IMLIFIDASE: ‘CHEMISCHE PLASMAFERESE’ BINNEN DE NEFROLOGIE

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DISCLOSURES

Speaker fee and advisory board fee HANSA Biopharma.

Research grant HANSA Biopharma.

Speaker fee Astellas BV.

imlifidase (Idefirix®)

EMA conditional approval:

desensibilisatie voor overleden donor niertransplantatie

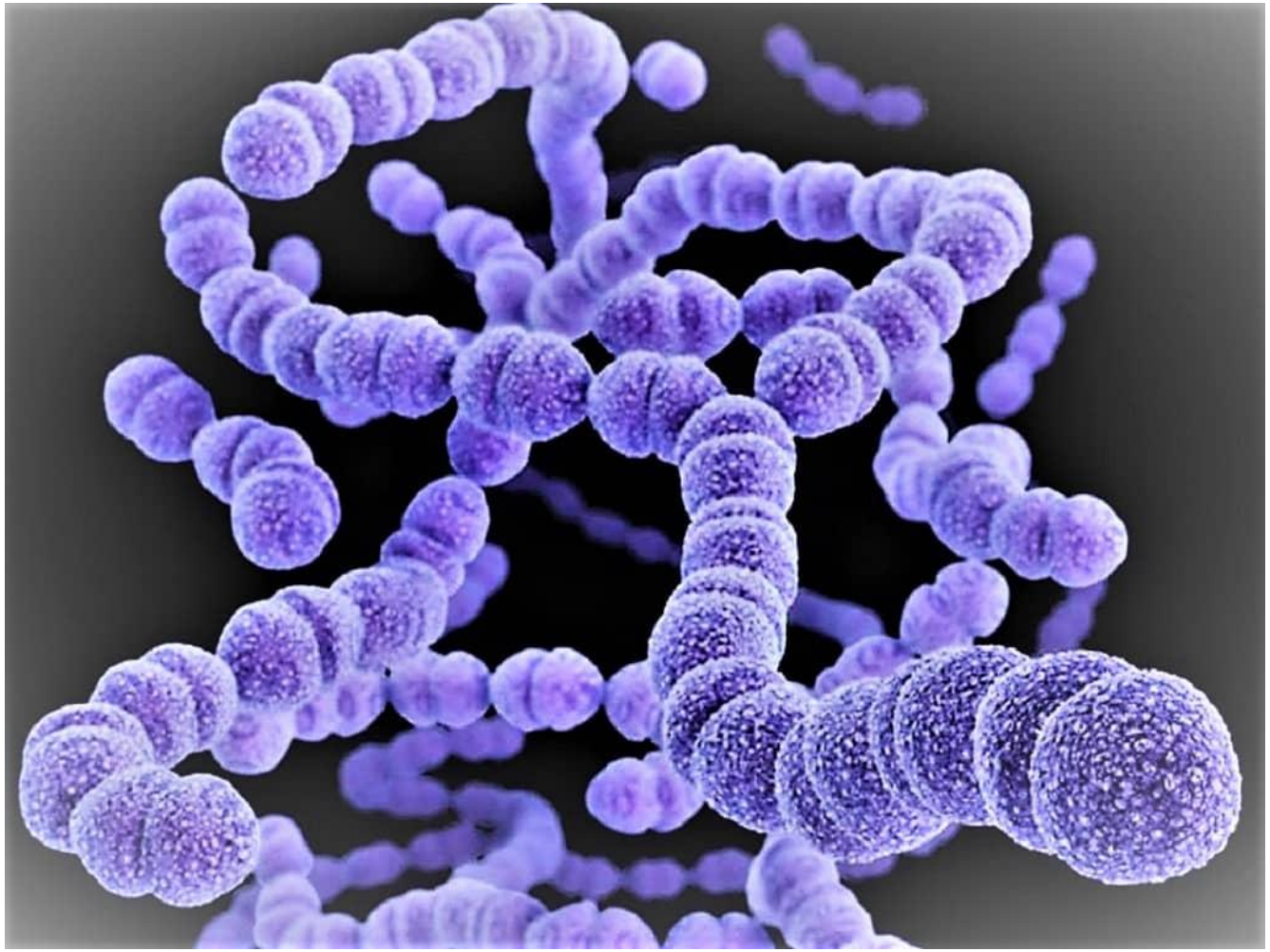
FDA: desensibilisatie RCT

studies:

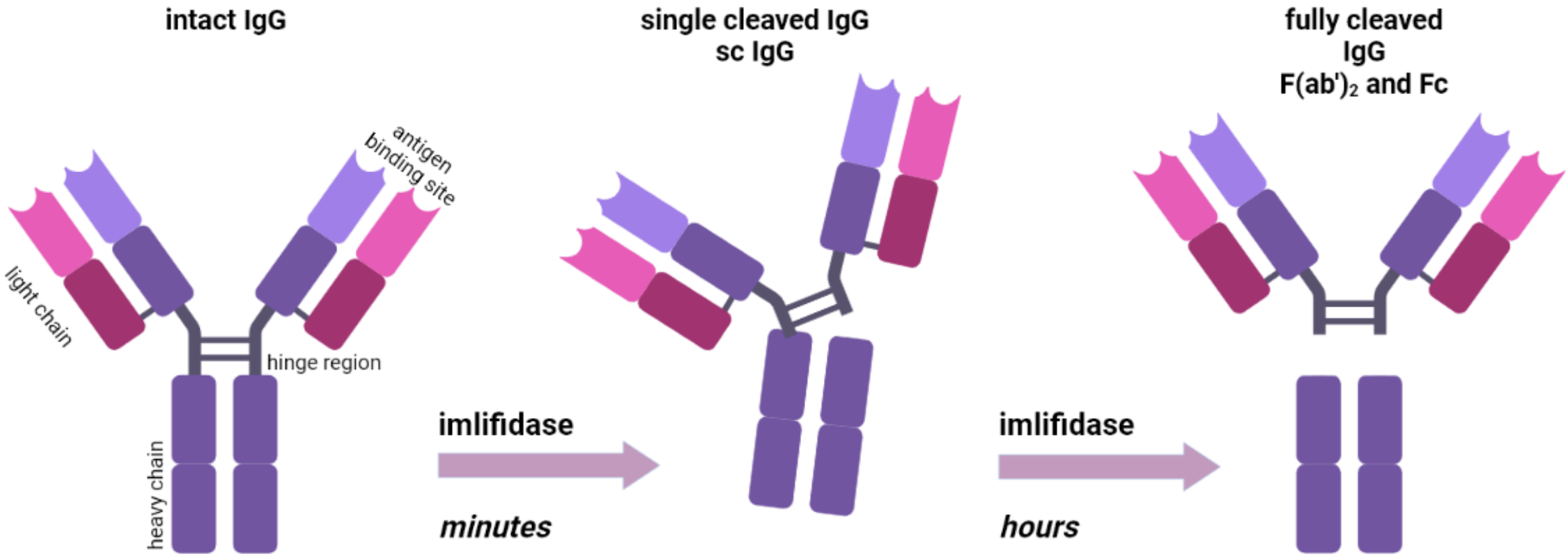
anti-GBM

ANCA-vasculitis

IdeS, 35 kDa cysteine protease

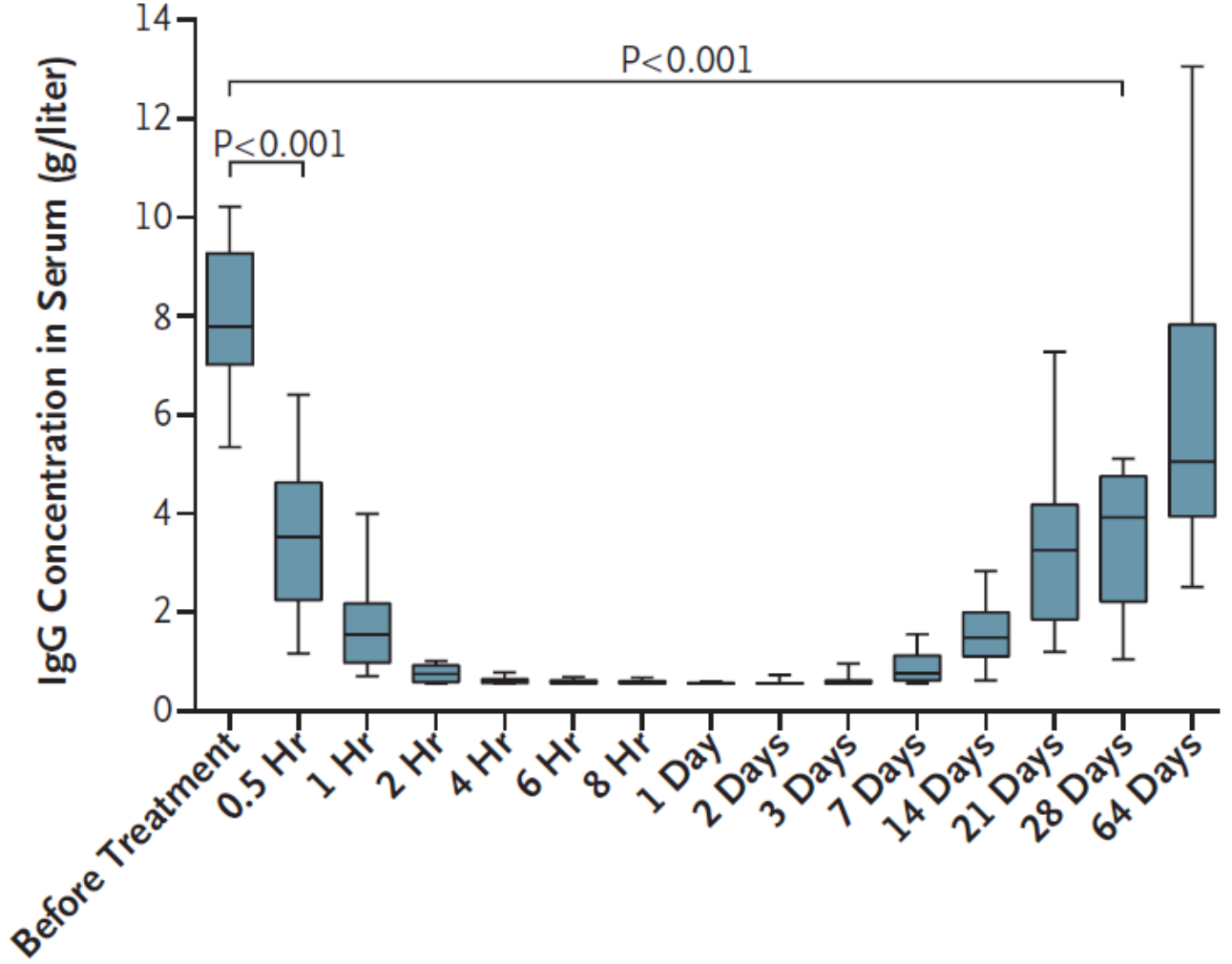


Imlifidase klieft (4 subclasses) IgG



De Weerd et al., submitted

IgG na 1-2 weken terug, 1-2 maanden richting uitgangsniveau



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Jordan et al., NEJM 2017.

“Chemische plasmaferese”

Geen complement en geen IgM

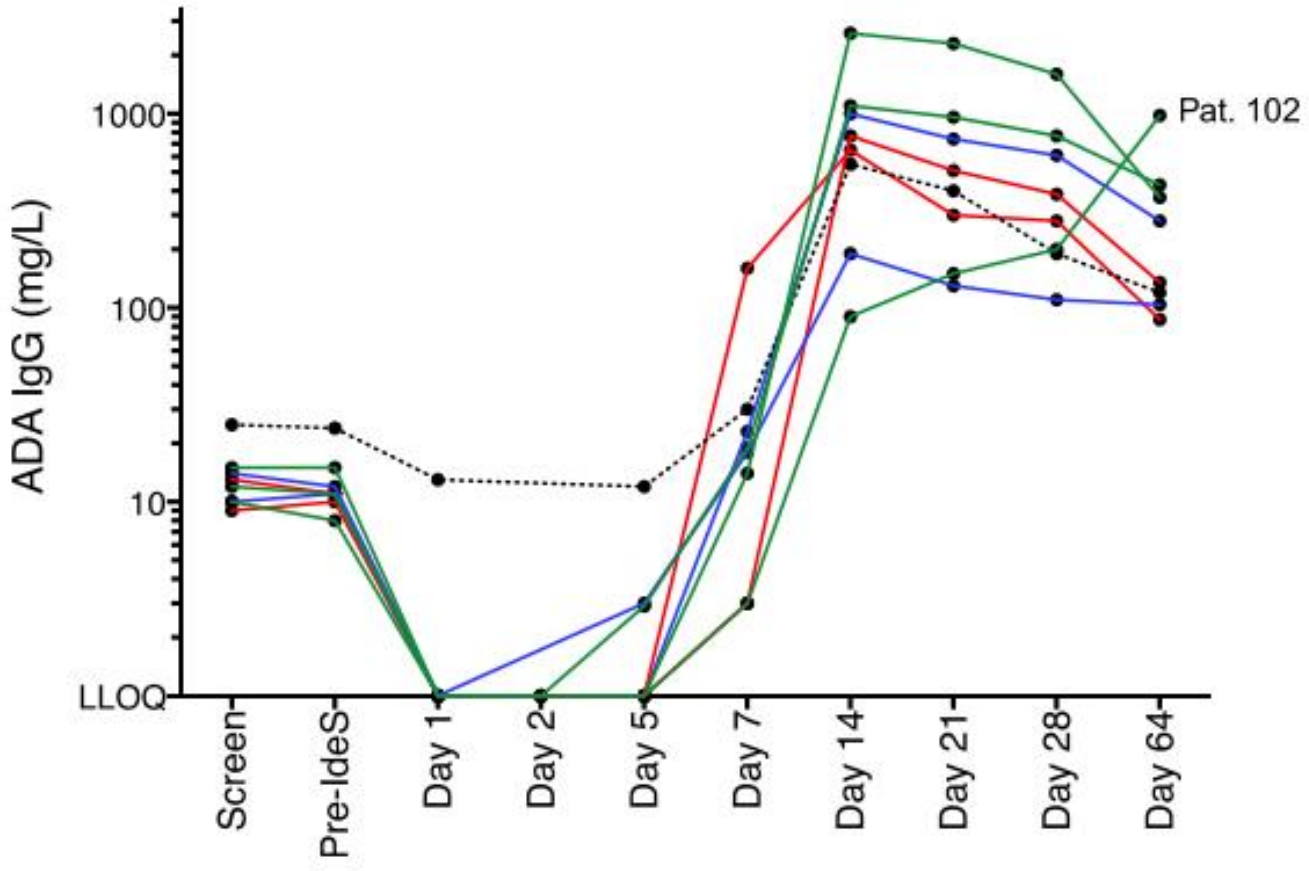
Extravasculair IgG

IgG gebonden aan B-cel receptor

Snel

Herhaalde toediening?

“van nature” anti-drug antibodies



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Winstedt et al, PLoS One 2015; Lorant et al., AJT 2018.

Pre-klinische studies

muis en rat IgG slechts gedeeltelijk gekliefd,

mens en konijn IgG wel geheel gekliefd

Diermodel:

ITP, Guillan-Barré, neuromyelitis optica, anti-GBM

Johansson et al., PLoS One 2008.; Wang et al. Exp Neurol 2017.; Tradtrantip et al., Mol Pharmacol 2013.; Yang et al. NDT 2010.

First-in human studies

proteïnurie na 24-48 u door eliminatie Fc fragments

terugkeer vaccinatie – IgG DKTP en *Haemophilus influenza* ≈ IgG pool

eliminatie gemiddeld 89 uur

Safety:

20% vrijwilligers ADA buiten arbitraire range → geëxcludeerd

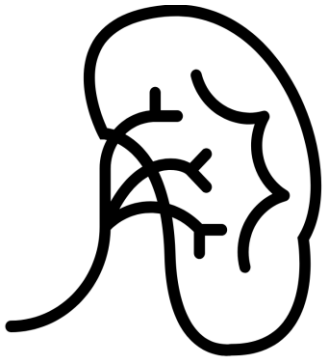
1/20 infusie reactie (geen IgE)

luchtweginfecties

Winstedt et al. PLoS One 2015.

Proof of concept studies

TTP by ADAMTS13-antibodies:
n=2 serum sickness



ANCA vasculitis, PR3-GPA
(ECMO, rituximab, cyclofosfamide, plasmeferese)
n=1

anti-GBM, open-label fase 2A
n=15

Stubbs et al. Br J Haematol 2019.; Enghard et al. Kidney Int 2021; Uhlin et al. JASN 2022.

n=15 vergeleken met historische controles

Characteristics	Men	Women	All	Historical Controls
Number, *n* (%)	9 (60)	6 (40)	15 (100)	50 (100)
Country: France/Sweden/Denmark Austria/Czech Republic, *n*	3/1/2/1/1	2/3/1/0/0	5/4/3/2/1	NA
Age years median (range)	60 (19–77)	66 (32–71)	61 (19–77)	63 (16–88)
ANCA MPO/PR3/none, *n* (%)	3/2/5 (33/22/56)	1/0/4 (17/0/67)	4/2/9 (27/13/60)	15[a]/7[a]/29 (30/14/58)
ANA positive, *n* (%)	3 (33%)	0	3 (20%)	NA
Renal function oliguria/dialysis/no dialysis, *n* (%)	4/4/1 (44/44/11)	1/1/4 (17/17/67)	5/5/5 (33/33/33)	41[7]/9 (82/18)
Pulmonary disease AH/other/none, *n* (%)[b]	1/2/6 (11/22/67)	1/2/3 (17/33/50)	2/4/9 (13/27/60)	21/NA/NA (42/NA/NA)
Smoking current/previous/never, *n* (%)	2/7/0 (22/78/0)	0/3/3 (0/50/50)	2/10/3 (13/67/20)	NA
Urinary albumin-creatinine, mg/g median (range) Reference range <27 mg/g[c]	2230 (434–30,531)	1932 (195–3540)	1982 (195–30,531)	NA
CRP mg/L median (range) Reference range <0.3 mg/dL[c]	3.4 (<0.07–5.2)	1.2 (<0.07–8.9)	3.2 (<0.07–8.9)	NA
Hb g/dL median (range)[c]	8.4 (6.9–11.1)	9.3 (7.3–11.5)	8.8 (6.9–11.5)	NA
Platelets 10^9/L median (range)[c]	318 (131–505)	320 (201–384)	320 (131–505)	NA
Berden class crescentic/mixed/sclerotic/focal, *n* (%)	6/2/0/0 (75/25/0/0)	3/2/1/0 (50/33/17/0)	9/4/1/0 (65/29/7/0)	25/3/1/0 (86/10/3/0)
Normal glomeruli, % median (range)	11% (0–29)	9% (0–35)	9.5% (0–35)	6.5% (0–43)
Linear staining for IgG, *n*/*n* (%)	5/8 (62)	6/6 (100)	11/14 (79)	27/29 (93)

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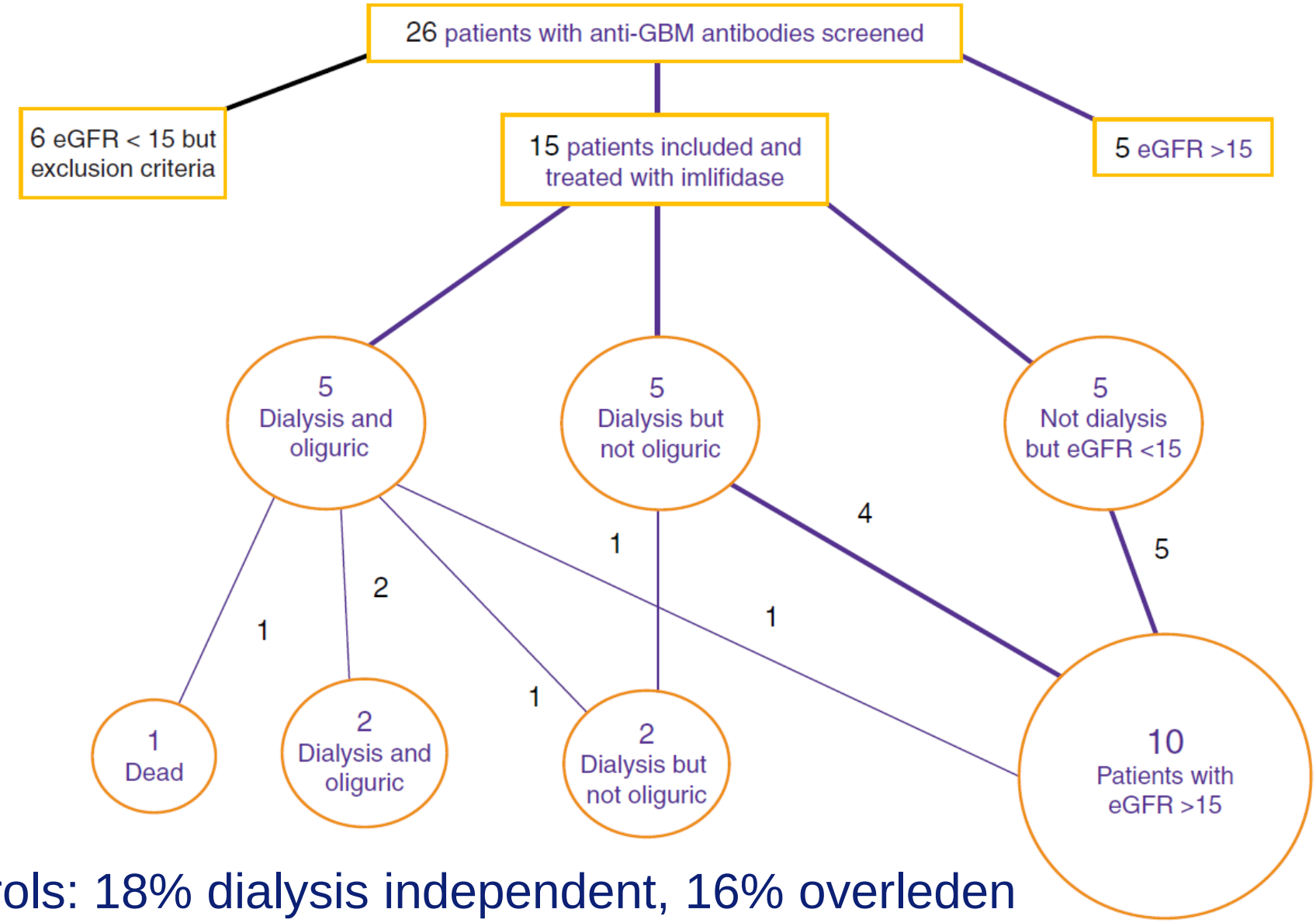
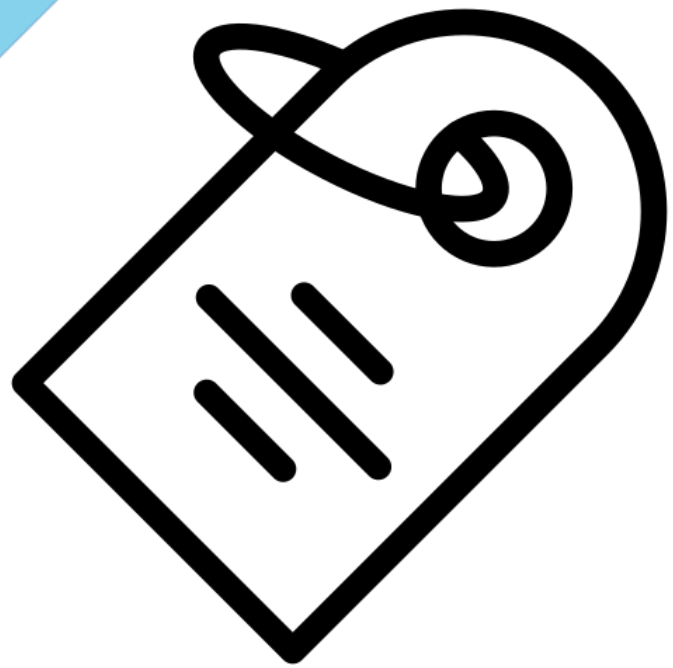
Uhlin et al., JASN 2022.



6 months

historical controls: 18% dialysis independent, 16% overleden

Uhlin et al., JASN 2022; McAdoo et al., CJASN 2017.



Desensibilisatie

voor

niertransplantatie

bij

hoog-geïmmuniseerden

met een

positieve kruisproef

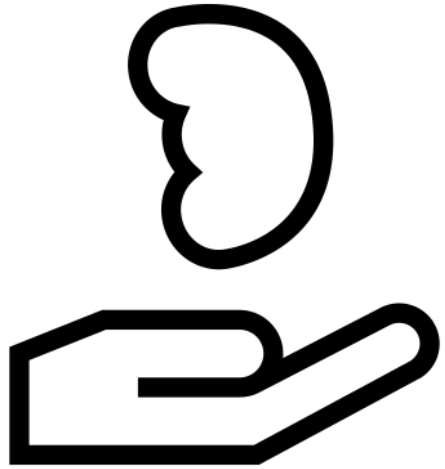
tegen een

overleden donor

met

weinig kansen in huidige allocatieprogramma's

Desensibilisatie studies



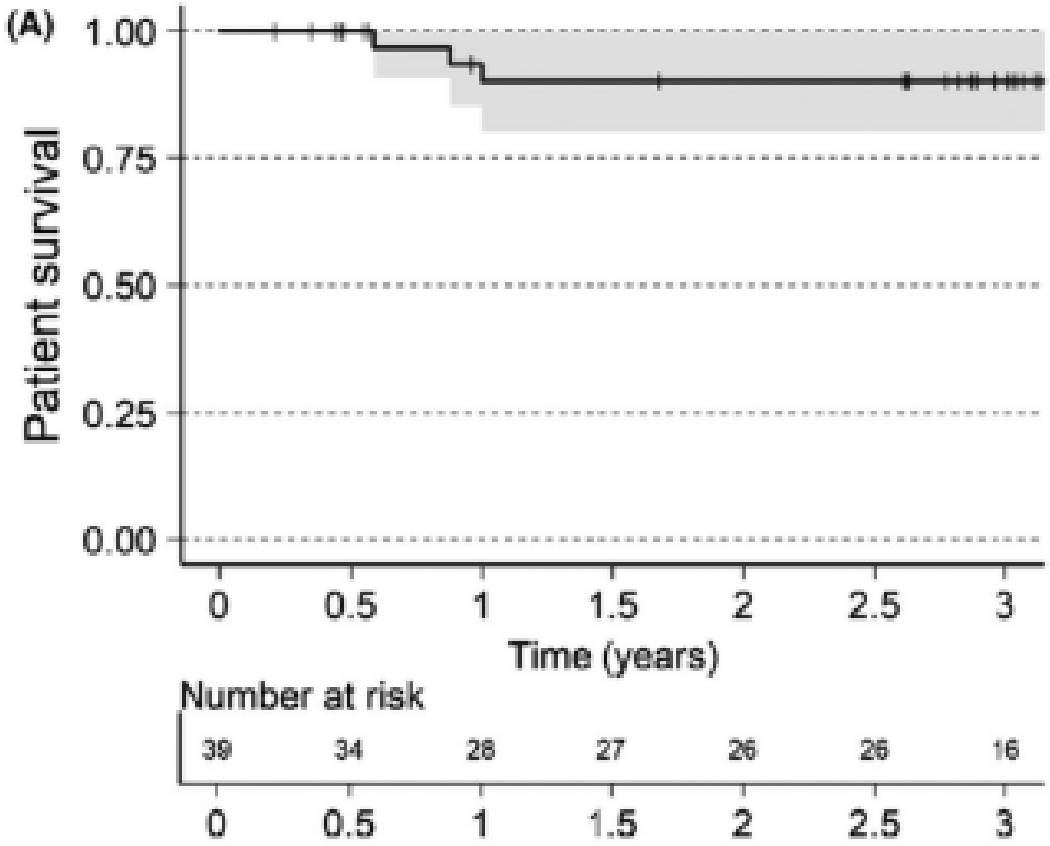
n=46 (2014-2017)

3-year follow-up: n=39 FACS+ crossmatch

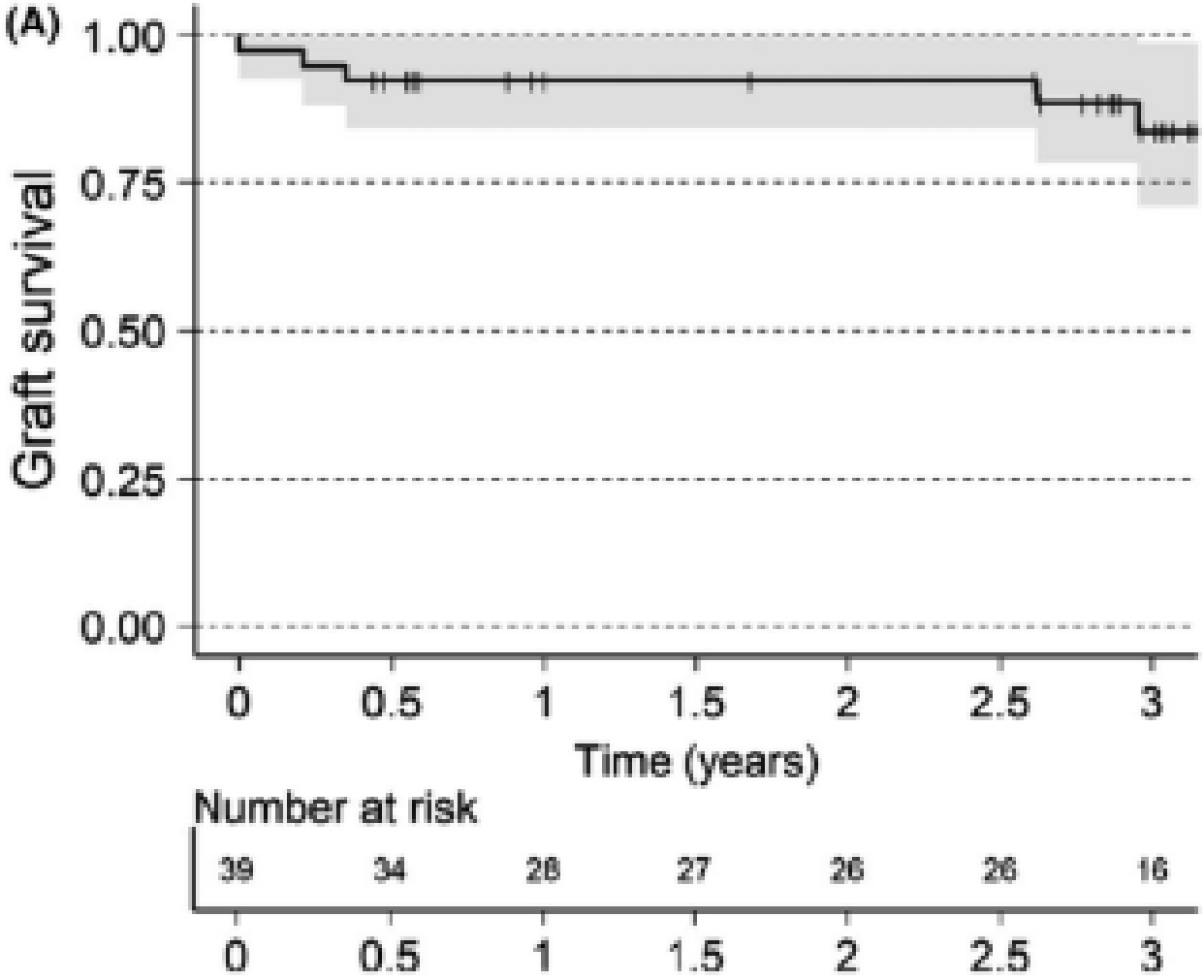
gemiddeld 43 jr, PRA 99,6%, 6.4 jaar dialyse
82% overleden donor, 69% retransplantaties
immunodominante DSA MFI 7791 (median, OneLambda)

Kjellman et al. AJT 2021.

patient overleving 90% na 3 jaar



transplantaat overleving 84% na 3 jaar



ABMR 38%

ABMR+: iDSA MFI 13.009

ABMR -: iDSA MFI 5727

Rebound na +/– 2 weken max 80% van pre-imlifidase levels

“……immunodominant DSA pre-Imlifidase was more often of class II, with higher initial levels and higher rebound in general than class I…….”

maart 2022 in NL
mw H. getransplanteerd

vrouw, 29 jaar
congenitaal nefrotisch syndroom
bg A, vPRA 100%
niertransplantaties 1999 en 2007
AM 2018
HU: vascular access

Anti-HLA antistoffen: Memory ++, current SAB +/–

Wegstrepen: delisting unacceptables

HLA-A locus

	A1	A2	A3	A9		2403	A10				A11	A19						A28		A36	A43	A80
				23	24		25	26	34	66		29	30	31	32	33	74	68	69			
typ zelf		Z											Z									
typ Tx											ntx			ntx								
CDC	C		C: 2004				C	C			C											
LSA cur	1k						2k	2k	1k	1k	2k									1k	2k	1k
LSA his	5k				7k		7k	6k	5k	6k	9k			6k	1k	2k	6k			4k	6k	4k
AM				AM								AM						AM	AM			
	UNAC				in 2004						UNAC											
Imli-AM			ja		ja		ja	ja	ja	ja				ja	ja	ja	ja			ja	ja	ja
														want CDC nooit pos	waren niet unacc	waren niet unacc						

	Z	ntx	aantoonbaar in CD
		C	
		20K	verkaarbaar
	AM	AM	Acceptabele mism
Imli-AM			onder current MFI

HLA-B locus

	B5*		B7	B8	B12*		B13*	B14		B15*					B16*		B17*		B18*	B21*		B22			B27	B27 08
	51	52			44	45		64	65	62	63	75	76	77	38	39	57	58		49	50	54	55	56		
typ zelf	Z																		Z							
typ Tx																							ntx			
CDC																										
LSA cur			3k				2k																1k		2k	4k
LSA his 17			11k				9k																	4k	10k	
AM				AM	AM	AM		AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM		AM	AM	AM				
Imli-AM			UNAC				ja																ja	ja	ja	UNAC

UNACC!! ! Ivm 2708

	B35*	B37*	B40		B41	B42	B46*	B47	B48	B53*	B59	B67	B70*		B73	703	B78	B81	B82	B83	7b*	Bw4	Bw6
			60	61									71	72									
typ zelf																							
typ Tx	ntx							ntx															
CDC																							
LSA cur			3k	3k		1k		2k	1k			1k			1k	3k		3k					
LSA his 17		4k	12k	12k	3k	8k		5k	9k			7k			5k			13k	6k				
AM	AM									AM	AM		AM	AM			AM						
Imli-AM		ja	UNAC	UNAC	ja	ja		ja	ja			ja			ja	ja		UNAC	ja				

AM donor frequentie 0.000% Delisting → ETKAS 3.95%

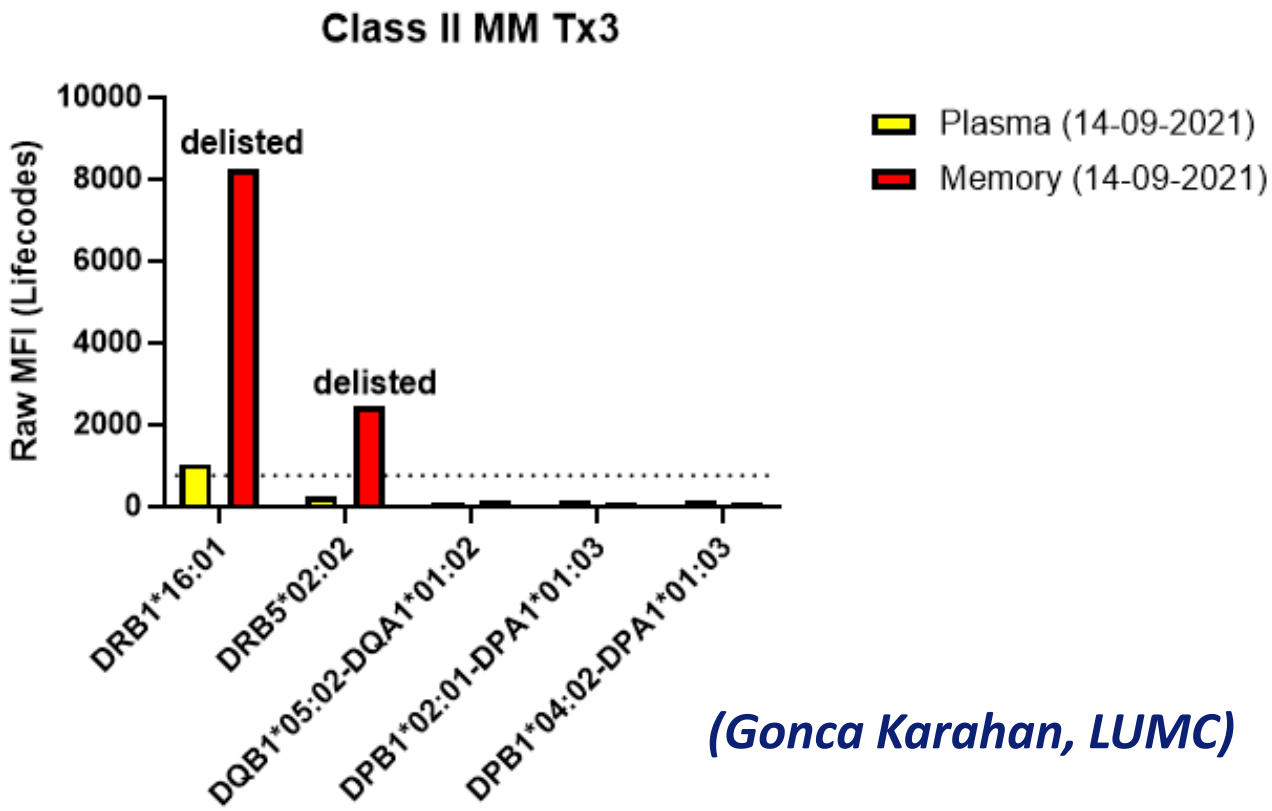
NIERAANBOD

High urgency DBD

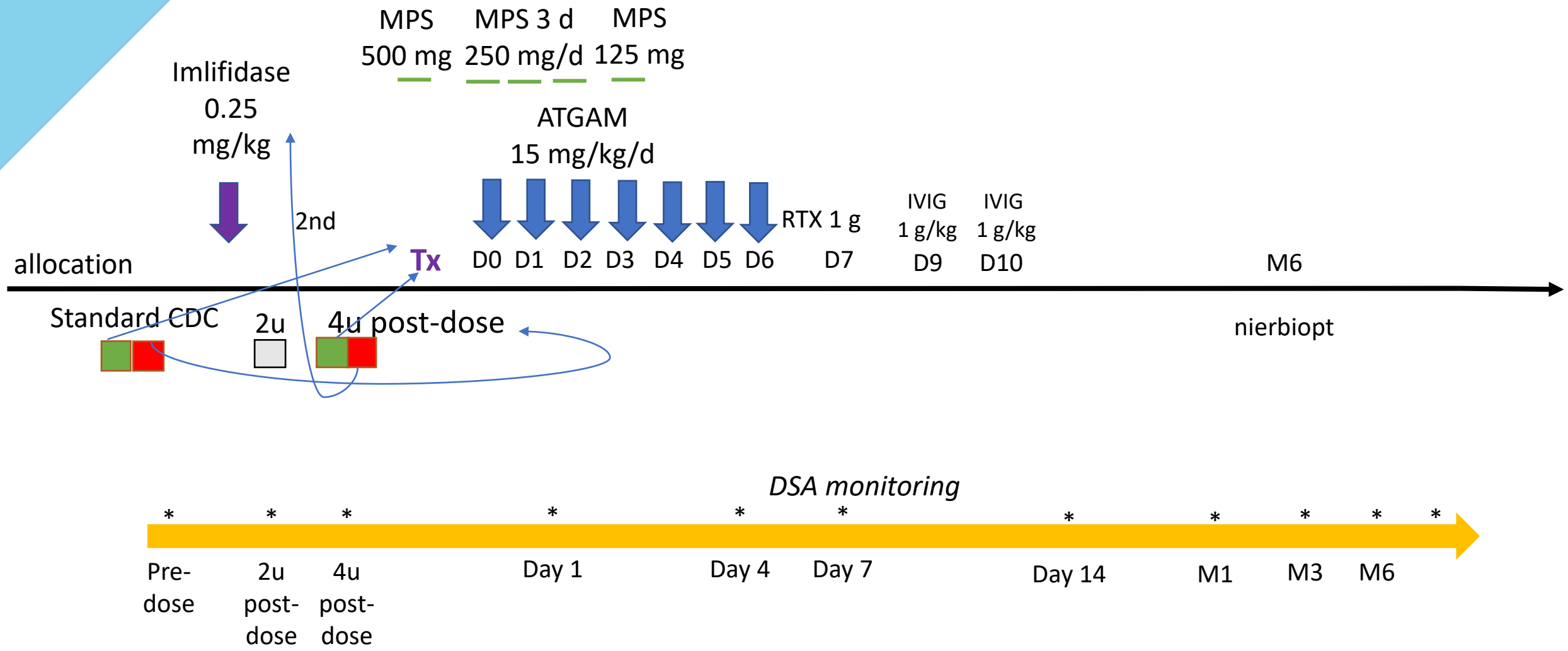
Mismatch A68, B44, B39, Cw12, **DR16, DR51**, DQ5

Virtual crossmatch +

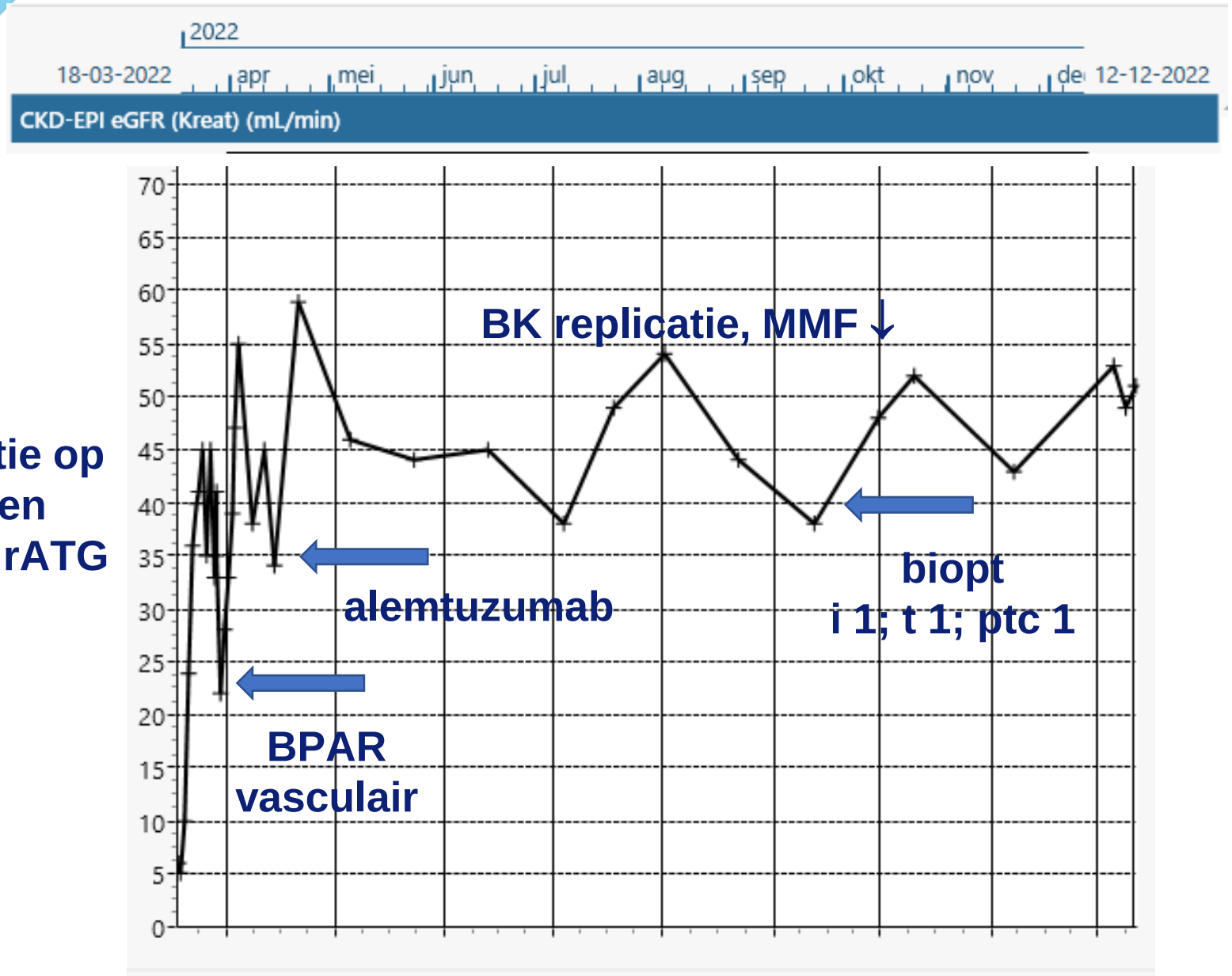
	DR16	DR51
current	2.5k	2k
historisch	11k	5k



(Gonca Karahan, LUMC)

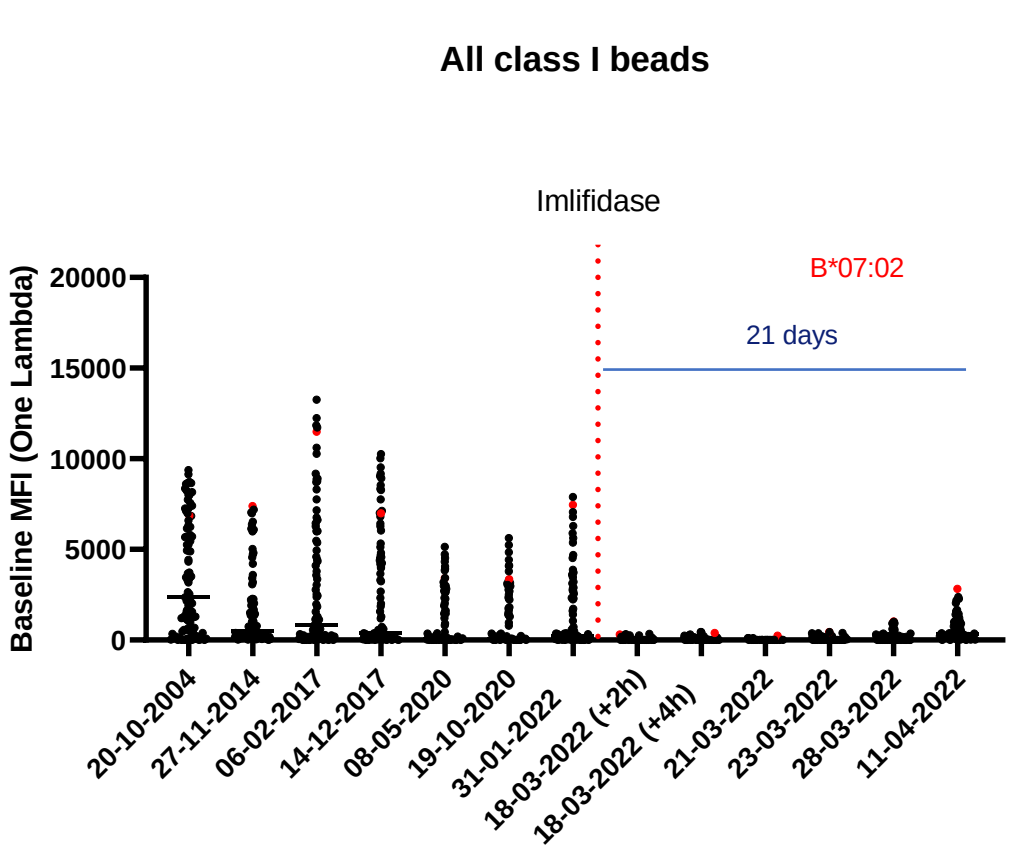

MPS
500 mg
MPS 3 d
250 mg/d
MPS
125 mg
Imlifidase
0.25
mg/kg
ATGAM
15 mg/kg/d
2nd
RTX 1 g
IVIG
1 g/kg
IVIG
1 g/kg
allocation
Tx
D0 D1 D2 D3 D4 D5 D6
D7
D9
D10
M6
Standard CDC
2u
4u post-dose
nierbiopt
DSA monitoring
Pre-
dose
2u
post-
dose
4u
post-
dose
Day 1
Day 4
Day 7
Day 14
M1
M3
M6

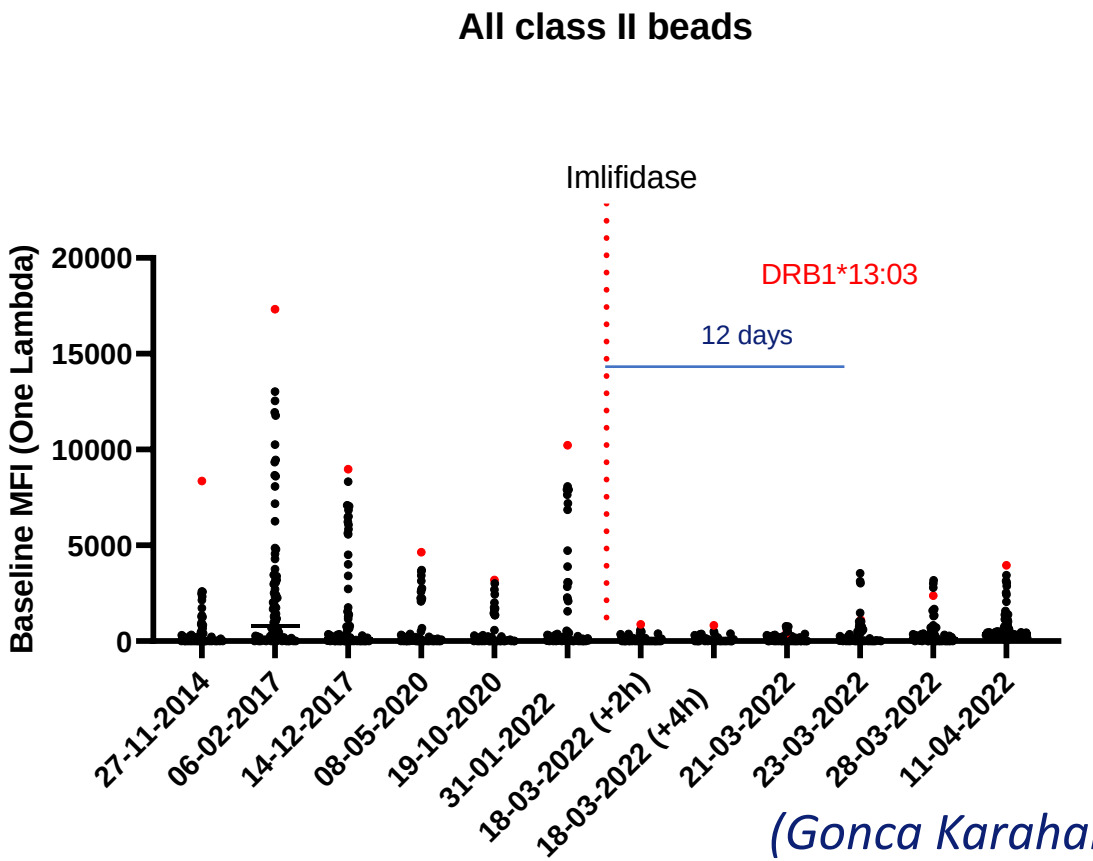
geen depletie op paarden ATG }rATG



Anti-HLA antistoffen One Lambda Luminex SAB

HLA class II eerder rebound dan class I





(Gonca Karahan, LUMC)

COMMISSIE IMLIFIDASE
add-on

potentiële kandidaten? — **vPRA ≥85% (99-100) en ≥2j AM**

‘delist’ strategie — **streef naar FACS+/CDC− kruisproef**

protocol — **≈ PAES**

TIMING IMLIFIDASE

uitslagen kruisproeven ↔ koude ischemie tijd

zekerheid dat donatieprocedure doorgaat?

wanneer komt donoraanbod na delisten?

ALLOCATIE
reguliere programma, buiten AM

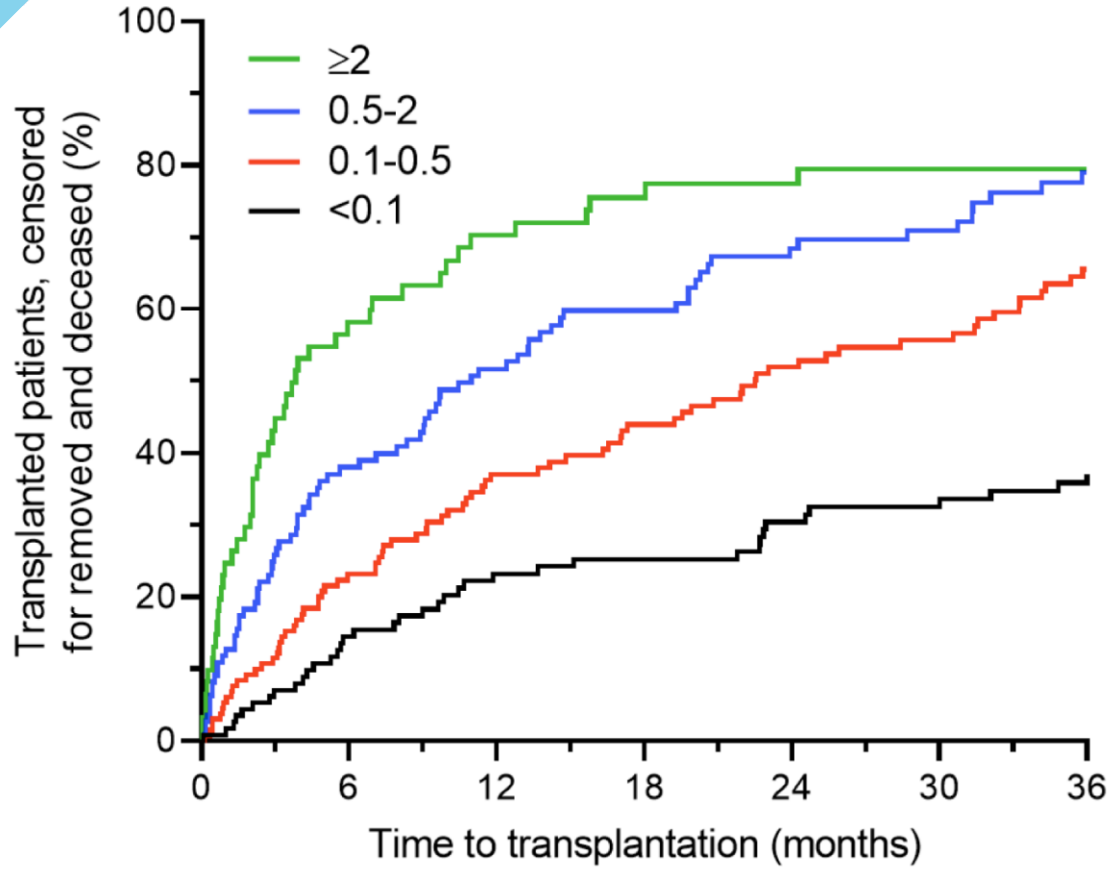
Nabije toekomst:

2de allocatie laag AM

<u>Eurotransplant donoraanbod:</u>

1. AM
2. Langwachtende AMers met Imlifidase delisted unacceptables
3. ETKAS HLA MM 0-0-0
4. ETKAS

BEHOUD 'PRIORITY ALLOCATION'
vooral AMers met extreme lage donorfrequentie zullen profiteren



# at risk							
≥2.0	61	25	17	13	11	10	9
0.5-2.0	110	66	49	39	27	23	15
0.1-0.5	131	98	75	65	53	46	34
<0.1	115	91	78	73	67	62	54

Donor frequency <0.1%

Heidt S, et al. Front Immunol. 2021

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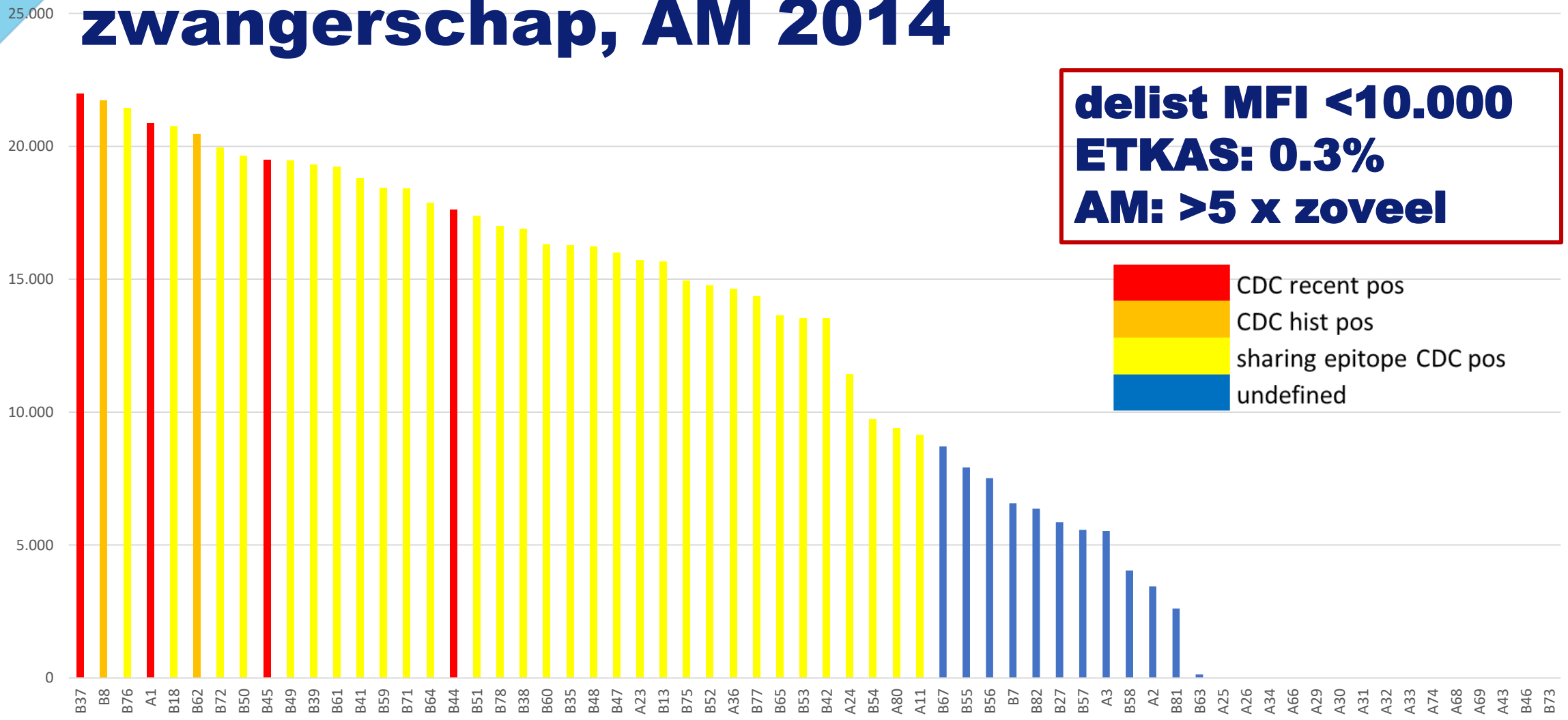
vrouw 30j, bg B, vPRA 100%, zwangerschap, AM 2014



IMLIFIDASE pijplijn

NIH U.S. National Library of Medicine
ClinicalTrials.gov

niertransplantatie:

- desensibilisatie:
  - PAES (EMA) n=50
  - RCT (FDA) ConfIdeS n=64
  - NCT05049850 Belatacept en bortezomib voor Imlifidase
- ABMR n=30

Guillan-Barré

anti-GBM?

IMLIFIDASE ? ?

Transplanteren “immunologisch niet-te transplanteren patiënten”

donoraanbod door delisten ⇔ rebound

“Delisten unacceptables die zonder desensibilisatie een te immunologisch groot risico *lijken te* vormen…..”

IMLIFIDASE

Hoge prijs

Uniek werkingsmechanisme voor IgG-gemedieerde aandoeningen, maar deze zijn meestal geen aan/uit fenomeen (anti-GBM?)

Verankering recombinant IdeS aan ‘target’ cellen

next-level interactie nefrologen en immunologen
Harmonistaie immunologisch beleid

Lynch et al. Blood 2022.

VRAGEN?

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