New Developments in Desensitization Protocols: Is There a Standard of Care?

Robert A. Montgomery, M.D., D.Phil.
Professor of Surgery
Director of the NYU Langone Transplant Institute

Disclosures:

Served on Advisory Boards for Genentech Scientific/ROCHE, True North/iPierian, Alexion, Novartis, and Hansa Medical

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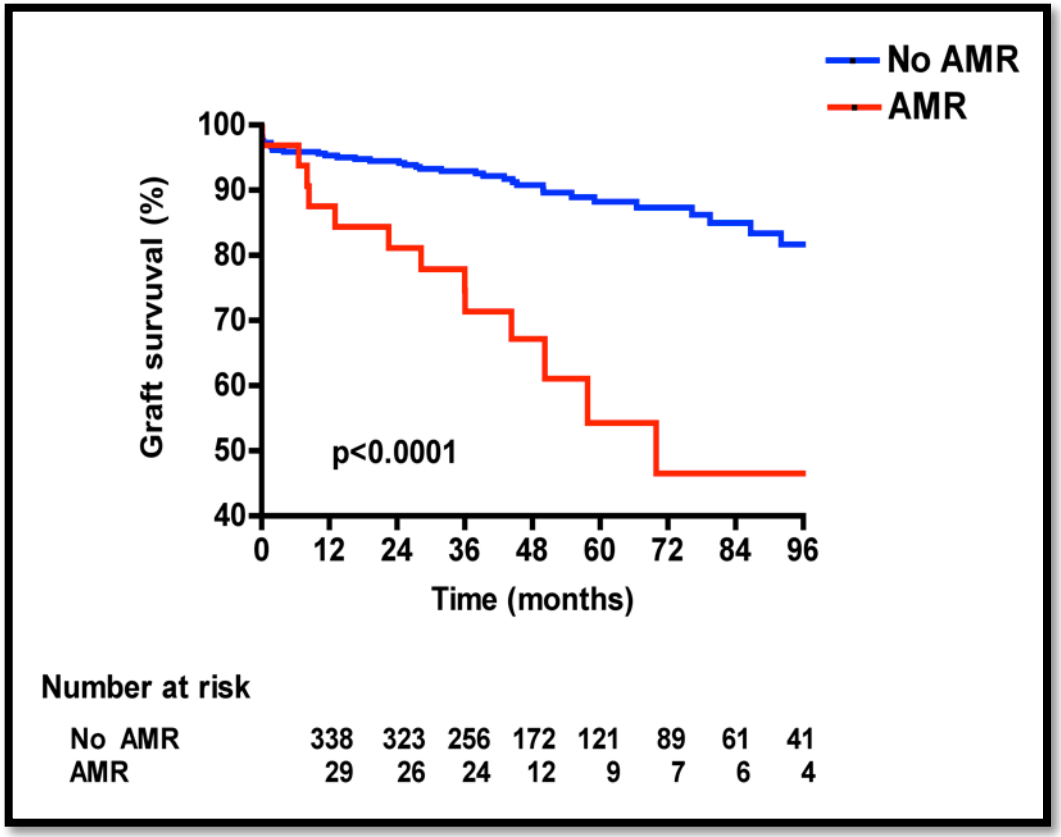
Involved in clinical trial design for some of the off label drugs I will be discussing:

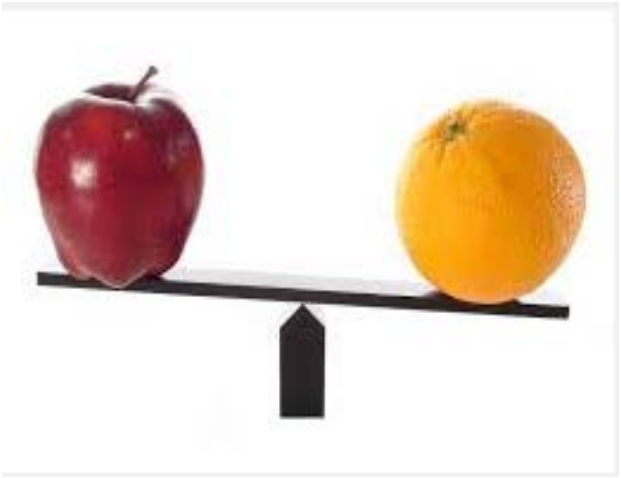
anti-CD20
IdeS
C5 inhibitor

AMR Is Associated With A Poor Outcome[1]



[1]Lefaucheur C et al. *J Am Soc Nephrol*. 2010.21:1398-1406.

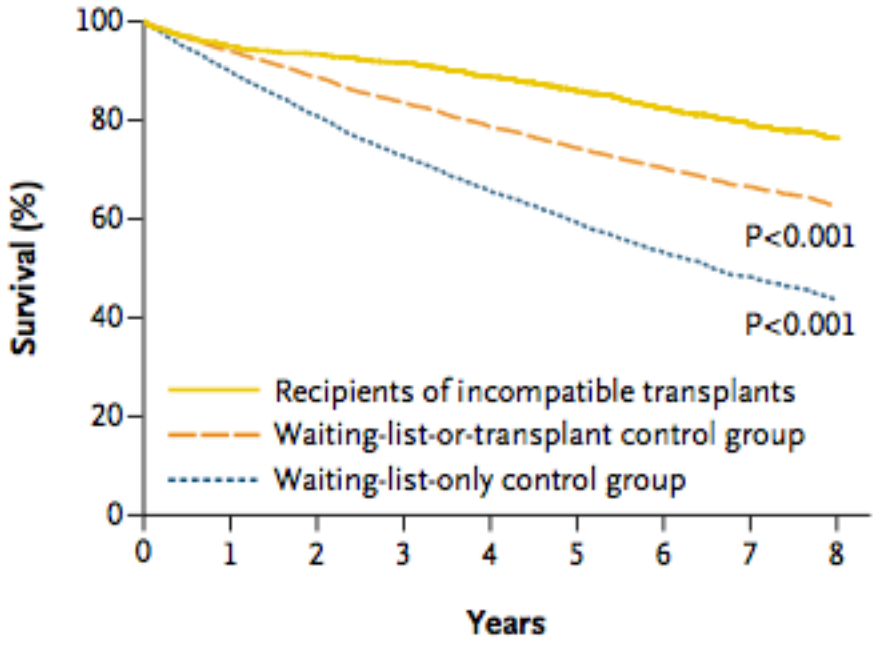
Compare Apples To Apples



- Outcomes of desensitization protocols need to be compared to options that are actually available to the patient

- For a patient with a CPRA of 100% receiving a compatible kidney has not been a realistic option and this should not be the reference intervention

Survival Advantage of Desensitization Over Remaining on the Waitlist[1]



No. at Risk					
Recipients of incompatible transplants	1025	958	832	584	327
Waiting-list-or-transplant control group	5125	4546	3673	2493	1414
Waiting-list-only control group	5125	4141	3024	1810	916

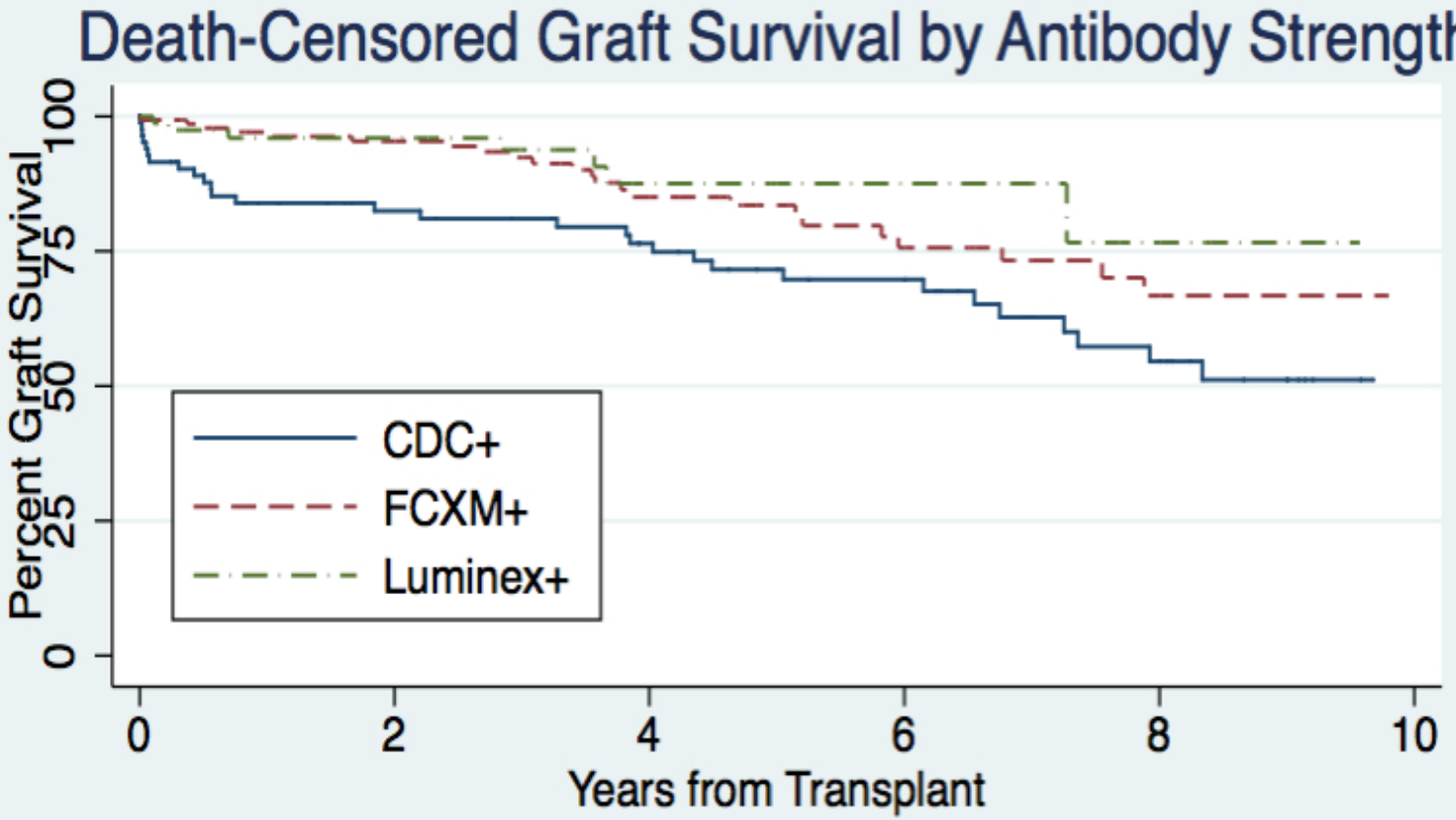
Orandi et al. N Engl J Med. 2016 Mar 10;374(10):940-50.

DSA Fate By Specificity After Plasmapheresis[1]

Specific	Eliminated	Persistent
cI	74%	26%
cII (DR, DQ)	56%	44%
DR51, 52, 53	20%	80%
Isoagglutinins	0%	100%

[1]Zachary, et al. Transplantation. 2003 Nov 27;76(10):1519-25.

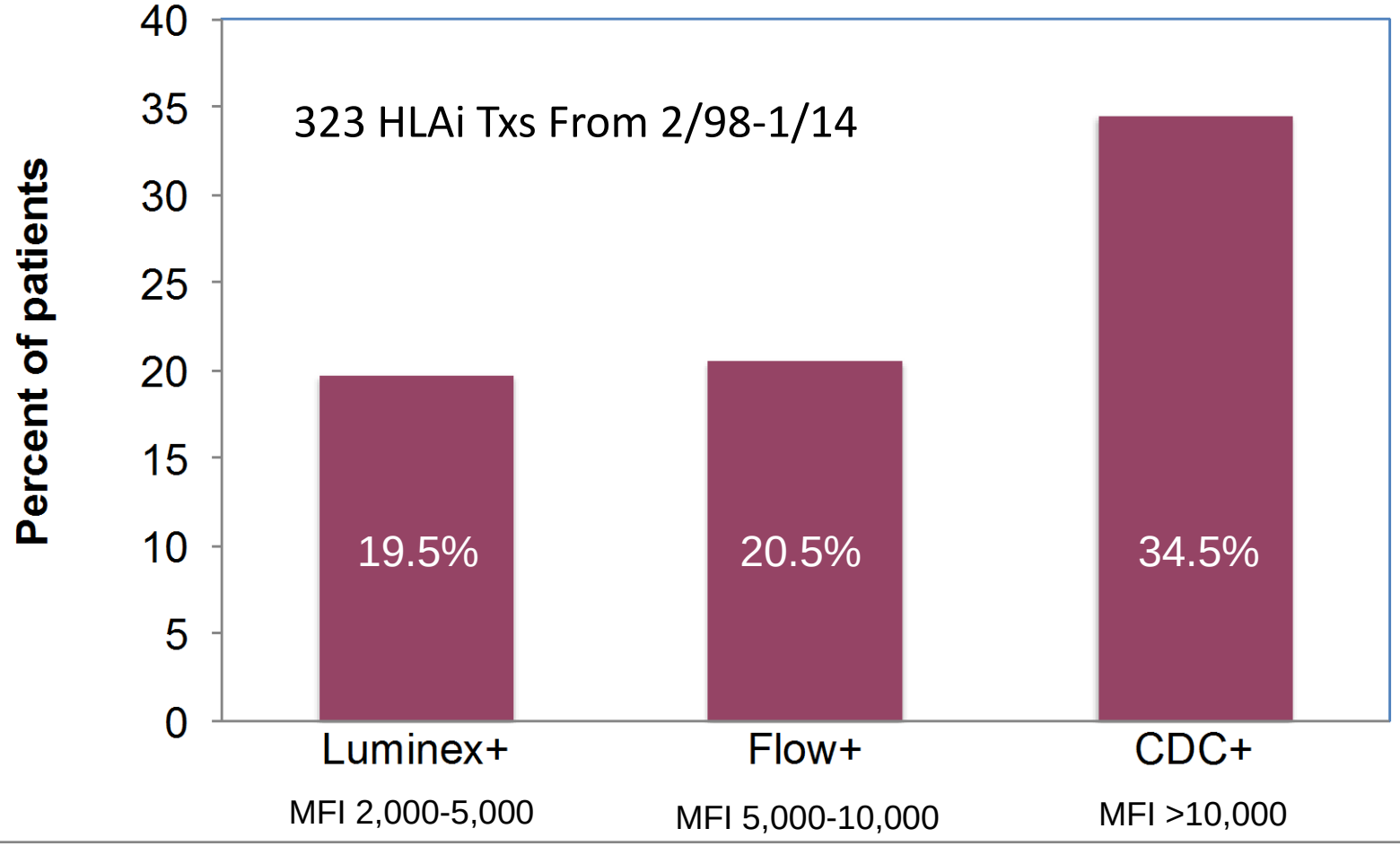
Graft survival Is Related To DSA Strength



Number at risk

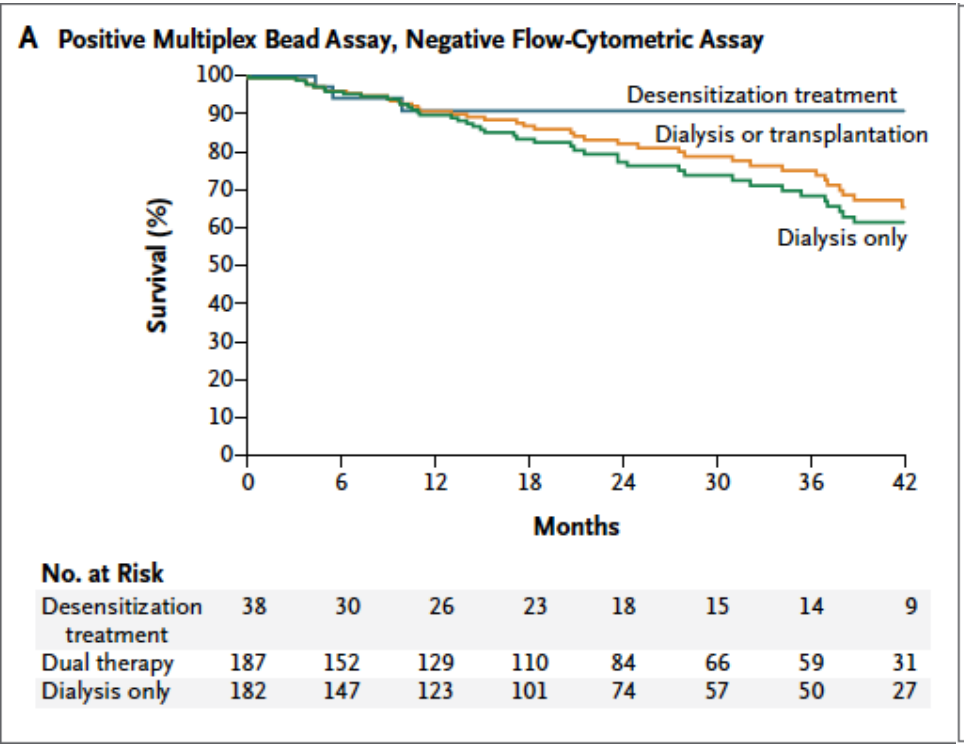
CDC+	83	64	57	54	48	42	37	24	20	14	5
FCXM+	146	121	105	87	64	49	37	27	20	14	12
Luminex+	81	61	55	41	27	22	13	11	5	1	0

Risk Of AMR In Desensitized Patients By HLA DSA Strength[1]

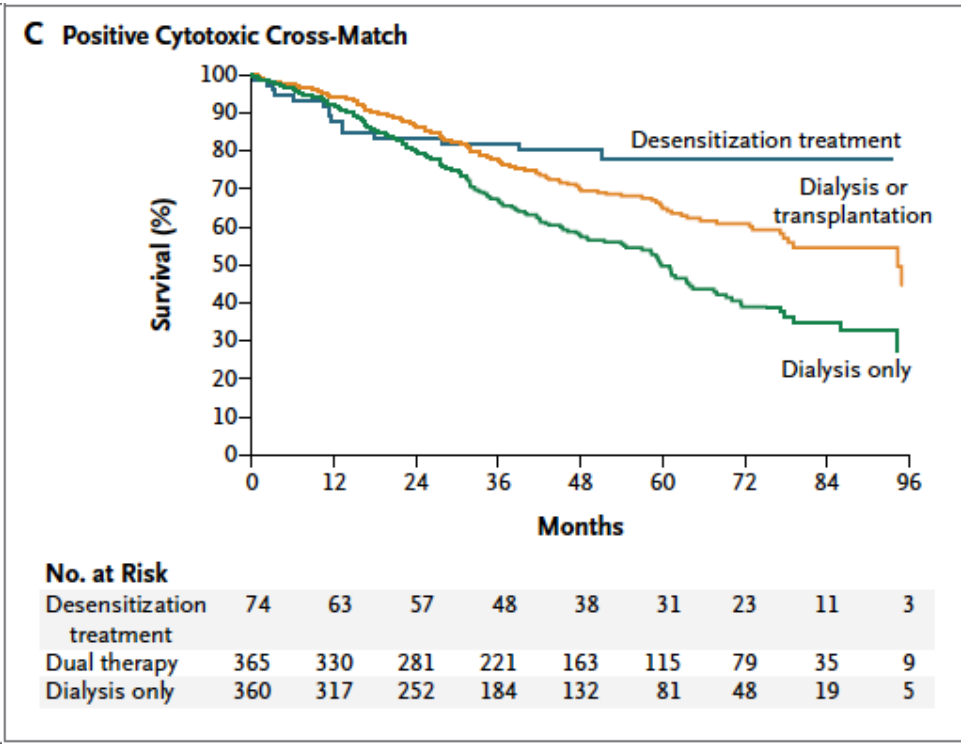


[1]Montgomery RA et al. unpublished.

Marked Survival Advantage of Desensitization vs. Other Available Options Even At CDC+ Strength[1]



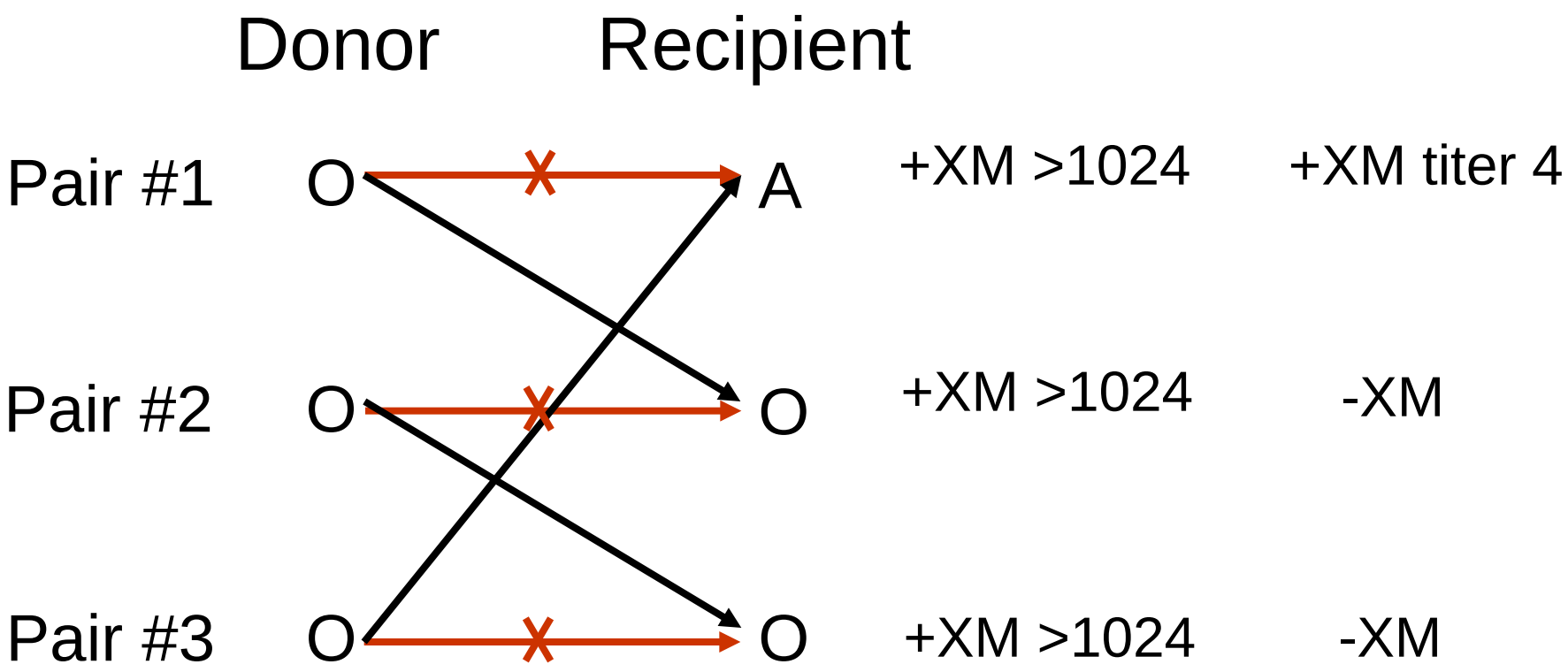
No. at Risk								
Desensitization treatment	38	30	26	23	18	15	14	9
Dual therapy	187	152	129	110	84	66	59	31
Dialysis only	182	147	123	101	74	57	50	27



No. at Risk									
Desensitization treatment	74	63	57	48	38	31	23	11	3
Dual therapy	365	330	281	221	163	115	79	35	9
Dialysis only	360	317	252	184	132	81	48	19	5

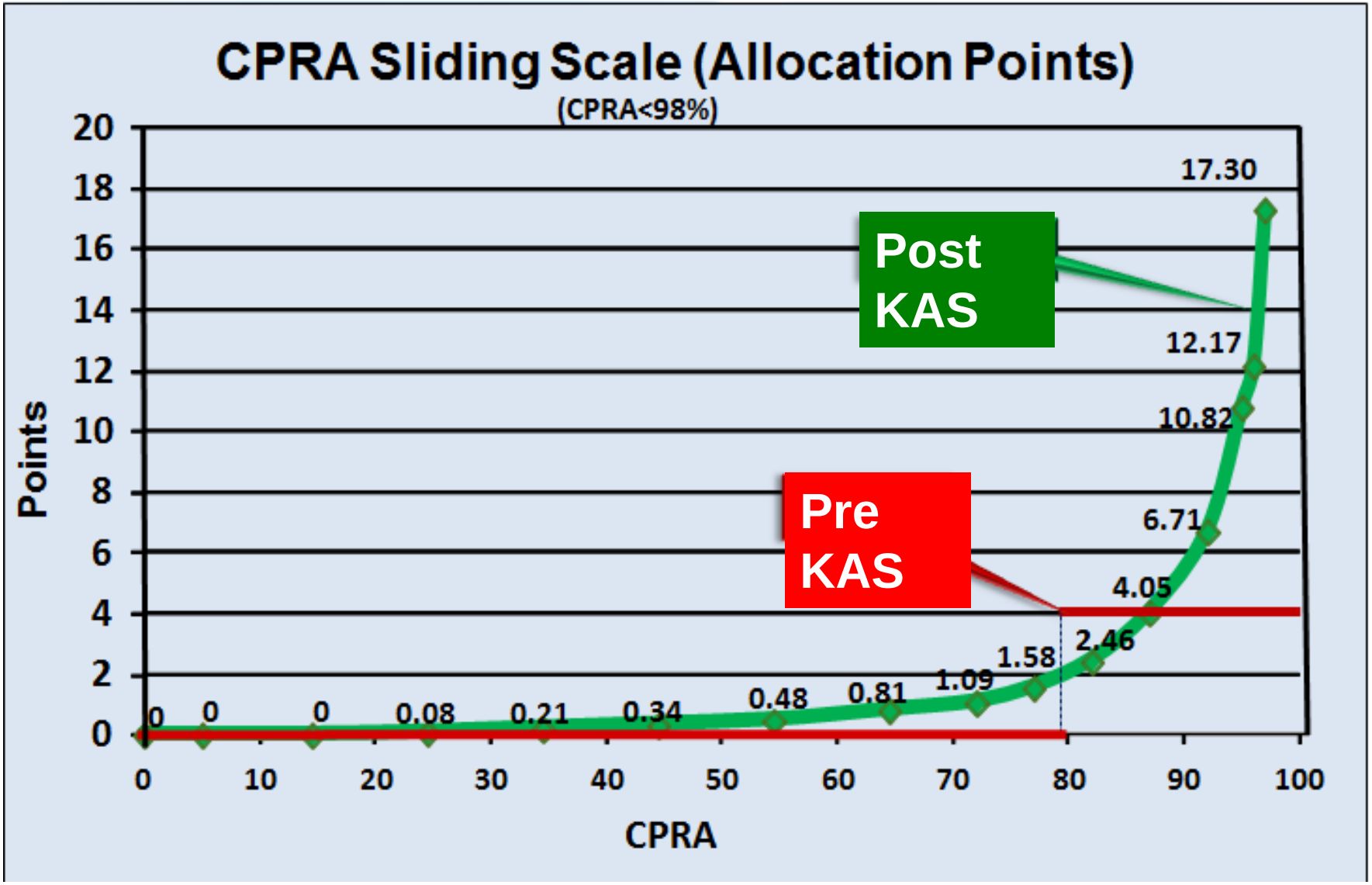
[1]Montgomery et al., N ENGL J MED 365;4 NEJM.ORG JULY 28, 2011

Combining Paired Donation With Desensitization

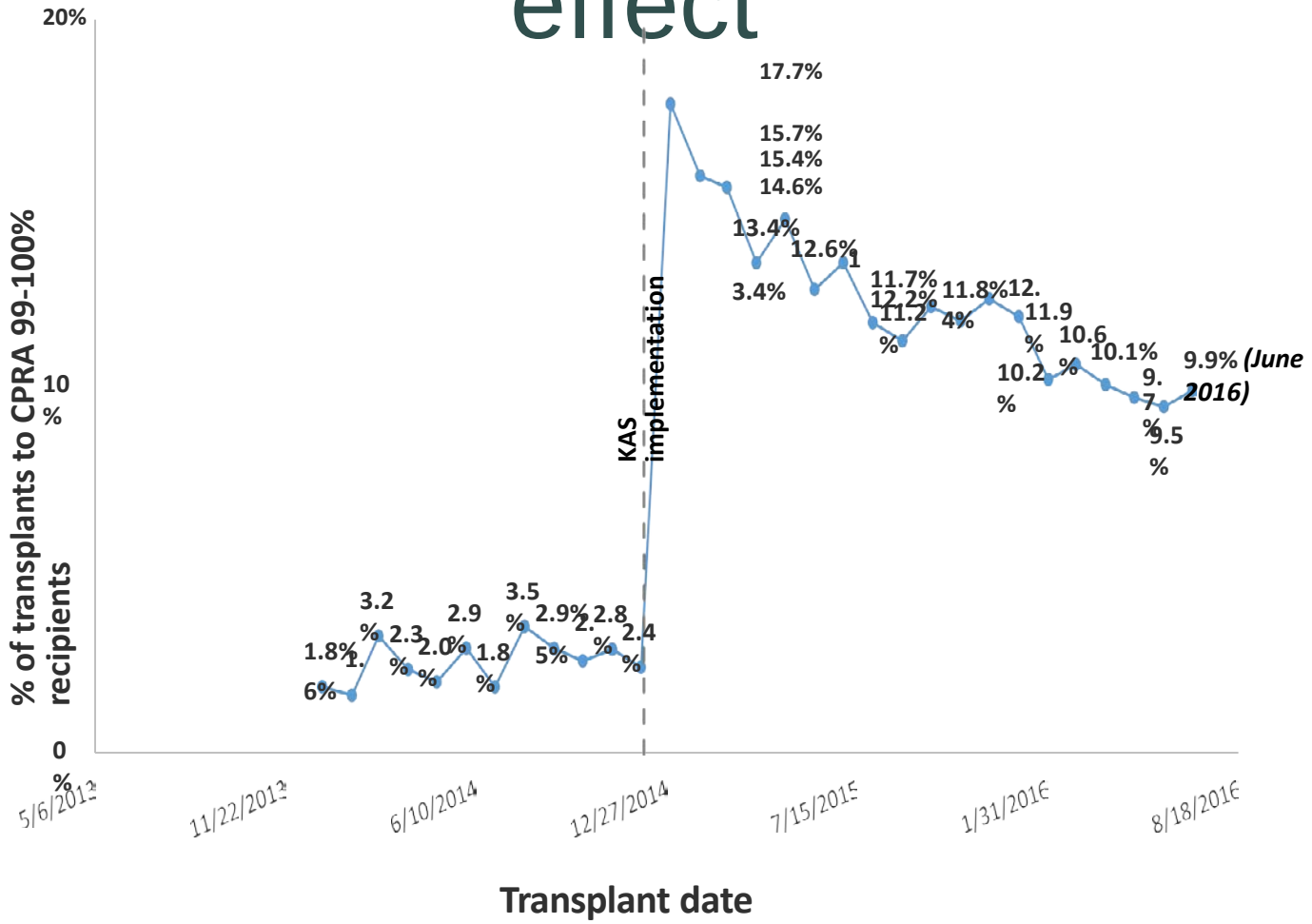


Montgomery et al. *JAMA*. 2005; 294:1655.

Point Changes: Sensitization



CPRA 99-100% recipient "≈2 yrs bolus effect"



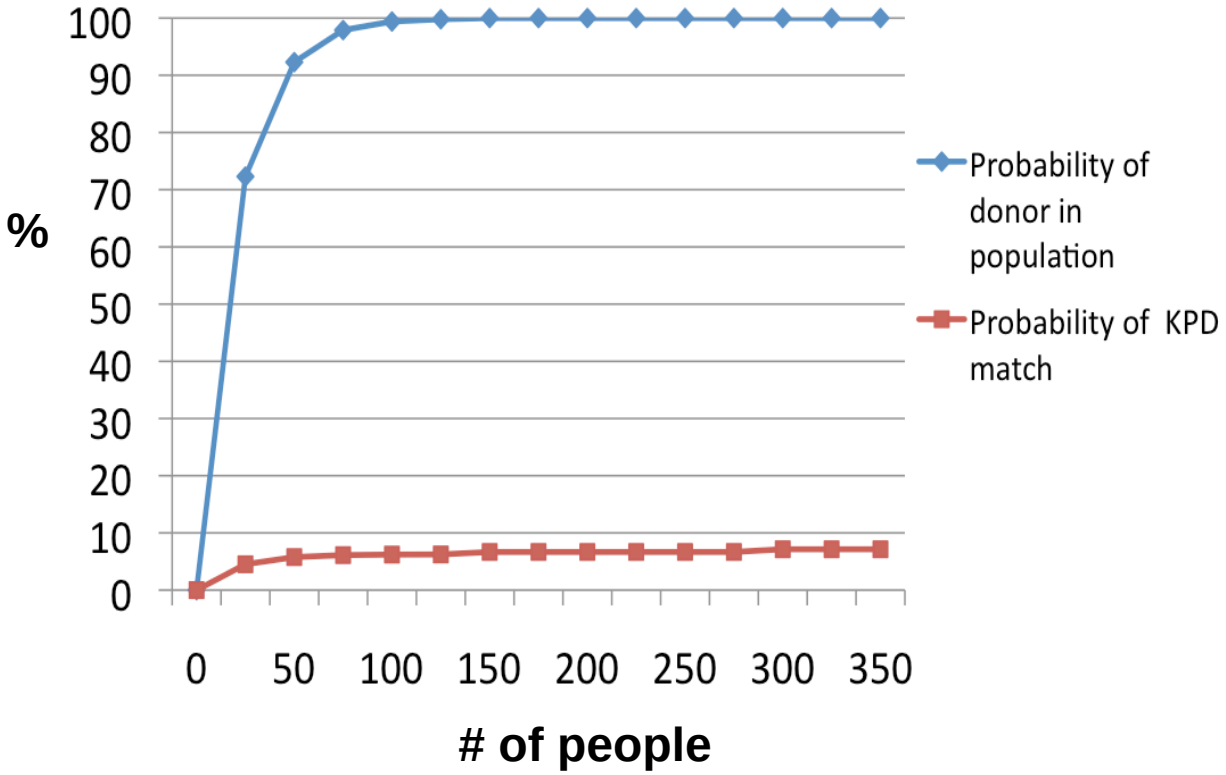
Transplants to CPRA 99-100% rose sharply after KAS; tapered to 10%

SRTR

KAS Priority For Highly Sensitized Candidates: Hopkins Data

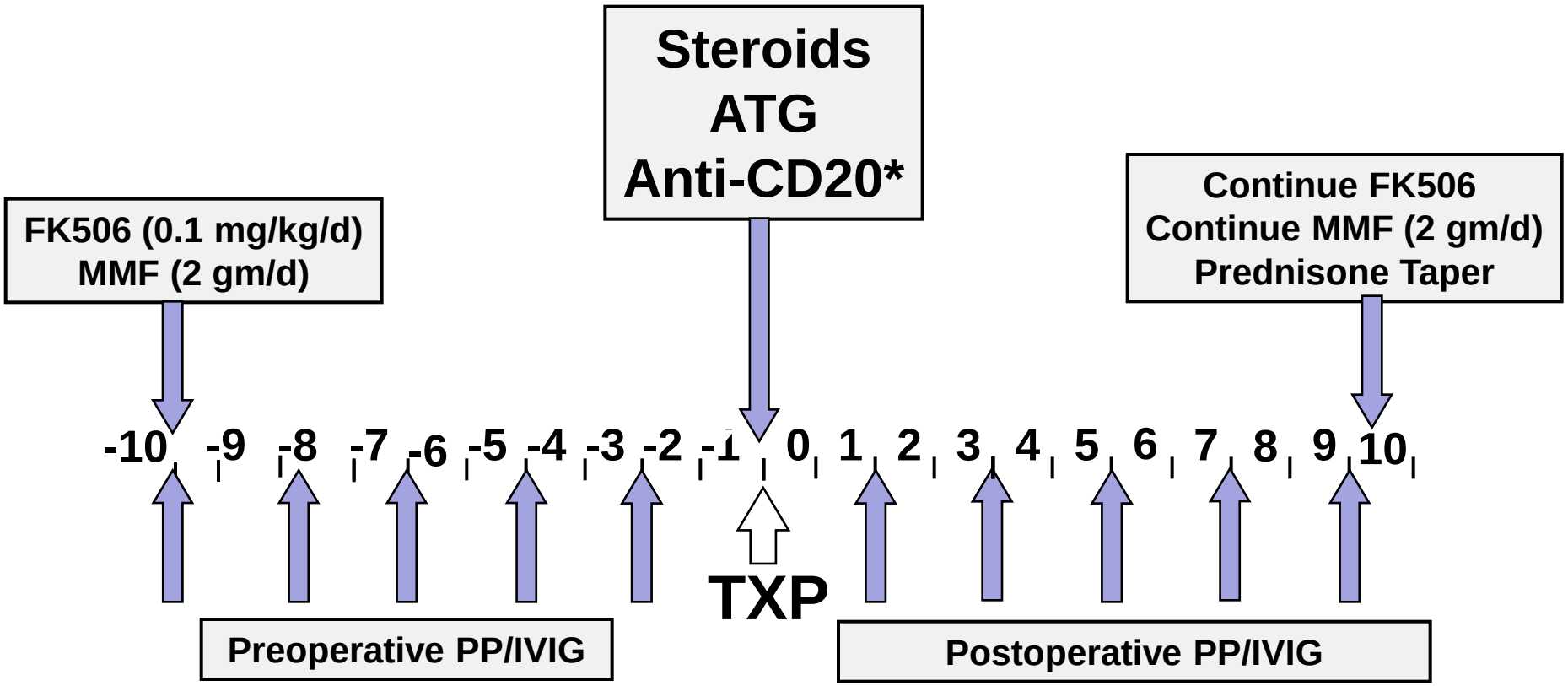
- Current Waiting list (active & inactive): 1338 patients
- CPRA 98-100%: 164 candidates (12%)
- Since new KAS: CPRA ≥ 98%
  - DDRT 66 patients transplanted
  - 64/66 of them had CPRA 100%
  - LDRT HLA incompatible 25 patients (normally > 50)

Competition For The Same Rare Genotypes Results In A Low KPD Match Rate[1]



[1]Montgomery/Jackson. Curr Opin Organ Transplant. 2011. 16(4):439-43.

Plasmapheresis Based SOC Desensitization for HLAi LD Recipients [1,2]



Goal is a (–) Cyto XM

Goal is a (–) Flow XM

*For repeat mismatches and CDC+XM

1. Montgomery RA. *Transplantation* 2000:70:887.
2. Montgomery RA. *Am J Transplant*. 2010;10:449.

Does Rituximab Prevent An Anamnestic Response[1]

Post-Transplant Antibody Production to Antigens With Elevated B-Cell Frequencies[a]

Made Antibody to Tetramer Antigen[b]	Treated With Rituximab		
	Yes	No	
Yes	0	13	$X^2_1 = 16.2$ $P = .00006$
No	10	3	

- Tetramers used to determine the frequencies of B cells with HLA specificities that are not producing soluble antibody
- Tetramers are available only for a limited number of HLA molecules

[a] There was not detectable antibody to the tested tetramer antigen prior to transplantation. [b] Made antibody to the tetramer antigen after transplantation.

1. Zachary AA et al. *Transplantation*. 2013;95:701-704.

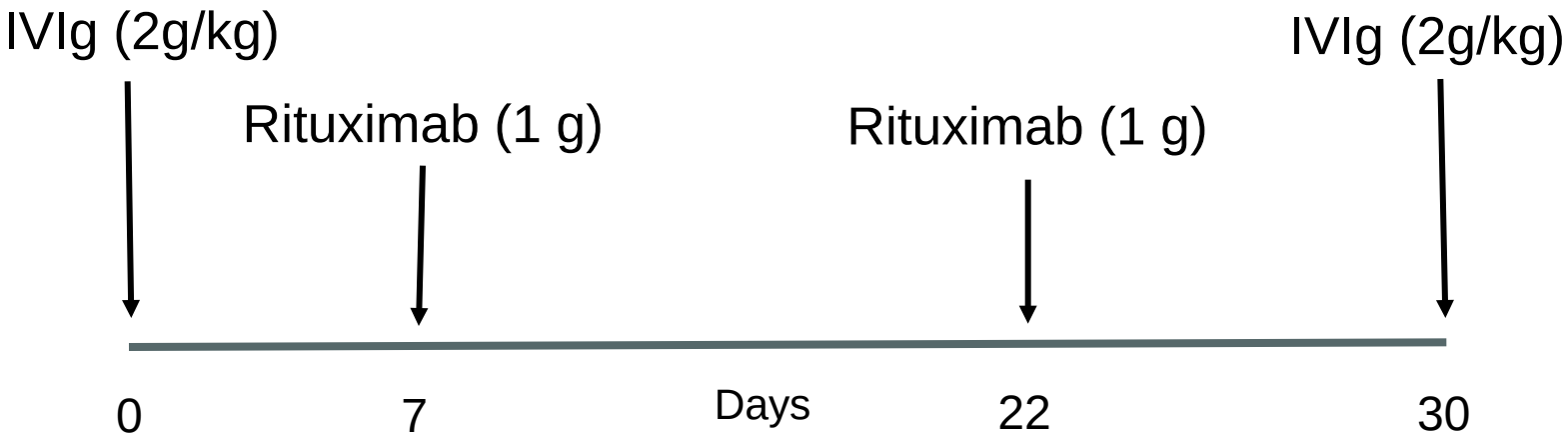
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

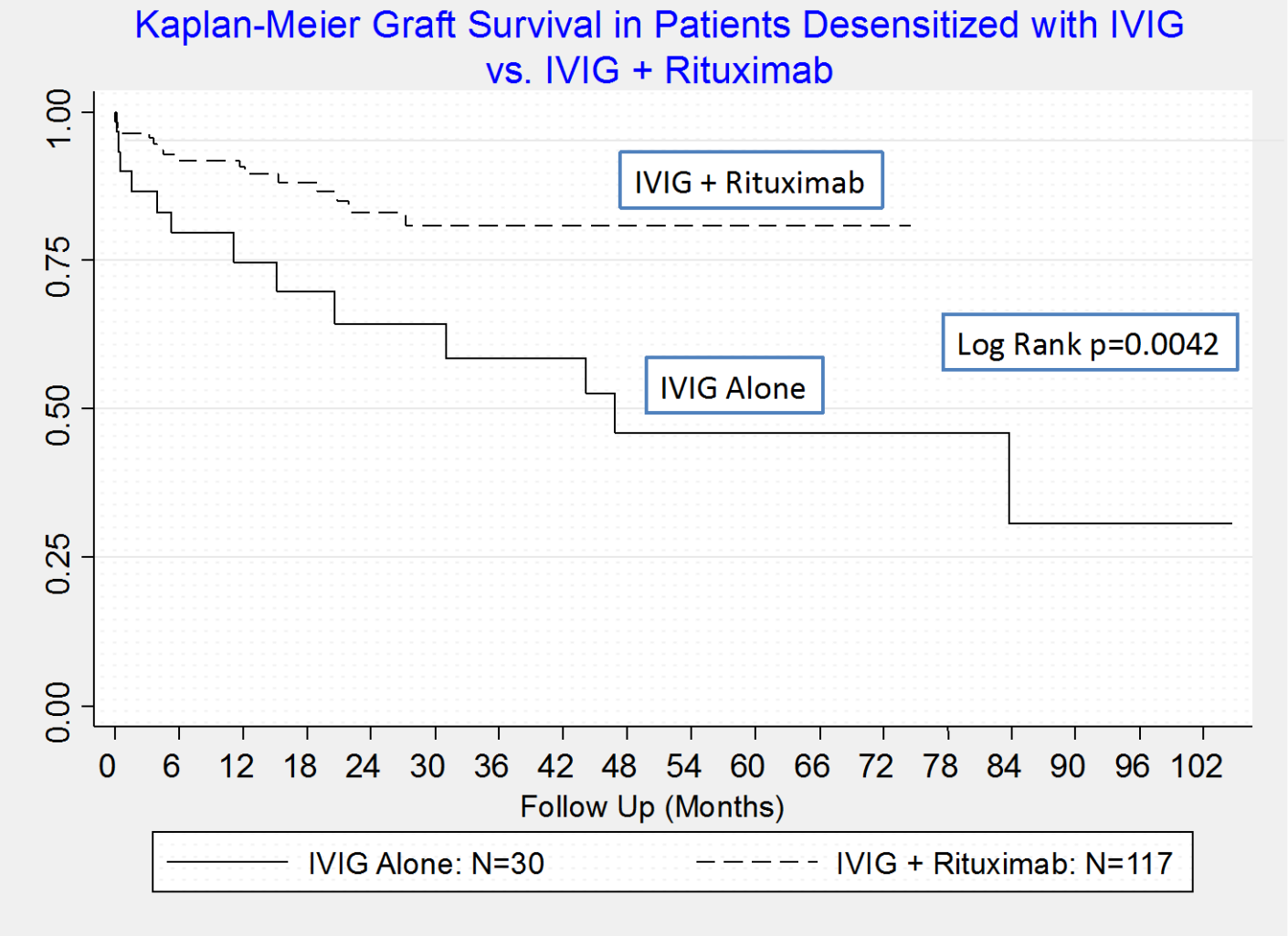
Rituximab and Intravenous Immune Globulin for Desensitization during Renal Transplantation

Ashley A. Vo, Pharm.D., Marina Lukovsky, Pharm.D., Mieko Toyoda, Ph.D., Jennifer Wang, M.D., Nancy L. Reinsmoen, Ph.D., Chih-Hung Lai, Ph.D., Alice Peng, M.D., Rafael Villicana, M.D., and Stanley C. Jordan, M.D.

80% Transplant rate and 94% graft survival



Outcomes of IVIg Desensitization With and Without Anti-CD20[1]



Vo et al. ATC 2013 Abstract #841

Courtesy of S. Jordan

Therapies and Intervention For HLA DSA

The Tackle Box

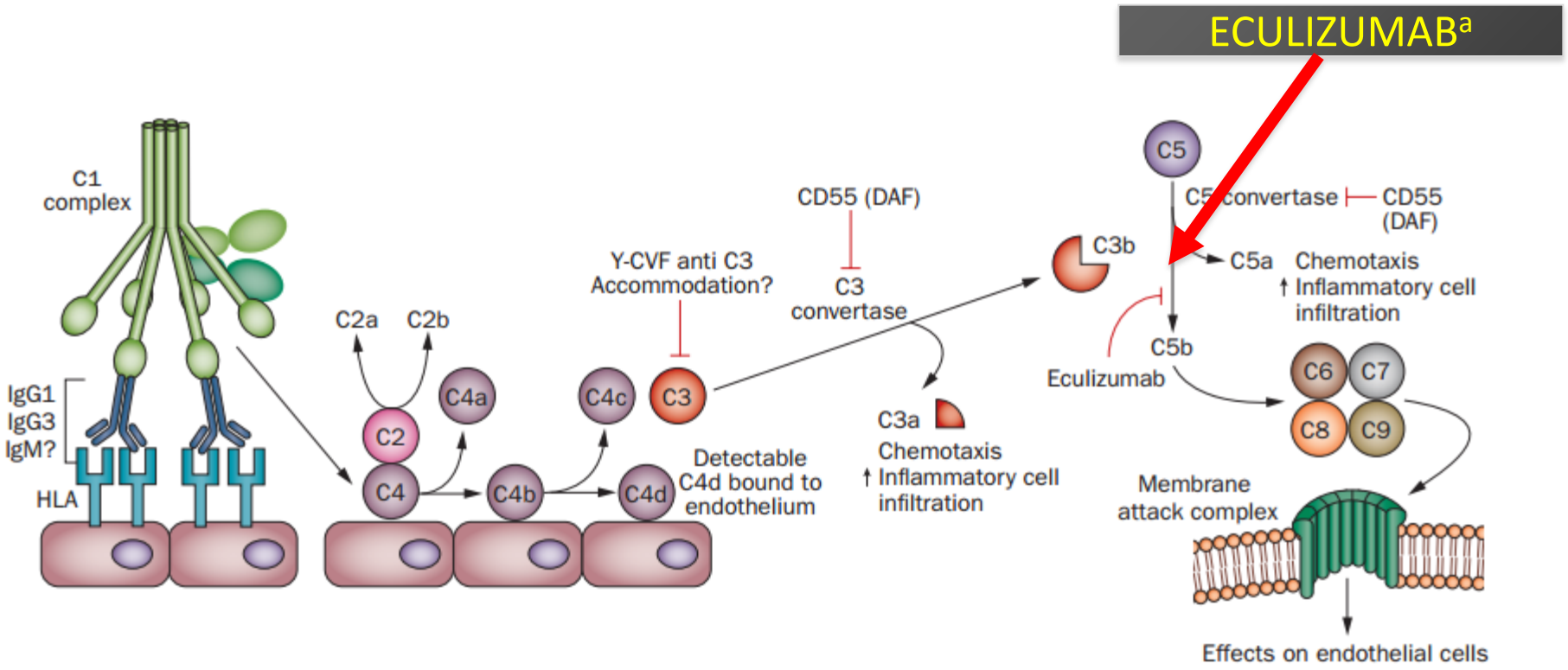
Standard of Care (SOC)

- Plasmapheresis
- Immunoabsorption
- IVIg (high or low dose)
- Steroids or ATG
- [Rituximab]
- Splenectomy

Add-ons to SOC

- Anti-CD20
- Complement Inhibitors (eculizumab and C1INH)
- Proteosomal Inhibitors
- Tocilizumab (anti-IL-6R)
- IdeS
- Splenic Irradiation

Classical Complement Pathway in Acute AMR in Sensitized KTRs[1]



[a] FDA approved for PNH and aHUS.

AMR, antibody-mediated rejection; DAF, decay-accelerating factor; DSAs, donor-specific antibodies, HLA, human leukocyte antigen; Y-CVF, Yunnan-cobra venom factor..

[1]Stegall MD et al. *Nat Rev Nephrol.* 2012;8:670–678.

Positive Crossmatch Kidney Transplant Recipients Treated With Eculizumab: Outcomes Beyond 1 Year

L. D. Cornell[1], C. A. Schinstock[2], M. J. Gandhi[3], W. K. Kremers[2] and M. D. Stegall[2,*]

AJT (2015) 5:1293-1302

Decreased ABMR 6.7% vs. 43.8% but no effect on TG at 2 years

Transplant Glomerulopathy in Controls versus Eculizumab			
	3-4 months	1 year	2 years
Eculizumab*	**0%** (0/28)	**26.7%** (8/30)	**45.4%** (10/22)
Control	**9.3%** (4/43)	**39.5%** (15/38)	**63.6%** (21/33)
P-value	**0.15**	**0.31**	**0.27**

*Residual DSA was not removed after the transplant

IdeS characteristics in humans

- IdeS treatment inhibits Fc-mediated activities
  - IgG mediated CDC
  - IgG mediated ADCC
  - IgG mediated phagocytosis
- IdeS only cleaves IgG (not IgM, IgA, IgD or IgE)
- IdeS has selective species specificity (human & rabbit)
- IdeS cleaves all forms of IgG: free, bound to antigen and membrane bound (BCR)
- PK of IdeS
  - Alpha phase (distribution): 5 h
  - Beta phase (elimination): 70 h
- IdeS is immunogenic and not novel to the immune system

IdeS: IgG-degrading enzyme of *Streptococcus pyogenes*

Highly specific for human IgG

$(ab')_2$

Glu-Leu-Leu-Gly236↓Gly-Pro

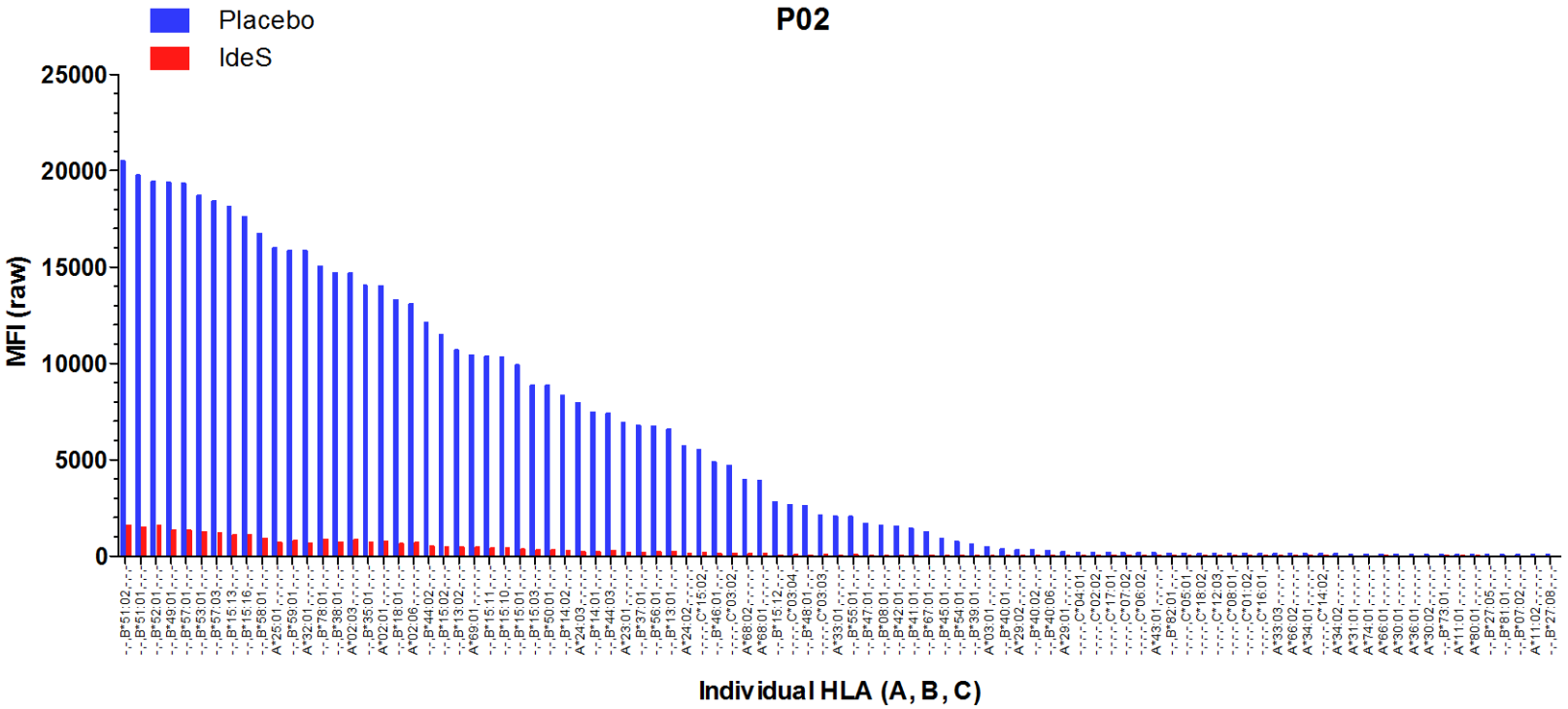
2 hrs

4 hrs

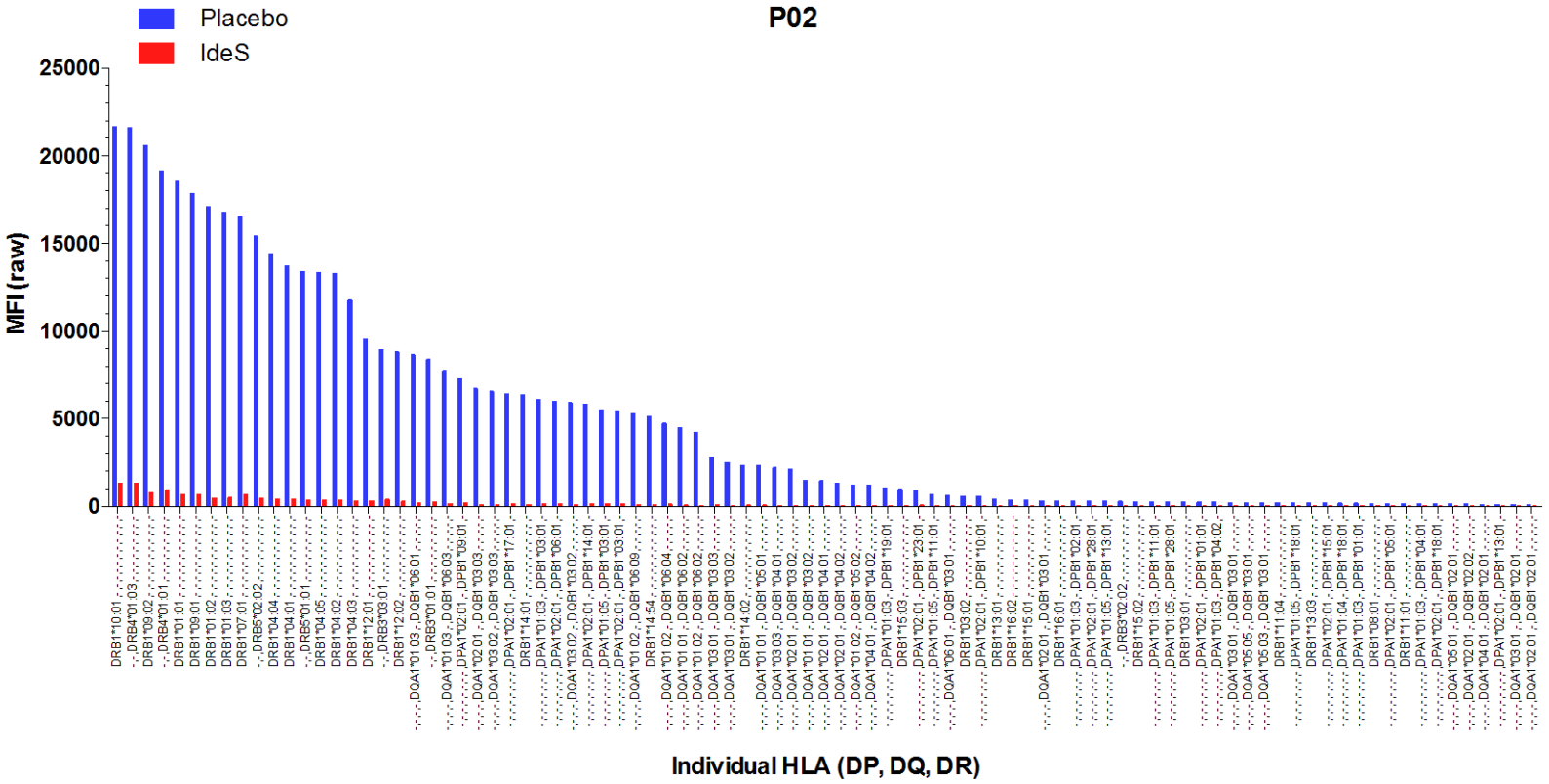
*

***Single-cleaved IgG (scIgG)**

IdeS Effect on Class I Antibody In A Sensitized Patient

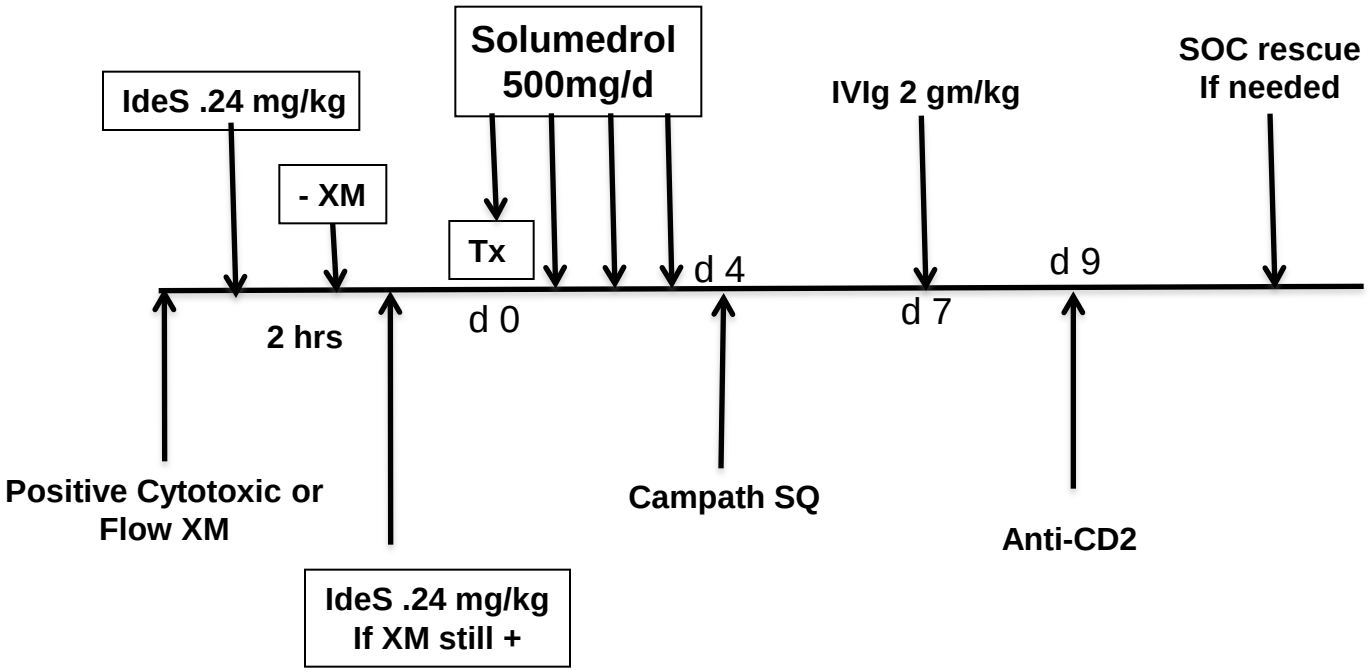


IdeS Effect on Class II Antibody In A Sensitized Patient



Trouble in paradise: IgG rebounds by day 14 and patient cannot be given more than 2 doses because of antibody formation

HLA Incompatible Donor IdeS Protocol



IdeS Desensitization: NYU Patient #2

Pre-IdeS 2 hr Post-IdeS

DONOR FLOW CROSSMATCH	Flow Cytometry	
	Recipient Untreated Serum	
	4/6/2017	4/7/2017
Donor B Cell	Pos (275)	Pos (133)
Donor T Cell	Pos (264)	Pos (110)

45 yo patient with 20 years on HD and 100% CPRA.
We eliminated as unacceptable all HLA ab with MFI < 20,000 and she still had a 100% CPRA. Received an import offer for a 41 yo DBD with a + CDC XM.

Pre-IdeS

RELATION	ABO*	HLA TYPING — Typing results are the most probable serological equivalents for low/intermediate molecular (DNA) testing. NT: Not typed for the HLA locus.																	
		A		B		Bw 4	Bw 6	C		DR B1	DR B1	DR B3	DR B4	DR B5	DQ B1	DQ B1	DP B1	DP B1	DQA A1	DQA A1
SELF	O	2	33	53		+		4		7	8		53		2	7	NT	NT	02	04
DECEASED	O	1	2	27	38	+		9	12	8	13	52			4	6	02:01	03:01	01	04:01
s I & II Ab: 6/2017 0528	Peak MFI Values	24,103	0	23,721	5,985			23,107	21,625	0	749	1,531			321	4,898	* 1517	* 1090	* 4898	* 277
		A serum is scored POSITIVE for an antigen if the MFI value is greater than or equal to 2000.																	

2 hr Post-IdeS

	ABO*	HLA TYPING — Typing results are the most probable serological equivalents for low/intermediate molecular (DNA) testing. NT: Not typed for the HLA locus.																	
		A		B		Bw 4	Bw 6	C		DR B1	DR B1	DR B3	DR B4	DR B5	DQ B1	DQ B1	DP B1	DP B1	DQA A1	DQA A1
	O	2	33	53		+		4		7	8		53		2	7	NT	NT	02	04
	O	1	2	27	38	+		9	12	8	13	52			4	6	02:01	03:01	01	04:01
Peak MFI Values		10,271	0	7,736	662			5,530	4,532	0	3	10			0	530	* 69	* 58	* 530	* 0
		A serum is scored POSITIVE for an antigen if the MFI value is greater than or equal to 2000.																	

48 hrs Post-IdeS

RELATION	ABO*	HLA TYPING — Typing results are the most probable serological equivalents for low/intermediate molecular (DNA) testing. NT: Not typed for the HLA locus.																	
		A		B		Bw 4	Bw 6	C		DR B1	DR B1	DR B3	DR B4	DR B5	DQ B1	DQ B1	DP B1	DP B1	DQA A1	DQA A1
SELF	O	2	33	53		+		4		7	8		53		2	7	NT	NT	02	04
DECEASED	O	1	2	27	38	+		9	12	8	13	52			4	6	02:01	03:01	01	04:01
s I & II Ab: 9/2017 0780	Peak MFI Values	3,318	0	2,358	18			1,127	715	0	0	0			0	32	* 0	* 0	* 32	* 0
		A serum is scored POSITIVE for an antigen if the MFI value is greater than or equal to 2000.																	

5 days Post-IdeS

RELATION	ABO*	HLA TYPING — Typing results are the most probable serological equivalents for low/intermediate molecular (DNA) testing. NT: Not typed for the HLA locus.																	
		A		B		Bw 4	Bw 6	C		DR B1	DR B1	DR B3	DR B4	DR B5	DQ B1	DQ B1	DP B1	DP B1	DQA A1	DQA A1
SELF	O	2	33	53		+		4		7	8		53		2	7	NT	NT	02	04
DECEASED	O	1	2	27	38	+		9	12	8	13	52			4	6	02:01	03:01	01	04:01
s I & II Ab: 0/2017 0903	Peak MFI Values	2,092	0	1,517	0			602	308	0	0	0			0	0	0	0	0	0
		A serum is scored POSITIVE for an antigen if the MFI value is greater than or equal to 2000.																	

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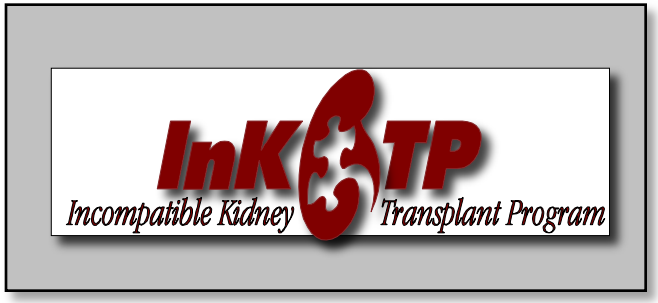

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