High efficacy and excellent safety profile of Actalycabtagene autoleucel, a humanized CD19 CAR-T product in r/r B-cell malignancies: A phase II pivotal trial

Hasmukh Jain[1*], *Atharva Karulkar*[2], *Devanshi Kalra*[2], *Smrithi Ravikumar*[2], *Netra Ghandade*[2], *Ruchira Patil*[2], *Shreshtha Shah*[2], *Afrin Firfiray*[2], *Juber Pendhari*[3], *Rushikesh Patil*[2], *Manivasagam S*[2], *Neha Sharma*[1], *Alok Shetty*[1], *Lingaraj Nayak*[1], *Bhausaheb Bagal*[1], *Shripad Banavali*[1], *Gaurav Narula*[1], *Sameer Melinkeri*[4], *Anil Aribandi*[5], *Narendra Agrawal*[6], *Lovin Wilson*[7], *Preeti Desai*[1], *Anisha Navkudkar*[1], *Prashant Tembhare*[1], *Navin Khattry*[1], *Epari Sridhar*[1], *Nikhil Patkar*[1], *Sumeet Gujral*[1], *Tanuja Shet*[1], *Uma Sakhadeo*[1], *Papagudi Ganesan Subramanian*[1], *Jayshree Thorat*[2], *Anamika Prashant*[1], *Sachin Punatar*[1], *Anant Gokarn*[1], *Kinjalka Ghosh*[1], *Archi Agrawal*[1], *Yash Jain*[1], *Venkatesh Rangarajan*[1], *Shashank Ojha*[1], *Shilpushp Bhosle*[1], *Siddhartha Laskar*[1], *Sangeeta Kakoti*[1], *Sumeet Mirgh*[1], *Sumathi Hiregoudar*[1], *Minal Poojary*[1], *Nitin Shetty*[1], *Vasundhara Patil*[1], *Akshay Baheti*[1], *Sanjay Biswas*[1], *Gaurav Salunkhe*[1], *Kunal Gala*[1], *Manju Sengar*[1], *Nirali N. Shah*[8], *Sattva S. Neelapu*[9], *Rahul Purwar*[2*]

1.Tata Memorial Centre, Mumbai, 2. Immunoadoptive Cell Therapy Private Limited (ImmunoACT), 3. Indian Institute of Technology, Bombay, 4. Deenanath Mangeshkar Hospital & Research Centre, 5. American Oncology Institute, Hyderabad, 6. Rajiv Gandhi Cancer Institute & Research Institute, New Delhi, 7. SMBT Hospital, Nasik, 8. National Cancer Institute, 9. The University of Texas MD Anderson Cancer Center(MDACC)

INTRODUCTION AND AIM

- Commercially approved CD19 CAR-T cell therapies are effective in r/r B cell malignancies but are associated with significant albeit manageable toxicities.
- These toxicities contribute to significant morbidity.
- We have developed a novel, humanized CD19 CAR-T cell therapy, Actalycabtagene autoleucel (Actaly-cel) and previously reported the safety in Phase I study (Jain H et.al., 4641 ASH 2022)
- Here, we present the pooled results from Phase I and Phase II study evaluating Actaly-cel.
- Recently received market authorization by regulatory authorities of India (Brand name: NexCAR19).

MATERIALS AND METHODS

- Manufacturing Site: Immunoadoptive Cell Therapy Pvt. Ltd (ImmunoACT)
- Clinical Trial Sites: Tata Memorial Hospital, DMHRC, AOI, RGCI, SMBT hospital.

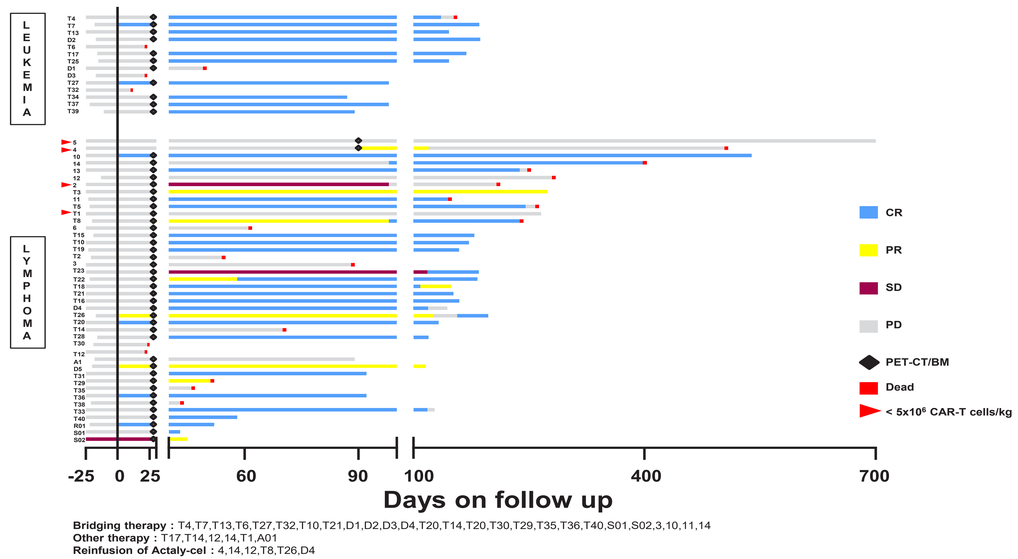
	Phase I	Phase II
Study Setting	Single -Centre	Multi centric
Population	High Grade Lymphoma	r/r B Cell Malignancies
Primary Objective	Safety and tolerability	Objective response rate
Dose	1 x 10^9 to 2 x 10^9	≥ 5 x 10^6 /kg
CTRI Registration	CTRI/2021/04/032727	CTRI/2022/12/048211

- Patients above the age of 15 with ECOG status 0-1, adequate organ function and no CNS involvement were screened for the study.
- Patients with relapsed/ refractory B-cell malignancies were included in the study.
- A lymphodepleting chemotherapy regimen of Fludarabine at 30mg/m2/day and cyclophosphamide at 500 mg/m2/day was administered.
- After 2 days rest period the patients were infused on day 0 with Actaly-cel.
- The response assessment was scheduled at day 28.

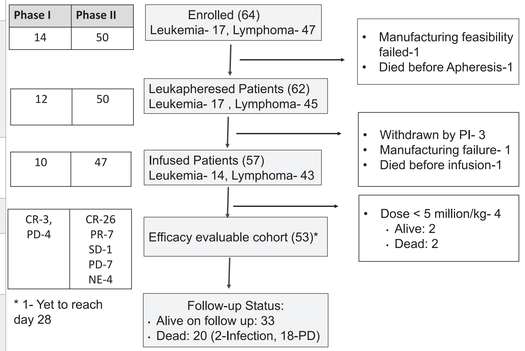
RESULTS

Table 1: Baseline Characteristics

Baseline Characteristics	Patients (N = 64)
Age Median (Range)	44 (16-71)
Gender n (%)	
Male	50 (78%)
Female	14 (22%)
ECOG	
0	2 (3%)
1	60 (94%)
2	2 (3%)
Diagnosis	
R/R DLBCL	43 (67%)
B-ALL	17 (27%)
Indolent lymphoma	4 (6%)
Disease Status at enrolment (Lymphoma)	
PD	43 (92%)
PR	2 (4%)
SD	2 (4%)
Disease Status at enrolment (Leukaemia)	
Relapsed	2 (12%)
Refractory	15 (88%)
Bulky Disease (>/= 7cm) n(%)	10 (21%)
Blast%, median (range)	61% (5-98)
Line of therapies Median (range)	2 (1-6)
Extranodal sites n (%)	
1	12 (25%)
>/=2	12 (25%)



Bridging therapy : T4,T7,T13,T6,T27,T32,T10,T21,D1,D2,D3,D4,T20,T14,T20,T30,T29,T35,T36,T40,S01,S02,3,10,11,14
Other therapy : T17,T14,12,14,T1,A01
Reinfusion of Actaly-cel : 4,14,12,T8,T26,D4



* 1- Yet to reach day 28

Responses	Efficacy Evaluable Cohort (n=53)	Lymphoma (n= 38)	Leukemia (n=15)*
ORR	36 (67%)	26 (68%)	10 (72%)
CR	29 (52%)	19 (37%)	10 (72%)
PR	7 (15%)	7 (18%)	0 (0%)
SD	1 (2%)	1 (3%)	0 (0%)
PD	11 (23%)	9 (24%)	2 (14%)
NE	4 (8%)	2 (5%)	2 (14%)

Actaly-cel showed robust in vivo expansion and persistence

Table 2: Toxicities & responses

Toxicities	N = 57
Adverse Events of Special Interest	
Cytokine Release Syndrome (Grade I/II)	40 (70%)
Cytokine Release Syndrome (Grade III)	3 (5%)
ICANS	0 (0%)
Hypogammaglobulinemia	21 (37%)

CONCLUSIONS

- Actaly-cel (NexCAR19) is highly effective with a very favorable safety profile in relapsed/refractory B-cell malignancies.
- The absence of ICANS, shorter duration of cytopenias and a lower incidence of grade 3/4 CRS makes it one of the safest CD19 CAR-T cell therapy products.
- Actaly-cel (NexCAR19) can improve the ease of delivery of CAR T-cell therapy in a wide-range of settings.

REFERENCES

1. Dwivedi A, Karulkar A, Ghosh S, Srinivasan S, Kumbhar BV, Jaiswal AK, Kizhakeyil A, Asija S, Rafiq A, Kumar S, Nisar A. Robust antitumor activity and low cytokine production by novel humanized anti-CD19 CAR T cells. Molecular Cancer Therapeutics. 2021 May;20(5):846-58
2. Jain H, Karulkar A, Sharma N, Sengar M, Jaiswal A, Shah S, Khan A, Firfiray A, Asija S, Suvasia P, Suvasia P. Phase I Trial of Humanized CD19 CART-Cell Therapy Developed in India: Safe, Active and Feasible for Outpatient Therapy. Blood. 2022 Nov 15;140(Supplement 1):10332-4.
3. Karulkar A, Jain H, Shah S, Khan A, Jaiswal A, Firfiray A, Suvasia P, Suvasia P, Pendhari J, Asija S, Chowdury A. Making Anti-CD19 CAR-T Cell Therapy Accessible and Affordable: First-in-Human Phase I Clinical Trial Experience from India. Blood. 2022 Nov 15;140(Supplement 1):4610-1.

ACKNOWLEDGEMENTS

- Immunoadoptive Cell Therapy Private Limited (ImmunoACT)
- Funding received from Indian Council of Medical Research (ICMR)
- NCG CRO team for monitoring the study
- Dr. Nitin Jain, MDACC

CONTACT

- Dr. Hasmukh Jain

Email: dr.hkjain@gmail.com

- Dr. Rahul Purwar

Email: rahul.purwar@immunoact.com