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A FIH phase I dose escalation study of YH001, an anti-CTLA-4 mAb, in combination with Toripalimab in patients with advanced solid tumors

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Background

- Cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) is an immune checkpoint that is expressed by activated T cells. As member of the immunoglobulin superfamily, CTLA-4 plays a key role in the down-regulation of the immune system through the transmission of an inhibitory signal to T cells.
- The therapeutic blockade of CTLA-4 has been demonstrated to enhance T-cell reactivity to tumor-specific antigens, translating to significant improvement in overall survival in certain patients.
- CTLA-4 inhibitor, such as ipilimumab, is approved, as mono or combination therapy with anti-PD1 mAb, for the treatment of solid tumors. However, significant adverse reactions are reported both from clinical trials and post market usage which have limited its use and therefore the therapeutic potential.
- YH001 is a humanized anti -hCTLA-4 IgG1 mAb. Pre-clinical data have shown potent anti-cancer activity when combined with anti-PD-1 mAb, and favorable safety profile compared with ipilimumab.

Experiment

Overall Design and Objective:

This is a first-in-human (FIH), open-label, phase I dose escalation study designed to evaluate the safety, tolerability and pharmacokinetics of YH001 in combination with Toripalimab (an anti-PD1 mAb) injection in subjects with advanced solid tumors.

The primary endpoint is the overall safety and tolerability of YH001 in combination with Toripalimab. The MTD, if any, will be determined based on the data of safety and tolerability.

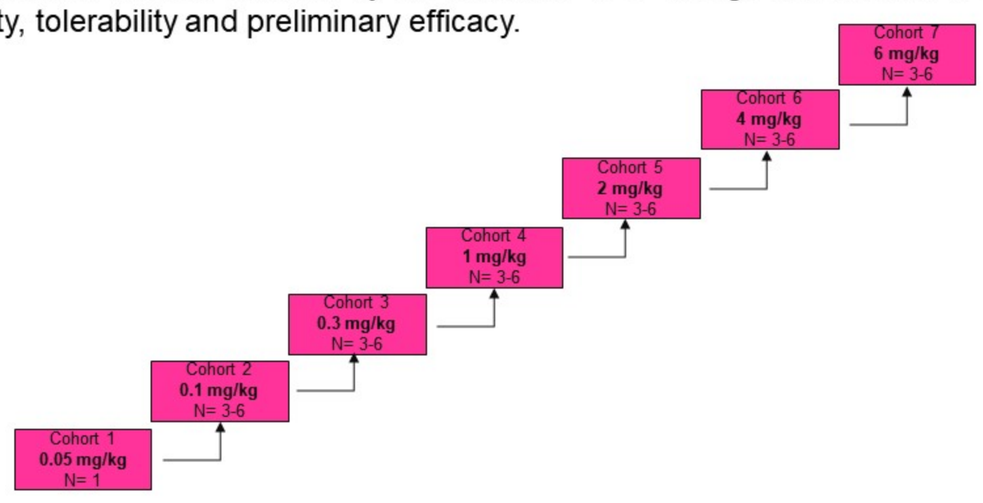
The secondary endpoints are PK parameters, incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) and objective response rate (ORR), duration of response (DOR) per RECIST v1.1, Time to response (TTR), disease control rate (DCR), and duration of disease control (DDC).

Study population:

- To be eligible for participation in the study, patients aged ≥ 18 years must have
  - ✓ advanced histologically or cytologically confirmed solid tumor;
  - ✓ progressed on after treatment with standard therapies or intolerant of standard care, or not accessible to standard therapy due to any reason;
  - ✓ at least 1 unidimensional measurable target lesion per RECIST v1.1. Target lesions situated in a previously irradiated or post locoregional treatment area are considered measurable if progression has been demonstrated in such lesions.
  - ✓ ECOG performance status score 0 or 1;
  - ✓ life expectancy of at least 12 weeks based on investigator's judgement;
  - ✓ adequate organ and bone marrow function
- Patients will be excluded from the study if they have:
  - ✓ prior anti-CTLA-4 mAb treatment;
  - ✓ intolerate to PD-1/L1 therapy;
  - ✓ a history of ≥ Grade 3 immune-related adverse events resulted from previous immunotherapy or an AE of any grade that resulted in discontinuation of prior immunotherapy.

Treatment

Patients received YH001 by IV administration at 0.05 to 6.0 mg/kg for 1 cycle (21 days) then in combination with Toripalimab at 240 mg Q3W for 4 cycles. An initial accelerated titration followed by the standard "3+3" design was utilized to evaluate safety, tolerability and preliminary efficacy.



Results

As cut-off date of 9 Aug2021, Twenty-one patients were enrolled and treated at 0.05 mg/kg (n=2), 0.1 mg/kg (n=3), 0.3 mg/kg (n=3), 1 mg/kg (n=5) ,2 mg/kg (n=5) and 4mg/kg (n=3). The median age was 58.8 years (range 45-86). Twelve (57.1%) were Male and nine (42.9%) were Female. Thirteen cases (61.9%) had a baseline ECOG score of 0, and eight cases (38.1%) had a baseline ECOG score of 1.

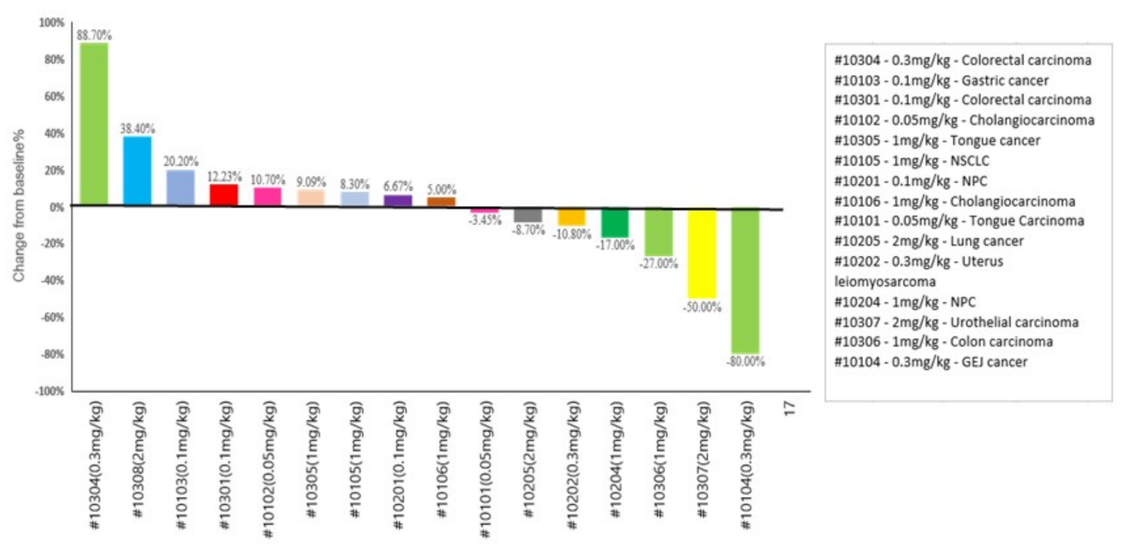
Safety and Tolerability

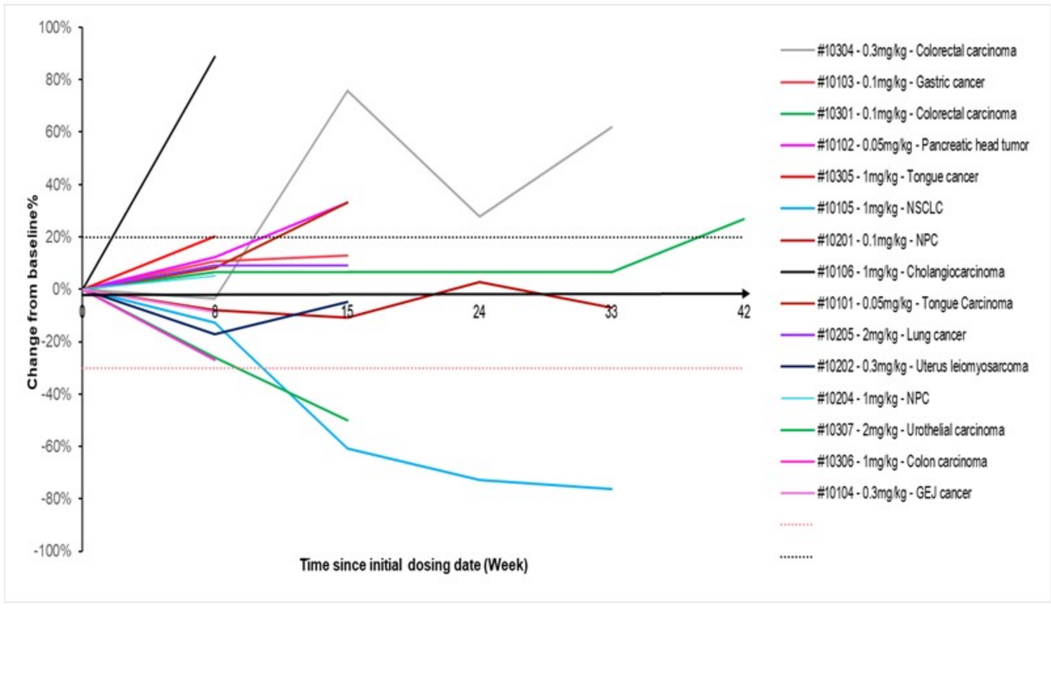
- Thirteen subjects (61.9%) had 32 drug-related adverse events (AEs) of any level, including 11 cases of grade 2 AEs, such as hypothyroidism (0.1 mg / kg), infusion reaction (0.3 mg/kg and 1.0 mg/kg) and elevated transaminase (1.0 mg/kg).
- Only one drug-related SAE occurred at 0.3 mg/kg, which was grade 3 colitis and recovered after treatment.
- There were no death events due to drug-related AEs.
- No dose limiting toxicity (DLT) was observed to date.

	Cohort 1 (0.05mg/kg) N=2	Cohort 2 (0.1mg/kg) N=3	Cohort 3 (0.3mg/kg) N=3	Cohort 4 (1mg/kg) N=5	Cohort 5 (2mg/kg) N=5	Total N=18
Any YH001 drug-related TEAEs	5	6	6	11	4	32
Grade 1	5	5	3	3	4	20
Grade 2	0	1	2	8	0	11
≥Grade 3	0	0	1	0	0	1
DLT	0	0	0	0	0	0
Drug-related SAE	0	0	1	0	0	1
AE leading to discontinuation	0	0	1	0	0	1
AE leading to death	0	0	0	0	0	0

Clinical Response

As cut-off date of 9 Aug2021, among 16 patients having imaging tumor assessment by RECIST v1.1. One patient with adenocarcinoma at the gastroesophageal junction in the 0.3mg/kg dose group, achieved PR and the largest tumor volume reduction was 80% compared with the baseline. Another patient with urothelial carcinoma in the 2mg/kg dose group, achieved PR and the largest tumor volume reduction was 50% compared with the baseline. This subject entered into this study after the failure of Zimberelimab (anti-PD-1 mAb) treatment. In addition, 7 subjects were evaluated as SD in 0.05 mg / kg dose group (1 case), 0.1 mg / kg dose group (1 case), 0.3 mg / kg dose group (1 case), 1.0 mg / kg dose group (4 cases).





Discussion and Conclusion

YH001 is a recombinant humanized anti-CTLA-4 IgG1 mAb that specifically binds to human CTLA-4. Binding of YH001 to CTLA-4 blocks the interactions of CTLA-4 with CD80 and CD86 and release the ligands to CD28. As a result, CD28-dependent T cell stimulation and overall T cell-mediated immune response against tumors are enhanced. Moreover, YH001 can mediate effector functions including both antibody-dependent cell- mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) to eliminate CTLA-4 expressing cells, particularly Treg cells.

In vivo toxicology studies in cynomolgus monkeys showed that YH001 was well tolerated with a single dose of up to 98 mg/kg. YH001 was demonstrated stronger anti-tumor activities when combined with pembrolizumab. In addition, YH001 combined with pembrolizumab demonstrated better efficacy compared to ipilimumab combined with pembrolizumab.（ASCO 2018）

The preliminary data from the Phase I clinical trial show that YH001 is well tolerated and has a favorable safety profile, which enable continuous dosing and is expected to benefit patients in treatment efficacy.

In conclusion, YH001 combined with Toripalimab is safe and tolerable up to 2 mg/kg dose level. In addition, YH001 combined with Toripalimab showed preliminary antitumor effect.