

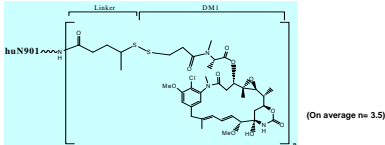
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Introduction

IMG901 (huN901-DM1; BB-10901) is a novel anticancer agent consisting of a potent cytotoxic maytansinoid, DM1, attached to a CD56-binding monoclonal antibody, huN901, using an engineered linker. Once bound to CD56 on a cancer cell, the conjugate is internalized and releases DM1. About 70% of multiple myeloma (MM) cases have surface expression of CD56. In preclinical settings, IMG901 showed significant *in vitro* and *in vivo* anti-myeloma activity as a single agent and in combination with approved drugs such as lenalidomide.

Figure 1. IMG901 (Maytansinoid DM1 conjugated to huN901 antibody)



Objectives

Primary
To determine the dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of IMG901 when given to patients with relapsed or refractory CD56-positive MM by IV infusion weekly for 2 consecutive weeks every 3 weeks
Secondary
To determine the qualitative and quantitative toxicities of IMG901 administered on this schedule
To evaluate the pharmacokinetics of IMG901
To recommend a dose for Phase II clinical studies
To observe any evidence of anti-tumor activity with IMG901
Objectives of MTD Expansion Cohort
To evaluate response rate including overall response rate (ORR) and complete response rate (CRR), and duration of response (DOR)
To further assess time to progression (TTP), progression free survival (PFS), and overall survival (OS)

Methods

Eligibility
Major Inclusion Criteria
-Patient was previously diagnosed with MM based on standard criteria
-CD56-positive, relapsed or refractory MM
-Age ≥ 18 years
-ECOG performance status ≤ 2
-Informed consent
-Women of child-bearing potential must have a negative pregnancy test
-Any chemotherapy or radiotherapy must be completed ≥ 4 weeks prior to Day 1
-Absolute neutrophil count (ANC) > 1000 cells/mm³, Hb ≥ 8.5 g/dL, and platelet count ≥ 75,000/mm³
-AST (SGOT) and ALT (SGPT) ≤ 3 x upper limit of normal (ULN) and total bilirubin ≤ 1.5 x ULN
-Creatinine ≤ 2 mg/dL
-Left ventricular ejection fraction ≥ lower limit of normal on MUGA scan.
-Amylase and lipase levels must be within normal limits

Major Exclusion Criteria
-Concomitant therapy with corticosteroids (except as indicated for other medical conditions or as pre-medication for blood products or study drug)
-Concomitant therapy with other antineoplastic treatments
-Peripheral neuropathy ≥ grade 3; painful grade 2 neuropathy
-Significant cardiac disease
-History of multiple sclerosis or other demyelinating disease, hemorrhagic or ischemic stroke within the last 6 months, central nervous system injury with residual neurological deficit
-Treatment with another investigational agent during the study or within 4 weeks prior to Day 1

Methods Cont'd

Major Exclusion Criteria Cont'd
-Previous monoclonal antibody therapy
-Subjects who have any known recent biochemical or clinical evidence of pancreatitis or extensive metastatic disease involving the pancreas
Trial Design
New cohorts of 3 patients received increasing doses of IMG901. The occurrence of a DLT triggers cohort expansion to 6 patients. MTD is defined as the highest dose at which ≤ 1 of 6 patients has a DLT.
Efficacy Assessments:
Responses are assessed using the European Blood and Bone Marrow Transplantation (EBMT) criteria.
Pharmacokinetics and Assessments of Immunogenicity:
Plasma was evaluated for the presence of humoral responses against the huN901 antibody component (HAHA) or against the DM1 component (HADDA). Pharmacokinetic analyses were performed using standard algorithms of the non-compartmental pharmacokinetic analysis (WinNonLin 4.2, Pharsight).

Baseline Demographics and Disease Characteristics (n=25^a)

Median Age in Years (range)	61 (43-82)
ECOG Performance Status	
• 0	19
• 1	5
• 2	1
Male, n (%)	12 (48%)
Female, n (%)	13 (52%)
Caucasian	22 (88%)
Black/African American	2 (8%)
Other: Indian	1 (4%)
Prior Chemotherapy	
• 1 prior regimen, n (%)	4 (16%)
• 2-3 prior regimens, n (%)	2 (8%)
• 4-5 prior regimens, n (%)	3 (12%)
• 6-7 prior regimens, n (%)	11 (44%)
• ≥ 8 prior regimens, n (%)	5 (20%)
Prior Radiation Therapy	
• 1 prior radiotherapy, n (%)	8 (32%)
• 2-3 prior radiotherapy, n (%)	3 (12%)
• 4-5 prior radiotherapy, n (%)	1 (4%)
Stem Cell Transplant	
• Yes, n (%)	10 (40%)
• No, n (%)	15 (60%)

^a 26 patients have been enrolled on the study as of November 5, 2009. Information for one patient is not yet in the study database.

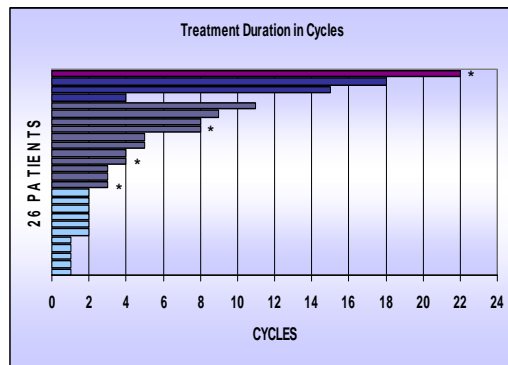
Summary of Patient Enrollment in Study 003

IMG901 Dose Level (mg/m ² /week)	Number of Patients	Total Number of Cycles	Patients with DLT	
			First Cycle	All Cycles
40	3	4	0/3	0/4
60	3	29	0/3	0/29
75	3	7	0/3	0/7
90	3	17	0/3	0/17
112 ^a	8 ^b	45 ^c	0/8	0/45
140	6	35 ^c	2/6	2/35

^a The study has defined 112 mg/m²/week as MTD.
^b Includes 2 patients enrolled after the MTD was declared.
^c There are 3 active patients at the dose of 112 mg/m²/week and 1 active patient at 140 mg/m²/week as November 5, 2009.
^d 2 patients had DLTs. 1 patient had grade 3 fatigue and another patient had grade 3 acute renal failure and fatigue.

Anti-Myeloma Activity

Treatment Duration



Best Response (By Investigator Assessment) * Treatment Ongoing as of November 16, 2009
 Partial response (PR) Minor response (MR)
 Stable disease (SD) Progressive disease (PD)

Patients Whose Duration of Treatment with IMG901 Exceeds that of Previous Treatment Regimen

Patient #	Tumor Cell CD56 Staining: Archived / Fresh Biopsy	# Prior Chemo-therapy Regimens	IMG901 Therapy		Duration on Last Regimen with Approved Drugs (Days) ^a
			Dose (mg/m ² /week)	Best Response	
201	NA ^a / 3 Homo	8	60	SD	131
202	NA / 3 Homo	6	60	MR	359
205	3 Homo / 2 Hetero	4	60	SD	226
209	3 Hetero / 0	10	75	SD	43
212	2 Focal / 3 Homo	10	90	MR	154
213	3 Homo / NA	6	90	SD	246
218	3 Homo / 3 Homo	7	112	MR	422
226 ^d	3 Hetero / 3 Hetero	1	140	PR	387

^a Not available.
^b The total duration of treatment on IMG901 among the 8 patients is approximately 1968 days (281 weeks) as of October 14, 2009.
^c The total duration of treatment on the last prior therapy among the 8 patients is approximately 486 days (69 weeks).
^d treatment is still ongoing for this patient.

Data presented in this poster are preliminary and unaudited

Safety

Representative Adverse Events Assessed to be Treatment Related (n= 26)^a

Adverse Event	Number of Patients with AE			
	Grade 1	Grade 2	Grade 3	Grade 4
Headache	7	1		
Nausea	2			
Diarrhea	1	1		
Fatigue	3	3	2	
Neuropathy	4	2	1	
Neutropenia			1	
Renal Failure/Insufficiency			1	

Lab Abnormalities Assessed to be Treatment Related (n= 26)^a

Lab Abnormality	Number of Patients with Lab Abnormalities			
	Grade 1	Grade 2	Grade 3	Grade 4
Increased AST ^b	6			
Increased ALT ^b	3			
Increased Amylase	1			
Increased Creatinine			1 ^c	
Increased Alk Phos ^b	2			
Increased Uric Acid	4			
Decreased Uric Acid	1			

^a Considered at least possibly or probably related to study drug.
^b AST: aspartate aminotransferase; ALT: alanine transferase; Alk Phos: alkaline phosphatase.
^c In same patient with reported renal failure/insufficiency.

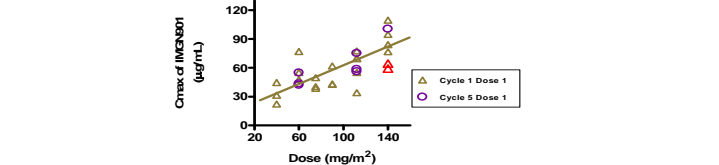
Pharmacokinetics

Pharmacokinetic Parameters of IMG901

Parameter	Dose					
	40 mg/m ²	60 mg/m ²	75 mg/m ²	90 mg/m ²	112 mg/m ²	140 mg/m ²
	N=3	N=3	N=3	N=3	N=6	N=6
Cmax (µg/mL)	32.8 ± 11.3	53.3 ± 12.8	42.9 ± 6.0	49.3 ± 10.9	60.2 ± 15.4	81.5 ± 19.9
t _{1/2} (hr)	16.7 ± 5.2	18.3 ± 1.5	17.1 ± 5.1	16.5 ± 0.8	21.1 ± 4.9	23.7 ± 2.6
AUC (hr.µg/mL)	791 ± 406	1406 ± 317	1012 ± 50	1202 ± 326	1736 ± 667	2289 ± 656
CL (mL/hr/m ²)	63.9 ± 40.3	44.4 ± 9.4	74.2 ± 3.7	78.3 ± 18.8	73.1 ± 28.4	66.5 ± 22.8
V _{ss} (mL/m ²)	1295 ± 739	1118 ± 248	2106 ± 164	1718 ± 392	1966 ± 642	1971 ± 424

All values are mean ± SD calculated from Cycle 1, Dose 1; except for 1 patient each at 60 mg/m² and 112 mg/m² are cycle 5, dose 1

Maximal Observed Plasma Concentration for IMG901. Cmax of Patients with Dose-Limiting Toxicity Are Highlighted in Red.



Conclusions

-IMG901 has demonstrated encouraging activity as monotherapy in patients with heavily pretreated CD56-positive MM.
-The MTD has been identified (112 mg/m²/week) and will be explored for activity in a less heavily pretreated patient population in an expansion cohort.
-An investigator-reported PR was observed in a patient treated at 140 mg/m²/week and the patient has remained on treatment for over a year. Three MRs were reported in 1 patient each at doses of 60, 90, and 112 mg/m²/week, with two of these sustained for 45 weeks or longer. The third patient terminated early due to a broken leg interfering with continuation in the study.
-Eleven patients had SD, with 4 of these patients having remained on treatment for 24 weeks or longer.
-Ten patients had IMG901 treatment duration in excess of some regimens used earlier in the course of their disease
-8 of these 10 patients had IMG901 treatment duration longer than the most recent regimen used to treat their disease (Total treatment duration with IMG901 = 281 weeks for these 8 patients vs total treatment duration on most previous myeloma regimen = 69 weeks).
-Mild to moderate headache, fatigue, and neuropathy, and some mild, transient lab abnormalities are the most commonly reported AEs related to IMG901.
-Most noteworthy is the lack of significant myelosuppression (only one event of grade 3 neutropenia), which should allow for combination with standard anti-myeloma regimens.
-Maximal plasma concentration of IMG901 generally increases with increasing dose. Elimination half-life is similar at all dose levels.
-The single agent efficacy and the favorable safety profile observed in Study 003 as well as findings from preclinical combination studies support continued investigation of this novel agent in patients with MM, including in combination with approved anti-myeloma agents such as lenalidomide and dexmethasone.