Genomic Profiling in Patients with Higher Risk Myelodysplastic Syndrome (HR MDS) Following HMA Failure: Baseline Results from the INSPIRE Study (04-30)

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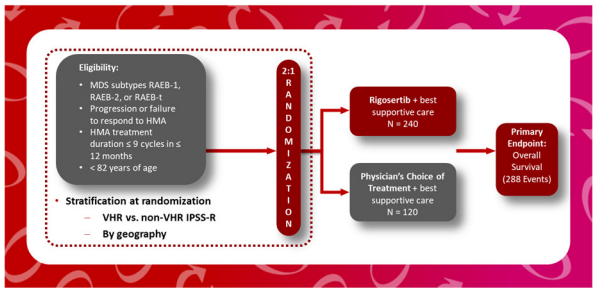
Submitted Abstract

Background:
More than 45 mutations have been identified in association with HR MDS. In the majority of patients with MDS (80%) co-mutations are present and the prognostic contribution of each individual mutation remains elusive, especially after adjusting for clinical variables such as IPSS-R score. *N-RAS* and *K-RAS* mutations as well as regulators of the Ras pathway (e. g. PTPN11, NF1) are frequently observed (15-20%) in HR MDS, however their clinical impact is unclear, especially in *de novo* MDS. Rigosertib (RGS) is a non-ATP-competitive small molecule RAS-mimetic that has the potential to block RAS-RAF-MEK-ERK and PI3K-AKT-mTOR signaling pathways (Athuluri-Divakar 2016). Rigosertib has the potential to also inhibit wildtype upregulation of RAS. We report here genomic profiling at the time of study entry in the ongoing phase 3 randomized global study (known as INSPIRE) in patients with HR MDS after failure of HMA therapy.
Methods:
INSPIRE (NCT02562443) is a global randomized Ph3 trial in pts with HR-MDS after HMA failure with an overall target enrollment of 360 pts with currently 298 pts randomized. Pts are randomized 2:1 to rigosertib or physician's choice of treatment. The primary endpoint is overall survival (OS). All pts failed to respond or progressed on HMA therapy. Key inclusion criteria includes: age < 82 years, RAEB-1, RAEB-2 or RAEB-t; intermediate risk (IR), high risk (HR) and very high risk (VHR) per IPSS-R; ≥ 1 cytopenia; duration of prior HMA ≤ 9 cycles within 12 months; last dose of HMA ≤ 6 months before enrollment; baseline blast counts between 5-29% and one of the following: progression any time after initiation of HMA treatment, intolerance to HMA, failure to achieve complete remission (CR), partial remission (PR), or hematologic improvement (HI) after six 4-week cycles of AZA or either four 4-week or four 6-week cycles of DAC, or relapse after initial CR, PR or HI. Bone marrow samples were collected at study baseline and throughout the study for mutational analysis as an exploratory endpoint. Baseline blast counts are described as % reported in bone marrow aspirate at screening. Genomic DNA was extracted from diagnostic bone marrow or peripheral blood samples and targeted capture deep sequencing of 295 genes were performed (median sequencing depth 500x) using Agilent's SureSelect custom panel. ModifiedMutect and Pindel were used to identify high-confidence somatic mutations.
Results:
All data is presented as blinded aggregate results for both arms of the study. Baseline mutations are presented for 114 pts; 92 pts were randomized, and 22 pts were screen failures. Median age is 72 years (59-81). The IPSS-R scores for the pts randomized were: Intermediate 5(5%), High 30 (32%) and VHR 56 (60%). In total 48 different mutations were identified at baseline prior to pts receiving study treatment. The most common mutations identified in pts were *ASXL1* 40%, *STAG2* 26%, *TP53* 24%, *RUNX1* 22%, *SRSF2* and *TET2* each 18%. Average number of mutations per pt was 3.06. At baseline, 4 pts (4%) had no mutations, 17 pts (18%) had only 1 mutation while 17 pts (18%) had between 6-8 mutations. *N-RAS* and *K-RAS* mutations occurred in 4 pts each (7% of pts) and all in the presence of other mutations. Mutations involving regulators of the Ras pathway (*N-RAS, K-RAS, PTPN11, NF1*) occurred in 12 (13%) of patients. Of note, 23 pts (25%) had *IDH1* (6 pts) or *IDH2* (17 pts) and the majority of these pts (68%) were High/VHR with an average blast count of 15% (range 5-27%) at study entry. The high proportion of IDH1/2 mutations observed is most likely due to inclusion of patients with RAEB-1. These results will be updated at the meeting with blinded baseline mutational analyses for all pts randomized into the study.
Conclusion:
The baseline mutational analyses from the INSPIRE study provides important initial insights into the genomic profile of pts with HMA failure, especially for the subset with VHR. Following an analysis of the primary endpoint, it is anticipated that correlation of overall survival and clinical response with mutational status will be possible, including changes in mutations following therapy. Given the number of mutations involving the Ras pathway the efficacy of rigosertib in patients with this group of mutations will also be examined.

Background

- More than 45 mutations have been identified in association with HR MDS and the number of mutations increases and changes following HMA failure and leukemic transformation (Haferlach Leukemia 2014, Lindsley NEJM 2017);
- In the majority of patients with MDS (80%) co-mutations are present and the prognostic contribution of each individual mutation remains elusive, especially after adjusting for clinical variables such as IPSS-R score. Only a few mutations are predictive of poor prognosis (e.g. TP53, SF3B1) (Haferlach Leukemia 2014);
- N-RAS and K-RAS mutations as well as regulators of the Ras pathway (e.g. PTPN11, NF1) are frequently observed (15-20%) in HR MDS, however their clinical impact is unclear, especially in de novo MDS (Haferlach Leukemia 2014);
- Rigosertib (RGS) is a non-ATP-competitive small molecule RAS mimetic that has the potential to block RAS-RAF-MEK-ERK and PI3K-AKT-mTOR signaling pathways (Athuluri-Divakar 2016). Rigosertib has the potential to also inhibit wildtype upregulation of RAS;
- We report here the genomic profile of XX patients with HMA failure HR MDS at the time of study entry prior to receiving rigosertib in the INSPIRE study, an ongoing phase 3 randomized global study evaluating IV rigosertib vs Physicians Choice (PC) in patients with HR MDS post HMA failure;

INSPIRE (04-30) Study



- Primary Objective: To compare the overall survival (OS) of patients in the rigosertib group vs PC arm in all patients and a sub-group of patients with IPSS-R very high risk;
- Exploratory Objective: Correlation of overall survival and clinical responses with mutational status;

Acknowledgement and Thanks to all those who have participated in the INSPIRE Study
The Patients and their families
The Referring Physicians and Study Investigators
Research Coordinators and Study Site Staff

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Key Inclusion Criteria

- INSPIRE (NCT02562443) is a global randomized Ph3 trial in pts with HR-MDS after HMA failure with an overall target enrollment of 360 pts with currently 298 pts randomized.
- Pts are randomized 2:1 to rigosertib or physician's choice of treatment. The primary endpoint is overall survival (OS). All pts failed to respond or progressed on HMA therapy.
- Key inclusion criteria includes:
  - age < 82 years,
  - RAEB-1, RAEB-2 or RAEB-t and ≥ 1 cytopenia;
  - Intermediate risk (IR), high risk (HR) and very high risk (VHR) per IPSS-R;
  - Duration of prior HMA ≤ 9 cycles within 12 months and last dose of HMA ≤ 6 months before enrollment;
  - Baseline blast counts between 5-29% and one of the following: progression any time after initiation of HMA treatment, intolerance to HMA, failure to achieve complete remission (CR), partial remission (PR), or hematologic improvement (HI) after six 4-week cycles of AZA or either four 4-week or four 6-week cycles of DAC, or relapse after initial CR, PR or HI.

Methodology

- Bone marrow samples were collected at study baseline and at Months 2, 4 and 6, and every 6 months thereafter as well as at the end of treatment for mutational analysis as an exploratory endpoint;
- In this abstract we report the genomic characterization of baseline samples from 159 patients (123 were randomized patients and 36 were screen failures). Complete patient demographics are available for 123 randomized patients. Future analyses will report baseline and longitudinal assessment while on therapy as well as at the time of disease progression (approximately 360 patients);
- Genomic DNA was extracted from diagnostic bone marrow or peripheral blood samples and targeted capture deep sequencing of 295 genes was performed (median sequencing depth 500x) using Agilent's SureSelect custom panel;
- Modified Mutect and Pindel were used to identify high-confidence somatic mutations;

Table 1. Pretreatment Characteristics of Sample

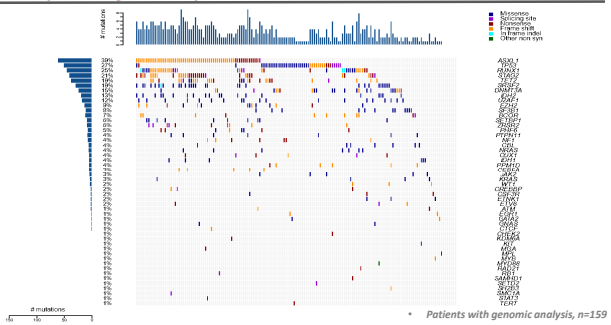
		Number of patients (%)
Sex	Female	39 (32)
	Male	84 (68)
Race	Asian	16 (13)
	Black	1 (1)
	Hispanic	9 (7)
	White	90 (73)
	Unknown	7 (6)
Age (yr)	Median	73
	Range	54 - 81
ECOG performance Status	0	31 (25)
	1	74 (60)
	2	18 (15)
MDS type	Primary (de novo)	113 (92)
	Secondary	10 (8)
WHO/FAB classification	RAEB-1	39 (32)
	RAEB-2	62 (50)
	RAEB-t	22 (18)
Failure type after the last HMA therapy	Progression	45 (37)
	Failure	55 (45)
	Relapse	18 (15)
	Intolerance	5 (4)
Revised IPSS score	Low	0 (0)
	Intermediate	6 (5)
	High	35 (28)
	Very High	81 (66)
	Unknown	1 (1)

** Patients with complete demographic data (n=123, 78% of total) are shown*

Table 2. Genomic profiling at study baseline in patients with HR MDS with HMA Failure undergoing screening for INSPIRE study

	N = 159 (%)
No mutations	3%
One mutation	11%
6-8 mutations	11%
N-RAS and K-Ras mutations	6%
Mutations in regulators of RAS pathway	19%
IDH1/2 mutations	14%

Genomic profiling in 159 pts w HMA Failure at baseline in INSPIRE

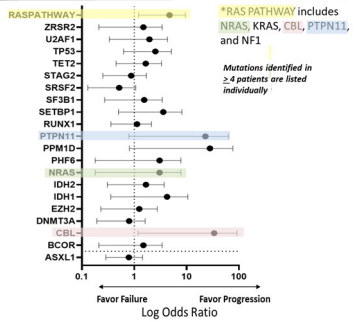


** Patients with genomic analysis, n=159*

Genomic profiling in patients with HMA Failure at baseline assessment for INSPIRE study

- Data is presented as blinded aggregate results for both arms of the study;
- Baseline mutations are presented for 159 patients of which 123 were randomized and 36 were screen failures;
- Median age is 73 years (59-81). IPSS-R scores for the patients randomized were: Intermediate 6 (5%), High 35 (28%) and VHR 81 (66%). There were no patients with low risk MDS and 1 patient with unknown IPSS-R at study entry;
- In total 50 different mutations were identified at baseline prior to pts receiving study treatment with either IV rigosertib or PC and the average number of mutations per pt was 3;
- The most common mutations identified in pts were ASXL1 39%, TP53 27%, RUNX1 25%, STAG2 21%, SRSF2 19%, TET2 19%, DNM3A 15%, IDH2 13% and U2AF1 12%;
- In total 31 patients (19%) had mutations that are part of RAS pathway (NRAS, 4 pts; KRAS, 5 pts; CBL, 7 pts; PTPN11, 7 pts; NF1, 8 pts);

Mutational results according to disease progression or HMA failure at time of study entry



Summary

- Baseline mutational 159 patients with HR MDS and HMA failure from the INSPIRE study were analyzed and provide potentially new information regarding the genomic profile of patients with HMA failure, especially those patients with VHR;
- Approximately 19% of patients had mutations involving the RAS pathway. The results showed that mutations in the RAS pathway were enriched in patients with disease progression following prior HMA failure;
- Future genomic analyses of the INSPIRE study will expand the data set (N=360) and will evaluate the correlation between changes in mutational status and clinical responses to treatment with rigosertib;
- It is anticipated that these analyses will provide important new information into the role of select mutations, including but not exclusively mutations of the RAS pathway.

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