Use of Quantitative System Pharmacology (QSP) Modeling to Optimize Dosing Frequency and Interval for Nemvaleukin Alfa (Nemvaleukin), an Investigational Cancer Immunotherapy

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^At time of study

INTRODUCTION

Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel engineered cytokine

- Nemvaleukin is designed to selectively bind the intermediate-affinity interleukin-2 receptor, preferentially expanding antitumor CD8+ T and natural killer (NK) cells, with minimal effect on immunosuppressive regulatory T cells (T_{regs})[1]

Nemvaleukin showed activity of interest in the ARTISTRY-1 trial

- In ARTISTRY-1 (NCT02799095), intravenous (IV) nemvaleukin on days 1-5 (QD×5) in a 21-day cycle showed antitumor activity across multiple tumor types as monotherapy at the recommended phase 2 dose of 6 µg/kg/d and as combination therapy at a dose of 3 µg/kg/d or 6 µg/kg/d with pembrolizumab[2]
- Expansion of circulating CD8+ T and NK cells was observed, with minimal effect on T_{regs}[2]
- An optimal IV dosing schedule would be the fewest doses in a treatment cycle to increase recovery time between doses and simplify administration when given as monotherapy or in combination with current standard-of-care treatments

Objective

- QSP modeling was applied to predict less frequent IV dosing regimens that result in expansion of CD8+ T and NK cells similar to that achieved with 3 µg/kg/d and 6 µg/kg/d QD×5

METHODS

QSP model description (Figure 1)

- A QSP model for nemvaleukin was developed using MATLAB® and SimBiology® (Mathworks.com) by leveraging published literature data
- The model comprises 6 compartments; target binding occurs mainly in the blood, lymph node, and tumor compartments
- Cell expansion occurs in lymph node compartment and increased cells are distributed into blood compartment
  - Drug binds to the beta-gamma subunit of the interleukin (IL)-2 receptor, which triggers phosphorylation of phospho-signal transducer and activator of transcription 5 (pSTAT5)
  - pSTAT5 on each cell type in lymph node is linked to cell expansion
  - pSTAT5 by drug treatment stimulates the synthesis of each cell type in lymph node (implemented as a maximal effective concentration [E_{max}] model)
- Number of biochemical species: 16 each in blood and lymph node compartments (including 3 active biological species) and 10 species in tumor compartment

Figure 1: QSP model diagram

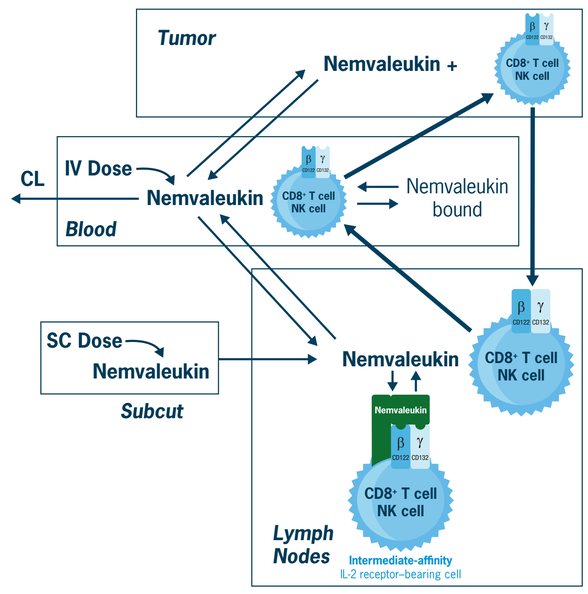


Table 1: Key model input parameters

Parameter	Definition	Calibration
Kon2	Association rate constant of the drug to the beta-gamma subunit	Manually calibrated with in vitro data (pSTAT5 assay)
ksp_CD8+i	STAT5 phosphorylation rate constant on CD8+ in lymph node compartment	Fitted with in vitro EC_{50} (pSTAT5 assay)
ksp_T_{reg}i	STAT5 phosphorylation rate constant on T_{reg} in lymph node compartment	Fitted with in vitro EC_{50} (pSTAT5 assay)
ksp_NKi	STAT5 phosphorylation rate constant on NK in lymph node compartment	Fitted with in vitro EC_{50} (pSTAT5 assay)
Base_CD8+_blood	baseline CD8+ count in blood compartment	Fitted with clinical CD8+ count data
Base_T_{reg}–blood	baseline T_{reg} count in blood compartment	Fitted with clinical T_{reg} count data
Base_NK_blood	baseline NK count in blood compartment	Fitted with clinical NK count data
AMP1	Relative E_{max} of drug effect on CD8+ expansion in lymph node compartment	Fitted with clinical CD8+ count data
EC_{50}–pSTAT_CD8+	EC_{50} of pSTAT5 on CD8+ in lymph node	Fitted with clinical CD8+ count data
AMP2	Relative E_{max} of drug effect on T_{reg} expansion in lymph node compartment	Fitted with clinical T_{reg} count data
EC_{50}–pSTAT_T_{reg}	EC_{50} of pSTAT5 on T_{reg} in lymph node	Fitted with clinical T_{reg} count data
EC_{50}–pSTAT5_NK	EC_{50} of pSTAT5 on NK in lymph node	Fitted with clinical NK count data
AMP3	Relative E_{max} of drug effect on NK expansion in lymph node compartment	Fitted with clinical NK count data
CL_ALKS	Clearance of drug	Fitted with clinical PK data
F	Bioavailability for SC dosing	Fitted with clinical PK data
peri2	Peripheral compartment	Fitted with clinical PK data

EC_{50}, half maximal effective concentration; PK, pharmacokinetic; SC, subcutaneous.

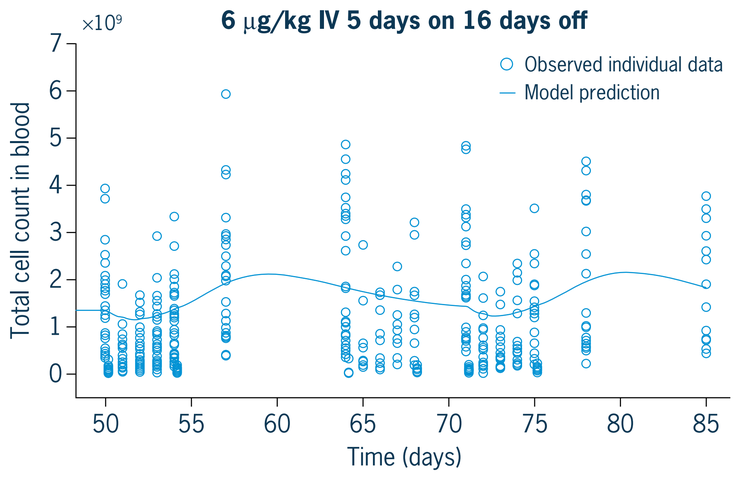
Parameters (Table 1)

- All parameters calibrated with in vitro or clinical data from ARTISTRY-1 (IV) and ARTISTRY-2 (SC)
- Nine parameters calibrated with clinical cell count data, 4 with in vitro pSTAT5 assay data, and 3 with clinical PK data
- Each calibration process was conducted separately
  - PK parameters (CL_ALKS, F and peri2) calibrated first with the clinical PK data
  - In vitro calibration
    - PK profile after SC dosing was back-checked after Kon refinement (target-mediated drug disposition [TMDD])
    - Drug binding kinetics to the β-γ subunit and phosphorylation of pSTAT parameters
- In vivo calibration
  - "Drug effect"–related parameters on synthesis of cells in lymph node (Production of cell = rate of synthesis [Ksyn],cell * [1+ drug effect on CD8+] = AMP1*pSTAT5_CD8+_LN/(EC_{50}_pSTAT_CD8+pSTAT5_CD8+_LN)
  - Same formula applied to other cell types

Model validation/verification

- The observed individual data for CD8+, NK, and T_{reg} cell counts from ARTISTRY-1 (6 µg/kg) were well described by the model prediction
- Figure 2 displays the data for CD8+ in blood; similar results were obtained for NK and T_{reg} cell counts (data not shown)

Figure 2: QSP model validation for CD8+ in blood



RESULTS

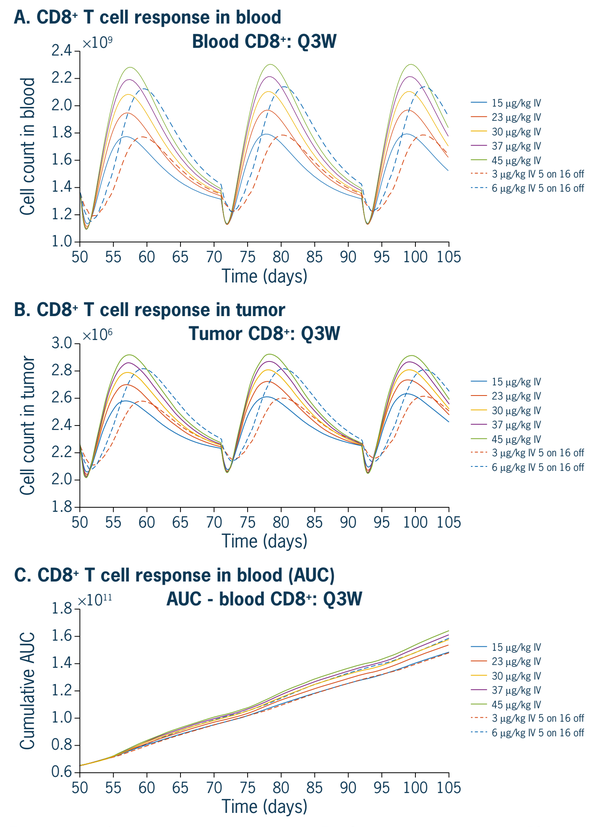
Criteria for identifying target doses and dosing schedules

- We sought to identify doses/dosing schedules such that the maximal response (R_{max}), the time to achieve R_{max}, and the area under the curve (AUC) would be similar or slightly better than QD×5 dosing

Dosing simulations

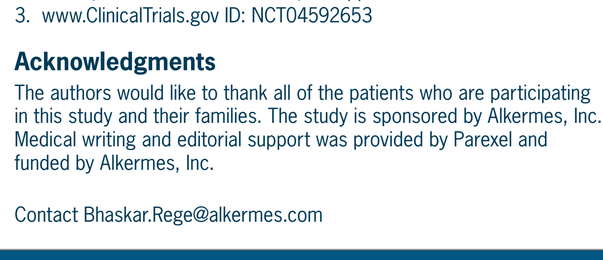
- 1 dose on day 1 was compared with 3 and 6 µg/kg IV QD×5 on days 1-5 in a 21-day cycle
  - Figure 3 shows cell counts over time in blood (A) and in tumor (B)
  - Figure 3C shows AUC in blood (results in tumor were similar)
- 2 doses administered on days 1 and 4 (Figure 4) and on days 1 and 8 (Figure 5) were compared with 3 µg/kg and 6 µg/kg IV QD×5 on days 1-5 in a 21-day cycle
  - Figures show results in blood; results in tumor were comparable (data not shown)
  - AUC results were comparable to those shown in Figure 3C (data not shown)
- 3 doses on days 1, 4, and 8 and 3 doses on days 1, 8, and 15 were compared with 3 µg/kg and 6 µg/kg IV QD×5 on days 1-5 in a 21-day cycle (data not shown)
- All dosing schedules were evaluated for expansion of NK cells and the results were similar to those shown here for CD8+ T cells

Figure 3: 1-dose regimen on day 1 compared with dosing QD×5 on days 1-5 in a 21-day cycle



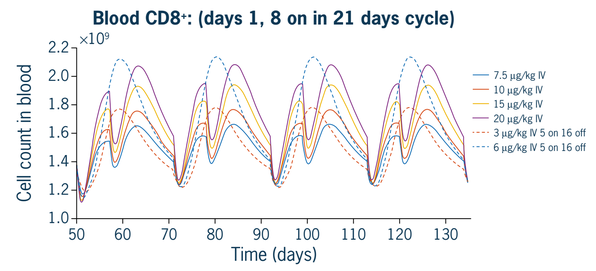
Time in days refers to the model simulation only. The first dose was given on day 50 to allow the model to reach the proper initial condition.

Figure 4: 2 dose regimen on days 1 and 4 compared with QD×5 on days 1-5 in a 21-day cycle



Time in days refers to the model simulation only. The first dose was given on day 50 to allow the model to reach the proper initial condition.

Figure 5: 2-dose regimen on days 1 and 8 compared with QD×5 on days 1-5 in a 21-day cycle



Time in days refers to the model simulation only. The first dose was given on day 50 to allow the model to reach the proper initial condition.

- Based on all the simulations, dose ranges for each less-frequent dosing regimen were identified that were predicted to result in target immune cell expansion similar to or slightly better than the established regimens of 6 µg/kg and 3 µg/kg QD×5 on days 1-5 (Table 2)
- As shown in Figure 3, the 1 dose regimen can achieve a better response than the established regimens on all 3 assessment criteria (R_{max}, time to R_{max}, and AUC)

Table 2: Summary of results for 21-day cycle simulations

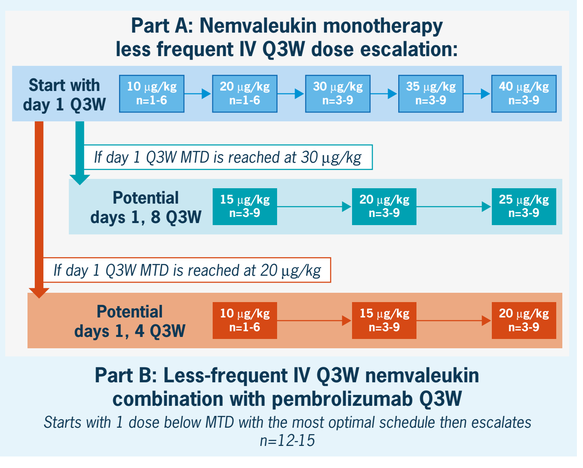
Simulated dosage regimen[a]	Dose (range)	Comparator dose[a] (regimen = QD×5 on days 1-5)
1 dose, on day 1	30-40 µg/kg	6 µg/kg
	15 µg/kg	3 µg/kg
2 dose, on day 1 and day 4	15-20 µg/kg	6 µg/kg
	7.5-10 µg/kg	3 µg/kg
2 dose, on day 1 and day 8	15-25 µg/kg	6 µg/kg
	7.5-10 µg/kg	3 µg/kg
3 dose, on day 1, day 4, and day 8	10-15 µg/kg	6 µg/kg
	5-7.5 µg/kg	3 µg/kg

[a]All doses administered IV.

QSP modeling informs dosing strategy in ARTISTRY-3

- ARTISTRY-3 (NCT04592653) is a phase 1/2, open-label study with 2 cohorts that will evaluate clinical and immunologic activity and impact on the tumor microenvironment of nemvaleukin alfa with a less-frequent IV dosing schedule as monotherapy and in combination with pembrolizumab in patients with solid tumors[3]
- QSP modeling study data were applied to identify a less frequent schedule for nemvaleukin monotherapy and combination
- The proposed dosing schedule is shown in Figure 6

Figure 6: ARTISTRY-3 Cohort 2 dosing schedule



CONCLUSIONS

- QSP modeling was found to be a useful tool to describe the exposure-response relationships of nemvaleukin and predict the pharmacodynamic profile in lymph nodes and tumor, which are difficult to sample in clinical studies
- QSP simulations predicted that a higher single IV dose in a 21-day cycle could match or exceed the target pharmacodynamic response observed with dosing at 3 and 6 µg/kg/d QD×5
  - Additionally, a 2-dose regimen in a 21-day cycle with administration on days 1 and 4 or days 1 and 8 may achieve target cell expansion at a lower dose compared with the single-dose schedule
- These modeling data were used to inform ARTISTRY-3 dosing strategy in which nemvaleukin will be administered at various doses and schedules to identify an optimal less frequent IV dosing schedule for nemvaleukin monotherapy and for combination with pembrolizumab[3]

REFERENCES AND ACKNOWLEDGMENTS

References

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Acknowledgments

The authors would like to thank all of the patients who are participating in this study and their families. The study is sponsored by Alkermes, Inc. Medical writing and editorial support was provided by Parexel and funded by Alkermes, Inc.

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ClinicalTrials.gov ID: NCT02799095