Clinical trials in progress

### A PHASE 1 EVALUATION OF TEBOTELIMAB, A BISPECIFIC PD-1 X LAG-3 DART® MOLECULE, IN COMBINATION WITH MARGETUXIMAB IN PATIENTS WITH ADVANCED HER2+ NEOPLASMS

1Manish Patel*, 2Jason Luke, 3Erika Hamilton, 4Bartosz Chmielowski, 5George Blumenschein, 6Hedy Kindler, 7Shakeela Bahadur, 8Cesar Santa-Maria, 9Jichao Sun, 10Sanjeev Kaul, 11Francine Chen, 12Xiaoyu Zhang, 5George Blumenschein, 6Hedy Kindler, 7Shakeela Bahadur, 8Cesar Santa-Maria, 9Jichao Sun, 10Sanjeev Kaul, 11Francine Chen, 12Xiaoyu Zhang

**Background**

Tebotelimab, also known as MGD013, is an investigational, Fc bearing bispecific tetravalent DART molecule designed to bind PD-1 and LAG-3 and sustain/restore the function of exhausted T cells. Margetuximab, an investigational Fc-engineered anti-HER2 monoclonal antibody, has similar HER2 binding and antiproliferative properties to trastuzumab, but with enhanced Fc-mediated effector function. In vitro studies have demonstrated upregulation of LAG-3/PD-L1 expression on immune cells after margetuximab exposure, along with enhanced lytic activity of immune cells primed by margetuximab in the presence of tebotelimab.

**Methods**

This study characterizes safety, PK/PD, and preliminary antitumor activity of tebotelimab plus margetuximab in patients with advanced HER2+ malignancies. A one-step 3+3 dose escalation phase of tebotelimab (300 and 600 mg) combined with margetuximab 15 mg/kg, both every 3 weeks, was followed by cohort expansion of patients with breast, gastric or gastroesophageal, and other HER2+ tumors.

**Results**

At data-cutoff, 31 patients (2.0 median lines of prior therapy; 64.5% with prior HER2-directed therapy) were treated. Median duration of treatment is 10.3 weeks with 17 patients remaining on treatment. No maximum tolerated dose was defined. Treatment-related adverse events (TRAEs) occurred in 23/31 (74.2%) patients, most commonly diarrhea (n=6), nausea, ALT increased (n=5, each), AST increased, and myalgia (n=4, each). The rate of Grade 3 TRAEs was 19.4%, with no Grade 4—5 TRAEs observed. Immune-related AE were consistent with events observed with anti-PD-1 antibodies and were manageable with supportive treatment. Among 20 response-evaluable patients (i.e., received on-treatment scan), 8 objective responses (6 confirmed) per RECIST v1.1 have been observed, including a confirmed complete response (cholangiocarcinoma) and 7 partial responses (breast [2], microsatellite stable colorectal cancer [2], esophageal adenocarcinoma [1], ovarian cancer [1], and microsatellite stable gastroesophageal junction carcinoma). Immunohistochemistry (IHC) of available baseline tumor specimens (n=17) demonstrated low PD-L1 expression with combined positive scores of either 0 (n=16) or 1 (n=1, colorectal cancer). Investigations into other potential correlative biomarkers, including LAG-3 and PD-1 by IHC and gene expression profiling by NanoString, remain ongoing.

**Conclusions**

Tebotelimab in combination with margetuximab has demonstrated an acceptable safety profile and encouraging early evidence of anti-tumor activity, with a preliminary overall response rate (ORR) of 40% (8/20) [including unconfirmed responses] among late-line patients with various advanced HER2+ malignancies.

**Trial Registration**
NCT03219268

**Ethics Approval**
This study was approved by each Institution’s Ethics Board prior to enrollment of subjects.

REFERENCE


### WO180 NOVEL ANTI-VISTA ANTIBODY: RATIONALE FOR TARGET PATIENT POPULATION AND FIRST-IN-HUMAN TRIAL DESIGN IN MONOTHERAPY AND IN COMBINATION WITH ANTI-PD1 ANTIBODY

1Ignacio Melero, 2Carlos Gomez-Roca, 3Pierre Ferre, 3Eric Chetaille, 4Aurelien Marabelle, 5Isaac Boudribila, 6Marta Pawlik, 7Aurelien Marabelle, 8Centro de Investigacion de Medica Applic, Pamplona, Spain; 9Institut Universitaire du Cancer, Toulouse, France; 10Pierre Fabre Research Institute, Toulouse, France; 11Institut Gustave Roussy, Villejuif, France

**Background**

V-domain Ig suppressor of T cell Activation (VISTA) is a negative checkpoint regulator of T cell response. VISTA is expressed within the tumor microenvironment, where its blockade can enhance antitumor immune responses. Furthermore, an increase in VISTA expression has been reported after treatment by anti-PD1/L1 and anti-CTLA4.

**Methods**

This study characterizes safety, PK/PD, and preliminary antitumor activity of tebotelimab plus margetuximab in patients with advanced HER2+ malignancies. A one-step 3+3 dose escalation phase of tebotelimab (300 and 600 mg) combined with margetuximab 15 mg/kg, both every 3 weeks, was followed by cohort expansion of patients with breast, gastric or gastroesophageal, and other HER2+ tumors.

**Results**

At data-cutoff, 31 patients (2.0 median lines of prior therapy; 64.5% with prior HER2-directed therapy) were treated. Median duration of treatment is 10.3 weeks with 17 patients remaining on treatment. No maximum tolerated dose was defined. Treatment-related adverse events (TRAEs) occurred in 23/31 (74.2%) patients, most commonly diarrhea (n=6), nausea, ALT increased (n=5, each), AST increased, and myalgia (n=4, each). The rate of Grade 3 TRAEs was 19.4%, with no Grade 4—5 TRAEs observed. Immune-related AEs were consistent with events observed with anti-PD-1 antibodies and were manageable with supportive treatment. Among 20 response-evaluable patients (i.e., received on-treatment scan), 8 objective responses (6 confirmed) per RECIST v1.1 have been observed, including a confirmed complete response (cholangiocarcinoma) and 7 partial responses (breast [2], microsatellite stable colorectal cancer [2], esophageal adenocarcinoma [1], ovarian cancer [1], and microsatellite stable gastroesophageal junction carcinoma). Immunohistochemistry (IHC) of available baseline tumor specimens (n=17) demonstrated low PD-L1 expression with combined positive scores of either 0 (n=16) or 1 (n=1, colorectal cancer). Investigations into other potential correlative biomarkers, including LAG-3 and PD-1 by IHC and gene expression profiling by NanoString, remain ongoing.

**Conclusions**

Tebotelimab in combination with margetuximab has demonstrated an acceptable safety profile and encouraging early evidence of anti-tumor activity, with a preliminary overall response rate (ORR) of 40% (8/20) [including unconfirmed responses] among late-line patients with various advanced HER2+ malignancies.

**Trial Registration**
NCT03219268

**Ethics Approval**
This study was approved by each Institution’s Ethics Board prior to enrollment of subjects.

REFERENCE

Abstracts

This confirms that VISTA may play a key role as a mechanism of resistance to the currently used immunotherapies. VISTA/PSGL1 pH-selective biochemical interaction has been recently demonstrated.1 VISTA and PSGL1 expression pattern, their correlation and their relationship to myeloid infiltrates have been evaluated in samples from patients with solid tumors. K01401-020 (W0180) is a novel anti-VISTA antibody that has the potential to activate T cells when given as a monotherapy6, and thus to generate added activity when combined with anti-PD/L1 antibodies in cancer patients.

Methods

This phase I/IIb for W0180 consists of 2 parts: an initial dose escalation phase I followed by an expansion cohorts phase IIb. In the dose escalation phase, 2 cohorts of patients will be assessed in parallel: the first cohort will be given W0180 as a single agent and the second cohort will receive W0180 in combination with pembrolizumab. The first dose and the schedule of administration of W0180 in combination with pembrolizumab will be determined using safety and pharmacokinetic data generated in monotherapy. The phase I will allow to determine the Maximum Tolerated Dose and Schedule (MTDS), to characterize Dose-Limiting Toxicities (DLTs) and explore pharmacodynamic activity of W0180 in monotherapy and combination with pembrolizumab. The dose-toxicity relationships will support the dose escalation process and will be used to assess the MTDS and recommended doses for expansion. Following completion of the dose escalation phase, the expansion phase will enroll cohorts of patients with homogeneous tumors to validate the dose/schedule, assess preliminary activity and to explore the potential relationship with VISTA and PSGL1 expression.

Results

N/A

Conclusions

N/A

Trial Registration

N/A

Ethics Approval

The study was approved by National French Ethnic committee (CPP Ile de France V) and National Spanish Ethnic committee (Comité Ético de Investigación Clínica de Navarra) and was registered in the European database (EudraCT: 2019-002299-15).

Consent

N/A

REFERENCES


http://dx.doi.org/10.1136/jitc-2020-SITC2020.0315

316 EVICTION STUDY: PRELIMINARY RESULTS IN SOLID TUMOR PATIENTS WITH ICT01, A FIRST-IN-CLASS, GAMMA9 DELTA2 T CELL ACTIVATING ANTIBODY TARGETING BUTYROPHILIN-3A

1Aurelien Marabelle, 2Christiane Jungels, 3Joahn De Bono, 4Nobert Vey, 5Martin Wernike, 6Elena Garalda, 7Aude de Gassart, 8Patrick Brune, 9Emmanuel Valentin, 6Marina Ichi, 10Daniel Olive, 11Paul Frohna. 1Gustave Roussy, Villejuif, France; 2Institut Jules Bordet, Brussels, Belgium; 3The Institute for Cancer Research, London, UK; 4Institut Paul-Papillot, Calmettes, Marseille, France; 5Medical Faculty Carl Gustav Carus, Dresden, Germany; 6 Vall d’Hebron Institute of Oncology, Barcelona, Spain; 7ImmCheck Therapeutics, Marseille, France; 8Life Consulting, Paris, France; 9Centre de recherche en Cancérologie, Marseille, France

Abstracts

This confirms that VISTA may play a key role as a mechanism of resistance to the currently used immunotherapies. VISTA/PSGL1 pH-selective biochemical interaction has been recently demonstrated.1 VISTA and PSGL1 expression pattern, their correlation and their relationship to myeloid infiltrates have been evaluated in samples from patients with solid tumors. K01401-020 (W0180) is a novel anti-VISTA antibody that has the potential to activate T cells when given as a monotherapy6, and thus to generate added activity when combined with anti-PD/L1 antibodies in cancer patients.

Methods

This phase I/IIb for W0180 consists of 2 parts: an initial dose escalation phase I followed by an expansion cohorts phase IIb. In the dose escalation phase, 2 cohorts of patients will be assessed in parallel: the first cohort will be given W0180 as a single agent and the second cohort will receive W0180 in combination with pembrolizumab. The first dose and the schedule of administration of W0180 in combination with pembrolizumab will be determined using safety and pharmacokinetic data generated in monotherapy. The phase I will allow to determine the Maximum Tolerated Dose and Schedule (MTDS), to characterize Dose-Limiting Toxicities (DLTs) and explore pharmacodynamic activity of W0180 in monotherapy and combination with pembrolizumab. The dose-toxicity relationships will support the dose escalation process and will be used to assess the MTDS and recommended doses for expansion. Following completion of the dose escalation phase, the expansion phase will enroll cohorts of patients with homogeneous tumors to validate the dose/schedule, assess preliminary activity and to explore the potential relationship with VISTA and PSGL1 expression.

Results

N/A

Conclusions

N/A

Trial Registration

N/A

Ethics Approval

The study was approved by National French Ethnic committee (CPP Ile de France V) and National Spanish Ethnic committee (Comité Ético de Investigación Clínica de Navarra) and was registered in the European database (EudraCT: 2019-002299-15).

Consent

N/A

REFERENCES


http://dx.doi.org/10.1136/jitc-2020-SITC2020.0315