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Factors Associated with Refractoriness or Relapse after Varnimcabtagene Autoleucel (IMN-003A) in Patients with Relapsed Refractory B Cell Malignancies: Phase 2 First-in-India Industry (IMAGINE) Study

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Background: Varnimcabtagene autoleucel (IMN-003A) is an anti-CD19 CAR-T cell immunotherapy for patients with relapsed refractory B cell malignancies (RR BCM) in the Phase 2 IMAGINE study. Some patients (pts) do not respond or relapse early after CD19 directed CAR-T cell therapy. This abstract reviews the factors associated with disease relapse to help improve patient outcomes and development of novel strategies.

Methods: Patients (pts) aged 3 to 45 years (B-ALL) and ≥ 18 years (B-NHL) with RR BCM were eligible for IMAGINE study if they had measurable disease, as assessed by lymphoid blasts (B-ALL) or metabolic tumour bulk (B-NHL), received ≥1 prior regimen, refractory to the last line of treatment with good performance status (ECOG 0 to 1).

Multiple characteristics for disease progression were reviewed (n=36) and risk stratified as: 1) Baseline parameters (age, lines of treatment, bridging therapy, cytogenetics, blasts, total metabolic tumour volume (TMTV), sum of perpendicular diameter (SPD), refractory, relapse within 6 months, laboratory parameters - haemoglobin, neutrophil count, lymphocyte count, platelet count, CRP, LDH, ferritin, baseline interleukin-6 (IL-6), baseline total T cells, CD4, and CD8 subsets in peripheral blood); 2) Apheresis parameters (total T cells, naïve / central memory in CD4 and CD8 subsets); 3) Final Product characteristics [total CAR+ cells, naïve / central memory

Skip to Main Content

SPD), product doubling time] and 4) Post Infusion factors (CAR peak & persistence, B cell aplasia, hypogammaglobulinema, infections and intravenous immunoglobulin (IVIg) replacement).

These parameters were analyzed using chi-square and appropriate multivariant odds ratio (OR) to examine the association with disease relapse.

Results: At data cut-off, of 25 pts enrolled (median age 31 yrs, range 3 - 66) with RR BCM (n=13 B-ALL; n=12 B-NHL), 24 pts received var-cel (1 withdrawal). Median follow-up after IMN-003A administration was 205 days (range 12 - 434).

Overall response rate (ORR) was 91.7% (22/24) at D+28 (B-ALL 91.7%; B-NHL 91.7%) and 80.9% (17/21) at D+90 (B-ALL 80%; B-NHL 81.8%). Median progression free survival (PFS, range 12-NR), duration of response (DOR, range 0-NR) and overall survival (OS) were not reached (range 12-NR). Treatment related mortality was 4.2% (n=1/24); 3 pts died of disease progression.

Nine pts had relapsed disease (B-ALL 4; B-NHL 5; overall 37.5%; CD19+ 7 pts; CD19- 2 pts; B-ALL: CD20 variable; CD22+ n=4/4; B-NHL PDL1 n=1/5) with median PFS of 178 days (range 28-319). For relapsed pts, median duration of B cell aplasia after primary infusion was 270 days (range 70-NR); var-cel was detected in 1 pt (n=1/4) at relapse and hypogammaglobulinema (IgG <4g/L) was seen in 4 pts.

For the 36 multiple parameters studied, age, high risk cytogenetics / genomic aberrations, refractoriness / early relapse <6m, blasts burden in B-ALL, absolute lymphocyte count, inflammatory markers (LDH, ferritin) and baseline T cell subsets did not show association with disease relapse.

Ten variables showing some association with disease progression on univariant analysis were: SPD, baseline haemoglobin, platelets, CRP, Apheresis CD8+ T_{N+CM}, Final Product doubling time, CAR-T dosage (B-NHL), CD8 CAR+ T_{N+CM} (weight & dose adjusted), Post Infusion Cmax and IVIg replacement.

Multivariant analysis of these parameters showed some statistical significance for following variables: Baseline Platelet count <200 x 10^9/L (overall); Final Product doubling time ≥1 day (B-ALL); baseline SPD ≥2000 mm^2, Hb <12 g/dL, Platelet count <200 x 10^9/L and post infusion IVIg replacement (B-NHL), Table1 & Figure 1. Of these variables, statistically significant association was seen with Final Product doubling time ≥1 day (B-ALL) and baseline SPD ≥2000 mm^2 with Hb <12 g/dL and Platelet count <200 x 10^9/L (B-NHL). The impact of IVIg replacement on efficacy needs further study.

Conclusions: In the IMAGINE study, with ORR 80.9% at primary endpoint and median PFS not reached, relapse was seen in 37.5% pts with median PFS of 178 days. Multivariant analysis has identified factors which may predict disease relapse. Further research is needed to identify strategies such as reinfusion or CAR-T targeting a different antigen to achieve cure.

Disclosures

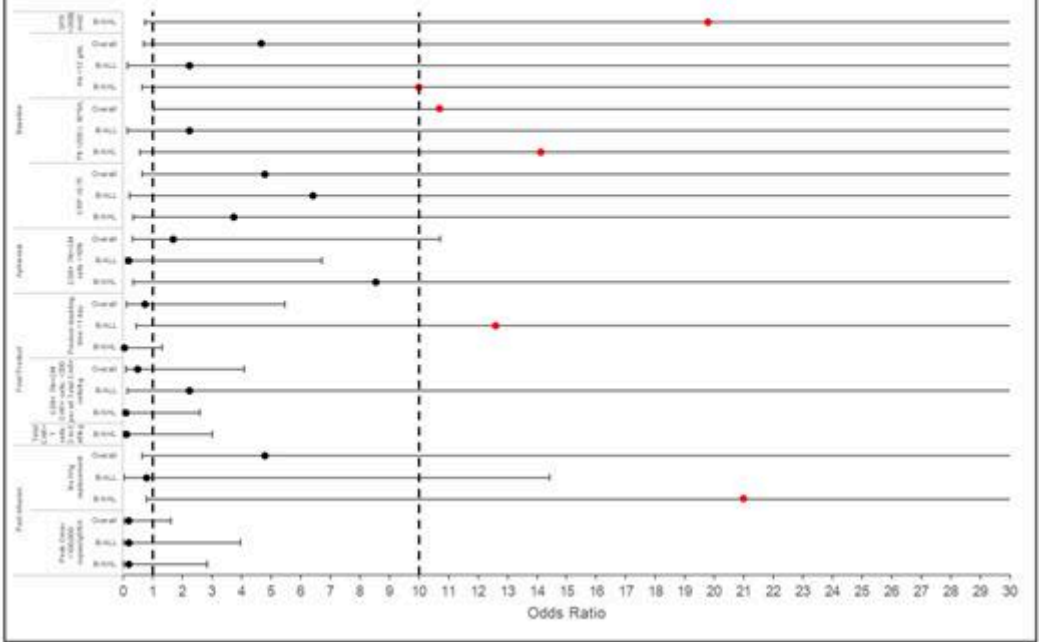
Raju:*Immuneel Therapeutics Private Limited:* Current Employment. **Arasu:***Immuneel Therapeutics Private Limited:* Current Employment. **Elluru:***Immuneel Therapeutics Private Limited:* Current Employment. **Akheel:***Immuneel Therapeutics Private Limited:* Current Employment. **Kamat:***Immuneel Therapeutics Private Limited:* Current Employment.

Figure 1

Table 1: Parameters analyzed for risk-stratification of patient for disease progression

	Parameters	Cohort	OR	95% CI	p
Baseline	SPD ≥2000 mm²	B-NHL	19.8	0.74,527.29	0.07
	Hb <12 g/dL	Overall	4.67	0.70,31.03	0.11
		B-ALL	2.25	0.15, 33.93	0.56
		B-NHL	10.0	0.65,154.4	0.10
	Platelet count <200 x 10^9/L	Overall	10.7	1.03,109.95	0.04
		B-ALL	2.25	0.15, 33.93	0.56
		B-NHL	14.1	0.57,352.03	0.11
	CRP >0.75 mg/dL	Overall	4.8	0.65,35.19	0.12
		B-ALL	6.43	0.21,201.08	0.29
		B-NHL	3.8	0.33,42.47	0.29
Apheresis	CD8+ T_{N+CM} cells <10%	Overall	1.7	0.31,9.01	0.55
		B-ALL	0.2	0.09,6.51	0.40
		B-NHL	8.6	0.34,212.95	0.19
Final Product	Total CAR+ T cells: 3 to 5 e6/kg	B-NHL	0.1	0,2.91	0.19
	CD8+ T_{N+CM} CAR+ cells: <200 per e6 Total CAR+ cells/kg	Overall	0.5	0.08,3.59	0.53
		B-ALL	2.25	0.15,33.93	0.56
		B-NHL	0.1	0,2.51	0.16
	Product doubling time ≥1 day	Overall	0.74	0.12,4.73	0.75
		B-ALL	12.6	0.45,356.38	0.13
		B-NHL	0.0	0,1.28	0.07
Post infusion	Peak Cmax <100,000 copies/gDNA	Overall	0.2	0.03,1.42	0.11
		B-ALL	0.2	0.02,3.77	0.32
		B-NHL	0.2	0.01,2.66	0.22
	No IVIg replacement	Overall	4.8	0.65,35.20	0.12
		B-ALL	0.8	0.05,13.63	0.90
		B-NHL	21.0	0.78,564.18	0.07

Figure 1: Multivariant Risk Analysis for Disease Relapse: Forest Plot



Skip to Main Content