NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis

Generic Drug Name

None assigned

Therapeutic Area of Trial

Oncology – solid tumors

Approved Indication

Not applicable

Protocol Number

CTAS266X2101

Title

A phase I, open-label dose escalation study with safety expansion of TAS266 administered by IV infusion to patients with advanced solid tumors

Study Phase

Phase I

Study Start/End Dates

06Jun2012 – 05Sep2012

Reason for Termination

The study was terminated early following the occurrence of dose limiting toxicities (DLTs) in three of four patients who received study drug.

Study Design/Methodology

This was an open-label, multicenter, single-arm, phase I, dose escalation study with safety expansion of TAS266 administered IV. The study was designed to assess the safety (including immunogenicity), tolerability, PK profile, preliminary clinical efficacy, and MTD or RDE of weekly TAS266 in patients with relapsed/refractory solid tumors for which no effective treatment was available. Patients received TAS266 IV over 1 hour (± 10 minutes) on Days 1, 8, 15 and 22 of a 28-Day Treatment Cycle. The planned provisional treatment groups were 3, 10, 15 and 20 mg/kg, with an option to reduce the dose to 1 mg/kg or administer intermediate doses based on review and analyses of safety/tolerability, PK, and Bayesian logistics regression model (BLRM) recommendations. Due to early study termination, enrollment into treatment groups other than 3 mg/kg in the dose escalation portion of the study and enrollment in the safety expansion portion did not occur.

Centers

USA (4)

Outcome Measures

Safety: Safety assessments consisted of collecting all AEs and serious AEs (SAEs). They included the regular monitoring of vital signs, physical condition, body weight, performance status, cardiac data (ECG) and laboratory parameters for hematology, blood chemistry and urinalysis.

Pharmacokinetics: Primary PK parameters included $AUC_{0-\infty}$, AUC_{0-last}, Cmax, and Tmax. Secondary PK parameters included $t_{1/2}$, CL, V, and Cmin.

Immunogenicity: presence of anti-TAS266 antibodies

Biomarkers: Anti-apoptotic biomarkers (Safety expansion portion only). No samples were collected for Biomarkers due to early termination of study after enrollment in the dose escalation phase.

Efficacy: Tumor evaluations using RECIST v1.1

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

TAS266 3 mg/kg Solution for Infusion administered by IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle.

Statistical Methods

The data for each patient receiving study treatment with respect to demographic and baseline characteristics, efficacy and safety observations and measurements, and all relevant PK and PD measurements, was presented in either listing or table format in the CSR.

The full analysis set (all patients who received at least 1 dose of TAS266) was the primary analysis set for all patient demographic and safety analyses. The dose-determining set (DDS) was defined as all patients who received at least 1 dose of TAS266, had at least 1 valid post-baseline safety assessment, met the minimum exposure criterion, and had sufficient safety evaluations or discontinued early due to a DLT. The DDS was used in the analysis of the posterior probability of DLT rate by dose level.

The PK set was used for all PK analyses and consisted of all patients who had at least 1 blood sample providing evaluable PK data. The primary and secondary PK parameters for TAS266 were determined in serum using non-compartmental methods.

For Immunogenicity, a listing of immunogenicity evaluations by patient was generated which included date/time of sample collection, presence of anti-TAS266 antibody, optical density and whether immunogenicity was high or low.

Study Population: Inclusion/Exclusion Criteria and Demographics

Main inclusion criteria

1. Confirmed diagnosis of solid tumors.
2. 18 years or older.

3. ECOG performance status of 0, 1 or 2
4. Adequate bone marrow, hepatic and renal function
5. Obtained written informed consent

Main exclusion criteria

1. Patients with primary CNS tumor or CNS tumor involvement. However patients with CNS metastases may be allowed if certain conditions are met.
2. Major surgery within 4 weeks before study treatment
3. Prior anaphylactic or other severe infusion reactions to human immunoglobulin or antibody formulations
4. Impaired cardiac functions
5. Previous hepatitis viral infection such as hepatitis B or hepatitis C
6. Diagnosis of HIV infection
7. Pregnant or nursing (lactating) women

Participant Flow

Patient disposition

Six patients were screened for this study, of which five were enrolled into the study. Of the five enrolled patients, four patients received TAS266. The fifth patient was screened, but was discontinued from the study before receiving any study drug due to halt of study enrollment. The study was terminated early following the occurrence of dose-limiting toxicities (DLT) in three of four patients receiving study drug.

Baseline Characteristics

All four patients were of same sex and race, over 50 years of age and had a WHO performance status of either 0 or 1.The tumor types included colon signet ring cell adenocarcinoma, rectal adenocarcinoma, malignant melanoma and head and neck squamous cell carcinoma. All patients had extensive metastatic disease at study entry with all patients having at least 2 target lesions and 1 non-target lesion for evaluation. Most patients had received multiple prior anti-neoplastic regimens as well as prior surgeries and radiotherapy.

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Clinical Trial Results Website

Safety Results

Adverse Events

Subject	SAE	Adverse event (REPORTED/ Preferred/ System organ class)	Start date/ study day	Stop date/ study day	Duration (days)	Grade	Related to study drug	Action taken	DLT/ Infusion reaction
Patient A		ELEVATED ALT/ Alanine aminotransferase increased/ Investigations			8	3	Susp	2	Yes/No
Patient B		ELEVATED ALT/ Alanine aminotransferase increased/ Investigations			4	2	Susp	None	No/No
		ELEVATED AST/ Aspartate aminotransferase increased/ Investigations			4	3	Susp	1	Yes/No
	Yes	ELEVATED AST/ Aspartate aminotransferase increased/ Investigations			5	4	Susp	2	No/No
	Yes	ELEVATED ALT/ Alanine aminotransferase increased/ Investigations			2	4	Susp	2	No/No
		EDEMA LEFT LOWER EXTREMITY/ Oedema peripheral/ General disorders and administration site conditions			35	1	Susp	3	No/No
		DYSGEUSIA/ Dysgeusia/ Nervous system disorders			2	1	Susp	None	No/No
		ELEVATED CREATININE/ Blood creatinine increased/ Investigations			5	2	Susp	None	No/No
		WEIGHT GAIN/ Weight increased/ Investigations				2	Susp	None	No/No
	Yes	ELEVATED AST/ Aspartate aminotransferase increased/ Investigations			11	1	Susp	None	No/No
	Yes	ELEVATED ALT/ Alanine aminotransferase increased/ Investigations			7	3	Susp	None	No/No
	Yes	ELEVATED ALT/ Alanine aminotransferase increased/ Investigations			8	2	Susp	None	No/No
		ELEVATED CREATININE/ Blood creatinine increased/ Investigations				1	Susp	None	No/No
		DRY COUGH/ Cough/ Respiratory, thoracic and mediastinal disorders				1	Not susp	None	No/No
		RASH, MACULOPAPULAR) FACE/ Rash maculo-papular/ Skin and subcutaneous tissue disorders			16	1	Not susp	3	No/No
		FATIGUE/ Fatigue/ General disorders and administration site conditions				1	Not susp	None	No/No
		NAUSEA/ Nausea/ Gastrointestinal disorders			9	1	Susp	None	No/No
		NAUSEA/ Nausea/ Gastrointestinal disorders			8	2	Susp	3	No/No

Subject	SAE	Adverse event (REPORTED/ Preferred/ System organ class)	Start date/ study day	Stop date/ study day	Duration (days)	Grade	Related to study drug	Action taken	DLT/ Infusion reaction
Patient D (continued)		MUSCULOSKELETAL, RIGHT SIDED CHEST PAIN/ Musculoskeletal chest pain/ Musculoskeletal and connective tissue disorders			5	2	Susp	None	No/No
		DIZZINESS/ Dizziness/ Nervous system disorders			3	1	Susp	None	No/No
		ELEVATED AST/ Aspartate aminotransferase increased/ Investigations			3	3	Susp	2	Yes/No
		ELEVATED ALT/ Alanine aminotransferase increased/ Investigations			3	3	Susp	2	Yes/No
		ELEVATED ALKALINE PHOSPHATASE/ Blood alkaline phosphatase increased/ Investigations				1	Susp	None	No/No
		ELEVATED AST/ Aspartate aminotransferase increased/ Investigations				1	Susp	None	No/No
		ELEVATED ALT/ Alanine aminotransferase increased/ Investigations			2	2	Susp	None	No/No
		ELEVATED ALT/ Alanine aminotransferase increased/ Investigations				1	Susp	None	No/No

Action taken: 0=No action taken, 1=Study drug delayed/temporarily interrupted; 2=Study drug permanently discontinued due to this AE; 3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization.
Study day is relative to the first day of treatment (day 1)
Ca, Caucasian; DLT, dose-limiting toxicity; SAE, serious adverse event; Susp, suspected.

Secondary Outcome Measure

Summary of primary PK parameters of TAS266 3 mg/kg on Cycle 1 Day 1 (PK Set)

Treatment	Statistics	$AUC_{0\text{-}inf}$, (ug*hr/mL)	$AUC_{0\text{-}last}$, (ug*hr/mL)	Cmax (ug/mL)	Tmax (h)
TAS266 3 mg/kg	n	4	4	4	4
	Mean (SD)	467.64 (121.242)	463.93 (119.015)	69.63 (12.000)	
	CV% mean	25.93	25.65	17.24	
	Median	497.34	495.48	70.35	1.06
	Min, Max	300.3, 575.6	298.4, 566.4	56.1, 81.7	1.0, 1.1

CV%, coefficient of variation (CV%=standard deviation/mean*100); SD, standard deviation.

Summary of secondary PK parameters of TAS266 3 mg/kg on Cycle 1 Day 1 (PK Set)

Treatment	Statistics	$t_{1/2}$ (h)	CL (L/h)	V (L)	Cmin (ug/mL)
TAS266 3 mg/kg	n	4	4	4	4
	Mean (SD)		0.47 (0.120)	3.13 (1.081)	0.15 (0.091)
	CV% mean		25.74	34.48	61.47
	Median	14.29	0.44	2.71	0.12
	Min, Max	9.7, 22.8	0.3, 0.6	2.4, 4.7	0.1, 0.3

CV%, coefficient of variation (CV%=standard deviation/mean*100); SD, standard deviation.

Immunogenicity, TAS266 3 mg/kg (Full Analysis Set)

Immunogenicity to TAS266 was present in three of the four patients at baseline. The fourth patient did not have pre-existing immunogenicity however, at End of Treatment, the patient was positive for immunogenicity after receiving 4 doses of TAS266.

Date of Clinical Trial Report

28-May-2013