NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis

Generic Drug Name

Not applicable

Trial Indication(s)

Adult patients with advanced solid tumors, including epithelial ovarian cancer and renal cell carcinoma

Protocol Number

CHKT288X2101

Protocol Title

A Phase I, multicenter, open-label dose escalation and expansion study of HKT288, administered intravenously in adult patients with advanced solid tumors, including epithelial ovarian cancer and renal cell carcinoma

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

Study Start Date: December 2016 (Actual)
Primary Completion Date: September 2017 (Actual)
Study Completion Date: September 2017 (Actual)

Reason for Termination (If applicable)

Given the adverse event profile observed with HKT288, which included two suspected-related neurologic adverse events, Novartis decided to terminate the study.

Study Design/Methodology

This was a Phase I, multicenter, open-label study conducted to determine the MTD/RDE as well as the safety/tolerability and PK of HKT288 in subjects with serous epithelial ovarian cancer and advanced clear cell or papillary RCC who had progressed on standard therapy or were intolerant to standard therapy, and for whom there was no curative therapy.

This study used Bayesian Logistic Regression Model (BLRM), a well -established method to estimate the MTD/RDE in cancer subjects. The decisions on new dose levels were made by the Investigators and Novartis study personnel and were based upon the recommendations made by the BLRM, tolerability and safety, PK, pharmacodynamics, and efficacy information available at the time of the decision. Following determination of the MTD/RDE in the dose escalation part, a dose expansion part was to be conducted. However, due to the early termination of the study, the dose expansion part was not conducted.

Centers

7 centers in 6 countries: Australia(1), Belgium(2), Japan(1), Switzerland(1), Spain(1), United States(1)

Objectives:

Primary objective:

- To characterize the safety and tolerability of HKT288 and to identify maximum tolerated dose/recommended dose for expansion (MTD/RDE)

Secondary objectives:

- To characterize the pharmacokinetic (PK) profile of HKT288
- To assess the preliminary anti-tumor activity of HKT288 in subjects with advanced serous epithelial ovarian cancer and clear cell or papillary renal cell carcinoma (RCC)
- To assess immunogenicity (IG) following one or more intravenous infusions of HKT288
- To assess cadherin-6 (CDH6) expression in subjects with advanced serous epithelial ovarian cancer and clear cell or papillary RCC and correlate with anti-tumor activity

Test Product (s), Dose(s), and Mode(s) of Administration

HKT288 was administered intravenously (IV) and was assigned to two treatment cohorts. Cohort 1 was treated with 0.3 mg/kg IV once every 3 weeks and Cohort 2 was treated with 0.75 mg/kg IV once every 3 weeks.

Statistical Methods

Assessment of safety was based on the type and frequency of AEs, as well as incidence of dose limiting toxicities (DLTs) in the first 21-day cycle. The Safety set was used for summaries and listings of safety data. AE summaries included all AEs occurring during on-treatment period. AEs were summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using Medical dictionary for regulatory activities (MedDRA) coding. Evaluation of anti-tumor activity was based on local Investigator assessment of overall lesion response according to RECIST v1.1. In this report, only best overall response (BOR) is summarized. Percentage change in tumor size from baseline and overall response by assessment cycle were listed. The other planned efficacy endpoints, overall response rate (ORR), disease control rate (DCR), duration of response (DOR) and progression free survival (PFS), were not evaluated, as the study was terminated early. Results of PK analyses are reported for two major analytes, tAb and tADC. Summaries were based on the pharmacokinetic analysis set (PAS), except for the listing of PK concentrations, which was based on the Safety set. PK concentration data were summarized by treatment, analyte, and time point. Immunogenicity and biomarkers data were not summarized due to early termination of the study.

Study Population: Key Inclusion/Exclusion Criteria

Main Inclusion Criteria:
-Advanced (metastatic or locally advanced) serous epithelial ovarian, serous fallopian tubal or serous primary peritoneal cancer or advanced clear cell or papillary renal cell carcinoma who have received or are intolerant to all therapy known to confer clinical benefit for their disease, as determined by the investigator.
-Tumor sample is available for retrospective CDH6 expression testing
-Eastern Cooperative Oncology Group (ECOG) Performance status ≤2

Main Exclusion Criteria:
-Patient has central nervous system metastatic involvement. Patients with previously treated CNS metastases are also excluded.
-Patient with any active or chronic corneal disorders
-Patients with monocular vision or have media opacities or any other condition that precludes monitoring of the retina or fundus.
-Patients with a history of serious allergic reactions

-Patients with QTcF >470 msec at screening ECG or congenital long QT syndrome
-Any prior history of treatment with maytansine (DM1 or DM4)-based ADC
-Patient have received anti-cancer therapies within the following time frames prior to the first dose of study treatment:
• Conventional cytotoxic chemotherapy: ≤4 weeks (≤ 6 weeks for nitrosoureas and mitomycin-C)
• Biologic therapy (e.g., antibodies): ≤4 weeks
• Non-cytotoxic small molecule therapeutics: ≤5 half-lives or ≤2 weeks (whichever is longer)
• Other investigational agents: ≤4 weeks
• Radiation therapy (except for localized radiotherapy for analgesic purpose or for lytic lesions at risk of fracture): ≤4 weeks
• Radiation therapy (localized radiotherapy for analgesic purpose or for lytic lesions at risk of fracture) ≤2 weeks
• Major surgery: ≤2 weeks

Participant Flow Table

Overall Study

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg
Started	6	3
Completed	0	0
Not Completed	6	3
Physician Decision	1	1
Lack of Efficacy	5	0
Adverse Event	0	1
Withdrawal by Subject	0	1

Baseline Characteristics

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg	Total
Number of Participants [units: participants]	6	3	9
Age Continuous (units: years) Mean ± Standard Deviation			
	61.8±15.51	68.7±6.81	64.1±13.18
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)			
Female	2	2	4
Male	4	1	5
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)			
Caucasian	5	2	7
Asian	1	1	2

Summary of Efficacy

Primary Outcome Result(s)

Incidence of dose limiting toxicities (DLTs) in the DLT evaluation period

	Dose escalation	Dose escalation

	part HKT288 0.3 mg/kg	part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3
Incidence of dose limiting toxicities (DLTs) in the DLT evaluation period (units: participants) Count of Participants (Not Applicable)		
	0	1

Tolerability as assessed by numbers of dose changes or interruptions

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3
Tolerability as assessed by numbers of dose changes or interruptions (units: participants) Count of Participants (Not Applicable)		
AE leading to discontinuation	0	1
AE leading to dose interruption	1	0

Safety assessed by severity of adverse events (AEs) and serious adverse events (SAEs)

	Dose escalation	Dose escalation

	part HKT288 0.3 mg/kg	part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3
Safety assessed by severity of adverse events (AEs) and serious adverse events (SAEs) (units: participants) Count of Participants (Not Applicable)		
Adverse events (AEs)	6	2
AEs with grade ≥ 3	1	1
SAEs	2	2

Secondary Outcome Result(s)

Concentration vs. time profiles of total antibody (tAb)

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3
Concentration vs. time profiles of total antibody (tAb) (units: hr*ng/mL; ng/mL; hr) Geometric Mean (Geometric Coefficient of Variation)		
AUC inf (hr*ng/mL)	691000 (56.7%)	1650000 (0%)
AUC last (hr*ng/mL	631000 (52.9%)	1400000 (13.3%)
Cmax (ng/mL)	5800 (21.9%)	15400 (18.2%)
T1/2 (hr)	126.0 (40.1%)	90.6 (0%)

Objective response rate

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3
Objective response rate (units: participants) Count of Participants (Not Applicable)		
	NA[]	NA[]

Duration of response

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3
Duration of response (units: participants) Count of Participants (Not Applicable)		
	NA[]	NA[]

Progression-free survival

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg

Number of Participants Analyzed [units: participants]	6	3
Progression-free survival (units: participants) Count of Participants (Not Applicable)		
	NA[]	NA[]

Disease Control Rate

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3
Disease Control Rate (units: participants) Count of Participants (Not Applicable)		
	NA[]	NA[]

Best overall response

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3

Best overall response (units: participants) Count of Participants (Not Applicable)		
complete response	0	0
partial response	0	0
stable disease	3	0
progressive disease	2	0
non complete response/ non progressive disease	1	0
not assessed	0	3

Presence of anti-HKT288 antibodies.

	Dose escalation part HKT288 0.3 mg/kg	**Dose escalation part HKT288 0.75 mg/kg**
Number of Participants Analyzed [units: participants]	6	3
Presence of anti-HKT288 antibodies. (units: participants) Count of Participants (Not Applicable)		
	NA[]	NA[]

CDH6 expression level

	Dose escalation part HKT288 0.3 mg/kg	**Dose escalation part HKT288 0.75 mg/kg**

Number of Participants Analyzed [units: participants]	6	3
CDH6 expression level (units: participants) Count of Participants (Not Applicable)		
	NA[]	NA[]

Pharmacokinetics (PK) parameter (AUC) for HKT288

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3
Pharmacokinetics (PK) parameter (AUC) for HKT288 (units: hr*ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
AUC inf	632000 (36.1%)	1580000 (0%)
AUC last	611000 (35.0%)	1280000 (19.3%)

PK parameter (Cmax) for HKT288

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3
PK parameter (Cmax) for HKT288		

(units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	5950 (27.9%)	13100 (22.5%)

PK parameter (Tmax) for HKT288

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3
PK parameter (Tmax) for HKT288 (units: hour) Median (Full Range)		
	2.1 (2.0 to 5.2)	2.2 (2.1 to 4.9)

PK parameters (half-life) for HKT288

	Dose escalation part HKT288 0.3 mg/kg	Dose escalation part HKT288 0.75 mg/kg
Number of Participants Analyzed [units: participants]	6	3
PK parameters (half-life) for HKT288 (units: hour) Geometric Mean (Geometric Coefficient of Variation)		

	97.0 (28.4%)	87.9 (0%)

Summary of Safety

Safety Results

All-Cause Mortality

	HKT288 0.3 mg/kg Q3W N = 6	HKT288 0.75 mg/kg Q3W N = 3	All patients N = 9
Total participants affected	0 (0.00%)	1 (33.33%)	1 (11.11%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit up to approximately 9 months.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment

	HKT288 0.3 mg/kg Q3W N = 6	HKT288 0.75 mg/kg Q3W N = 3	All patients N = 9

Total participants affected	2 (33.33%)	2 (66.67%)	4 (44.44%)
Cardiac disorders			
Angina pectoris	1 (16.67%)	0 (0.00%)	1 (11.11%)
Immune system disorders			
Cytokine release syndrome	1 (16.67%)	0 (0.00%)	1 (11.11%)
Nervous system disorders			
Encephalopathy	0 (0.00%)	1 (33.33%)	1 (11.11%)
Partial seizures	1 (16.67%)	0 (0.00%)	1 (11.11%)
Seizure	0 (0.00%)	1 (33.33%)	1 (11.11%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit up to approximately 9 months.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	HKT288 0.3 mg/kg Q3W N = 6	**HKT288 0.75 mg/kg Q3W N = 3**	**All patients N = 9**
Total participants affected	6 (100.00%)	2 (66.67%)	8 (88.89%)

Blood and lymphatic system disorders			
Anaemia	1 (16.67%)	1 (33.33%)	2 (22.22%)
Cardiac disorders			
Tachycardia	1 (16.67%)	0 (0.00%)	1 (11.11%)
Eye disorders			
Conjunctival hyperaemia	1 (16.67%)	0 (0.00%)	1 (11.11%)
Eye pain	1 (16.67%)	0 (0.00%)	1 (11.11%)
Gastrointestinal disorders			
Abdominal discomfort	1 (16.67%)	0 (0.00%)	1 (11.11%)
Abdominal pain upper	1 (16.67%)	0 (0.00%)	1 (11.11%)
Constipation	3 (50.00%)	1 (33.33%)	4 (44.44%)
Dry mouth	0 (0.00%)	1 (33.33%)	1 (11.11%)
Nausea	1 (16.67%)	1 (33.33%)	2 (22.22%)
Stomatitis	1 (16.67%)	0 (0.00%)	1 (11.11%)
Vomiting	2 (33.33%)	1 (33.33%)	3 (33.33%)
General disorders and administration site conditions			
Chills	1 (16.67%)	0 (0.00%)	1 (11.11%)
Fatigue	3 (50.00%)	0 (0.00%)	3 (33.33%)
Oedema peripheral	1 (16.67%)	0 (0.00%)	1 (11.11%)
Pain	1 (16.67%)	0 (0.00%)	1 (11.11%)
Pyrexia	4 (66.67%)	0 (0.00%)	4 (44.44%)
Infections and infestations			

Lower respiratory tract infection	1 (16.67%)	0 (0.00%)	1 (11.11%)
Rhinitis	1 (16.67%)	0 (0.00%)	1 (11.11%)
Upper respiratory tract infection	1 (16.67%)	0 (0.00%)	1 (11.11%)
Metabolism and nutrition disorders			
Decreased appetite	1 (16.67%)	0 (0.00%)	1 (11.11%)
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (16.67%)	0 (0.00%)	1 (11.11%)
Back pain	1 (16.67%)	0 (0.00%)	1 (11.11%)
Bone pain	1 (16.67%)	0 (0.00%)	1 (11.11%)
Musculoskeletal stiffness	1 (16.67%)	0 (0.00%)	1 (11.11%)
Myalgia	1 (16.67%)	0 (0.00%)	1 (11.11%)
Pain in extremity	0 (0.00%)	1 (33.33%)	1 (11.11%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Paget's disease of nipple	1 (16.67%)	0 (0.00%)	1 (11.11%)
Nervous system disorders			
Aphasia	0 (0.00%)	1 (33.33%)	1 (11.11%)
Neuralgia	0 (0.00%)	1 (33.33%)	1 (11.11%)
Neuropathy peripheral	1 (16.67%)	0 (0.00%)	1 (11.11%)

Respiratory, thoracic and mediastinal disorders			
Bronchospasm	1 (16.67%)	0 (0.00%)	1 (11.11%)
Dysphonia	1 (16.67%)	1 (33.33%)	2 (22.22%)
Dyspnoea	2 (33.33%)	0 (0.00%)	2 (22.22%)
Dyspnoea exertional	1 (16.67%)	0 (0.00%)	1 (11.11%)
Hypoxia	1 (16.67%)	0 (0.00%)	1 (11.11%)
Sputum discoloured	1 (16.67%)	0 (0.00%)	1 (11.11%)
Skin and subcutaneous tissue disorders			
Dermatitis acneiform	1 (16.67%)	0 (0.00%)	1 (11.11%)
Pruritus	1 (16.67%)	0 (0.00%)	1 (11.11%)
Rash	1 (16.67%)	0 (0.00%)	1 (11.11%)
Skin discolouration	1 (16.67%)	0 (0.00%)	1 (11.11%)
Vascular disorders			
Hypertension	1 (16.67%)	0 (0.00%)	1 (11.11%)
Hypotension	1 (16.67%)	0 (0.00%)	1 (11.11%)

Other Relevant Findings

Conclusion:

Given the adverse event profile observed with HKT288, which included two suspected-related neurologic adverse events, Novartis decided to terminate the study. Due to early study termination, the Maximum Tolerable Dose and Recommended Dose for Expansion could not be determined. Due to limited data, efficacy conclusions could not be drawn.

Date of Clinical Trial Report

3-Aug-2018