Selective Expansion of Regulatory T Cells in Patients with Systemic Lupus Erythematosus by a Novel IL-2 Conjugate, NKTR-358

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BACKGROUND

- Compared with recombinant human interleukin-2 (rIL-2), PEG-conjugated NKTR-358 is less antigenic and has a prolonged half-life.
- An altered binding profile, with a lower binding affinity for IL-2R, is a characteristic of NKTR-358.
- Treg levels peaked at Day 10 after the first NKTR-358 dose and remained above baseline for 20–30 days following the last dose.

METHODS

- Study design: A randomized, double-blind, multiple-dosing study (MAD Phase I) of subcutaneous NKTR-358 in patients with pre-moderate to mild SLE.
- Assessments: Immunophenotyping by multicolor flow cytometry to quantify multiple immune cell subsets, using whole blood collected pre- and post-NKTR-358 administration.

RESULTS

- Safety and tolerability:
  - No dose-limiting toxicities, deaths, or clinically significant adverse events were observed.
  - No adverse events were reported.

- Baseline demographics and characteristics:
  - Mean age: 39.9 years, median age: 38.0 years.
  - Mean disease duration: 7.2 years.

CONCLUSIONS

- NKTR-358 was safe and well tolerated, with a similar safety profile for single and repeat doses.
- A novel, dose-dependent expansion of CD25+FoxP3+ Tregs was observed, which was maintained through multiple NKTR-358 administrations.
- Treg induction was further supported by a correlation between the number of Tregs and the extent of demethylation.
- Increases in Treg activation markers (CD25, Helios, and CTLA-4) and genes associated with Treg regulation were observed.
- Low-level increases in NK cell numbers occurred in patients at the highest NKTR-358 dose; the CD56 bright population was more sensitive than the CD56 dim population.
- A dose-dependent reduction in CLASI-A score was seen with NKTR-358 treatment, which warrants further exploration.
- These data provide strong support for continued testing of NKTR-358 in patients with SLE and other inflammatory diseases.
- A Phase 2 trial of NKTR-358 in patients with SLE is currently recruiting (NCT04433365).

Note: All data are from the MAD Phase I study of NKTR-358 in patients with SLE.