

# Ex Vivo Nicotinamide-Expanded (NAM-Expanded) Unrelated Cord Blood (UCB) Transplantation for Refractory Severe Aplastic Anemia Results in Rapid Engraftment and Expedites Immune Recovery

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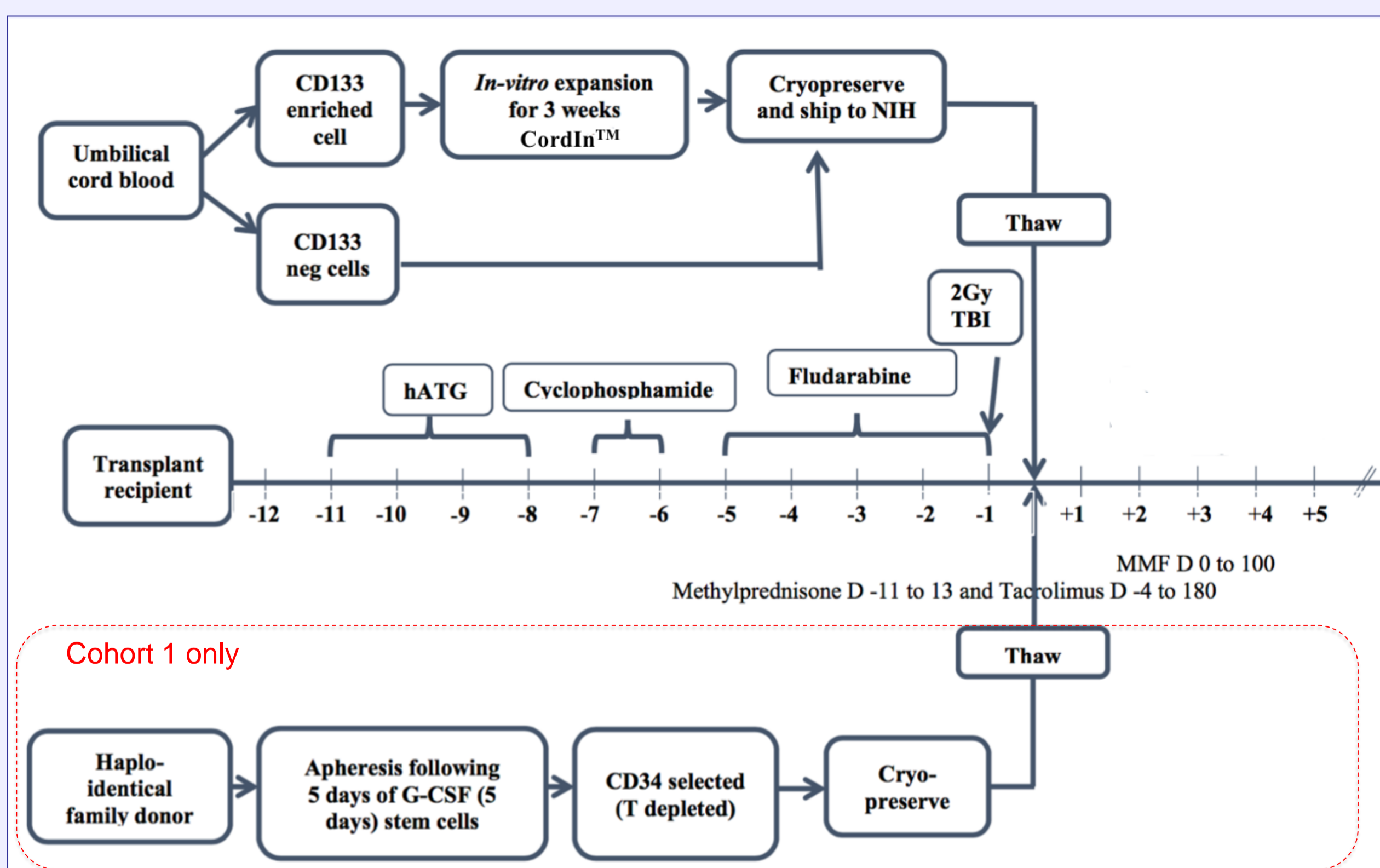
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## INTRODUCTION

- Allogeneic hematopoietic stem cell transplantation using UCB (UCBT) is an alternative approach for severe aplastic anemia (SAA) patients lacking an HLA matched donor.
- However, UCBT is associated with delayed engraftment, and high rates of graft failure and mortality.
- Ex-vivo expanded UCB using nicotinamide (NAM) can engraft in NOD/SCID mice, and in patients with hematological malignancies in pilot studies.
- Here we investigated whether NAM-expanded UCBT would accelerate engraftment and immune reconstitution in refractory SAA patients.

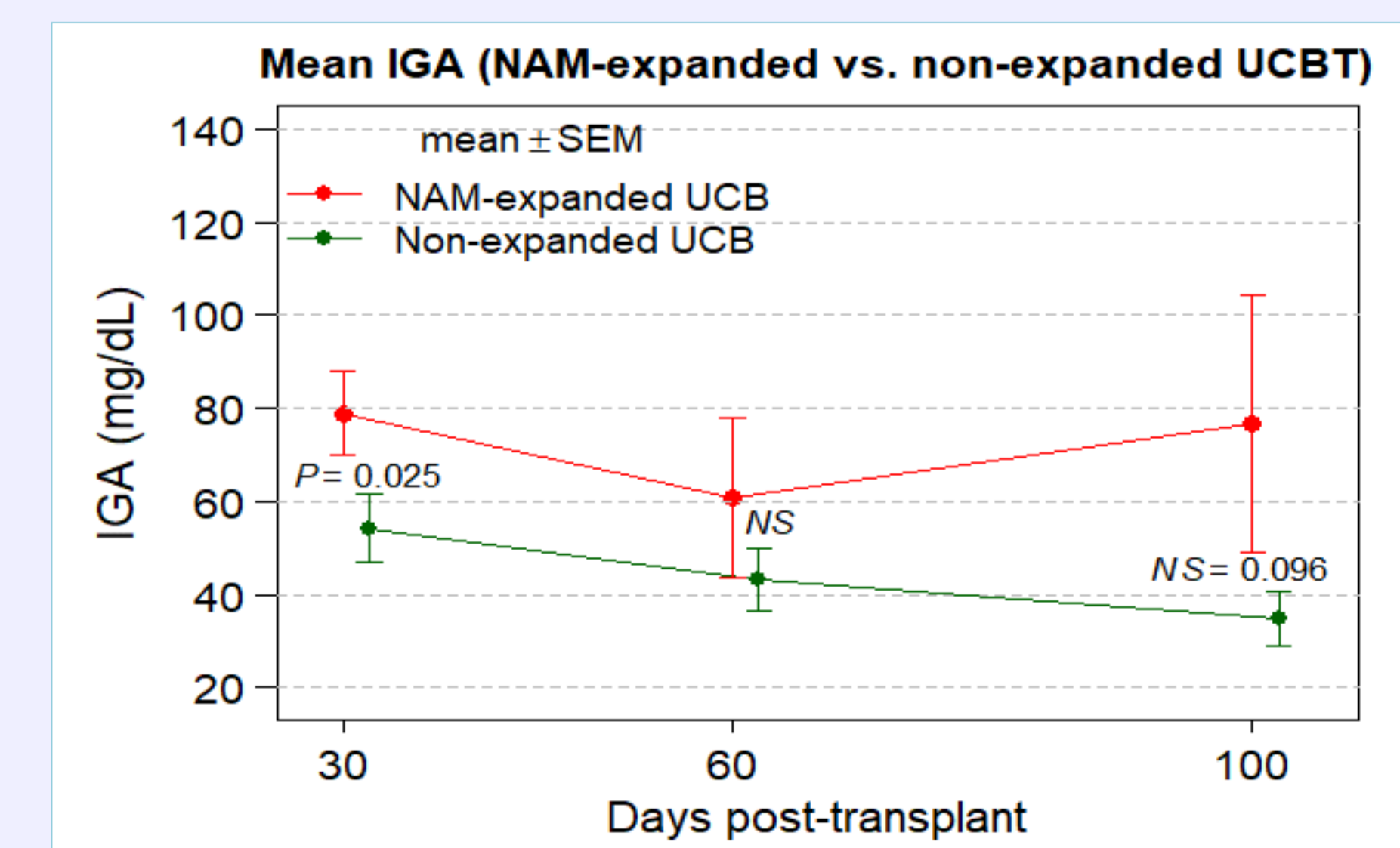
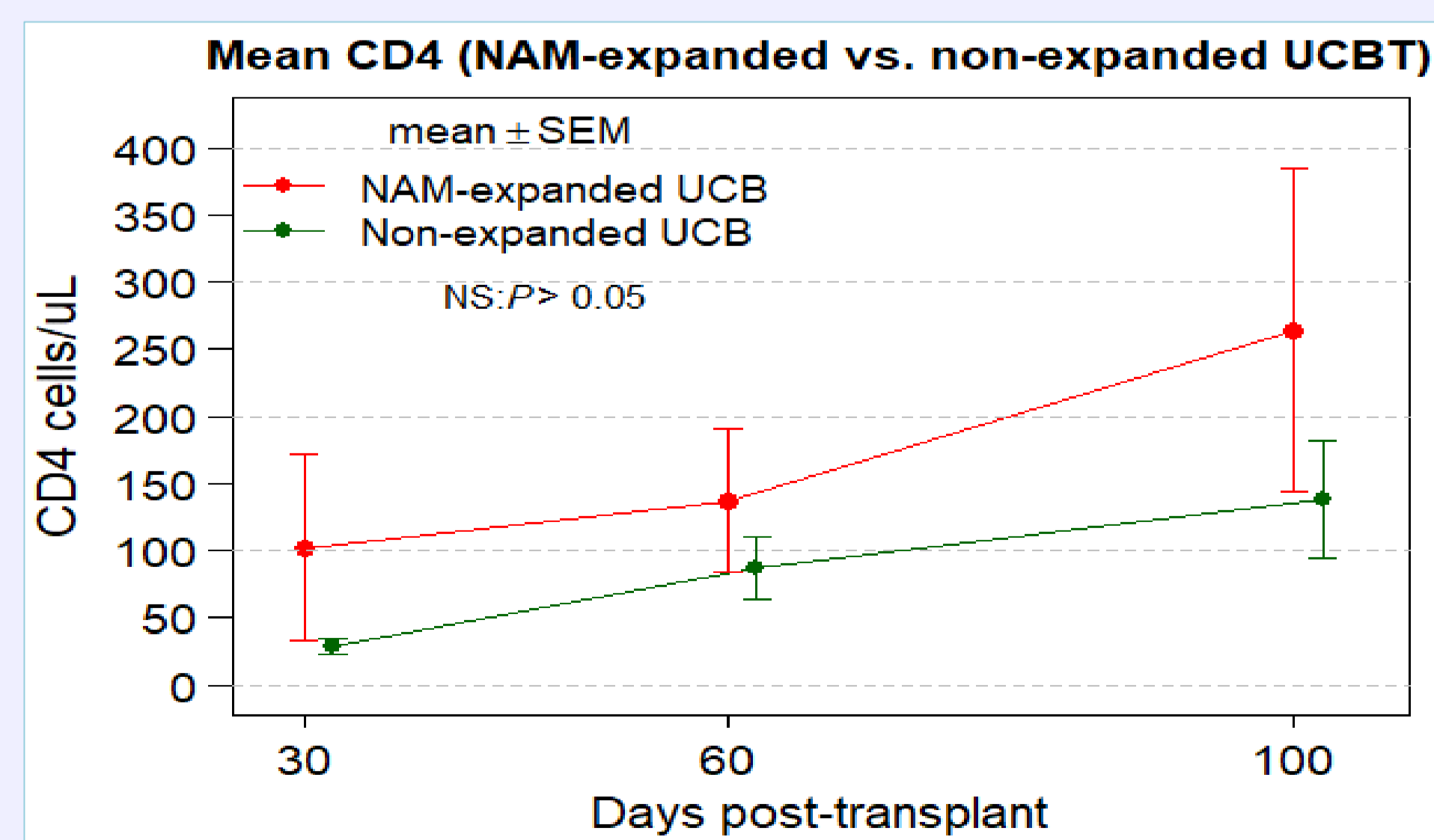
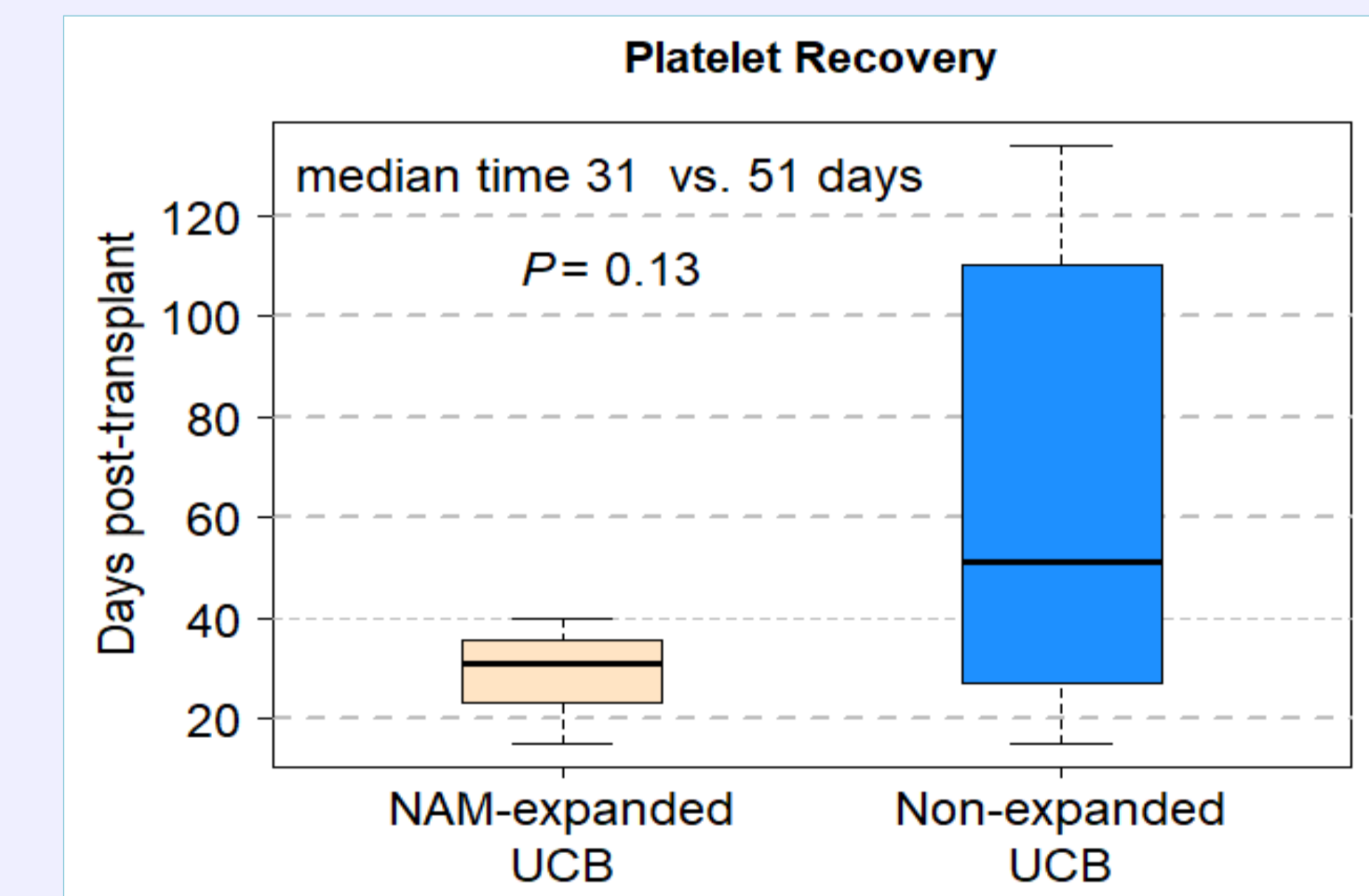
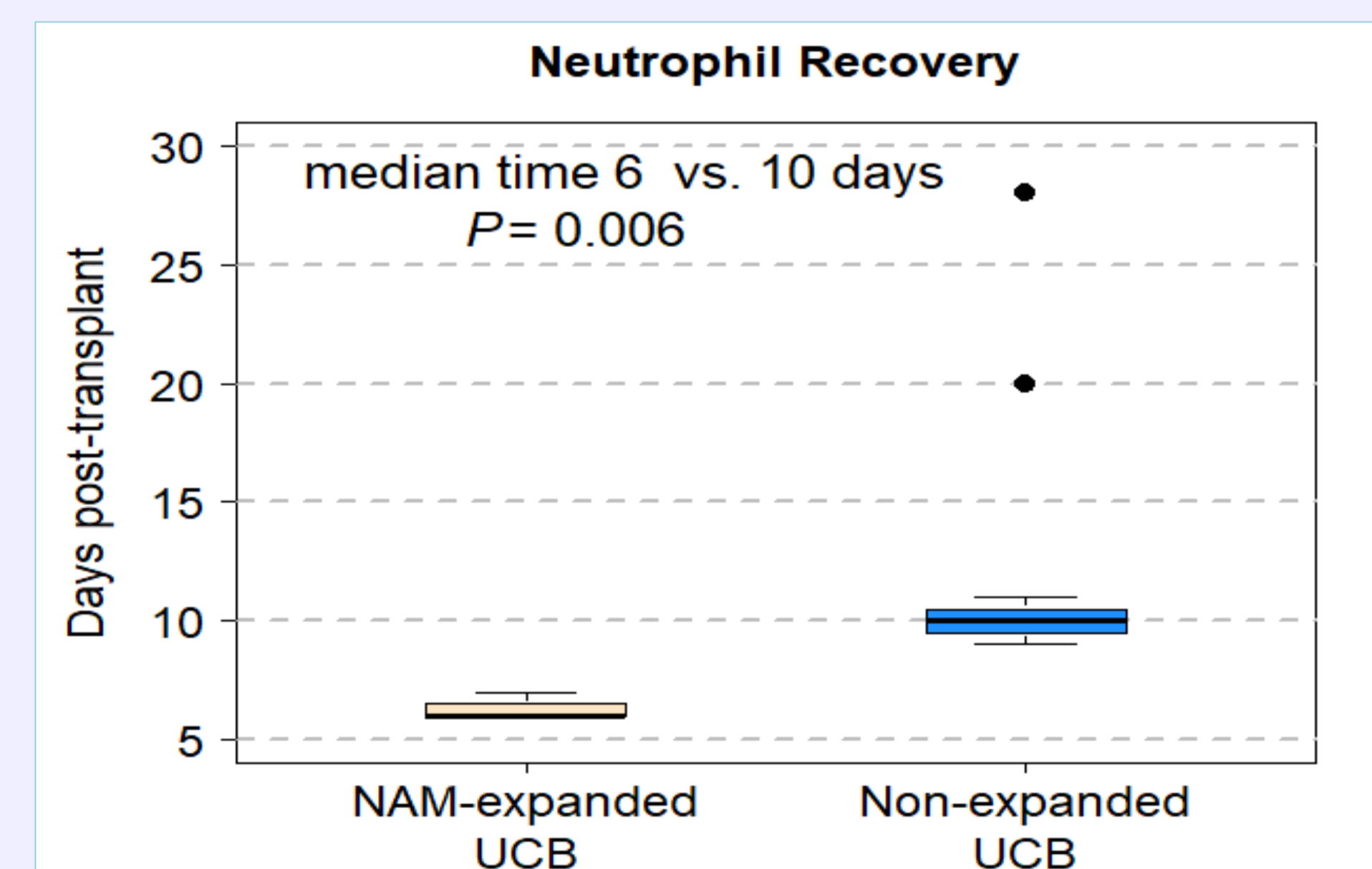
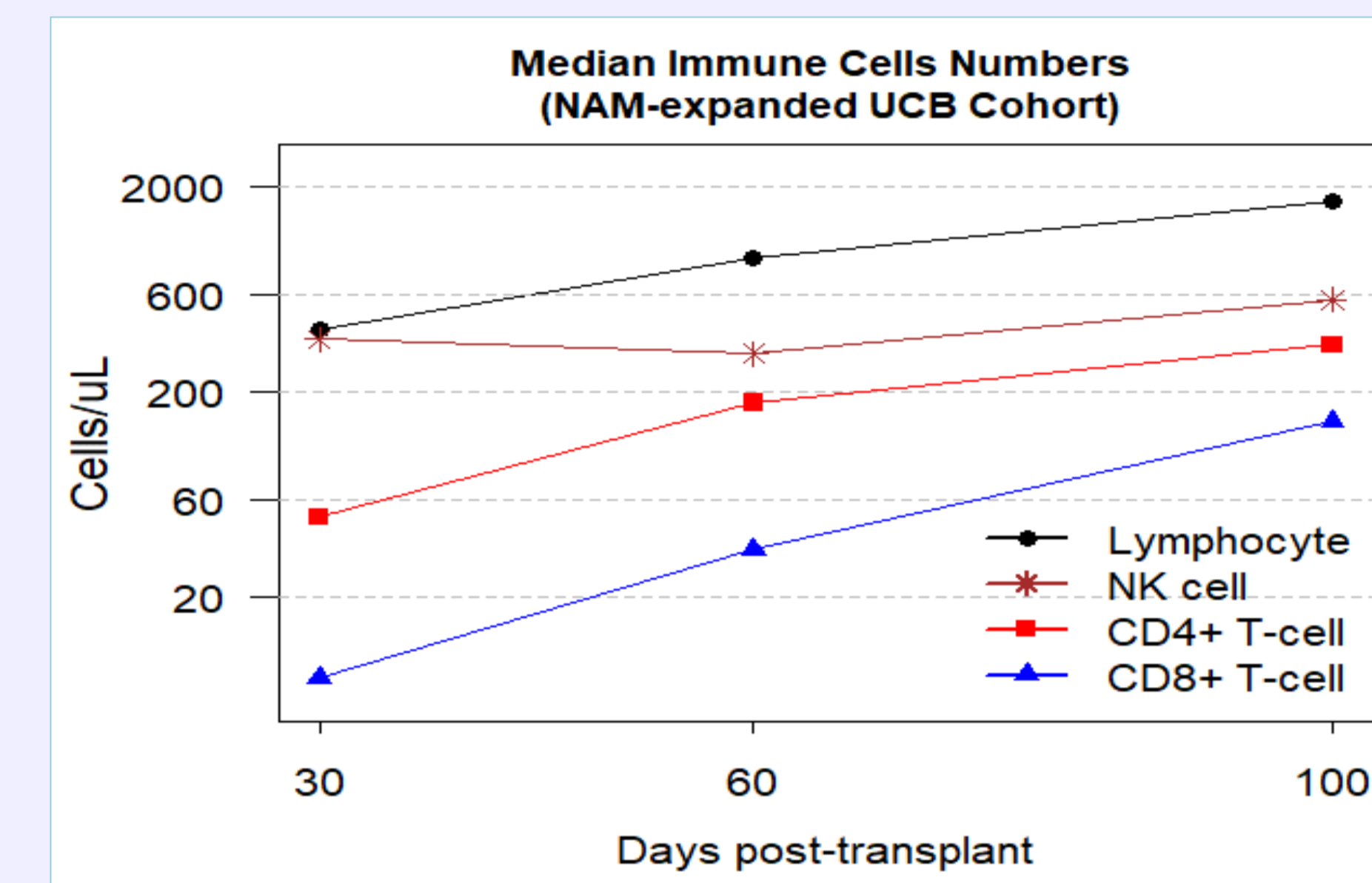
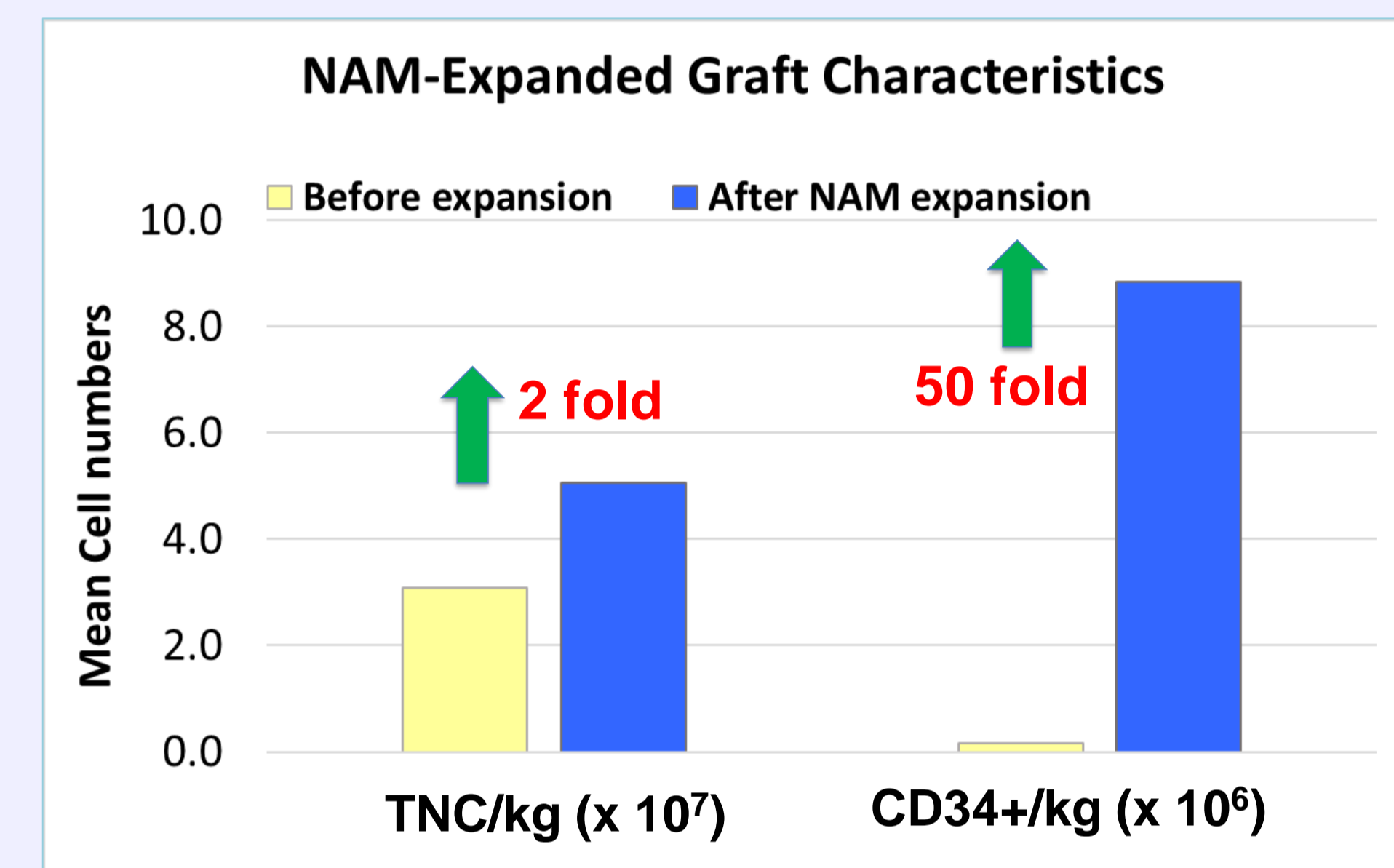
## STUDY DESIGN

- Eligible SAA patients with severe neutropenia who failed immunosuppressive therapy underwent a NAM-expanded UCBT at a single center in a phase II trial.
- Patients were conditioned with cyclophosphamide (60 mg/kg x 2), horse ATG (40 mg/kg x 4), fludarabine (25 mg/m<sup>2</sup> x5) and 200cGy of TBI. GVHD prophylaxis included tacrolimus and MMF.
- Cohort 1** is designed to transplant 3-6 patients with a single NAM-expanded unit combined with 3 x 10<sup>6</sup> CD34+ cells/kg from a haploidentical donor as a stem cell backup.
- Once adequate cord engraftment is established (defined as 3 of the first 3-4 patients or 4 of 6 patients with ANC >500 cells/ul by day 26 and cord ANC >500 cells /ul by day 42 sustained at day 100), **Cohort 2** will transplant up to 20 SAA patients with a NAM-expanded unit alone.



## RESULTS

- Here we assessed the engraftment and immune recovery of NAM-expanded UCBT patients in Cohort 1 and compared their outcome with a conventional single unexpanded UCBT with haploidentical CD34+ cells using the same conditioning & GVHD prophylaxis.
- From 2017 to 2018, three SAA patients (age/gender: 22M, 45F, 22F) with a pre-transplant ANC ≤500/uL, all who failed ATG/CSA/eltrombopag, successfully underwent a single 5/8 or 6/8 HLA-matched NAM-expanded UCBT combined with haploidentical CD34+ cells.



## RESULTS (CONT)

- UCB units before expansion contained a mean total nucleated cell (TNC) dose of 3.1 x 10<sup>7</sup>/kg and 1.7 x 10<sup>5</sup> CD34+ cells/kg. Transplanted NAM-expanded units contained a mean 5.1 x 10<sup>7</sup> TNCs/kg and 88.4 x 10<sup>5</sup> CD34+ cells/kg, representing a mean TNC and CD34+ cell expansion of nearly 2-fold and 50-fold, respectively.
- For NAM expanded transplants, the median time to neutrophil and platelet recovery was 6 days (range 6-7) and 31 days (15-40), with >95% cord donor myeloid at 6 days and >95% T-cell chimerism occurring 26 days post-transplant, respectively.
- All three patients achieved cord engraftment (a calculated cord ANC >500/uL) at median 6 days which was sustained at day 100.
- At median follow-up of 11 months (range 4-18), all NAM expanded patients were alive and GVHD-free.
- Immune recovery was brisk: at day 100, mean CD4+ cells were 264/μL and IGA 77 mg/dL. In two of the three patients, an absolute CD4+ > 200 cells/μL occurred at 17 and 60 days.
- Compared to 16 SAA patients who received a single unexpanded UCBT with haploidentical CD34+ cells at our institute from 2013 to 2016, engraftment and immune recovery were superior in SAA patients receiving a NAM-expanded UCBT.

## CONCLUSIONS

- These encouraging results show for the first time that NAM-expanded UCB can result in rapid cord engraftment, sustained hematopoiesis and accelerated immune recovery in treatment refractory, neutropenic SAA patients.
- The higher numbers of CD34+ progenitor cells transplanted in NAM-expanded grafts could potentially overcome graft failure which limits conventional UCBT for SAA, obviating the need to co-transplant haploidentical CD34+ cells as a stem cell back-up.
- Limitation: Our findings are based on small pilot study and limited by relatively large between-subject variability.
- Future study plan:** Cohort 1 is completed and we will proceed to Cohort 2 to evaluate engraftment and outcome of transplantation with the NAM-expanded unit alone in 20 SAA patients.

Disclosures: No relationships to disclose