2. JAEC Synopsis

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Clinical Study Report Synopsis: Study I5A-IE-JAEC

Title of Study: A Five-Tier, Phase 2 Open-Label Study of IMC-A12 Administered as a Single Agent Every 2 Weeks in Patients with Previously-Treated, Advanced or Metastatic Soft Tissue and Ewing's Sarcoma/PNET

Number of Investigators: This multicenter study included 20 principal investigators.

Study Centers: This study was conducted at 20 study centers in 7 countries.

Publication Based on the Study: Schoffski P, Adkins D, Blay J, Gil T, Elias AD, Rutkowski P, Pennock GK, Youssoufian H, Zojwalla NJ, Willey R, Grebennik DO. Phase II trial of anti-IGF-IR antibody cixutumumab in patients with advanced or metastatic soft-tissue sarcoma and Ewing family of tumors. Abstract 10004 presented at the American Society of Clinical Oncology Annual Meeting; June 3 – 7, 2011; Chicago, IL.

Length of Study:
Date of first patient enrollment: 21 July 2008
Date of last patient completed entire study: 29 February 2012

Phase of Development: 2

Objectives: The primary objective of this study was to determine the progression-free survival (PFS) rate assessed 12 weeks after the initiation of cixutumumab monotherapy, administered every 2 weeks to patients with previously-treated, advanced or metastatic soft tissue and Ewing's sarcoma/PNET. The secondary objectives of this study were (1) to evaluate the overall PFS rate; (2) to evaluate the objective response rate (ORR); (3) to determine the time to onset of response and the duration of response; (4) to determine overall survival (OS); (5) to determine the clinical benefit rate (CBR) and (6) to evaluate the safety, tolerability, and adverse event profiles of cixutumumab in the treatment of metastatic or advanced squamous sarcoma; and to assess the development of antibodies against cixutumumab

Study Design: This was a multicenter, open-label study. The patient population was stratified into 5 tiers according to sarcoma subtype: (1) Ewing's Sarcoma (ES)/PNET; (2) rhabdomyosarcoma (RMS); (3) leiomyosarcoma; (4) adipocytic sarcoma; and (5) synovial sarcoma. A total of 85 patients were to be enrolled initially, 17 in each tier. The Simon two-stage design was applied separately to each tier; safety and response in the initial 17 patients in each tier was used to determine whether to extend enrollment to the target total of 37 patients per tier.

Number of Patients:
Planned: 185
Enrolled: 113
Treated (at least 1 dose): 111

Diagnosis and Main Criteria for Inclusion: Patients ≥12 years with histologically or cytologically-confirmed sarcoma of one of the following histologies: (1) ES/PNET; (2) RMS; (3) leiomyosarcoma; (4) adipocytic sarcoma; or (5) synovial sarcoma that had relapsed or become refractory or metastatic at the time of entry were included. Eligible patients must have had measureable disease as defined by RECIST and a life expectancy > 3 months.

Cixutumumab, Dose, and Mode of Administration:
Cixutumumab 10 mg/kg supplied in single use 250 mg/50-ml vials or 500 mg/50 ml vials containing 5 mg/ml or 10 mg/ml vials was given over 1 hour every 2 weeks as an intravenous (I.V.) infusion.
Lot numbers: [redacted]

Duration of Treatment:
A treatment cycle was defined as 6 weeks. There was no interruption between treatment cycles. Patients continued to receive treatment until there was evidence of progressive disease, unacceptable toxicity, or withdrawal of consent.

Variables:
Efficacy: 12-week PFS rate, overall PFS, ORR, time to response, duration of response, OS and CBR
Safety: adverse events, physical examinations and clinical laboratory assessments

Statistical Evaluation Methods:

The sample size was based on Simon optimal two-stage design using 20% as a futility level for 12 week PFS rate and 40% or above as a "continue development" level, with $\alpha = 0.10$ and $\beta = 0.10$. A 12-week PFS rate between these two values was considered inconclusive. The resulting Stage 1 sample size was 17 for each tier. Four or more patients without PD or death at 12 weeks were required in order for the tier to continue to Stage 2 where an additional 20 patients were to be enrolled per tier.

The primary statistical analysis used all enrolled patients who received any study treatment [Intention-to-Treat (ITT) population]. Safety analyses were performed on all patients who received cixutumumab. Adverse events (AEs) that were unrelated to treatment and that occurred more than 30 days after the administration of the last dose of treatment were not reported or analyzed.

Efficacy: 12-week PFS rate was measured as a binary variable , ie, patients with a response of stable disease (SD) or better at Week 12 tumor assessment versus those who did not. Patients were considered "successful" if radiological evaluation performed at the 12 week visit (Cycle 2 Week 6), indicated a response of SD, PR, or CR as defined by RECIST. The binomial outcome was independently summarized for each tier and was presented with a two-sided 95% confidence interval (CI). Median PFS and OS were calculated using the Kaplan-Meier method with 95% CI independently for each tier. For PFS, patients who did not progress were censored at their last objective tumor response and for OS, living patients were censored at the last date at which they were known to be alive. ORR was equal to the proportion of patients achieving either a best overall response of partial or confirmed response (PR + CR). ORR was calculated with two-sided 95% CI. Median time to response and duration of response were analyzed by the Kaplan-Meier method with 95% CI.

Safety: Adverse events (AEs) were summarized by MedDRA system organ class and preferred term, classified from verbatim terms. The incidence and percentage of patients with at least one occurrence of a preferred term were included according to the most severe NCI-CTCAE Version 3.0 grade. Laboratory results were also classified according to NCI-CTCAE Version 3.0. Incidence of laboratory abnormalities were summarized; laboratory results not corresponding to an NCI-CTCAE Version 3.0 term were not graded.

Summary:

Of the 113 patients who entered the study, 111 patients received treatment. The most common reasons for early discontinuation were progressive disease (84 patients, 74.3%) followed by symptomatic deterioration (12 patients, 10.6%). In the RMS tier, 1 patient was withdrawn for non-compliance. Patient [redacted] did not return after receiving Cycle 1 treatment. The ES/PNET (18 patients), RMS (17 patients), leiomyosarcoma (24 patients) and synovial sarcoma (17 patients) tiers were closed after the first stage due to futility. The adipocytic sarcoma tier was fully enrolled at 37 patients (Table JAEC.1).

Table JAEC.1 Patient Disposition (Enrolled Patients)

	Number of Patients					
	Ewing's Sarcoma/ PNET (N = 18)	**Rhabdomyosarcoma (N = 17)**	**Leiomyosarcoma (N = 24)**	**Adipocytic Sarcoma (N = 37)**	**Synovial Sarcoma (N = 17)**	**All Tiers (N = 113)**
Enrolled	18 (100.0)	17 (100.0)	24 (100.0)	37 (100.0)	17 (100.0)	113 (100.0)
Treated	18 (100.0)	17 (100.0)	22 (91.7)	37 (100.0)	17 (100.0)	111 (98.2)
Not Treated	0	0	2 (8.3)	0	0	2 (1.8)
ITT Population	18 (100.0)	17 (100.0)	22 (91.7)	37 (100.0)	17 (100.0)	111 (98.2)
As Treated (Safety Population)	18 (100.0)	17 (100.0)	22 (91.7)	37 (100.0)	17 (100.0)	111 (98.2)
On Study*	0	0	0	0	0	0
Off Study	18 (100.0)	17 (100.0)	22 (91.7)	37 (100.0)	17 (100.0)	111 (98.2)
Reason for Discontinuation						
AE	1 (5.6)	0	0	4 (10.8)	0	5 (4.4)
Death	0	0	1 (4.2)	1 (2.7)	1 (5.9)	3 (2.7)
PD per RECIST	12 (66.7)	14 (82.4)	16 (66.7)	29 (78.4)	13 (76.5)	84 (74.3)
Symptomatic Deterioration	2 (11.1)	2 (11.8)	3 (12.5)	2 (5.4)	3 (17.6)	12 (10.6)
Withdrawal of Consent	0	0	2 (8.3)	0	0	2 (1.8)
Non compliance	0	1 (5.9)	0	0	0	1 (0.9)
Other	3 (16.7)	0	0	1 (2.7)	0	4 (3.5)

The majority of patients in this study were white (101 patients, 91.0%). The median age was 47.0 years with the youngest population in the ES/PNET tier (median age 27.5 years) and the eldest population in the adipocytic sarcoma tier (median age 59.0 years). Overall, across all tiers combined, the number of male and female patients was similar (57 male patients, 54 female patients). Differences were seen in the ES/PNET tier which was predominantly male (13 patients, 72.2%) while the leiomyosarcoma tier was predominantly female (21 patients, 95.5%). The median duration of disease was 30.2 months from diagnosis to first dose with a range from 2.6-299.5 months. The median duration of disease across the individual tiers was 20.3 months (range 7.8-149.8 months) in the ES/PNET tier, 16.3 months (range 6.0-100.8 month) in the RMS tier, 29.2 months (range 7.0-101.9 months) in the leiomyosarcoma tier, 45.9 months (7.0-299.5 months) in the adipocytic sarcoma and 26.6 months (range 2.6-184.2 months) in the synovial sarcoma tier. Lung was the most common site of metastatic disease across all tiers.

Efficacy:

Of the 18 patients treated in the ES/PNET tier and 17 patients treated in the RMS tier, 2 patients each (11.1% and 11.8%, respectively) had a response of SD or better at Week 12. Of the 22 patients enrolled in the leiomyosarcoma tier and 17 patients enrolled in the synovial sarcoma tier, 3 patients each (13.6% and 17.6%, respectively) had a response of SD or better at Week 12. Of the 37 patients enrolled in the adipocytic sarcoma tier, 12 patients (32.4%) had a response of SD or better at Week 12. In this group, 21 out of 37 patients had either a partial response (PR), (1 patient) or durable SD (20patients) and a decrease in tumour volume was observed in 12 out of 37 patients at either the 6- or 12-week evaluation.

Table JAEC.2 Analysis of Progression Free Survival and Overall Survival

Kaplan-Meier Estimates	Ewing's Sarcoma/ PNET (N = 18)	Rhabdomyosarcoma (N = 17)	Leiomyosarcoma (N = 22)	Adipocytic Sarcoma (N = 37)	Synovial Sarcoma (N = 17)	All Tiers (N = 111)
PFS						
Number Progressed (%)	15 (83.3)	16 (94.1)	18 (81.8)	31 (83.8)	14 (82.4)	94 (84.7)
Number censored (%)	3 (16.7)	1 (5.9)	4 (18.2)	6 (16.2)	3 (17.6)	17 (15.3)
PFS (weeks)						
Median	6.4	6.1	6.0	12.1	6.4	6.7
Min-Max	(0.1+, 47.3)	(0.1+, 41.9)	(0.1+, 23.4)	(0.1+, 105.4+)	(0.1+, 23.9)	(0.1+, 105.4+)
95% CI of the Median	5.1, 12.1	5.1, 7.3	5.4, 11.0	6.0, 17.7	5.6, 11.9	6.0, 11.0
12 Week PFS (%)	27.3	12.5	25.4	50.0	21.4	31.9
95% CI (%)	8.5, 50.4	2.1, 32.8	8.4, 46.8	32.9, 64.9	5.2, 44.8	23.0, 41.1
OS						
Number Progressed (%)	13 (72.2)	13 (76.5)	10 (45.5)	26 (70.3)	12 (70.6)	74 (66.7)
Number censored (%)	5 (27.8)	4 (23.5)	12 (54.5)	11 (29.7)	5 (29.4)	37 (33.3)
OS (weeks)						
Median	24.1	23.6	-[a]	46.4	56.3	38.4
Min-Max	(2.4, 105.1+)	(6.6+, 99.9+)	(5.9, 79.1+)	(2.4, 112.9+)	(2.9, 94.9)	(2.4, 112.9+)
95% CI of the Median	12.6, 37.6	8.9, 52.1	25.7, -	31.3, 61.1	22.3, 71.3	31.1, 52.0
12 Week Survival(%)	77.8	61.4	85.9	89.2	94.1	83.4
95% CI (%)	51.1, 91.0	33.3, 80.5	62.4, 95.2	73.7, 95.8	65.0, 99.1	74.9,89.2

+ indicates a censored value

a Median OS could not be mathematically calculated due to an inadequate number of deaths

One patient [redacted] in the ES/PNET tier had a PR. The time to response was 6.0 weeks and the duration of response was 41.4 weeks. One patient [redacted] in the adipocytic sarcoma tier also had a PR. The time to response for this patient was 6.1 weeks and the duration of response was 12.1 weeks. The CBR was 33.3%, 23.5%, 40.9%, 56.8% and 35.3% for ES/PNET, RMS, leiomyosarcoma, adipocytic sarcoma and synovial sarcoma tiers, respectively.

Safety:

The majorty of patients experienced a TEAE in the study (108, 97.3%). Overall, nausea (29 patients, 26.1%), fatigue (26 patients, 23.4%), diarrhea (25 patients. 22.5%) and hyperglycemia (22 patients, 19.8%) were the most frequently reported AEs across all tiers. In the ES/PNET tier thrombocytopenia, nausea, diarrhea, constipation, fatigue, disease progression, and hyperglycaemia (5 patients each, 27.8%) were the most frequently reported AEs. In the RMS tier, back pain (5 patients, 29.4%) followed by disease progression and anemia (4 patients each, 23.5%) were the most frequently reported AEs. In the leiomyosarcoma tier, diarrhea (10 patients, 45.5%) followed by nausea (8 patients, 36.4%) and fatigue and anorexia (7 patients each, 31.8%) were the most frequently reported AEs. In the adipocytic sarcoma tier, nausea and hyperglycemia (11 patients each, 29.7%) followed by muscle spasms (10 patients, 27.0%) were the most frequently reported AEs, and in the synovial sarcoma tier, fatigue (5 patients, 29.4%) followed by nausea, asthenia, cough, decreased weight, chest pain and haemoptysis (3 patients each, 17.6%) were the most frequently reported AEs. Two of the patients who experienced haemoptysis had underlying lung metastases.

Overall, 55 patients (49.5%) experienced treatment emergent SAEs. Of these, 11 patients (9.9%) experienced SAEs related to cixutumumab. There were no SAEs related to cixutumumab reported in the RMS and leiomyosarcoma

tier. Overall, 10 patients (9.0%) experienced TEAEs that led to discontination from the study. Disease progression (4 patients, 3.6%) was the most frequently reported AE resulting in discontinuation from the study. Two patients in the adipocytic sarcoma tier discontinued due to SAEs that were considered related to cixutumumab (Table JAEC.3).

Table JAEC.3 Summary of Adverse Events (Safety Population)

	Ewing's Sarcoma/ PNET (N = 18)	Rhabdomyosarcoma (N = 17)	Leiomyosarcoma (N = 22)	Adipocytic Sarcoma (N = 37)	Synovial Sarcoma (N = 17)	All Tiers (N = 111)
Any TEAE	18 (100)	16 (94.1)	22 (100)	36 (97.3)	16 (94.1)	108 (97.3)
Serious TEAE	10 (55.6)	10 (58.8)	7 (31.8)	18 (48.6)	10 (58.8)	55 (49.5)
Study Drug Related TEAE	15 (83.3)	4 (23.5)	15 (68.2)	26 (70.3)	9 (52.9)	69 (62.2)
Study Drug Related Serious TEAE	2 (11.1)	0	0	8 (21.6)	1 (5.9)	11 (9.9)
TEAE Led to Discontinuation	2 (11.1)	1 (5.9)	1 (4.5)	5 (13.5)	1 (5.9)	10 (9.0)
TEAE Led to Held/Modified	2 (11.1)	2 (11.8)	1 (4.5)	7 (18.9)	2 (11.8)	14 (12.6)
TEAE Led to New or Prolonged Hospitalization	10 (55.6)	10 (58.8)	7 (31.8)	13 (35.1)	10 (58.8)	50 (45.0)
CTC Grade 3 TEAE	6 (33.3)	11 (64.7)	7 (31.8)	18 (48.6)	7 (41.2)	49 (44.1)
CTC Grade 4 TEAE	3 (16.7)	2 (11.8)	3 (13.6)	4 (10.8)	2 (11.8)	14 (12.6)
CTC Grade 5 TEAE	5 (27.8)	4 (23.5)	1 (4.5)	2 (5.4)	1 (5.9)	13 (11.7)

There were 12 deaths (10.8%) reported on study or within 30 days of last dose. Of these, 10 patients (83.3%) died due to disease progression. Two patients (16.7%) died of other causes. There was 1 death [redacted] that was considered related to cixutumumab in the adipocytic sarcoma tier (cardiac arrest).

Conclusions:

In this population of patients with advanced or metastatic soft tissue or ES/PNET sarcoma cixutumumab 10 mg/kg once every 2 weeks was generally safe and well tolerated.

Only the adipocyctic sarcoma tier met the protocol- specified criteria and was fully enrolled. In this group 21 out of 37 patients had either a partial response (1 patient) or durable stable disease (20 patients) and a decrease in tumour volume was observed in 12 out of 37 patients at either the 6- or 12-week evaluation. The ES/PNET tier, RMS tier, leiomyosarcoma and synovial sarcoma tier failed the futility analysis and enrollment was stopped after Stage 1 of the study.