De novo DSA and ABMR:

Surrogate Endpoints and Clinical Trial Design

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Relevant Financial Relationship Disclosure Statement

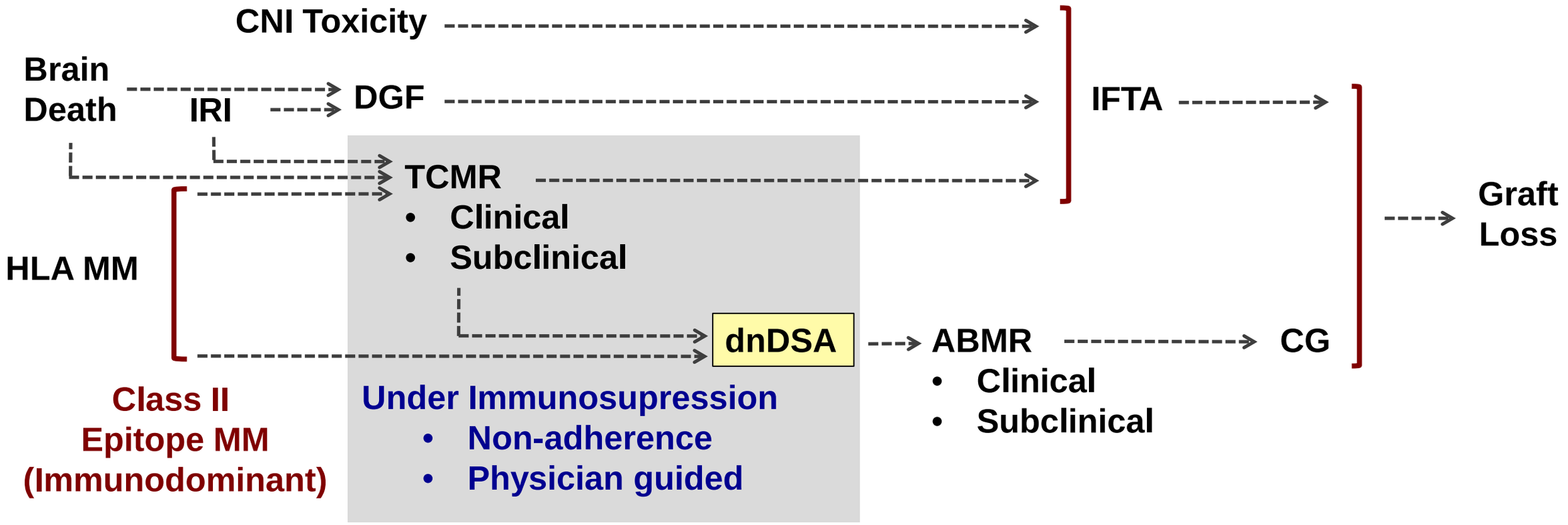
Peter Nickerson, University of Manitoba, Winnipeg, Canada

Astellas consultant and core investigator providing central laboratory support for the FKC-014 Canadian clinical trial

AND

My presentation does not include discussion of off-label or investigational use of drugs

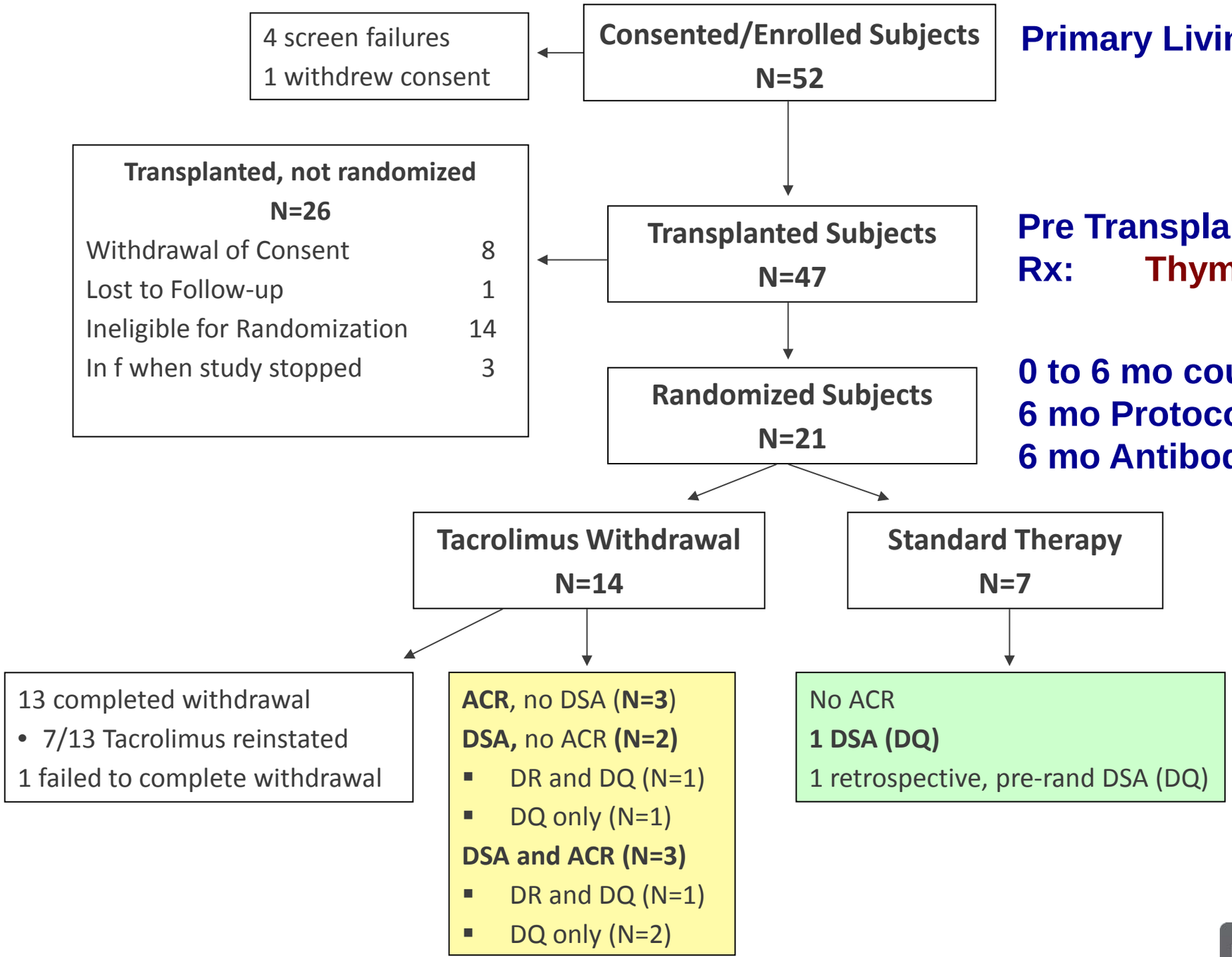
De novo DSA as a Surrogate Endpoint



- **Enrichment strategies to increase endpoint frequency**
  - **Prognostic Biomarker – Class II HLA epitope mismatch**
- **Confounder to control for**
  - **Medication Non-Adherence (MNA)**

(Requires an objective measure)

CTOT-09: Tacrolimus Withdrawal in Immune Quiescent, Low-risk, Kidney Transplant Recipients



Primary Living Donor Transplants

Pre Transplant Antibody: no DSA, PRA <30%
Rx: Thymo, Tacrolimus, MMF, Prednisone

0 to 6 mo course: No Acute Rejection
6 mo Protocol Biopsy: Normal Histology
6 mo Antibody Screen: No DSA

What predicts DSA?

Hricik et al., JASN (2015) ePub

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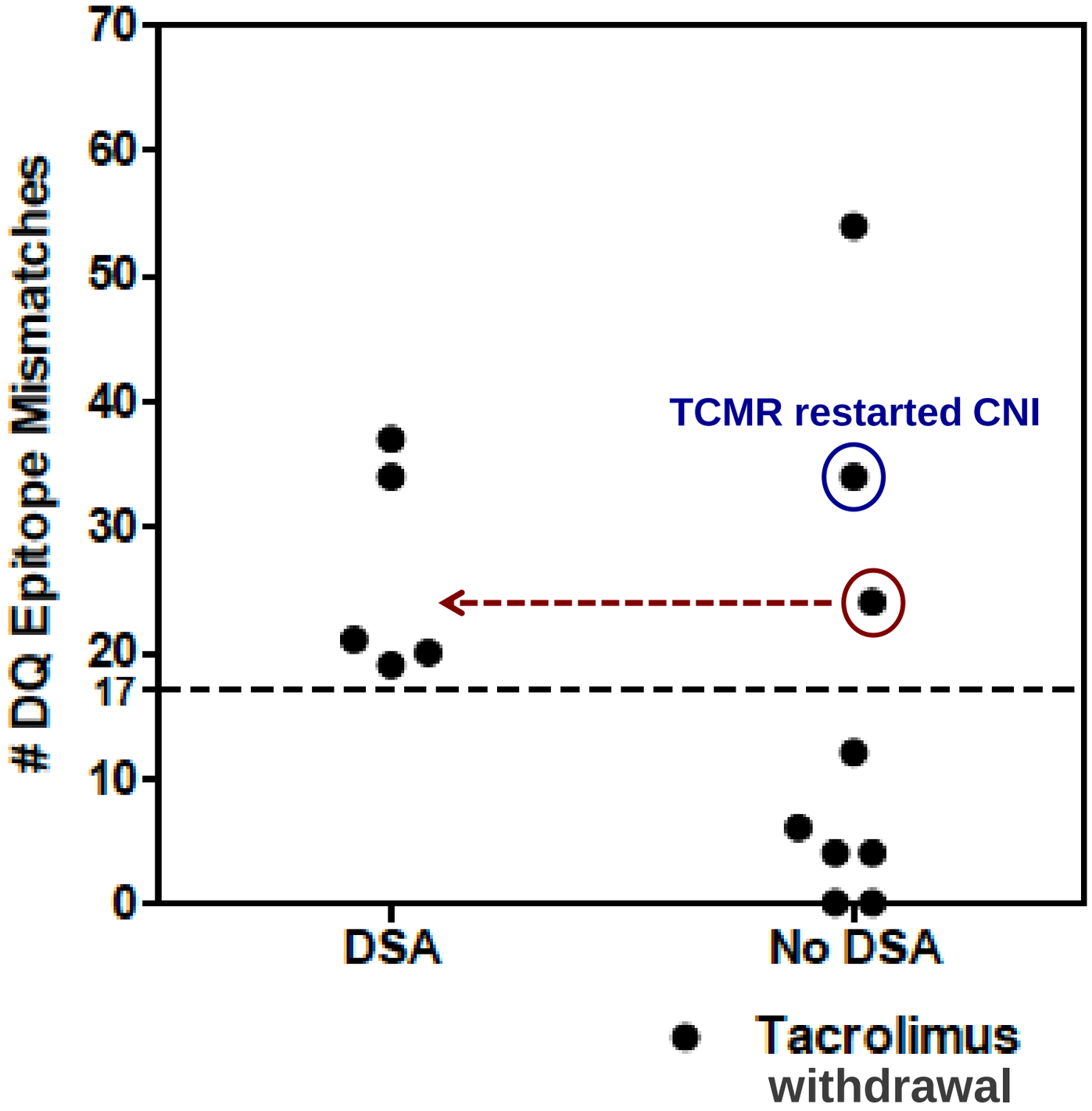


***De novo DQ* DSA associated with high Epitope MM load (≥ 17)**

5/8 in Tac withdrawal (P=0.0310)

6/8 in longer follow-up (P=0.0096)

Hricik et al., JASN (2015) ePub

National Institute of Allergy and Infectious Diseases

CTOT Clinical Trials in Organ Transplantation

Predictive Patterns of Early Medication Adherence in Renal Transplantation

Thomas E. Nevins,[1,4] William N. Robiner,[2] and William Thomas[3]

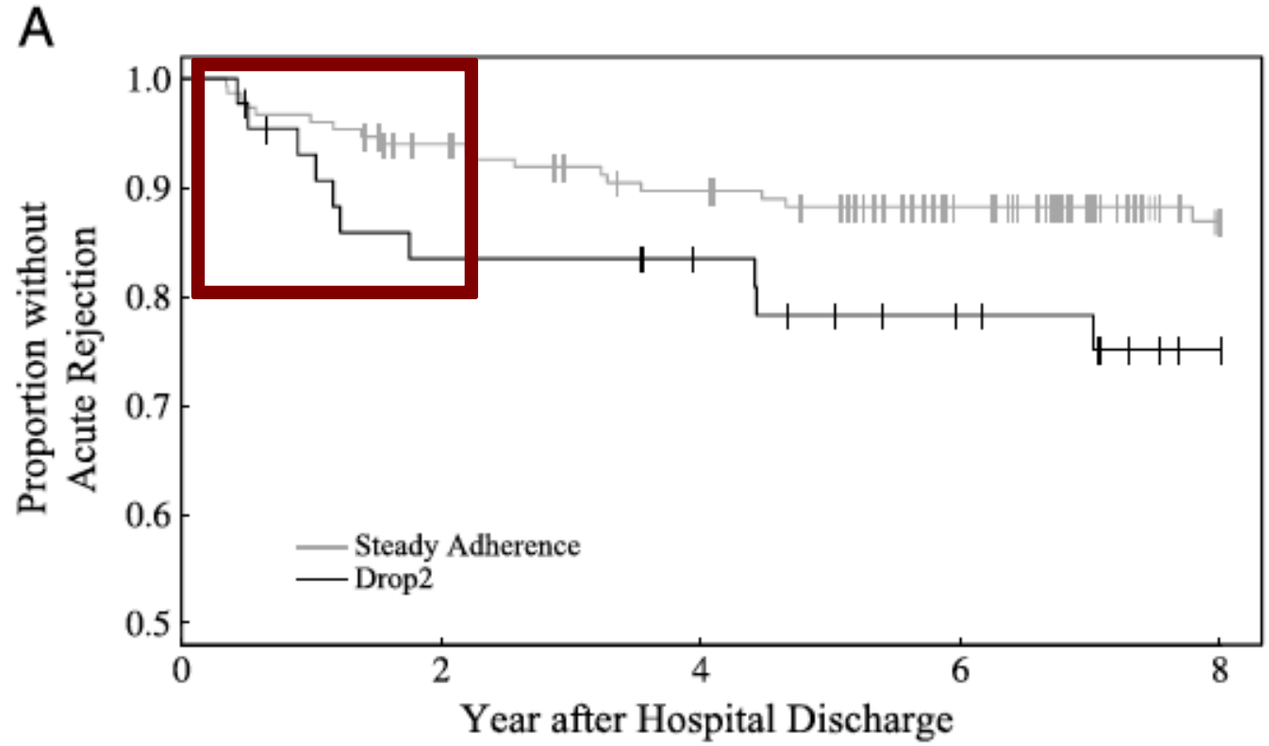
MEMS
(Medication Event Monitoring System)

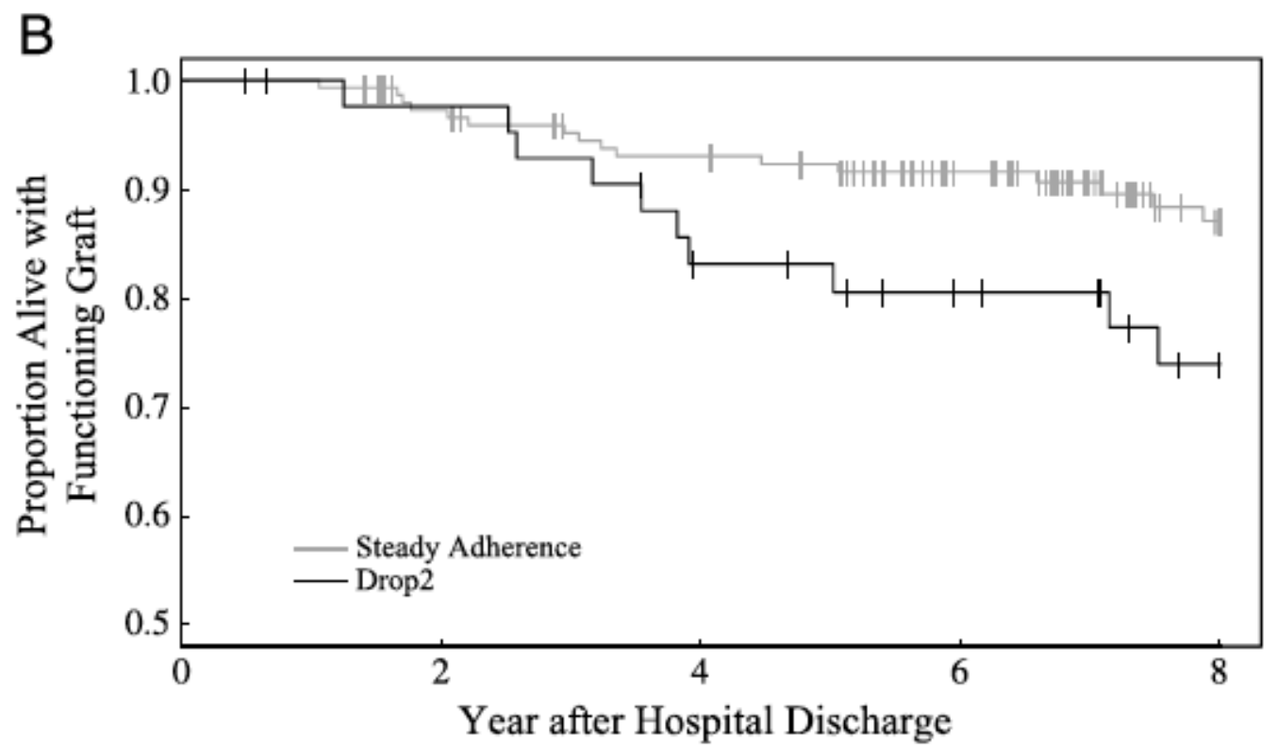
195 patients

- **44 (22.6%)** decreased adherence by 7% or more in **month 2** post tx

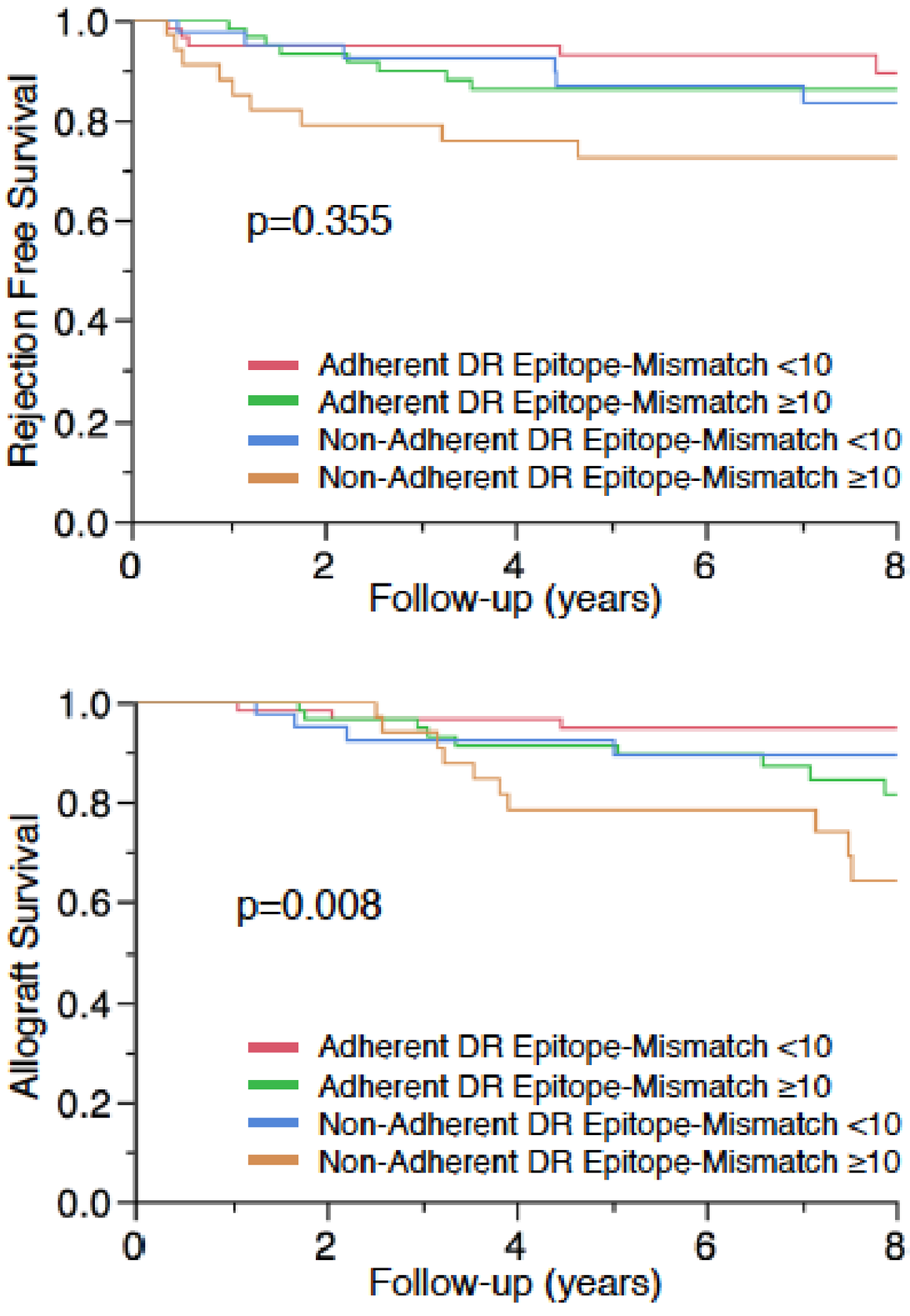
  → **Late Acute Rejection**
  → **Early Graft Loss**

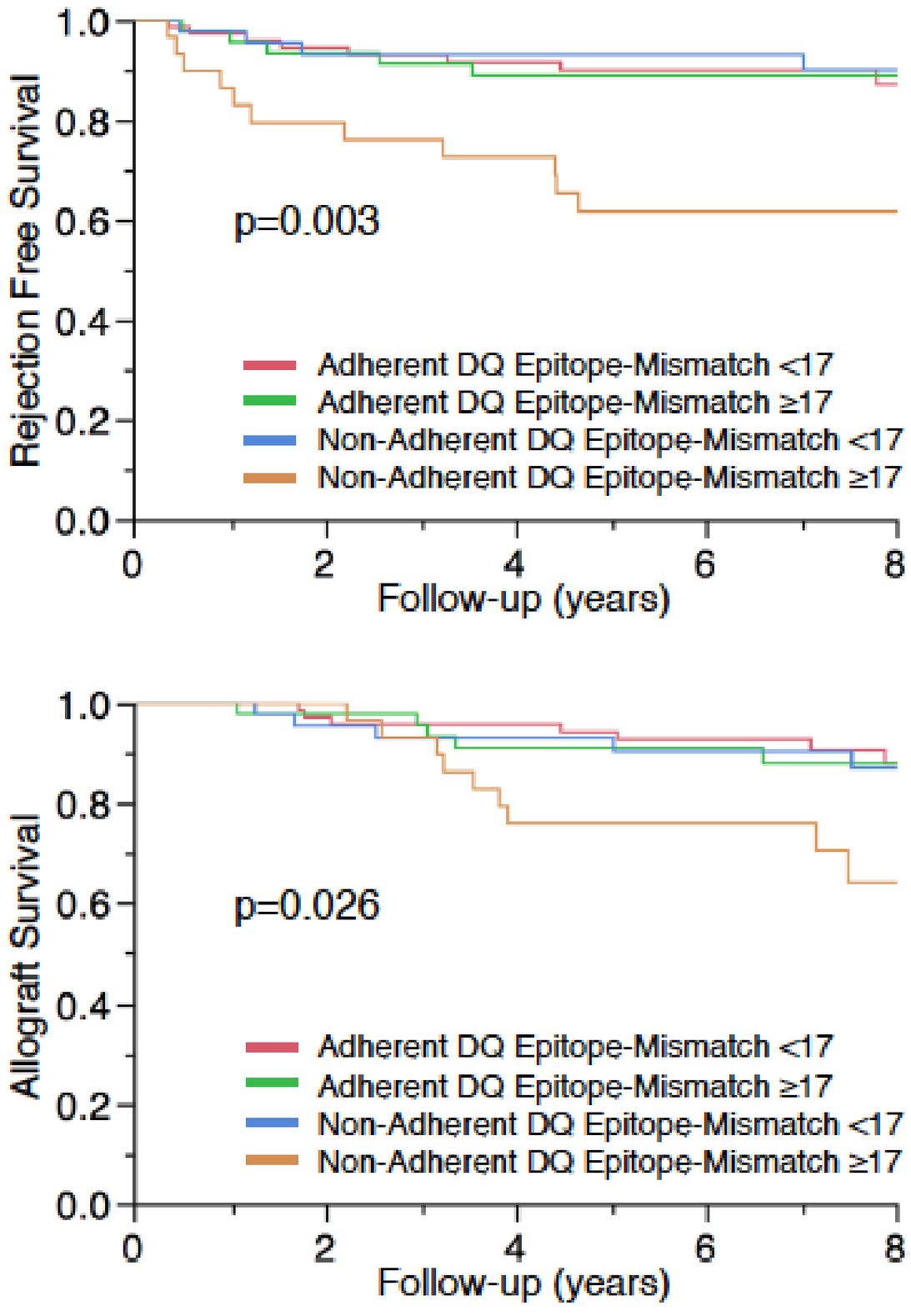
Transplantation (2014) 98:878-884





Synergistic Effect of Non-Adherence and EPITOPE MM Load





Wiebe et al., AJT (2015) 15:2197

HLA-DR and -DQ Eplet Mismatches and Transplant Glomerulopathy: A Nested Case–Control Study

R. Sapir-Pichhadze[1,2,3,*,†] K. Tinckam[1,4], K. Quach[1,5], A.G. Logan[1,2,3], A. Laupacis[2,6], R. John[4], J. Beyene[2,6,7] and S.J. Kim[1,2,3,8]

American Journal of Transplantation 2015; 15: 137–148

Odds Ratio of Developing TG based upon Total Eplet Threshold

	Univariate	**Multivariate ****
DR + DQ: ≥36 vs. <36	2.01[1.01-4.01]	3.21 [1.26-7.56]
DQ: ≥18 vs. <18	1.50 [0.75,3.00] NS	2.42 [1.03,5.70]
DR: ≥15 vs. <15	2.44 [1.16,5.12]	3.64 [1.42,9.37]

** Model includes Eplet exposure, recipient age, sex, peak PRA, race, induction and donor type.

De novo DSA as a Surrogate Endpoint

Unselected Population

Epitope MM Load		DQ	
		0-16	17-69
DR	0-9	37%	11%
	10-57	17%	35%

Exclude 0 A, B, DR MM

Epitope MM Load		DQ	
		0-16	17-69
DR	0-9	30%	11%
	10-57	19%	40%

Caveats for Study Design

Be strict in ruling out pre-existing DSA

- Set low threshold for MFI
- Assess more than one pre-transplant sera

Control for MNA

- May require MEMS monitoring

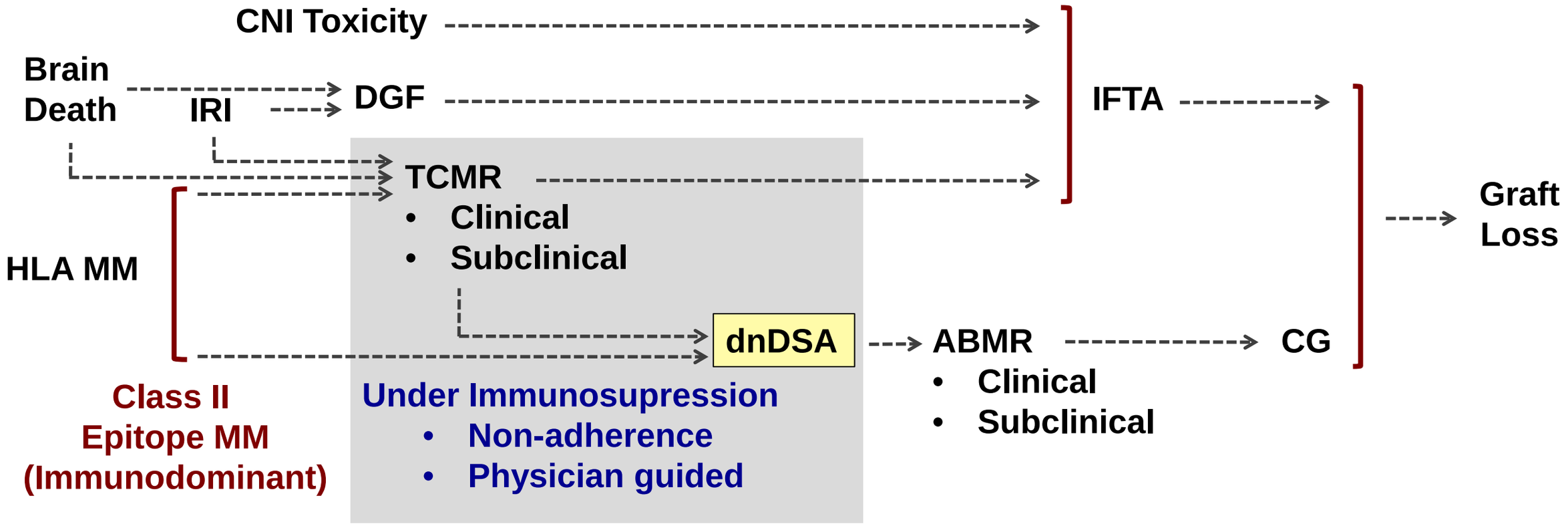
Enrich for “at risk” patients

- Target high Class II epitope MM loads

Greatest utility in Clinical Trials maybe for:

- MNA intervention studies
- Physician-guided minimization studies

Clinical Trial Design for *de novo* DSA patients



- **Enrichment strategies to increase endpoint frequency**
  - **Prognostic Biomarkers – DSA titer, MNA, tubulitis, Banff CG score**
- **Endpoints**
  - **Clinical – Graft loss**
  - **Surrogate – eGFR, Banff CG score**

Prognostic Biomarkers to ⇧ Endpoint Frequency

A. Clinical Predictors (n=64)		Univariate Predictors HR (95%CI)	Univariate Predictors p value	Multivariate Predictors HR (95%CI)	Multivariate Predictors p value
Recipient Age (per year)		0.98 (0.95-0.99)	0.0465	-	
Donor Age (per year)		1.00 (0.97-1.02)	0.7745	-	
HLA-A/B/DR/DQ Mismatch (per mismatch)		0.87 (0.6-1.2)	0.3833	-	
Cold Ischemic Time (per hour)		1.06 (0.99-1.3)	0.0674	-	
Delayed Graft Function (yes vs. no)	**DGF**	3.78 (1.2-10.0)	0.0250	6.21 (1.9-18.7)	0.0047
TCMR Episodes ≤12 months (per episode)		1.74 (1.0-2.9)	0.0505	-	
Non-Adherence (yes vs. no)	**MNA**	5.51 (2.3-15.1)	<0.0001	5.57 (2.3-15.5)	<0.0001
dnDSA Phenotype (clinical vs. subclinical)		4.96 (2.2-11.5)	<0.0001	-	
MFI_{sum} (per 1000 MFI)	**"DSA Titer"**	1.01 (1.0-1.03)	0.0993	1.02 (1.0-1.04)	0.0286

Wiebe et al., AJT (2015) ePub

DSA MFI Caveats

- **Not an FDA approved quantitative assay**
- **May not be linearly related to outcome**
- **Weak correlate with graft outcome**
- **Change in MFI may be a surrogate endpoint but needs prospective study demonstrating drop in MFI correlates with improved graft survival**

MNA Caveats

- **Ideal is to objectively define (i.e. MEMS)**
- **Without strategy to improve adherence clinical trials which include these patients may be futile as MNA can persist**
- **Focusing on adherent patients to avoid error of a trial reporting a negative effect due to MNA will increase sample size**

Prognostic Biomarkers to ⇧ Endpoint Frequency

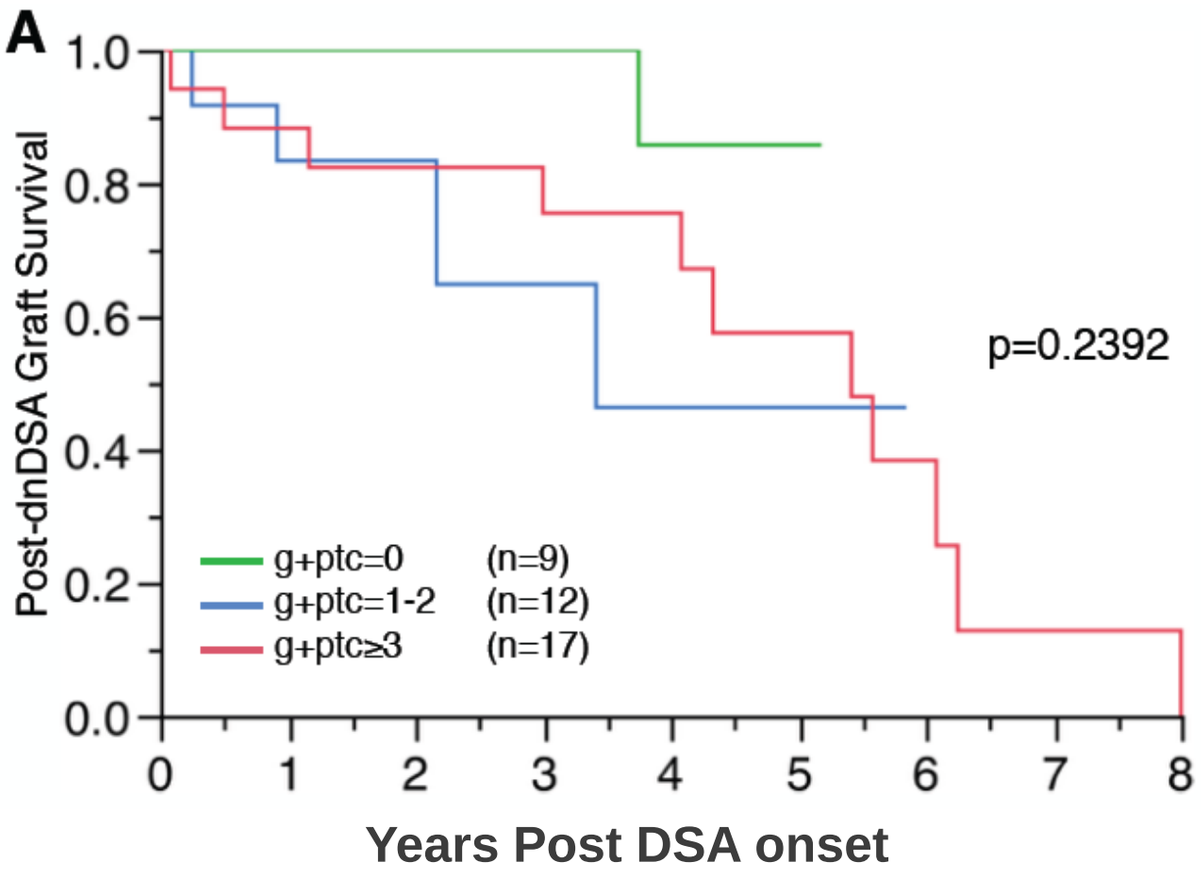
University of Manitoba

Microvascular inflammation (MVI) is present in majority of those who progress, but

Grade of MVI does not predict risk for graft loss

CNI + MMF + Pred + 16% Thymo

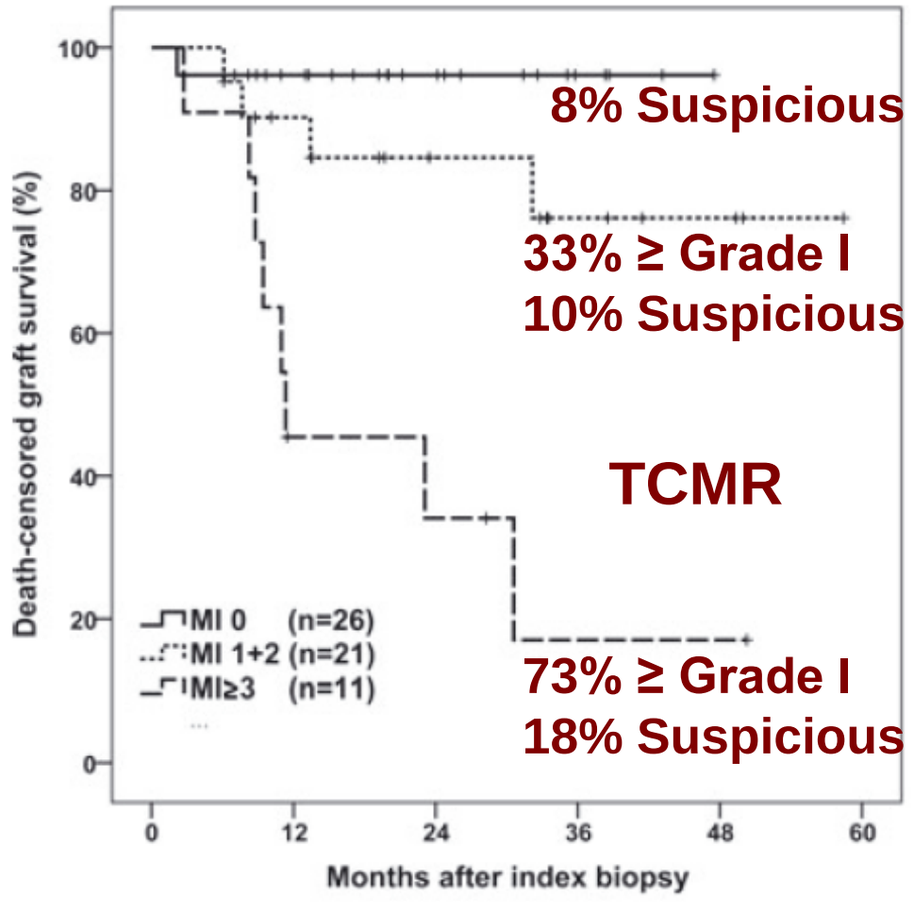
DSA onset 49 mo (IQR 25 – 77)



Wiebe et al., AJT (2015) ePub

90% Alemtuzumab + $Tac_{monotherapy}$

DSA onset 3.8 mo (IQR 0.6 – 10.8)

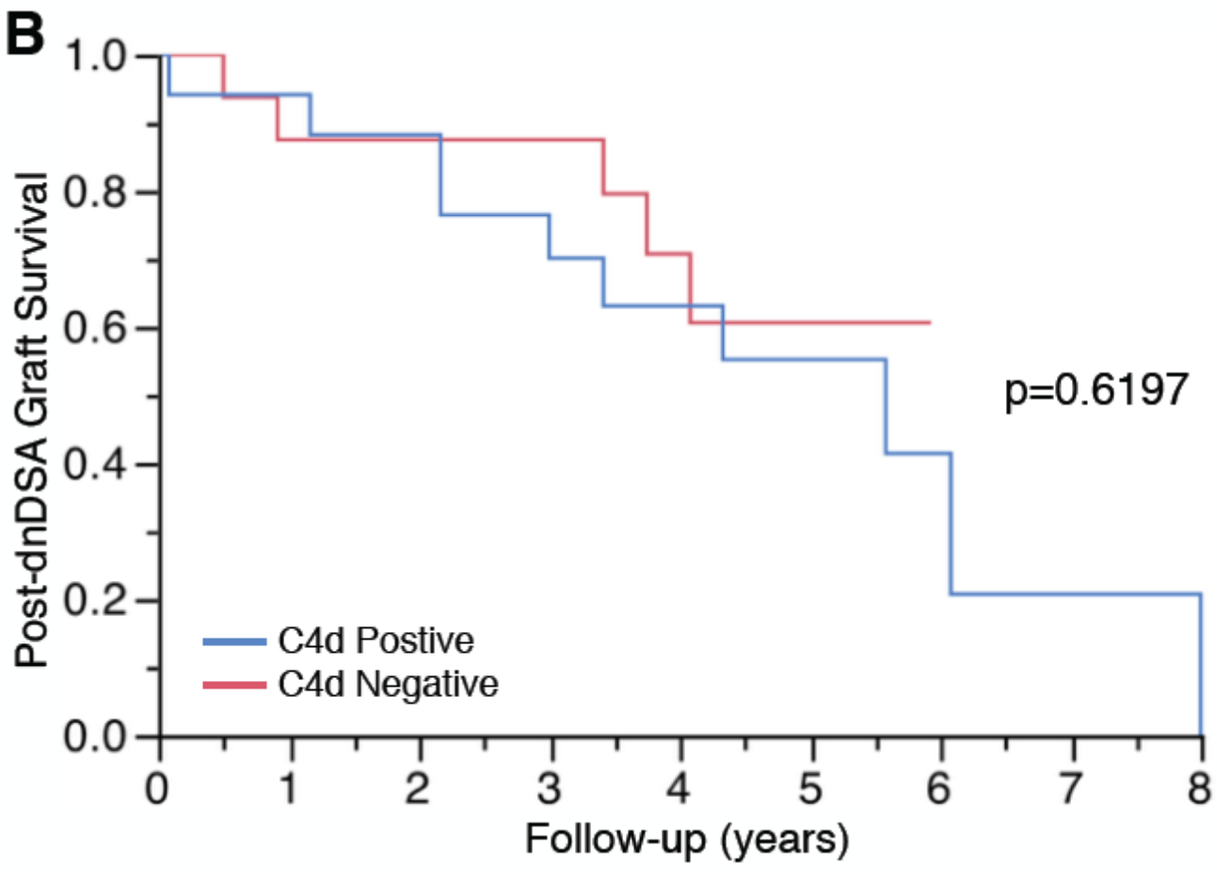


de Kort et al., AJT 2013;13:485

Prognostic Biomarkers to ⇧ Endpoint Frequency

UNIVERSITY OF MANITOBA

C4d does not predict graft loss



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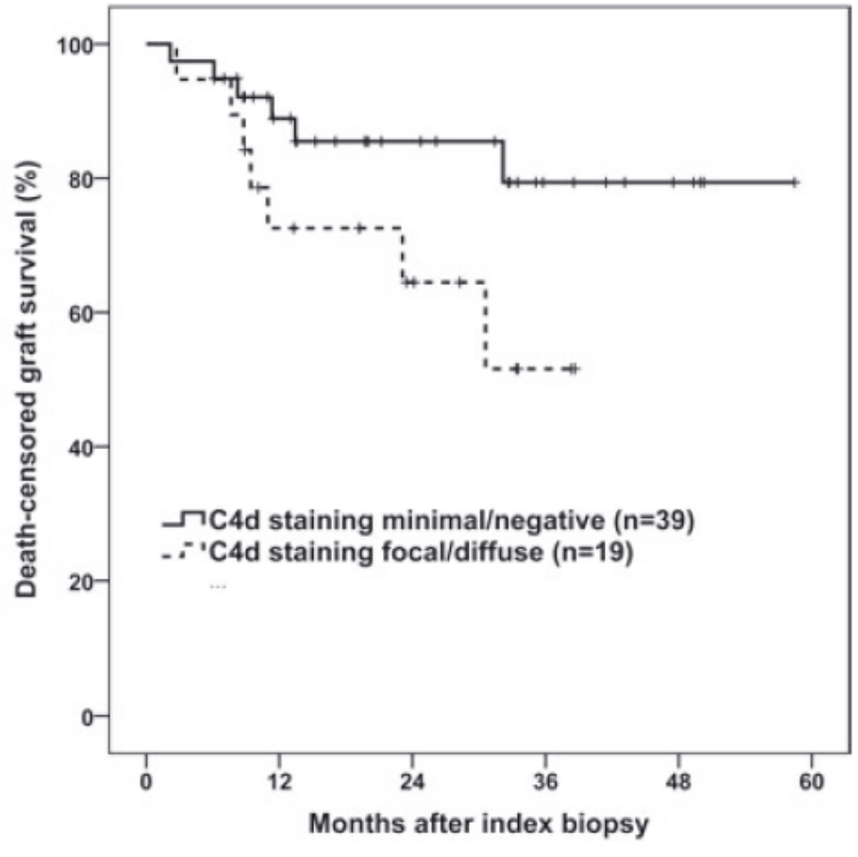


de Kort et al., AJT 2013;13:485

Clinical Endpoint Graft Survival

De novo DSA clinical trial with 5 yr graft survival as endpoint

(sample size for power 80%, α 0.05, drop-out 10%)

dnDSA Group	Median 5 year Graft Survival	Risk Reduction in Graft Loss 25%	35%	50%
All dnDSA	60%	601	306	150
Clinical dnDSA	28%	243	108	79
Subclinical dnDSA	75%	1591	590	377

Caveat

- **90% of clinical *de novo* DSA patients are non-adherent**

Wiebe et al., AJT (2015) ePub

Surrogate Endpoint eGFR

In CKD trials, FDA will consider as an ESRD surrogate endpoint:

- Doubling of serum creatinine (57% decline in eGFR), or
- A 40% decline in eGFR over 2 years, assuming a baseline of 50 ml/min

Thompson et al., AJKD (2014) 64:836

For each 1.0 ml/min/1.73m^2 decrease in eGFR at 3 years post-subclinical dnDSA onset, the risk of graft loss increased (HR 1.06 [1.03-1.09], p<0.0001)

Wiebe et al., AJT (2015) ePub

Subclinical *de novo* DSA clinical trial with eGFR as surrogate endpoint

Study Duration	Mean eGFR Decline (ml/min/ 1.73m^2)	Risk Reduction in eGFR Decline 50%	70%
2 years	7.83±15.6	550 (23%)	282 (31%)
3 years	10.8±20.3	490 (27%)	251 (35%)

* Power=80%, Alpha=0.05, Drop out=10%

** sample size (predicted risk reduction for graft loss)

Surrogate Endpoint — Banff CG Score

University of Manitoba

Rationale for CG

- Correlates strongly with *de novo* DSA
- Infrequent at the onset of *de novo* DSA
- Increases in grade after the onset in *de novo* DSA (**1 grade /3 yrs**)
- Is a prognostic biomarker of graft loss

Caveat

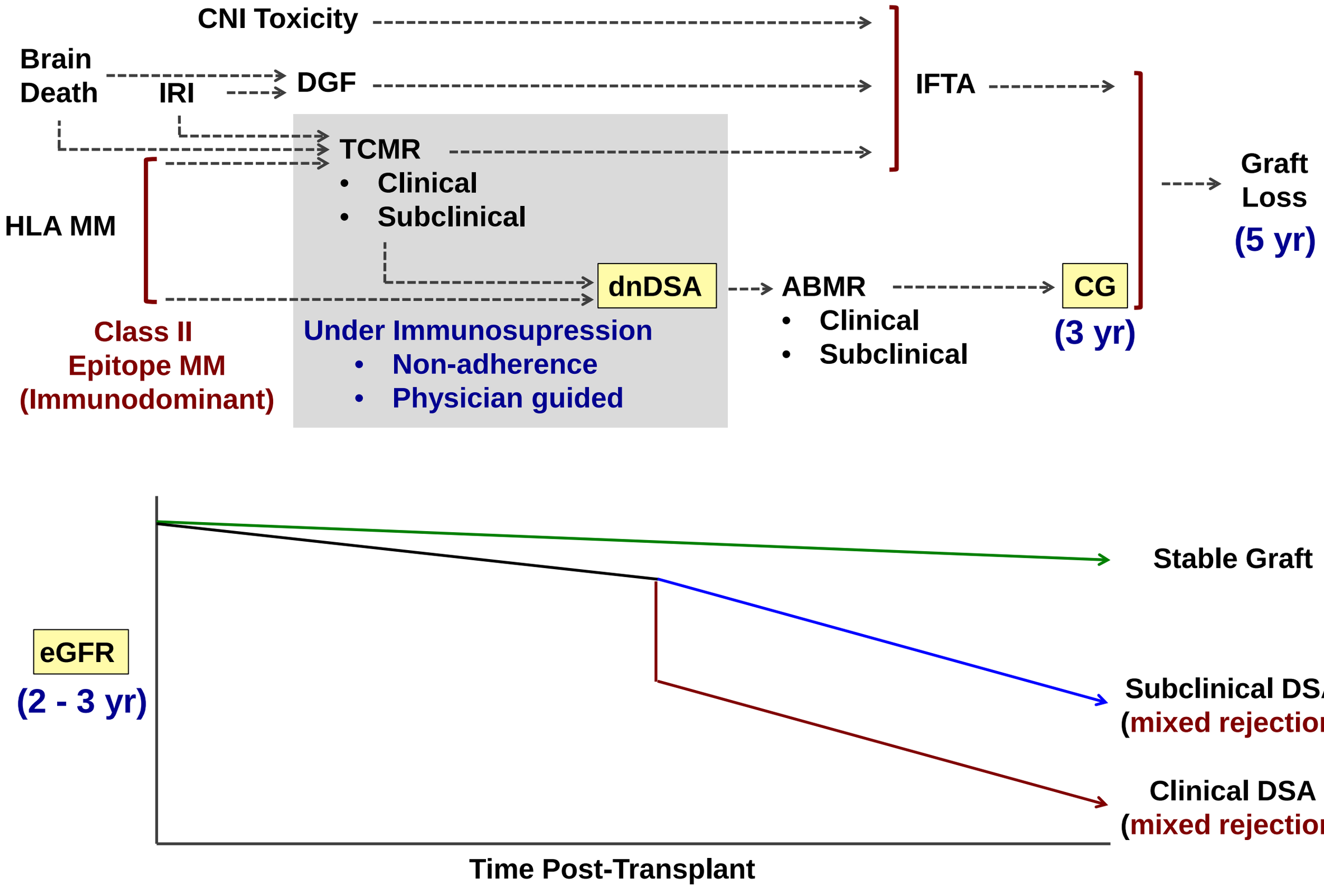
- Validation that preventing the development and/or progression in response to treatment correlates with improved graft survival is required

Key Consideration

- **Electron Microscopy** many be a useful tool to detect changes with more sensitivity (earlier) than Light Microscopy

Wiebe et al., AJT (2015) ePub

Potential New Surrogate Endpoints



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