aCD154mAb (TNX-1500) alone, or in combination with rapamycin, MMF, or aCD28mAb (VEL-101) prolongs cynomolgus cardiac allograft survival

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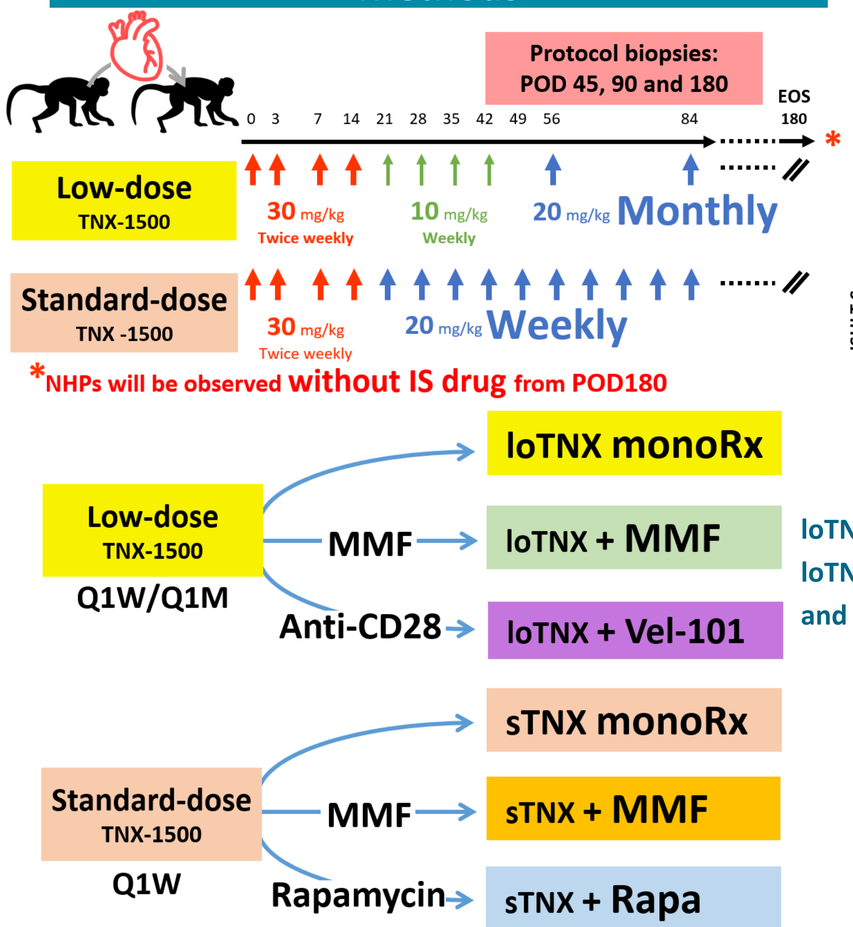
Introduction

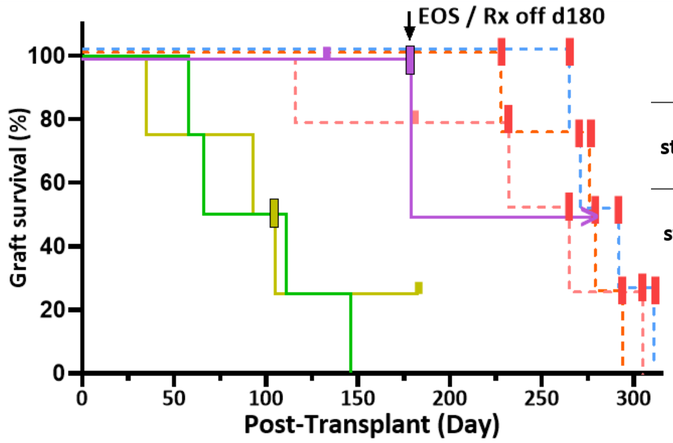
- TNX-1500 (TNX) is a novel humanized anti-CD154 mAb that contains the hu5c8 Fab region and an IgG4 Fc region engineered to decrease FcγR2A binding.
- TNX-1500 was designed to reduce the risk of thromboembolic events observed with hu5c8 IgG1 (ruplizumab) in previous clinical trials.
- The efficacy of TNX-1500 when combined with conventional IS has not been previously described.

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

Methods



Results



stTNX vs	IoTNX	*p = 0.057*
	IoTNX+MMF	*p = 0.01*
stTNX+MMF vs	IoTNX	*p = 0.04*
	IoTNX+MMF	*p = 0.006*
stTNX+Rapa vs	IoTNX	*p = 0.045*
	IoTNX+MMF	*p = 0.006*

Explant of beating graft
ACR3 graft explanted with animal issue
Graft failure after cessation of all IS treatment

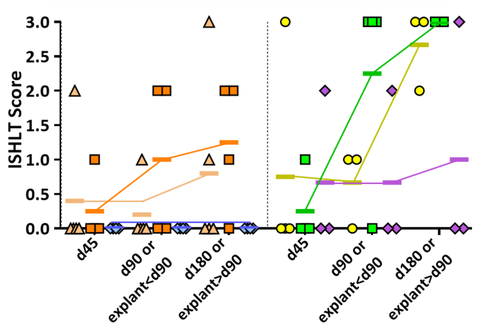
Median survival (day)

IoTNX	99	stTNX	265
IoTNX+MMF	88.5	stTNX+MMF	277.5
IoTNX+VEL101	203	stTNX+Rapa	281.5

IoTNX+Vel-101 prolonged graft survival, but there is no significant difference in IoTNX groups. All grafts of stTNX survived over 6 months, except one graft got an infection. After Rx cessation on d180, grafts kept beating for 2-4 months.

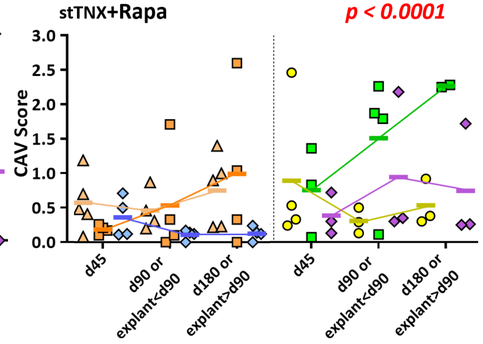
ISHLT score

stTNX+Rapa vs IoTNX *p = 0.053*
stTNX+Rapa vs IoTNX+MMF *p < 0.0001*



CAV score

IoTNX vs stTNX *p = 0.042*
IoTNX+MMF vs stTNX *p = 0.015*
stTNX+Rapa *p < 0.0001*



IoTNX monoRx had high ISHLT acute rejection score, but low CAV score. IoTNX+MMF had high ISHLT and CAV scores. IoTNX+Vel-101 had stable low ISHLT and CAV scores. stTNX+Rapa showed no evidence of rejection at all time points

DSA elaboration

	Anti-donor IgM	Anti-donor IgG
IoTNX	1/4 (MHC I + II)	2/4 (MHC I + II)
IoTNX+MMF	2/4 (MHC I)	0/4
IoTNX+Vel-101	0/2	0/2
sTNX	0/5	0/5
stTNX+MMF	1/4 (MHC I)	0/4
stTNX+Rapa	0/4	0/4

IoTNX combined with either MMF or Vel-101 Rx prevented class-switching (no IgG DSA); and IoTNX+Vel-101 suppressed IgM DSA elaboration. No DSA elaboration in stTNX monoRx and stTNX+Rapa. One stTNX+MMF recipient had anti-donor MHC class1 IgM.

Discussion & Conclusion

- The preliminary results indicates that TNX-1500 efficacy is similar to hu5c8 parent molecule with no evidence for procoagulant phenotypes
- 'Standard' dosing as monotherapy consistently prevents graft loss during Rx
- Combination Rx with MMF is associated with higher incidence & severity of ACR score in both IoTNX and stTNX
- stTNX-1500 combined with Rapa prolonged graft survival with no evidence of pathologic and humoral rejection