SYNOPSIS

Primary Clinical Study Report for Study CA224083

TITLE OF STUDY: A Phase 1/2a Study to Evaluate the Safety, Tolerability, and Efficacy of Relatlimab Administered in Combination with Ipilimumab or Ipilimumab Alone in Participants with Unresectable or Metastatic Melanoma Who Have Progressed on Anti-PD-1 Therapy

PURPOSE: This study was designed as a Phase 1/2a, open-label study of relatlimab plus ipilimumab in subjects with unresectable or metastatic melanoma who experienced progressive or recurrent disease on prior anti-PD-1 therapy. The study was comprised of 2 parts: a dose escalation phase (Part 1 [redacted]) and a randomized dose expansion phase (Part 2) comparing relatlimab plus ipilimumab to ipilimumab monotherapy.

On 26-May-2022, the Sponsor (Bristol-Myers Squibb) made a decision to terminate CA224083 [redacted]. This decision was not based on any safety concern. Subjects already enrolled in Part 1 (Cohort 1 and Cohort 2) continued to receive study treatment per protocol and completed the post-treatment Clinical Follow-up. Further enrollment into Part 1 was terminated. [redacted] Part 2 of the study (Phase 2a) were not initiated.

The purpose of this primary clinical study report (CSR) for Study CA224083 is to provide the safety results of Part 1 (Cohorts 1 and 2). This primary CSR is prepared in a synoptic format, due to the limited enrollment and data collected given the early termination of the study.

This CSR includes data collected from the 07-Oct-2019 first patient first visit (FPFV) through the 26-Jul-2023 last patient last visit (LPLV), with a final database lock (DBL) of 13-Sep-2023.

NUMBER OF SUBJECTS:

[redacted].

Enrolled: 19 subjects were enrolled.

Treated: 11 subjects were treated:

- Cohort 1 (relatlimab 360 mg with ipilimumab 3 mg/kg for 4 cycles, followed by relatlimab 360 mg for 30 cycles; administered as intravenous [IV] infusion every 3 weeks [Q3W]): 5 subjects.
- Cohort 2 (relatlimab 720 mg with ipilimumab 3 mg/kg for 4 cycles, followed by relatlimab 720 mg for 30 cycles; administered as IV infusion Q3W): 6 subjects.

The early termination of this study resulted in small sample sizes per treatment group.

DISPOSITION:

At the time of the DBL, all subjects were off treatment, and no subjects were continuing in the study. One subject in Cohort 2 completed the full treatment course of 34 cycles; the remaining subjects discontinued treatment, primarily due to disease progression. The coronavirus disease 2019 (COVID-19) pandemic did not have any noticeable impact on study disposition.

Table 1: End of Treatment Period Subject Status Summary - All Treated Subjects

Status (%)	Rela 360 mg + Ipi N = 5	Rela 720 mg + Ipi N = 6	Total N = 11
COMPLETED TREATMENT	0	1 (16.7)	1 (9.1)
DISCONTINUED TREATMENT	5 (100.0)	5 (83.3)	10 (90.9)
REASON FOR DISCONTINUATION OF TREATMENT			
ADVERSE EVENT	2 (40.0)	0	2 (18.2)
DISEASE PROGRESSION	3 (60.0)	3 (50.0)	6 (54.5)
STUDY DRUG TOXICITY	0	2 (33.3)	2 (18.2)
DISCONTINUED STUDY	5 (100.0)	6 (100.0)	11 (100.0)
REASON FOR DISCONTINUATION OF STUDY			
DEATH	1 (20.0)	2 (33.3)	3 (27.3)
LOST TO FOLLOW-UP	1 (20.0)	0	1 (9.1)
SUBJECT WITHDREW CONSENT	1 (20.0)	1 (16.7)	2 (18.2)
OTHER	0	1 (16.7)	1 (9.1)
FOLLOW-UP NO LONGER REQUIRED PER PROTOCOL	2 (40.0)	2 (33.3)	4 (36.4)
DISCONTINUED TREATMENT DUE TO COVID-19	0	0	0
DISCONTINUED STUDY DUE TO COVID-19	0	0	0

Cohort 1: Rela 360 mg + Ipi; Cohort 2: Rela 720 mg + Ipi

Percentages were based on subjects entering period.

Subjects displayed as discontinued due to Covid-19 were a subset of the overall subjects those discontinued.

Abbreviations: Rela = Relatlimab, Ipi = Ipilimumab

DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Baseline disease characteristics were in keeping with a population of subjects with Stage III or Stage IV melanoma who have progressed on anti- programmed cell death protein 1 (PD-1) therapy (Table 3). A majority of subjects had tumors with primary resistance to prior anti-PD-1 therapy.

Table 2: Demographic Characteristics Summary - All Treated Subjects

	Rela 360 mg + Ipi N = 5	Rela 720 mg + Ipi N = 6	Total N = 11
AGE (YEARS)			
N	5	6	11
MEAN	65.2	62.0	63.5
MEDIAN	67.0	59.5	64.0
MIN , MAX	[redacted]	[redacted]	[redacted]
SD	6.6	11.2	9.1
SEX (%)			
MALE	3 (60.0)	3 (50.0)	6 (54.5)
FEMALE	2 (40.0)	3 (50.0)	5 (45.5)
RACE (%)			
[redacted]			11 (100.0)
ETHNICITY (%)			
[redacted]			
COUNTRY BY GEOGRAPHIC REGION (%)			
[redacted]			11 (100.0)
			11 (100.0)

Cohort 1: Rela 360 mg + Ipi; Cohort 2: Rela 720 mg + Ipi

Abbreviations: min = minimum, max = maximum, [redacted]

Table 3: Baseline Disease Characteristics Summary - All Treated Subjects

	Number of Subjects (%)		
	Rela 360 mg + Ipi N = 5	Rela 720 mg + Ipi N = 6	Total N = 11
INITIAL DISEASE STAGE			
STAGE I	0	1 (16.7)	1 (9.1)
STAGE II	1 (20.0)	0	1 (9.1)
STAGE III	3 (60.0)	4 (66.7)	7 (63.6)
STAGE IV	0	1 (16.7)	1 (9.1)
UNKNOWN OR NOT REPORTED	1 (20.0)	0	1 (9.1)
AJCC (8TH EDITION) STAGE AT STUDY ENTRY			
UNRESECTABLE STAGE III	0	1 (16.7)	1 (9.1)
METASTATIC STAGE IV	5 (100.0)	5 (83.3)	10 (90.9)
BASELINE AJCC (8TH EDITION) M STAGE			
M0/M1A	2 (40.0)	2 (33.3)	4 (36.4)
M1B/M1C/M1D	3 (60.0)	3 (50.0)	6 (54.5)
NOT REPORTED	0	1 (16.7)	1 (9.1)
BASELINE TYPE OF RESISTANCE TO PRIOR ANTI-PD-1 THERAPY			
PRIMARY RESISTANCE	3 (60.0)	3 (50.0)	6 (54.5)
ACQUIRED RESISTANCE	2 (40.0)	1 (16.7)	3 (27.3)
NOT APPLICABLE	0	2 (33.3)	2 (18.2)
BASELINE LAG-3 EXPRESSION			
>=1%	4 (80.0)	5 (83.3)	9 (81.8)
<1%	1 (20.0)	1 (16.7)	2 (18.2)

Cohort 1: Rela 360 mg + Ipi; Cohort 2: Rela 720 mg + Ipi

Primary Resistance: no clinical benefit while receiving anti-PD-(L)1 therapy, with PD as best overall response. Assumes participant did not discontinue treatment very early (≤ 8 weeks) due to intolerance. Acquired Resistance: clear clinical benefit (CR/PR/SD) from anti-PD-(L)1 with supportive documented evidence (per RECIST 1.1 criteria).

Abbreviations: AJCC = American Joint Commission on Cancer, CR = complete response, LAG-3 = lymphocyte-activation gene 3, PD = progressive disease, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease

SUMMARY OF SAFETY RESULTS:

The safety profile of relatlimab (at 360 mg or 720 mg) administered IV Q3W with ipilimumab 3 mg/kg (4 cycles) followed by relatlimab monotherapy (30 cycles) in subjects with unresectable or metastatic melanoma who progressed on anti-PD-1 therapy was consistent with the known mechanisms of action of relatlimab and ipilimumab. There were no new safety signals identified, and there has been no change in the understanding of the safety profile of relatlimab or ipilimumab based on the results of this study.

The frequency of dose limiting toxicities (DLTs) was higher in Cohort 2 than Cohort 1. The frequencies of all causality and drug-related adverse events (AEs), AEs leading to discontinuation, and serious AEs (SAEs) were similar for any grade and high grade (Grade 3/4) events. The most commonly reported all causality AEs and drug-related AEs (> 50%) were diarrhea, nausea (in Cohort 1), and pruritus (in Cohort 2). No deaths due to study drug toxicity and no Grade 5 AEs were reported.

Due to the small sample size, the results should be interpreted with caution.

Table 4: Overall Safety Summary - All Treated Subjects

Safety Parameters	Cohort 1: Rela 360 mg + Ipi N=5			Cohort 2: Rela 720 mg + Ipi N=6		
Deaths (%)	2 (40.0)			3 (50.0)		
Primary Reason for Death						
Disease	1 (20.0)			3 (50.0)		
Study Drug Toxicity	0			0		
Unknown	1 (20.0)			0		
Other	0			0		
Subjects Who Died Within 30 Days of Last Dose	0			0		
	Any Grade	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**
SAEs, n (%)	2 (40.0)	2 (40.0)	0	3 (50.0)	3 (50.0)	0
Drug-related SAEs, n (%)	1 (20.0)	1 (20.0)	0	2 (33.3)	1 (16.7)	0
AEs leading to DC, n (%)	1 (20.0)	1 (20.0)	0	2 (33.3)	1 (16.7)	0
Drug-related AEs leading to DC, n (%)	1 (20.0)	1 (20.0)	0	2 (33.3)	1 (16.7)	0
All causality AEs, n (%)	5 (100.0)	3 (60.0)	0	6 (100.0)	3 (50.0)	0
Drug-related AEs, n (%)	5 (100.0)	2 (40.0)	0	6 (100.0)	1 (16.7)	0

MedDRA Version: 26.0

CTCAE Version: 5.0

Included events reported between first dose and 30 days after last dose of study therapy.

Abbreviations: DC = discontinuation

Table 5: DLT Summary - All Treated Subjects

Treatment Group	Number of Treated	Number of DLT Evaluable	[redacted]	Number of Subjects that Experienced DLT within DLT Period [2]	DLT Rate within DLT Period (%) [2]
RELA 360 MG + IPI	5	4		0	0
RELA 720 MG + IPI	6	6		1	16.7
TOTAL	11	10		1	10.0

[redacted]

[2] DLT Period was 28 days.

DATE OF REPORT: 05-Dec-2023