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CNDO-109-Activated Allogeneic Natural Killer Cells in Patients with High Risk Acute Myeloid Leukemia in First Complete Remission (CR1): A Phase 1 Study

CNDO-109 Overview

- Clinical-grade lysate of the human leukemia cell line CTV-1
- Expresses priming but not triggering ligands
- Primes autologous or allogeneic NK cells *ex-vivo*
- Straightforward, 2-day manufacturing process
  - Incubation with cytokines is not required
- Secure and proven cold supply chain

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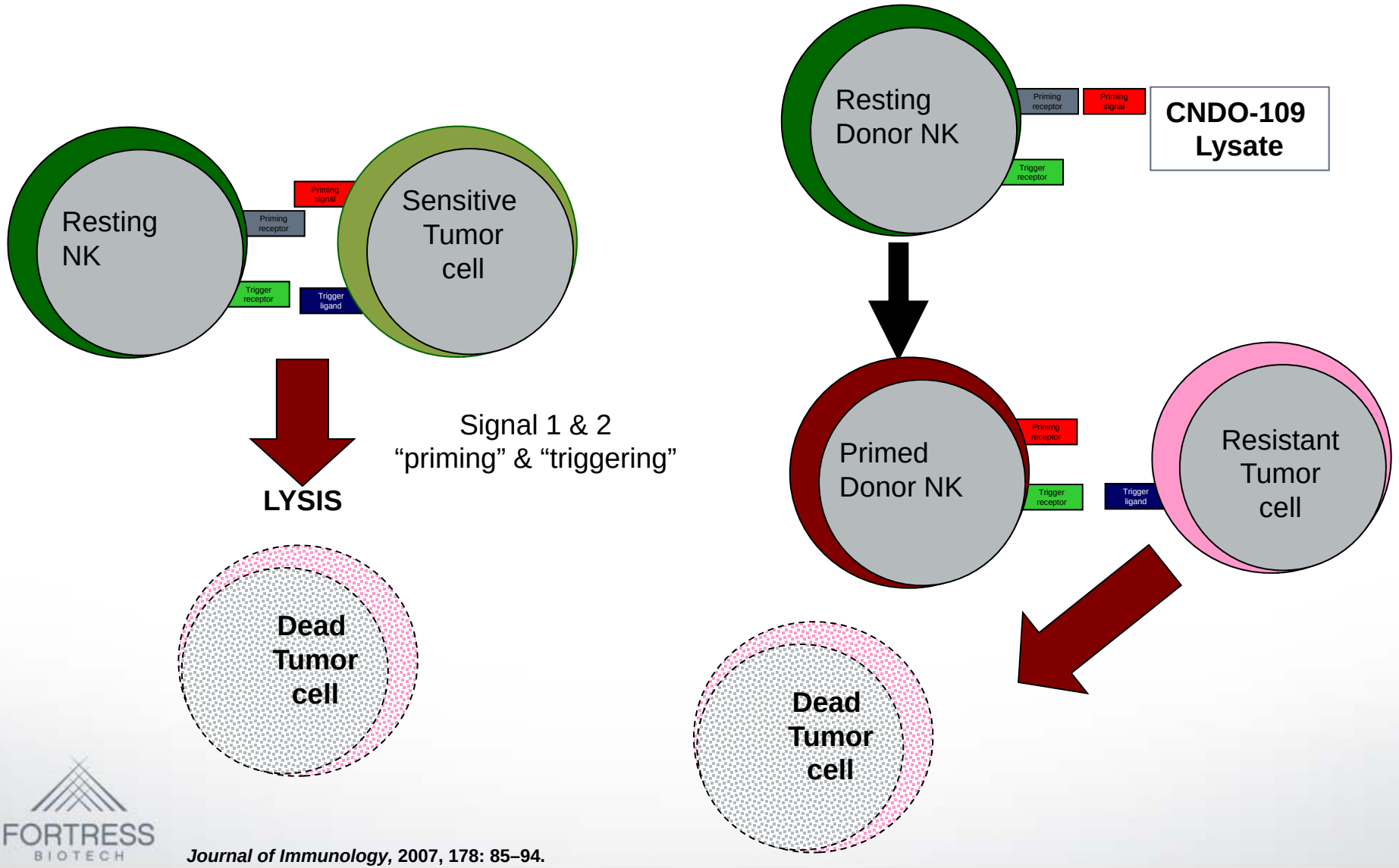
NK Cell Activation by CNDO-109



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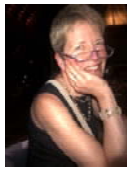
Journal of Immunology, **2007, 178: 85–94.**

Manufacture and Supply Schema

Patient



Donor

Apheresis

NK selection

NK Priming with CNDO-109 Lysate

Cryopreserve

QC test and Release

Ship to clinical site

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CNDO-109 aNK Cells: Release Specifications

- Cell viability > 70%
- CD56+/CD3- >50%
- Viable aNK cells/kg – per protocol
  - max. dose tested is $3x10^6$ cells/kg
- T cell dose (CD56-/CD3+) < 10^4 cells/kg
- Endotoxin < 7.5 EU/ml
- Gram stain, Mycoplasma, Sterility – negative
- Potency: aNK vs rNK killing > 0%
- CD69+, CD25+ expression (report value only)
- **Other markers in development**

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UCL Phase 1 Study

Two-Stage Priming of Allogeneic Natural Killer Cells for the Treatment of Patients with Acute Myeloid Leukemia: A Phase I Trial

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UCL Phase 1 Study

- High-risk AML patients
- Prep regimen: Fludarabine + TBI
- Dose = a *single* infusion of CNDO-109-primed NK cells
- 7 patients treated
- Profound myelosuppression (median neutrophil recovery day = 55)
- Median overall survival = 400 days post infusion (range 141–910)
- 4 patients remained in CR after treatment for longer than their most recent previous CR
- NK engraftment was shown in all evaluable patients

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CNDO-109-001:

A Phase 1/2 Study of CNDO-109-Activated Allogeneic Natural Killer Cells in patients with High Risk Acute Myeloid Leukemia in First Complete Remission (CR1)

ClinicalTrials.gov Identifier: NCT01520558

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CNDO-109-001: Study Objectives

- Primary objective = define acceptable dose
  - Determination of MTD or max dose tested
- Secondary objectives
  - Safety profile
  - RFS and OS through 12 months
- Exploratory objectives
  - Determine the chimerism and persistence of donor NK cells as well as evaluate presence of minimal residual disease (MRD)

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Study Design – Stage 1

Stage 1/Escalation 3+3 design (3-6 patients per cohort):

- Cohort 1 received 3×10^5 activated NK cells/kg
- Cohort 2 received 1×10^6 activated NK cells/kg
- Cohort 3 received 3×10^6 activated NK cells/kg

Stage 1/Expansion Enrolled additional subjects to ensure that a total of 6 patients were treated at the provisional MTD

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Key Eligibility Criteria

- Patients with AML in CR1 w/in 16 weeks of screening
  - Repeated testing to confirm CR1 w/in 21 days of prep regimen [consolidation therapy was allowed]
- At high risk of relapse:
  - High risk cytogenetics (-5, -7, del(5q), abnormal 3q, 11q23 translocations, complex cytogenetics) or if cytogenetics are normal the presence of a FLT3 mutation without a NPM1 mutation
  - Age > 60 years
  - Antecedent hematological disorder (AHD)
  - AML that is considered to be therapy-related
  - FAB subtype M0 (minimally differentiated acute myeloblastic leukemia), M6 (acute erythroid leukemias, including erythroleukemia (M6a) and pure erythroid leukemia (M6b), or M7 (acutemegakaryoblastic leukemia)
- Not considered candidates for stem cell transplant at current time
- Recovered from prior toxicities
- Relatively normal/stable clinical condition
- Has a haploidentical NK cell donor (first degree or second degree relative)
  - Minimum testing will be for HLA-A, HLA-B, and HLA-DR with donors matched for 3/6, 4/6 or 5/6 antigens

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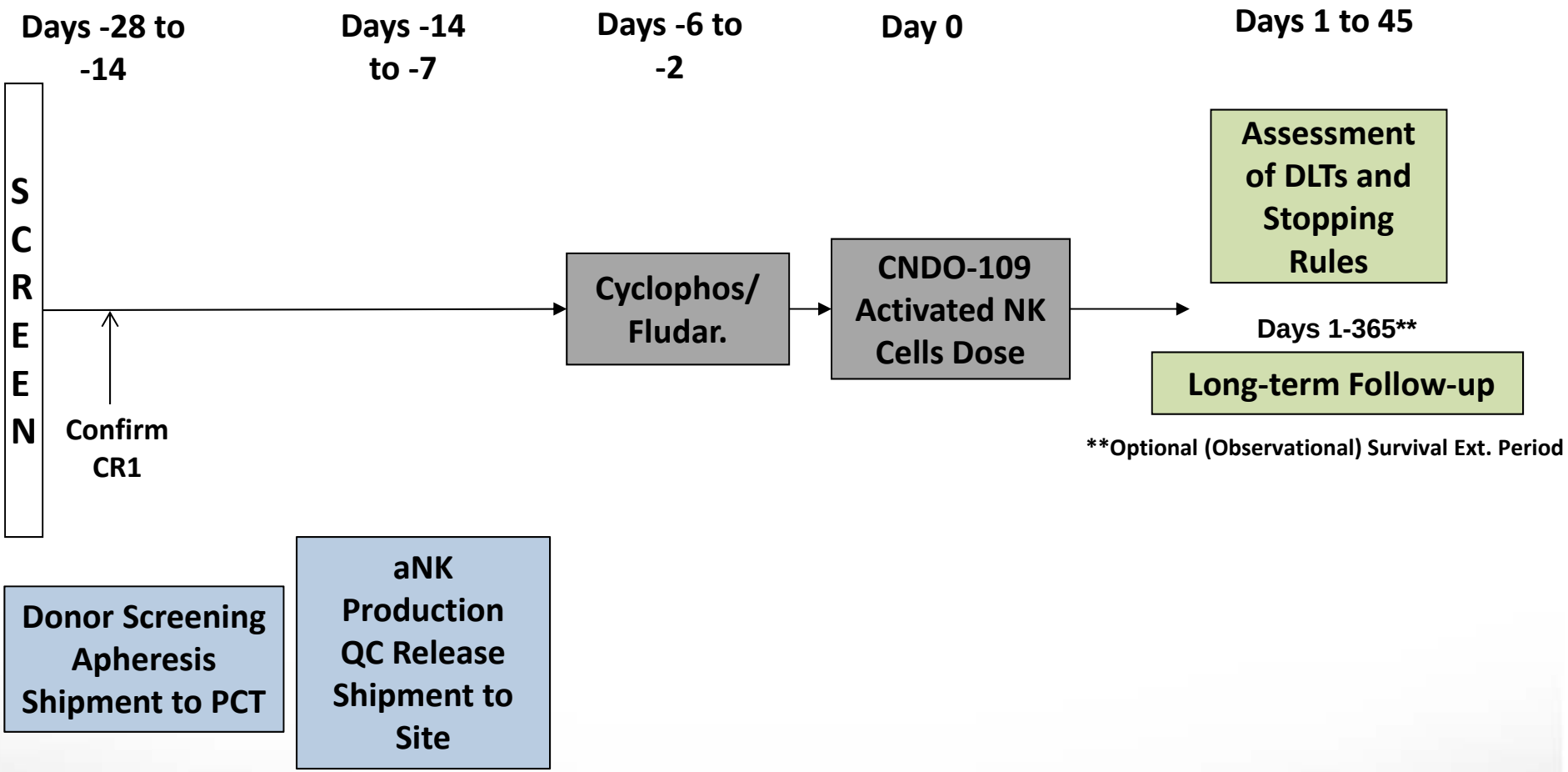
CNDO-109-001: Study Schematic



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Enrollment by Site

Clinical Site (Site #)	Principal Investigator	# of Patients Enrolled
Washington University in St. Louis School of Medicine (03)	Todd Fehniger	5
USC Hollings Cancer Center (08)	Robert Stuart	4
University of Minnesota (02)	Sarah Cooley	2
City of Hope (05)	Amandeep Salhotra	1

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CNDO-109-001: Patient Enrollment & Dosing

- 12 patients enrolled
  - Dose Group 1 (3×10^5 NK cells/kg) = 3 patients
  - Dose Group 2 (1×10^6 NK cells/kg) = 3 patients
  - Dose Group 3 (3×10^6 NK cells/kg) = 6 patients*

- All products met release criteria*
  - Median Purity = 71.8% [range 55.5%-93.8%]
  - Median Viability = 96.4% [range 92.5%-99.2%]

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* 1 patient received an actual dose of 2.5×10^6 due to an inadequate yield of donor NK cells
** 1 patient excluded in Dose Group 1 and 1 in Dose Group 3

CNDO-109-001: DLTs & Safety

- No DLTs were reported during the study
- MeTD = 3×10^6 cells/kg patient body weight
- As expected, all patients experienced transient myelosuppression consequent to conditioning, with recovery over approx. 2 weeks
- Administration of CNDO-109-NK cells was well tolerated
  - No infusion-related events were reported, and no patient developed GVHD

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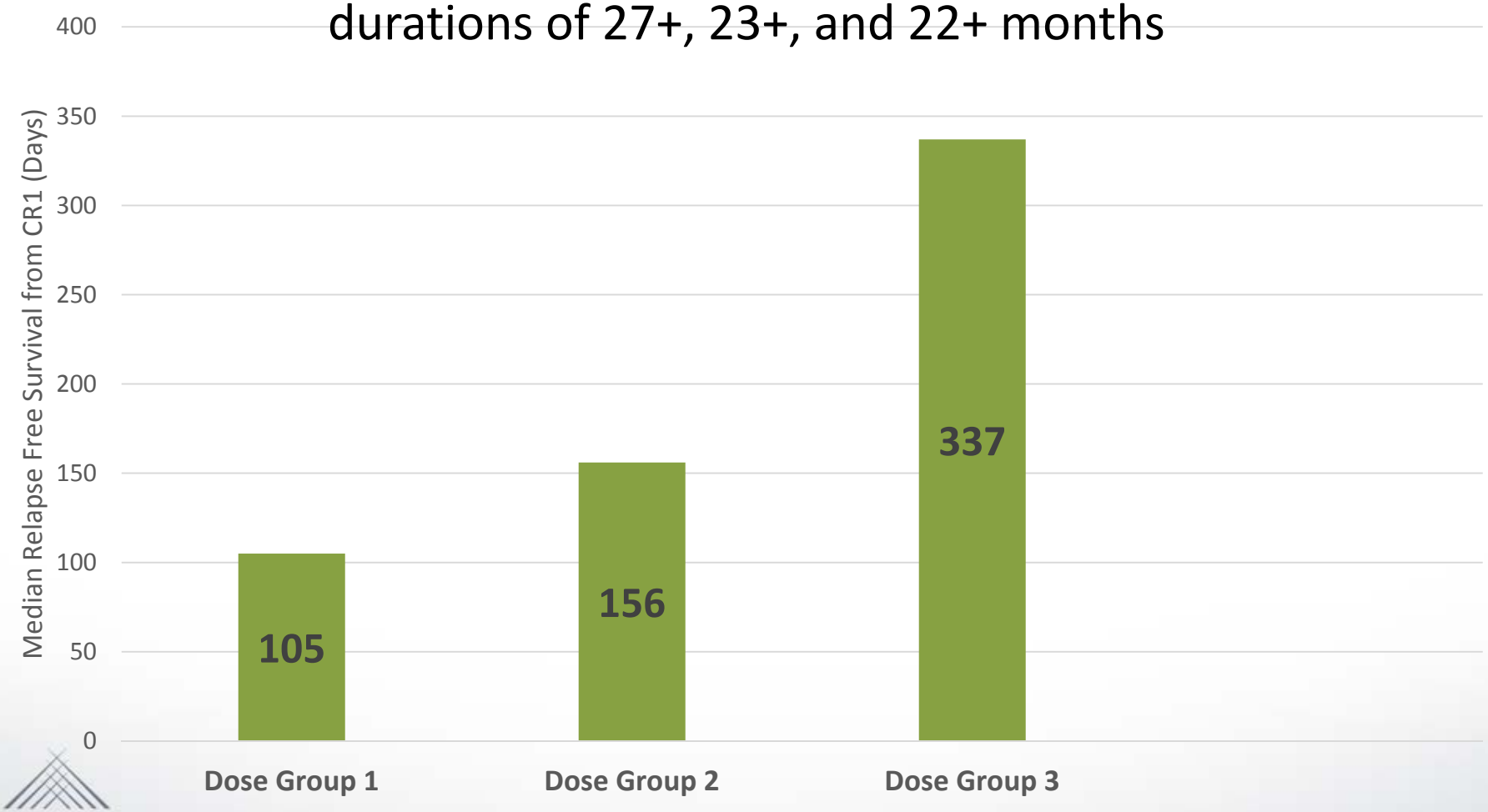
CNDO-109-001: Relapse Free Survival

3 patients remain relapse-free in post-study follow-up: RFS durations of 27+, 23+, and 22+ months



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CNDO-109-001: Immune Monitoring

- 2 chimerism methods utilized
  - Molecular DNA chimerism with STR genotyping
  - Flow cytometry
- 8 patients had detectable donor activated NK cells on Day 7
- 3 patients had detectable donor activated NK cells on Day 14 or later
- 1 patient had detectable donor activated NK cells in blood on Days 14, 28, and 56 and in bone marrow on Day 56
- 4 patients had an increase from baseline in CD69 expression on NK cells at Day 7, which was sustained through Day 28 or 56

Patient ID	Donor NK Cell % (Day 7)
1	<1%
2	<1%
3	ND
4	16%
5	ND
6	1%
7	84%
8	ND
9	66%
10	ND
11	7%
12	15%

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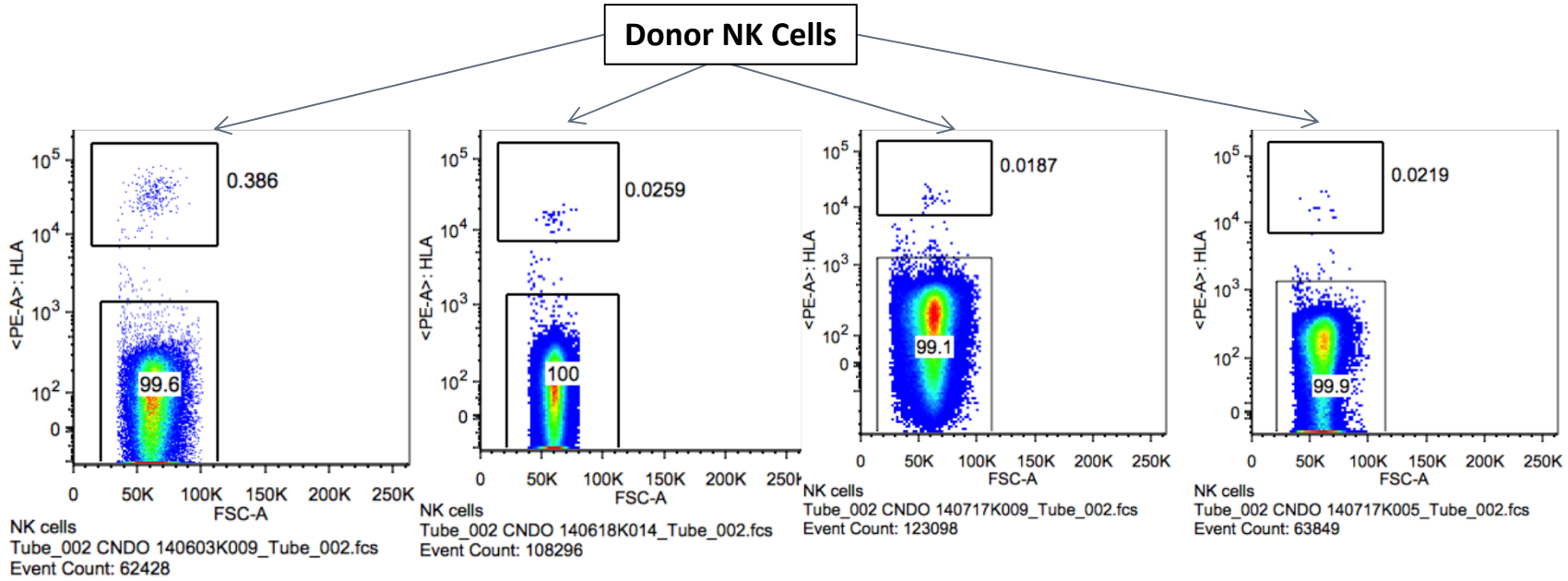
Patient 7 (Dose Group 3) Flow Plots



Day 14 blood | Day 28 blood | Day 56 blood | Day 56 marrow

All of the plots above are gated on NK cells (CD56+CD3-). The donor is HLA-A2+ and the recipient is HLA-A2neg so anti-HLA-A2 antibody was used to identify donor cells.

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Patients with Longer RFS

ID	Site ID	Risk Factor	RFS* (mos.)	Consolid.	KIR L MM in GVL vector	Chimerism	Dose Level
5	02-001	79 yo	>27.5	No	C2	D7 (2%)	2
10	05-001	57 yo FLT3-ITD mutation w/o NPM1 mutation	>22.6	No	No	None	3
11	03-006	67 yo AML considered to be therapy-related	>22.3	No	No	D14 (15-2%)	3

* Calculated from time of CR1

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CNDO-109-001: Conclusions

- Maximum tested dose was defined: $3x10^6$ aNK cells/kg
- Product safety was confirmed with no infusional toxicity, adverse events attributed to NK therapy, nor GvHD reported.
- Transient persistence of donor NK cells with lasting microchimerism for > 1 month
- Evidence of activation of endogenous NK cells in patients
- Longer than expected complete remissions (CRs) in some high risk patients

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UCL: Mark Lowdell, Janet North

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- University of Minnesota, Masonic Cancer Center, Translational Cell Therapy

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Questions?

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