



Combined blockade of CD154 and CD28 co-stimulation pathways attenuates pathogenic alloimmunity and prolongs survival in cynomolgus cardiac allografts

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Background

- 1st generation anti-CD154 mAb
prolonged graft survival in NHP Tx model (heart/Kidney/Islets/skin)

- Major thrombotic events in the clinical trial

hu5c8 mAb forms **immune complexes** with soluble-CD154 via **FcγRIIa**
crosslinked sCD154:hu5c8 via **FcγRIIa** activates platelets

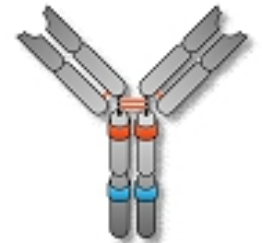
(Robles-Carrillo L et al 2010)

- 2nd generation aCD154 reduced efficacy

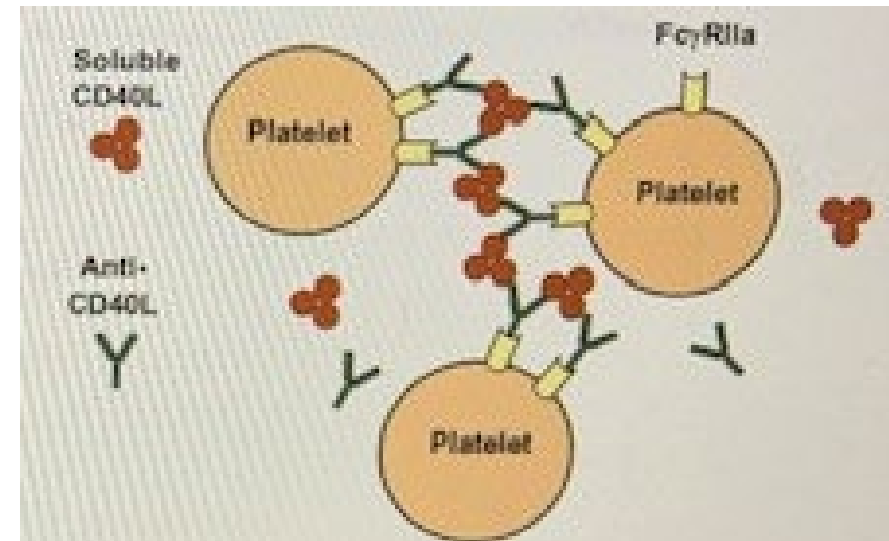
Aglycosyl IgG1 aCD154 Ab (NHP allo islet)
(Ferrant et al 2004)

FcγR silenced aCD154 domain Ab (NHP allo kidney)
(Kim et al 2016)

First-generation
anti-CD40L mAbs



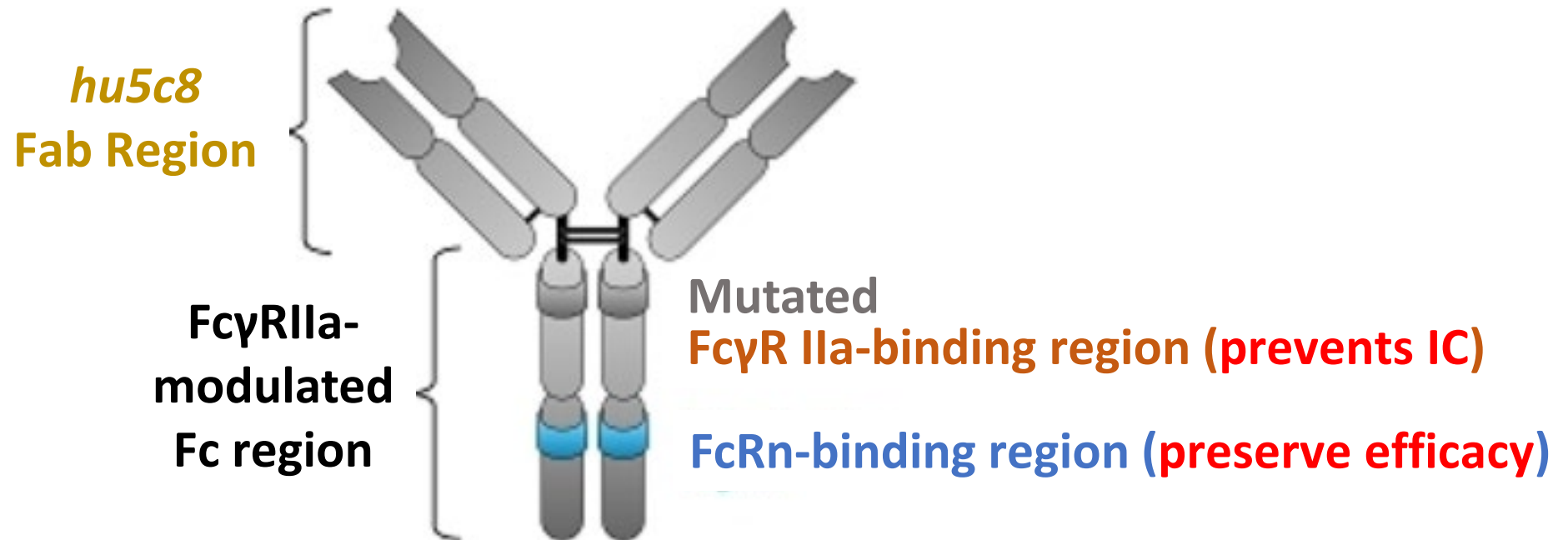
hu5c8



TNX-1500: α CD154 IgG4 with retained hu5c8 Fab

- 3rd generation: Fc-modified α CD154 mAb

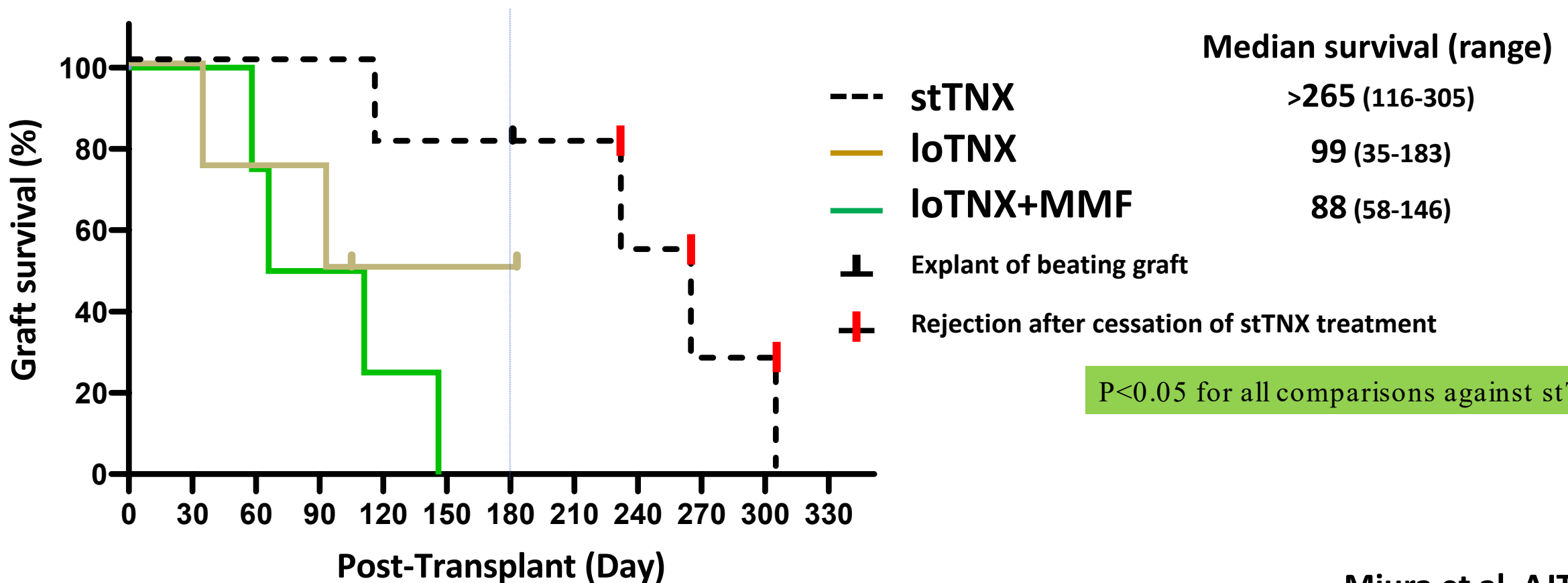
TNX-1500 reduced binding to Fc γ RIIa and retained FcRn binding.
(prevents IC) (preserved efficacy)



*TNX-1500 is an investigational new biologic and has not been approved for any indication

Costimulation Blockade: aCD154

NHP Heart Allograft Survival was significantly prolonged with standard dose TNX-1500 (stTNX) vs low-dose (loTNX)



■ TNX-1500

Safe, Effective at 20 mg/kg weekly (Standard Dose)

Equivalent to 5c8 at 20 mg/kg monthly (Low Dose)

Miura et al, AJT 2023

Heart Tx model in NHP study

■ VEL-101 (FR 104): anti-CD28 PEGylated monovalent Fab molecule

Safe, Effective at 5 or 10 mg/kg weekly

Poirier et al, Sci Trans Med 2012

Kidney Tx model in NHP study

■ Synergy between VEL-101 and TNX-1500 or 5c8 explored with TNX-1500/5c8 at 20 mg/kg monthly ('Low Dose')

Methods – Cyno Hetero Heart AlloTx

Anti-CD154 monoRx 'Low Dose'

hu5c8

TNX

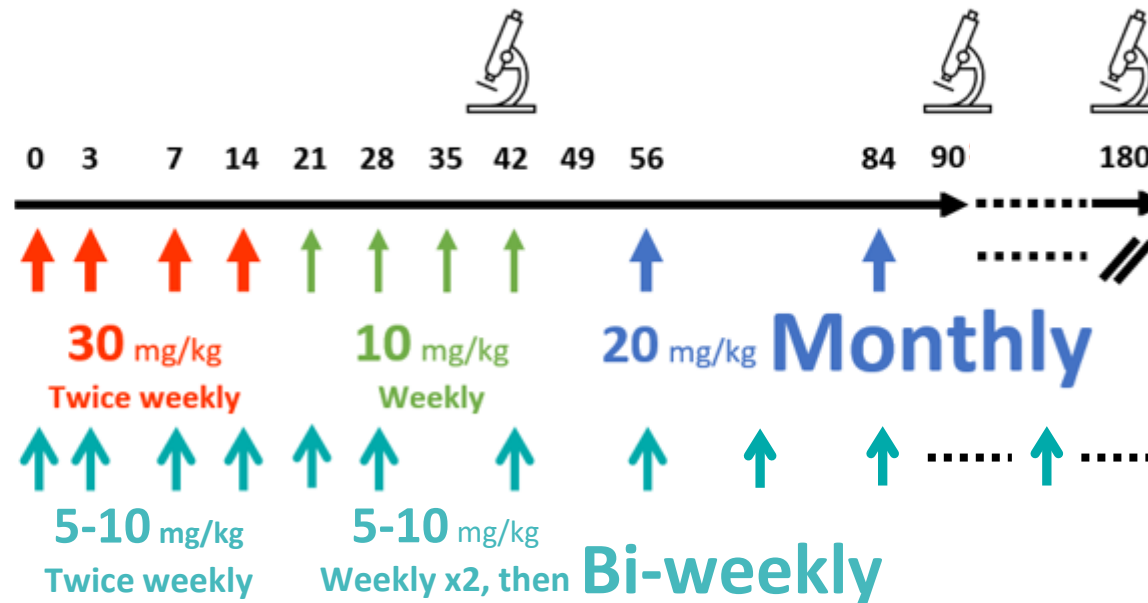
Anti-CD28 monoRx

VEL-101

Anti-CD154 + Anti-CD28

5c8+VEL-101

TNX+VEL-101



Low-dose α CD154
5c8 or TNX-1500

VEL-101

Protocol Biopsies

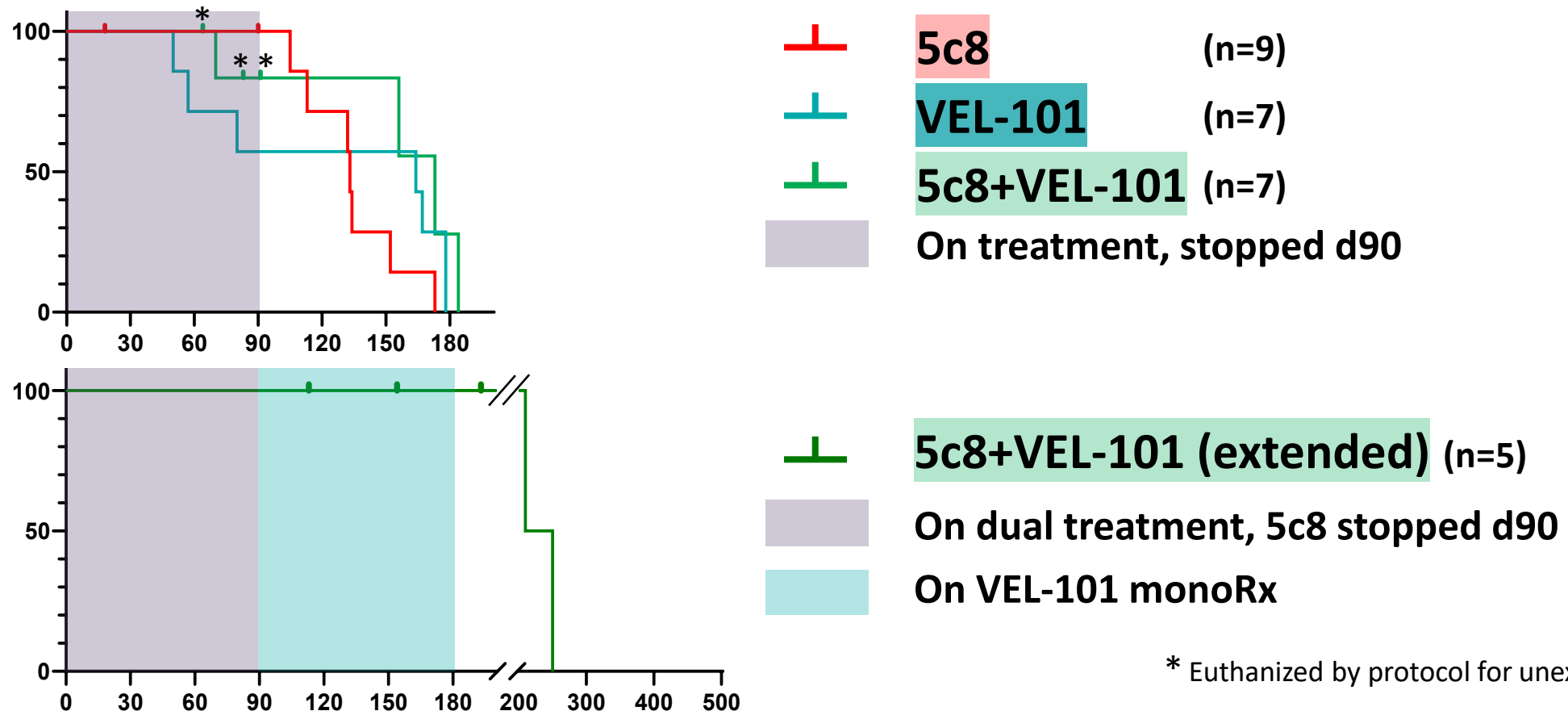
Rx stopped at 90-180d

Rx stopped at 90-400d

Results

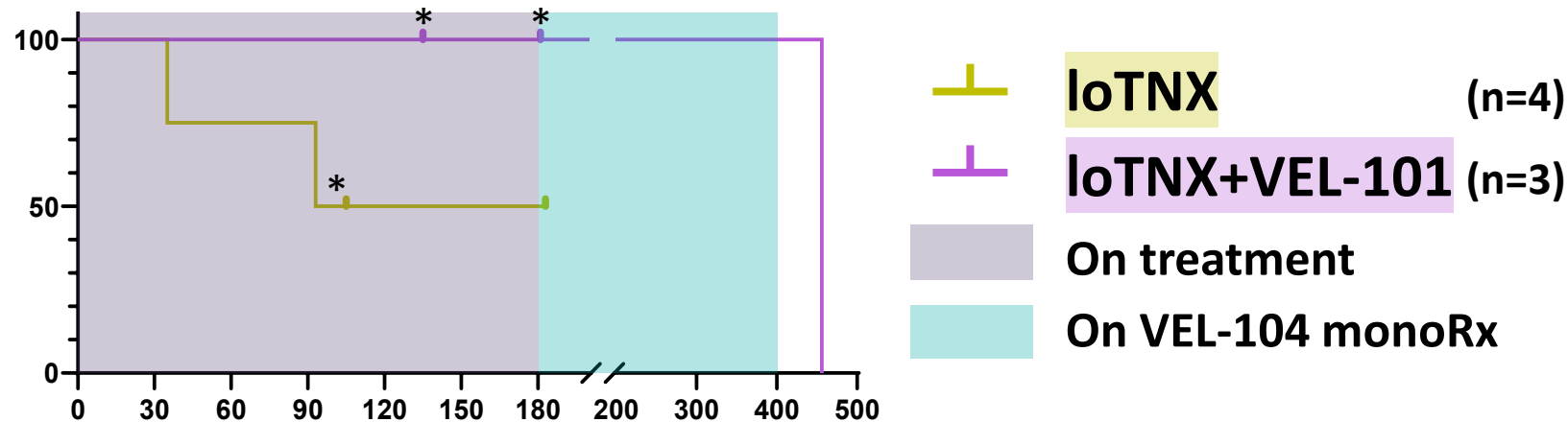
Vel-101+5c8 prevented graft loss during Rx period

Vel-101 monoRx after dual Rx 'induction' prolonged graft survival



Vel-101+TNX prevented graft loss during Rx period

Vel-101 monoRx after dual Rx 'induction' prolonged graft survival
No alloantibody, generally low ISHLT ACR and CAV scores



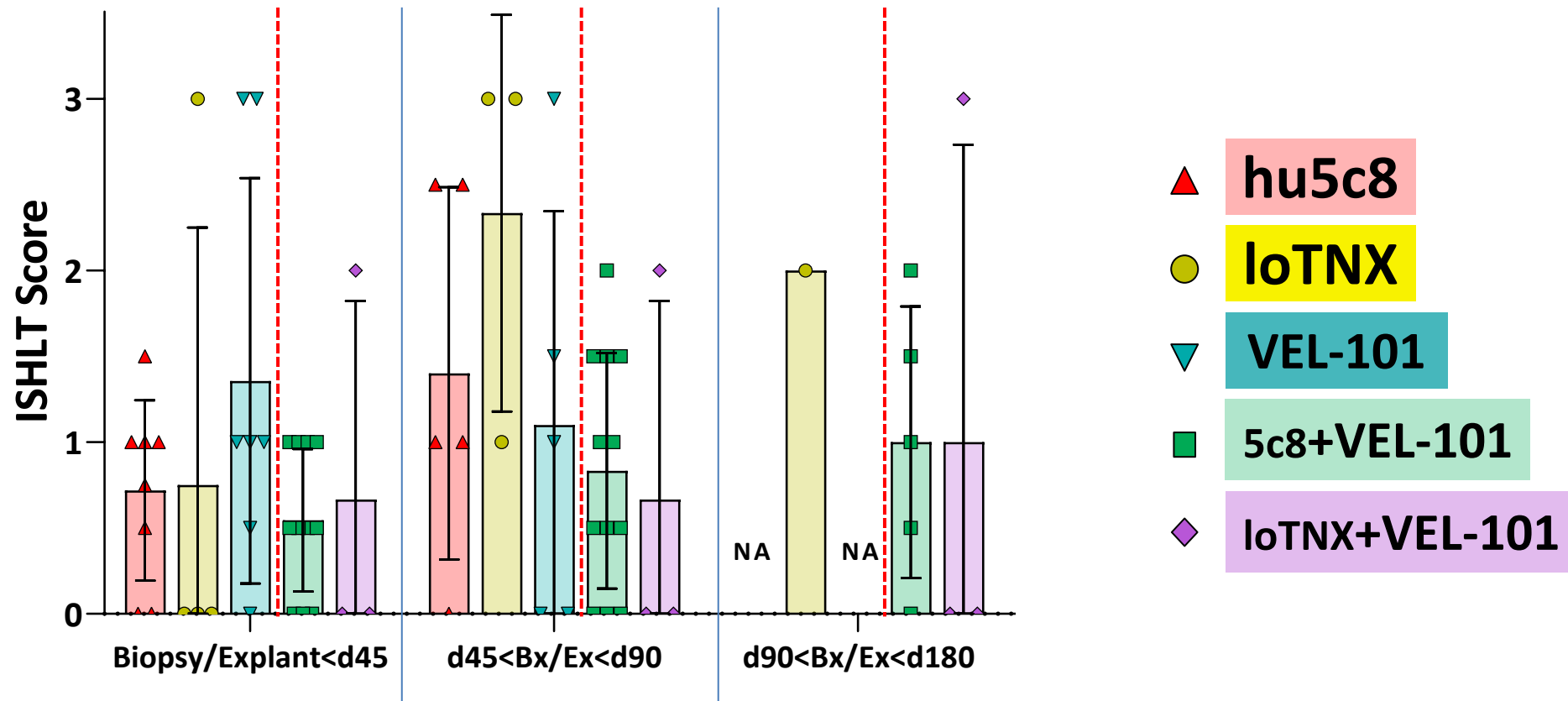
* Euthanasia with beating graft
(surgical complication, unexplained weight loss)

TNX-1500 or hu5c8 with VEL-101 inhibited alloantibody elaboration, class switching

	Anti-donor IgM	Anti-donor IgG
hu5c8	0/5	0/5
IoTNX	1/4 (MHC I + II)	2/4 (MHC I + II)
VEL-101	2/7 (MHC I)	2/7 (MHC I + II)
5c8+VEL-101	0/5	0/5
IoTNX+VEL-101	0/3	0/3

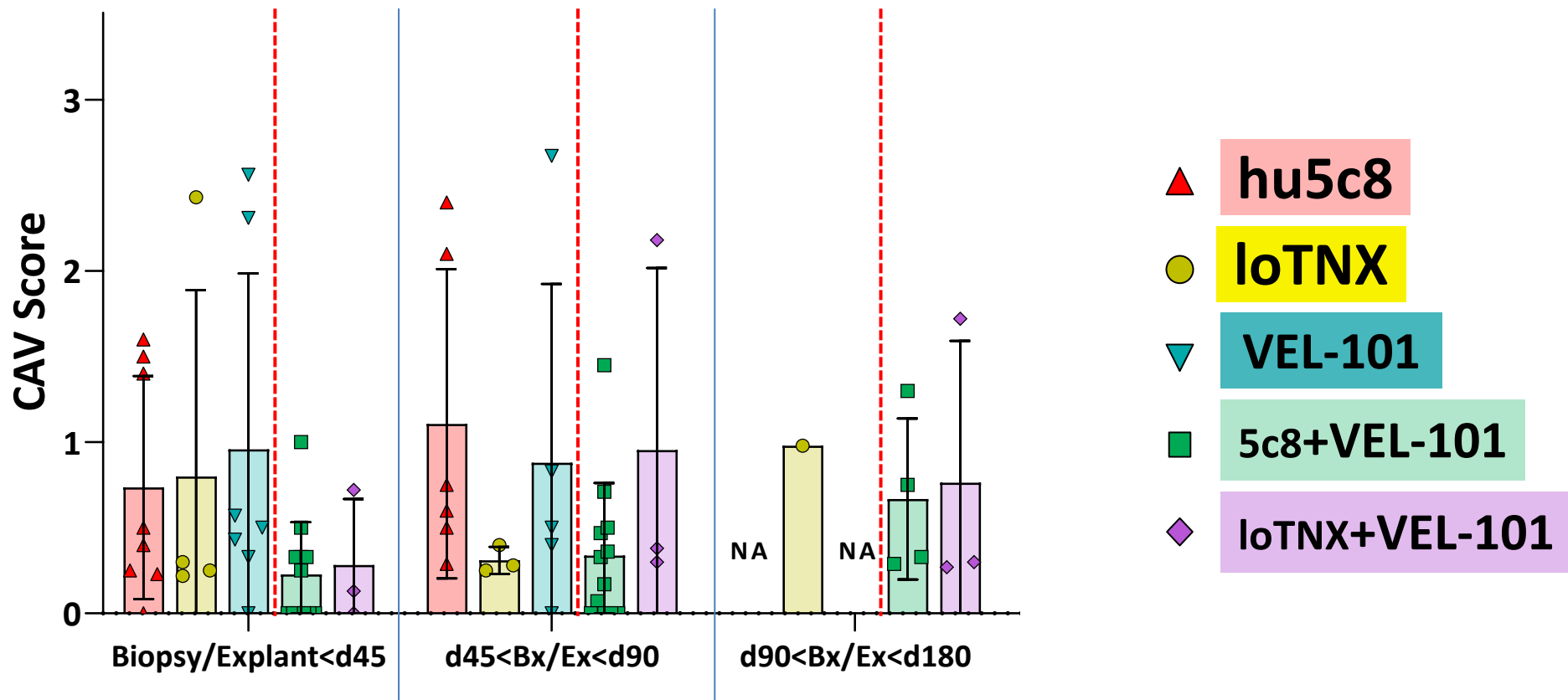
*NB: Assay in older h5c8 studies was less sensitive than in contemporary VEL/TNX studies

VEL-101 with either 5c8 or IoTNX reduced ISHLT ACR score



VEL-101 with 5c8 reduced CAV score

Further study of TNX+VEL-101 is warranted



Conclusions

- **TNX-1500 efficacy is similar to hu5c8 parent molecule in NHP study**
 - **No procoagulant phenotype**
 - **Well tolerated: no increase in viral infections or PTLD**
- **α CD154 with α CD28 has synergistic effects**
 - **durable protection from pathogenic allo-immunity**
 - **promising for clinical translation.**



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