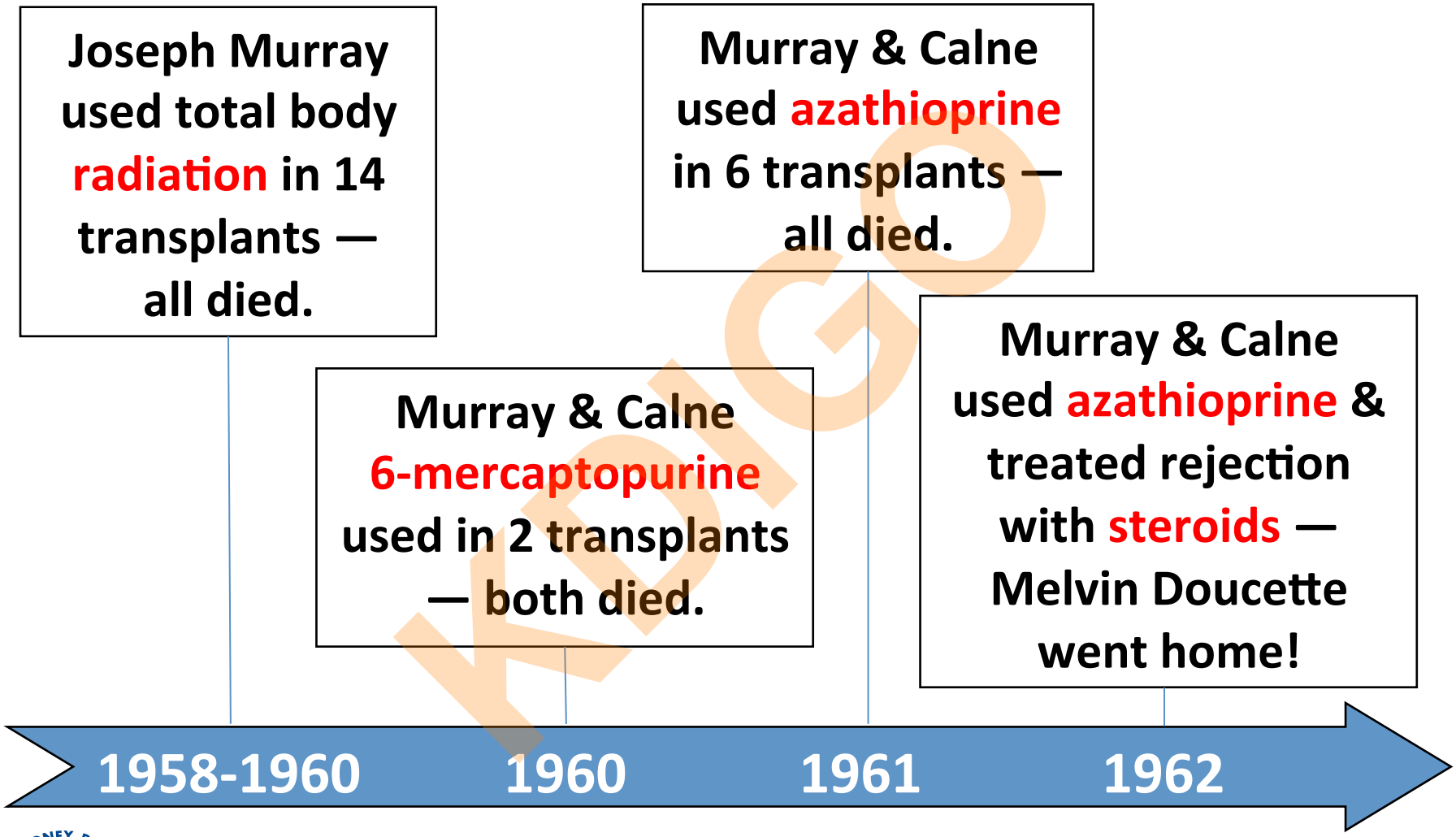
New Immunosuppression Horizons in Kidney Transplantation

Mumbai, India, February 9, 2014

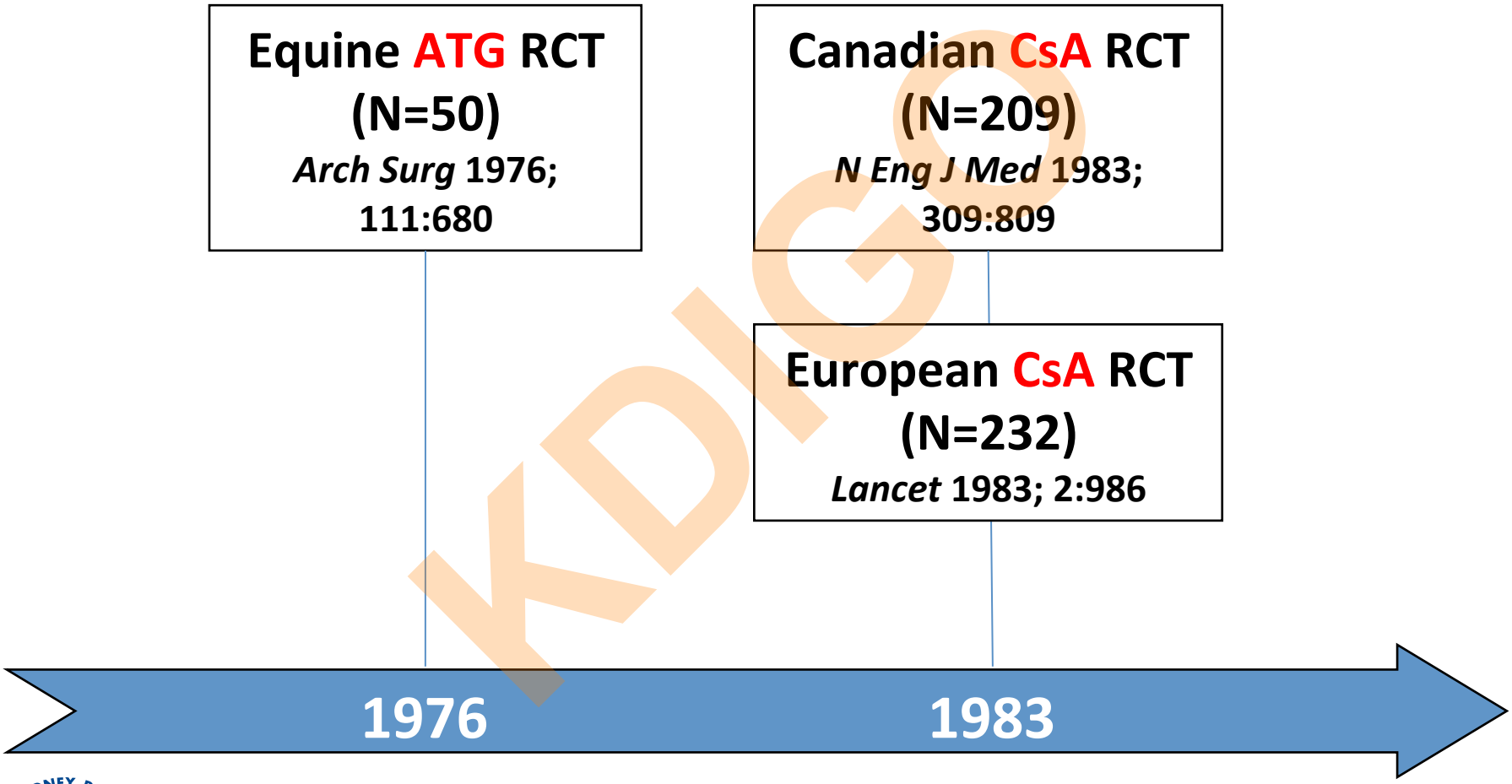
New Immunosuppression Horizons

- "Golden Era" of RCTs
- KDIGO Guideline 2009
- Current Clinical Practice
- Recent Randomized Trials
- New Drug Development

Initial Immunosuppression Attempts



Beginning the Era of RCTs



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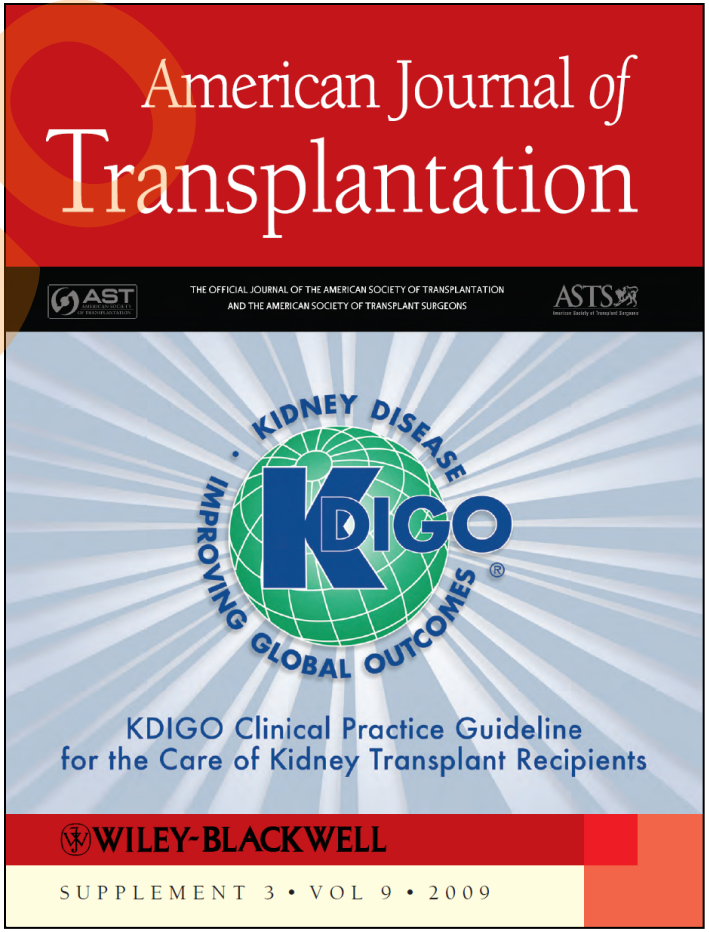
KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients

- Systematic reviews by the ERT:
  1985 through January 2007
- Evidence updated through:
  November 2008
- GRADE system used
  Strength of Recommendations:
  1 or 2
  Strength of Evidence:
  A, B, C, D
  "Not Graded" recommendations



Question 1

A 55 year old women with ESRD from diabetes has a living donor for her 1st kidney transplant. PRA 0%; no DSA. You would use the following induction:

A. No antibody induction
B. IL-2 receptor antagonist
C. Rabbit ATG
D. Alemtuzumab
E. Other

Question 2

A 55 year old women with ESRD from diabetes has a living donor for her 2nd kidney transplant. PRA 50%; no DSA. You would use the following induction:

A. No antibody induction
B. IL-2 receptor antagonist
C. Rabbit ATG
D. Alemtuzumab
E. Other

Induction Therapy

1.2: We recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. *(1A)*

1.2.1: We recommend that an IL2-RA be the first-line induction therapy. *(1B)*

1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk. *(2B)*

Maintenance Immunosuppression

2.2: We suggest that tacrolimus be the first-line CNI used. *(2A)*

2.3: We suggest that mycophenolate be the first-line antiproliferative agent. *(2B)*

2.4: We suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation. *(2B)*

Am J Transplant Jan 2009; 9 (Suppl 3): S1

Maintenance Immunosuppression

3.2: We suggest that CNIs be continued rather than withdrawn. *(2B)*

3.3: If prednisone is being used beyond the first week after transplantation, we suggest prednisone be continued rather than withdrawn. *(2C)*

Am J Transplant Jan 2009; 9 (Suppl 3): S1

Treatment of Acute Cellular Rejection

6.3: We recommend corticosteroids for the initial treatment of acute cellular rejection. *(1D)*

6.3.1: We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. *(2D)*

6.3.2: We suggest using lymphocyte-depleting antibodies or OKT3 for acute cellular rejections that do not respond to corticosteroids, and for recurrent acute cellular rejections. *(2C)*

Am J Transplant Jan 2009; 9 (Suppl 3): S1

Treatment of AMR

6.4: We suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids *(2C)*:

- **plasma exchange;**
- **intravenous immunoglobulin;**
- **anti-CD20 antibody;**
- **lymphocyte-depleting antibody.**

Am J Transplant Jan 2009; 9 (Suppl 3): S1

Treatment of Chronic Allograft Injury

7.2: For patients with CAI and histological evidence of CNI toxicity, we suggest reducing, withdrawing, or replacing the CNI. *(2C)*

7.2.1: For patients with CAI, eGFR >40 mL/min/1.73 m^2, and urine total protein excretion <500 mg/g creatinine (or equivalent proteinuria by other measures), we suggest replacing the CNI with a mTORi. (*2D*)

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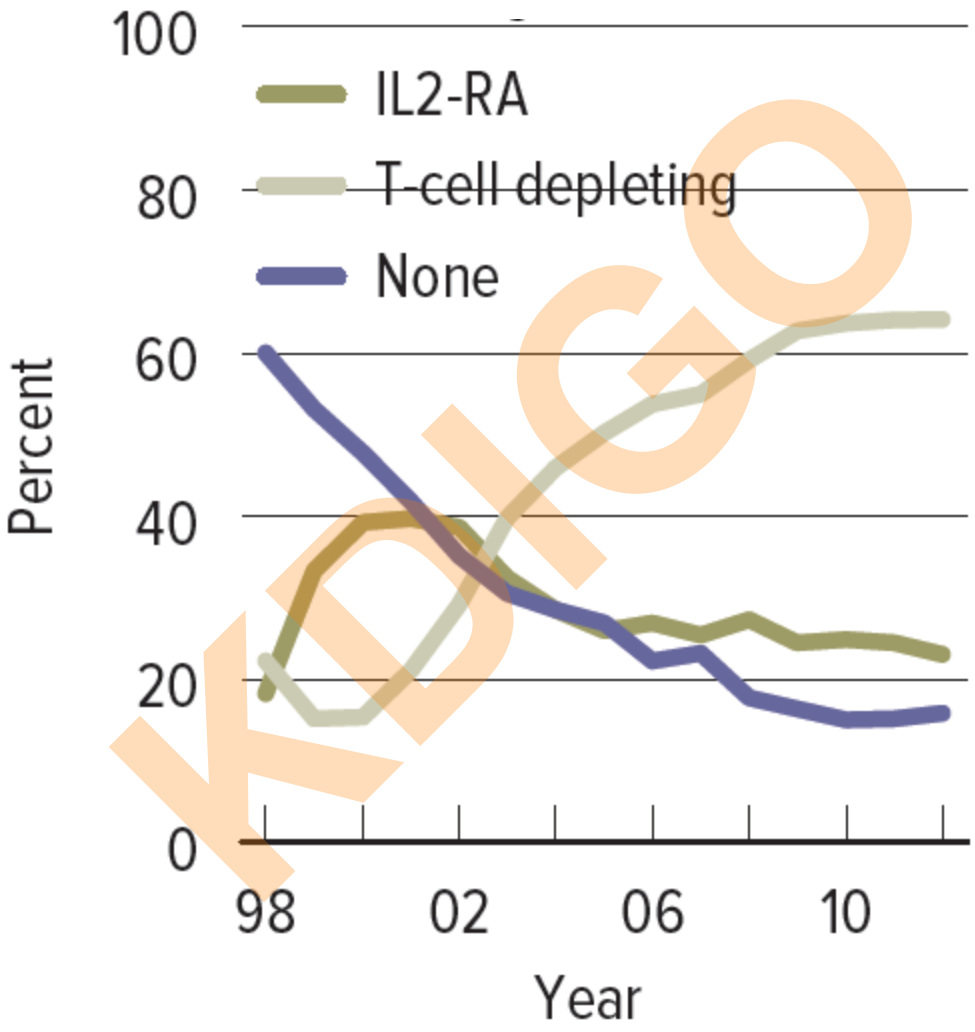
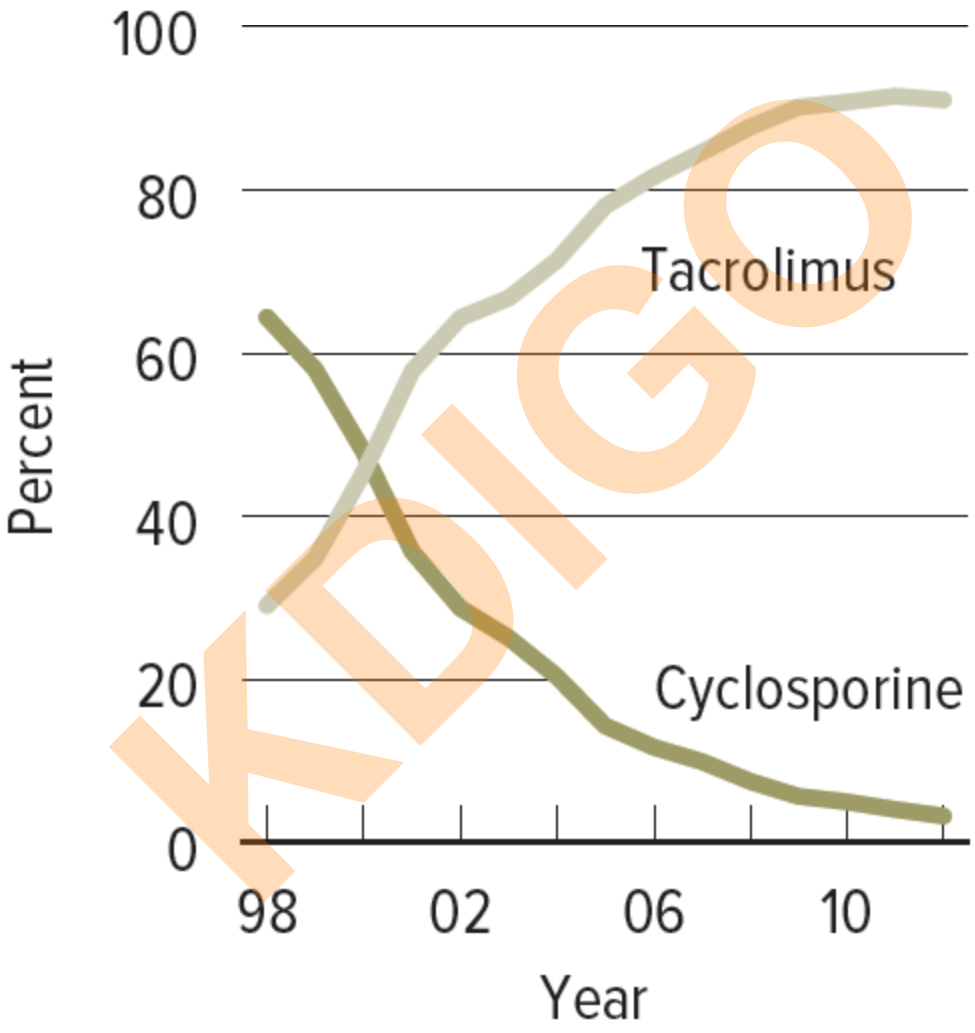
Induction Therapy



Kidney Disease: Improving Global Outcomes

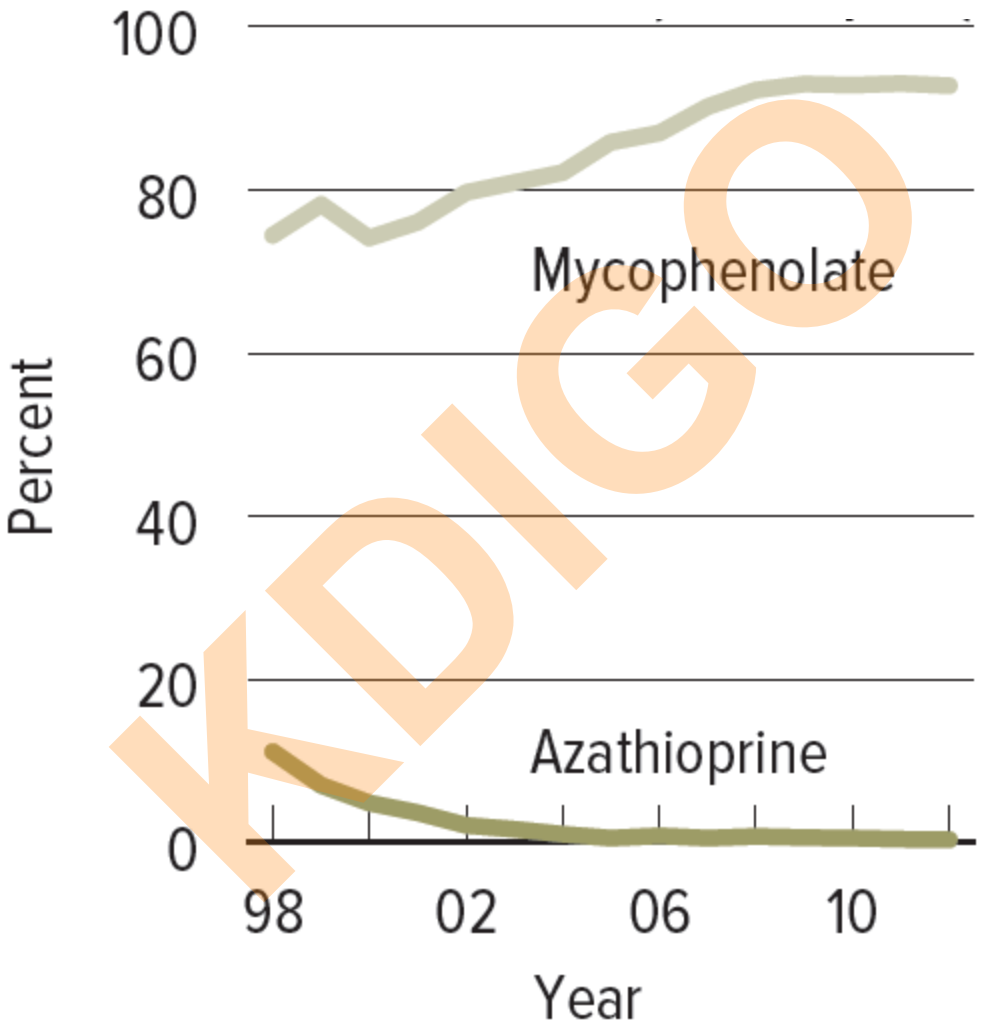
OPTN / SRTR Annual Data Report *Am J Transplant* Jan 2014

Maintenance CNI Use



OPTN / SRTR Annual Data Report *Am J Transplant* Jan 2014

Maintenance Antimetabolite Use



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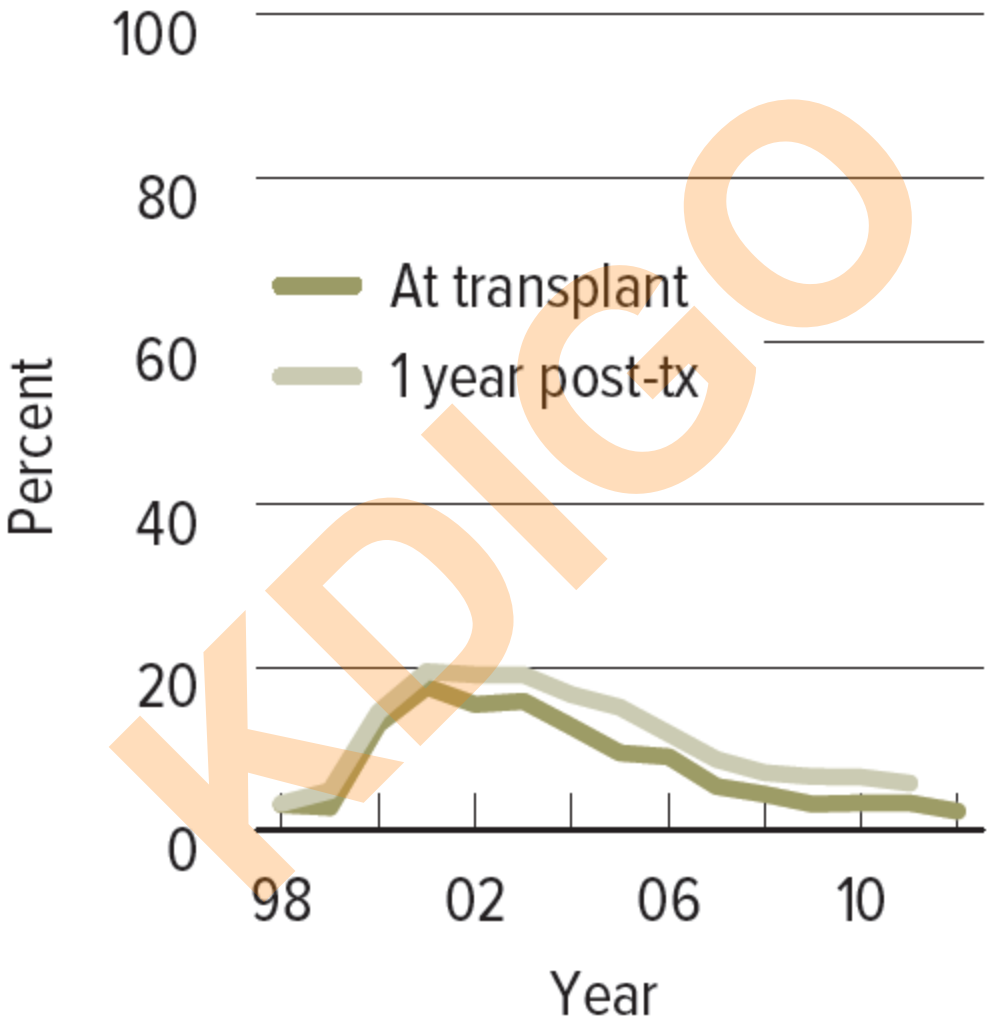
Maintenance mTOR Inhibitor Use



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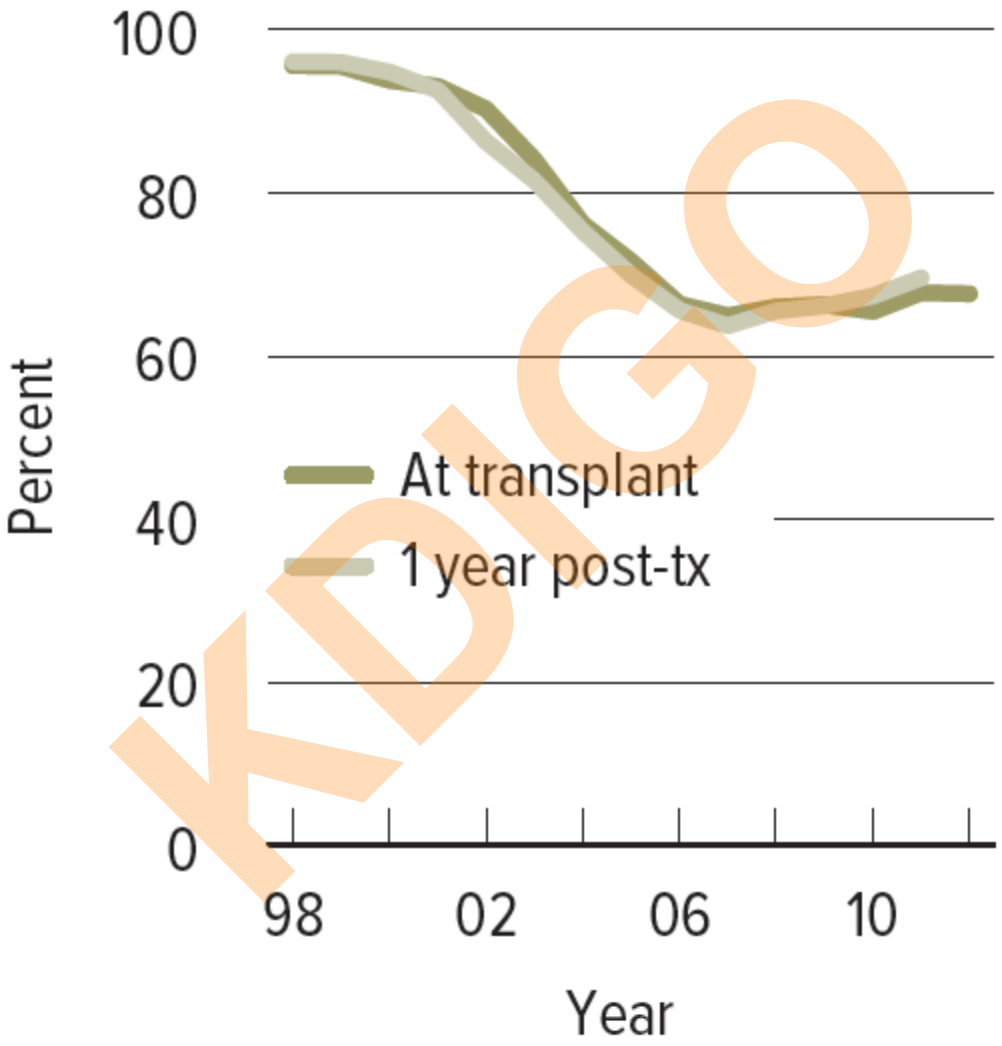
Maintenance Corticosteroid Use



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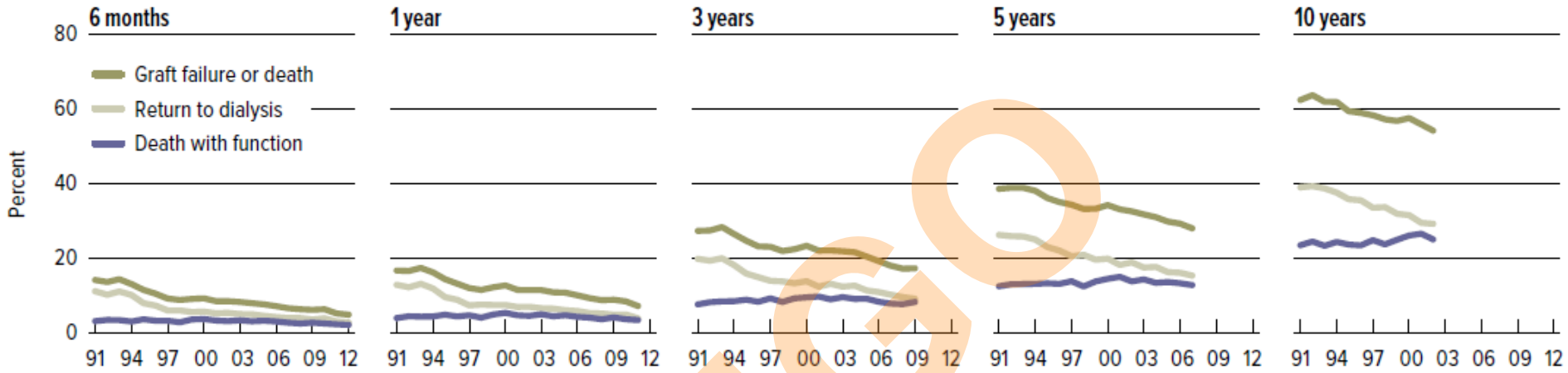
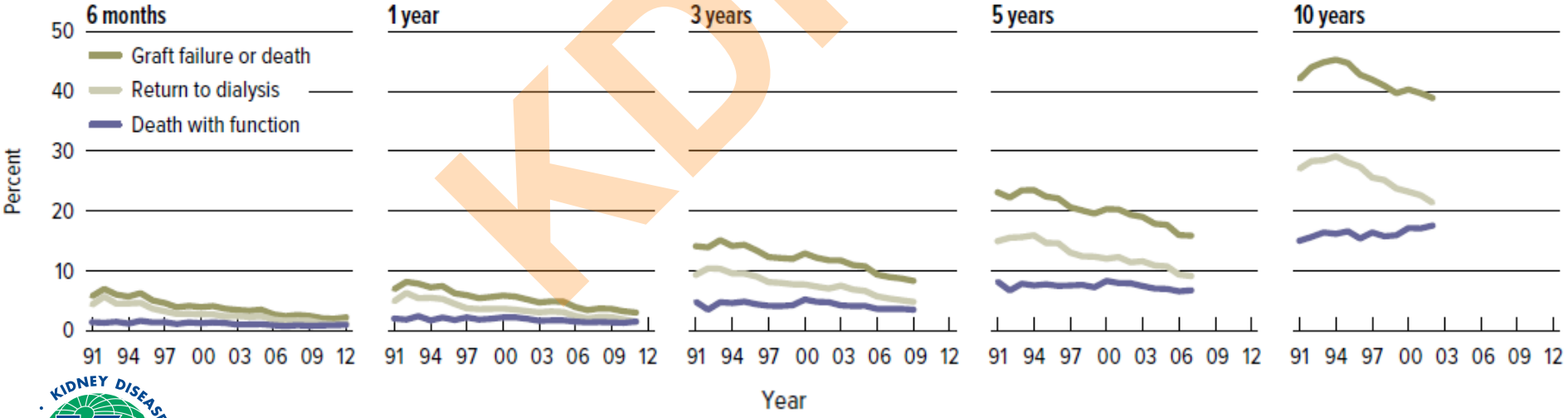
Adult US Kidney Transplant Outcomes

Deceased Donor Transplants



Living Donor Transplants



Kidney Disease: Improving Global Outcomes

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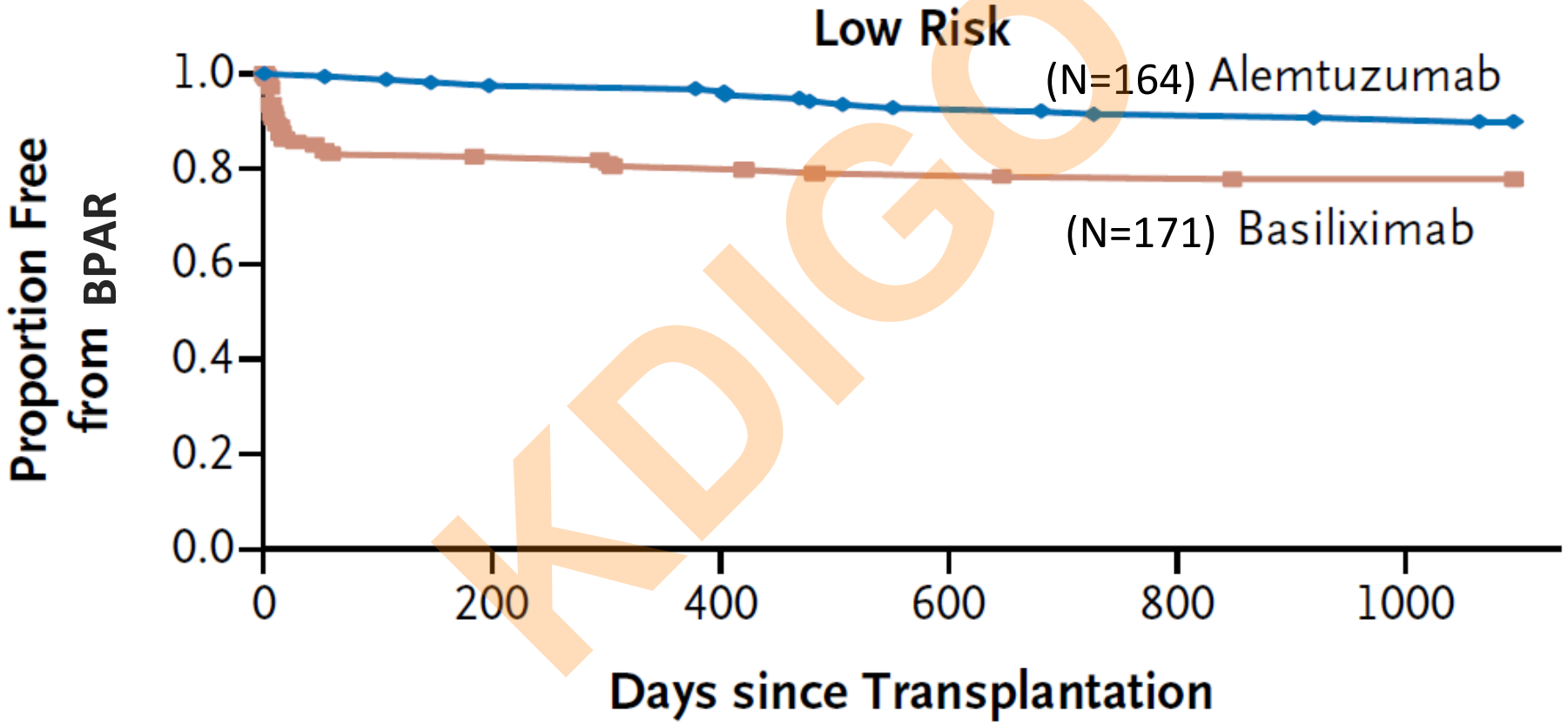
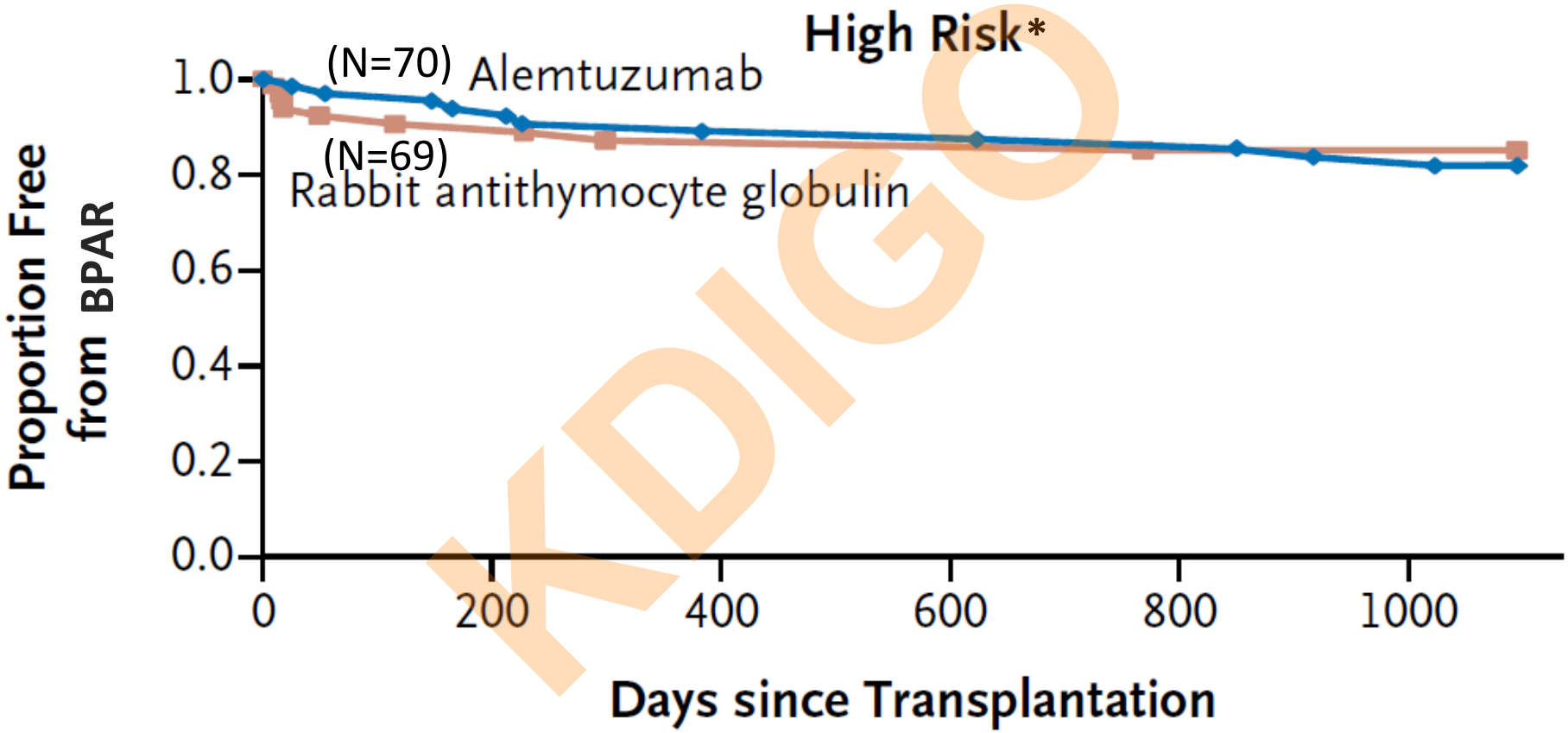
Alemtuzumab: Anti-CD52 T-Cell & B-Cell–Depleting Monoclonal Antibody



MJ Hanaway, ES Woodle, et al. *N Engl J Med* 2011;364:1909

Alemtuzumab: Anti-CD52 T-Cell & B-Cell–Depleting Monoclonal Antibody



*High-risk: repeat transplant, a peak or current value PRA > 20%, or black race.

Kidney Disease: Improving Global Outcomes MJ Hanaway, ES Woodle, et al. *N Engl J Med* 2011;364:1909

Acute Rejection in BENEFIT & BENEFIT-EXT

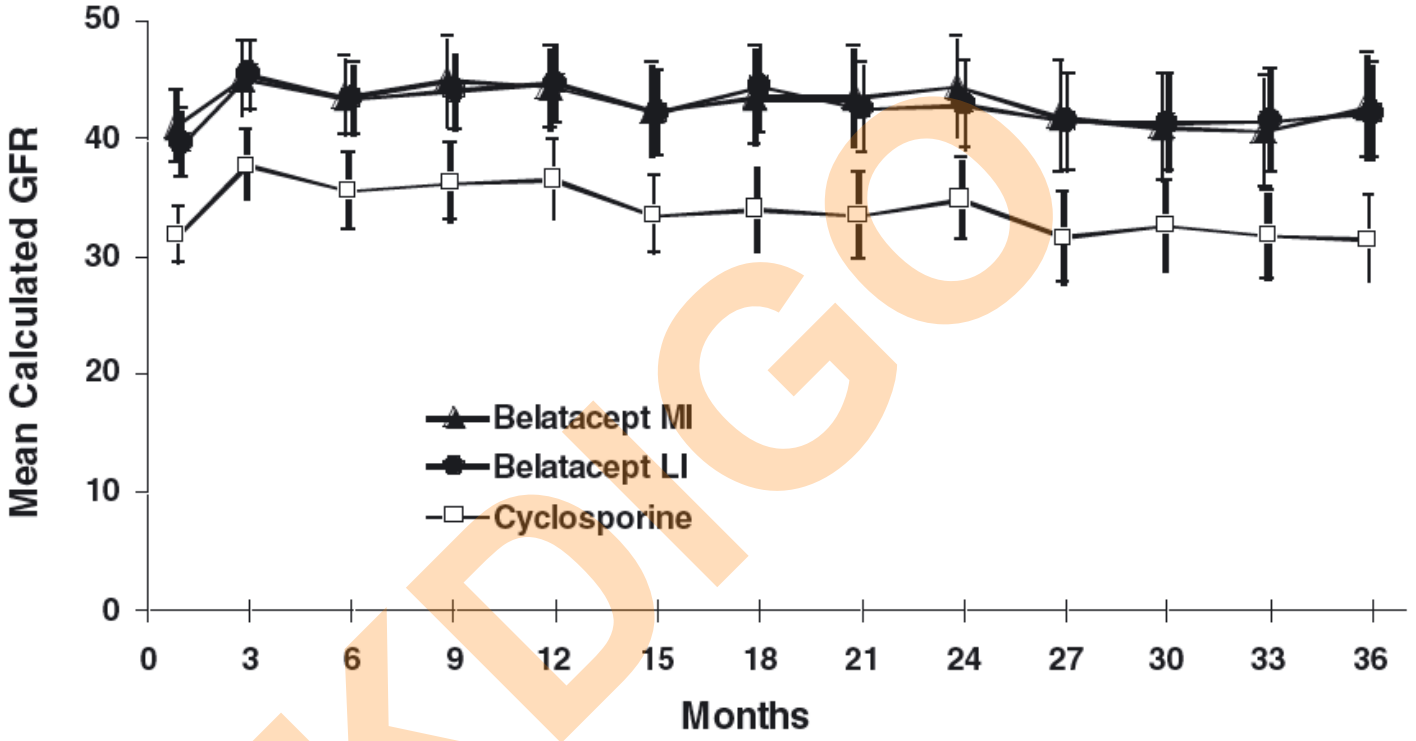
	Belatacept MI (N=219)	Belatacept LI (N=226)	Cyclosporine A (N=221)
Acute Rejection	49 (22%)	39 (17%)	16 (7%)
Banff grade IIA	17 (8%)	16 (7%)	6 (3%)
Banff grade IIB	20 (9%)	10 (4%)	2 (1%)

	Belatacept MI (N=184)	Belatacept LI (N=175)	Cyclosporine A (N=184)
Acute Rejection	33 (18%)	31 (18%)	26 (14%)
Banff grade IIA	10 (5%)	17 (10%)	17 (9%)
Banff grade IIB	16 (9%)	8 (5%)	5 (3%)

F Vincenti, et al. *Am J Transplant* 2010; 10:535

A Durrbach, et al. *Am J Transplant* 2010; 10:547

Estimated GFR in BENEFIT-EXT



Patients with Measurements													
Bela MI	182	177	161	153	165	145	143	140	152	129	136	139	152
Bela LI	173	168	152	149	157	140	142	144	158	139	140	132	154
CsA	184	172	153	147	159	139	140	137	154	126	132	133	143

JO Medina-Pestanta, et al. *Am J Transplant* 2012; 12:630

Safety Results in BENEFIT & BENEFIT-EXT

Complication	Belatacept MI (N=403)	Belatacept LI (N=401)	Cyclosporine A (N=405)
PTLD	5	6	2
Tuberculosis	6	6	1

C Larsen, et al. ATC May 2, 2011

Late Switch from CNI to Belatacept

- **Randomized, open-label trial:**
  - Stable 6-36 months post-transplant
  - Group 1 (N=89): continue CNI
  - Group 2 (N=84): change to belatacept

Complication	Belatacept (N=84)	Continue CNI (N=89)
Acute rejection	6 (7%)	0
Banff grade IIA	3 (4%)	0
Banff grade IIB	1 (1%)	0

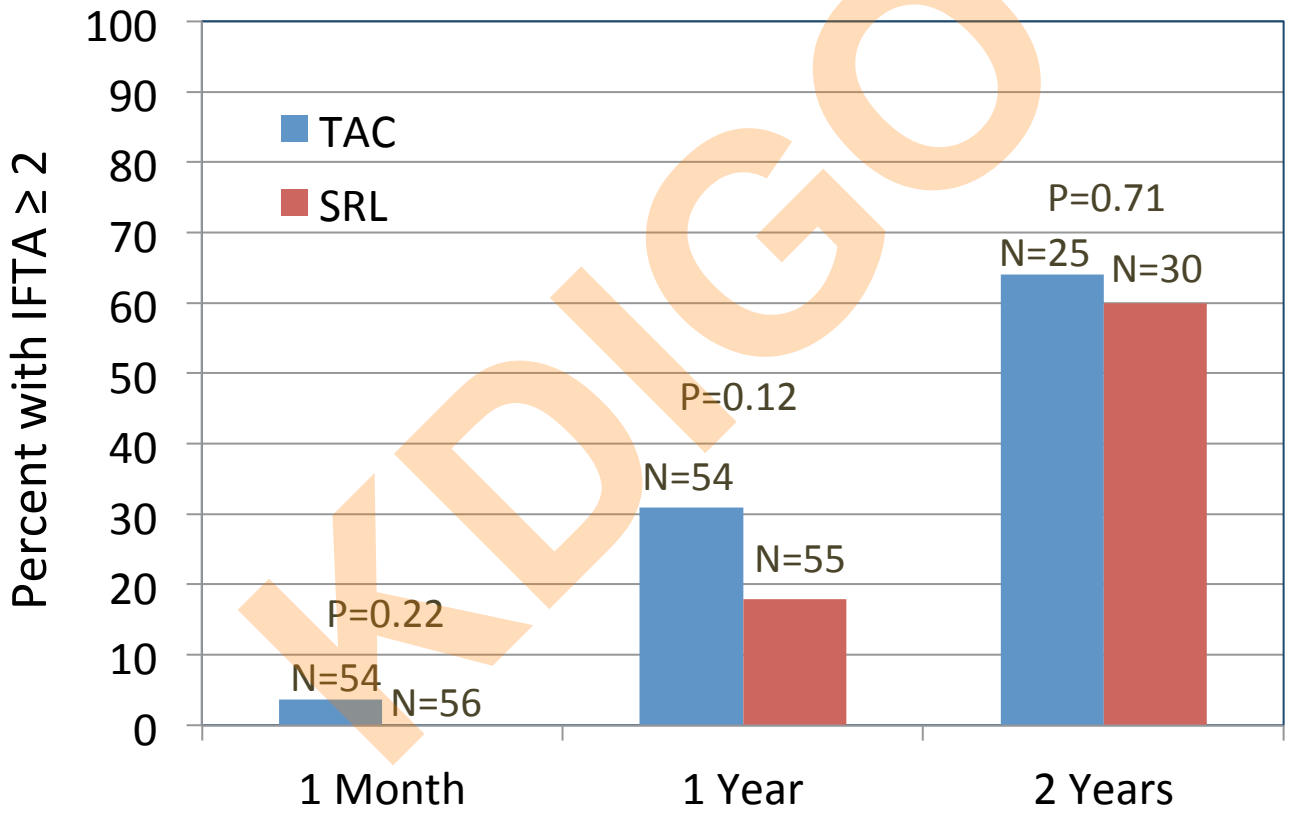
L Rostaing, et al. *Clin J Am Soc Nephrol* 2011; 6:430

Question 3

A 40 year old 1 year after a deceased donor kidney transplant is on tacrolimus, mycophenolate and prednisone 2.5 mg daily. You would consider switching tacrolimus to an mTOR inhibitor for decreasing eGFR from 60 to 50 mL/min/1.73m^2 with Banff Grade 1-2 interstitial fibrosis.

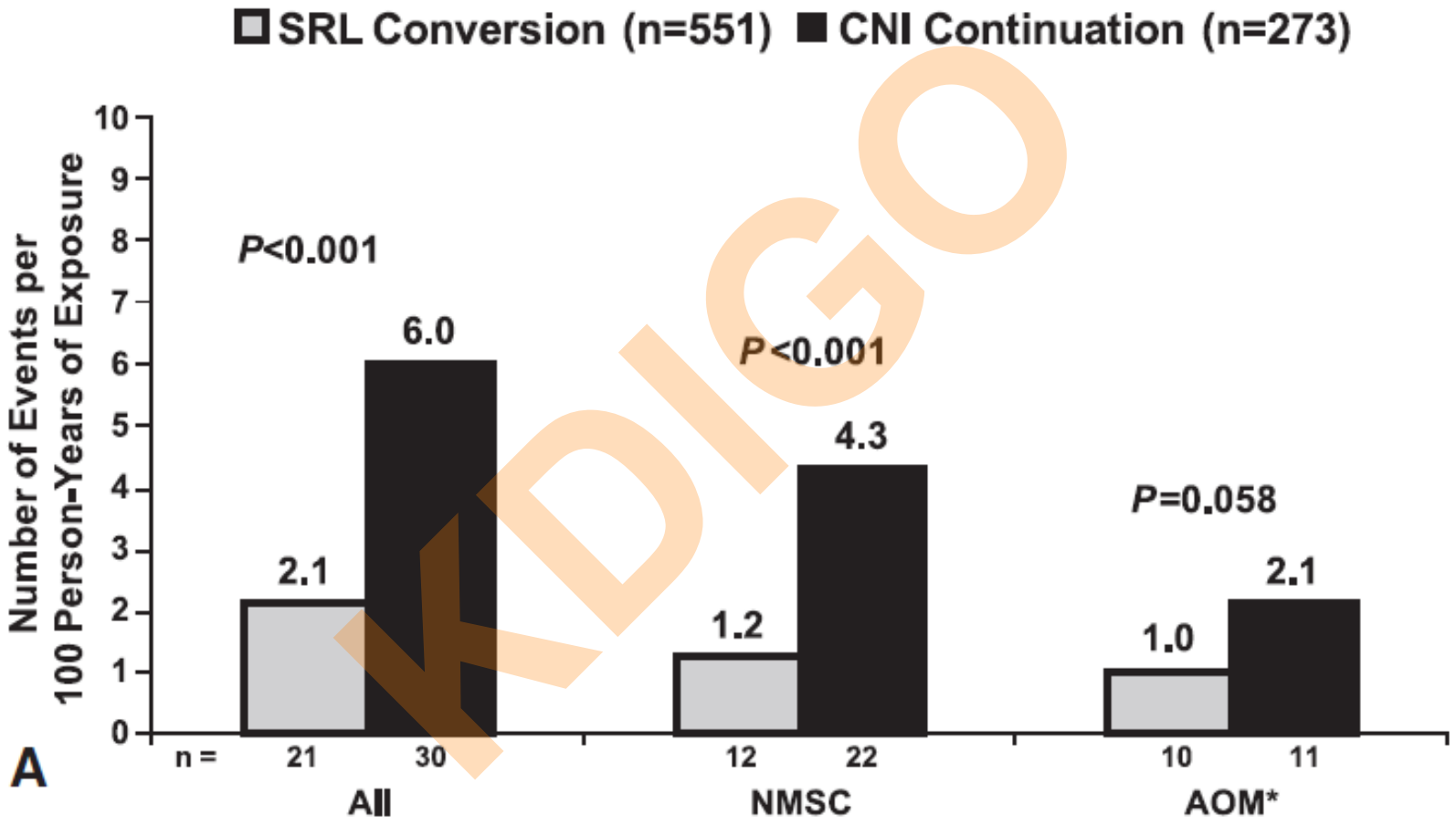
A. Yes
B. No
C. Unsure

Effect of Rapamycin Conversion at 1 Month on Interstitial Fibrosis at 1 and 2 Years



RL Heilman, et al. *Transplantation* 2012;93: 47

Effect of Rapamycin Conversion on Cancer



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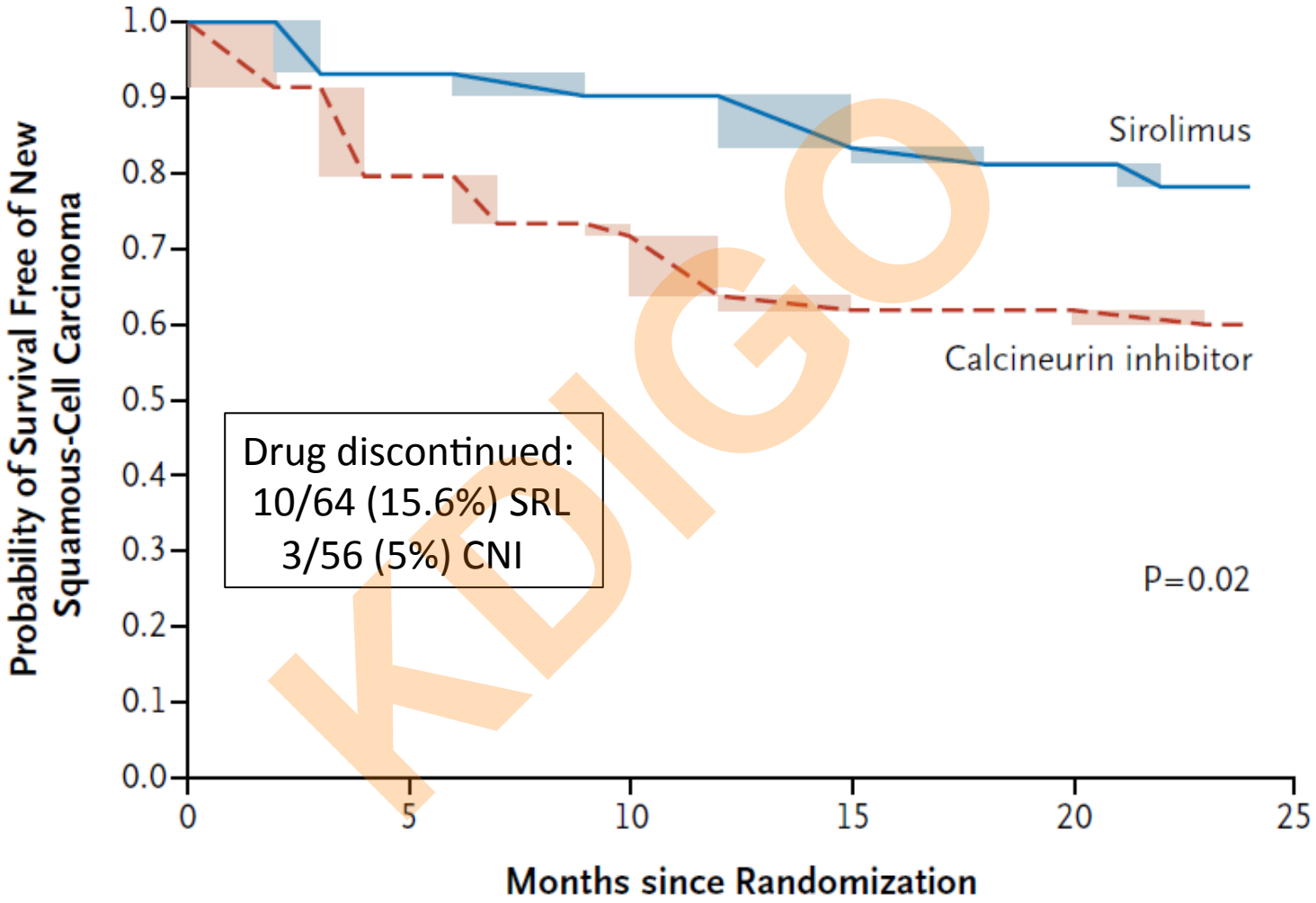
J Alberu et al. T*ransplantation* 2011; 92:303

Rapamycin in Patients with Skin Cancer



Shaded boxes indicate 95% confidence intervals.

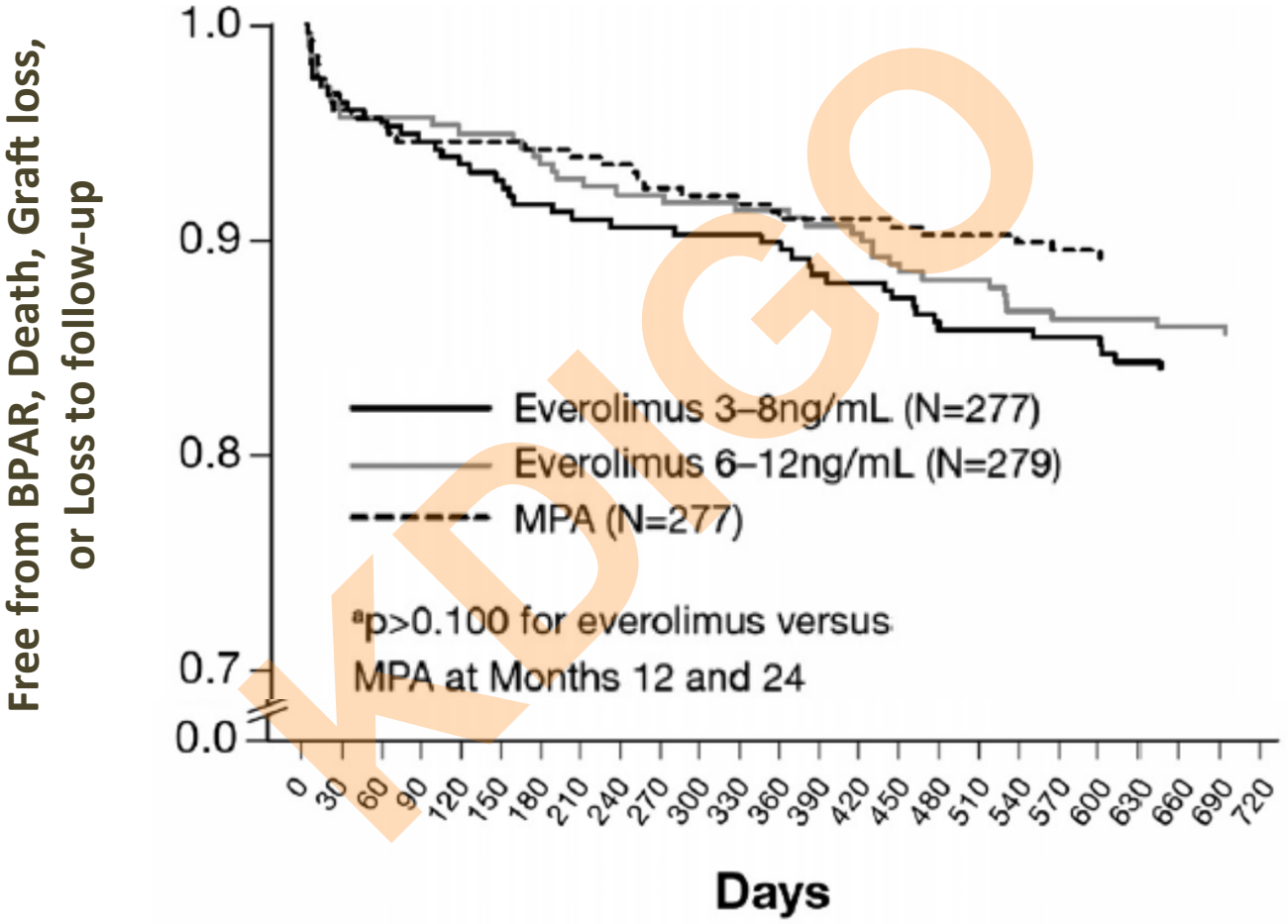
S Euvrard, et al. *N Eng J Med* 2012; 376(4):329

Question 4

A 40 year old 3 years after a deceased donor kidney transplant is on tacrolimus, mycophenolate and prednisone 2.5 mg daily. You would consider switching tacrolimus to an mTOR inhibitor for new onset diabetes.

A. Yes
B. No
C. Unsure

Everolimus for CNI Minimization



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D Cibric, et al. *Transplantation* 2013; 95:933

Late Conversion from CNI to Everolimus

	EVR + CNI Elimination (N=127)	EVR + CNI Minimization (N=144)	Controls (N=123)
BPAR	7 (5.5%)	8 (5.6%)	3 (2.4%)
Serious Adverse Events	72 (56.7%)*	78 (54.2%)	52 (42.3%)
Proteinuria > 3.5 g/L	10 (7.9%)	15 (10.4%)	5 (4.1%)
Hyperlipidemia	36 (28.3%)*	34 (23.6%)*	11 (8.9%)
mGFR (mL/min/1.73m^2)	48.0±22.0	46.6±21.1	46.0±20.4

*P<0.05 v. Controls

H Holdass, et al. *Transplantation* 2011

Question 5

A 32 year old with no rejection 6 months after a living donor kidney transplant, develops diarrhea. He is on tacrolimus, mycophenolate mofetil (MMF) and prednisone. Evaluation for treatable causes of diarrhea is negative. You would:

A. Reduce the dose of MMF
B. Change MMF to EC-mycophenolate sodium
C. Change MMF to azathioprine
D. Use symptomatic treatment only

Effect on GI Symptoms of Conversion to Enteric-Coated Mycophenolate Sodium

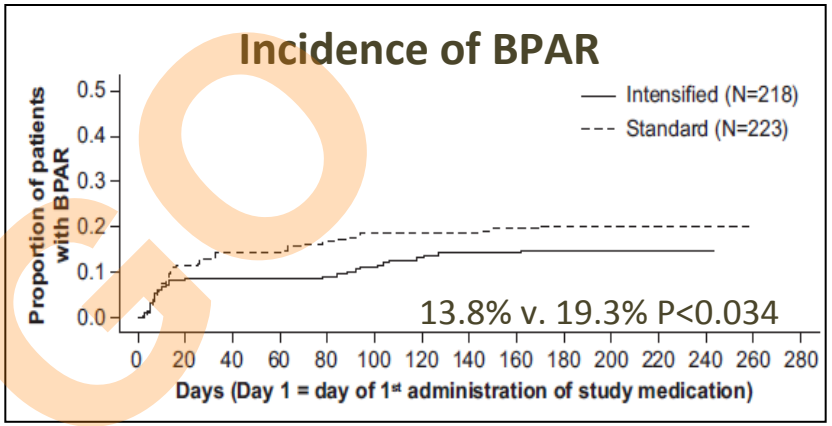
	Treatment group		
	EC-MPS (N=199), n (%)	MMF (N=197), n (%)	*P*
Patients with at least one GI AE[a]	77 (38.7)	91 (46.2)	0.1545
Abdominal distension	27 (13.6)	31 (15.7)	0.5719
Diarrhea	22 (11.1)	19 (9.6)	0.7420
Dyspepsia	19 (9.5)	17 (8.6)	0.8616
Nausea	11 (5.5)	23 (11.7)	0.0320
Flatulence	11 (5.5)	19 (9.6)	0.1325
Eructation	9 (4.5)	20 (10.2)	0.0348
Abdominal pain upper	9 (4.5)	18 (9.1)	0.0754
Abdominal pain lower	11 (5.5)	14 (7.1)	0.5426
Intestinal functional disorder	10 (5.0)	14 (7.1)	0.4079
Gastroesophageal reflux disease	13 (6.5)	9 (4.6)	0.5115
Constipation	7 (3.5)	15 (7.6)	0.0829
Vomiting	6 (3.0)	11 (5.6)	0.2258

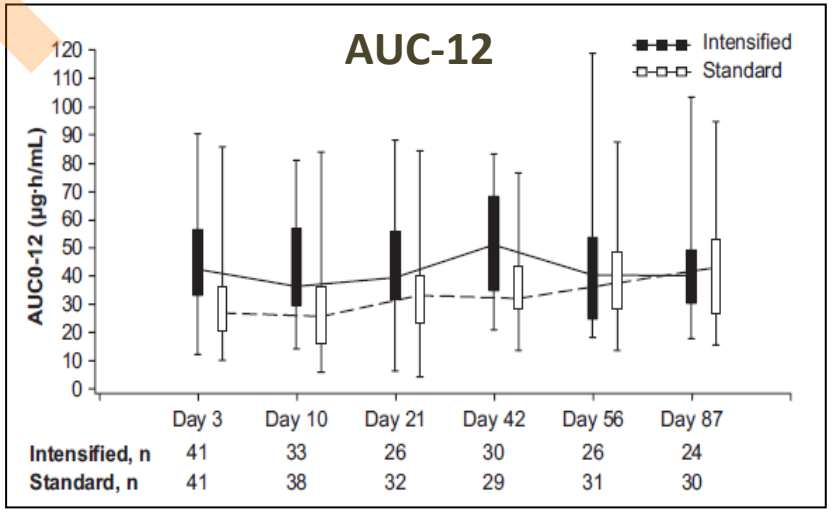
[a] A patient with multiple occurrences of an AE is counted only once in the AE category for that treatment.

AJ Lagone, et al. *Transplantation* 2011; 91:470

Intensified Mycophenolate

- 2 open-label RCTs (N=441)
  - EC-MMF
  - 2w 2880/d; 4w 2160/d then 1440/d
  - Standard 1440/d
- Other:
  - IL2-RA (74%), CsA, steroids
- AEs causing dose reduction:
  - Intensified: 67 (31.5%)
  - Standard: 45 (20.5%) P=0.011





K Budde, et al. *Transplantation* 2011;

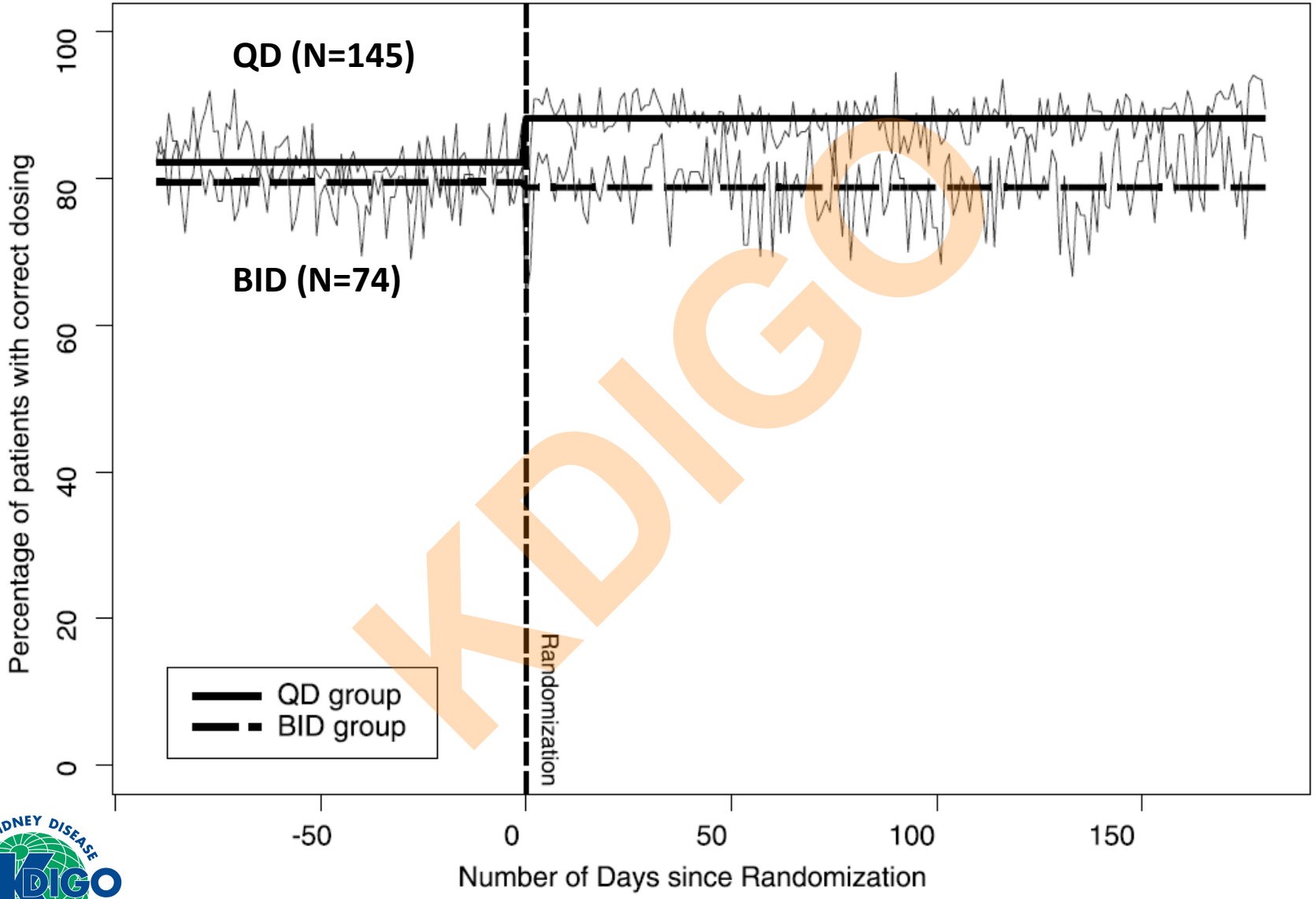
Conversion to Once Daily Tacrolimus

Event at 12 Months	Once Daily (N=162)	Twice Daily (N=162)	P-Value
Efficacy failure*	4(2.5%)	4 (2.5%)	N.S.
Discontinuation	20 (12.3%)*	4 (2.5%)	0.028
Adverse events	135 (82.7%)	133 (81.6%)	N.S.
Serious adverse events	36 (22.2%)	26 (16%)	N.S.

*Death, graft failure, locally read biopsy-proven acute rejection , or loss to follow-up

S Bunnapradist, et al. *Am J Transplant* 2013; 13(3): 760

Once v. Twice Daily Tacrolimus Adherence



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DRJ Kuypers, et al. *Transplantation* 2013;95: 333

Key RCT Results since the KDIGO Guideline

Alemtuzumab: similar to rATG, possibly less expensive

Belatacept: role unclear

Rapamycin: role unclear except to prevent skin cancer

Everolimus: similar to rapamycin

Enteric-coated mycophenolate sodium: role unclear

Intensified mycophenolate: role unclear

Once daily tacrolimus: may improve adherence

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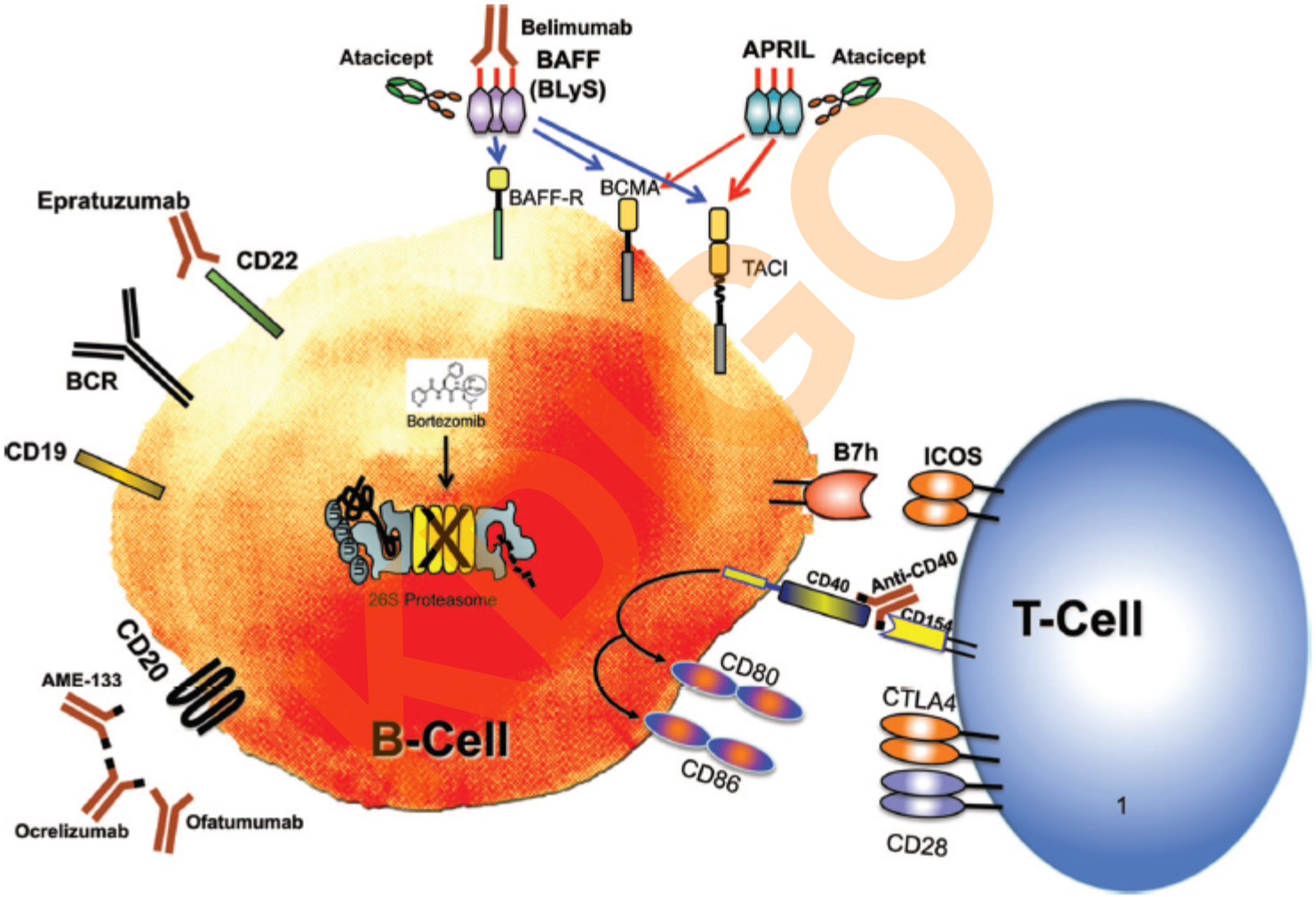
Question 6

A 40 year old 3 years after a deceased donor kidney transplant on low-dose tacrolimus, mycophenolate and prednisone 2.5 mg daily, develops decreasing eGFR 60 to 50 mL/min/1.73m^2 over 12 months. Biopsy shows Banff Grade 2 interstitial fibrosis, inflammation in areas of fibrosis, C4d(-), and arteriolar hyalinosis. A single DSA is positive in low titer. This is most likely:

A. Chronic antibody-mediated rejection
B. CNI toxicity
C. Non-adherence
D. A combination of the above

New Immunosuppression Horizons



A Webber, et al. *Transplantation* 2011; 91:1057

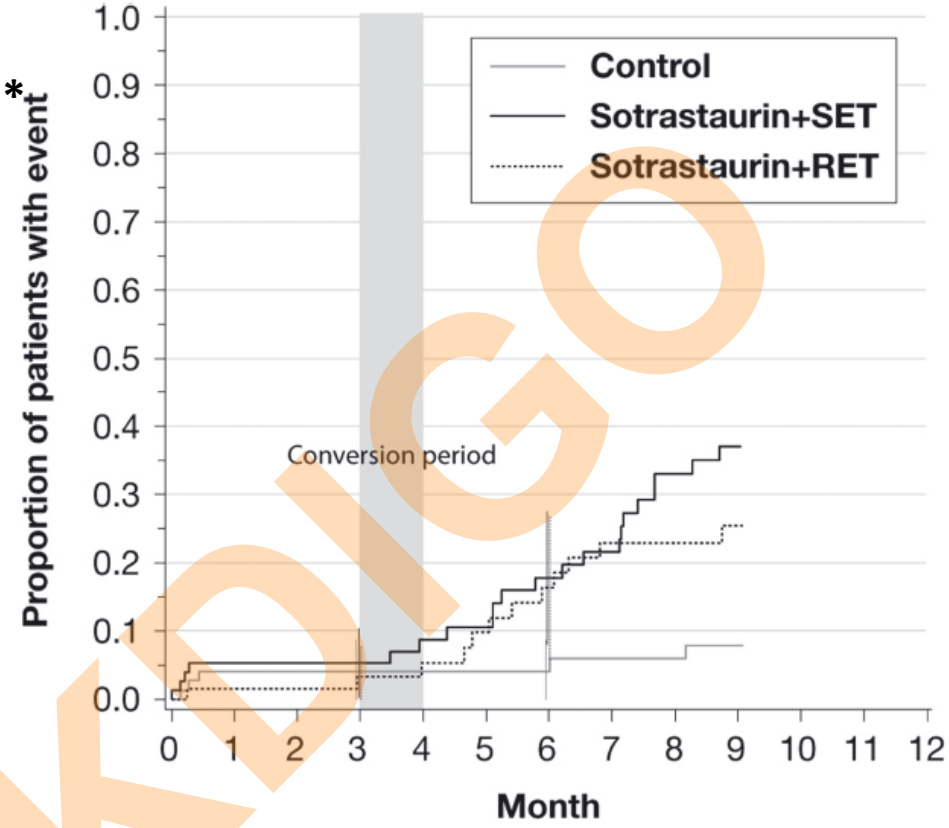
Tofacitinib versus CsA

Complication	CsA (N=109)	CP MI (N=106)	CP LI (N=107)
BPAR at Month 12	18.8%	17.4%	15.4%
mGFR (mL/min)	53.9	64.6*	64.7*
CMV disease	4.5%	19.5%*	13.3%*
PTLD	0	2#	1

*p<0.05 vs. CsA; #2 more cases of PTLD after 12 mo.

F Vincenti, et al. *Am J Transplant* 2012; 12(9):2446

Sotrastaurin with Tacrolimus Minimization



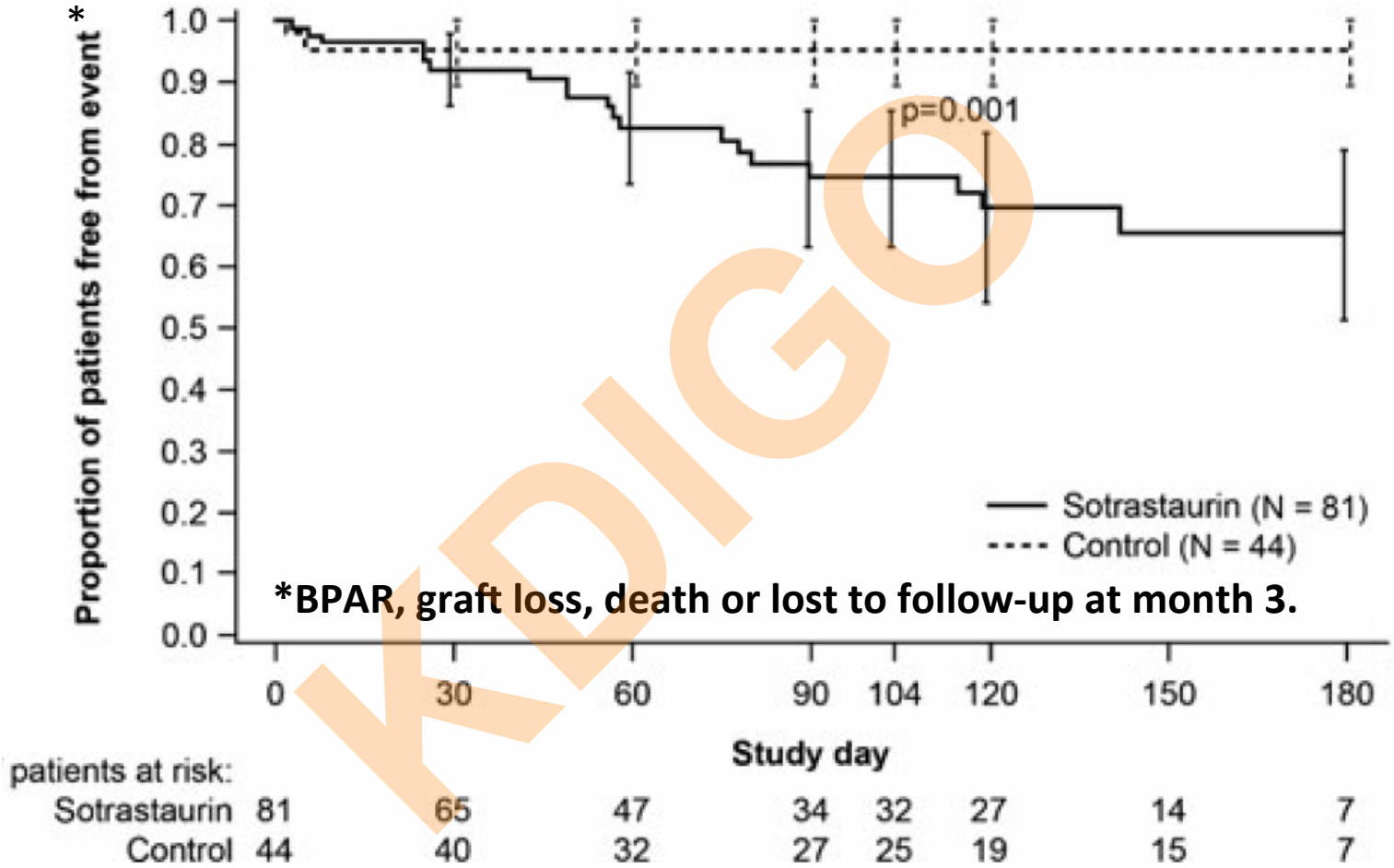
Treatment	No. of patients at risk			
Control	74	60	52	45
Sotrastaurin+SET	76	63	45	30
Sotrastaurin+RET	66	56	38	27

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

Kidney Disease: Improving Global Outcomes

K Budde, et al. *Am J Transplant* 2010; 10:571

Sotrastaurin versus Tacrolimus



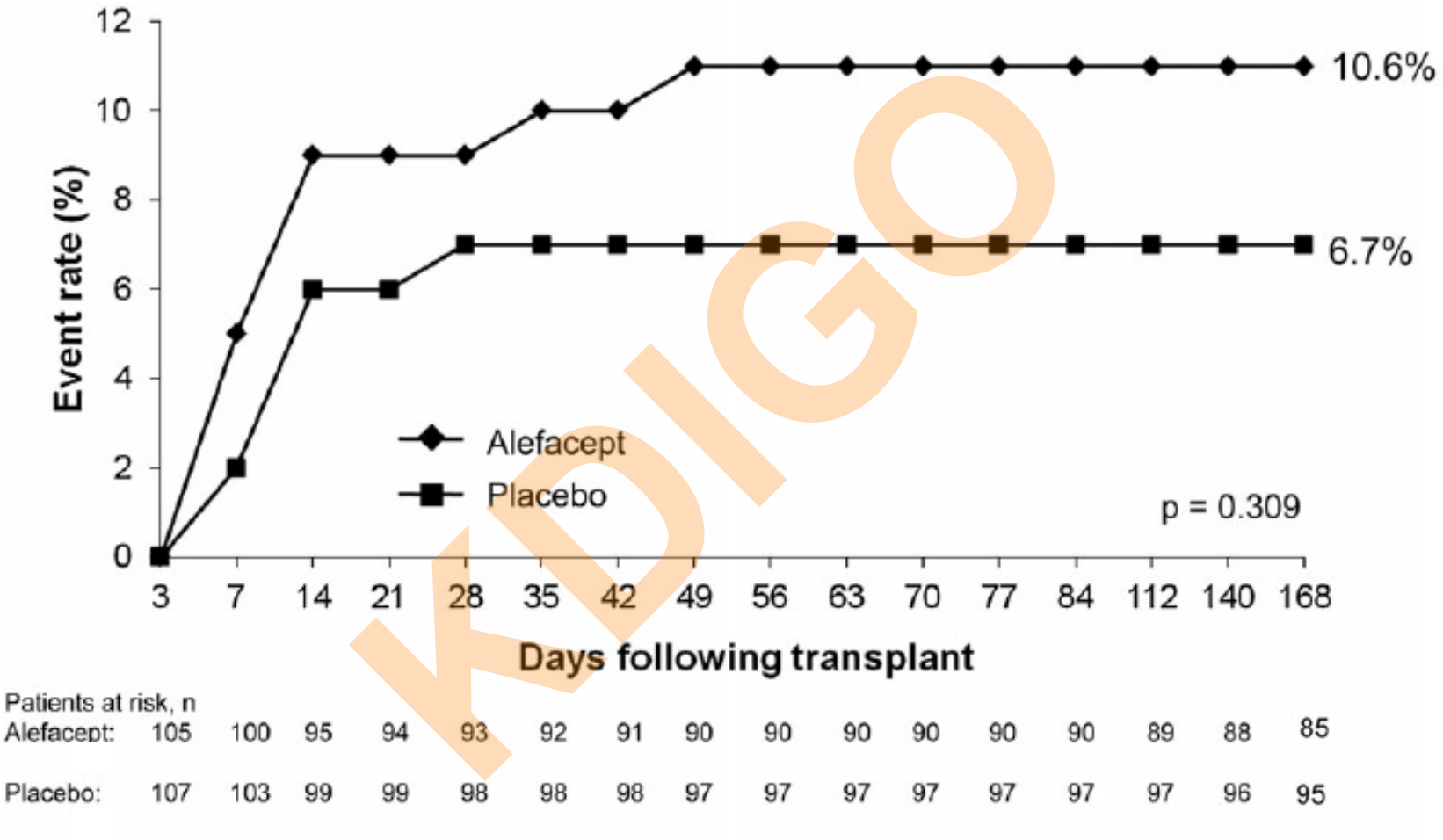
S Friman, et al. Am J Transplant 2011; 11(7): 1444

Alefacept Phase II RCT

Parameter	Control (N=79)	A+Low Tac (N=77)	A+Tac (N=75)	A(qow)+Low Tac (N=78)
BPAR (%)	12.7	26.3*	18.8	16.7
CD4+ T memory (cells/mm3)	538.6	335.2*	330.9*	268.8*
CD8+ T memory (cells/mm3)	146.3	84.8*	92.0*	56.2*

*P<0.05 versus control

Alefacept Phase II RCT



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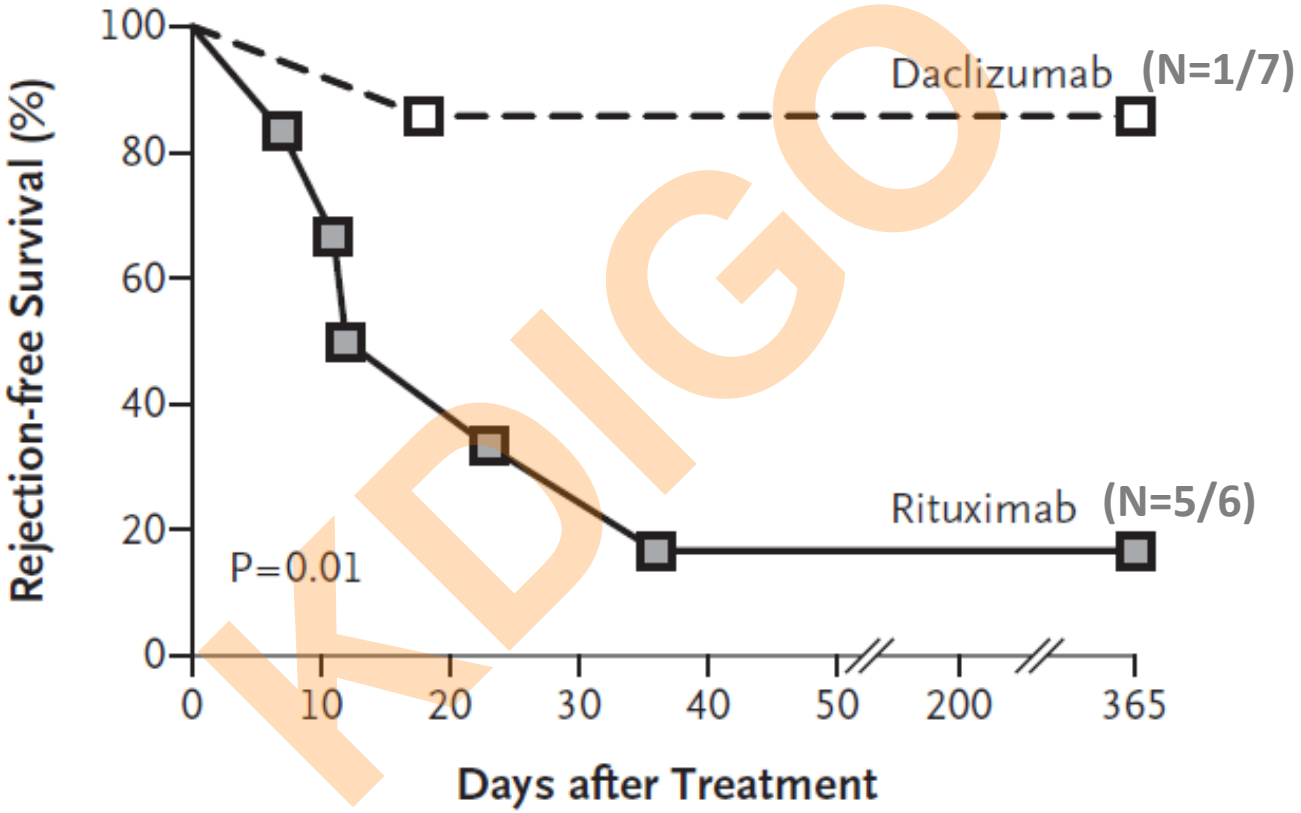
L Rostaing, et al. *Am J Transplant* 2013; 13(7):1724

Rituximab Induction



MR Clatworthy, et al. *N Eng J Med* 2009; 360:2683

Rituximab Induction

	Rituximab (N=68)	Placebo (N=68)	P-Value
Treatment failure* at 6 months	10 (14.7%)	14 (20.6%)	0.348
BPAR at 6 months	8 (11.6%)	12 (17.6%)	0.317

*Acute rejection, graft loss, or death during the first 6 months

G Tyden, et al. *Transplantation* 2009;87: 1325

Rituximab Induction

	Rituximab (N=138)	Placebo (N=142)	P-Value
BPAR at 6 mo.	15.9%	21.8%	0.15
BPAR at 6 mo. in N=62 with PRA>6 or re-transplant	17.9%	41.1%	0.039
Patient survival at 24 mo.	92.3%	92.8%	0.87
Graft survival at 24 mo.	88.7%	87.7%	0.93

M. van den Hoogen, et al. ATC 2013 (abstract 266.1)

Systematic Review of AMR Treatment

Therapy	Action	Evidence supporting the treatment[a]
Plasmapheresis (PP)[b]	Decrease the titer and block the effect of DSA	Low, benefit not consistently demonstrated
Immunoadsorption (column)	Decrease the titer of DSA	Low, seems beneficial
IVIG	Decrease the titer and block the effect of DSA	Very low
Bortezomib	Decrease production of DSA	Very low
Corticosteroids	Decrease inflammation caused by DSA in graft and decrease production of DSA, suppression of T cells	Very low
Anti-thymocyte preparations	Reduce production of DSA by decreasing Helper T cells, suppression of T cells	Very low
Eculizumab	Block complement activation resulting from DSA activation	Very low
Mycophenolate	Block the effect and decrease production of DSA, suppression of T cells	Very low
Rituximab	Decrease production of DSA	Very low
Cyclophosphamide	Decrease production of DSA	Very low
Deoxyspergualin	Decrease production of DSA, suppression of T cells	Very low
Splenectomy	Decrease production of DSA	Very low
Tacrolimus	Decrease production of DSA, Suppression of T cells	Very low

DM Roberts et al. *Transplantation* 2012;94: 775

Rituximab Treatment of Acute Cellular Rejection with B-Cell Infiltrates

- Rituximab in acute cellular tubulointerstitial rejection with B-cell infiltrates (RIACT).
- Randomized, double-blind, placebo-controlled, parallel group Phase III study.
- Addition to standard treatment with steroids
- Endpoint: 1-year kidney function
- N=180

L Schiffer et al. *Trials* 2012; 13:199

Ongoing Phase II Bortezomib Trials

- Prevention of AMR in sensitized patients
- Treatment of late AMR

Ongoing Phase II Eculizumab Trials

- Prevention of AMR in sensitized patients
- Prevention of AMR in XM(+) patients
- Treatment of acute AMR
- Treatment of chronic AMR
- World's most expensive drug?
  (Matthew Herper, Forbes, Feb. 22, 2010)

Promising Pipeline?

Tofacitinib: higher rate of PTLD versus CsA

Sotrastaurin: more rejection versus tacrolimus

Alefacept: more rejection versus tacrolimus

Rituximab: phase III induction & AMR treatment trials

Bortezomib: phase II induction & AMR treatment trials

Eculizumab: phase II induction & AMR treatment trials

New Immunosuppression Horizons

- "Golden Era" of RCTs
- KDIGO Guideline 2009
- Current Clinical Practice
- Recent Randomized Trials
- New Drug Development