Poster 1124

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Novel benchmark scaling method for first-in-human starting dose of CAR-T therapies

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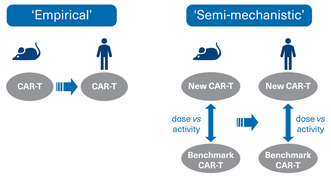
KEY FINDINGS AND CONCLUSIONS

- The proposed method to calculate FIH starting dose mitigates the current limitation in preclinical-to-clinical translation in CAR-T therapy. Examples of two CAR-Ts with different targets and indications demonstrated the utility of the approach.



- The preclinical studies should be designed carefully, for example, appropriate animal models should be selected to represent the patient condition, as the animal model and experimental details may impact the assessment of CAR-T function.
- The major limitation in this approach is that it is applicable only to new CAR-Ts for which clinical information from other CAR-T therapy with the same or functionally similar target(s) or minimally for the same indication is available.
- Additionally, this approach does not utilize preclinical toxicity data. It is assumed that the safety profile (e.g. types of side effects) is mainly target driven, and the severity of toxicity should be taken into account by the calculated activity difference.

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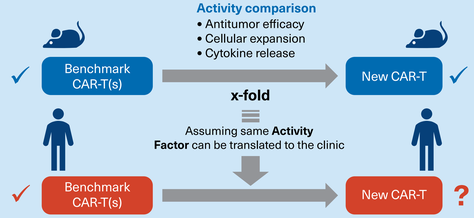
INTRODUCTION

- Despite several approved CAR-T therapies, the first-in-human (FIH) dose for new therapies in clinical development is often determined empirically.
- Establishing a starting dose for dose escalation studies for novel CAR-T therapies remains a challenge, due to the lack of preclinical-to-clinical translational methods.
- For example, allometric scaling, a general method for traditional modalities, may not be applied directly to CAR-T. In addition, the PK/PD relationships for CAR-T are complicated by variable factors.
- Finally, there is no established animal model to assess safety.

METHODS

- To mitigate the current limitations in preclinical-to-clinical translation of CAR-T therapy, a novel method of starting dose selection is proposed by scaling from benchmark CAR-T(s) with an activity factor.
- The benchmark CAR-T(s) should bind to the same or functionally similar target(s) and have clinical safety or efficacy data available.
- The activity factor is
  - derived by comparing the benchmark CAR-T(s) with the novel CAR-T in relevant animal models, eg, xenograft mice, and is based on the time course of anti-tumor activity, cellular expansion, and serum cytokine secretion. Statistical analysis or mathematical modeling may be utilized to make the comparison.
  - assumed to be translatable from preclinical studies to the clinic.
- Leveraging the clinical dose-safety or dose-efficacy information of the benchmark CAR-T(s), a dose predicted to be tolerable and with some clinical activity can be derived for the new CAR-T.

Figure 1. Scheme of proposed FIH dose method based on benchmark CAR-T(s)



CAR-T, chimeric antigen receptor T cell; FIH, first-in-human.

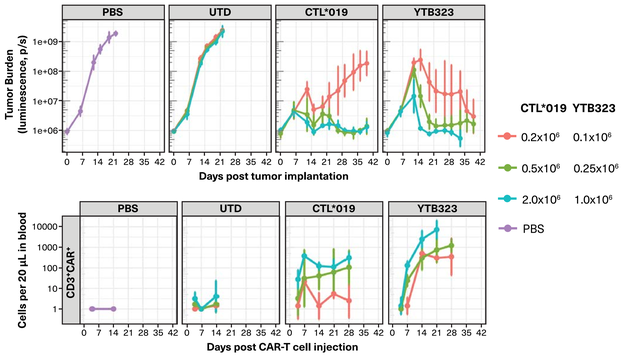
RESULTS

- The development of a CD19-targeted CAR-T (YTB323)[1] and a BCMA-targeted CAR-T (PHE885)[2] manufactured with the T-Charge™ platform are used as examples. The FIH clinical doses were derived based on the method described. Both CAR-Ts showed acceptable safety profile with some clinical activity at the chosen starting dose[3,4], supporting the general application of the proposed method.

Example 1 - YTB323 FIH dose strategy

- In a xenograft immunodeficient NOD scid gamma (NSG) mouse model of leukemia (Nalm-6 B-ALL cell line), YTB323 appeared more potent than the reference CAR-T CTL*019[1] with 40-fold higher C_{max} and approximately 2 to 5-fold higher tumor inhibition.
- For safety reasons, an activity factor of 40 was chosen for YTB323 starting dose calculations, based on the largest margin derived from these preclinical cellular kinetics measurements.
- Scaling from the CTL019 dose of 3×10^8 cells (median active dose in DLBCL, high range of ALL doses) by the activity factor and applying an additional 3-fold safety factor resulted in a starting dose of 2.5×10^6 viable CAR$^+$ T cells for YTB323 for treatment of B cell malignancies.
- Early activity and good safety observed at the proposed starting dose in patients with DLBCL in a phase I dose-escalation study (NCT03960840)[3].

Figure 2. Tumor killing and cellular expansion of YTB323 and CTL*019 in Nalm6 B-ALL tumor model



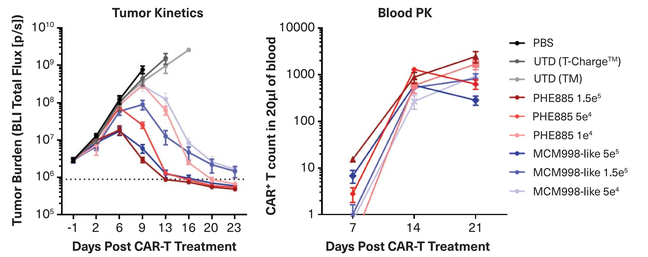
Tumor inhibition	2–5 fold higher
Cellular expansion	40 fold higher

CAR-T, chimeric antigen receptor T cell; PBS, phosphate buffered saline; UTD, control T cells.

Example 2 - PHE885 FIH dose strategy

- PHE885 showed 5-fold higher activity compared to MCM998 (benchmark CAR-T) in the KMS11 multiple myeloma tumor model[2].
- Scaling from the tolerated MCM998 dose of 500×10^6 by the activity factor and an additional 10-fold safety factor resulted in a starting dose of PHE885 at 10×10^6 cells with a range of 5-10×10^6 cells proposed for r/r MM patients.

Figure 3. Tumor killing and cellular expansion of PHE885 and MCM998 in a KMS11 model



PHE885 vs MCM998

Tumor inhibition	3–5 fold higher
Cellular expansion	2–3 fold higher

BLI, bioluminescence imaging; CAR-T, chimeric antigen receptor T cell; PBS, phosphate buffered saline; UTD, control T cells

- High cellular expansion and promising clinical activity were observed in the first few patients treated with PHE885 at the lower end of the target dose range of 5×10^6 cells in r/r MM patients (NCT04318327), with higher doses currently being explored[4].

Figure 5. Derivation of PHE885 dose based on MCM998 clinical information

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Disclosures

All authors, except NB and LB, are employees of Novartis with stock options. NB was a full-time employee of Novartis at the time of the study. Currently he is employed with BMS. LB was a full-time employee of Novartis at the time of the study. Currently she is employed with AstraZeneca.

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