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EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

Imlifidase una nuova opzione per il paziente altamente immunizzato in attesa di trapianto renale: il ruolo dell'istocompatibilità

Giovanni Rombolà
SSD Immunogenetica dei Trapianti
Azienda Ospedaliero-Universitaria di Parma

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Disclosure

Nessun conflitto di interessi da dichiarare

Indicazione approvata di imlifidase*

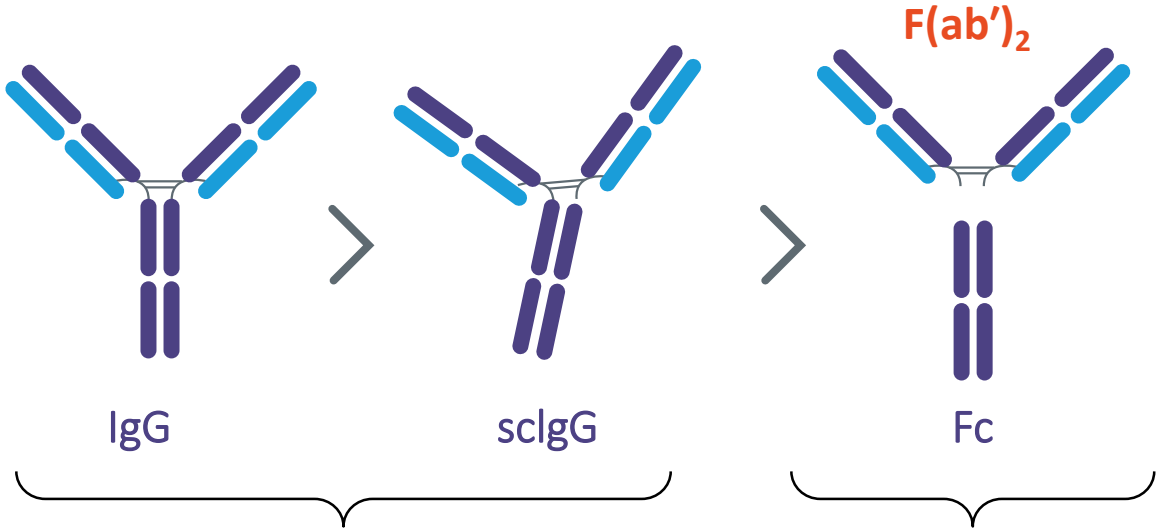
Imlifidase è indicato per il trattamento di desensibilizzazione di pazienti adulti altamente sensibilizzati che necessitano di trapianto di rene con un crossmatch positivo contro un donatore deceduto disponibile.

L'uso di imlifidase deve essere riservato ai pazienti che hanno poche probabilità di essere sottoposti a trapianto nell'ambito del sistema di allocazione dei reni disponibili, compresi i programmi di assegnazione di priorità per i pazienti altamente sensibilizzati.

*RCP imlifidase - May 2024

Imlifidase specifically cleaves IgG

IgG is cleaved in a two-step process[1,2]



STEP 1: scIgG with one intact heavy chain is generated

STEP 2: one $F(ab')_2$ fragment and one Fc fragment generated

- Cleaves IgG at the lower hinge region to form $F(ab')_2$ and Fc fragments[1,3]
- Cleaves all forms of IgG (free, bound to antigen and membrane bound)[3]
- Effectively neutralises IgG Fc-dependent effector functions, including ADCC, ADCP and CDC[1–3]
- Highly specific towards IgG[2–4]

Other molecules (i.e. IgA, IgD, IgE and IgM) are not cleaved[4]

Imlifidase è l'unico trattamento approvato per la desensibilizzazione di pazienti adulti altamente sensibilizzati sottoposti a trapianto di rene con crossmatch positivo contro un donatore deceduto disponibile

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ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; Fc, fragment crystallisable; Ig, immunoglobulin; scIgG, single cleaved immunoglobulin G

1. Winstedt L, el al. PLoS One. 2015;10(7):e0132011; 2. Vindenbro R, et al. FEBS Letters. 2013;567:1818-22. 3. Jarnum S, et al. J Immunol. 2015;195:5592-601. 4. von Pawel-Rammingen U, et al. EMBO J. 2002;21(7):1607-15.

Safety and efficacy of imlifidase in highly-sensitized kidney transplant recipients: results from the International phase II study

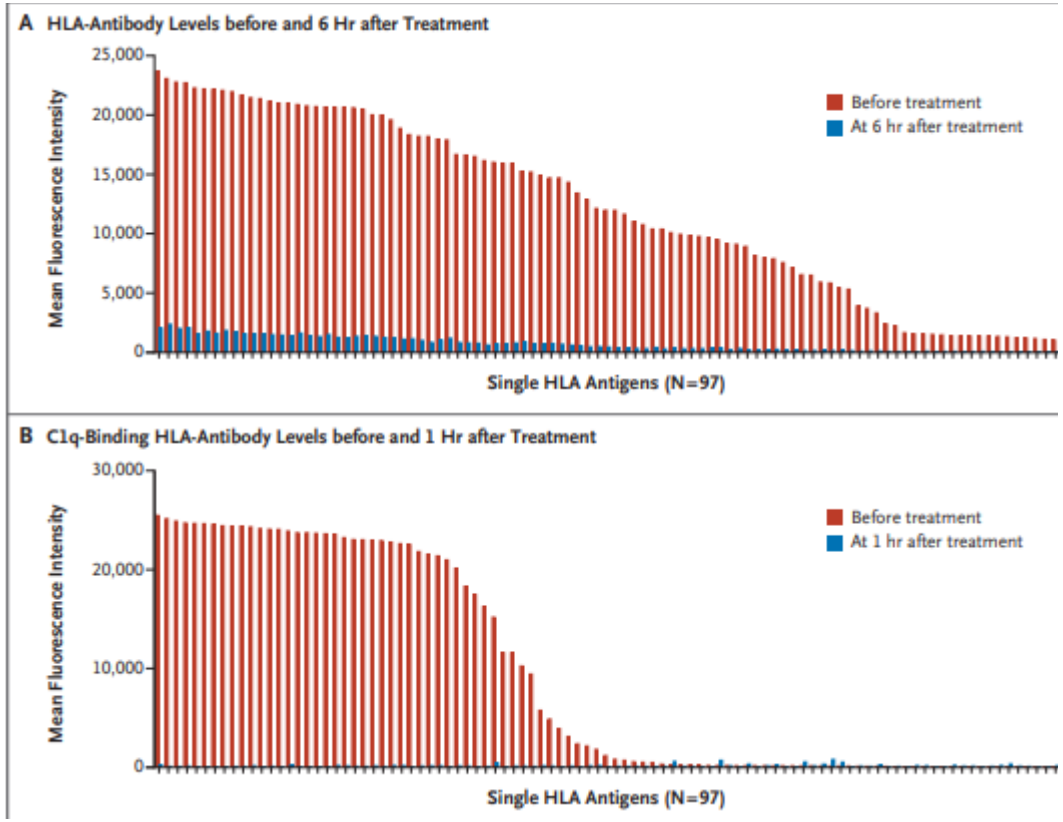
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation

S.C. Jordan, T. Lorant, J. Choi, C. Kjellman, L. Winstedt, M. Bengtsson, X. Zhang, T. Eich, M. Toyoda, B.-M. Eriksson, S. Ge, A. Peng, S. Järnum, K.J. Wood, T. Lundgren, L. Wennberg, L. Bäckman, E. Larsson, R. Villicana, J. Kahwaji, S. Louie, A. Kang, M. Haas, C. Nast, A. Vo, and G. Tufveson

ABSTRACT

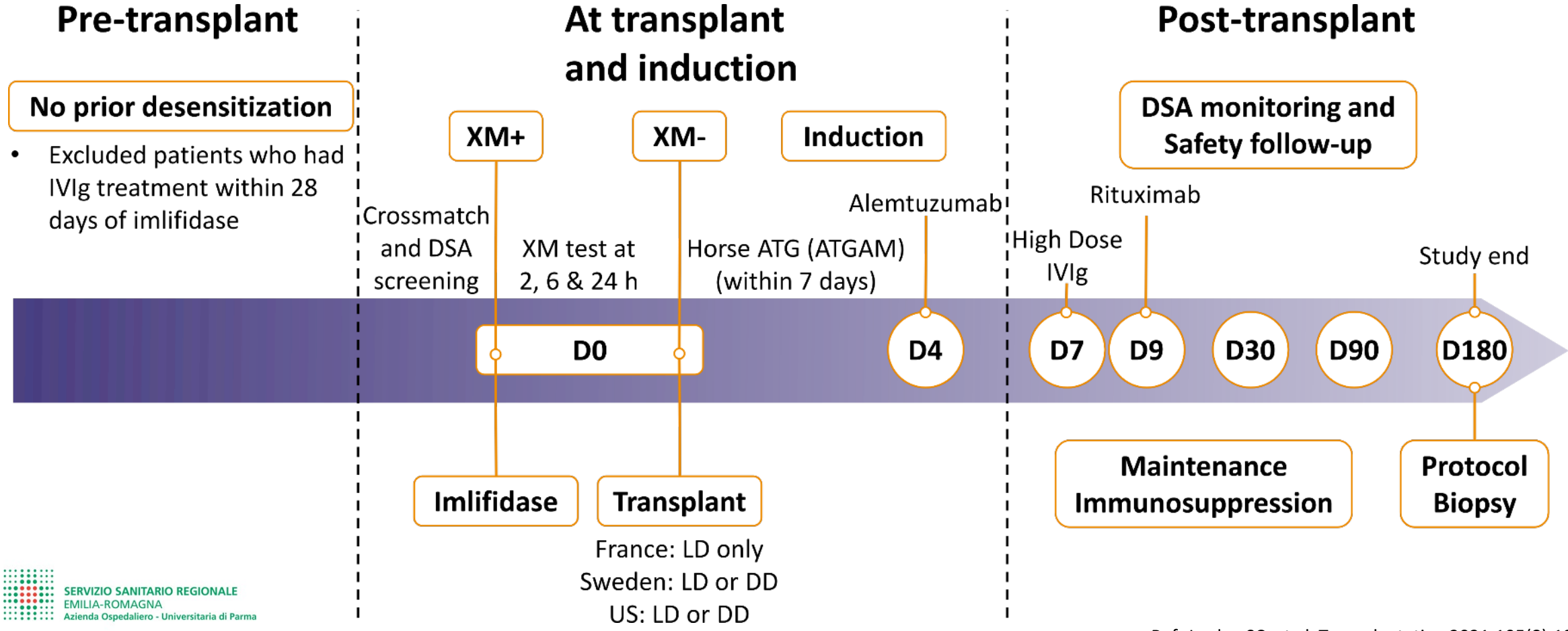


Ref: Jordan SC et al. *New Engl J med*. 2017;377:442-53.

Imlifidase Desensitization in Crossmatch-positive, Highly Sensitized Kidney Transplant Recipients: Results of an International Phase 2 Trial (Highdes)

Stanley C. Jordan, MD,[1] Christophe Legendre, MD,[2] Niraj M. Desai, MD,[3] Tomas Lorant, MD,[4,5] Mats Bengtsson, MD,[4] Bonnie E. Lonze, MD,[6] Ashley A. Vo, PharmD,[1] Anna Runström, MSc,[5] Lena Laxmyr, PhD,[5] Kristoffer Sjöholm, PhD,[5] Åsa Schiött, PhD,[5] Elisabeth Sonesson, PhD,[5] Kathryn Wood, MD,[5] Lena Winstedt, PhD,[5] Christian Kjellman, PhD,[5] and Robert A. Montgomery, MD[6]

Study 06 design



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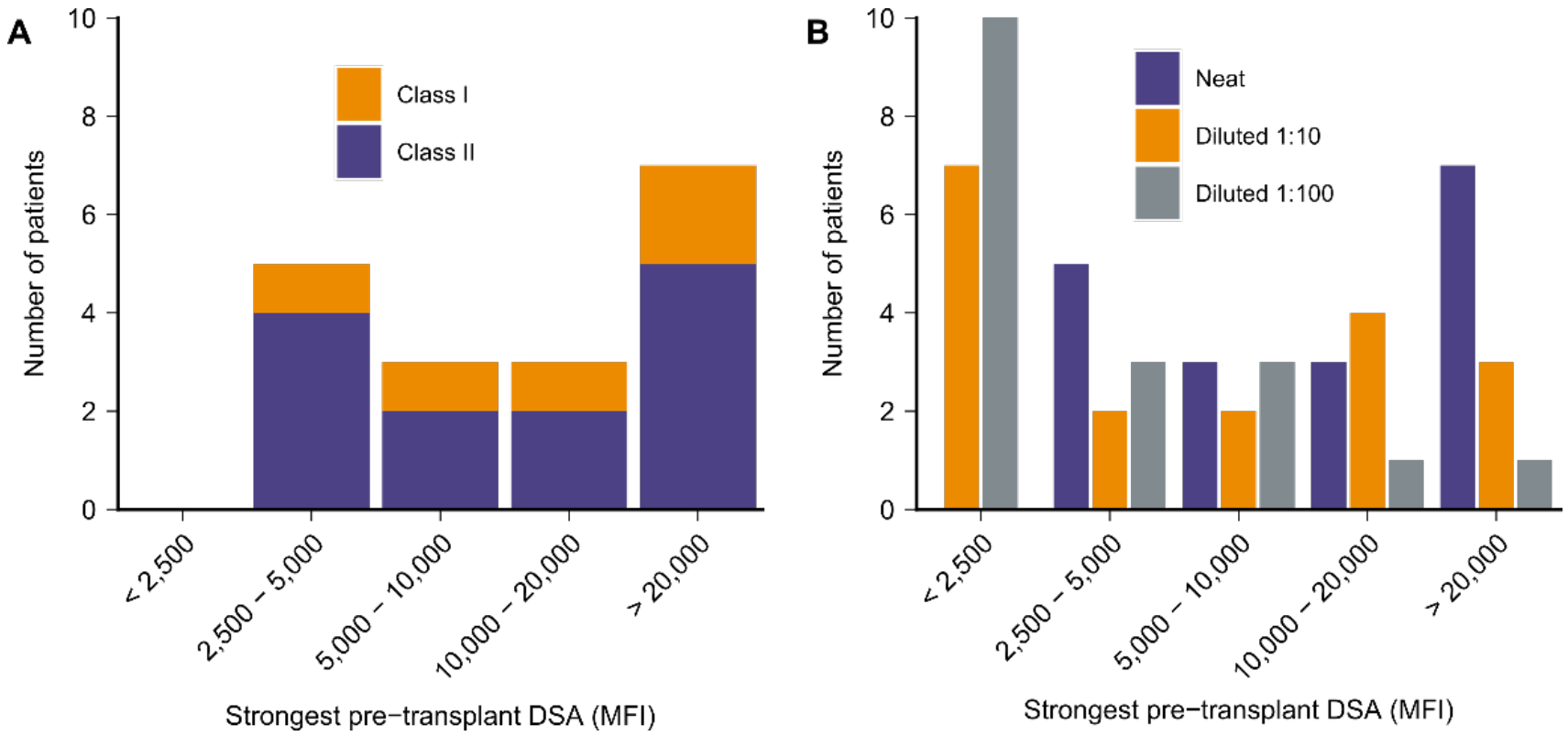
XM, crossmatch

Ref: Jordan SC, et al. Transplantation 2021;105(8):1808-1817

Pre-transplant antibody data

Number of recipients by DSA level



DSA were present in all individuals
Median recipient cPRA:

99.8%

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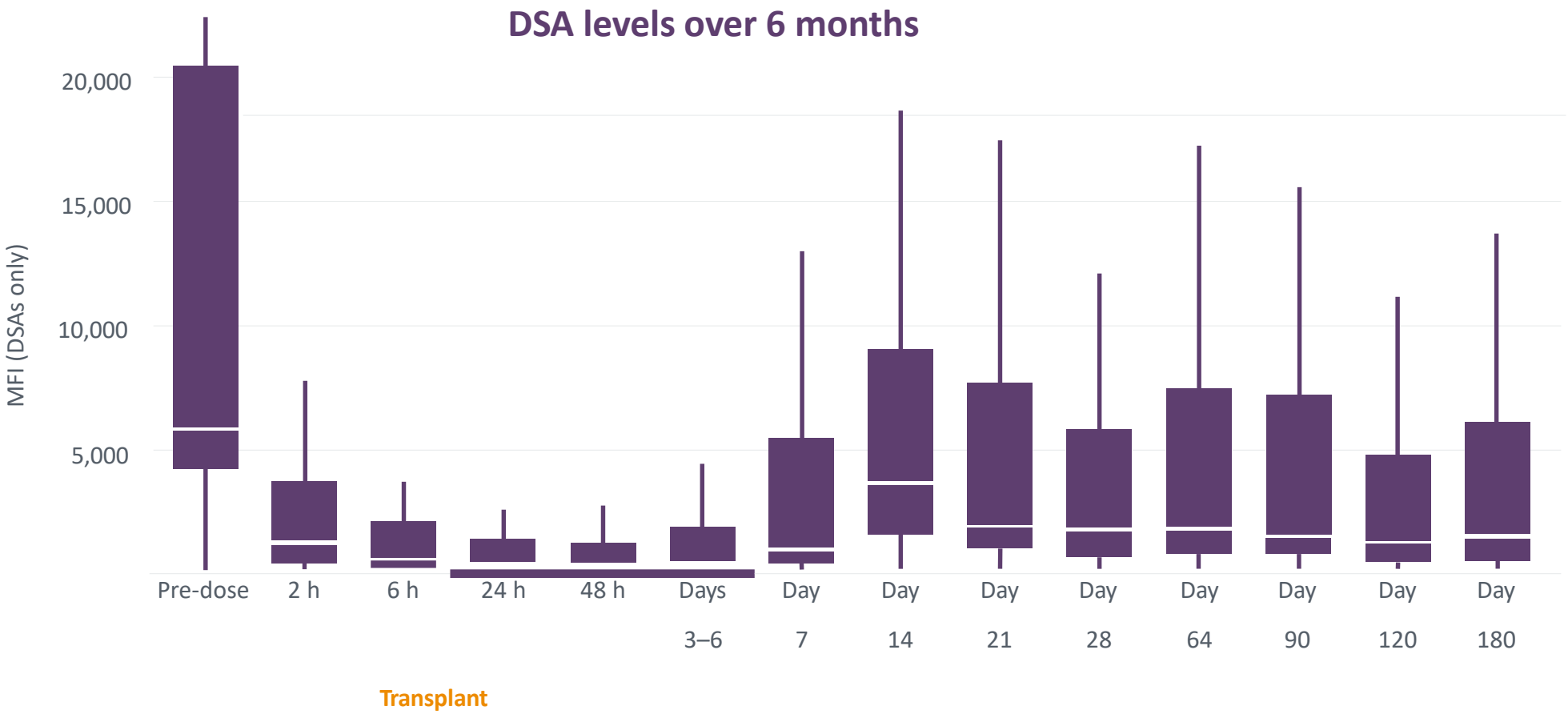
cPRA, Calculated panel reactive antibody

Ref: Jordan SC, et al. *Transplantation* 2021;105(8):1808-1817.

DSA pre- and post-imlifidase



Patient Survival
100%

Graft Survival
89%
(two Primary non-function)

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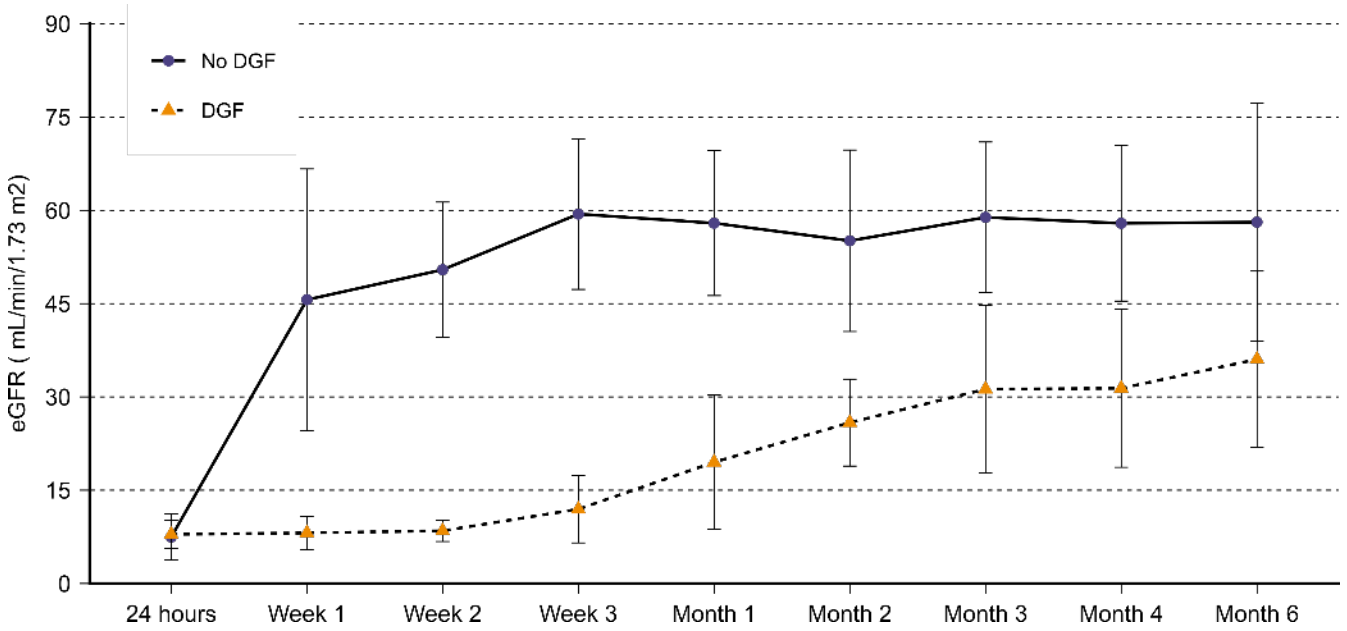
Ref: Jordan SC, et al. *Transplantation* 2021;105(8):1808-1817.

Graft function

eGFR calculated from serum creatinine



Median eGFR at 6 months:
47 mL/min/1.73 m^2

Mean eGFR at 6 months with DGF
36 mL/min/1.73 m^2

Mean eGFR at 6 months without DGF
58 mL/min/1.73 m^2

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eGFR, estimated glomerular filtration rate; DGF, Delayed graft function

Ref: Jordan SC, et al. *Transplantation* 2021;105(8):1808-1817.

Long-term Follow Up Of imlifidase Desensitized Kidney Transplant Recipients: 5 Year Pooled Analysis

- 4 single-arm,
  open-label, phase 2 studies: 02, 03, 04, 06
- 46 adult patients
  treated with imlifidase prior to kidney transplantation
- 39
  XM-positive patients
  included in this analysis

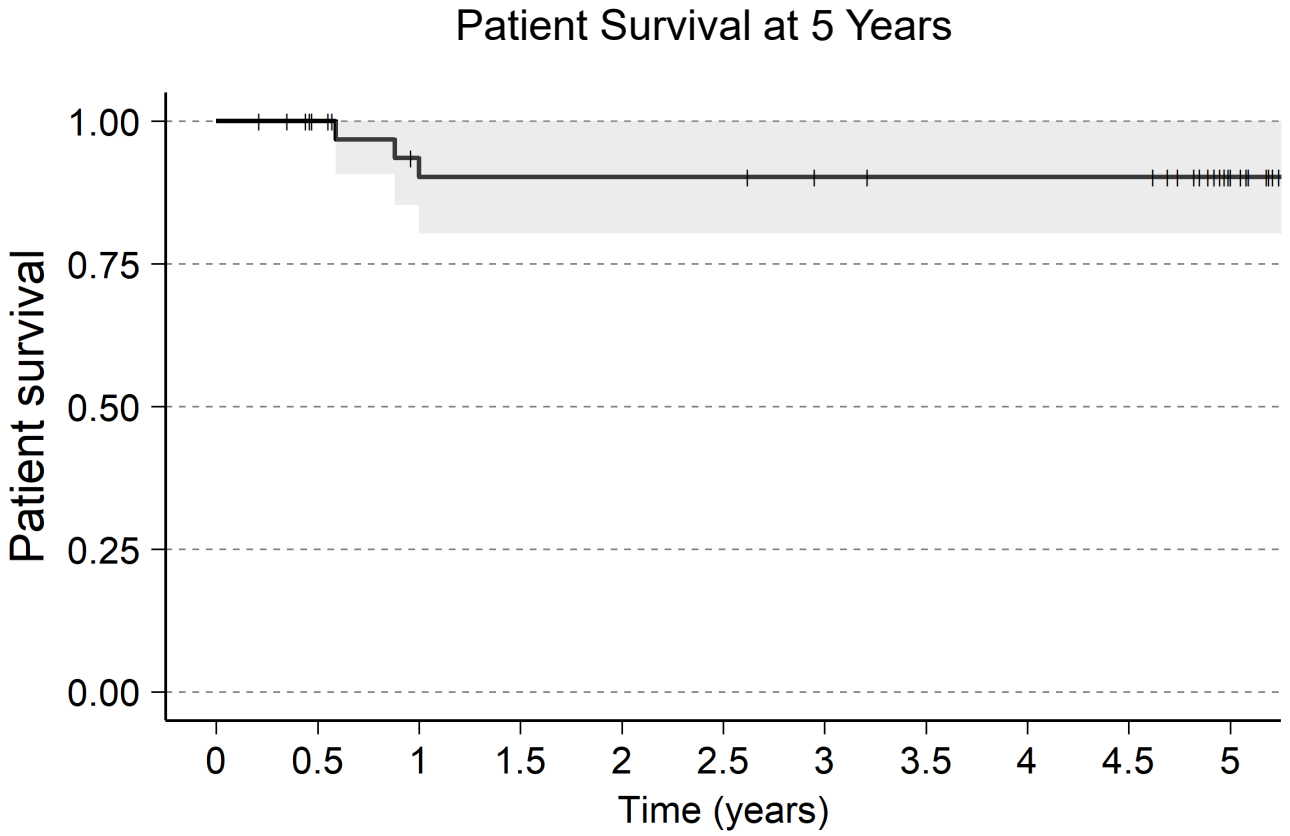
https://clinicaltrials.gov/search?term=NCT03611621 Kjellman C. et al. Am J Transplant. 2021;21:3907–3918 & non-published internal data
S. Jordan et al abstract #1330 ATC20204

Patient Survival at 5 Years = 90%

Patient survival at 6-months: 100%

Patient survival at 3 and 5 years: 90%

- 3 deaths occurred between 6 months and 1 year:
  - 1 death was attributed to pseudomonas bacteremia/influenza,
  - 1 due to cardiac arrest;
  - the cause of the third death was unknown.
- No deaths occurred between 1 and 5 years



Patient survival estimated with Kaplan-Meier. Alive patients are censored at last known visit, indicated in graphic as a thin vertical line

https://clinicaltrials.gov/search?term=NCT03611621 Kjellman C. et al. Am J Transplant. 2021;21:3907–3918 & non-published internal data
S. Jordan et al abstract #1330 ATC20204

5 Year Pooled Analysis

Death-Censored Graft Survival at 5 Years = 82%

3 graft losses in the feeder studies:

- 1 non-IgG mediated hyperacute rejection
- 2 due to primary non-functioning grafts

2 graft losses occurred between 2 and 3 years:

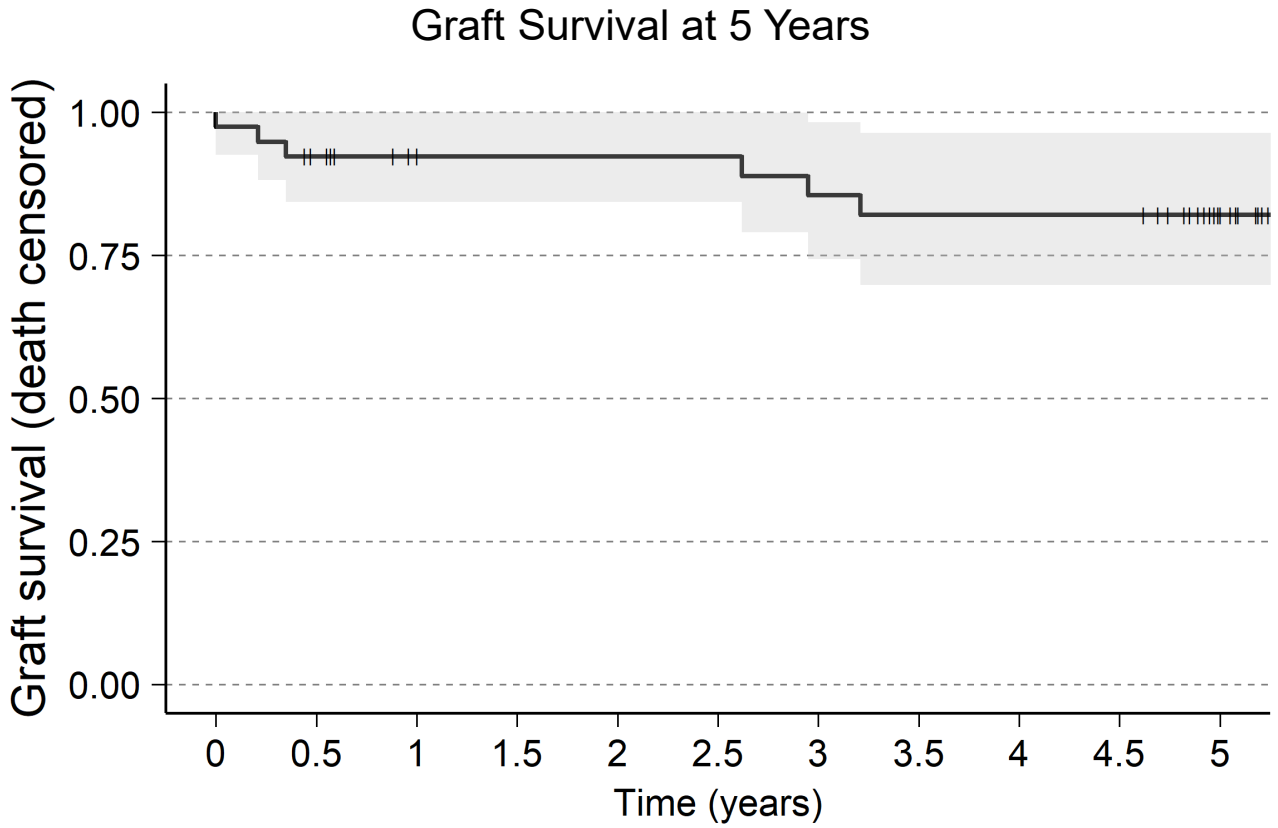
- 1 due to reduction of immunosuppression secondary to an infection
- 1 due to immunosuppression medication non-adherence

1 graft loss occurred between 3 and 5 years:

- 1 due to decline in graft function over time

3-year allograft survival, XM+: 84%

5-year allograft survival, XM+: 82%



Graft survival estimated with Kaplan-Meier. Patients without graft loss are censored at last known visit or death, indicated in graphic as a thin vertical line

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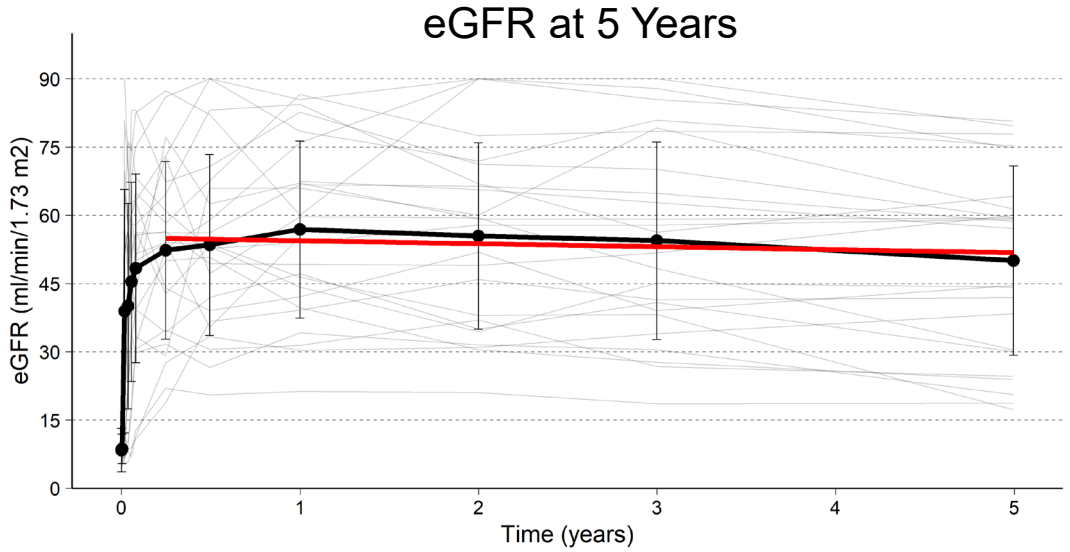
https://clinicaltrials.gov/search?term=NCT03611621 Kjellman C. et al. Am J Transplant. 2021;21:3907–3918 & non-published internal data
S. Jordan et al abstract #1330 ATC20204

5 Year Pooled Analysis

eGFR by MDRD at 5 Years = 50 mL/min/m2

eGFR at 3 years: 54 mL/min/1.73 m²
(n=23 patients with functioning graft and available data at 3y)

eGFR at 5 years: 50 mL/min/1.73m²
(n=24 patients with functioning graft and available data at 5y)



eGFR with individual patient data (thin gray lines), mean (black line), standard deviation (error bars), and red line is a linear regression from 30 days up 5 years.
Only subjects with data in follow-up included (N=24) and only timepoints with atleast N=20 subjects included

eGFR (mL/min/1.73 m²), N=24	Year 1, N (%)	Year 2, N (%)	Year 3, N (%)	Year 5, N (%)
15-30	1 (4%)	1 (4%)	3 (12%)	5 (21%)
30-45	7 (29%)	7 (29%)	6 (25%)	6 (25%)
45-60	5 (21%)	6 (25%)	6 (25%)	6 (25%)
>60	11 (46%)	10 (42%)	8 (33%)	7 (29%)
Missing	0 (0%)	0 (0%)	1 (4%)	0 (0%)

https://clinicaltrials.gov/search?term=NCT03611621 Kjellman C. et al. Am J Transplant. 2021;21:3907–3918 & non-published internal data S. Jordan et al abstract #1330 ATC20204

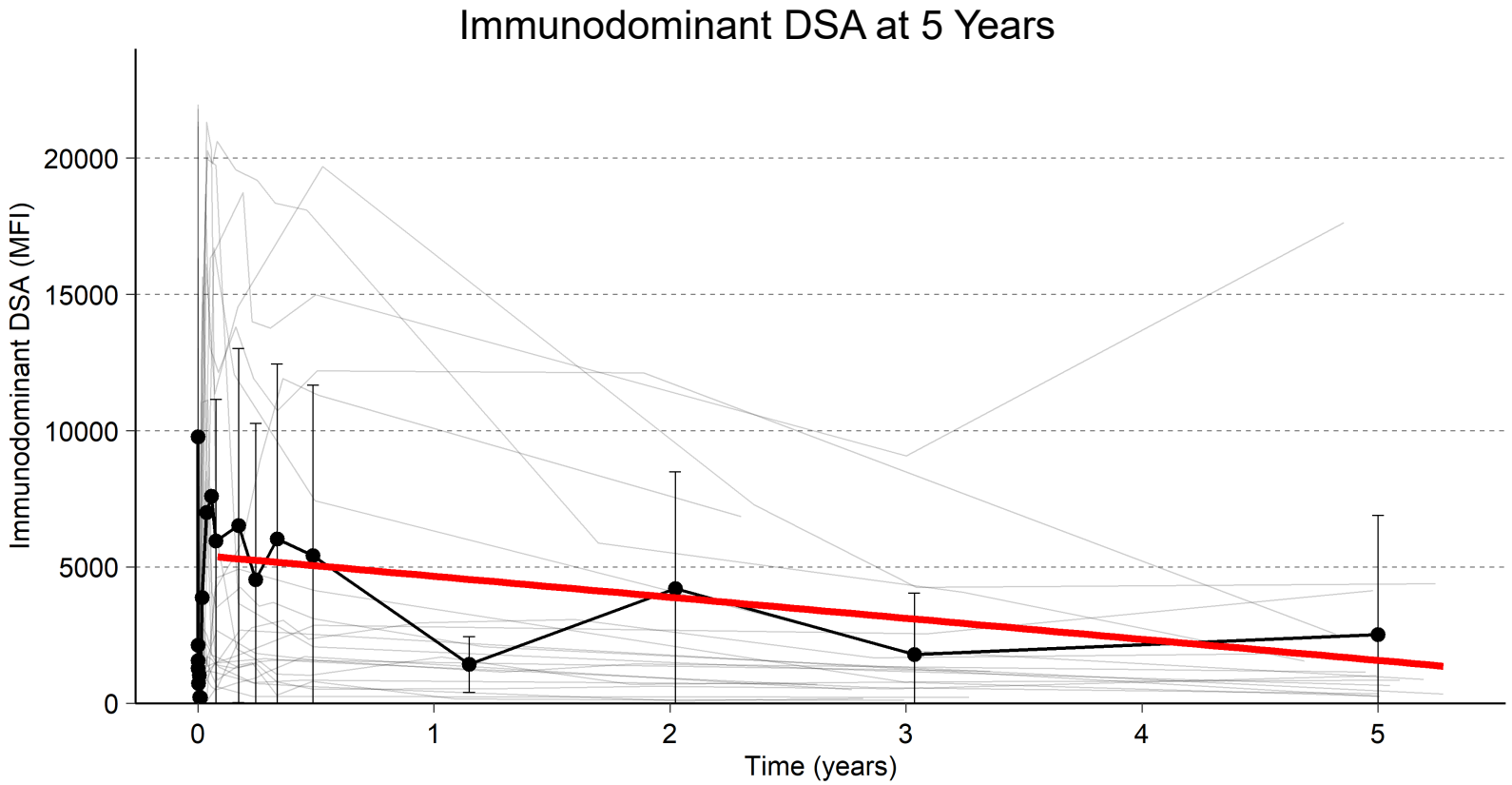
5 Year Pooled Analysis
Analysis of Immunodominant Donor Specific Antibody at 5 Years

Median MFI for immunodominant DSA levels pretreatment:

6552 (IQR: 4225, 15,944)

General trends:

- **MFI remained low ~ 1 week**
- **Rebounded to ~80% of pre-treatment levels**
- **DSA levels progressively decreased over time**



DSA with individual patient data (thin gray lines), mean (black line), standard deviation (error bars), and red line is a linear regression from 30 days up 5 years.
Only subjects with data in follow-up included (N=22)

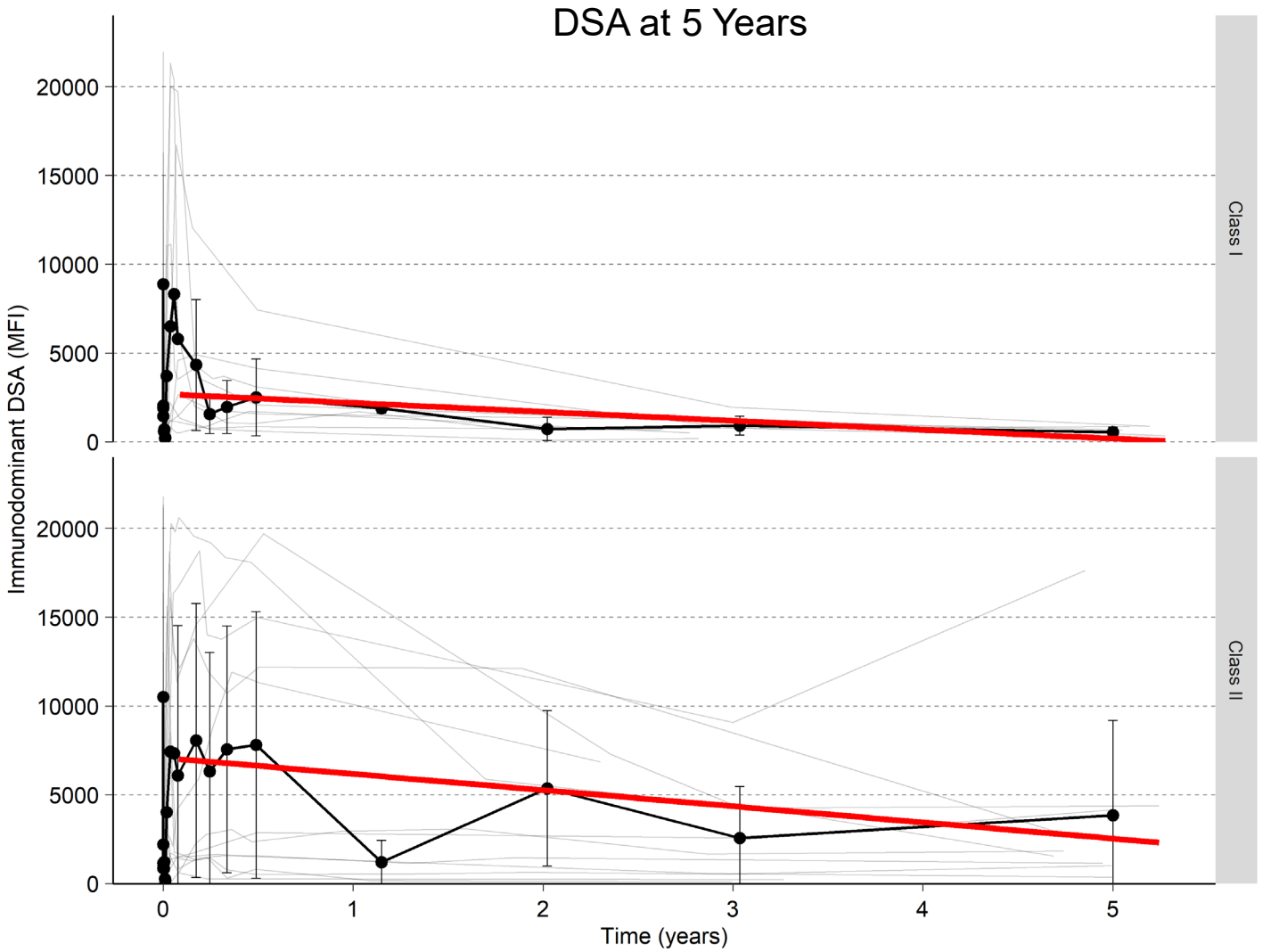
https://clinicaltrials.gov/search?term=NCT03611621 Kjellman C. et al. Am J Transplant. 2021;21:3907–3918 & non-published internal data
S. Jordan et al abstract #1330 ATC20204

5 Year Pooled Analysis

Analysis of Donor Specific Antibody at 5 Years

Median MFI for immunodominant DSA levels pretreatment:

- **Class I**
  7258 median (IQR: 3709, 13,427)
- **Class II**
  6193 median (IQR: 4438, 17,549)



DSA with individual patient data (thin gray lines), mean (black line), standard deviation (error bars), and red line is a linear regression from 30 days up 5 years. Only subjects with data in follow-up included (Class I N=10, Class II N=12)

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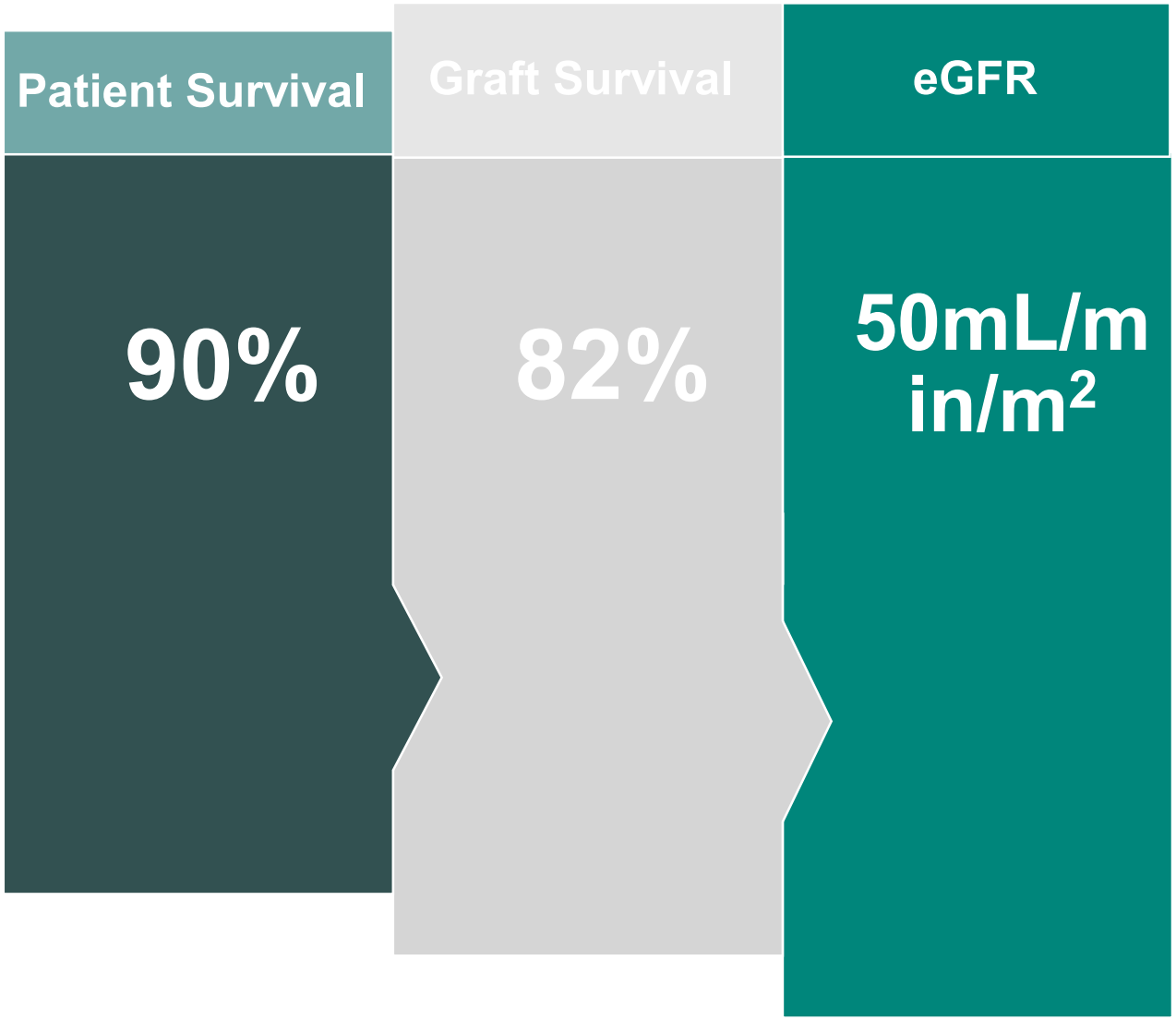
https://clinicaltrials.gov/search?term=NCT03611621 Kjellman C. et al. Am J Transplant. 2021;21:3907–3918 & non-published internal data
S. Jordan et al abstract #1330 ATC20204

Summary

Five years after imlifidase-enabled desensitization and transplantation



The highest risk for AMR is during the first weeks

Both early and late AMR responded to treatment with no attributable graft losses

The majority of the grafts continue to function well up to 5 years

Imlifidase is a potential option to enable transplantation for highly sensitized patients for whom lifetime dialysis, and its accompanying morbidity may be the only alternative.

https://clinicaltrials.gov/search?term=NCT03611621 Kjellman C. et al. Am J Transplant. 2021;21:3907–3918 & non-published internal data
S. Jordan et al abstract #1330 ATC20204

Requirements for selecting a patient

Patients eligible for this treatment
- cPRA ≥ 98% (on the last serum)
- Age ≤ 65 years
- Time on the waiting list ≥ 3 years
- Number of previous kidney transplantation from: 0 to 2 (multidisciplinary consensus required beyond 2 grafts)
- Kidney graft biopsy with a low risk of complication
- Patient information

Transplant unit profile
Access to plasmapheresis 7 days a week

Delisting of HLA antibodies
Allow only HLA antibodies with MFI not exceeding 5000 after 1:10 dilution

Organ offer

Donor profile: Avoid
elderly donors
donation after cardiac death
long ischemia time
acute kidney injury

DSA
MFI of immunodominant DSA A, B, DRB1, DQB1 > 6000 except for Cw and DP

Pre-Imlifidase virtual positive crossmatch on recent serum
(No cell crossmatch)

Imlifidase 0.25 mg/kg

4 to 6 hours after Imlifidase infusion

Cell crossmatches
- Prospective post-Imlifidase negative complement-dependent cytotoxicity crossmatch
- Prospective (or retrospective) flow cytometry crossmatch on recent, and day 0 pre- and post-Imlifidase sera

Transplantation

Timeline

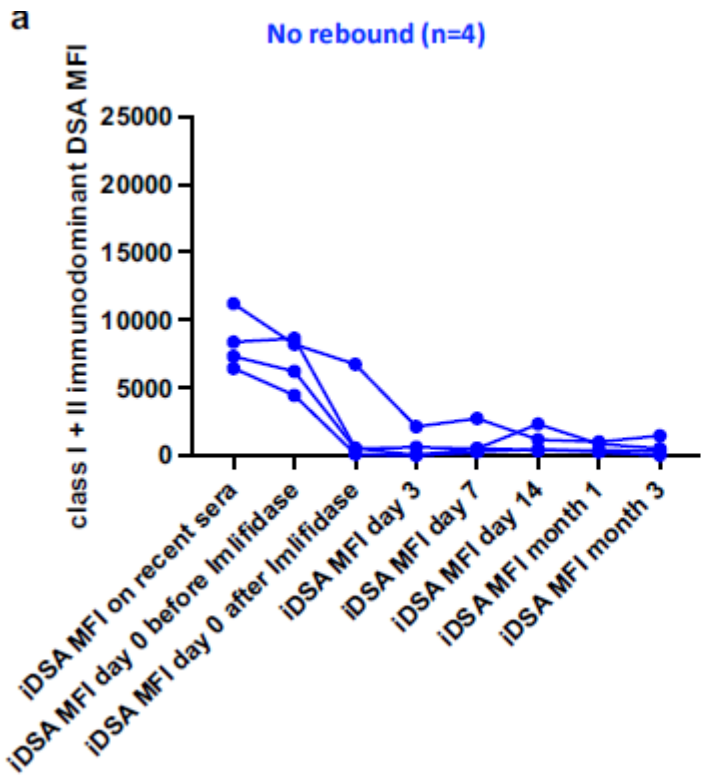
Imlifidase for Kidney Transplantation of Highly Sensitized Patients With a Positive Crossmatch: The French Consensus Guidelines

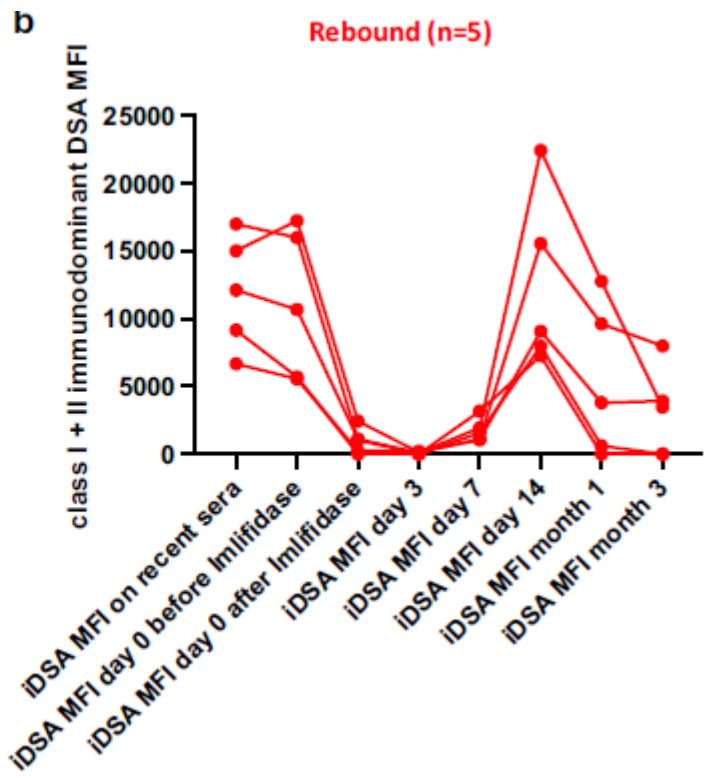
Couzi, Transpl Int 2023

Imlifidase in Highly Sensitized Kidney Transplant Recipients With a Positive Crossmatch Against a Deceased Donor

- 9 PAZIENTI, >3M F-U
- PRA>99% (2), PRA>100% (7); iDSA medMFI 9153; mDSA n=4
- Pre-imlifidase: FCXM POS (9), CDC XM POS (2)
- 5 DSA REBOUND: 2 ABMR, 2 SUBCLINICAL ABMR, 1 C4d POS
- NO GRAFT LOSS, NO PATIENT LOSS

Kamar, KIreports 2024

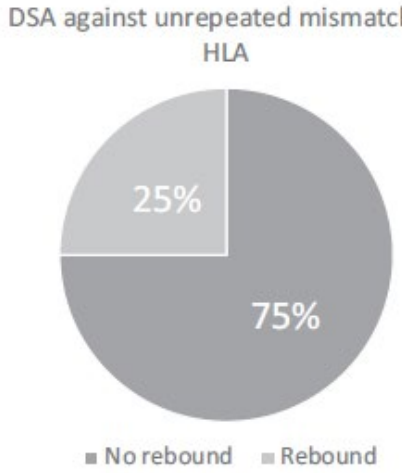


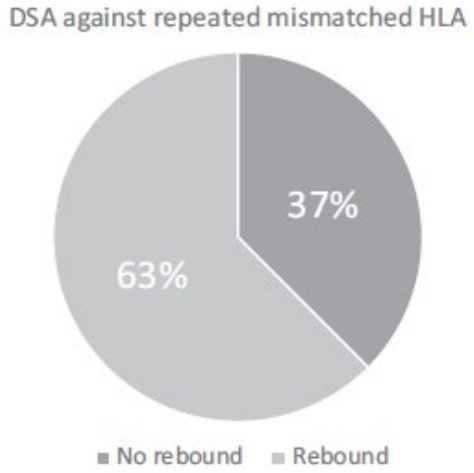


5/9 REBOUND

4/9 ABMR

P5: CDC XM POS
+7d: sMFI 97000. creatinina 600
ABMR, ECU, subcl AMR





rMM DSA: 5/8 rebound
NO r MM DSA: 7/28 rebound

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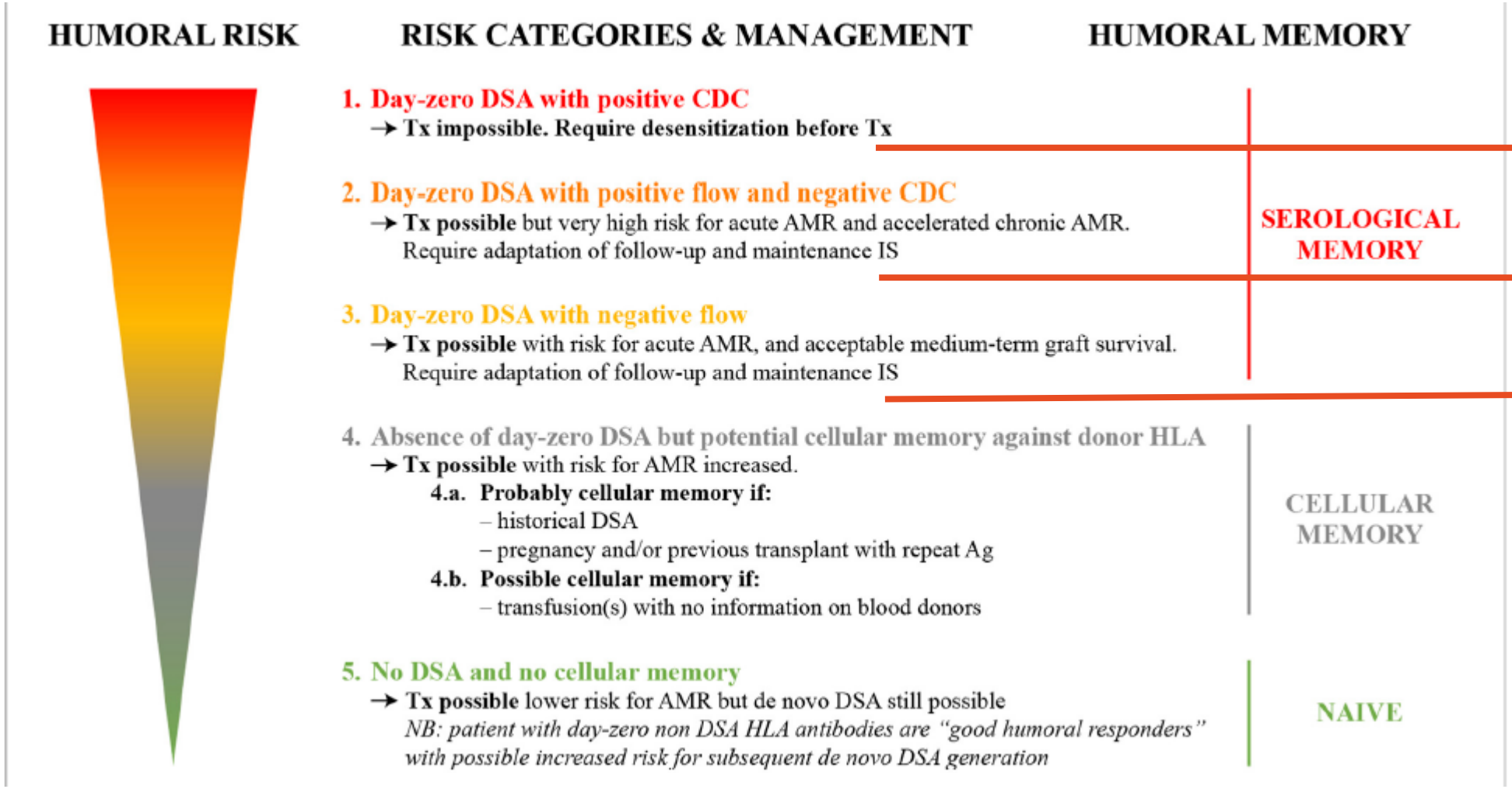
Kamar, KIreports 2024



In Italia

Cat1. No Transplant
Note di raccomandazioni CNT

Cat2. IMLIFIDASE

Cat3. PNI

European Consensus on the Management of Sensitized Kidney Transplant Recipients: A Delphi Study

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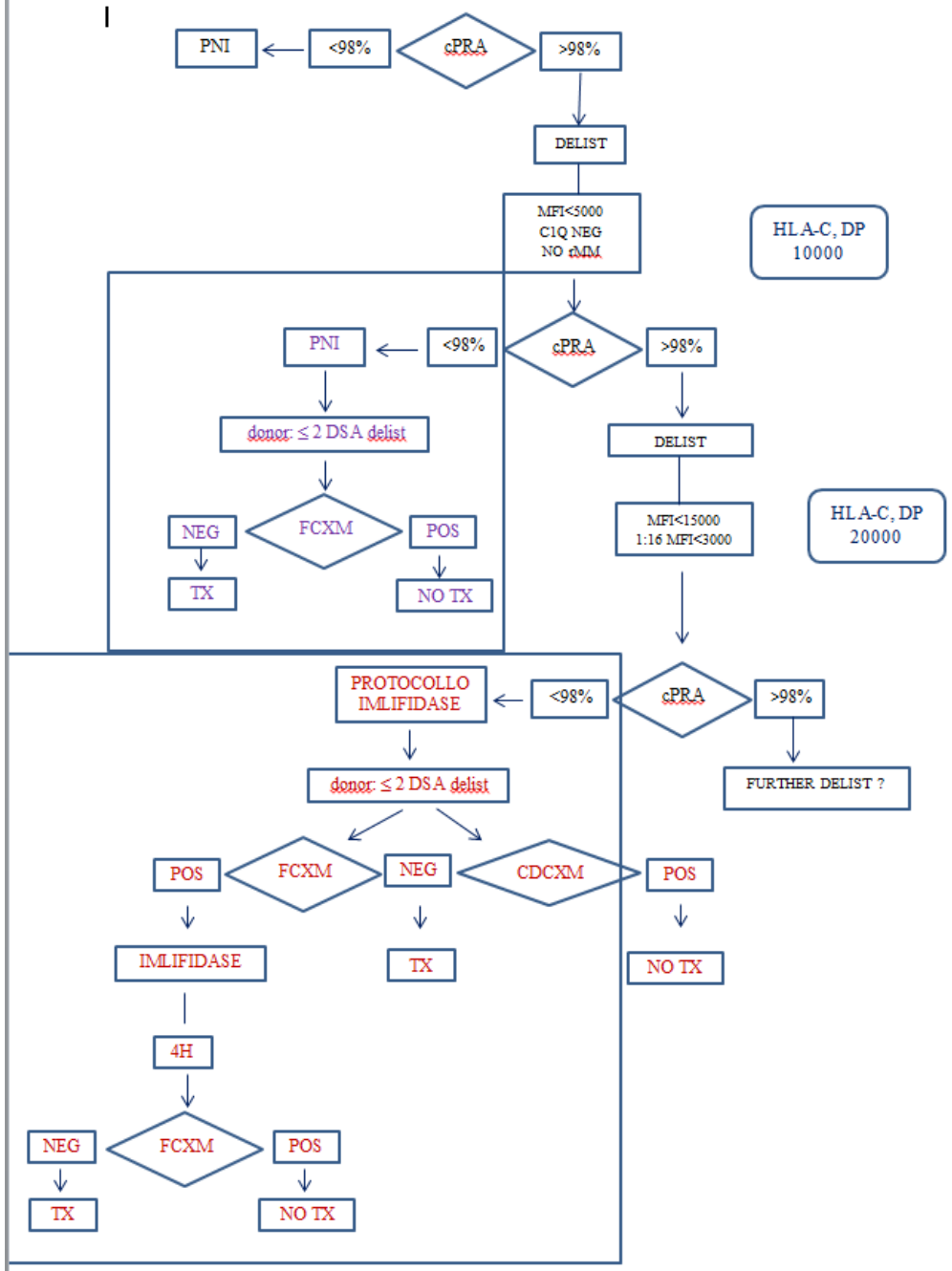
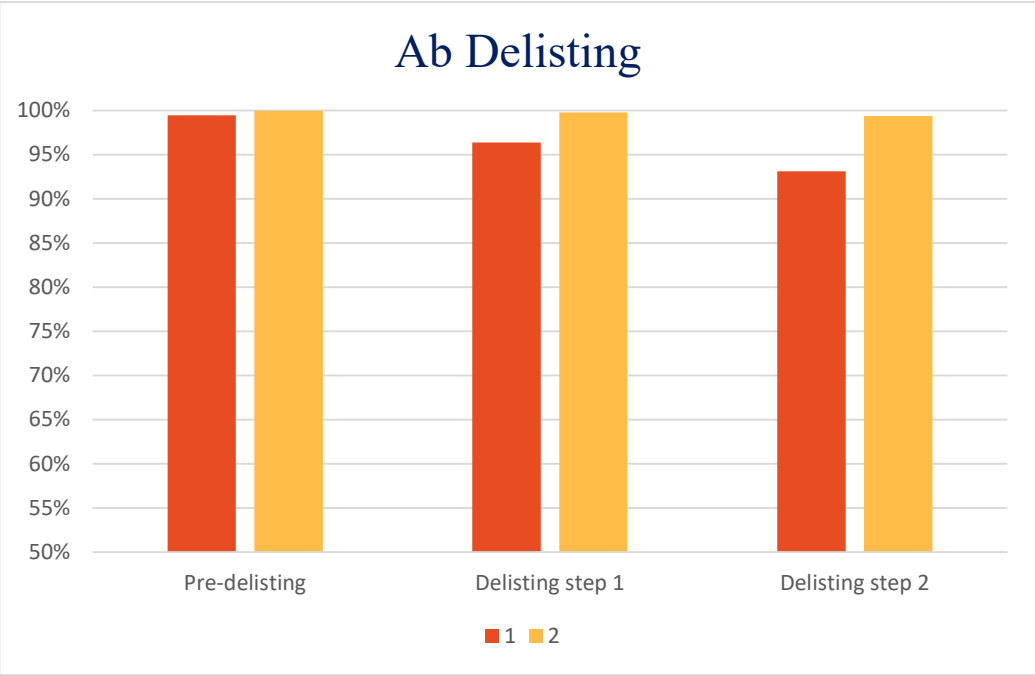
Bestard, Transpl Int 2021 Mamode, Transpl Int 2022 Furian, Transpl Int 2024



PROTOCOLLO DELISTING EMILIA-ROMAGNA PNI E IMLIFIDASE



Patient	Pre-delisting	DelIsting step 1	Delisting step 2
	I + II	I + II	I + II
1	99.48%	96.40%	93.13%
2	99.98%	99.79%	99.39%

OBIETTIVO: PRA<98%
STEP 1: PNI
STEP 2: IMLIFIDASE

Centro Nazionale Trapianti

PROTOCOLLO NAZIONALE IPERIMMUNI

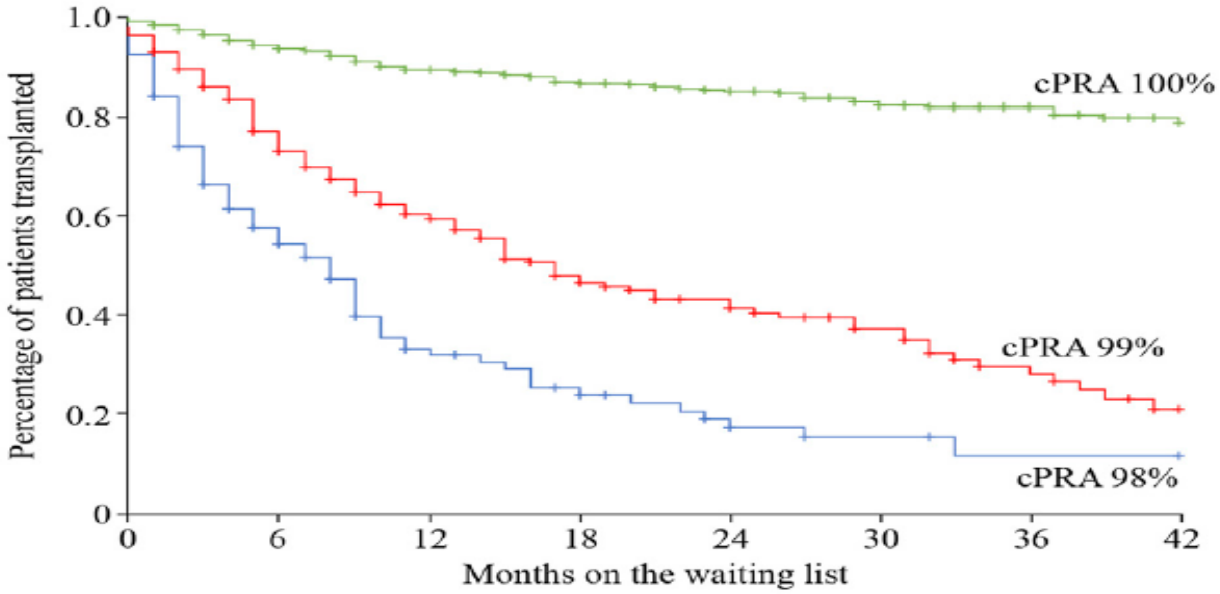
Criteri di accesso al PNI 3.0

L'inserimento del malato nel PNI 3.0 richiede obbligatoriamente:

I. **Anzianità di dialisi di almeno 8 anni**
II. **Soddisfacimento dei seguenti criteri immunologici:**
    - cPRA massimo >90%
    - Inoltro al CNT della lista degli antigeni proibiti (referto del laboratorio di riferimento)
III. **Firma di un consenso informato specifico**

CNT, PNI

ONT.es, PATHI



PNI – tempo medio attesa Tx

- 2011-2023: 0.87 A
- 2011: 0.3 A
- 2023: 1.6 A

PNI – iscritti (31/12/23)

267

217 (81%) PRA 99-100%

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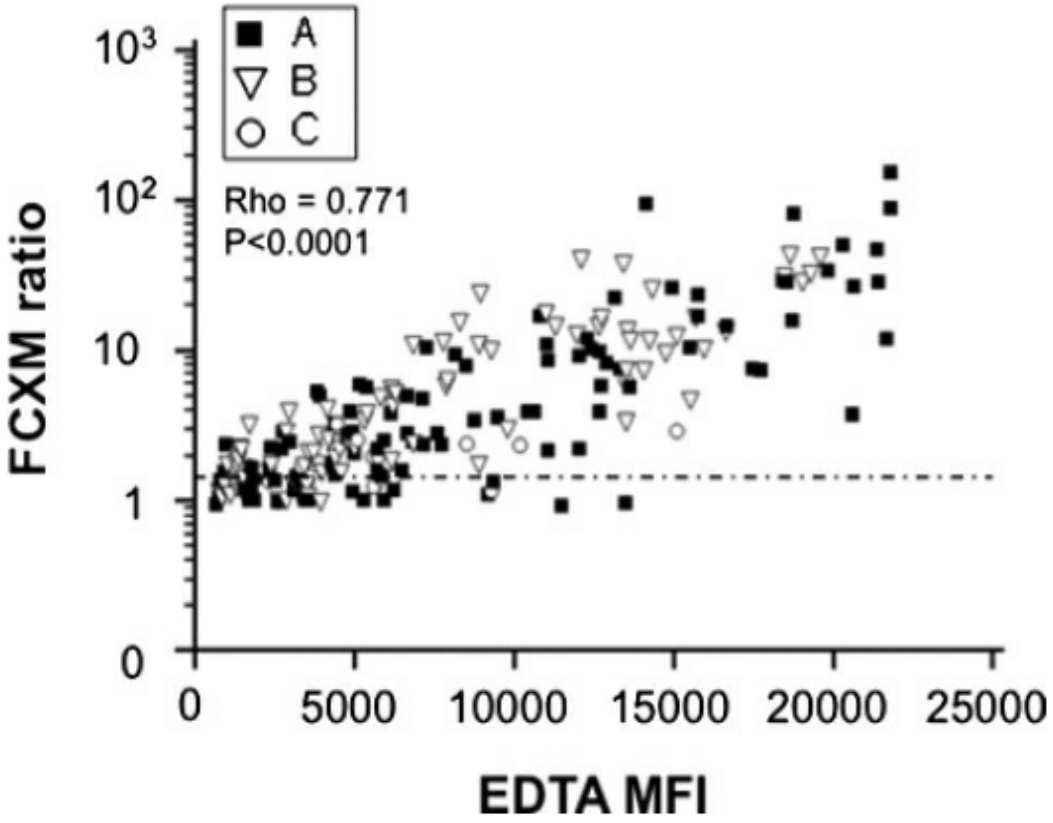
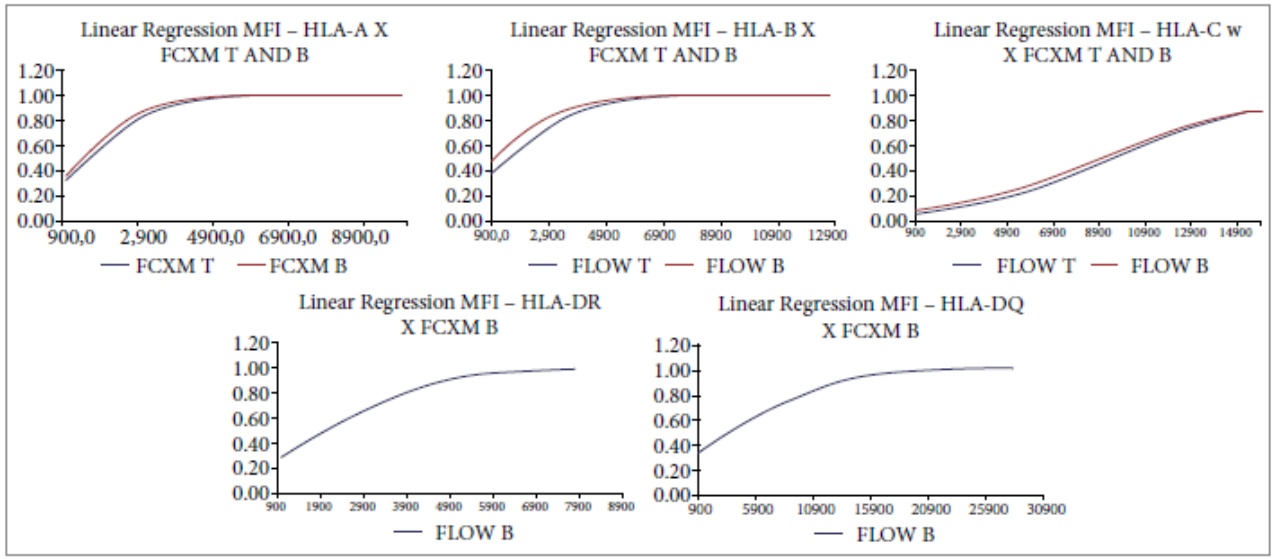
CNT - Centro Nazionale Trapianti

Mamode, Transpl Int 2022

MFI PREDITTIVI FCXM





SAB One Lambda

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Visentin, Transplantation 2017 Schiavo, BJT 2023

cPRA>98%

↓

DELIST

↓

MFI<5000
C1q NEG
NO rMM

DONOR

NEG → TX

<98% → FCXM ◇

cPRA ◇

POS → NO TX

>98% → Second step of delisting

DELISTING PER PNI

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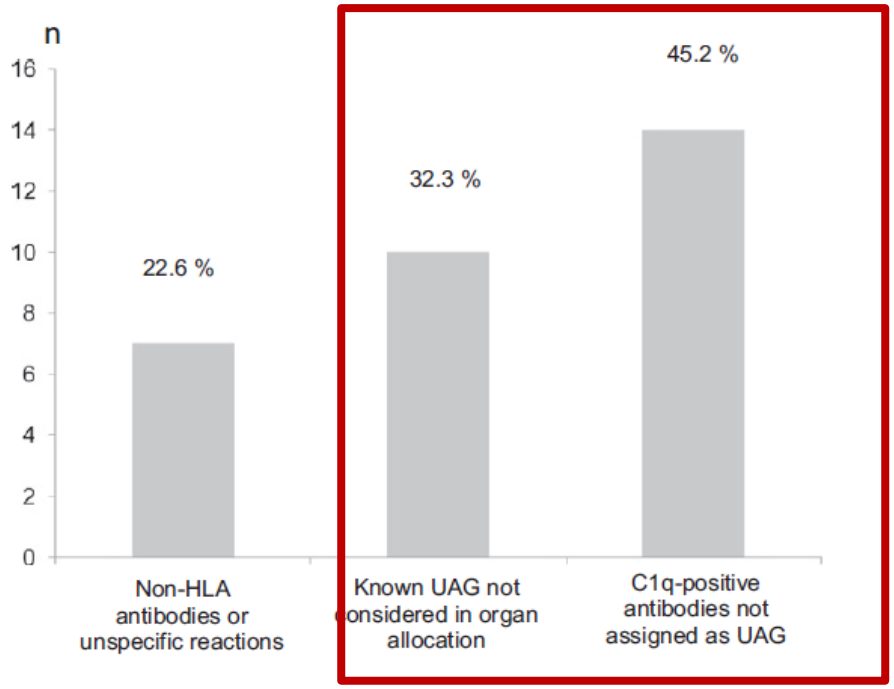
NOTA DI INDIRIZZO PER LA SELEZIONE DEI PAZIENTI IPERIMMUNIZZATI CANDIDATI AL TRAPIANTO DI RENE DOPO TRATTAMENTO DESENSIBILIZZANTE CON IDEFIRIX

1) La somministrazione di Idefirix è consentita solamente ai candidati al trapianto di rene con una età minima di 18 anni
2) I potenziali riceventi devono essere in dialisi da almeno 4 anni
3) I potenziali riceventi devono avere un PRA/cPRA uguale o superiore al 90%
4) Nei potenziali riceventi deve essere dimostrata la presenza di almeno un anticorpo donatore-specifico diretto contro il potenziale donatore deceduto disponibile. Nei confronti del potenziale donatore deceduto disponibile, il potenziale ricevente dovrà dimostrare una condizione di positività al cross-match virtuale, citofluorimetrico o citotossico complemento-dipendente (CDC-crossmatch).

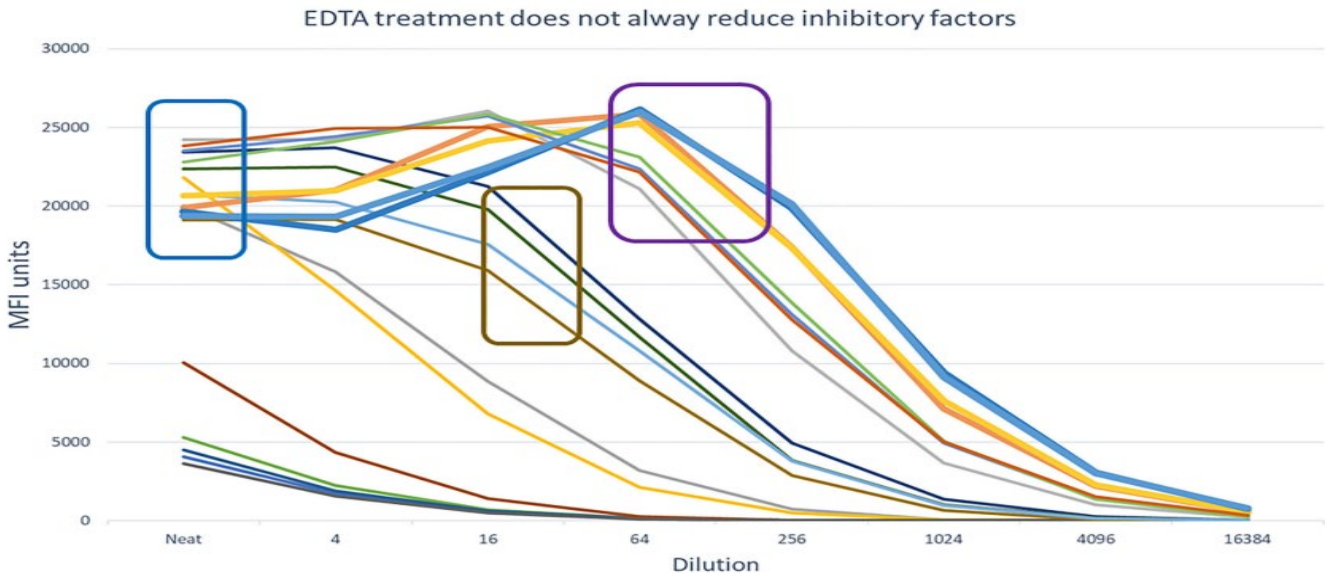
C1Q/C3D PREDITTIVO CDC-XM

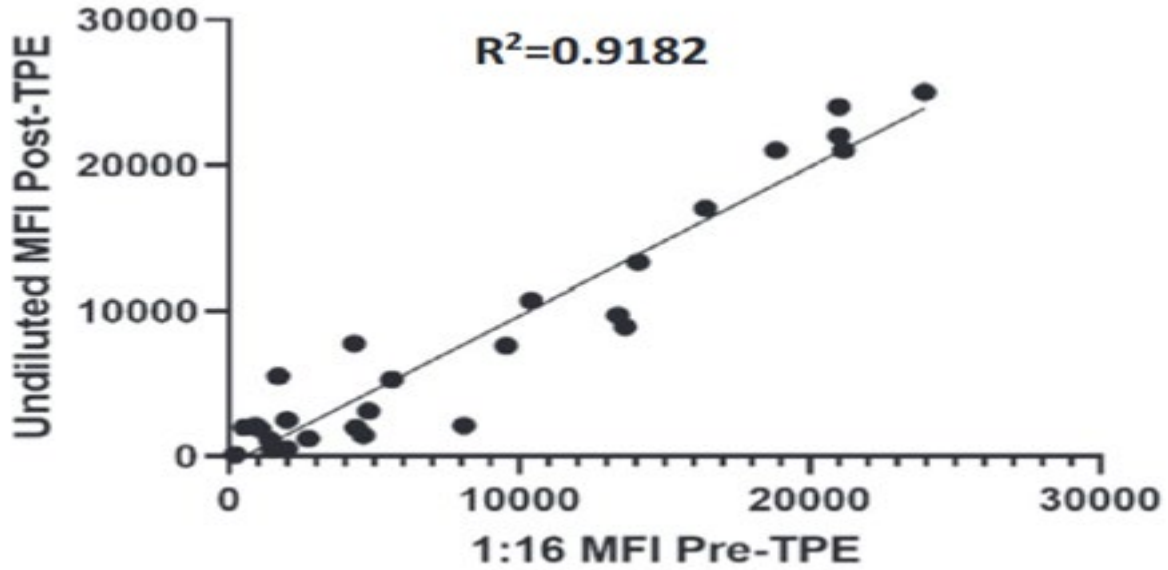


	T-cell CDC +	T cell CDC –
C3d-binding +	58	12
C3d-binding –	3[a]	104

	B-cell CDC +	B cell CDC –
C3d-binding +	44	6
C3d-binding –	4	39

Juhl, Transpl Imm 2017 Wong, HLA 2023





DIL 1:16

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Tambur, HLA 2022 Timofoeva, Transpl Int 2021

DELISTING PER IMLIFIDASE

cPRA>98%

↓

DELIST

↓

MFI<15000
DIL 1:16, MFI<3000
C1q NEG
NO rMM

↗

cPRA ◇

<98% → IMLIFIDASE

>98% → FURTHER DELIST?

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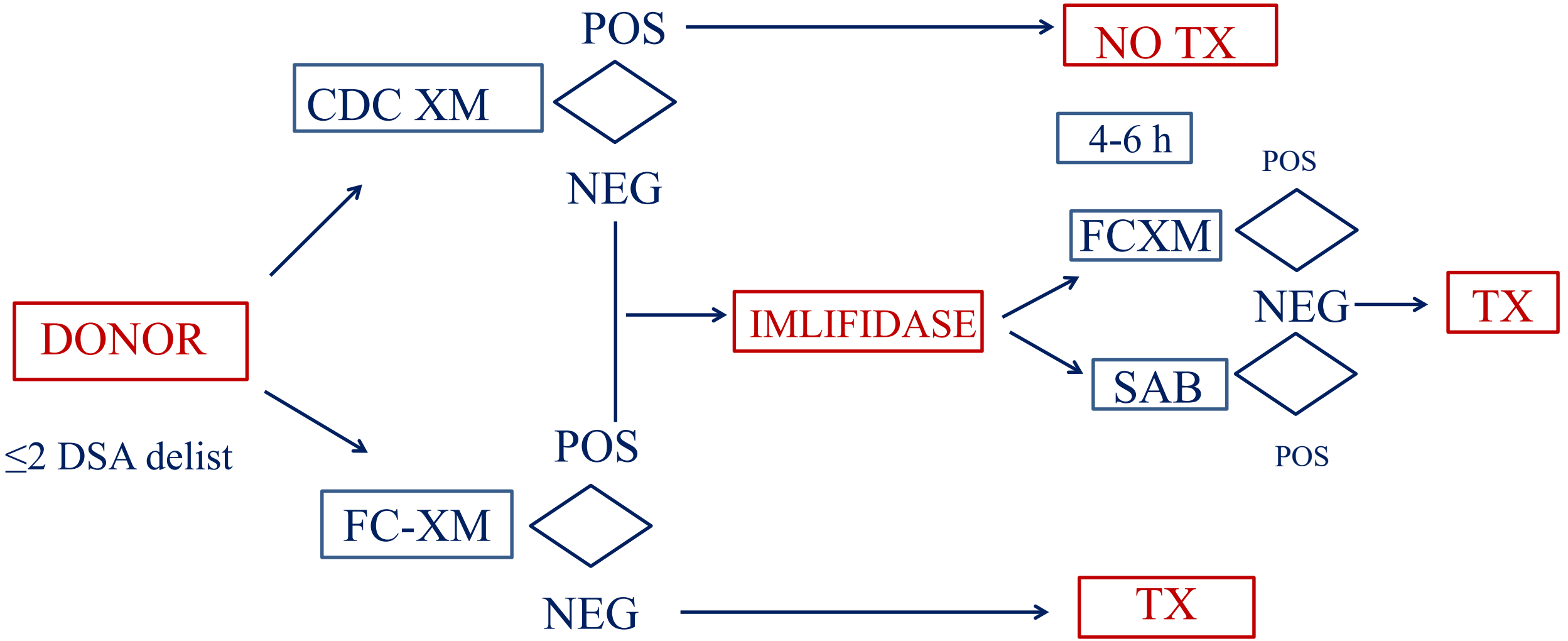

PROTOCOLLO IMLIFIDASE

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