A phase 1b/2 open label study of IMU-131 HER2/Neu peptide vaccine plus cisplatin and either 5-fluorouracil or capecitabine chemotherapy in patients with HER2/Neu overexpressing metastatic or advanced adenocarcinoma of the stomach or gastroesophageal junction

Ursula Wiedermann[1], Anthony J Good[2], Erika Garner-Spitzer[1], Yee Chao[3], Iurie Bulat[4], Arunee Dechaphunkul[5], Wichit Arpornwirat[6], Chaiyut Charoentum[7], Chia-Jui Yen[8], Thomas Cheung Yau[9], Marina Maglakelidze[10], Suebpong Tanasanvimon[11], Jedzada Maneechavakajorn[12], Aumkhae Sookprasert[13], LiYuan Bai[14], Wen-Chi Chou[15], Teerapat Ungtrakul[16], Leslie Chong[2], Nick Ede[2]

1. Medical University Vienna, Vienna, Austria 2. Imugene, Sydney, Australia 3. Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan 4. ARENSIA Exploratory Medicine Research Unit, Institute of Oncology, Chisinau, The Republic of Moldova 5. University of Alberta, Edmonton, AB, Canada 6. National Cancer Institute, Bangkok, Thailand 7. Maharaj Nakorn Chiang Mai Hospital, Mueang Chiang Mai District, Thailand 8. National Cheng Kung University Hospital, Tainan, Taiwan 9. Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, Hong Kong 10. ARENSIA Exploratory Medicine LLC, Tbilisi, Georgia 11. King Chulalongkorn Memorial Hospital, Bangkok, Thailand 12. Rajavithi Hospital, Bangkok, Thailand 13. Srinagarind Hospital, Khon Kaen, Thailand 14. China Medical University Hospital, Taichung, Taiwan 15. Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan 16. Faculty of Medicine and Public Health, HRH Princess Chulabhorn College of Medical Science, Bangkok, Thailand

Abstract

Background: Gastric cancer is the 5th most frequently diagnosed cancer and the 3rd leading cause of cancer deaths. HER2/neu is overexpressed in 15% to 25% of patients with gastric cancer and associated with a poor prognosis. Monoclonal antibodies against HER2/neu have been shown to be effective but alternative treatments are needed due to cost and global availability issues. IMU-131 is a B-cell peptide vaccine composed of 3 B cell epitopes derived from the extracellular domain of HER2/neu. Polyclonal antibodies against IMU-131 peptides binding 3 separate regions of HER2/neu have been shown to elicit antitumor activity in vitro and a phase I study demonstrated safety and immunogenicity in Her-2 +/++ metastatic breast cancer patients. Fusion of the single peptides into a hybrid peptide conjugated to CRM197 in conjunction with the adjuvant Montanide (P467-CRM-Montanide) improved formulation and stability of the vaccine. With the present Phase 1b/2 trial performed in patients with HER2/neu overexpressing gastric or gastroesophageal junction (GEJ) adenocarcinoma, it is hypothesized that administration of IMU-131 in addition to chemotherapy is safe and immunogenic, and will prolong survival and may delay tumor progression and/or reduce tumor burden.
Methods: This study is an international open-label multicenter study performed in 16 Asian and Eastern European sites with up to 18 patients enrolled in Phase 1b. This dose escalation study is designed to assess safety, tolerability, immunogenicity and recommended phase 2 dose of IMU-131. Each patient will recieve 3 injections of IMU-131, at a single dose level on Days 0, 14, and 35, accompanied by cisplatin and 5-fluorouracil or capecitabine every 21 days. The RP2D will be evaluated in the dose expansion Phase 2 study with 68 patients being enrolled.
Results: The study is ongoing with the completion of the phase 1b portion in 4Q18.
Conclusions: No conclusions can be drawn at this time.

Background

IMU-131 is being developed as a therapeutic vaccine for the treatment of gastric cancer in patients with HER-2/neu-overexpressing advanced adenocarcinoma of the stomach or gastroesophageal junction (GEJ). 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[3]. HER-2/neu is a tumor-associated protein that is overexpressed in several malignancies and has been proposed as a human cancer vaccine target[1]. Overexpression of HER-2/neu in human breast and gastric carcinomas correlates with a more aggressive course of disease[2] with poorer overall survival than in patients without overexpression of HER-2/neu[4].
IMU-131 may complement or replace the high-dose passive immunization induced by trastuzumab with a persistent humoral response to HER-2/neu. The immunological proof of principle has been demonstrated in mice by administering the 3 HER-2/neu epitopes as either individual or collinear peptides conjugated to different carriers and formulated with or without adjuvants. 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[3][5].

Study Drug

IMU-131 is supplied in 2 vials: an aqueous solution of the peptide antigen conjugated to the carrier protein CRM197 (a nontoxic mutant of diphtheria toxin) and the adjuvant Montanide. The components are mixed in a 1:1 ratio for intramuscular (IM) injection. The IMU-131 vaccine will be administered into the deltoid region of the upper arm with a 0.60 x 25 mm 23G needle.

Study Design

The phase1b/2 protocol is made up of 2 sections, a 1b dose escalation and a Phase 2 evaluation of clinical activity submitted as an amendment after completion of Phase 1b. Patients must have metastatic gastric or GEJ adenocarcinoma, or disease not amenable to surgical resection and have HER2/neu overexpression (3+ by immunohistochemistry (IHC) or IHC 2+ confirmed by fluorescent in situ hybridization (FISH) or chromogenic in situ hybridization (CISH)).
In the Phase 1b section dose escalation of 3 injections of IMU-131 at a particular dose was given to patients on days 0, 14, and 35, with chemotherapy cycles every 21 days starting 14 days ($\pm$1 day) after first IMU-131 vaccination. The doses tested were 10, 30 and 50 μg (peptide P467 antigen equivalent) with injection volumes of 0.1, 0.3 and 0.5 mL.
Chemotherapy included the following treatments

- Cisplatin, IV (80 mg/m^2 on Day 14, then every 21 days) and either
  - 5-FU, 4000 mg/m2 CIV (1000 mg/m^2/day infusion for 96 hrs on days 14-17, then every 21 days)
  - Capecitabine for 14 days at 2000 mg/m2/day, orally (1000 mg/m^2 twice daily on days 14-27, then every 21 days).

Patients will be evaluated on every dosing visit and final assessments were done on day 56 and included

- Clinical laboratory assessments and Vaccination site evaluation
- Cellular (analysis of regulatory and effector T and B cells) and humoral immunity (anti-P467 and anti-HER2 antibodies)
- Radiographic assessment to evaluate disease progression (RECIST 1.1)

Patients who complete Day 56 will continue in long term maintenance with administration of IMU-131 on Day 98 then every 84 days.

References

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