R289, a Dual IRAK 1/4 Inhibitor, in Patients with Relapsed/Refractory (R/R) Lower-Risk Myelodysplastic Syndrome (LR-MDS): Initial Results from a Phase 1b Study

G GARCIA-MANERO[1], YF MADANAT[2], MA SEKERES[3], H CARRAWAY[4], M CUSNIR[5], J McCLOSKEY[6], K NAQVI[7], G SCHILLER[8], L YAN[9], T GORDI[9], L ROJKJAER[9], LR SILVERMAN[10]

1. Department of Leukemia, MD Anderson Cancer Center, University of Texas, Houston, TX; 2. Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX; 3. Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; 4. The Cleveland Clinic, Cleveland, OH; 5. Mount Sinai Comprehensive Cancer Center (MSCCC), Miami Beach, FL; 6. Hackensack University Medical Center, John Theurer Cancer Center, Hackensack, NJ; 7. Division of Hematology/Oncology, Department of Medicine, Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA; 8. David Geffen School of Medicine at UCLA, Los Angeles, CA; 9. Rigel Pharmaceuticals Inc. South San Francisco, CA; 10. Icahn School of Medicine at Mount Sinai, New York, NY

INTRODUCTION

- Interleukin receptor-associated kinases (IRAK) 1 and 4 are critical for downstream signaling of IL-1R family and most toll-like receptors (TLR) (Fig. 1), promoting proinflammatory cytokine production, bone marrow inflammation and cell death[1].
- Co-targeting both IRAK 1/4 may be necessary to maximally suppress inflammation and leukemic stem/progenitor cell function and restore hematopoiesis in MDS.
- R835 is a selective dual inhibitor of IRAK 1/4 that blocks TLR4 and IL-1R-dependent cytokine release in vitro and in vivo[2], and substantially suppressed LPS-induced cytokine release compared to placebo in healthy volunteers (HV)[3].

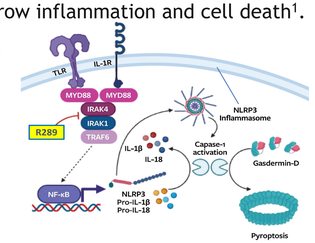


Fig. 1: TLR/IL-1R Signaling Pathway

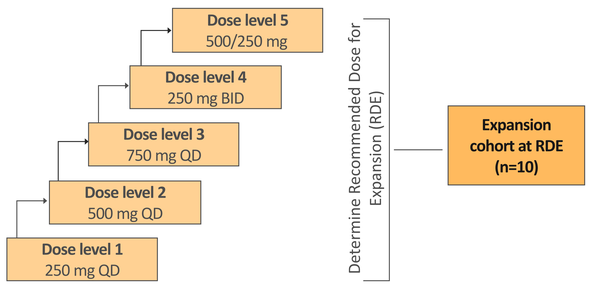
- We present the initial dose escalation results from a phase 1b, open-label, single arm study evaluating the safety and preliminary activity of the oral IRAK 1/4 inhibitor R289, a prodrug of R835, in LR-MDS patients (Fig. 2) (NCT05308264).

METHODS

Key Eligibility Criteria

- ≥18 years old, LR-MDS (IPSS-R ≤3.5, <5% marrow blasts); ECOG 0-2
- R/R or inadequate response to prior therapies. Del(5q): R/R to lenalidomide.
- Hemoglobin (Hgb) ≤9.0 g/dL and symptomatic anemia or transfusion dependent (TD: ≥2u RBCs/16wks)

Figure 2: Phase 1b Study Design (modified 3+3 design used in dose escalation)



Assessments:

- Bone marrow biopsies were performed at baseline, every 8 weeks until transfusion independence was achieved, then every 3-6 months as indicated.
- Hematologic responses [transfusion independence (TI) and HI-E] per IWG 2018 criteria[4] and other responses per IWG 2006 criteria[5], from 8 weeks.

Primary objective:

- Assess safety and tolerability of R289

Secondary objectives:

- Assess preliminary efficacy of R289
- Characterize PK

RESULTS

- Data on 22 patients (data cutoff: 25 Oct 24) are reported
- Median duration of treatment: 4.6 months (range: 0.9-22.4 months)

Table 1: Baseline (BL) Characteristics

	All patients (n=22)
Median age, years (range) ≥ 75 years	76 (50-84) 13 (59%)
Sex (M:F)	14 : 8
IPSS-R classification	
Low Intermediate	14 (64%) 8 (36%)
Median no. prior therapies	3 (1 - 8)
Prior hypomethylating agent (HMA)	16 (73%)
Prior luspatercept	17 (77%)
High transfusion burden (HTB) (≥ 8u RBCs/prior 16 wks)	16 (73%)
Low transfusion burden (LTB) (3-7u RBCs/prior 16 wks)	4 (18%)
Non-transfused (NT)	2 (9%)
Mean baseline ANC (range)	2.2 x 10^9/L (0.3-5.4 x 10^9/L)
Mean baseline platelet count (range)	168 x 10^9/L (31.5-509.5 x 10^9/L)

Safety

- R289 was generally well-tolerated; the most common AEs (≥20%) were diarrhea and fatigue (each 6,27%), chills, nausea and pruritis (all 5,23%); all G1/2. The most frequent G3/4 AEs were anemia, platelet count decreased, pneumonia and ALT increased (all n=2,9%). Treatment-related AEs are shown in Table 2.
- Serious AEs (SAEs) occurred in 8 patients (36%); SAEs in ≥2 patients were pneumonia and upper GI bleed (n=2 each; all unrelated).

Table 2: Treatment-related AEs occurring in ≥2 patients by dose level

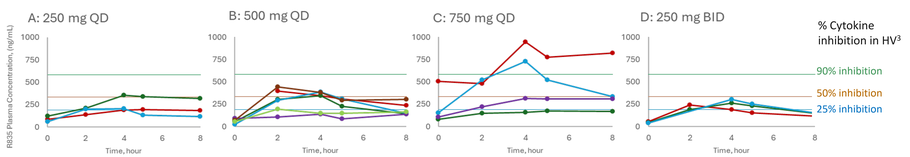
Preferred term	250 mg QD (n=3)		500 mg QD (n=6)		750 mg QD (n=6)		250 mg BID (n=6)		500/250 mg QD (n=1)		Total (n=22)	
	All	G3/4	All	G3/4	All	G3/4	All	G3/4	All	G3/4	All	G3/4
Diarrhea	0	0	1 (17%)	0	2 (33%)	0	0	0	0	0	3 (14%)	0
Dyspnoea	0	0	1 (17%)	0	2 (33%)	0	0	0	0	0	3 (14%)	0
Nausea	0	0	0	0	3 (50%)	0	0	0	0	0	3 (14%)	0
Neut. count decreased	0	0	0	0	2 (33%)	1 (17%)	0	0	1	0	3 (14%)	1 (4%)
ALT incr.*	0	0	0	0	2 (33%)	2 (33%)	0	0	0	0	2 (9%)	2 (9%)
AST incr.*	1 (33%)	0	0	0	2 (33%)	1(17%)	0	0	0	0	2 (9%)	1 (4%)
Constipation	0	0	0	0	2 (33%)	0	0	0	0	0	2 (9%)	0

**Dose limiting toxicity: G3/4 ALT/AST increase in 1 patient at 750 mg QD; incr = increased ; neut = neutrophil*

Pharmacokinetics

- R835 exposure increased with increasing R289 dose. At doses ≥500 mg QD, R835 steady state plasma concentrations reached or exceeded concentrations correlating with 50% or 90% LPS-induced cytokine inhibition (horizontal lines) previously observed in HV. (Fig. 3)

Figure 3: Plasma Concentration of R835 (administered as R289) by Dose Level



Efficacy

- 18 pts were evaluable for efficacy (≥1 dose of R289 with ≥1 efficacy assessment)
- 3 pts achieved RBC-TI ≥8 wks: 1 at 500 mg QD and 2 at 750 mg QD (Fig. 4). 2 pts achieved RBC-TI ≥ 24 wks (Table 3).The median duration of RBC-TI was 29 wks (range 12.7-51.9 wks)
- 1 HTB pt at 500 mg QD had a minor HI-E response (64% reduction in RBCs compared to BL)

Figure 4: RBC Transfusion Frequency by Dose Level

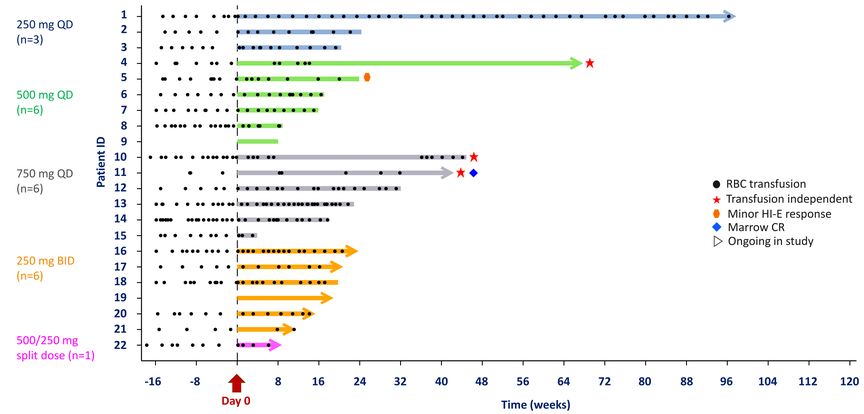


Table 3: Summary of Responders

Pt ID	Sex, age	Dose level	BL RBCs	Prior therapies	HI-E response	Response duration
4	76, M	500 mg QD	HTB	ESA, canakinumab, ALK2 inhibitor, decitabine	TI	51.9 w
5	75, M	500 mg QD	HTB	ESA, azacitidine, luspatercept, fostamatinib, anti-TIM-3 ab	Minor (64% RBC ↓)	16.9 w
10	59, M	750 mg QD	HTB	azacitidine, lenalidomide, luspatercept	TI	28.9 w
11	50, F	750 mg QD	LTB	darbopoetin, luspatercept	TI (+ marrow CR)	12.7 w

CONCLUSIONS

- R289 was well-tolerated in this heavily pretreated LR-MDS patient population, the majority of whom were HTB. The incidence of G3/4 cytopenias and infections was low.
- At doses ≥500 mg QD, R835 plasma concentrations at steady state in some pts were ≥ those correlating with 50% or 90% LPS-induced cytokine inhibition previously observed in HV[3].
- RBC-TI/HI-E responses occurred in 4/10 (40%) of evaluable TD patients receiving R289 doses ≥500 mg QD, with durable responses (>24 weeks) occurring in 2 HTB pts thus far. Both had received a prior HMA (Table 3).
- The expansion part of the study is planned to confirm a recommended phase 2 dose.

REFERENCES

1. Sallman DA, et al. Front Oncol. 2016;6
2. Lamagna C et al. Ann Rheum Dis 2020;79 (suppl 1)
3. Yan L et al. Ann Rheum Dis 2020;79 (suppl 1)
4. Platzbecker U et al. Blood 2019;133(10)
5. Cheson BD et al. Blood 2006;108

ACKNOWLEDGMENTS

We would like to thank the study site staff, the patients and their families.

CONTACT INFORMATION

Dr. Guillermo Garcia-Manero
(ggarciam@mdanderson.org)