Third Generation CD20 targeted CAR T-Cell therapy (MB-106) for Treatment of Patients with Relapsed/Refractory B-NHL

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Disclosures for Mazyar Shadman

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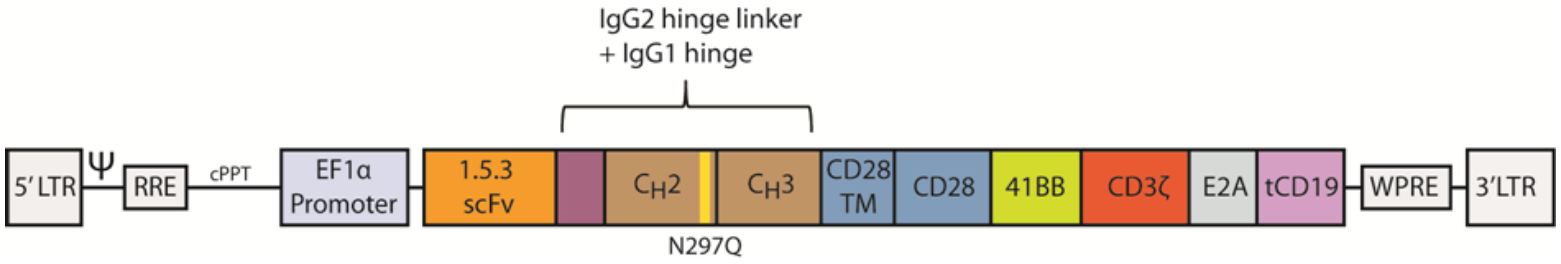
Background

- Chimeric antigen receptor (CAR) adoptive T cell therapy is effective for treatment of patients with relapsed/refractory B-NHL
- Only 30-40% of DLBCL patients have durable remissions with CD19 CARs and there is limited follow-up for MCL patients treated with CD19 CARs
- CD20 is a proven therapeutic target for B-NHL, supported by previously approved naked and radiolabeled anti-CD20 antibodies and promising efficacy from bispecific antibodies
- CD20-targeted CAR-T is another potential adoptive immunotherapy option that could be utilized in combination or in sequence with CD19 CAR-T
- We present interim results of our ongoing phase I/II clinical trial investigating safety and efficacy of a CD20 CAR-T for high-risk B-NHLs (NCT03277729)

CD20 CAR (MB-106)

- MB-106 is a fully human third-generation CD20 targeted CAR with both 4-1BB and CD28 costimulatory domains
- Modified IgG1 spacer eliminates FcR binding
- Truncated CD19 transduction marker
- Lentiviral vector



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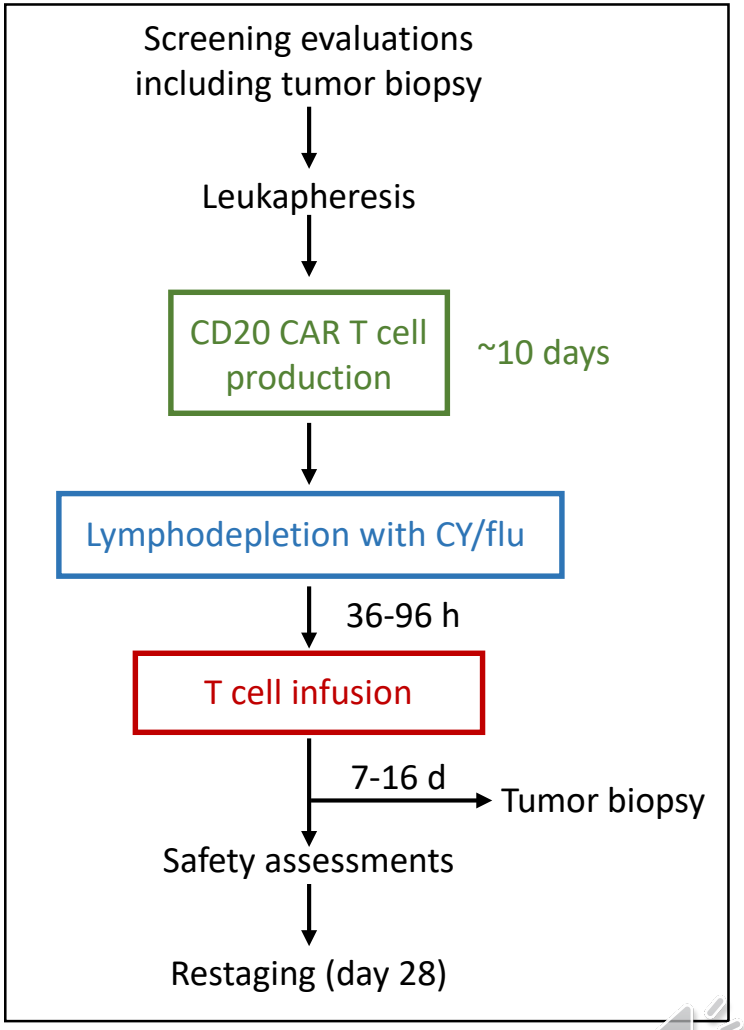
Study Design

- Single institution phase I/II study
- Eligibility: CD20^{+} B-NHLs
  - Large cell lymphoma after 2 lines of treatment
  - Follicular lymphoma and mantle cell lymphoma after at least 1 prior line of treatment
  - Other previously treated B-NHLs
  - Prior treatment with a CD19 CAR is allowed after recovery of normal B cells (≥ 20 B cells/µL)
- Lymphodepletion (LD):
  - Cyclophosphamide and Fludarabine (Cy-Flu)
- Dose levels (DL):
  - Dose level 0: 1 x 10^5 cells/kg
  - **Dose level 1: 3.3 x 10^5 cells/kg**
  - Dose level 2: 1 x 10^6 cells/kg
  - Dose level 3: 3.3 x 10^6 cells/kg
  - Dose level 4: 1 x 10^7 cells/kg



Study Timeline

- "Original" cell manufacturing process (2017-2019):
  - Separate culturing of $CD4^+$ and $CD8^+$ cells
  - Variable lymphodepleting regimens (Cy alone or in combination with Flu) were used
  - 7 pts (3 FL, 3 MCL, 1 hairy cell variant) were treated with best response being stable disease (SD)
  - Due to challenges in meeting target cell doses, poor CAR-T expansion, and lack of clinical responses, enrollment was placed on hold and cell manufacturing process underwent a major revision
- "Modified" cell manufacturing process
  - Starting 2019 (enrollment is ongoing)
  - Manufacturing process was changed to combined culture of $CD4^+$ and $CD8^+$ cells
  - **As of 11/18/2020, 10 patients have undergone leukapheresis and 9 patients have reached the day 28 assessment for safety and efficacy**
- **For this presentation, we present the safety data from both the original and modified processes (n=16) and the efficacy data from the modified process (n=9)**

Results: Patient Characteristics

Patients treated with "modified process" and had day 28 evaluation (**N=9**)

Age, median (range)	**57 (43-67)**
Female sex, n(%)	**5 (55%)**
Follicular Lymphoma n(%)	**7 (78%)**
POD24	5/7 (71%)
History of transformation	3/7 (43%)
Prior lines of therapy median (range)	4 (2-7)
Prior Pi3K inhibitor	2/7 (28%)
Mantle Cell Lymphoma n(%)	**2 (22%)**
Prior lines of therapy median (range)	6 (5-7)
Prior ASCT	2/2 (100%)
Prior BTK inhibitor	2/2 (100%)
Pretreatment LDH (U/L) median (range)	**140 (103-216)**

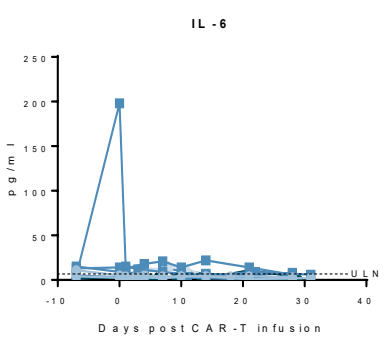
ASCT: Autologous stem cell transplant
BTK: Bruton tyrosine kinase
Pi3K: Phosphoinositide 3-kinases
POD24: Progression of disease within 24 months after last dose of first line chemotherapy for FL

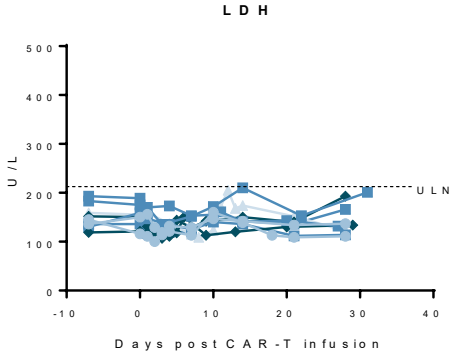
Results: Safety

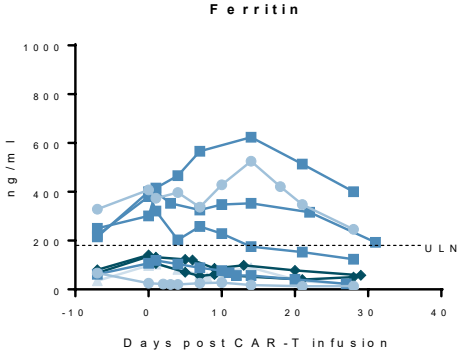
Patients treated with “original: and “modified” processes and had day 28 evaluation (**N=16**)

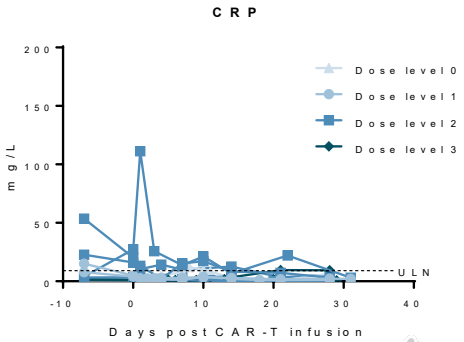
AE of interest	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All grades n (%)
Cytokine Release Syndrome[1]	1 (6%)	-	1† (6%)	-	-	2 (12%)
ICANS [2]	-	-	-	-	-	-
Tumor Lysis Syndrome	-	-	-	-	-	-
Infections	-	-	2 (12%)	-	-	2 (12%)
Neutropenia	-	1 (6%)	3 (18%)	9 (56%)		13 (81%)

† unexplained elevated alkaline phosphatase in the setting of fever









1- Lee et al, Blood, 2014 ; 2- Lee, et al, BBMT, 2019

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Results: Efficacy

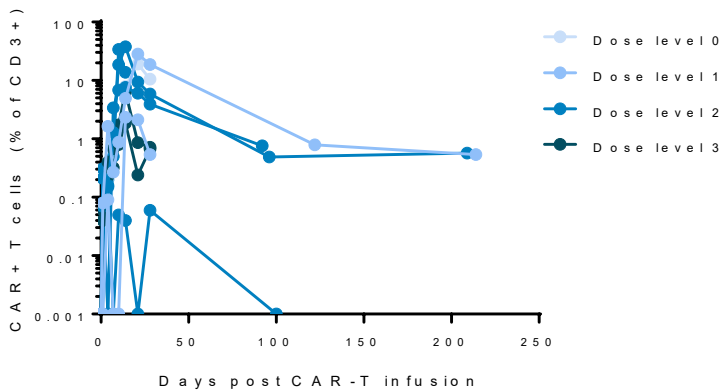
Patients treated with "modified process" and had day 28 evaluation (**N=9**)

Histology	**Response by Lugano PET criteria†**	**All dose levels**	Dose level 0 (n=1)	Dose level 1 (n=2)	Dose level 2 (n=4)	Dose level 3 (n=2)
			1 x 10^5 cells/kg	3.3 x 10^5 cells/kg	1 x 10^6 cells/kg	3.3 x 10^6 cells/kg
FL (n=7)						
	ORR, n(%)	**6/7 (85%)**	1/1	1/2	2/2	2/2
	CR, n(%)	**4/7 (57%)**	-	1/2	1/2	2/2
	PR,n (%)	**2/7 (28%)**	1/1	-	1/2	-
	SD,n (%)	**-**	-	-	-	--
	PD,n (%)	**1/7 (14%)**	-	1/2	-	-
MCL (n=2)						
	ORR, n(%)	**2/2 (100%)**	-	-	2/2	-
	CR,n(%)		-	-	-	-
	PR,n (%)	**2/2 (100%)**	-	-	2/2	-
	SD,n (%)		-	-	-	-
	PD,n (%)		-	-	-	-
All patients (n=9)						
	ORR, n(%)	**8/9 (89%)**	1/1 (100%)	1/2 (50%)	4/4 (100%)	2/2 (100%)
	CR, n(%)	**4/9 (44%)**		1/2 (50%)	1/4 (25%)	2/2 (100%)

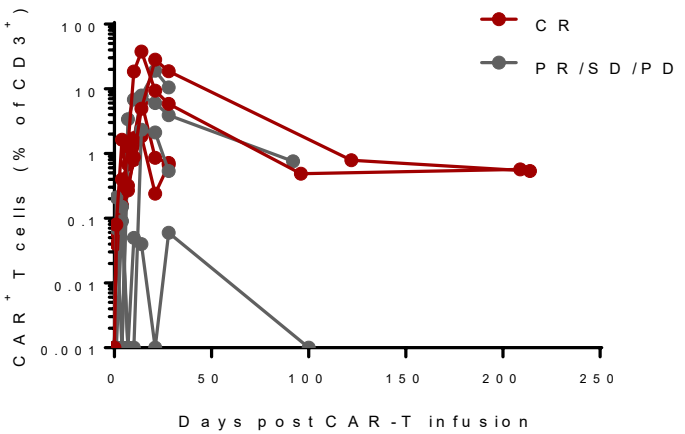
†Cheson, et al. J Clin Oncol, 2014

Results: CAR-T persistence

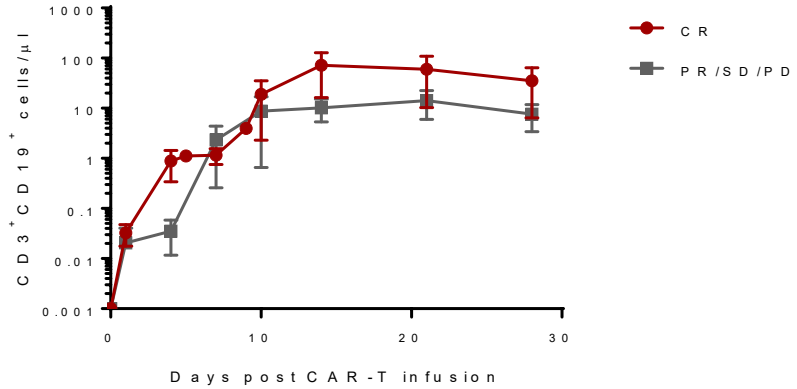
Expansion in individual patients by dose level



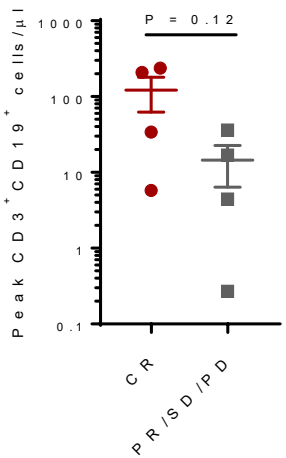
Expansion in individual patients by response

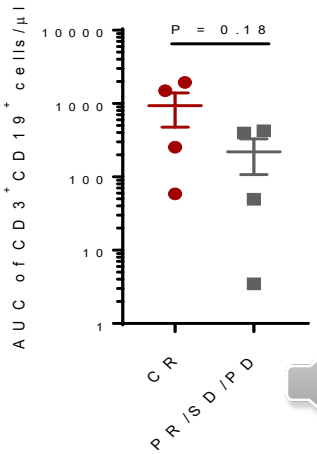


Expansion in all patients by response



Expansion in CR patients vs. others





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Summary

- MB-106 is a third generation fully human CD20 targeted CAR-T cell therapy for treatment of B-NHLs.
- Safety: Extremely favorable safety profile has been observed:
  - CRS in 2 of 16 patients (all grades)
  - no ICANS
- Efficacy: High overall and complete responses with “modified process”:
  - FL patients : ORR 85% ; CR 57%
  - All patients: ORR 89% ; CR 44%
  - Robust CAR-T expansion and persistence
- Enrollment continues for the current study. All CD20+ NHL are eligible. CLL pts are also eligible with the new amendment (NCT03277729)
- A multicenter phase 2 study is planned