354 **OPTIMIZATION OF DOSE AND REGIMEN OF LETETRESGENE AUTOLEUCEL FOR THE TREATMENT OF SYNOVIAL SARCOMA: SIMULATION OF DOSE DEPENDENCE AND SPLIT DOSING USING QUANTITATIVE SYSTEMS PHARMACOLOGY MODELING**

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Background Letetresgene autoleucel (lete-cel) is an autologous genetically modified T-cell therapy targeting NY-ESO-1 expressed by cancer cells in synovial sarcoma (SS). The aim of the work is to predict overall response rate (ORR) to lete-cel in SS for various doses and to investigate the effect of split dosing on ORR and cytokine peak levels using quantitative systems pharmacology (QSP) modeling.

Methods The developed QSP model consists of[1] lymphodepletion including pharmacokinetics (PK) of fludarabine and cyclophosphamide, their effects on lymphocytes and IL-7 and IL-15 levels[2]; tumor growth and microenvironment in SS including biomarkers in blood;[3] PK and distribution of lete-cel after intravenous infusion[4]; killing of NY-ESO-1 positive cancer cells by lete-cel and activation of engineered T-cells followed by their expansion and cytokine secretion (IFNg, TNFa, IL-6). The model was calibrated against in vitro data, baseline patient disease characteristics, and lete-cel clinical longitudinal data. Validation of the model was done against lete-cel clinical data on ORR and PFS.

Results ORR dose dependence was simulated for doses from 0.05 to 50 billion cells. Maximal ORR was 41% (95% CI: 33% - 57%). median peak IL-6 levels stayed below cytokine release syndrome thresholds.[2–4] Several 10 billion cell split-dose regimens were simulated: (1) 100% of dose on day 1; (2) 30% of dose on day 1 and 70% on day 8; (3) 10% on day 1, 30% on day 2, 60% on day 3; (4) 5% on day 1 and 95% on day 3. Regimen 3 showed almost similar median ORR to single dose (34.2% vs 36.7%), whereas regimens 2 and 4 showed lower median ORR (26.7% and 31.7%, respectively). All split dosing regimens resulted in lower peak levels of IL6 than single dose.

Conclusions Maximal ORR to lete-cel in SS was predicted to be 41% (95% CI: 33% - 57%) and . The optimal spilt-dose regimen among tested was 10% of the dose on day 1, 30% on day 2 and 60% on day 3. Split-dose cell therapy regimens may provide an improved safety profile while delivering comparable efficacy compared to single dose.

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