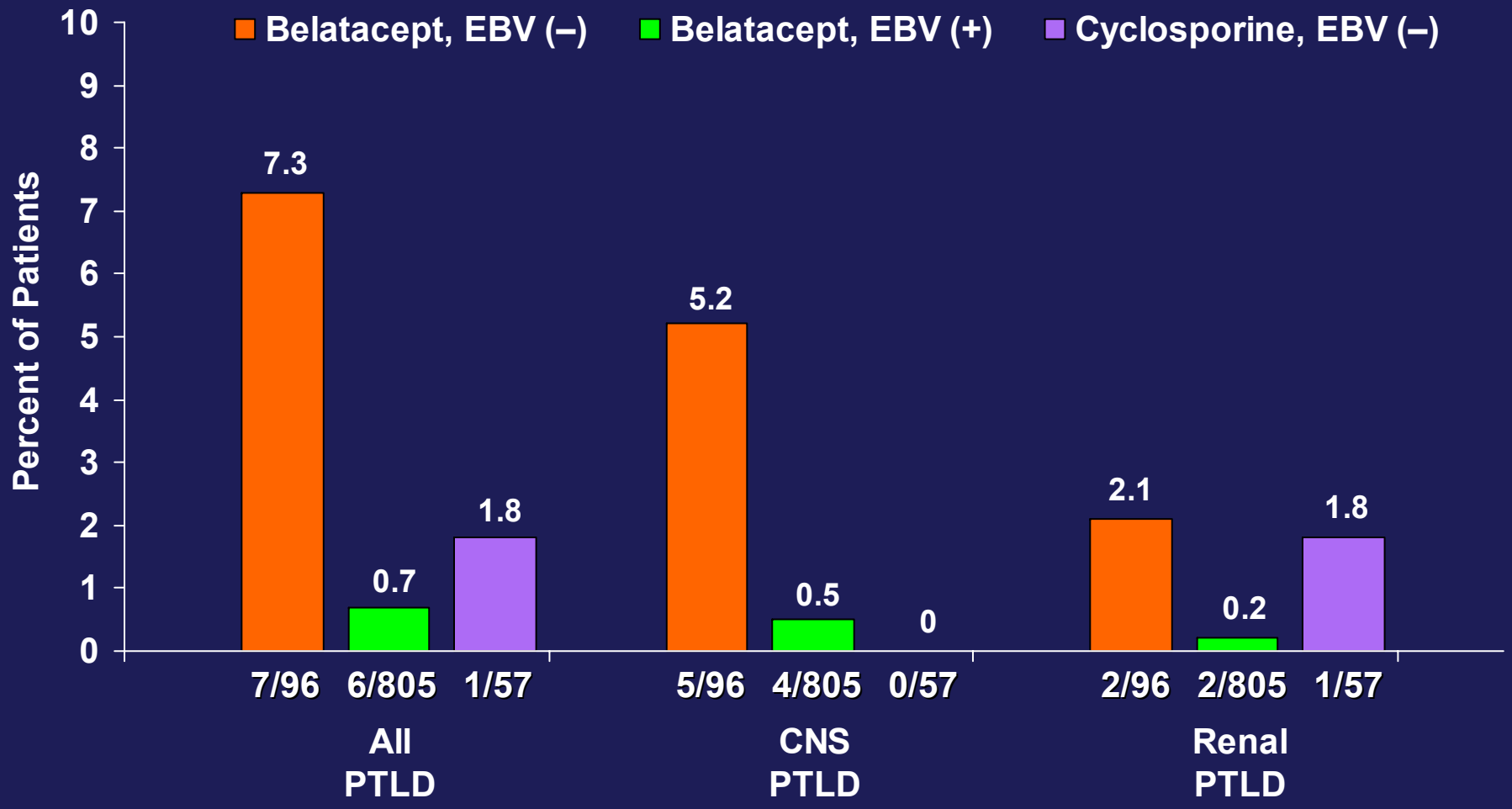
Opelz G, Döhler B. "Lymphomas after solid organ transplantation: a collaborative transplant study report" *Am J Transplant*. 2003;4:222-230

PTLD Cases in the Belatacept Core Studies

	Number of Patients with PTLD		
	Belatacept MI N=477	Belatacept LI N=472	Cyclosporine N=476
PTLD	8	6	2
Renal	2	3	2
EBV-negative	1	1	1
EBV-positive	0	2	0
EBV-unknown	1	0	1
Fatal	1	1	2
CNS	6	3	0
EBV-negative	4	1	0
EBV-positive	2	2	0
Fatal	3	3	0

* Includes one case reported after DBL

PTLD Risk Concentrated in EBV (–) Recipients*



*Does not include 1 EBV unknown patient in the belatacept MI group, and 1 EBV unknown in the cyclosporine group. There are no cases of PTLD in CsA EBV(+) patients.

PTLD 2-year Incidence Rates by Recipient EBV Serostatus

	Incidence rates per 100 p-y (95% CI)	
	EBV (+) recipients	EBV (–) recipients
CMS*	0.28 (0.22, 0.34)	1.03 (0.78, 1.36)
UNOS*	0.11 (0.08, 0.13)	0.70 (0.55, 0.87)
Belatacept core studies	0.33 (0.11, 0.77)	4.09 (1.64, 8.42)

* Including LDT induction, treatment with any immunosuppressant, 2000–2006

Increased CNS PTLD and CNS Infections in MI Arm

	Number (%) of Patients		
	Belatacept MI N=477	Belatacept LI N=472	CsA N=476
CNS PTLD	6 (1.3)	3 (0.6)	0
CNS Infections	7 (1.5)	1 (0.2)	1 (0.2)

- No non-PTLD malignancies involving CNS
- Selection of LI dose can mitigate risk of CNS presentation

* Includes one case reported after DBL

Summary of Belatacept Safety

- Belatacept's safety profile was consistent with its targeted immunosuppressant properties
  - Principal safety concerns are CNS PTLD and PML
  - Greatest risk observed in EBV (–) patients and in patients receiving the MI regimen
- LI has better overall safety profile than MI and is the recommended clinical dose
  - LI resulted in lower rates of deaths, serious infections including CNS infections/PML, and CNS PTLD than MI
- LI also has advantages over CsA with fewer deaths, serious infections, and off-target toxicities observed in the study

Risk Management Strategy

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Senior Vice President,
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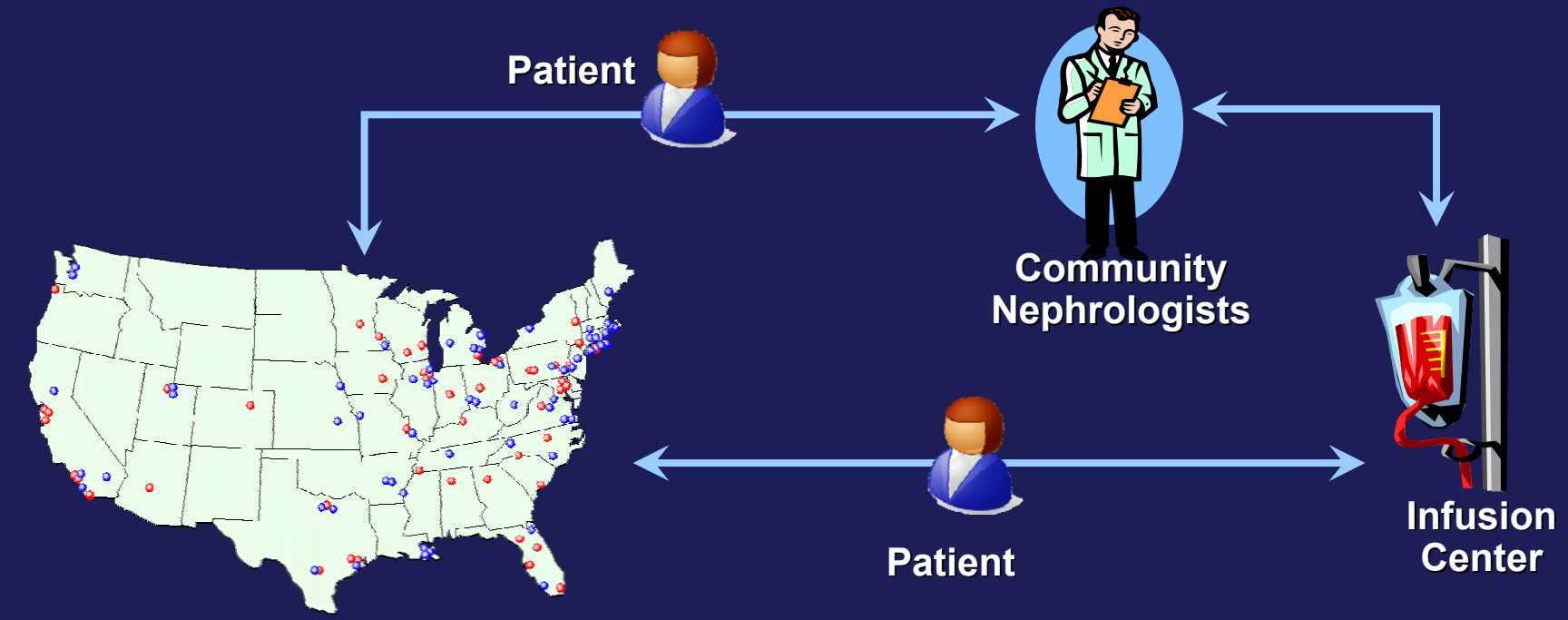
Goals of Risk Management

Risks	Goals	Label	REMS Elements
• PTLD • PML	• Minimize Occurrence • Mitigate Impact • Monitor and Assess	• Belatacept LI regimen • Contraindicate EBV (–) / unknown • Only experienced MDs should prescribe • CMV prophylaxis • Avoid higher than recommended IS • Detection / diagnosis of neurologic signs and symptoms	• Dear Healthcare Professional letter • Fact sheet • Medication guide • Surveys

Transplant Care: Belatacept



Transplant Center

- Immunosuppression Protocols
- Patient Education
- Regular site of care and infusions for at least first 3–6 months
- Continued connection to patient over life of graft

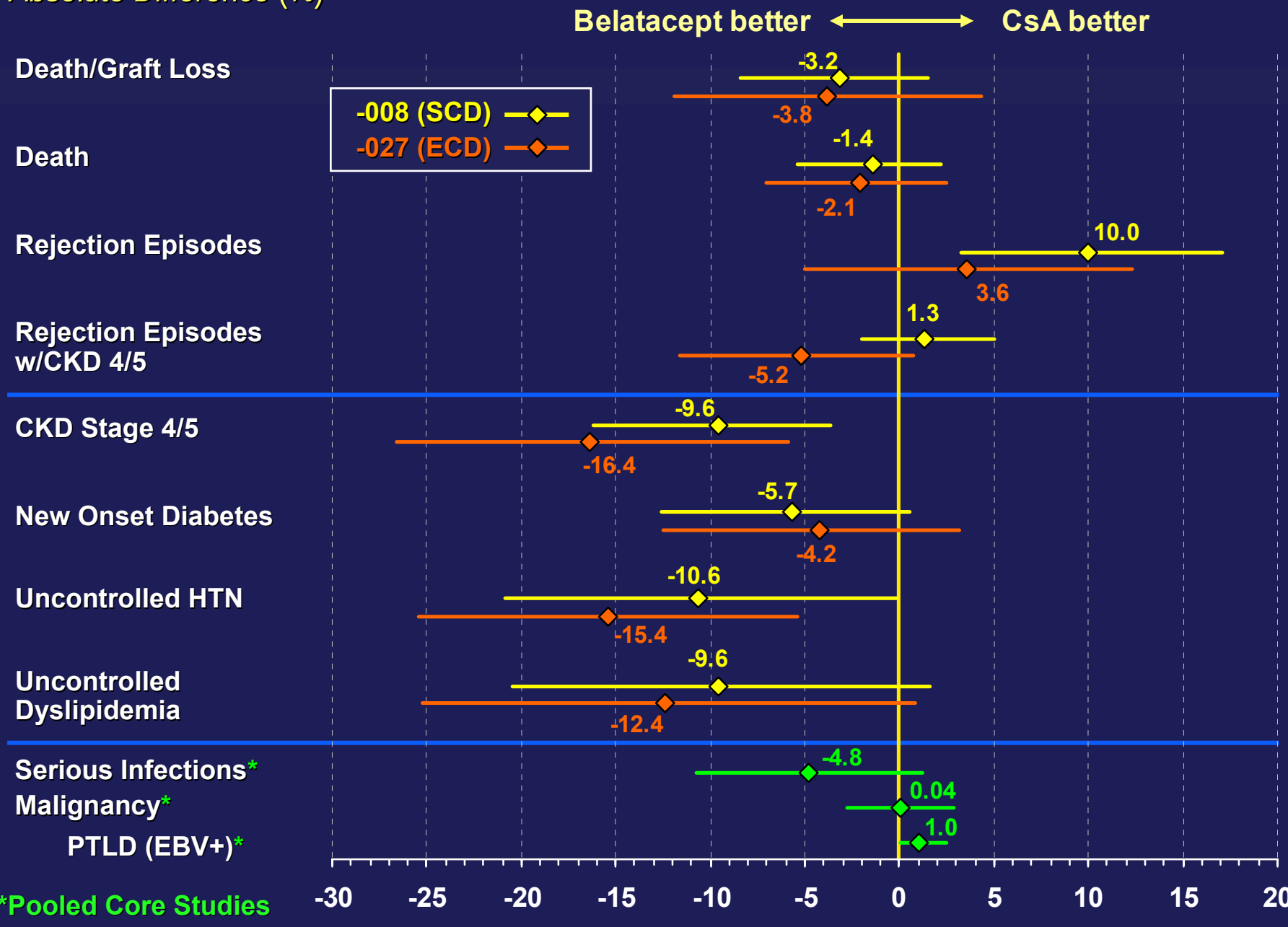
Community Setting of Care

- Long term follow up of patient care
  - Patient visits quarterly
- IV administration of Belatacept
  - Monthly visits

Benefit-Risk Assessment

Comprehensive Benefit-Risk Assessment: Belatacept LI vs CsA

Absolute Difference (%)



*Pooled Core Studies

BMS Commitment

Belatacept: Post-marketing Assessment

Pharmacoepidemiology studies

- Prospective Cohort Study of risks and benefits
  N = 3000 per arm
- PTLD Study: UNOS/OPTN database
  N = 5000 per arm
- Patterns of Use Study: UNOS/OPTN database
  N > 5000 per arm

Clinical trials

- Phase 3 Long-term Extensions: 7 years

Overall Conclusions

- Belatacept offers a new option for renal transplant patients
- LI regimen offers favorable benefit-risk profile in EBV (+) recipients
- Belatacept LI recommended for prophylaxis of organ rejection and preservation of a functioning allograft in adult patients receiving renal transplants

Belatacept in Clinical Context

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