A Phase 1b Study of IMU-131 HER2/neu Peptide Vaccine plus Chemotherapy in Patients with HER2/neu Overexpressing Metastatic or Advanced Adenocarcinoma of the Stomach or Gastroesophageal Junction

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Abstract

Background: HER2/neu is overexpressed in 15% - 25% of gastric cancers. IMU-131 is a B-cell peptide vaccine composed of 3 epitopes of the extracellular domain of HER2/neu. Antibodies against IMU-131 peptides elicit antitumor activity in vitro and a phase I study demonstrated safety and immunogenicity in Her-2 +/++ breast cancer patients.

Methods: IMU-131 was given to patients with HER2/neu positive gastric cancer in an open-label Phase 1b dose escalation trial with 14 Asian and Eastern European sites. Each patient received IMU-131 on Days 0, 14, and 35, with cisplatin and 5-fluorouracil or capecitabine every 21 days. Patients remained on study until disease progression. Ongoing patients received boosters at D98 then every 84 days.

Results: 14 patients were enrolled with 10 HER2 overexpressing (7 x HER2+++, 3 x HER2++ FISH positive) and 4 HER2++ expressing tumors. Mean age was 57 yo (range of 21 - 79) with ECOG scores of 0 or 1 in 7 patients each. There were 9 Asian and 5 Caucasian patients with 5 females and 9 males. Dose levels were 10, 30 and 50 μg with 3, 6, and 5 patients respectively. 11 patients received all 3 doses and 3 patients received only 2 doses due to disease progression. P467 and HER2 antibodies were generated at all dose levels with patients dosed at 50μg responding to the vaccine with equally high antibody levels. There were no DLTs or SAEs related to IMU-131. Of the 14 patients dosed 11 were evaluable for tumor progression at day 56 and later. Of those patients, the best response was 1 CR, 5 PR, 4 SD and 1 PD. Two patients, both dosed at 50μg IMU-131, remain on study after D266, with one patients tumor reduced by approximately 80% from 177mm at baseline to 37mm at D266.

Conclusions: Safety data indicate that IMU-131 is well tolerated with no significant local or systemic reactions. There were no dose-limiting toxicities observed, no significant injection site reactions and no IMU-131 related SAEs. The 50μg dose produced the most consistent P467 and HER-2 specific antibodies compared to 10 and 30μg doses with preliminary response data demonstrating 50μg of IMU-131 is associated with tumor size reduction.

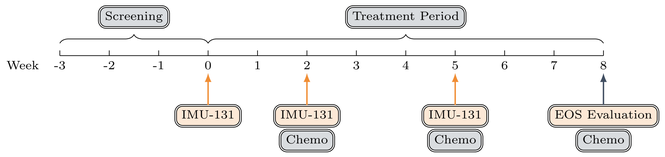
Background

IMU-131 contains a single peptide antigen composed of 3 individual linear B-cell epitope peptide sequences selected from HER-2/neu (P4/P6/P7) that induce the patient's own B-cells to produce anti-HER-2/neu antibodies[4]. IMU-131 may complement or replace the high-dose passive immunization induced by trastuzumab with a persistent humoral response to HER-2/neu. Vaccination of mice with 3 HER-2-peptides representing B-cell epitopes of the extracellular domain (ECD) of HER-2/neu induces HER-2/neu specific immunoglobulin G (IgG) antibodies with strong antitumor activity in vitro and in vivo[4][5].

Study Design

The doses tested were 10, 30 and 50 μg (peptide P467 antigen equivalent) on days 0, 14, and 35, with chemotherapy cycles every 21 days starting 14 days ($\pm$1 day) after first IMU-131 vaccination. Chemotherapy included Cisplatin, IV (80 mg/m^2 on Day 14, then every 21 days and either 5-FU, 1000 mg/m^2/day infusion for 96 hrs on days 14-17, then every 21 days) or Capecitabine for 14 days at 1000 mg/m^2 twice daily on days 14-27, then every 21 days). Patient's cellular (T_{reg}/T_{eff} and B_{reg}/B_{eff} cells), and humoral immunity (anti-P467 and anti-HER2 antibodies) were evaluated. Radiographic assessment evaluated disease progression (RECIST 1.1). Patients who completed Day 56 continued in long term maintenance with administration of IMU-131 on Day 98 then every 84 days.

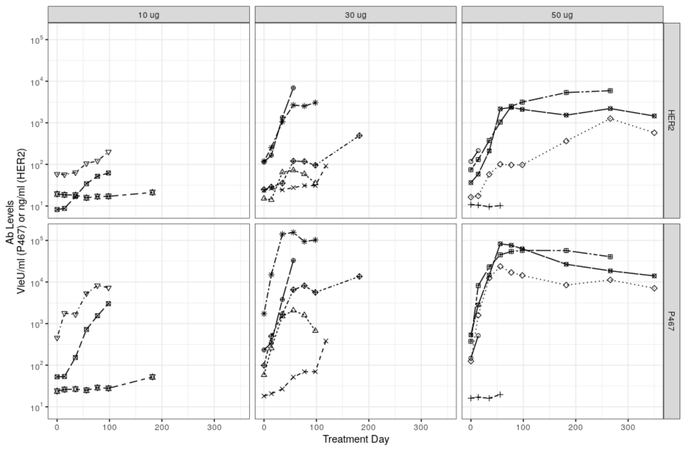
Study Design cont.



Results

Fourteen patients were enrolled from 14 sites in 5 countries (Georgia, Hong Kong, Republic of Moldova, Taiwan and Thailand). Three patients were enrolled in the 10 μg, 6 in the 30 μg and 5 in the 50 μg cohorts. Nine patients (64.3%) were Asian and 5 (35.7%) were Caucasian. All 14 patients were included in the safety population, 11 (78.6%) patients completed the treatment period, 3 (21.4%) patients discontinued treatment and 10 (71.4%) patients discontinued the study. Five patients were (35.7%) female and 9 (64.3%) male with a mean age of 57 $\pm$ 17 yrs. Tumor stages were IIIb (n=2), IIIc (n=1) and IV (n=11).

Immunogenicity: Antibodies that cross-reacted with HER2/neu extracellular protein and the p467 protein construct were measured. For both antibodies there were dose and time dependent increases. Antibody levels tended to increase with each dose administration and were at their highest levels at Day 56.

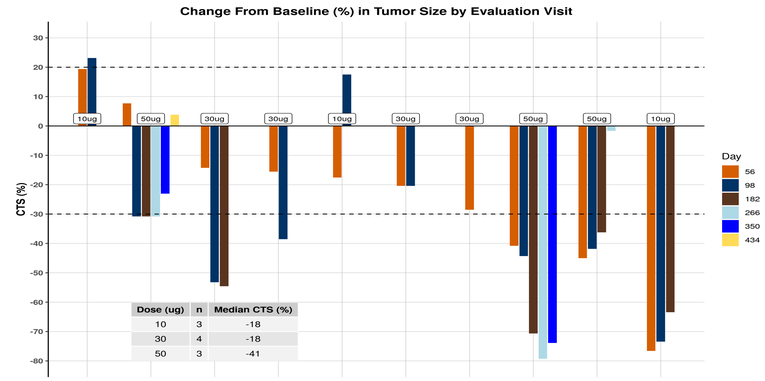


Tumor Response: Overall tumor size decreased from baseline over time. The overall mean percentage change at Visit Day 56 was -23.17% (SD = 27.10%), -25.10% (SD = 35.37%) at the start of long term maintenance Day 98 and -58.98% (SD = 6.28%) at long term maintenance Day 182. Tumor size decreases from baseline over time was also noted for all treatment groups.

Safety: Overall, over 200 TEAEs were reported by 14 patients with majority of the events assessed as Grade 1 to 3 severity and not related to IMU-131. Two Grade 1 vaccination site reactions (injection site reactions) (pruritus and erythema) were reported by 1 patient (50 μg group) and assessed as possibly related.

Results cont.

The TEAEs observed in this study were in line with and expected for the chemotherapy the patient received. A total of 9 patients reported 15 SAEs of which 5 TEAEs resulted in fatal outcomes. The TEAEs (convulsion, pneumonia, acute renal failure, dyspnea and acute respiratory failure) leading to fatal outcomes were not related to the study drug (IMU-131). No DLTs were observed and there were no events leading to study drug discontinuation. Clinical laboratory findings including vital signs, ECG and physical examinations were unremarkable and did not impact the overall safety results.



Patient Tumor and Response Data

Patient	Dose (μg)	HER2 Status	Tumor Size[a](RECIST) Baseline	Day 56	Day 98	Day 182	Day 266	Day 350	Day 434
TH02 001	10	2+/FISH-	97	80 (SD)	114 (PD)	Withdrawn			
TH03 001	10	2+/FISH-	268	320 (SD)	330 (PD)	Deceased			
TW02 002	10	3+	38	9 (CR)	10 (PR)	14 (PD)	Withdrawn		
TH05 013	30	2+/FISH+	49	39 (SD)	39 (SD)	Deceased			
TH05 015	30	3+	78	66 (SD)	36 (PR)	35 (PR)	Deceased		
GE01 004	30	3+	122	103 (SD)	75 (PR)	Deceased			
TW01 001	30	3+	56	40 (PD)[b]	Withdrawn				
MD01 003	30	3+	NTL[c]	NTL (SD)	NTL (PD)	Withdrawn			
TW02 003	50	2+/FISH+	66	36 (PR)	39 (PR)	42 (PR)[d]	65 (PD)	Withdrawn	
MD01 007	50	2+/FISH -	26	28 (SD)	18 (PR)	18 (PR)[d]	18 (SD)	20 (SD)	27 (SD)[d]
TW02 004	50	3+	177	105 (PR)	99 (PR)	52 (PR)	37 (PR)	43 (PD)	Withdrawn

[a] Sum of the diameters of the target lesions [b] Due to 2 new lesions [c] Non-target lesions [d] Ongoing in Study

Conclusion

The preliminary immunology and clinical response data are promising. Safety data indicate that IMU-131 is well-tolerated with no significant local or systemic reactions. There were no dose-limiting toxicities observed, no significant injection site reactions and no IMU-131 related SAEs. The 50 μg dose produced the most consistent P467 and HER-2 specific antibodies compared to 10 and 30 μg doses with preliminary response data demonstrating 50 μg of IMU-131 was associated with tumor size reduction. The 50 μg dose of IMU-131 is being used in the ongoing phase 2 study.

References

[1] In: *Oncogene* 9 (8 Aug. 1994).[2] In: *Journal of immunology* 156 (9 May 1996).[3] In: *Microsc Res Tech* 59 (2 Oct. 2002).[4] In: *Int J Cancer* 107 (6 Dec. 2003).[5] In: *Breast Cancer Res Treat* 106 (1 Nov. 2007).

Study Sponsor and COI

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