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Circulating Antibodies: What, When, Why to Use Desensitization Therapy

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CEOT CUTTING EDGE of **TRANSPLANTATION**

TRANSPLANT SUMMIT 2019

NO SIZE FITS ALL: *Uncovering the Potential of Personalized Transplantation*

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Disclosure

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- Consultant/Independent Contractor: Pfizer, Alnylam, Mallinckrodt Pharmaceuticals, AstraZeneca
- Honoraria: Alnylam, Akcea, Therakos

Learning Objectives

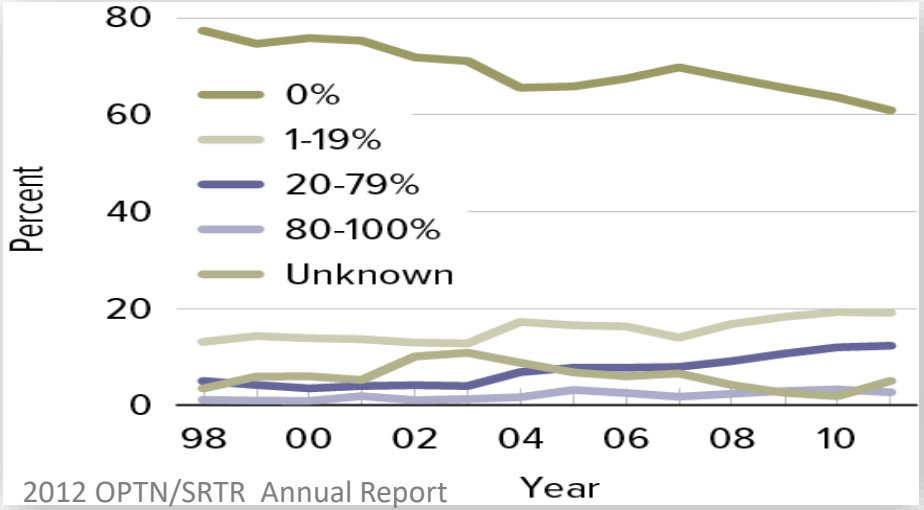
1) Defining the population which should be considered for desensitization therapy in heart transplantation

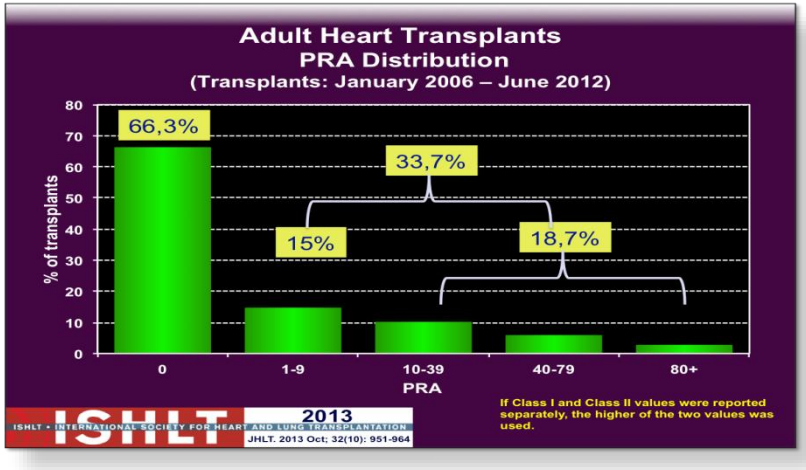
2) Discussing therapeutic options for management of circulating antibodies

3) Appraising efficacy of currently available treatment options

4) Reviewing potentially promising future therapies

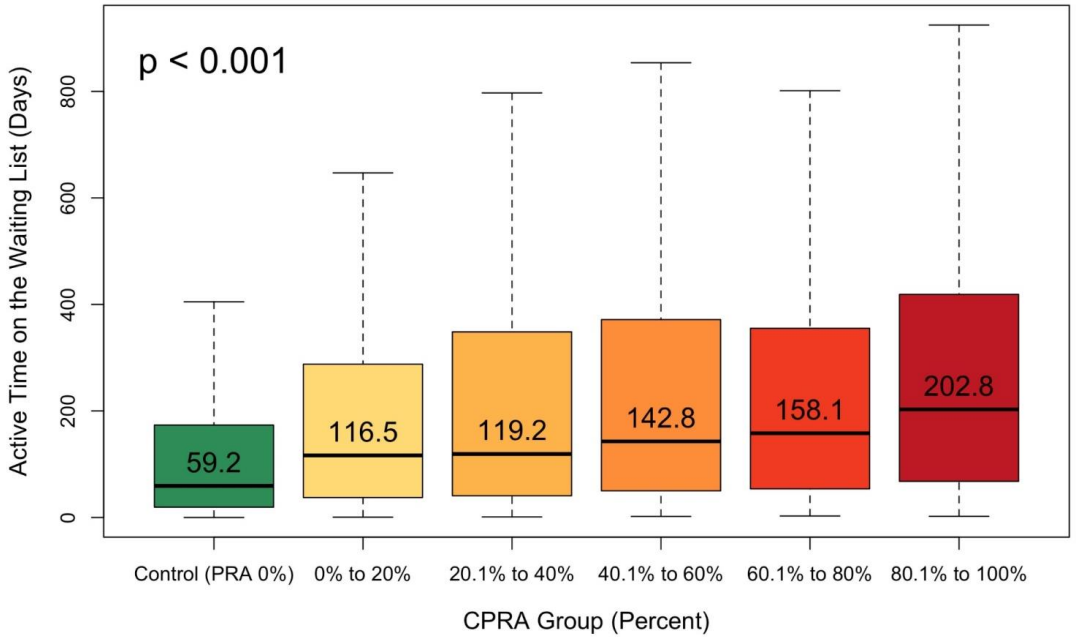
Who Needs Desensitization?





% Patients Awaiting Transplantation by PRA

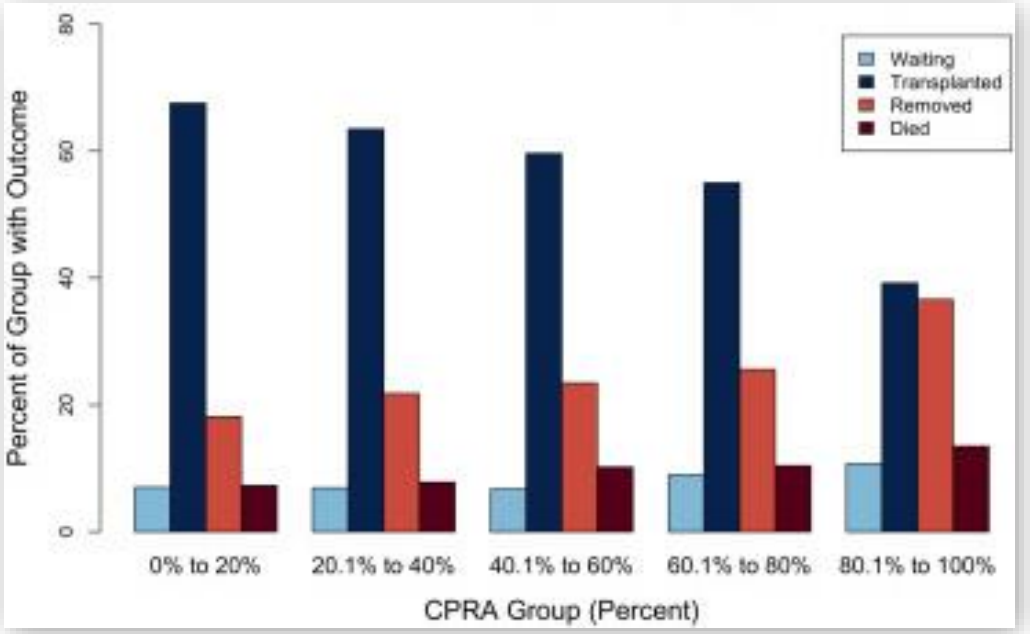
Sensitization Limits the Suitable Donor Pool..
Waiting Time by cPRA Group in Candidates Undergoing Heart Transplant



N=3855
UNOS Registry

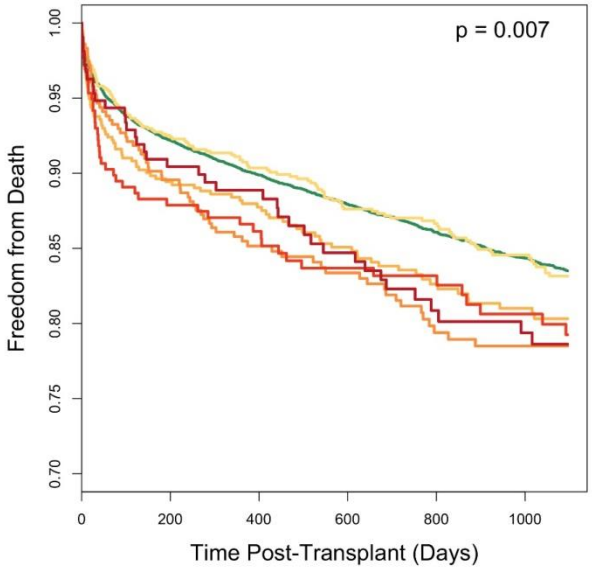
Kransdorf EP, Kittleson MM, Patel JK, Pando MJ, Steidley DE, Kobashigawa JA. JHLT. 2017 Feb 17

Outcomes on the Heart Transplant Waiting List by cPRA Group



Kransdorf EP, Kittleson MM, Patel JK, Pando MJ, Steidley DE, Kobashigawa JA. JHLT. 2017 Feb 17

Post-Transplant Mortality According to Pre-Transplant cPRA



Group	Transplant	Year 1	Year 2	Year 3
Control (PRA 0%)	8468	6997	5729	4582
CPRA 0% to 20%	910	726	528	369
CPRA 20.1% to 40%	518	404	304	203
CPRA 40.1% to 60%	357	281	202	147
CPRA 60.1% to 80%	259	192	144	108
CPRA 80.1% to 100%	214	162	125	95

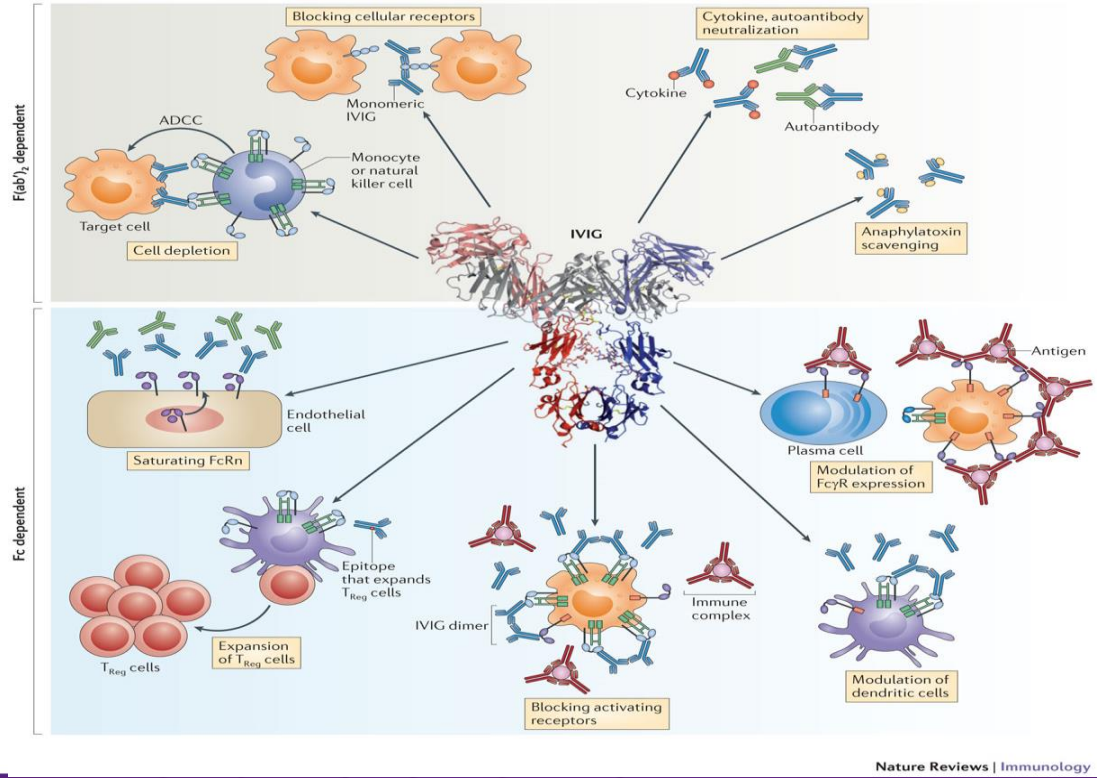
Kransdorf EP, Kittleson MM, Patel JK, Pando MJ, Steidley DE, Kobashigawa JA. JHLT. 2017 Feb 17

How Do We Do It? - Desensitization Therapies

Combined Strategies

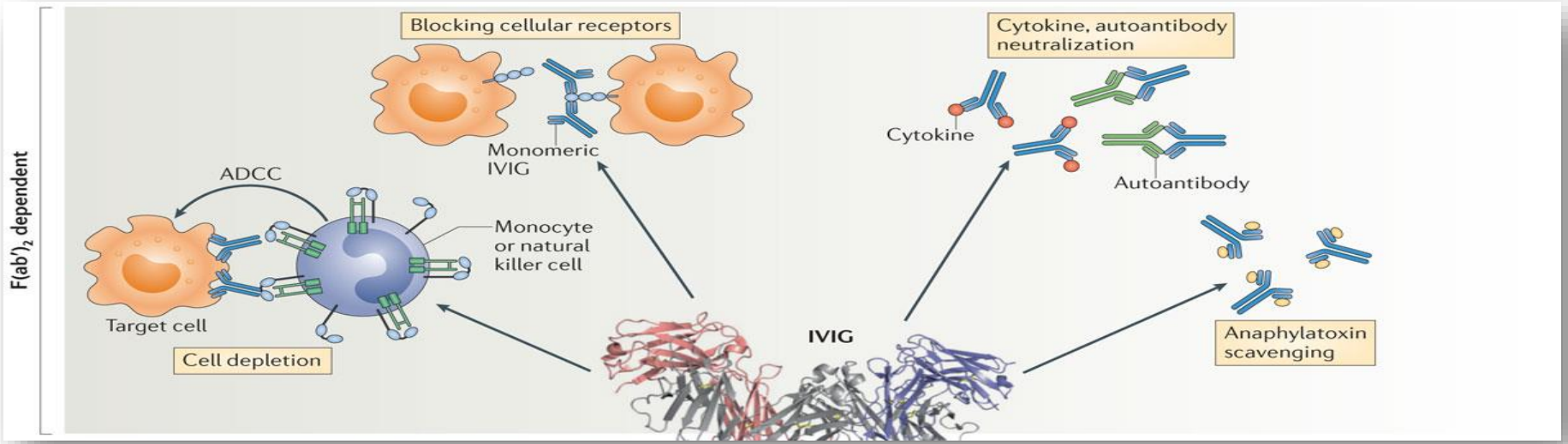
Approaches	Therapies
Antibody removal	Therapeutic Plasma Exchange, Immunoadsorption
To alter antibody production B cell modulation Plasma cell depletion	Rituximab/Obinutuzumab Bortezomib/Carfilzomib
Immunomodulation (Ab inactivation)	IVIG
Complement blockade	Eculizumab

Multimodal Mechanisms of IVIg Activity



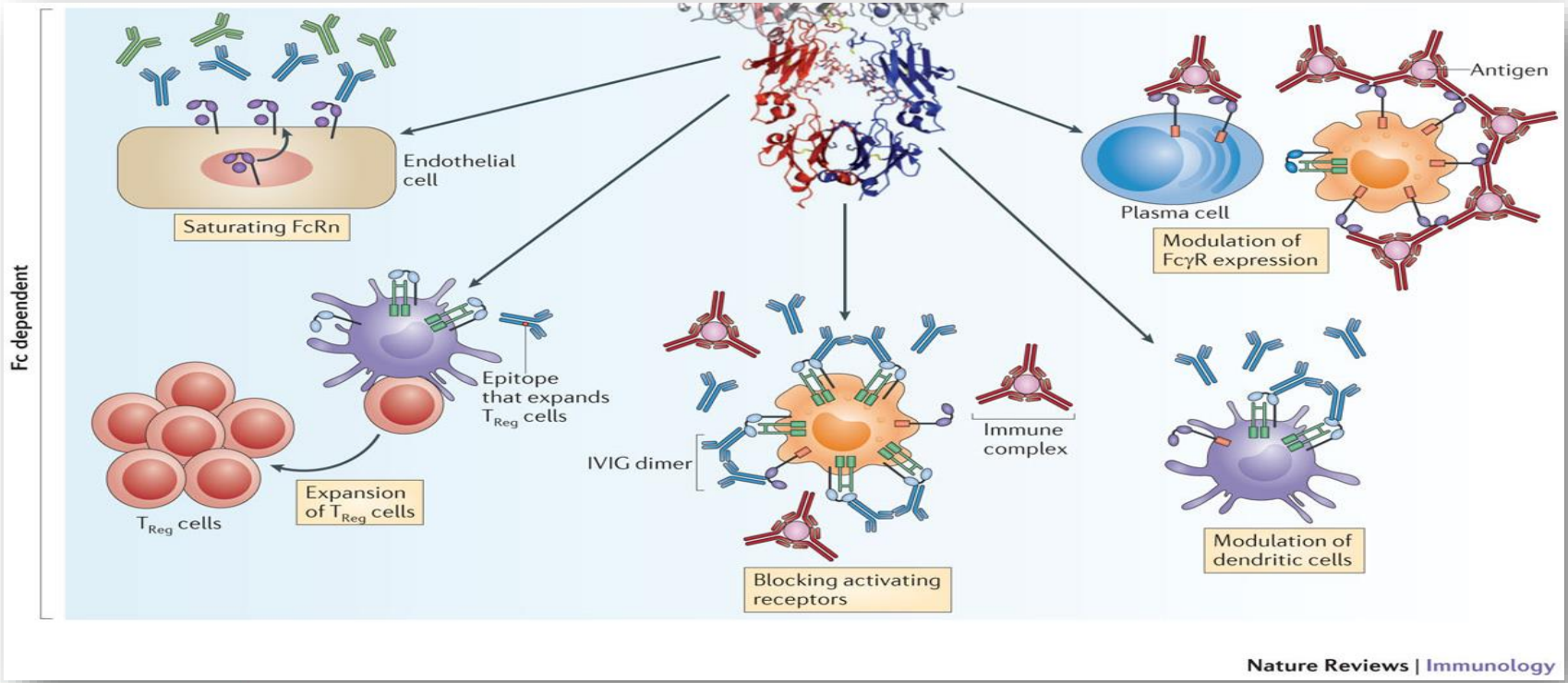
Schwab & Nimmerjahn, Nature Reviews Immunology 13, 176-189 (March 2013)

Mechanism of IVIg Activity - F(ab')$_2$ Dependent Pathway



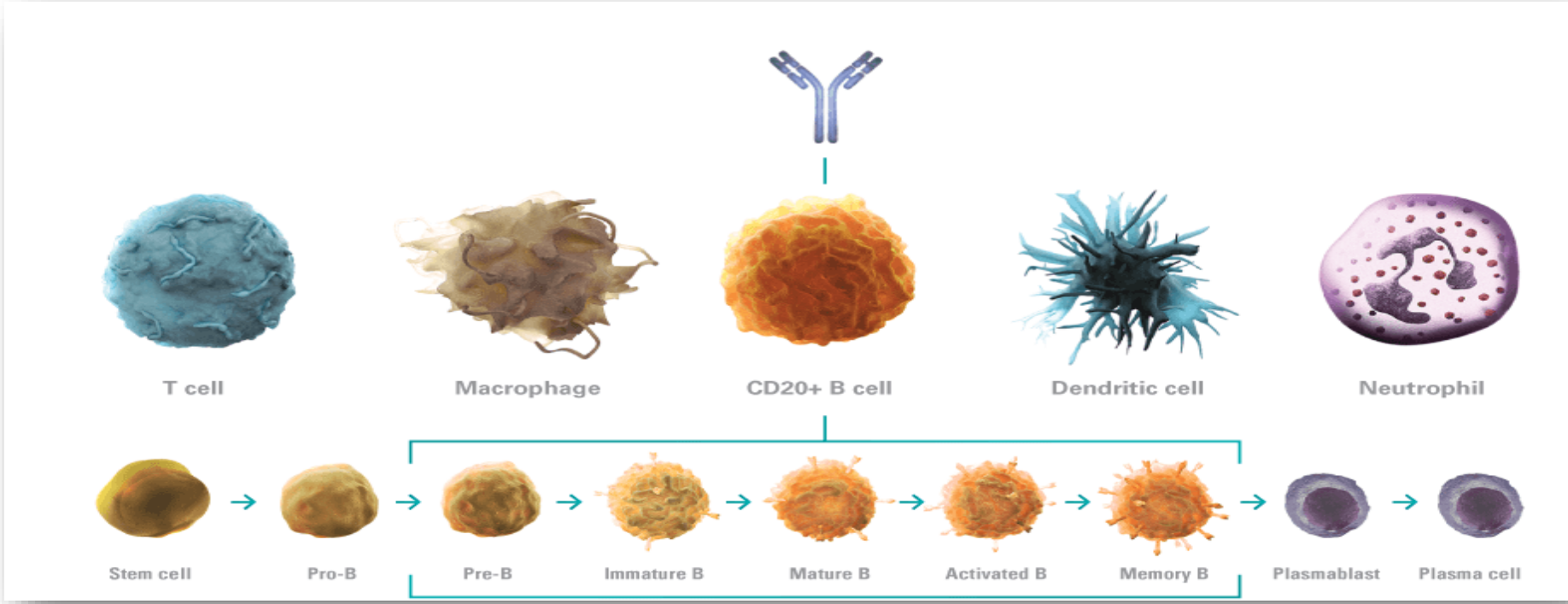
Schwab & Nimmerjahn, Nature Reviews Immunology 13, 176-189 (March 2013)

Mechanism of IVIg Activity - Fc-dependent Pathway

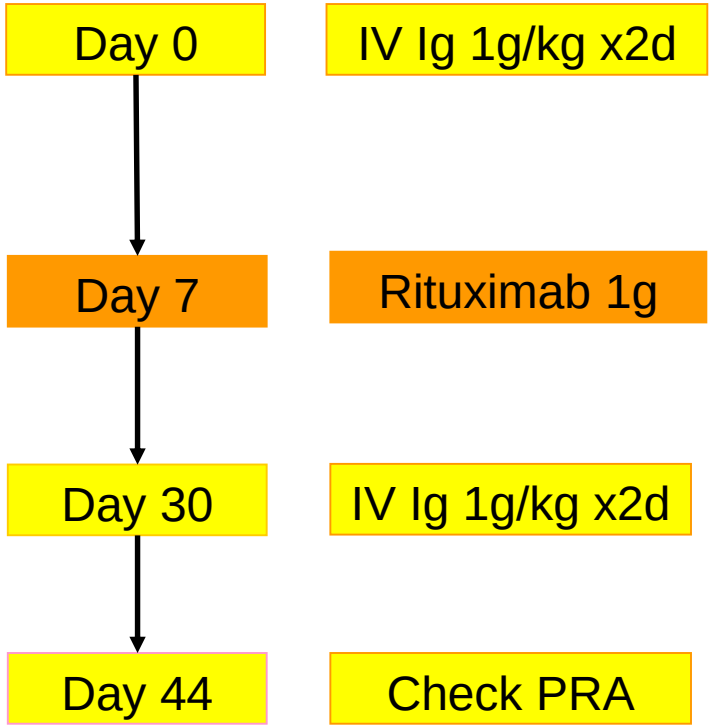


Schwab & Nimmerjahn, Nature Reviews Immunology 13, 176-189 (March 2013)

Rituximab/Obinutuzumab

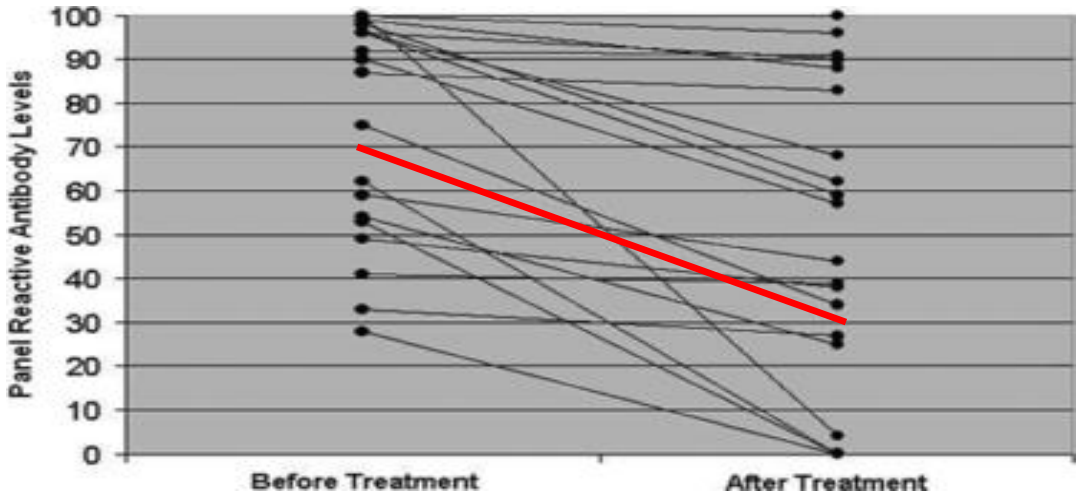


Desensitization Protocol – Rituximab/IVIG



Vo, A., Jordan S. et al NEJM

Desensitization



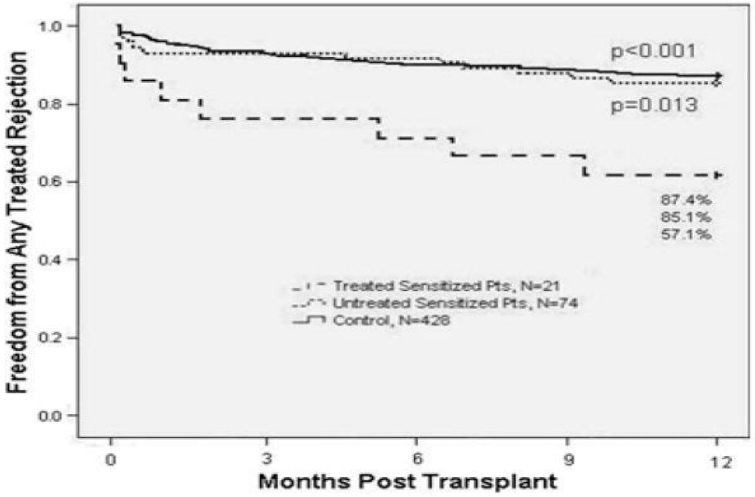
N=21

Individual reductions in mean PRA levels of treated sensitized heart transplant candidates.

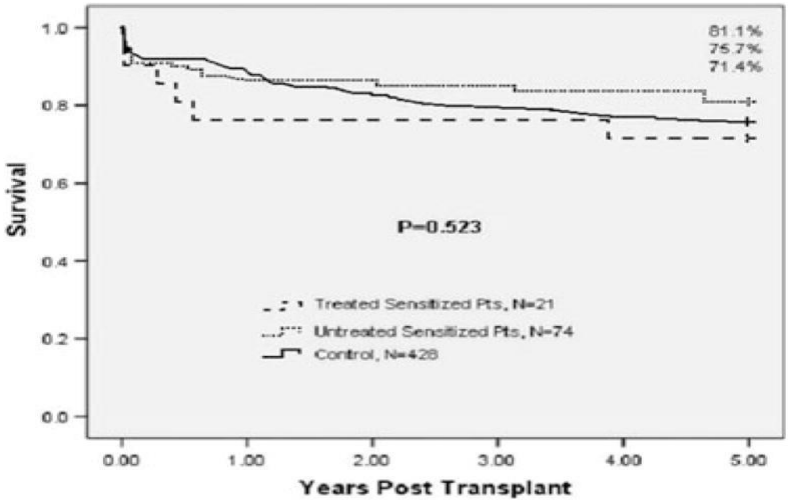
Treatments: plasma exchange, IVIg, rituximab

Kobashigawa, Patel et al: Clin Transplant. 2011 Jan;25(1):E61-7.

Desensitization – Post-transplant Outcomes



1-year Freedom From Any Treated Rejection



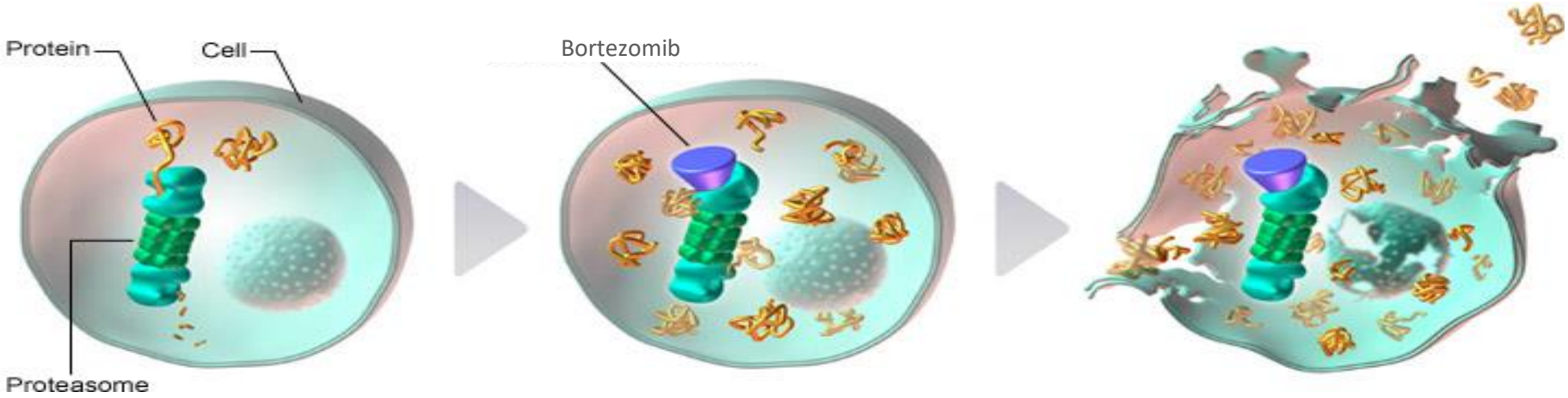
5-year Survival

Treatments: plasma exchange, IVIg, rituximab

Kobashigawa, Patel et al: Clin Transplant. 2011 Jan;25(1):E61-7.

Mechanism - Bortezomib

Proteasome inhibitor active against plasma cells

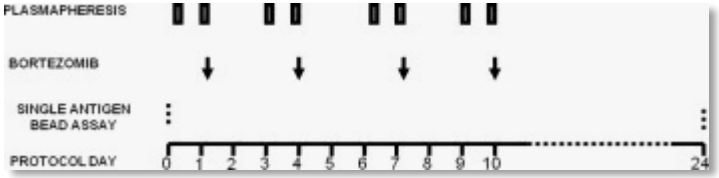


Normal breakdown of proteins

Bortezomib blocks the proteasome, causing an imbalance of proteins in the cells

Protein imbalance can lead to cell death

Refractory Antibodies – Plasmapheresis/bortezomib:



cPRA ≥ 50% after IVIg/ritux protocol

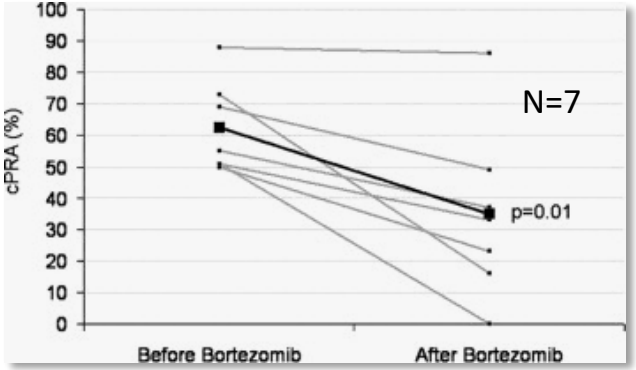
Days 1, 4, 7, 10

Plasmapheresis
Bortezomib 1.3 mg/m²

Day 24

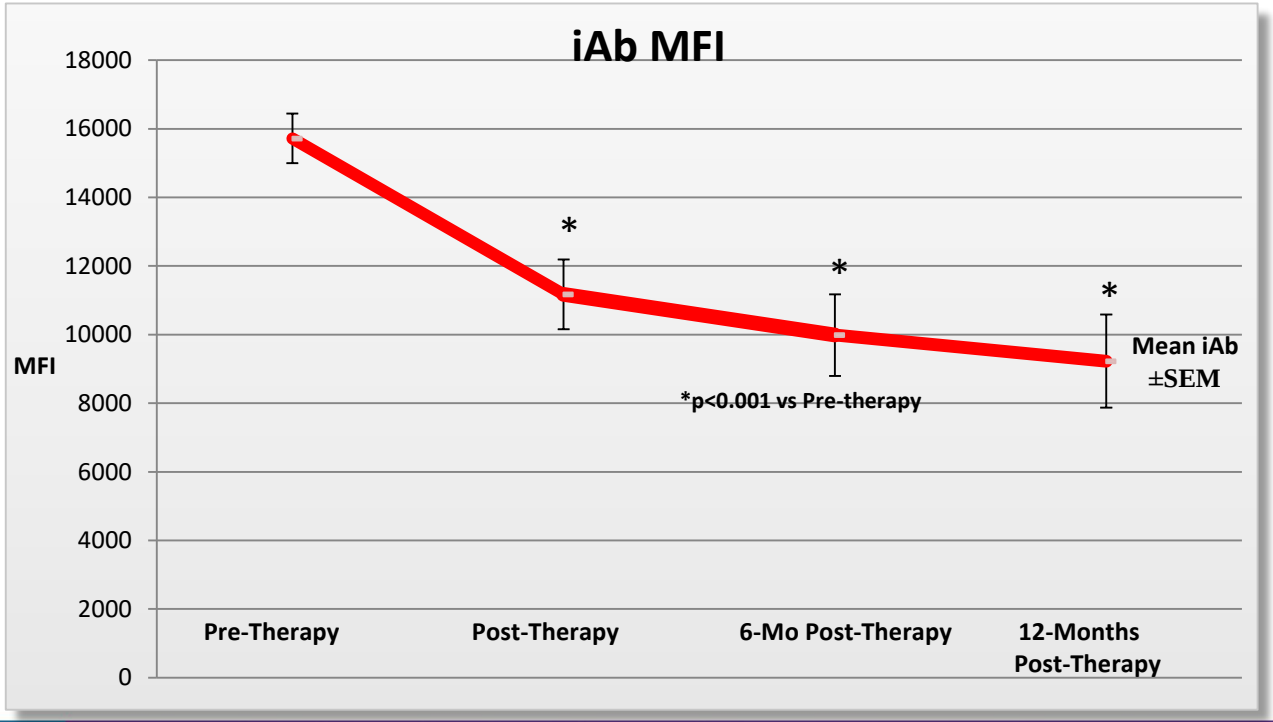
Check PRA

Repeat 2-wk cycle if cPRA ≥ 50%



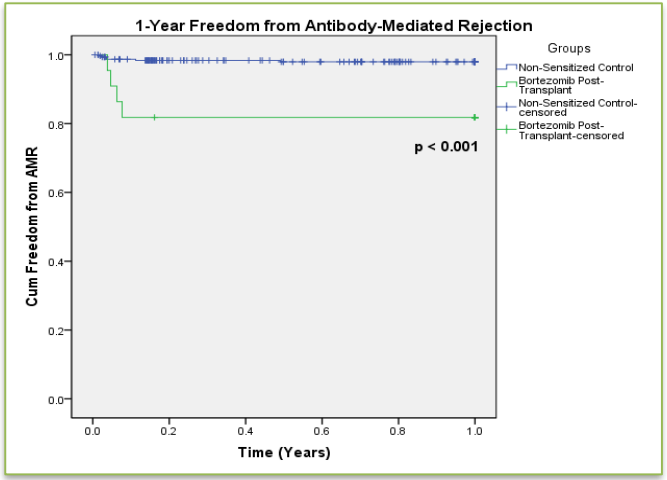
Patel JK et al: J Heart Lung Transplant. 2011 Dec;30(12):1320-6

Twelve-month follow-up for iAb MFI following desensitization with PP/BTZ (n=21)



Transplant outcomes for PP/BTZ desensitized patients vs. non-sensitized controls

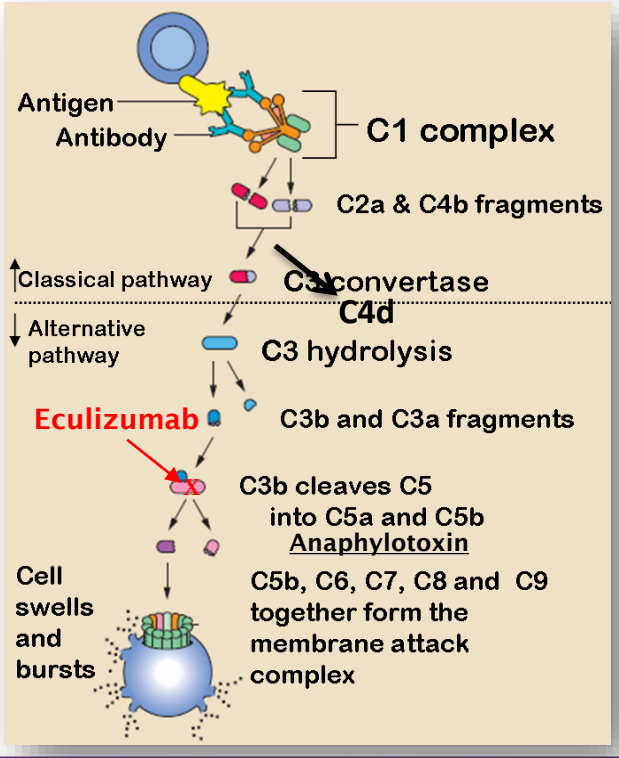
Endpoints	PP/BTZ Treated (n=22)	Non-Sensitized (n=315)	p-value
1-Year Survival	100.0%	88.9%	0.12
1-Year Freedom from Any-Treated Rejection	77.0%	82.8%	0.38
1-Year Freedom from Acute Cellular Rejection	89.5%	90.7%	0.91
1-Year Freedom from Antibody-Mediated Rejection	81.8%	98.0%	<.01
1-Year Freedom from Biopsy Negative Rejection	100.0%	92.5%	0.21
1-Year Freedom from Treated Infection (IV antibiotics)	70.9%	71.3%	0.88



Eculizumab

- Eculizumab is a humanized monoclonal antibody that binds and prevents activation of complement component C5 by the amplified C3 convertase molecules.

- Eculizumab is approved by the US Food and Drug Administration for treating paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (HUS).



Eculizumab Protocol – DUET Study

- Eculizumab Protocol:
  - Meningococcal vaccine ≥ 2 weeks prior to transplant or Gram Neg antibiotic prophylaxis
  - Methylprednisolone IV, Anti-thymocyte globulin (ATG) 1.5 mg/kg x 5 days followed by IVIG 1 gm/kg x 2 days
  - Eculizumab
    - Day 0: 1200 mg
    - Day 1,7,14,21: 900 mg
    - Day 28,42,56: 1200 mg
- Tacrolimus, mycophenolate, prednisone

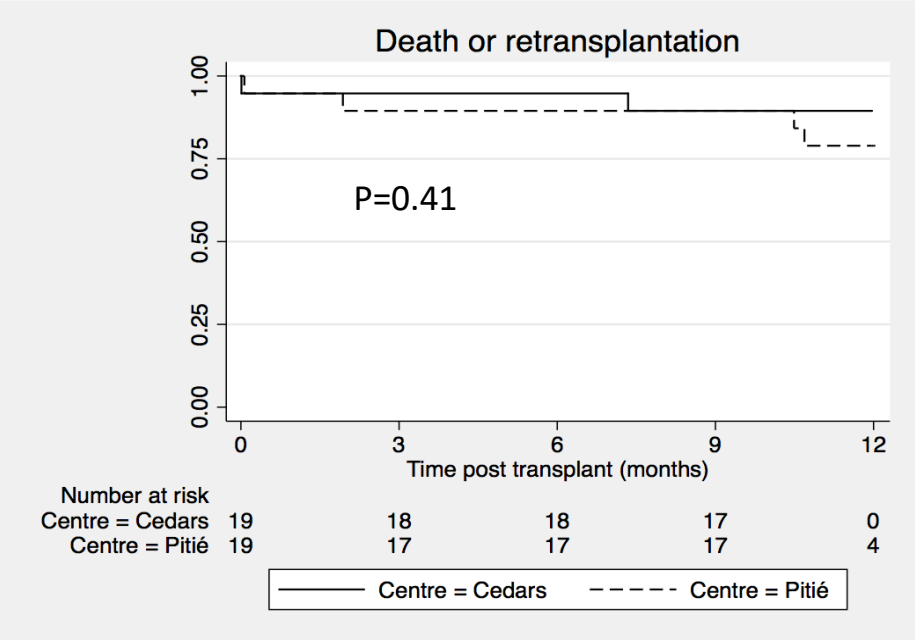
The De-novo Use of Eculizumab Alongside Conventional Maintenance Therapy in Presensitized Patients Receiving Cardiac Transplantation: An, Open-Label, Investigator-Initiated Pilot Trial: [The DUET Cardiac Trial]

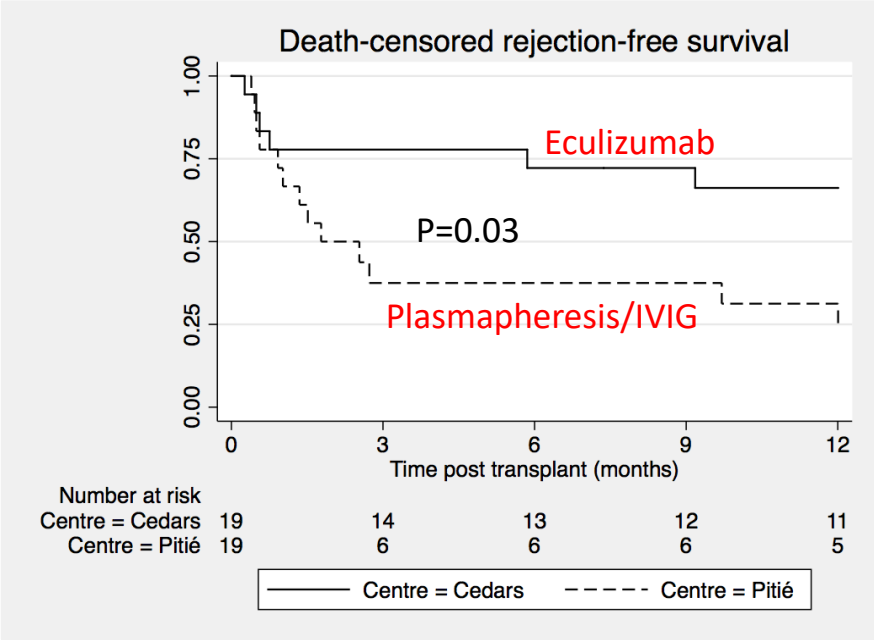
Preliminary Outcomes

Endpoints	N=18
1-Year Actuarial Survival	88.5%
1-Year Actuarial Freedom from Cellular Rejection (ISHLT ≥2R)	100.0%
1-Year Actuarial Freedom from Antibody-Mediated Rejection (AMR ≥2)	88.2%
1-Year Actuarial Freedom from Any Treated Rejection	88.2%
Average 6-Month Left Ventricular Ejection Fraction (%)*	63.5 ± 3.3
% of Patients with DSA at 1 Month Post-Transplant	77.8% (14/18)
1-Year Freedom from Treated Infection	50.0%

* No patient with reduced LVEF

Eculizumab vs Plasmapheresis/IVIG

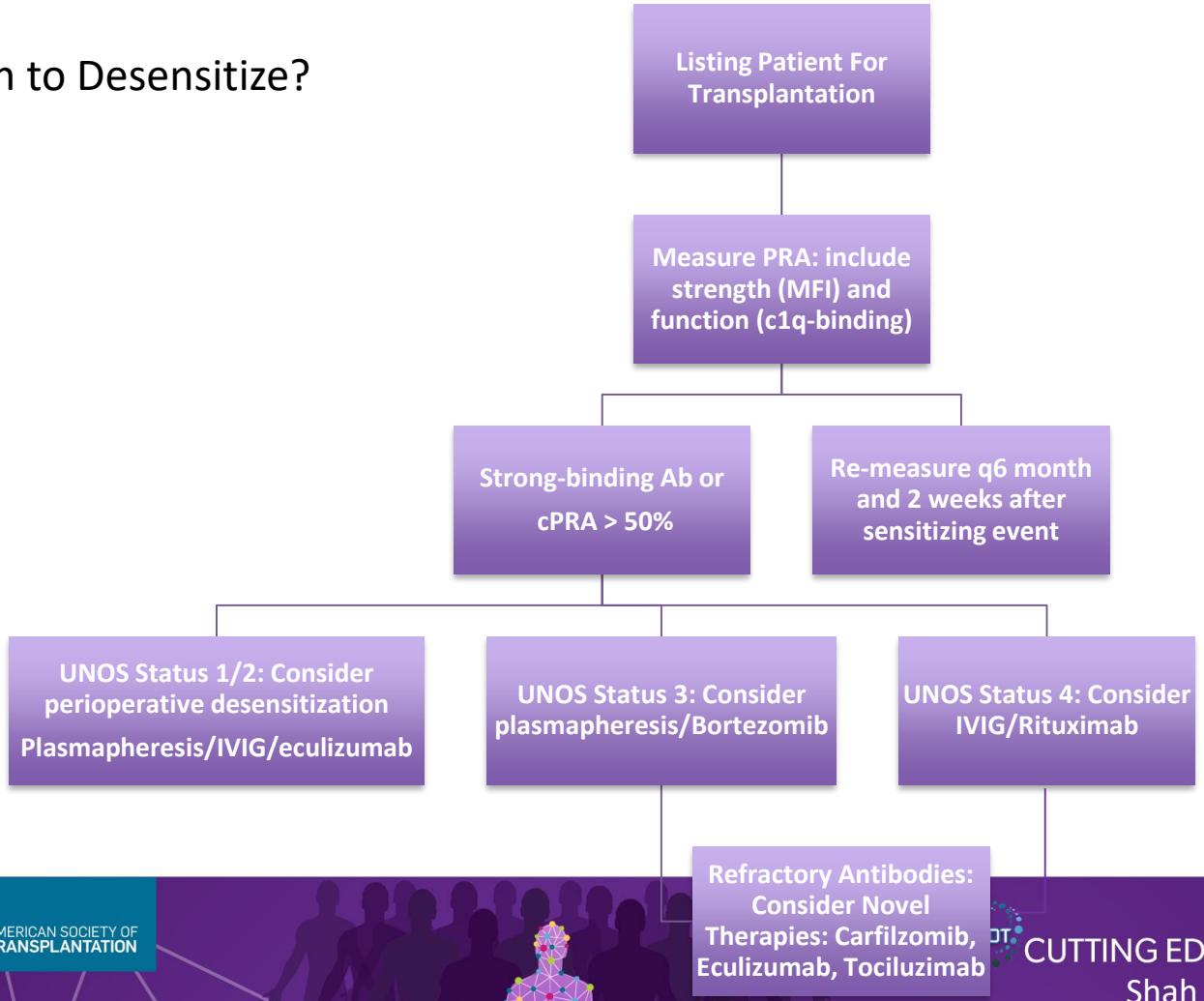




Courtesy A. Loupy

Biopsy proven AMR

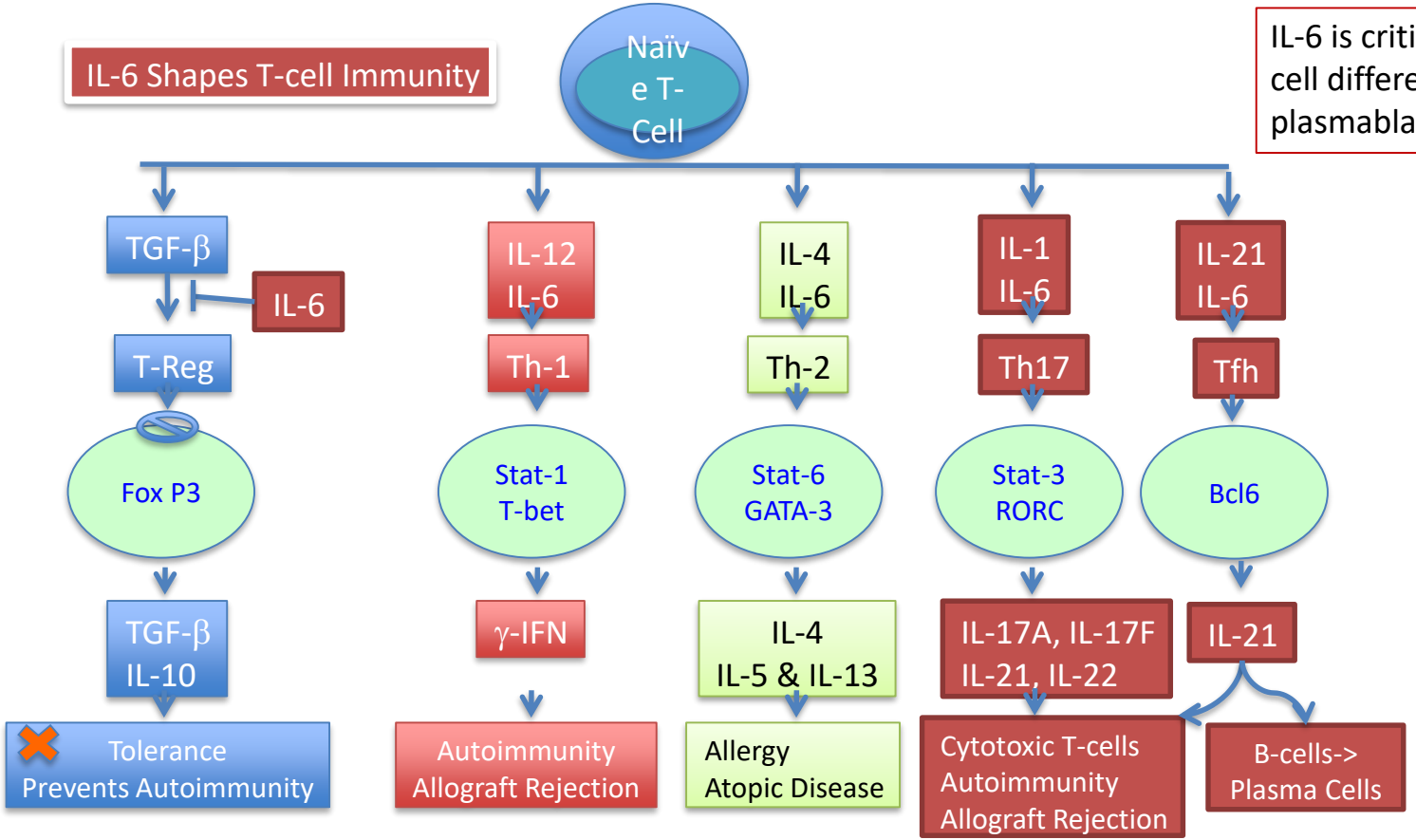
When to Desensitize?



Shah K., and Patel JK., submitted

Tocilizumab

- First-in-class, humanized, monoclonal antibody directed against the IL-6 receptor (IL-6R).
- FDA approved for the treatment of refractory inflammatory diseases such as RA, idiopathic juvenile arthritis and GVHD.
- Has shown impressive efficacy in RA patients who had failed to respond to first line immunosuppressive agents.



Jordan SC, **Choi** J, Kim I, Wu G, Toyoda M, Shin B, Vo A. Transplantation. 2016 Aug 19.

First Published Use of IL-6r mAb (Tocilizumab) in Human Organ Recipients

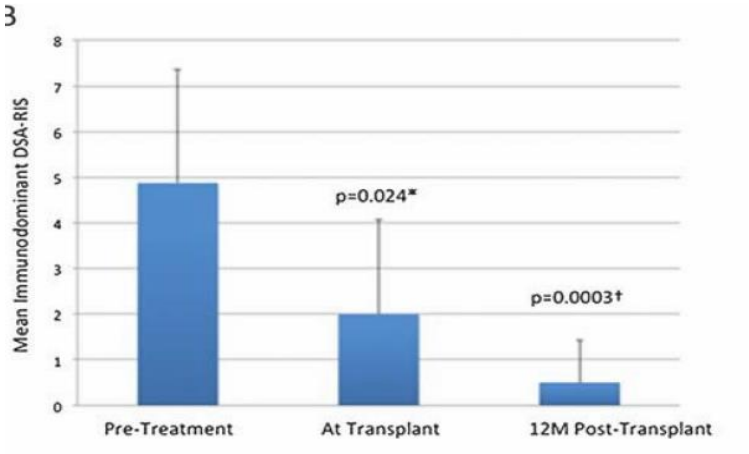
A Phase I/II Trial of the Interleukin-6 Receptor Specific Humanized Monoclonal (Tocilizumab) + Intravenous Immunoglobulin in Difficult to Desensitize Patients

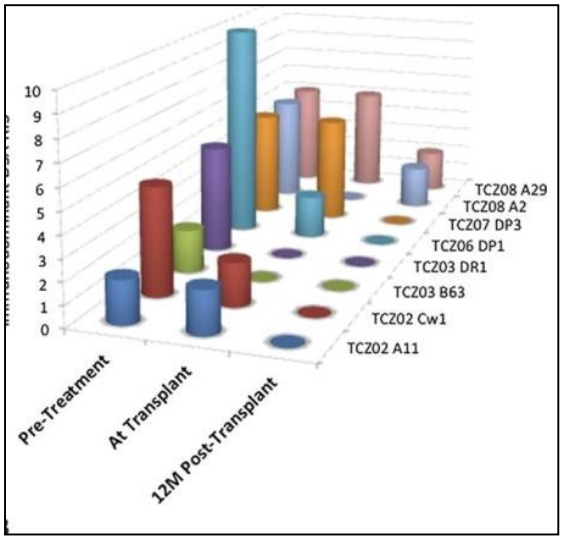
Ashley A. Vo, PharmD,[1] Jua Choi, PharmD,[1] Irene Kim, MD,[1] Sabrina Louie, MPH,[1] Kristen Cisneros, RN,[1] Joseph Kahwaji, MD,[1] Mieko Toyoda, PhD,[2] Shili Ge, PhD,[2] Mark Haas, MD,[3] Dechu Puliyanda, MD,[1] Nancy Reinsmoen, PhD,[4] Alice Peng, MD,[1] Rafael Villicana, MD,[1] and Stanley C. Jordan, MD[1]

- 25-30% or patients are resistant to standard desensitization (plasmapheresis, IVIg, rituximab).

(*Transplantation* 2015;99: 2356–2363)

Level of Immunodominant DSAs - Tocilizumab



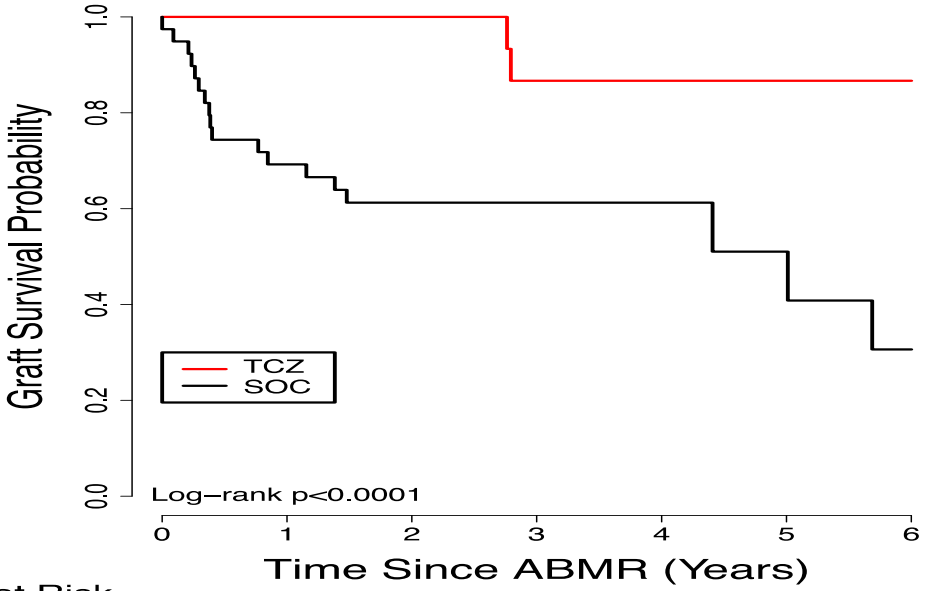


N=10

DSAs were eliminated in all but one patient who had 2 weak DSAs at 12mo but no ABMR on protocol Bx

Vo AA et al, *Transplantation* 2015;99:2356

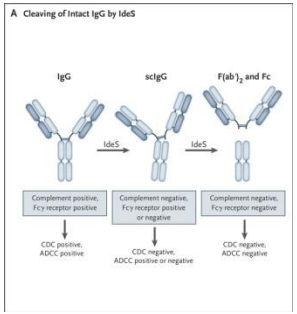
Allograft Survival Since Initial Biopsy: TCZ v. SOC

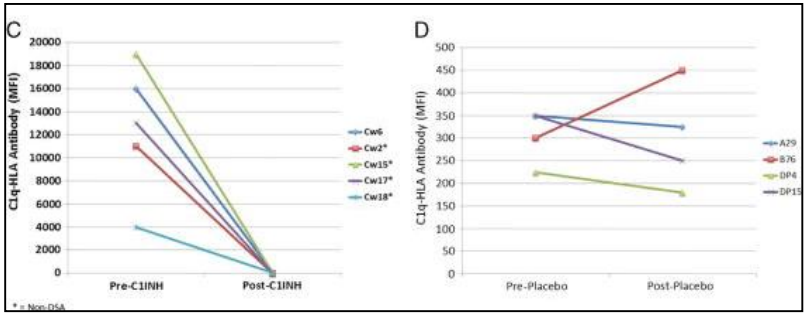


N at Risk							
TCZ	36	34	24	13	9	7	6
SOC	39	27	19	15	7	5	3

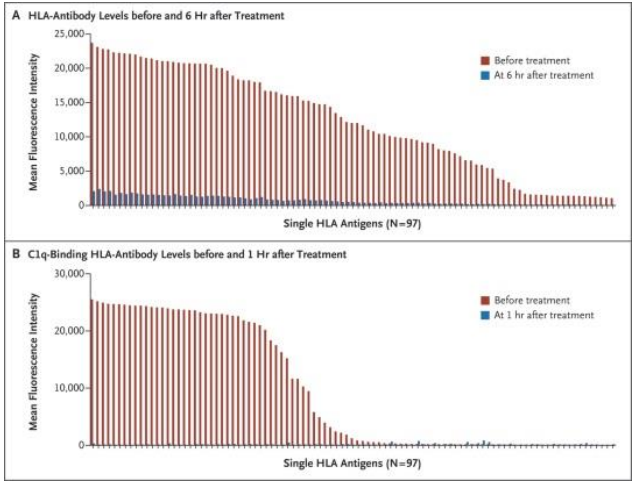
Choi J, et al.*Am J Transplant.* 2016; 16 (suppl 3).

Potential Therapies





C1 Esterase Inhibitors



IdeS

Vo A et al. Transplantation. 99(2):299-308, Feb 2015; Vo et al. Transplantation. 99(11):2356-2363,2015;
Jordan et al. N Engl J Med. 2017 Aug 3;377(5):442-453.

Summary

- The number of sensitized awaiting heart transplantation is increasing
- Desensitization strategies continue to evolve
- Therapies lack precision and target multiple pathways of the immune system
- Efficacy will be difficult to assess without robust clinical trials

- Desensitization strategies for heart transplant candidates will remain a priority in the U.S., as the revised allocation scheme has no provision to prioritize sensitized patients unlike the Kidney Allocation Score and the Canadian Cardiac Transplant Society Allocation Scheme