RESULTS OF A PHASE 2 STUDY OF AME-133v (LY2469298), AN Fc-ENGINEERED HUMANIZED MONOCLONAL ANTIBODY, IN LOW AFFINITY FcγRIIIa PATIENTS WITH PREVIOUSLY TREATED FOLLICULAR LYMPHOMA

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BACKGROUND

AME-133v (LY2469298) is a humanized monoclonal antibody with greater CD20 affinity and antibody-dependent cell-mediated cytotoxicity (ADCC) potency than rituximab in vitro. A Phase 2 study was conducted to assess the safety and efficacy of AME-133v in patients with previously treated follicular lymphoma (FL) who expressed a low-affinity variant of FcγRIIIa (158-FF or VF; F-carriers). The Phase 1 dose-escalation component of the Phase 1/2 clinical trial of AME-133v at doses ranging from 2 – 375 mg/m^2, demonstrated that AME-133v was safe and tolerable at all dose levels tested, and 375 mg/m^2 was chosen for further assessment.

STUDY OBJECTIVES

Primary Objective:

•To determine the safety and tolerability of repeat administration of AME-133v at 375 mg/m^2

Secondary Objectives:

•To determine the pharmacokinetic (PK) profile, objective response rate, and duration of response in patients who are F-carriers in one or both alleles that encode amino acid position 158 of the FcγRIIIa gene

STUDY DESIGN

Fifty previously treated FL patients were enrolled in the Phase 2 study. Based on the Phase 1 dose escalation results, AME-133v was administered at the highest previously tested dose of 375 mg/m^2 intravenously every week for 4 weeks. Patients received pre-medication with acetaminophen and diphenhydramine; corticosteroids were prohibited. Six patients were treated at 375 mg/m^2 during the dose escalation portion of this clinical trial and are included in this analysis as pre-specified in the protocol. Safety, PK, response, and progression free survival were assessed. Response was also assessed by an independent central reviewer.

ELIGIBILITY

Key Entry Criteria:

- Morphologically confirmed diagnosis of CD20+ follicular B-cell non-Hodgkin's lymphoma
- Have the low affinity form of FcγRIIIa (F/F or F/V at position 158) as determined by FcR genotyping
- Have measurable disease
- Have received prior treatment with chemotherapy, rituximab, or both for follicular lymphoma and;
- Be relapsed from or refractory to conventional chemotherapy given without rituximab OR
- Have not relapsed or progressed within 120 days (inclusive) of the last infusion of rituximab

DEMOGRAPHICS

TABLE 1. Demographics

Demographic	375 mg/m^2
No. of Patients	50
Age, years	
Median	61
Range	39-83
Sex	
Male	29 (58%)
Female	21 (42%)
Prior Chemotherapy Regimens	
Median	1.5
Range	0-6
Rituximab	
Prior Rituximab only	27 (54%)
Rituximab Naïve	2 (4%)

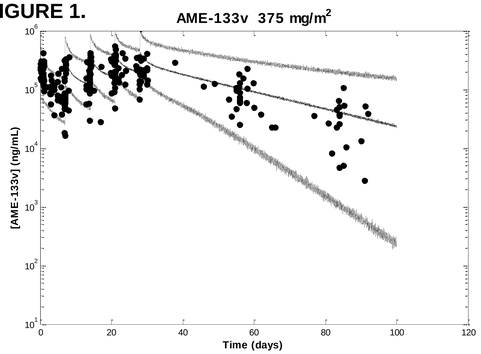
First patient enrolled: January 22, 2008
Last patient enrolled: December 29, 2008

TABLE 2. FcγR Genotype

FcγRIIa	Number of Patients (%)	FcγRIIIa	Number of Patients (%)
Arg/Arg	12 (24)	**Val/Val**	0
His/His	11 (22)	**Phe/Phe**	28 (56)
His/Arg	27 (54)	**Val/Phe**	22 (44)

PHARMACOKINETICS

FIGURE 1.



The serum concentration data from 30 patients dosed in the phase 2 part of the trial were analyzed by means of non linear mixed effect modeling (NONMEM). Observations below the limit of quantification as well as outliers were excluded from the analysis.

The PK of LY2469298 at a dose of 375 mg/m^2 were best described by a 2-compartment model (Non Linear Mixed Effect Modeling). Clearance (CL) was 0.26 L/day, and the volume of distribution of the central (V1) and peripheral (V2) compartments were 3.2 and 3.3 L, respectively. The latter correspond to a terminal elimination half-life (T1/2) of 18.6 days. Inter-patient variability was moderate to high, with CVs of 45.9, 43.7, and 49.8% for CL, V1, and V2, respectively. A positive covariate effect of BSA on V1 was detected but is not presented here.

Data does not include patient enrolled during dose escalation and excludes outliers N = 30.

SAFETY

TABLE 3. AEs Reported in ≥ 10% of Patients

Preferred Term	Grade 1	Grade 2	Grade 3	Total
Subjects with at least 1 Adverse Event				49 (98%)
Rigors	8	9	0	17 (34%)
Fatigue	13	4	0	17 (34%)
Nausea	9	2	1	12 (24%)
Pyrexia	10	0	0	10 (20%)
Constipation	7	0	0	7 (14%)
Dizziness	7	0	0	7 (14%)
Headache	7	0	0	7 (14%)
Abdominal Pain	0	4	1	5 (10%)
Arthralgia	2	2	1	5 (10%)
Back Pain	2	2	1	5 (10%)
Cough	4	1	0	5 (10%)
Diarrhea	2	3	0	5 (10%)
Vomiting	1	3	1	5 (10%)

TABLE 4. Grade 3*/4/5 AEs

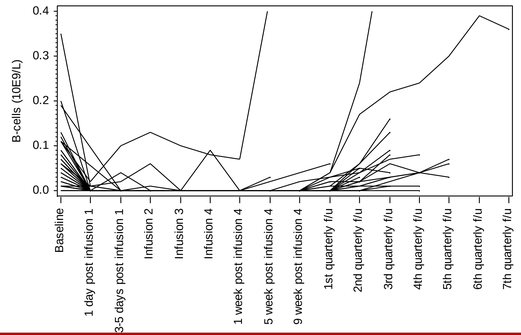
*Grade 3 AEs Reported in ≥ 2 Patients	
Anemia	2
Neutropenia	2
Thrombocytopenia	2
All Grade 4 AEs	
Oesophageal Achalasia	1
All Grade 5 AEs	
Aspiration Pneumonia	1

TABLE 5. SAEs

Treatment Emergent Serious Adverse Events	
Neutropenia	1
Cellulitis	1
E. Coli Septicemia	1
Abdominal Pain	1
Renal Failure	1
Abscess	1
Hypotension	1
Pyelonephritis	1
UTI	1
Back Pain	1
Oesophageal Achalasia	1
Lower GI Hemorrhage	1
Malnutrition	1
Nausea	1
Vomiting	1
Aspiration Pneumonia	1
COPD	1

FIGURE 2: Percent of Baseline B-cell (CD19)

N = 41 as baseline measurements were not available for all patients.



EFFICACY

TABLE 6. Overall Response and PFS

375 mg/m^2	CR	CRu	PR	SD	PD	Missing
Central Read	5	**0**	11	24	3	7
PI Assessed	4	**3**	8	23	7	3

FIGURE 3. Duration of Response and PFS

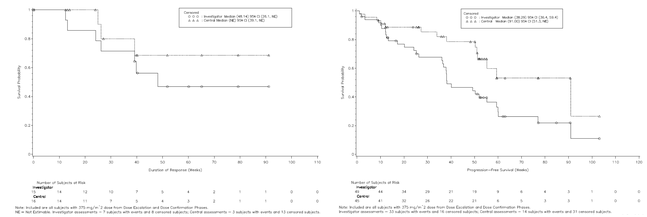
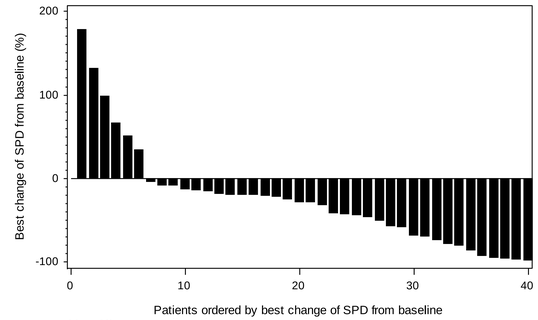


FIGURE 4. Best Change of SPD from Baseline



N = 40 as not all patients had baseline measurements

CONCLUSIONS

- **AME-133v was safe and well tolerated at the recommended Phase 2 dose of 375 mg/m^2**
- **Investigator assessed responses were observed in 15 (30%) of patients, including 7 (14%) patients with CR/CRu**
- **PK profile of AME 133v is similar to rituximab**
- **Lymphocyte subset analysis showed a significant selective and prolonged reduction of B cells**
- **AME 133v is active in previously treated FL patients who are F-carriers at amino acid position 158 in the FcγRIIIa gene**

AME-133v is now the property of MENTRIK Biotech, LLC,Dallas, Texas, USA.

For more information, e-mail info@mentrik.com.

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