Efficacy and Safety of a Third Generation CD20 CAR-T (MB-106) for Treatment of Relapsed/Refractory Indolent B-cell Non-Hodgkin Lymphoma: Phase-1 Results from a Multicenter Trial

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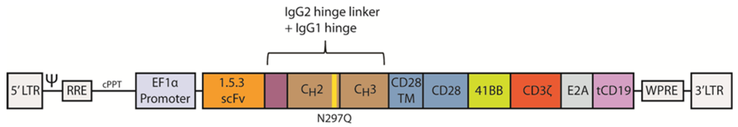
Introduction

Indolent B-cell non-Hodgkin lymphomas (NHL) remain incurable despite multiple therapeutic options, including chemoimmunotherapy, targeted therapies, bispecific antibodies, and CD19-targeted chimeric antigen receptor (CAR) T-cells.

MB-106 is a fully human 3rd-generation CD20-targeted CAR T-cell product with 4-1BB and CD28 costimulatory domains. A schematic of the transgene used in the production of MB-106 is below.



In a separate single institution trial (NCT03277729), follicular lymphoma (FL) patients who received MB-106 at doses ≥3.3×10^6 CAR T-cells/kg, had a high overall response rate (100%) and complete response rate (91%). The present trial (NCT05360238) seeks to replicate the favorable efficacy and safety profile in a multicenter setting with centralized manufacturing. This trial has been partially funded by NCI grant 5R44CA265616.

Study Design – Phase 1

A multicenter, open-label, non-randomized study of MB-106 in adult patients

Eligibility
- Relapsed or refractory indolent CD20+ B-cell NHL that has progressed after 2 or more standard therapies.
- Patients are eligible if progression occurred after 1 prior therapy, if there is no established standard of care for second line therapy (e.g., progression within 24 months [POD24] in patients with FL).
- Prior CD19 CAR T-cell therapy is allowed, provided CD19+ B-cell count has recovered to ≥20 cells/μL.

Primary Endpoint
- Assess safety, tolerability and feasibility of MB-106
- Determine recommended Phase 2 dose (RP2D)

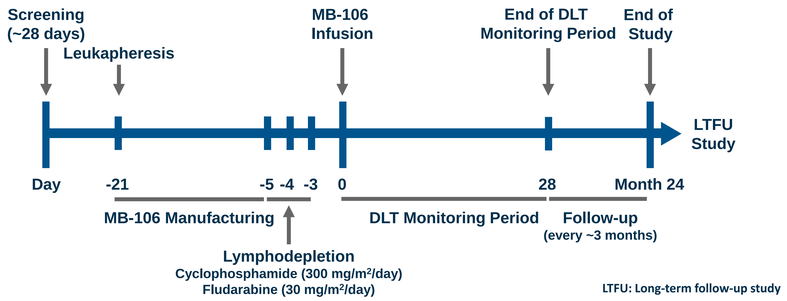
Dose Escalation
- 3+3 design, with at least 6 patients enrolled at the maximum tolerated dose.

Dose Levels

Dose level 1 (DL1): 3.3×10^6 CAR T-cells/kg body weight
Dose level 2 (DL2): 1.0×10^7 CAR T-cells/kg body weight

First patient treated at each dose level was hospitalized. All other patients were treated in an outpatient setting, if allowed by institutional guidelines.

Study Schema



LTFU: Long-term follow-up study

Baseline Patient Characteristics

Number of patients enrolled	9*
Age, median (range)	56 (39-79)
Sex, male (%)	7 (78%)
Histology • Follicular lymphoma (FL) • Waldenström macroglobulinemia (WM) • Hairy cell leukemia – variant (HCL-v)	 5 3 1
Prior lines of therapy, median (range)	4 (1-9)
Prior CD19 CAR T-cell therapy	2
Prior autologous stem cell transplant	1
POD24§	1

* One patient received non-conforming material (drug product that did not meet release criteria), following FDA authorization.
§ POD24: Progression of disease within 24 months of front-line chemoimmunotherapy. POD24 is a clinically significant endpoint to identify FL patients with a high risk of death.

Efficacy *[Combined results for DL1 (N=4) and DL2 (N=5)]*

Best Responses to Date‡	FL, N=5	WM, N=3
Overall response rate (ORR)†	100% (5/5)	100% (3/3)
Complete response (CR)	5 (100%)	0
Very good partial response (VGPR)#	N/A	1
Partial response (PR)	0	2
Minor response#	N/A	0
Stable disease (SD)	0	0

‡ In WM patients, responses are evaluated using the 11th International Workshop on WM (IWWM) criteria (Treon, 2023). In all other patients, PET-CT-based responses are evaluated using the Lugano Classification (Cheson, 2014).
† ORR is the rate of PR or better in FL. ORR is the rate of minor response or better in WM.
# **VGPR and minor response are WM-specific response categories.**
N/A = Not applicable

A heavily transfusion dependent HCL-v patient, treated on dose level 1, achieved transfusion independence and maintained stable disease.
Complete responses are rare in WM. Ibrutinib and zanubrutinib are both approved as single-agents for the treatment of WM despite the absence of complete responses.

Safety *[Combined results for DL1 (N=4) and DL2 (N=5)]*

CRS & ICANS

	Grade 1	Grade 2	Grade 3	Grade 4
CRS	5 (56%)	0	0	0
ICANS	0	0	0	0

CRS: Cytokine release syndrome
ICANS: Immune effector cell-associated neurotoxicity syndrome
Numbers in tables are individual patients, not number of events.
For each individual event, highest grade is reported per patient.

No related serious adverse events (SAEs) reported, apart from Grade 1 CRS.

No prophylactic tocilizumab or dexamethasone was administered.

Grade ≥3 Adverse Events (First 28 Days), Regardless of Causality

	Grade 3	Grade 4
Neutrophil count decreased	1	5
Febrile Neutropenia	0	0
Anemia	1	0
Appendicitis	1	0
Worsening Pain (Extremity Knees)	1	0
Blood bilirubin increased*	0	1

* Transient increase in bilirubin attributed to hemolysis related to underlying lymphoma. Not study drug related.

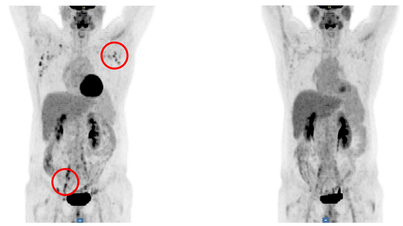
No prolonged (>28 days post-lymphodepletion) neutropenia to date, despite not using prophylactic G-CSF.

Complete Response in Follicular Lymphoma Patient with Prior CD19 CAR-T (Liso-cel) - Representative PET-CT

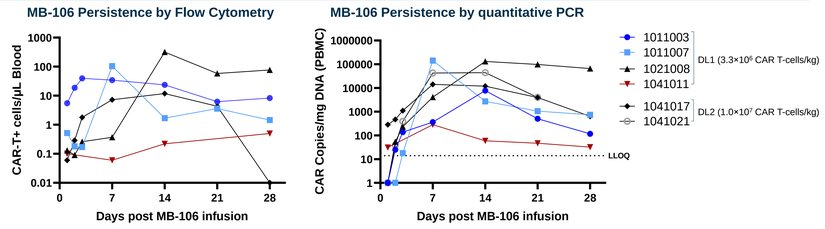
Best Response:
CR (Day 28) by PET-CT & bone marrow

Patient's first CR despite 6 prior therapies

Safety:
CRS: None
ICANS: None



CAR T-cell Expansion and Persistence



Conclusions

- Treatment with MB-106 resulted in high response rates, including complete responses.
- Complete responses have been observed in patients previously treated with CD19-targeted CAR-T in both this multicenter trial and the original single institution trial.
- MB-106 has a tolerable safety profile in patients with indolent NHL, with no occurrence of CRS above Grade 1, and no ICANS of any Grade, despite not using prophylactic tocilizumab or dexamethasone.
- Outpatient administration was allowed and was found to be feasible in this study.
- MB-106 expansion and persistence in patients has been demonstrated.
- Although the number of patients enrolled is too small to draw any definitive conclusions, no obvious differences in safety or efficacy were observed between the two dose levels.

Planned Registrational Phase 2 & Developmental Strategy

Planned FDA Meeting	Expect to complete dose level 2 with 1 final patient and to present 1.0×10^7 CAR T-cells/kg as treatment dose
Start of Phase 2	Registrational trial expected to start mid-2024
Eligibility	Relapsed or refractory WM. All patients must have progressed after 2 or more prior standard therapies, including chemoimmunotherapy (e.g., bendamustine + rituximab) OR proteasome inhibitor AND BTK inhibitor, or be intolerant to these therapies.
Primary Endpoint	% of patients achieving CR or VGPR, assessed by the Independent Review Committee
Enrollment	58 total patients over 20 North American sites
Future Expansion	Diffuse large B-cell lymphoma relapsed from prior CD19 CAR T-cell therapy Follicular lymphoma, POD24

References

1. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068. doi: 10.1200/JCO.2013.54.8800.
2. Treon SP, Tedeschi A, San-Miguel J, et al. Report of consensus Panel 4 from the 11th International Workshop on Waldenstrom's macroglobulinemia on diagnostic and response criteria. *Semin in Hematol*. 2023;60(2):97-106. doi: 10.1053/j.seminhematol.2023.03.009.