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Varnimcabtagene Autoleucel (IMN-003A): Pharmacokinetic Profile with Predominant Naïve and Central Memory Phenotype Demonstrates Sustained In Vivo Persistence and Durable Responses in a First-in-India Industry Phase-2 Study (IMAGINE)

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Background: Varnimcabtagene autoleucel (IMN-003A) is an autologous CD19 directed CAR-T cell product with a 4-1BB co-stimulatory domain and a non-FMC63 murine single chain variable fragment (A3B1 binder), manufactured in India, tested in the IMAGINE study (CTRI/2022/03/041162), a phase-2 clinical trial for patients (pts) with relapsed and/or refractory B cell malignancies (RR BCM). 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 Fludarabine-Cyclophosphamide lymphodepletion regimen (LR). Here we present var-cel pharmacokinetic data and correlation with efficacy.

Methods: Varnimcabtagene autoleucel was manufactured using a cGMP compliant closed system (CliniMACS Prodigy ®). The manufacturing data were obtained and analyzed, including % CAR transduction in the final product (FP) by flow cytometry (FC). 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 (BM) MRD (B-ALL) and PET-CT (B-NHL) was assessed at screening, D+28 and D+90 for efficacy. Minimal residual disease (MRD) was performed by FC with 10 $^{-4}$ sensitivity. Apheresis, FP, and PB/BM samples on D+28 were analyzed for T-cell subpopulations

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Results: Of 25 patients (pts) enrolled and apheresed, 24 pts received var-cel (1 withdrawal) with majority of infusions on Days 0, +3, +7. Median product doubling time and manufacturing time was 1.04d (range 0.74-2.12) and 14 days (range 10 - 27) with 100% success with T cell purity median 99.4% (range 96.3-99.9). The mean % transduction of var-cel was 33.12% (range 8.50 - 58.35) with median transgene copies / genome of 2.57 (range 0.76 - 4.16). The mean CD4/CD8 ratio at apheresis and final product was 0.47 and 2.58 respectively. There was reversal of CD4/CD8 ratio from apheresis to final product (CAR+ T cells) which was statistically significant ($p<0.01$). There was statistically significant increase ($p<0.01$) in the number of naïve (CCR7+ RA+) and central memory (CCR7+ RA-) T cell subsets between apheresis and final product (CAR+ T cells). There was predominance of naïve and central memory CAR+ T cell subsets in the FP (58.19%; Figure 1A). Median Apheresis to Infusion time was 25d (range 16 - 95). There was a statistically significant trend ($p<0.01$) towards reversal of CD4/CD8 ratio in the PB from D0 to D+90.

Var-cel showed maximum PB expansion (T_{max}) at D+10 (range 7 - 28 days) with median C_{max} 125,242 CAR copies / µg gDNA (range 18256 - 413,968). Among pts with 28-day and 90-day and last follow-up, 79.2%, 29.2% and 20.8% respectively had evidence of var-cel in PB, with median persistence of 28 days (range 10 - NR). Post-infusion, peak interleukin-6 level was median 42.3 pg/mL (range 6.71 - 17,481). B cell aplasia was observed in all pts concurrent with CAR-T expansion (Figure 1B). Median loss of B cell aplasia was not reached (range 42 - NR), with no apparent association with response at D+28 and D+90. Hypogammaglobulinemia was noted in 11 pts and 16 pts received IVIg. Of evaluable patients with CD4+ T-cell counts below 200/µL, recovery (>200/µL) was seen at median of 12 days (range 2 - NR) after var-cel infusion.

Overall response rate (ORR) was 91.7% (22/24) at D+28 (B-ALL 91.7%, MRD neg 83.3% (n=10/12); B-NHL 91.7%, CR 66.7%) and 80.9% (17/21) at D+90 [B-ALL 80%, MRD neg 80% (n=8/10); B-NHL 81.8% (9/11), CR 63.6%]. One B-NHL pt in PR at D+28 achieved CR at D+90. Three pts relapsed by D+90. Updated results will be presented at the meeting.

Conclusion: Varnimcabtagene autoleucel manufacturing process results in a drug product characterized by highly pure T cells, with high proportion of naïve and central memory polyfunctional cells. In this industry-led first-in-India phase-2 study, var-cel resulted in a cytokine response with sustained in vivo proliferation and persistence resulting in robust and durable responses.

Disclosures

Dhar:*Immuneel Therapeutics Private Limited:* Current Employment. **Joseph:***Immuneel Therapeutics Private Limited:* Current Employment. **Kumar MG:***Immuneel Therapeutics Private Limited:* Current Employment. **Kumar:***Immuneel Therapeutics Private Limited:* Current Employment. **Soares:***Immuneel Therapeutics Private Limited:* Current Employment. **Nahar:***Immuneel Therapeutics Private Limited:* Current Employment. **Gandikota:***Immuneel*

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Figure 1

A

Mean values (%) of T cell subpopulations obtained in Apheresis and Final Product

	Apheresis			Final Product (CAR+ T cells)		
	CD4	CD8	Total	CD4	CD8	Total
Naive (CCR7+ RA+)	25.99	17.27	18.47	38.72	51.98	42.78
Central Memory (CCR7+ RA-)	17.68	1.82	7.28	18.14	7.08	15.41
Effector Memory (CCR7- RA-)	44.73	17.39	24.80	17.72	7.25	14.84
EMRA (CCR7- RA+)	11.60	63.52	49.44	25.41	33.69	26.98

Mean values (%) of Naive and Central Memory (CD4 & CD8) cells obtained in Apheresis and Final Product

	Apheresis	Final Product (CAR+ T cells)	P value
Naive (CCR7+ RA+)	18.47	42.78	< 0.01*
Central Memory (CCR7+ RA-)	7.28	15.41	
Total Naive + Central Memory (CCR7+ RA+ / RA-)	25.75	58.19	

Mean values (%) of CD4 and CD8 cells obtained in Apheresis and Final Product

	Apheresis	Final Product (CAR+ T cells)	P value
CD4	29.24	70.47	< 0.01*
CD8	62.06	27.34	

Mean values (%) of lymphocyte repertoire (total) in peripheral blood

	D0	D+14	D+28	D+90	P value D0 & D+90
CD4	60.86	27.30	30.83	24.00	< 0.01*
CD8	28.95	59.48	53.14	64.69	
CD4/CD8	2.10	0.46	0.58	0.44	

B

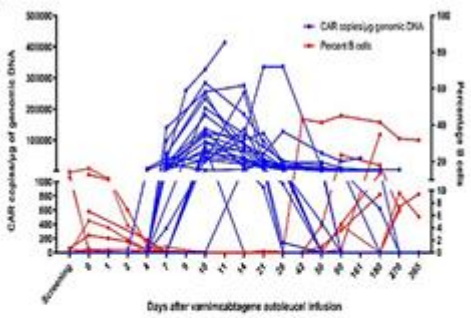

Figure 1: (A) T cell subpopulations in apheresis and FP; Lymphocyte repertoire (naïve and central memory T cell subsets) in apheresis and FP; Lymphocyte repertoire (CD4 and CD8 T cell subsets) in apheresis and FP; Lymphocyte repertoire (CD4 and CD8 T cell subsets) in peripheral blood at D0, +14, +28, +90
(B) Persistence and expansion of varnimcabtagene autoleucel and percentage B cell count.

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Potential Articles of Interest

Response, Peak and Persistence of Varnimcabtagene Autoleucel (IMN-003A), First-in-India Industry CD19-Directed CAR-T Cell Therapy, with Fractionated Infusions for Patients with Relapsed and/or Refractory B Cell Malignancies: Early Results (IMAGINE

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