Erfahrungen mit BELATACEPT-NULOJIX®

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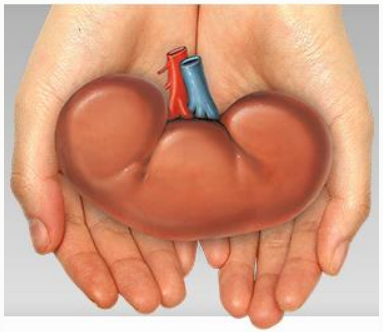
Transplantationsworkshop 27. – 29. Nov 2015

Aktuelle Situation / status quo



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Rejection-rate: <15%

1-year graft survival: >90%

ELITE-Symphonie-study

Long-term experience

CNI(Tac)
MMF
Steroids

-

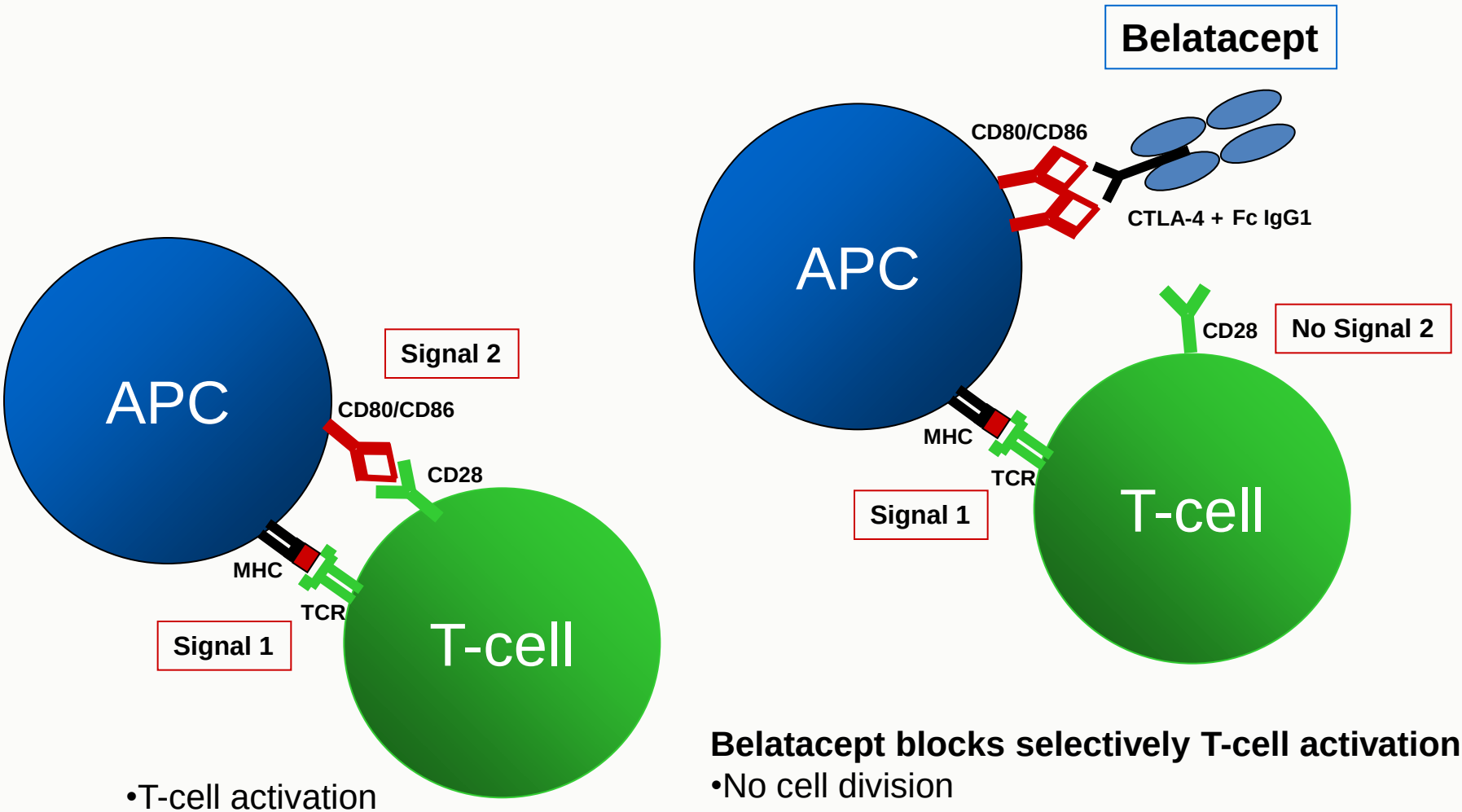
Cardiovascular events

Malignancies

Renal Toxicity

Metabolic disorders:
- Hypertension
- Dyslipidaemia
- PTDM

BELATACEPT – Co-Stimulation-blockade

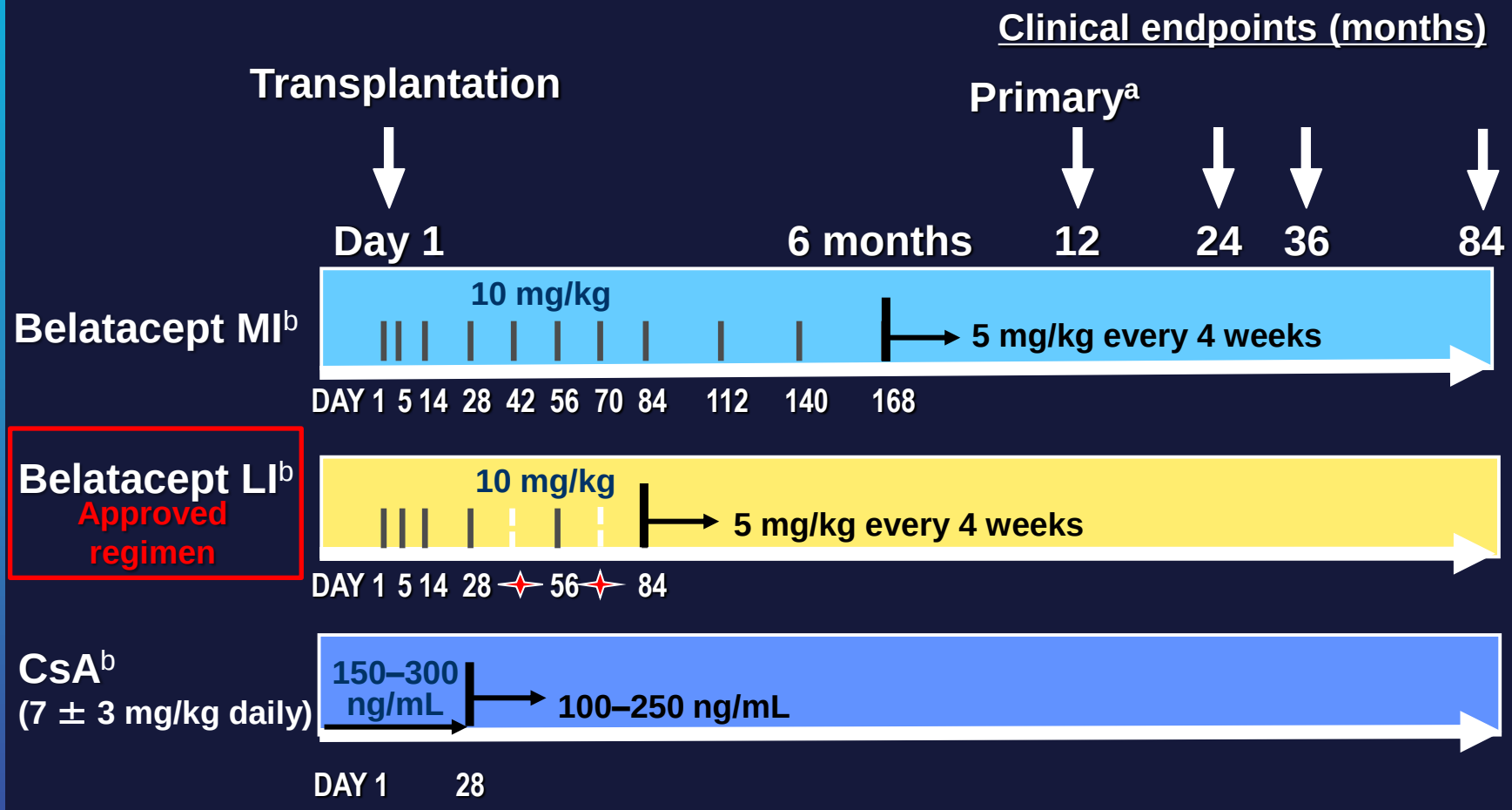


•T-cell activation
•IL-2 production
•Cell Proliferation

Belatacept blocks selectively T-cell activation:
•No cell division
•No cytokine production
•Anergy
•Apoptosis

BELATACEPT – de novo use (phase III: BENEFIT/BENEFIT-EXT)

Study Design and Dosing



Placebo infusions

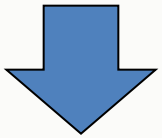
[a]Belatacept arms unblinded at 12 months.

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

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

BELATACEPT – de novo use

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



LTT – 7 years data

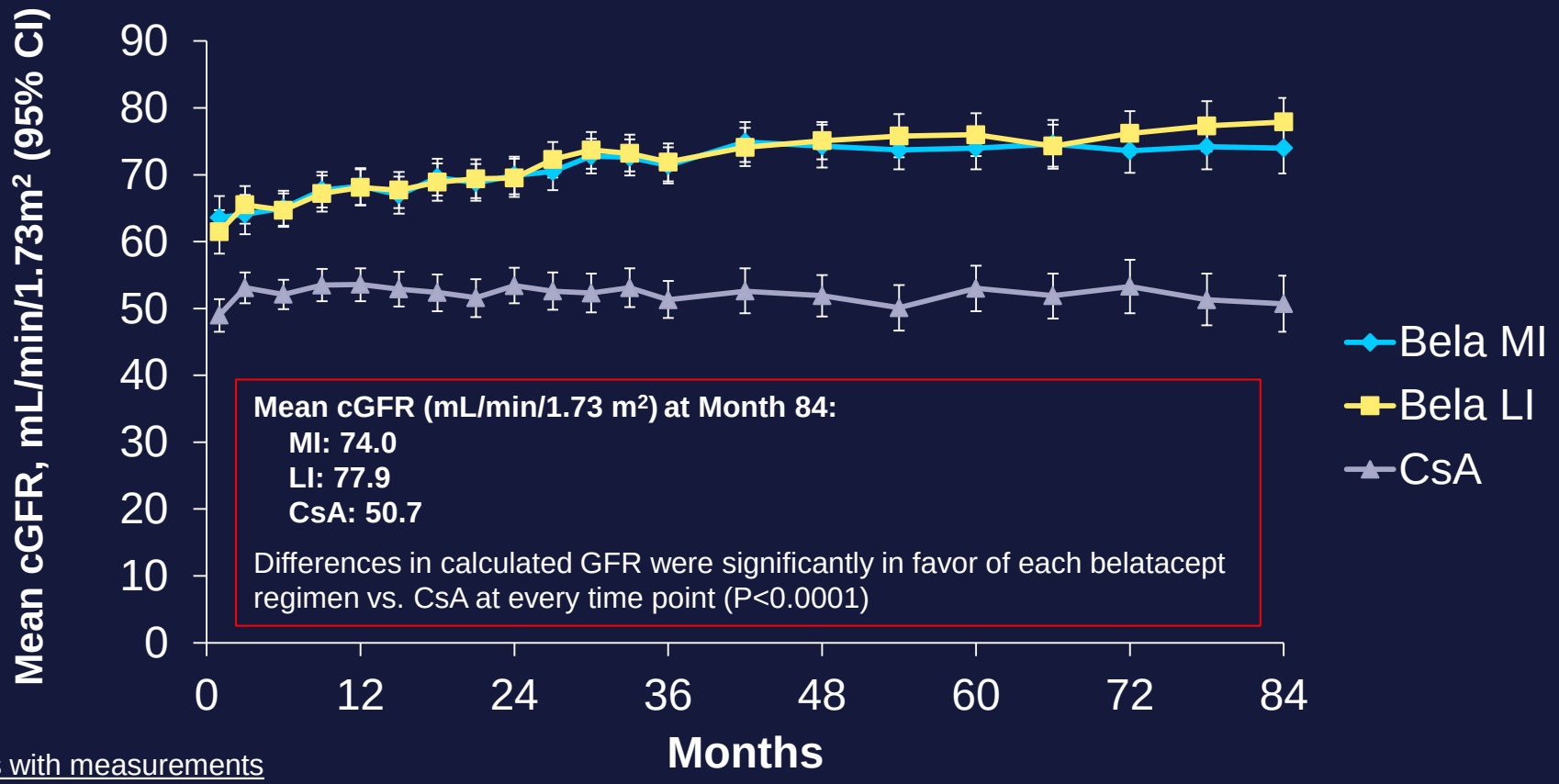
Belatacept-Treated Patients Had Better Graft Survival at 7-Years Post-Transplant Compared With Cyclosporine-Treated Patients: Final Results From BENEFIT

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

721DE15NP03348-04

Calculated GFR Over 84 Months*: Without Imputation

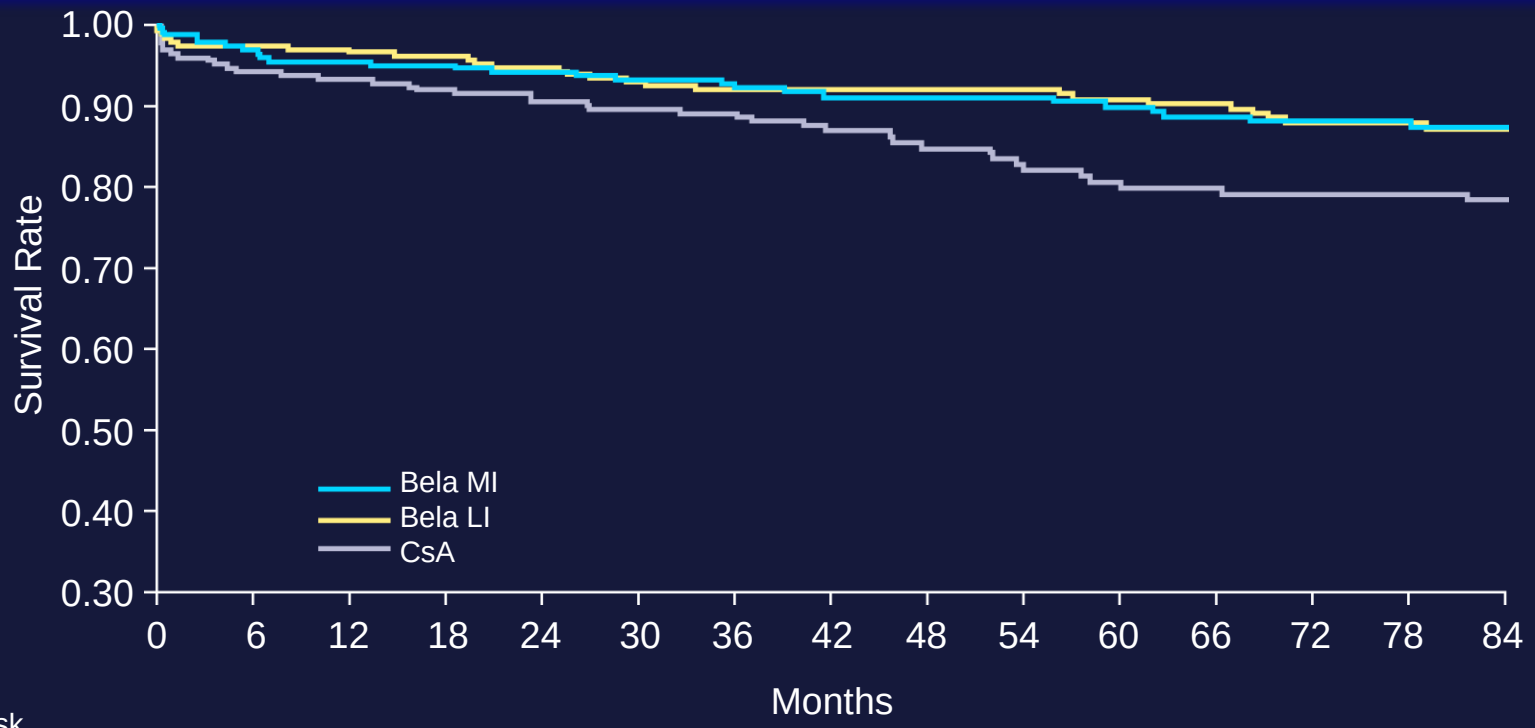


Patients with measurements

MI:	214	192	179	170	136	132	122	109
LI:	220	192	189	174	142	140	126	115
CsA:	210	186	163	149	107	98	93	74

*cGFR values are as observed. cGFR=calculated GFR; CI=confidence interval; CsA=cyclosporine A; GFR=glomerular filtration rate; LI=less intensive; MI=more intensive.

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	131	128
Bela 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)

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

BELATACEPT – de novo use (phase III: BENEFIT)

Acute Rejection

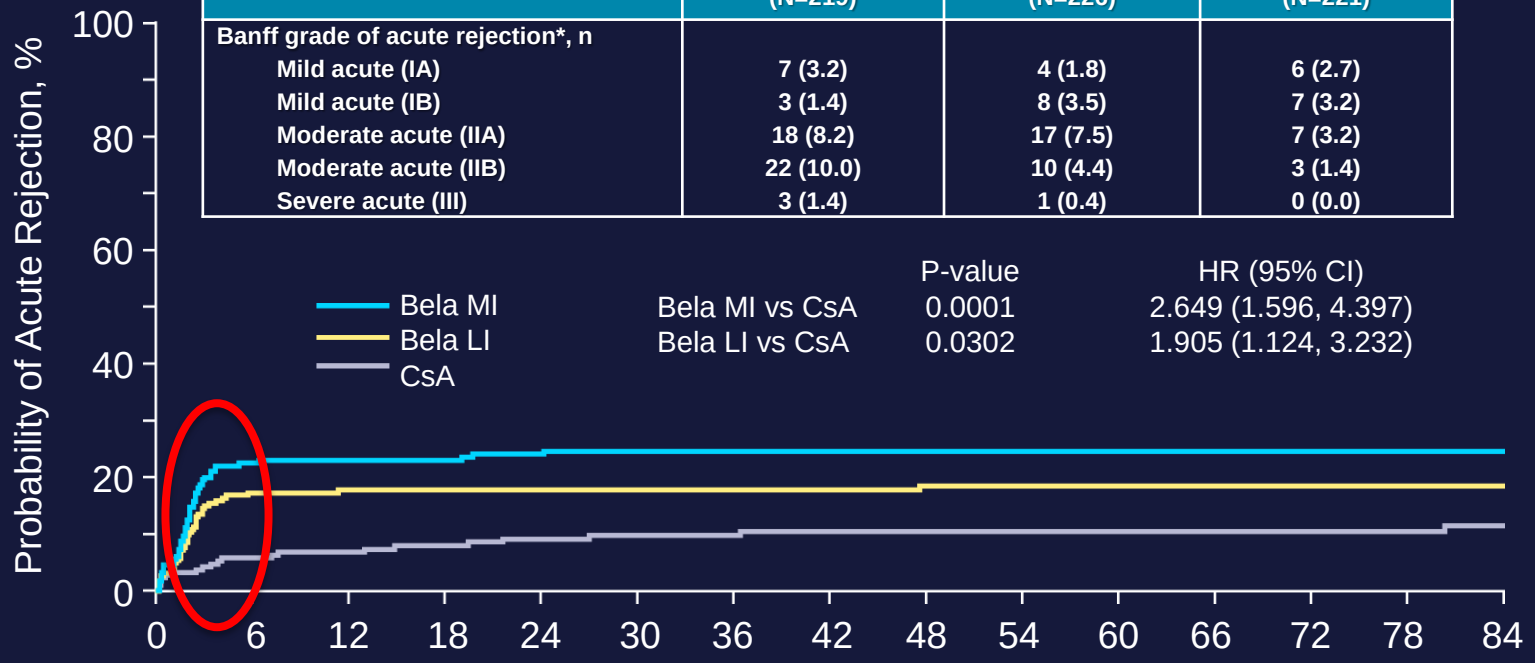
Acute Rejection by Month 36 - BENEFIT

Patients, n (%)	Belatacept MI (n=219)	Belatacept LI (n=226)	Cyclosporine (n=221)
Acute rejection	53 (24)	39 (17)	21 (10)
Banff 97 grade			
Mild acute (IA)	7 (3)	4 (2)	5 (2)
Mild acute (IB)	3 (1)	8 (4)	7 (3)
Moderate acute (IIA)	18 (8)	16 (7)	6 (3)
Moderate acute (IIB)	22 (10)	10 (4)	3 (1)
Severe acute (III)	3 (1)	1 (<1)	0

*Intent-to-treat population; LI=less intensive; MI=more intensive.

Acute Rejection - BENEFIT

	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	108	105
Bela 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.

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

BELATACEPT – de novo use (phase III: BENEFIT/BENEFIT-EXT)

Adverse Events

Safety Summary Up to Month 84 - BENEFIT

	Belatacept MI (N=219)	Belatacept LI (N=226)	CsA (N=221)
Serious adverse events, n (%)*	155 (70.8)	155 (68.6)	168 (76.0)
Incidence rate†			
Serious infections – total‡	10.6	10.7	13.3
Incidence rate†			
Any fungal infection*	7.8	6.7	7.6
Any viral infection– total*	16.2	14.2	15.7
BK polyomavirus	1.2	0.7	1.3
Cytomegalovirus	2.3	2.3	2.8
Herpes zoster	1.9	1.6	2.0
Any malignancy‡	2.1	1.8	2.6

*The exposure (patient-years) of a patient was calculated from the randomization date to the event date, to the date of last dose of study medication plus 56 days, or to Month 84, whichever was earliest.
†Incidence rate=per 100 person-years.
‡The exposure (patient-years) of a patient was calculated from the randomization date to the event date, to the date of last follow-up, or to Month 84, whichever was earliest.
CsA=cyclosporine A; LI=less intensive; MI=more intensive.

Safety Summary Up to Month 84- BENEFIT EXT

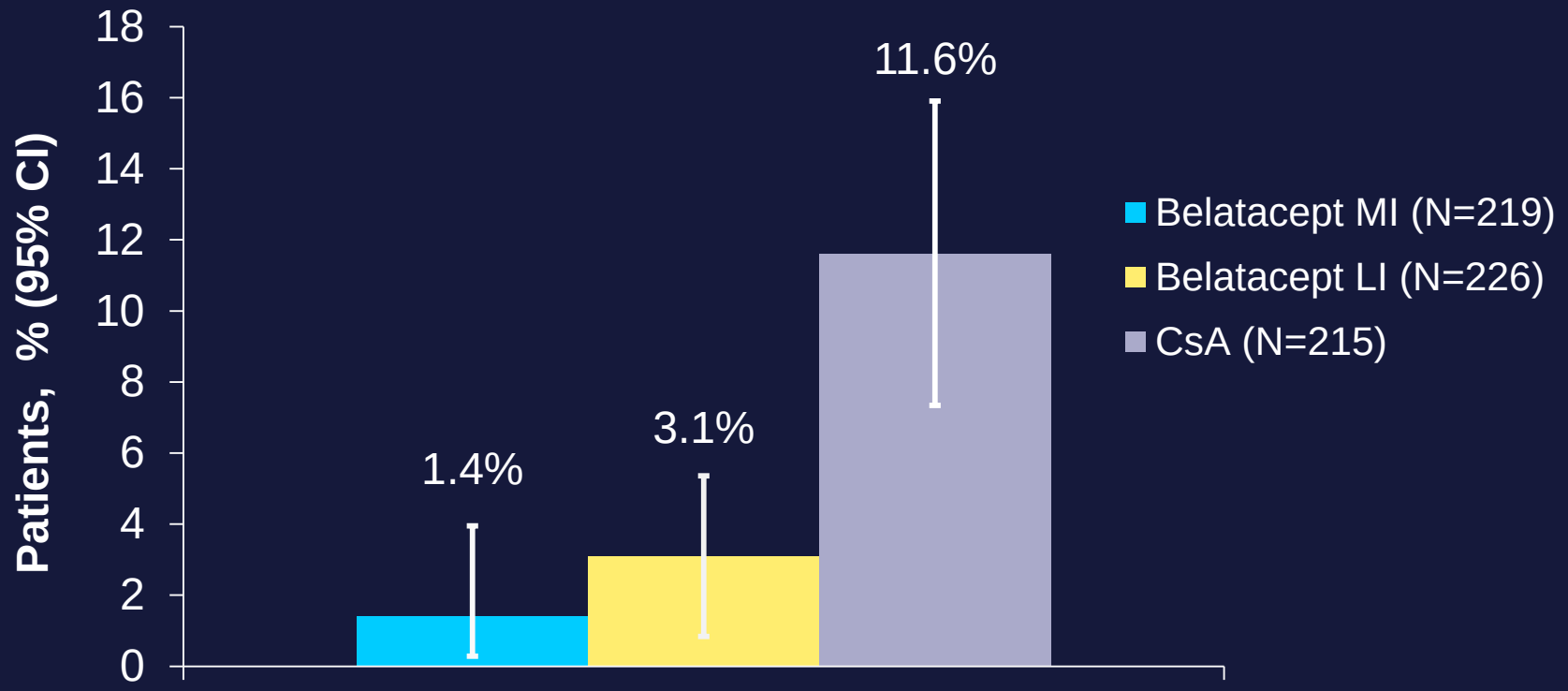
	Belatacept MI (N=184)	Belatacept LI (N=175)	CsA (N=184)
Serious adverse events, n (%)*	160 (87.0)	156 (89.1)	155 (84.2)
Incidence rate†			
Serious infections – total‡	22.67	16.52	20.32
Incidence rate†			
Any fungal infection*	9.79	6.93	11.00
Any viral infection – total*	20.98	17.45	19.05
BK polyomavirus	0.96	0.26	0.30
Cytomegalovirus	5.13	4.19	4.64
Herpes zoster	3.96	2.50	2.43
Any malignancy‡	3.80	3.23	3.64

*The exposure (patient-years) of a patient was calculated from the randomization date to the event date, to the date of last dose of study medication plus 56 days, or to Month 84, whichever was earliest.
†Incidence rate=per 100 person-years.
‡The exposure (patient-years) of a patient was calculated from the randomization date to the event date, to the date of last follow-up, or to Month 84, whichever was earliest.
CsA=cyclosporine A; LI=less intensive; MI=more intensive.

BELATACEPT – de novo use (phase III: BENEFIT/BENEFIT-EXT)

Donor-specific HLA-Antibodies (DSA)

BENEFIT: Incidence of De Novo DSAs



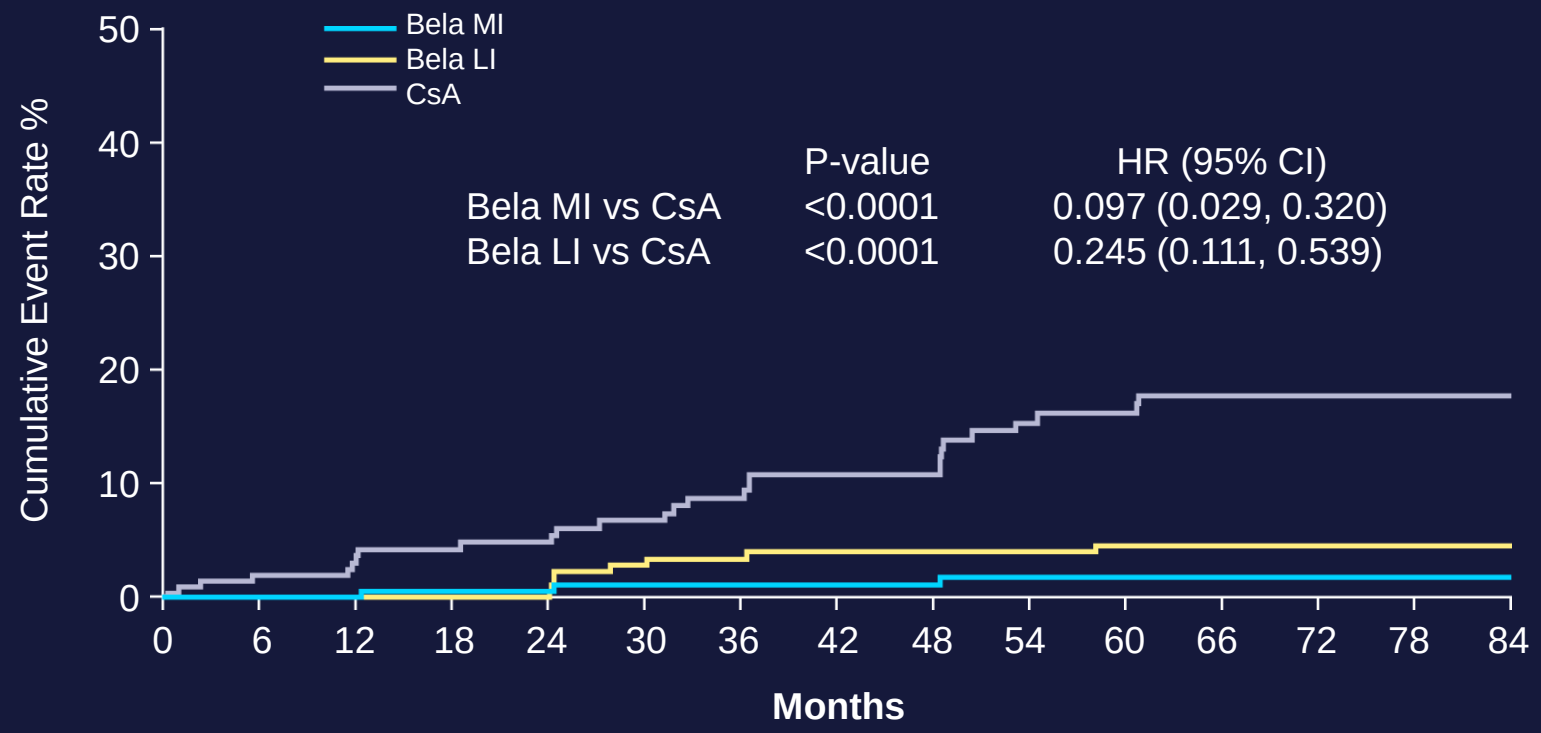
Specificity	Bela MI	Bela LI	CsA
Total, n	3	7	25
Class I DSA, n	1	3	7
Class II DSA, n	2	4	14
Class I and II, n	0	0	4

Analysis is based on all randomized, transplanted, and treated patients.

95% CI
MI: 0.28–3.95
LI: 0.84–5.36
CsA: 7.34–15.91

CI=confidence interval; CsA=cyclosporine A; DSA=donor-specific antibody; LI=less intensive; MI=more intensive.

BENEFIT: Kaplan-Meier Analysis of Cumulative De Novo DSA Over Time



N at risk

Bela MI	219	182	174	168	163	158	156	148	147	144	141	136	130	127	124
Bela 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

Analysis is based on all randomized, transplanted, and treated patients.

BELATACEPT – de novo use (phase II + III: BENEFIT/BENEFIT-EXT)

PTLD

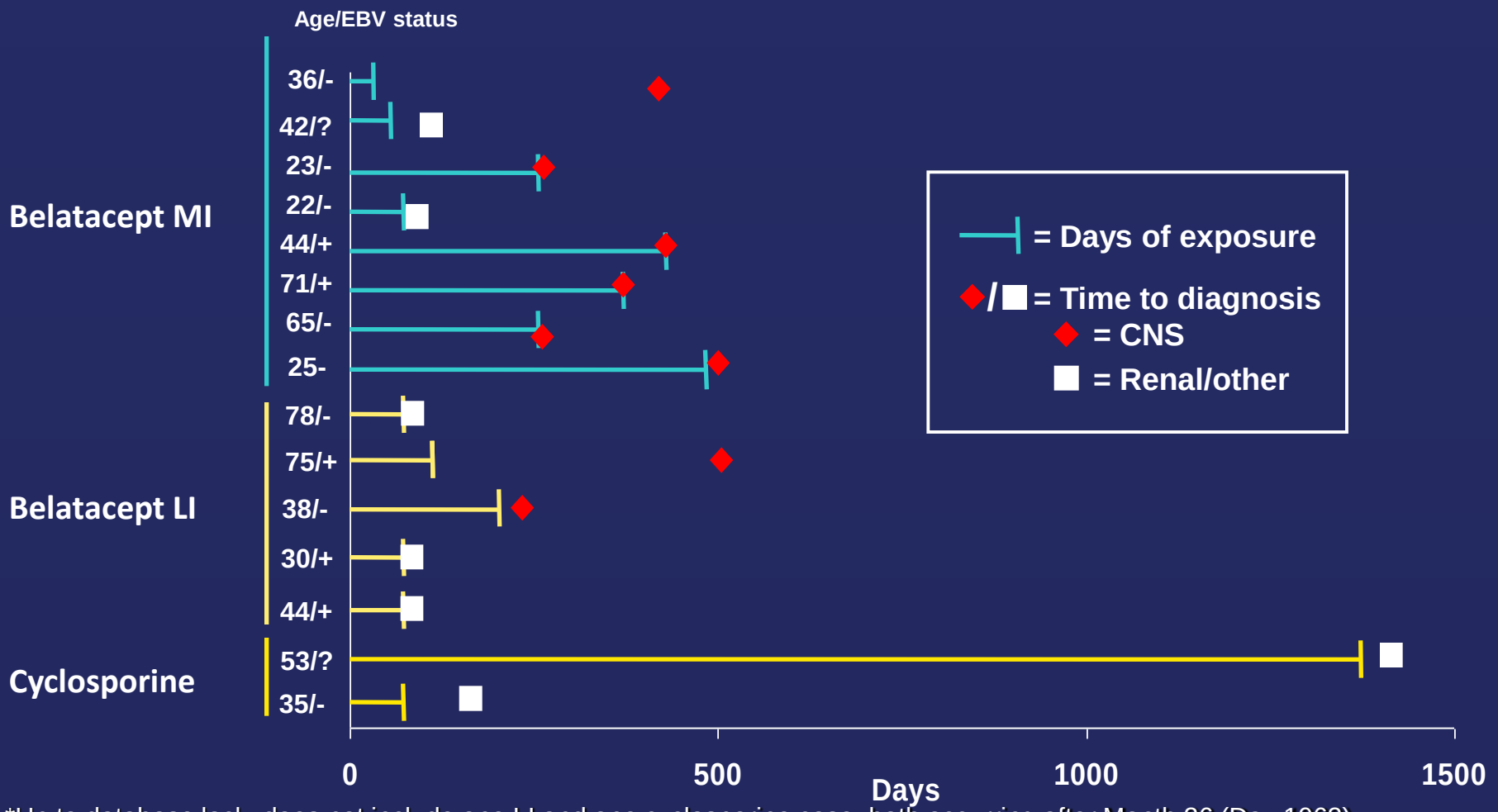
Table 5.5.3.4-1: Post-transplant Lymphoproliferative Disorder (Pooled Core Studies)

	Number of Subjects (%)		
	MI N = 477	LI N = 472	CsA N = 476
Cumulative up to Month 12	4 (0.8)	4 (0.8)	1 (0.2)
Cumulative to Oct 2011	8 (1.7)	8 (1.7)	3 (0.6)
Cumulative to May 2013	8 (1.7)	8 (1.7)	3 (0.6)
Renal allograft	2	3	0
Fatal	1	1	0
Disseminated	0	1	3
Fatal	0	0	3
Gastrointestinal	0	1	0
Fatal	0	1	0
CNS PTLD	6	3	0
Fatal	3	3	0
Total fatal PTLD cases	4	5	3

Source: Long-term data from Core Studies,[66] Program Sources /gbs/prod/clin/programs/im/103/008/csr05/rpt/rt-adae-ptld-inc-v01.sas 24AUG2011:14:02:51 and /gbs/prod/clin/programs/im/103/027/csr05/rpt/rt-adae-ptld-inc-v01.sas 20JUL2011:13:44:20, and supportive data based on information collected in the Clinical Safety Program.

Pooled core studies

PTLD Case Timeline*



*Up to database lock; does not include one LI and one cyclosporine case, both occurring after Month 36 (Day 1063); CNS=central nervous system; EBV=Epstein-Barr virus; LI=less intensive; MI=more intensive; PTLD=post-transplant lymphoproliferative disorder.

Risk Factors for PTLD development

- EBV-negative recipient status
- CMV-infection
- Use of Lymphocyte-depleting agents
- Recipient Age >60 years

Summary: de novo use of Belatacept

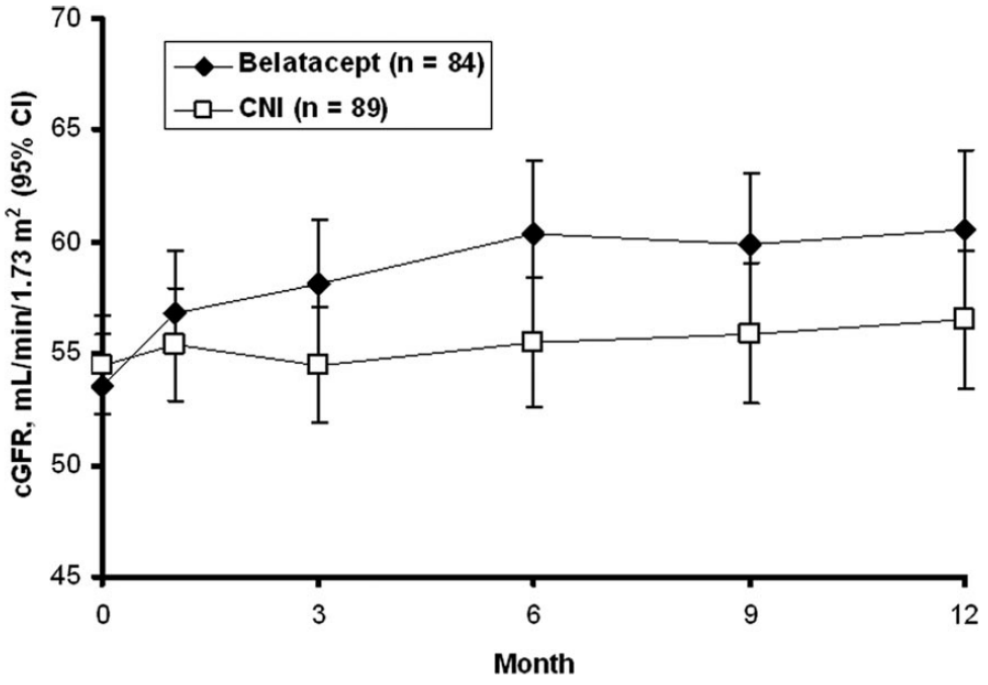
- Belatacept treated pts had significant better graft survival and renal function than CsA treated pts
- Incidence of Rejection is higher in the first 3 Months after Tx
- Lower frequency of DSA
- Higher risk of development of PTLD
- Lower Triglycerides

BELATACEPT – Conversion

Switching from Calcineurin Inhibitor-based Regimens to a Belatacept-based Regimen in Renal Transplant Recipients: A Randomized Phase II Study

Lionel Rostaing, Pablo Massari,† Valter Duro Garcia,‡ Eduardo Mancilla-Urrea,§ Georgy Nainan,‖ Maria del Carmen Rial,¶ Steven Steinberg,** Flavio Vincenti,†† Rebecca Shi,‡‡ Greg Di Russo,‡‡ Dolca Thomas,‡‡ and Josep Grinyó§§*

Conversion time after Tx 20 months



GFR +7ml

Clin J Am Soc Nephrol 6: 430–439, February, 2011

Table 3. Secondary outcomes at month 12

	Belatacept ($n = 84$)	CNI ($n = 89$)
Acute rejection incidence, *n* (%)	6 (7)	0
95% CI	1.6 to 12.7	
Banff grade, *n* (%)		
mild acute (IA)	1 (1)	0
mild acute (IB)	1 (1)	0
moderate acute (IIA)	3 (4)	0
moderate acute (IIB)	1 (1)	0
severe acute (III)	0	0
Patient/graft survival, *n* (%)	84 (100)	88 (99)
95% CI		96.7 to 100.0
Graft loss or death, *n* (%)	0	1 (1)
graft loss	0	0
death	0	1 (1)
death with functioning graft	0	1 (1)

Clin J Am Soc Nephrol 6: 430–439, February, 2011

BELATACEPT – Late Conversion Center Charité Mitte Experience

Patient characteristics

	N=79
Mean age ± SEM, years	53.9 ± 1.6
Mean time after transplantation ± SEM, months	69.0 ± 7.0
Male, n (%)	48 (60.8)
Mean estimated GFR ± SEM, mL/min/1.73 m^2	26.1 ± 1.7
Treatment prior to conversion, n (%)	
Tacrolimus (mean trough level ± SEM 4.8±0.31)	40 (50.6)
Cyclosporine (mean trough level ± SEM 72.2±3.9)	17 (21.5)
Everolimus (mean trough level ± SEM 4.7±0.34)	16 (20.2)
Sirolimus (mean trough level ± SEM xx±xx)	6 (7.6)
Reason for conversion, n (%)	
Biopsy-confirmed CNI-induced nephrotoxicity	46 (58.2)
Severe mTOR-i–induced adverse event (proteinuria n=6)	11 (13.9)
Biopsy-confirmed transplant vasculopathy	10 (12.7)
Severe CNI-induced adverse event	8 (10.1)
Compliance problem	4 (5.1)

*Three patients had hemolytic uremic syndrome.
CNI, calcineurin inhibitor; GFR, estimated glomerular filtration rate; mTOR-i, mammalian target of rapamycin inhibitor; SD, standard deviation; SEM, standard error of the mean.

Step-wise conversion to Belatacept

Belatacept 5 mg/kg was administered intravenously on days 1, 15, 29, 43, and 57 and then every 28 days thereafter.

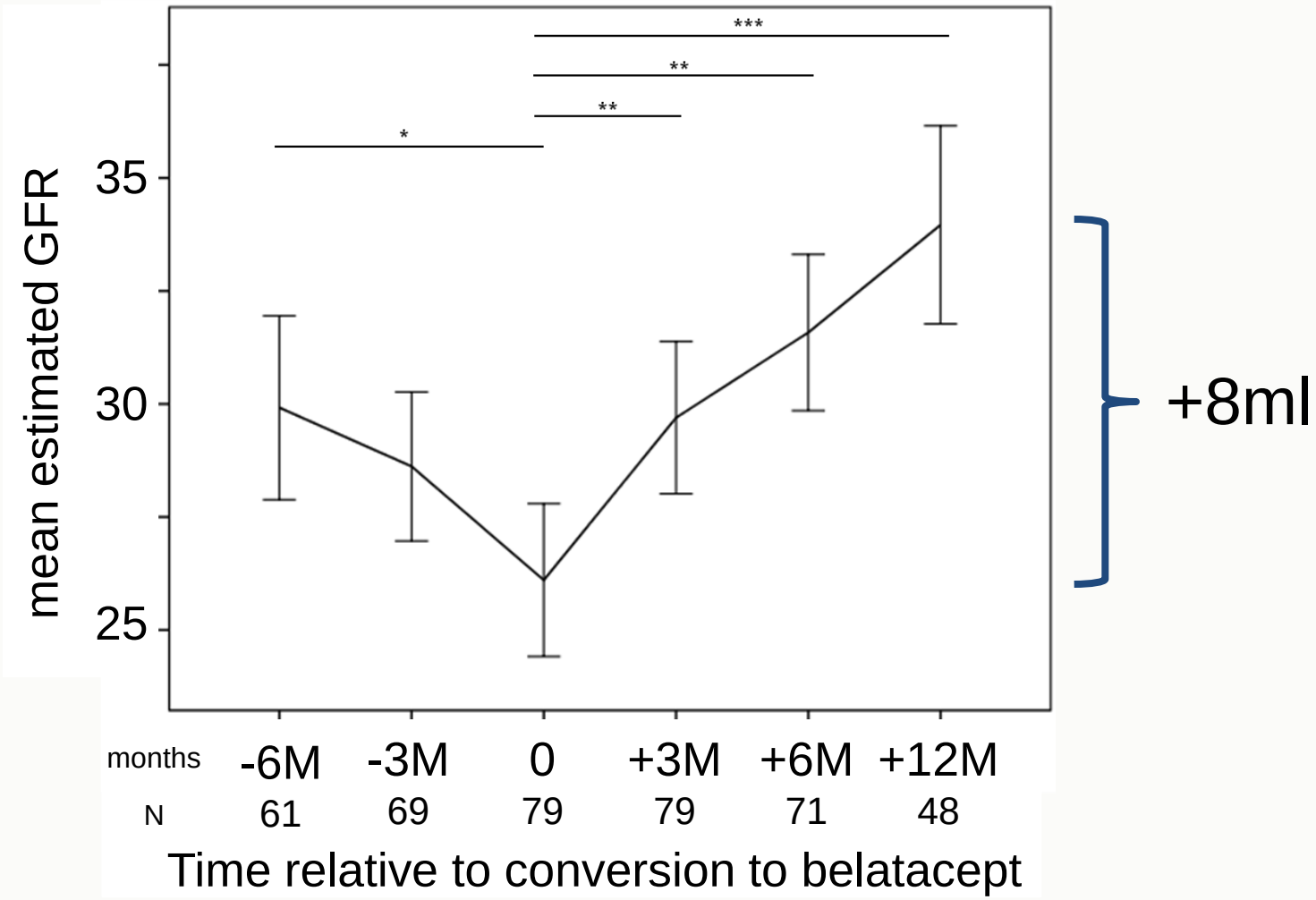
CNI Reduction scheme over conversion period to Belatacept:

At baseline:	**50%** of CNI dose based to baseline
After 2 weeks	**25%** of CNI dose based to baseline
After 4 weeks	complete withdrawal of CNI

mTORi Reduction scheme over conversion period to Belatacept:

At baseline:	**50-75%** of mTORi dose based to baseline
After 2 weeks:	**25-50%** of mTORi dose based to baseline
After 4 weeks:	complete withdrawal of mTORi

Renal Function all patients

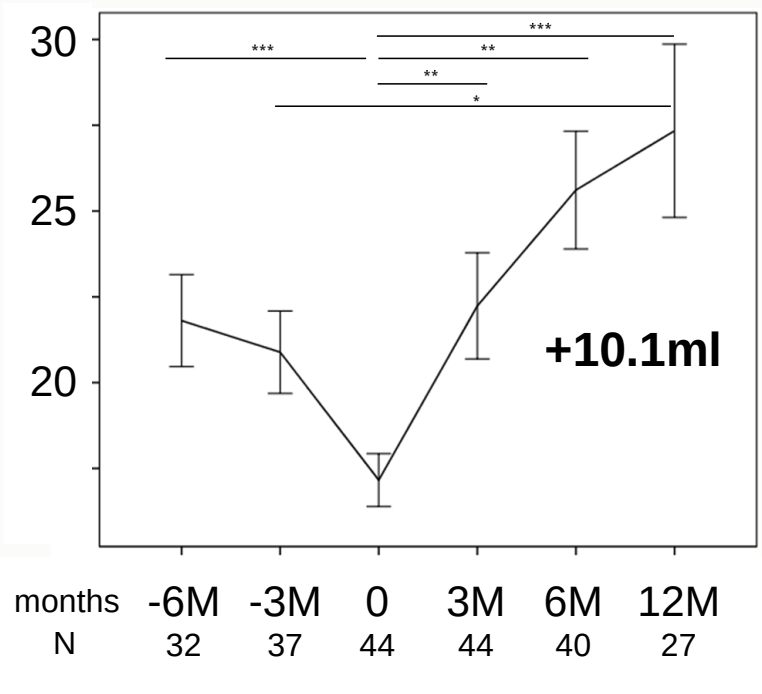


*p<0.05. **p<0.01. ***p<0.001. GFR, glomerular filtration rate;

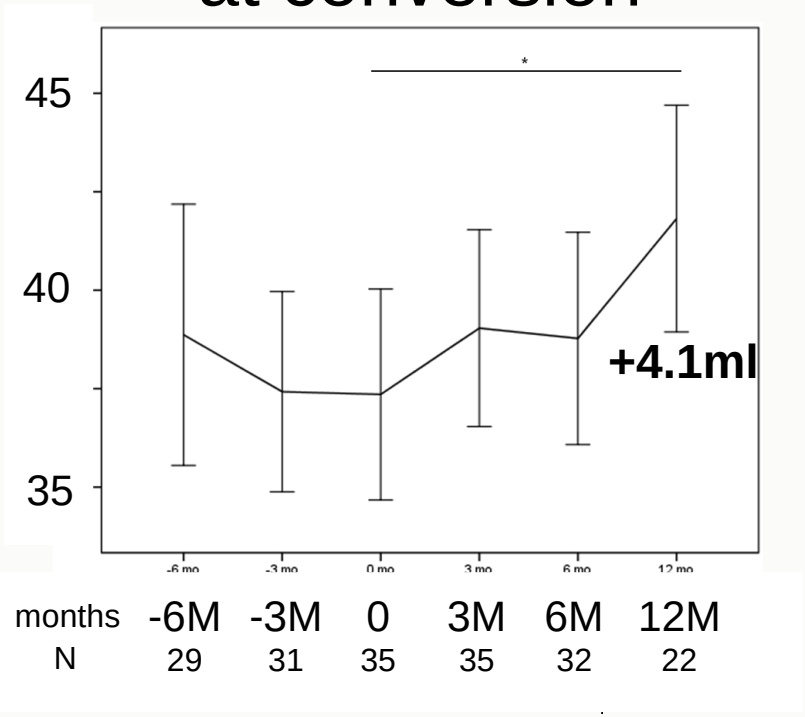
Brakemeier et al. Manuscript in preparation

Sub-group Analysis – Renal function

GFR <u>≤25ml/min</u> at conversion



GFR <u>≥25ml/min</u> at conversion



Time relative to conversion to belatacept

*p<0.05. **p<0.01. ***p<0.001. GFR, glomerular filtration rate;

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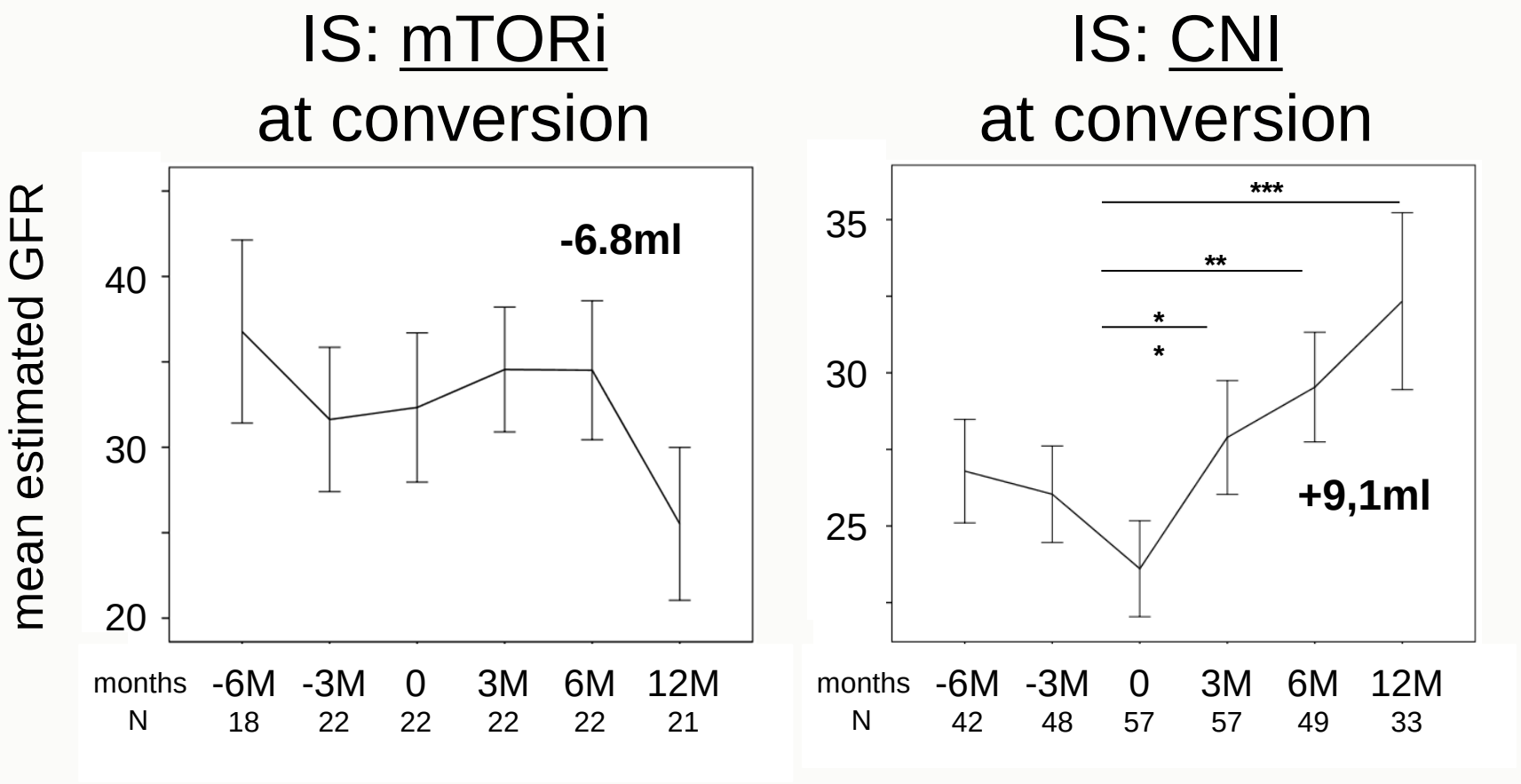
Sub-group Analysis – Renal function



Time relative to conversion to belatacept

*p<0.05. **p<0.01. ***p<0.001. GFR, glomerular filtration rate;

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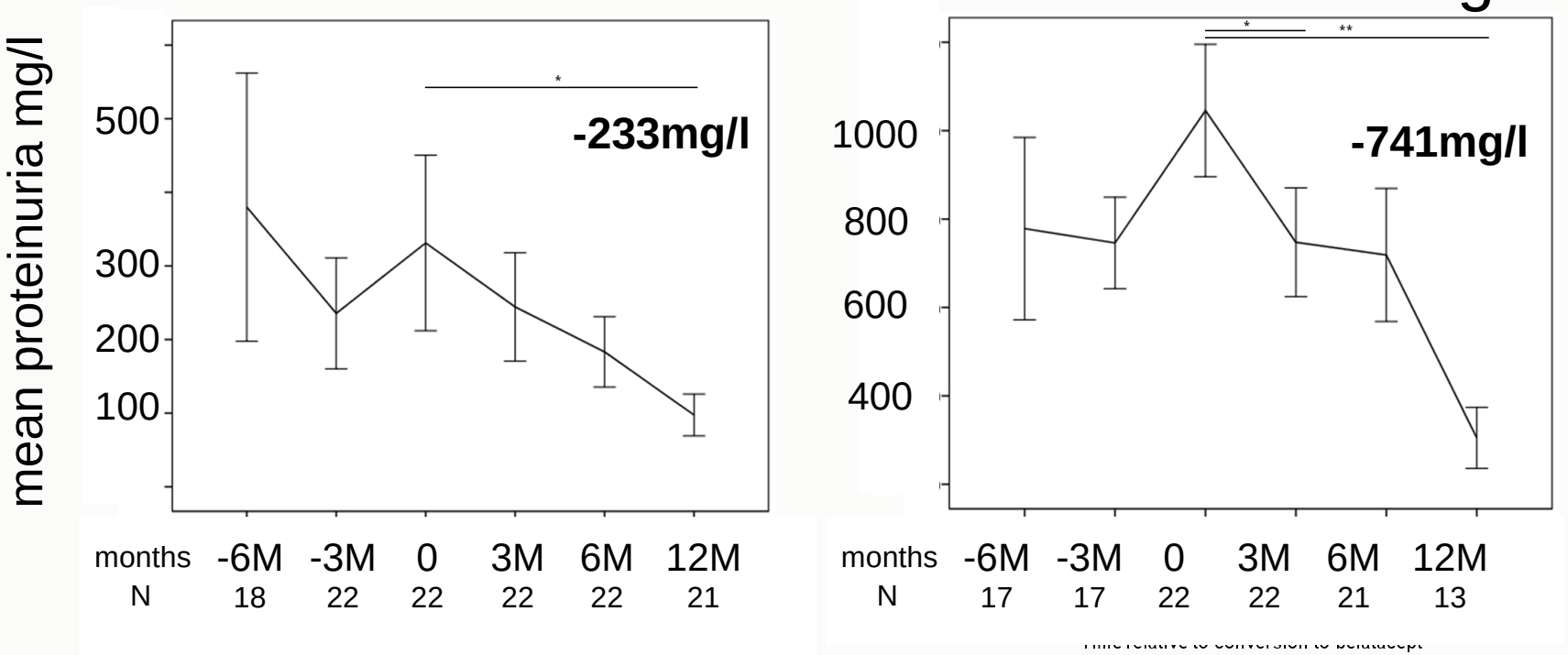
Sub-group Analysis – Proteinuria

IS: mTORi at conversion

IS: CNI (n=17), mTORi (n=5)

Proteinuria >500mg/l



Time relative to conversion to belatacept

*p<0.05. **p<0.01. ***p<0.001. GFR, glomerular filtration rate;

Brakemeier et al. Manuscript in preparation

EFFICACY

12 months results	
Patient survival	76 (96.2%)
Graft survival • Chronic allograft failure • Fulminant rejection	68 (86.1%) 6 2
Acute rejection	9 (11.4%)
• BANFF IB • BANFF IIA • BANFF IIB • BANFF III	4 1 3 1
Death • MI • NSCLC	3 2 1

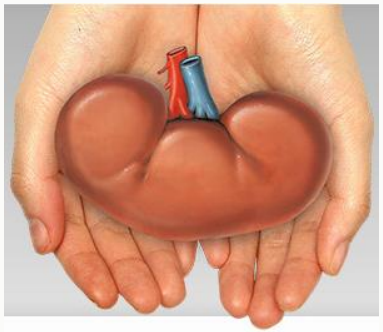
Adverse Events

	Events, n
Infections	
• Viral • Bacterial	18 (in 18 pts) 49 (in 49 pts)
Blood lymphatic system	
• Anemia • Leukopenia	36 (in 28 pts) 7 (in 7 pts)
Malignancy • NSCLC • Kaposi´s sarcoma • Basal cell carcinoma • PTLD (CNS)	4 1 1 1 1

Summary:
Late - Conversion to Belatacept

- Conversion from CNI or mTORi to Belatacept was found to be both effective and well tolerated
- Belatacept based therapy may be an alternative treatment for chronic transplant nephropathy or CNI-toxicity
- Need to evaluate the risk of rejection and infection

Belatacept alltagstauglich?



Belatacept
+MMF
+/-Steroide

+

1-year graft survival: >90%

-

Early Rejection-rate: >15%

Low incidence of DSA

7- years LTT experience
Superior renal function and graft survival

Malignancies
- **Higher incidence of PTLD**

Cardiovascular profile
Lower Bloodpressure
Lower incidence of PTDM
Lower Triglycerides

Side effects:
Infections
(CMV-Reactivation)

Danke für Ihre Aufmerksamkeit!

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