Abstract 165681

INSPIRE: A Randomized Phase III Trial of Intravenous Rigosertib in Patients with Higher-risk Myelodysplastic Syndromes (HR-MDS) after Failure of Hypomethylating Agents (HMAs) – Study Design Informed by Subgroup Analyses of ONTIME

Guillermo Garcia-Manero, MD; Aref Al-Kali, MD; Maria R. Baer, MD; Gail Roboz, MD; Uwe Platzbecker, MD; Abdulraheem Yacoub, MD; Lucy Godley, MD; Robert Collins, Jr, MD; Jamile Shammo, MD; Valeria Santini, MD; Azra Raza, MD; Lewis R. Silverman, MD; Nozar Azarnia, PhD; Steven Fruchtman, MD; Barbara Snyder, MA; Pierre Fenaux, MD

Background

Encouraging effects of rigosertib on overall survival (OS) seen in subgroups of patients in ONTIME[1] informed the design of a new pivotal trial (Study 04-30; INSPIRE). This Phase III, randomized study has been initiated in pts with HR-MDS failing HMA treatment, testing the hypothesis that a more homogenous HR-MDS patient population (based on prognostic factors defined in ONTIME) will benefit from rigosertib.

Methods

Major inclusion criteria: < 80 years of age; MDS classified as RAEB-1, RAEB-2 or RAEB-t; ≥1 cytopenia; failure of prior HMA; duration of prior HMA of ≤ 9 months; last dose of HMA ≤6 months before screening; ECOG status 0-2

Stratification

Randomization is stratified by the revised International Prognostic Scoring System[2] (IPSS-R) very high risk (VHR) vs non-VHR, and by geographic region.

Dosing

Rigosertib is administered as an 1800 mg/24 hr infusion for 72 hr every 2 weeks for 16 weeks, then every 4 weeks (N~150) vs physician's choice of treatment (N~75).

Endpoints

Primary: OS in the ITT population and in the IPSS-R VHR subgroup.
Secondary: OS in pts with monosomy 7 and/or trisomy 8 chromosomal aberrations, overall response and bone marrow blast response per IWG 2006, quality-of-life per EuroQol EQ-5D, hematologic improvement, and rigosertib population pharmacokinetics. Genomic studies will be performed at baseline and monitored in both arms.

Enrollment

Opened in December 2015 and is ongoing.

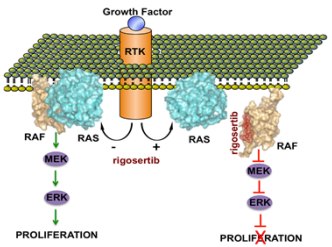
Current Locations

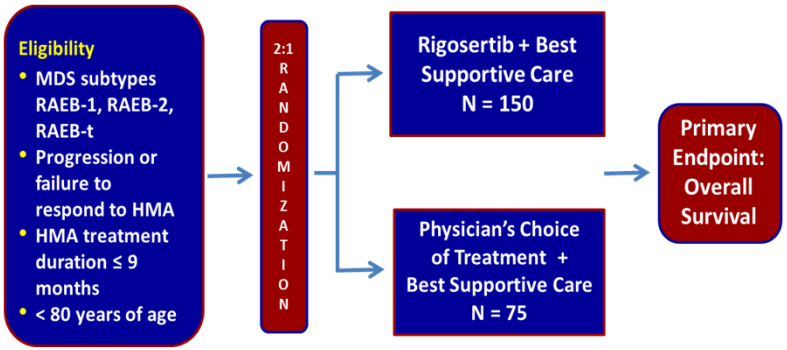
North America, Europe, Japan, Australia, Israel

Clinical trial registry number

NCT02562443.

Rigosertib Mechanism of Action[3]





Overall Survival Results in ONTIME Subgroups that Influenced the Study Design for INSPIRE

	Rigosertib		Best supportive care			
	N	Median (months)	N	Median (months)	Log-rank p-value	Hazard ratio (Rigosertib / BSC) (95% CI)
Duration of last HMA (months)						
≤ 9	103	7.7	46	4.5	0.0025	0.55 (0.37, 0.81)
>9	96	9.2	52	8.1	0.42	1.18 (0.79, 1.74)
Age (years)						
< 80	155	8.6	86	5.4	0.068	0.76 (0.57, 1.02)
≥ 80	44	4.5	14	6.8	0.21	1.57 (0.77, 3.20)
Months since last dose of HMA						
≤ 6	173	7.9	91	5.4	0.24	0.84 (0.63, 1.12)
> 6	26	9.8	8	11.9	0.99	1.00 (0.41, 2.44)
IPSS-R risk level						
Intermediate/	15	9.7	14	12.6	0.21	1.71 (0.56, 5.24)
Low	67	9.7	26	9.7	0.93	0.98 (0.49, 1.95)
High	93	7.6	41	3.2	0.015	0.61 (0.36, 1.03)
Very high						

References

[1] Garcia-Manero G, Fenaux P, Al-Kali A, et al for the ONTIME study investigators. Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial. Lancet Oncol; published online 8 Mar 2016.
[2] Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood 2012;120:2454-65.
[3] Athuluri-Divakar SK, Vasquez-Del Carpio R Dutta K, et al. A small molecule RAS-mimetic disrupts RAS association with effector proteins to block signaling. Cell. 2016;165(3):643-55.

Contact: ggarciam@mdanderson.org