PHARMACOKINETIC PROFILE OF VARNIMCABTAGENE AUTOLEUCEL (IMN-003A), FIRST-IN-INDIA INDUSTRY CD19-DIRECTED CAR-T CELL THERAPY FOR PATIENTS WITH RELAPSED / REFRACTORY B CELL MALIGNANCIES (IMAGINE STUDY)

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(Abstract release date: 05/11/23) EHA Library. Kamat A. 06/08/2023; 385812; P1364

Abstract: P1364

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Abstract Type: Poster Presentation

Session Title: Gene therapy, cellular immunotherapy and vaccination - Biology & Translational Research

Background:

Varnimcabtagene autoleucel (IMN-003A) is an autologous CD19 directed CAR-T cell product with a 4-1BB co-stimulatory domain and A3B1 binder, a non-FMC63 murine single chain variable fragment, manufactured in India and tested in the IMAGINE study (CTRI/2022/03/041162), a phase-2 clinical trial for patients (pts) with relapsed / refractory B cell malignancies. A fractionated infusion of 1 x 10^6 CAR+ cells (IMN-003A)/kg for B-ALL cohort and 5 x 10^6 CAR+ cells (IMN-003A)/kg for B-NHL cohort was administered over 3 days as 10%, 30% and 60% fractions after Flu-Cy lymphodepletion regimen. Safety and efficacy results are submitted in a separate abstract. Here we present the IMN-003A pharmacokinetic data and correlation with disease response.

Aims:

Study the pharmacokinetic profile of varnimcabtagene autoleucel (IMN-003A) and correlation with disease response.

Methods:

Peripheral blood (PB) samples were obtained after consent at screening and as per patient schedule after infusion. Persistence of IMN-003A was evaluated in PB after infusion by ddPCR. Safety and efficacy data were collected for analysis. Bone marrow minimal residual disease (MRD) was performed by flowcytometry (FC) at 10^{-4} sensitivity at screening, D+28 and D+90 for efficacy.

IMN-003A was manufactured using cGMP compliant closed system (CliniMACS Prodigy). The manufacturing data was analyzed, including % CAR transduction in the final product (FP) by FC. Apheresis, FP, and PB samples were analyzed for T-cell subpopulations and surface markers by FC.

Results:

Twenty-one pts underwent apheresis and selected T cells were transduced to achieve the FP with a median manufacturing time of 14d (range 10-27) with 100% success. Two pts underwent second apheresis. The mean % transduction of IMN-003A on autologous T cells was 33.59% (range 8.50 - 58.35) with median transgene copies / genome of 2.27 (range 0.76 – 4.16). The mean CD4/CD8 ratio at apheresis and final product was 0.81 and 1.03 respectively. The mean proportion of CD4 and CD8 positive naïve cells (CCR7+ RA+) was above 35% in the final product (Figure 1A). Median Product Doubling time and Apheresis to Infusion time was 1.04d (range 0.83 – 4.20) and 22d (range 16 - 95) respectively. Post IMN-003A infusion, there was a trend towards reversal of CD4/CD8 ratio.

IMN-003A CAR-T cells showed maximum PB expansion (T_{max}) at median 10d (range 7 – 21) with median C_{max} 135,693 CAR copies / µg gDNA (range 24,624 – 413,968). CAR-T cell persistence in PB was 94% at D+28 and 36% at D+90 (range 21 - NR). All pts had B-cell aplasia concurring with CAR-T expansion (Figure 1B); median not reached (range 42 - NR), with no apparent association with response at D+28 and D+90. Hypogammaglobulinemia was noted in 14 of 19 evaluable pts and 9 pts received IVIg. Of evaluable patients, CD4+ T-cell count recovery (>200/µL) was seen at median of 12 days (range 2 - 42) after infusion.

Overall response rate (ORR) was 88.2% at D+28 and 72.7% at D+90. Two pts relapsed by D+90. Of MRD-evaluable pts, response was 100% at day+28 (n=7) and 83.3% at D+90 (n=6). Updated results will be presented at the meeting.

Summary/Conclusion:

In this industry-led first-in-India phase-2 study, IMN-003A production in a cGMP closed system was 100% successful and rapid. The peak of CAR-T expansion occurs at median 10d of infusion. Responses at D+90 are sustained and deep.

A

Mean values (%) of T cell subpopulations obtained in Apheresis and Final Product				
	Apheresis		Final Product	
	CD4	CD8	CD4	CD8
Naïve (CCR7+ RA+)	27.24	16.17	35.69	36.87
Central Memory (CCR7+ RA-)	11.89	1.05	21.37	7.42
Effector Memory (CCR7- RA-)	49.07	16.63	23.86	18.83
EMRA (CCR7- RA+)	11.80	66.15	19.08	36.88

Mean values (%) of lymphocyte repertoire obtained in Apheresis and Final Product		
	Apheresis	Final Product
CD4	33.62	47.73
CD8	48.69	52.52

Mean values (%) of lymphocyte repertoire in peripheral blood				
	D0	D+14	D+28	D+90
CD4	63.55	25.57	27.38	24.55
CD8	30.96	63.01	59.34	53.68
CD4/CD8	2.05	0.41	0.46	0.46

B

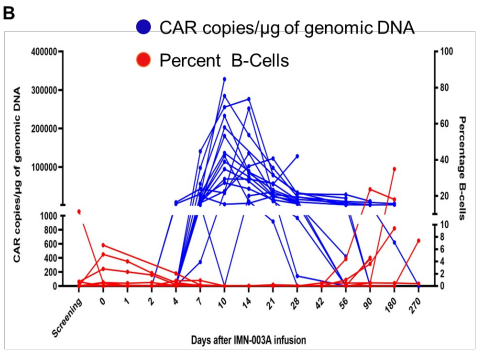

Figure 1: (A) T cell subpopulations in apheresis and FP; Lymphocyte repertoire in apheresis and FP; Lymphocyte repertoire in peripheral blood at D0, +14, +28,
(B) Persistence and expansion of IMN-003A and percentage B cell count.

Keywords: Acute lymphoblastic leukemia, Non-Hodgkin's lymphoma, CAR-T, Pharmacokinetic