HARVARD MEDICAL SCHOOL
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Monotherapy with TNX-1500, an Fc-modified anti-CD154 mAb, prolongs cardiac allograft survival in cynomolgus monkeys

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I have no financial relationships with commercial interests to disclose

AND

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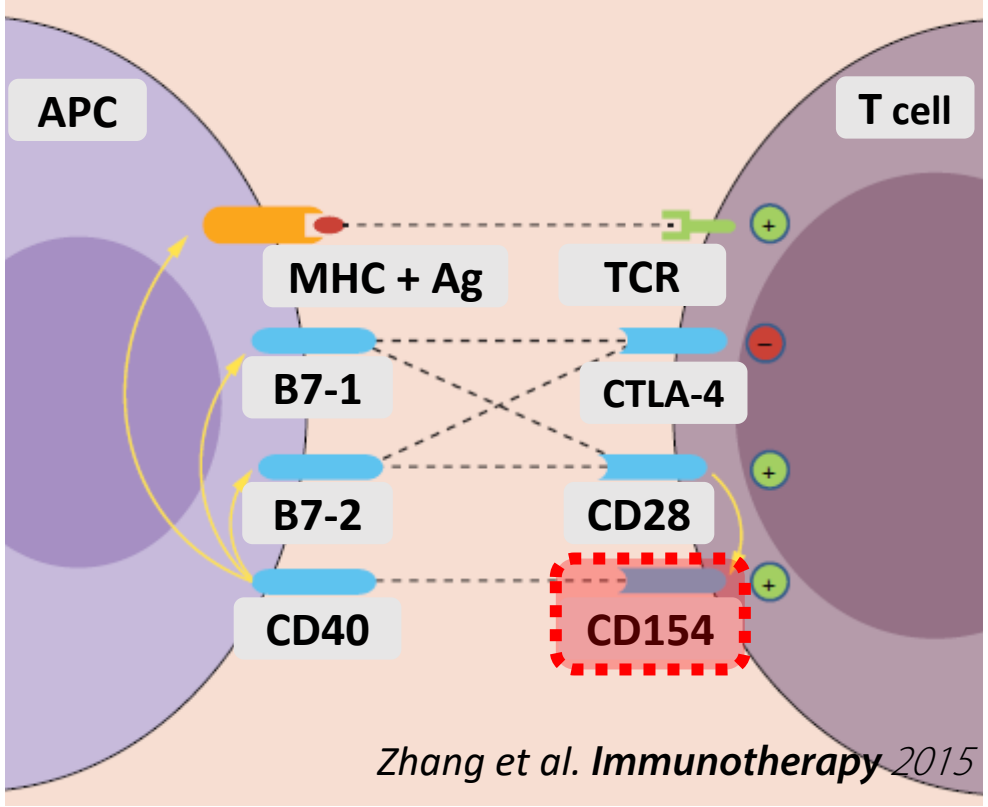
Emerging Costimulation Blockade: aCD154



Zhang et al. ***Immunotherapy*** *2015*

Transplantation. 1999 Dec 15;68(11):1800-5. doi: 10.1097/00007890-199912150-00026.

Prolongation of primate cardiac allograft survival by treatment with ANTI-CD40 ligand (CD154) antibody

R N Pierson 3rd [1], A C Chang, M G Blum, K S Blair, M A Scott, J B Atkinson, B J Collins, J P Zhang, D W Thomas, L C Burkly, G G Miller

ARTICLES

Treatment with humanized monoclonal antibody against CD154 prevents acute renal allograft rejection in nonhuman primates

Allan D. Kirk[1,2,3], Linda C. Burkly[4], D. Scott Batty[3], Roxanne E. Baumgartner[1], Justin D. Berning[1], Kelvin Buchanan[1], John H. Fechner, Jr.[2], Rhonda L. Germond[1], Robert L. Kampen[1], Noelle B. Patterson[1], S. John Swanson[3], Douglas K. Tadaki[1], Christopher N. TenHoor[4], Leonard White[1], Stuart J. Knechtle[2] & David M. Harlan[1]

Massachusetts General Hospital
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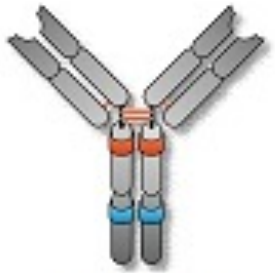
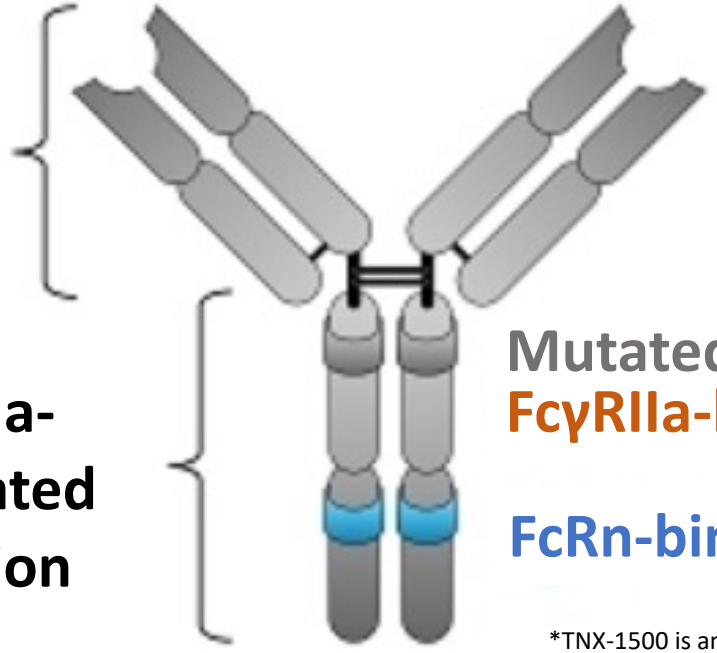
- 1st generation anti-CD154 mAb *hu5c8*
  prolonged graft survival in NHP Tx model(Hrt/Kid /islet/skin)



hu5c8

- Major thrombotic events in the clinical trial
  ∵ Activate platelets via FcγRIIa express CD154
  mAb form immune complexes with soluble-CA154 and them

- 3rd generation Fc-mod aCD154 mAb *TNX-1500**



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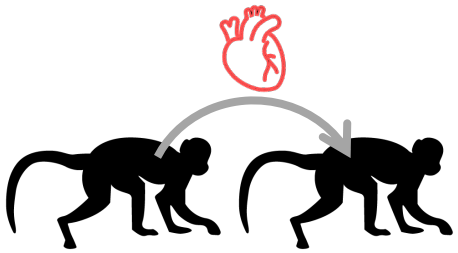
*TNX-1500 is an investigational new biologic and has not been approved for any indication

Methods- Heterotopic abdominal heart allotransplant model



Protocol biopsies: POD ~45 and 90

EOS: POD 180

0 3 7 14 21 28 35 42 49 56 63 70 77 84 91 98 105 112 119 126 133 140 147 154 161 168 175 180

Low-dose TNX-1500 monoRx (loTNX-1500, n=4)

- **30** mg/kg — Twice weekly
- **10** mg/kg — Weekly
- **20** mg/kg — Monthly

Low-dose TNX-1500 + MMF (loTNX-1500 + MMF, n=4)

- **30** mg/kg — Twice weekly
- **10** mg/kg — Weekly
- **20** mg/kg — Monthly
- **MMF 200 mg PO daily**

Standard-dose TNX -1500 monoRx (sTNX, n=5)

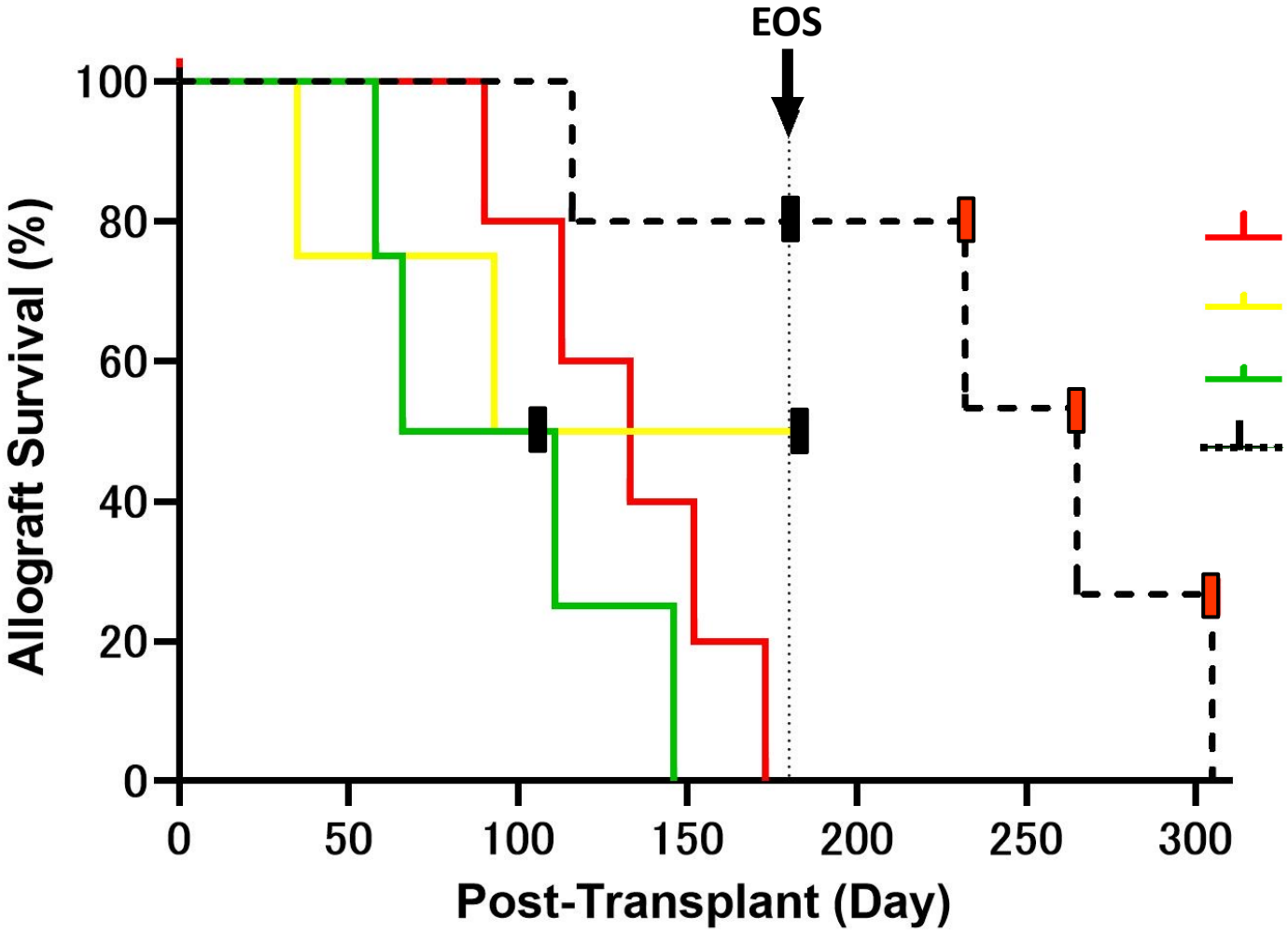
- **30** mg/kg — Twice weekly
- **20** mg/kg — Weekly

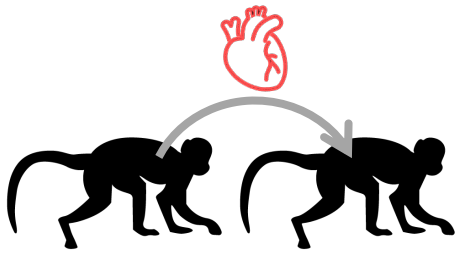
Primatized Hu5c8 monoRx (Reference, n=5)

- **30** mg/kg — Twice weekly
- **10** mg/kg — Weekly
- **20** mg/kg — Monthly

Results-

Heart Allograft Survival in NHPs is significantly prolonged with Standard dose TNX-1500 (stTNX)





	MST (range)
hu5c8 (n=4) (Rx off d90)	133 days (90-173)
IoTNX (n=4)	99 days (35-183)
IoTNX + MMF (n=4)	88 days (58-146)
stTNX (n=5) (Rx off d175)	>265 days (116-305)

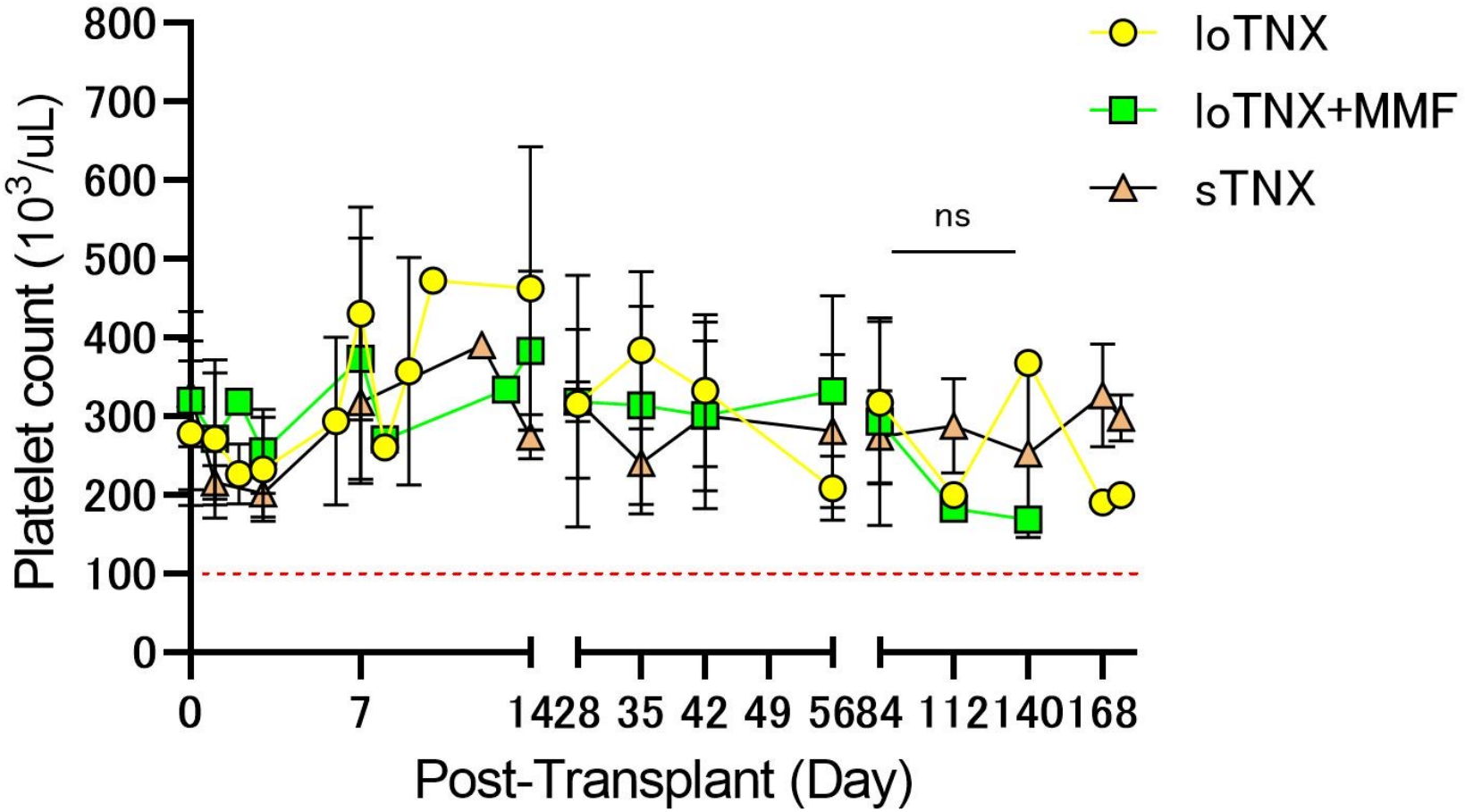
$P<0.05$ for all comparisons against stTNX

Explant of beating graft

Rejection after cessation of all IS treatment

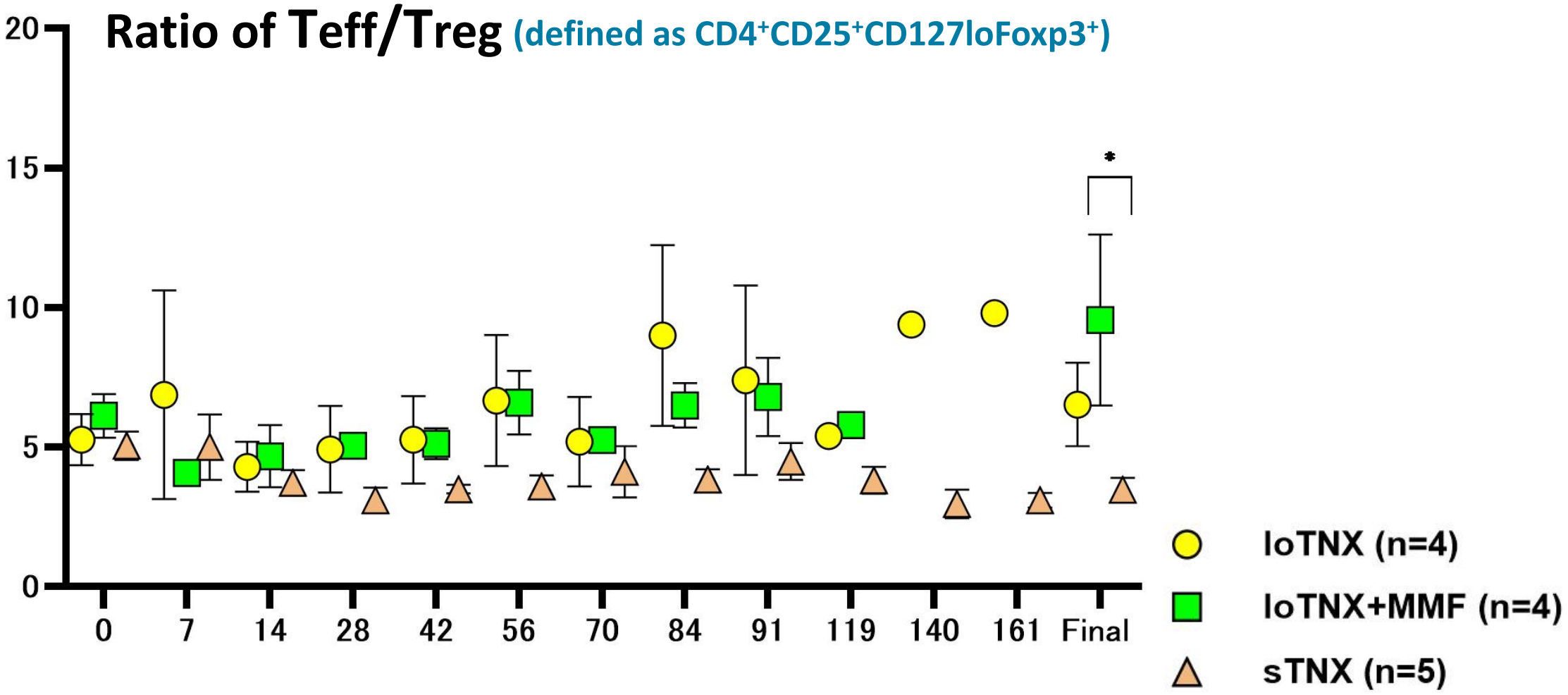
Results-

Platelet counts were stable and No thromboembolic complications were observed



Results-

stTNX suppressed the rise in Teff/Tregs ratio at the final time-point more effectively than loTNX+MMF

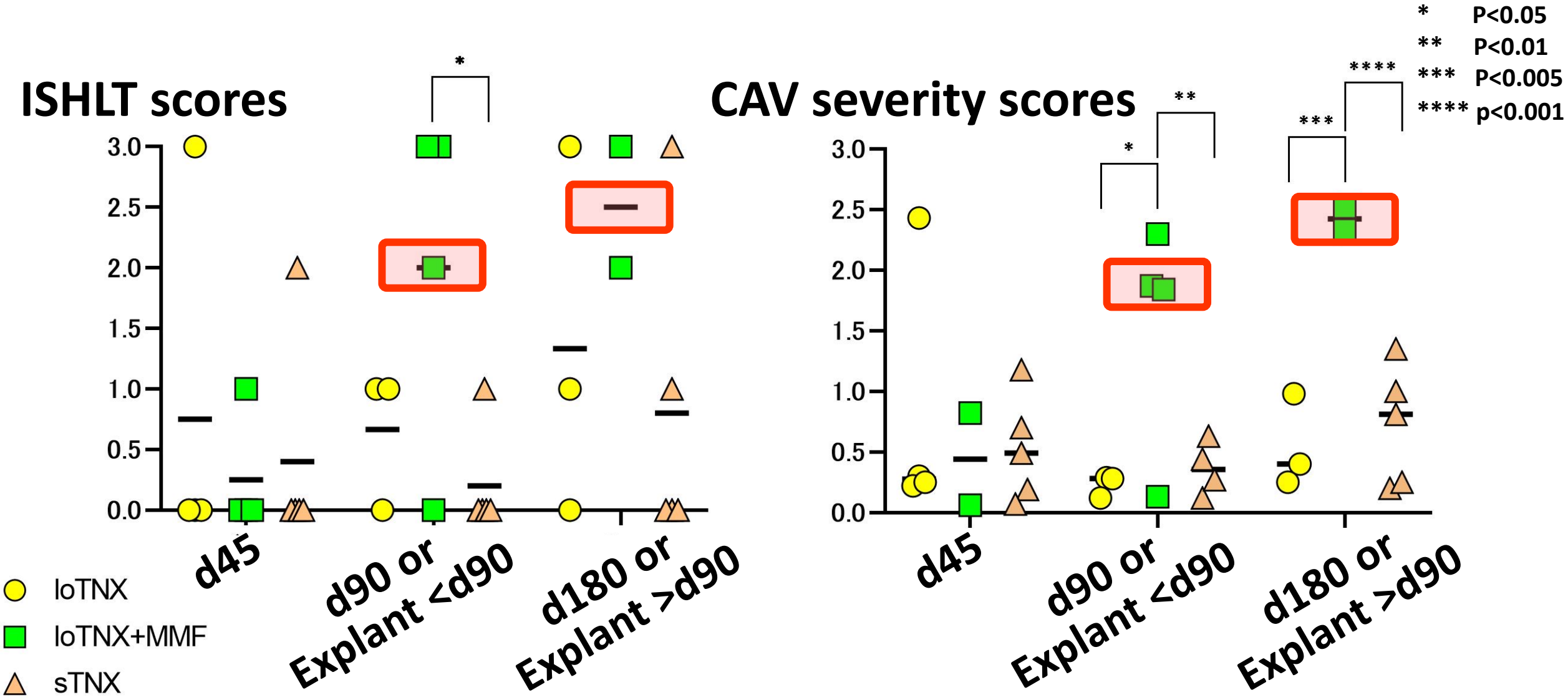


ISHLT; International Society for Heart and Lung Tx

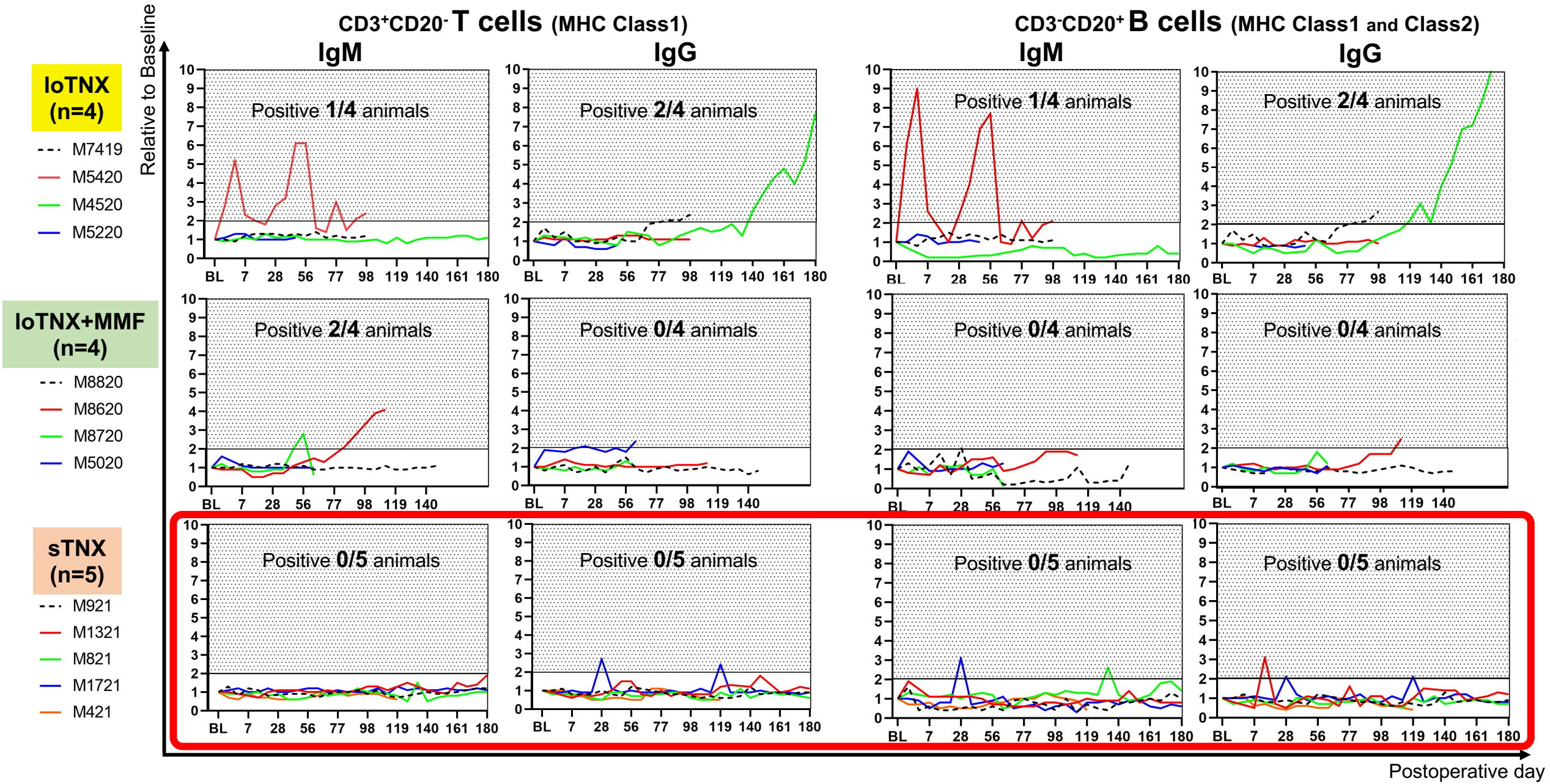
CAV; Cardiac Allograft Vasculopathy

Results-

CAV significantly more severe with IoTNX-1500+MMF



Results- TNX-1500 suppresses anti-donor-alloantibody elaboration



Conclusions

Thank you for your listening!

- **Standard-dose TNX-1500 inhibits pathologic alloimmunity in NHPs**
  - **Consistently prolonged NHP heart allograft survival**
    - ***No clinical thrombotic events***
    - ***Relative expansion of Tregs in peripheral blood***
    - ***No CMV activation (no prophylaxis)***
- **MMF does not improve heart results with low-dose TNX-1500**
  - **Does MMF interfere with Treg expansion, function under aCD154 Rx?**

(Kirk AD et al)

- **TNX-1500 inhibits alloantibody elaboration, class switching**
  - **Dose-dependent effect**

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