A Multicenter, Open-label, Phase I Clinical Study: Safety, Efficacy, and Pharmacokinetics of Oral Rigosertib in Japanese Patients with Recurrent/Relapsed or Refractory Myelodysplastic Syndromes (MDS):

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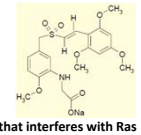
Introduction

Rigosertib sodium



Molecular formula : $C_{21}H_{24}NO_8SNa$

Molecular weight : 473.47

Structural formula :

- Rigosertib is a novel molecular entity that interferes with Ras binding domain containing proteins. Rigosertib induces G2/M arrest leading to the apoptosis of cancer cells and myeloblasts while causing minimal damage to normal cells.[1]
- Rigosertib interferes with the RAS-binding domains of RAF kinases and inhibits the RAS-RAF-MEK and PI3Ks pathways.[2]
- A Phase I study in the U.S. showed the safety and good tolerability of oral rigosertib in patients with low, intermediate-1, intermediate-2, or high risk myelodysplastic syndromes (MDS).[3]

Objectives

- Examine tolerability, investigate DLT and determine recommended dose (RD) for Phase II
- Explore pharmacokinetics and antitumor effect when rigosertib was orally administered to Japanese patients with recurrent/relapsed or refractory MDS

[Primary endpoint]

Number of patients experienced with dose-limiting toxicity (DLT) in the 1st cycle

[Secondary endpoints]

(1) Safety: Adverse events and changes in laboratory test values

(2) Efficacy:

1) Hematologic remission rate of the overall response per IWG 2006 [4]
2) Hematologic improvement rate of the overall response per IWG 2006
3) Cytogenetic response rate per IWG2006
(3) Pharmacokinetics: Pharmacokinetic parameters

Key Inclusion Criteria

1. Diagnosed with MDS and classified as one of followings (WHO[5] or FAB[6]): RA, RARS, RAEB-1, RAEB-2, RAEB-t or CMML
2. Reduction in at least one hemocyte parameter of the followings:
   - Neutrophil count: <1,800/mm3
   - Platelet count: <100,000/mm3
   - Hemoglobin level: <10 g/dL
3. Pts with previous MDS treatment who meet one of the followings:
   1) Failed to achieve complete remission, partial remission, or hematologic improvement
   2) Recurrence/relapse after achievement of complete remission, partial remission, or hematologic improvement
   3) Intolerance and discontinuation due to liver or renal disorder
4. Age: ≥20 years
5. ECOG PS: 0 to 2
6. Adequate major organ functions:
   - AST/ALT: ≤3.0-fold ULNR
   - Total bilirubin/: ≤1.5-fold ULNR
   - Serum creatinine: ≤1.5-fold ULNR

Treatment Scheme

1 cycle = 21 days

<Treatment> Twice-daily oral administration (Day 1 ~ Day 14)

<Observation> (Day 15 ~ Day 21)

Up to 6 cycles were allowed

- 280 or 560 mg/dose of oral rigosertib administered twice daily for 14 days every 21 days
- Dose-escalation performed by use of a modified 3+3 design

Definition and Assessment of DLTs

- Defined as adverse events developed within Cycle 1 as outlined below, of which causal relationship with the investigational drug could not be ruled out

1) Grade 3 or higher non-hematologic toxicities. However, nausea, vomiting, diarrhoea, pyrexia, stomatitis and esophagitis/dysphagia are excluded (Grade 3 nausea, vomiting, diarrhoea, and pyrexia that cannot be controlled with antiemetic, antidiarrheal, or antifebrile agents are regarded as DLTs)

2) Grade 3 or higher stomatitis, esophagitis, and dysphagia that persist for ≥4 days

- Assessed by the Data and Safety Monitoring Committee

Pharmacokinetics

- Blood samples were collected only during Cycle 1 as follows

Day	1 or 14									2 or 15
Hour[1)]	0	0.5	1	1.5	2	4	6	8	10	24[2)]
blood sampling	○	○	○	○	○	○	○	○	○	○

Day	8[3)]
Hour	0
blood sampling	○

1) Indicating the elapsed time from 1st dosing on Days 1 and 14 (time 0)
2) Just before the 1st dosing on Days 2 and 15
3) Just before the 1st dosing on Day 8

- Plasma rigoseritb concentrations were determined using a validated LC/MS/MS method (LLOQ=0.01 ng/mL)
- PK parameters were calculated from rigosertib concentration-time data using a non-compartmental model (WinNonlin Compiled Models: Model 200)

Analysis Sets

Patients who provided consent: 13 pts

- Patients enrolled: 10 pts
- Patients not enrolled: 3 pts

Safety analysis set (pts who received study drug): SAS: 9 pts (280 mg BID: 3/560 mg BID: 6)

Patients not administered: 1 pt (aggravation of the PS)

Full analysis set: FAS: 9 pts (280 mg BID: 3/560 mg BID: 6)

Patients excluded from FAS: 0 pt

Per-protocol set: PPS: 6 pts (280 mg BID: 2 / 560 mg BID: 4)

Patients excluded from PPS: 3 pts
- Antitumor effect not assessed (280 mg BID: 1/560 mg BID: 1)
- Received the investigational drug improperly (560 mg BID: 1)

Patient Demographics and Disease Characteristics (1)

Characteristics			Total (n=9)	280 mg BID (n=3)	560 mg BID (n=6)
Age	Median (range)		70 (52-80)	63 (63-76)	71.5 (52-80)
Sex	M/F		6/3	1/2	5/1
PS	0		7	2	5
	1		2	1	1
WHO[5]	RA		1	0	1
	RARS		2	0	2
	RCMD		1	1	0
	RAEB-1		3	1	2
	RAEB-2		2	1	1
FAB[6]	RA		2	1	1
	RARS		2	0	2
	RAEB		4	2	2
	RAEB-t		1	0	1
IPSS[7]	Int-1		4	1	3
	Int-2		5	2	3
	High		0	0	0
Transfusion (8 wks before treatment)	RCC	Yes	8	3	5
		No	1	0	1
	PC	Yes	1	0	1
		No	8	3	5
Prior chemotherapy	Yes		9	3	6

Patient Demographics and Disease Characteristics (2)

Dose group (mg)	Pt#	Age	FAB	Karyotype	IPSS[7]
280 (BID)	C01	63	RAEB	46,XX,del(20)(q17) [20]	Intermediate-2
	C02	76	RAEB	48,XY,+8,+19 [20]	Intermediate-2
	C03	63	RA	46,XX [20]	Intermediate-1
560 (BID)	C04	52	RAEB-t	46,XY,+1,der(1;7)(q10;p10) [19] 46,XY [1]	Intermediate-2
	C05	70	RAEB	45〜46,XY,-5,-6,del(7)(q22),add(10)(q26), -12,-19,-20,+4〜+5mar [18] 46,XY [2]	Intermediate-2
	C06*	80	RAEB	46,XY [20]	Intermediate-1
	C07	67	RARS	46,XY,t(6;10)(p11;p15),?12qh+ [1] 46,XY,?12qh+ [19]	Intermediate-1
	C08	80	RARS	46,XY,t(10;17)(q11;q11) [20]	Intermediate-1
	C09	73	RAEB	46,XX,t(1;3)(p36.3;q21) [3]	Intermediate-2
	C10	74	RA	46,XY [20]	Intermediate-1

*: Investigational drug was not administered due to aggravation of the PS during screening period

Observed DLTs by Dose Group

Dose group (mg)	Patient #	Administration (cycles)	DLT (Grade)
280 (BID)	C01	20**	-
	C02	6	-
	C03	1	Diabetes (3), Delirium nocturnum (4)
560 (BID)	C04	2	-
	C05	1	-
	C06*	-	-
	C07	1	Urinary tract infection (5)
	C08	1	QTc prolongation (3)
	C09	3	-
	C10	4	-

*: Investigational drug was not administered due to aggravation of the PS during the screening period
**: Enrolled in the extension study and administered until Cycle 20

Adverse Events Developed in ≧2 pts (n=9)

Event	280 mg BID No. of pts (%)	560 mg BID No. of pts (%)	Total (%)
No. of pts	3	6	9
Anaemia	0	2 (33.3%)	2 (22.2%)
Vomiting	1 (33.3%)	1 (16.7%)	2 (22.2%)
Nasopharyngitis	0	2 (33.3%)	2 (22.2%)
Alanine aminotransferase increased	1 (33.3%)	1 (16.7%)	2 (22.2%)
Aspartate aminotransferase increased	1 (33.3%)	1 (16.7%)	2 (22.2%)
Lymphocyte count decreased	1 (33.3%)	1 (16.7%)	2 (22.2%)
Neutrophil count decreased	1 (33.3%)	1 (16.7%)	2 (22.2%)

Grade 3 or Higher Adverse Events (n=9)

Event	280 mg Grade (No. of pts) 3	4	5	560 mg Grade (No. of pts) 3	4	5	Total (%)
No. of pts	3			6			9
Anaemia	0	0	0	2	0	0	2 (22.2%)
Cholecystitis	0	0	0	1	0	0	1 (11.1%)
Periodontitis	0	0	0	1	0	0	1 (11.1%)
Pneumonia	0	0	0	1	0	0	1 (11.1%)
Urinary tract infection	0	0	0	0	0	1*	1 (11.1%)
Soft tissue infection	0	0	0	1	0	0	1 (11.1%)
Alanine aminotransferase increased	0	0	0	1	0	0	1 (11.1%)
Aspartate aminotransferase increased	0	0	0	1	0	0	1 (11.1%)
Electrocardiogram QT prolonged	0	0	0	1	0	0	1 (11.1%)
Haemoglobin decreased	0	0	0	1	0	0	1 (11.1%)
Neutrophil count decreased	1	0	0	1	0	0	2 (22.2%)
Type 2 diabetes mellitus	1	0	0	0	0	0	1 (11.1%)
Delirium	0	1	0	0	0	0	1 (11.1%)

Hematologic Remission Effect (IWG 2006 Criteria)

Dose Group (mg/dose)	#of pts	Hematologic Remission Effect n (%) CR[a)]	PR[b)]	mCR[c)]	SD[d)]	Failure	Disease progression	NA[e)]	HR rate Rate[1)]	95%CI[2)]
Total (n=9)	9	0	0	1 (11.1%)	2 (22.2%)	0	3 (33.3%)	3 (33.3%)	1 (11.1%)	0.3-48.2
280 (n=3)	3	0	0	1 (33.3%)	1 (33.3%)	0	0	1 (33.3%)	1 (33.3%)	0.8-90.6
560 (n=6)	6	0	0	0	1 (16.7%)	0	3 (50.0%)	2 (33.3%)	0	0.0-45.9

1) CR, PR or mCR, 2) Exact 95% confidential interval based on binomial probability

a) Complete remission, b) Partial remission, c) Marrow complete remission, d) Stable disease, e) Not assessable

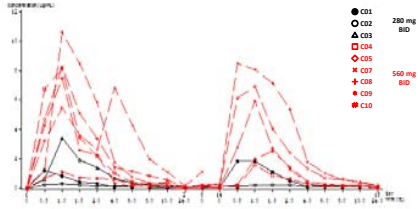
Hematologic Improvement Effect (IWG2006 Criteria)

Dose Group (mg/dose)	# of Pts	Hematologic Improvement Effect n (%) # of pts with HI effect HI-E[a)]	HI-P[b)]	HI-N[c)]	PD[d)]	Relapse	NA[e)]	HI rate Rate[1)]	95%CI[2)]
Total (n=9)	9	1 (11.1%)	0	1 (11.1%)	1 (11.1%)	0	7 (77.8%)	1 (11.1%)	0.3-48.2
280 (n=3)	3	1 (33.3%)	0	1 (33.3%)	0	0	2 (66.7%)	1 (33.3%)	0.8-90.6
560 (n=6)	6	0	0	0	1 (16.7%)	0	5 (83.3%)	0	0.0-45.9

1) HI-E, HI-P or HI-N, 2) Exact 95% confidential interval based on binomial probability

a) Hematologic Improvement Erythrocyte, b) Hematologic Improvement Platelet, c) Hematologic Improvement Neutrophile, d) Progressive disease, e) Not assessable

Plasma Rigosertib Concentration Following Oral Administration



Day 1, Day 2: Time elapsed in hour after starting administration on Day 1 (0 hr)
Day 8: 0 hr indicates just before administration on Day 8
Day 14: Time elapsed in hour after starting administration on Day 14 (0 hr)

Pharmacokinetic Parameters

Dose Group	Day		C_{max} (μg/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (μg·hr/mL)	CL/F (L/hr/m²)	Vz/F (L/m²)
280 mg BID	1 (n=3)	Mean	1.62	0.8	7.2	4.4	64.7	672.0
		S.D.	1.60	0.3	0.2	3.9	41.8	445.3
	14 (n=2)	Mean	1.02	1.0	13.5	4.5	45.0	859.7
		S.D.	—	—	—	—	—	—
560 mg BID	1 (n=6)	Mean	7.06	1.5	5.5	21.1	24.4	205.3
		S.D.	3.19	1.2	0.7	13.5	19.7	179.1
	14 (n=5)	Mean	5.08	1.0	9.9	15.4	31.6	461.5
		S.D.	2.93	0.4	2.0	11.2	18.3	293.7

—: Not Calculated

Summary

- DLTs were observed in 1/3 pts in the 280 mg BID group (type 2 diabetes mellitus and delirium) and in 2/6 pts in the 560 mg BID group (urinary tract infection and prolonged QT interval)
- A total of 57 events of adverse events developed in the 9 pts: The adverse events that developed in ≥2 pts included anaemia, vomiting, nasopharyngitis, alanine aminotransferase increased, aspartate aminotransferase increased, lymphocyte count decreased, and neutrophil count decreased
- One pt in the 560 mg BID group died of septic shock that had been caused by urinary tract infection during the study period
- The hematological remission rate was 11.1% (1 marrow CR: 1/9 pts) and the hematological improvement rate was 11.1% (1 HI-P: 1/9 pts)
- No cytogenetic response was seen
- Plasma concentrations of rigosertib increased rapidly after oral administration and there was no sign of accumulation of rigosertib after repeated administration

Conclusion

The present regimen of oral rigosertib was well tolerated.

Our study indicates that the recommended dose for a Phase II clinical study is 560 mg BID in Japanese patients with recurrent/relapsed or refractory MDS.

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- Kurashiki Central Hospital
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- NHO* Kyushu Cancer Center
- NHO* Nagoya Medical Center

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