Abstract #EP829:
Mutations in RAS pathway genes correlate with Type of Failure to Azacitidine: Genomic Analysis at Randomization onto the INSPIRE Trial

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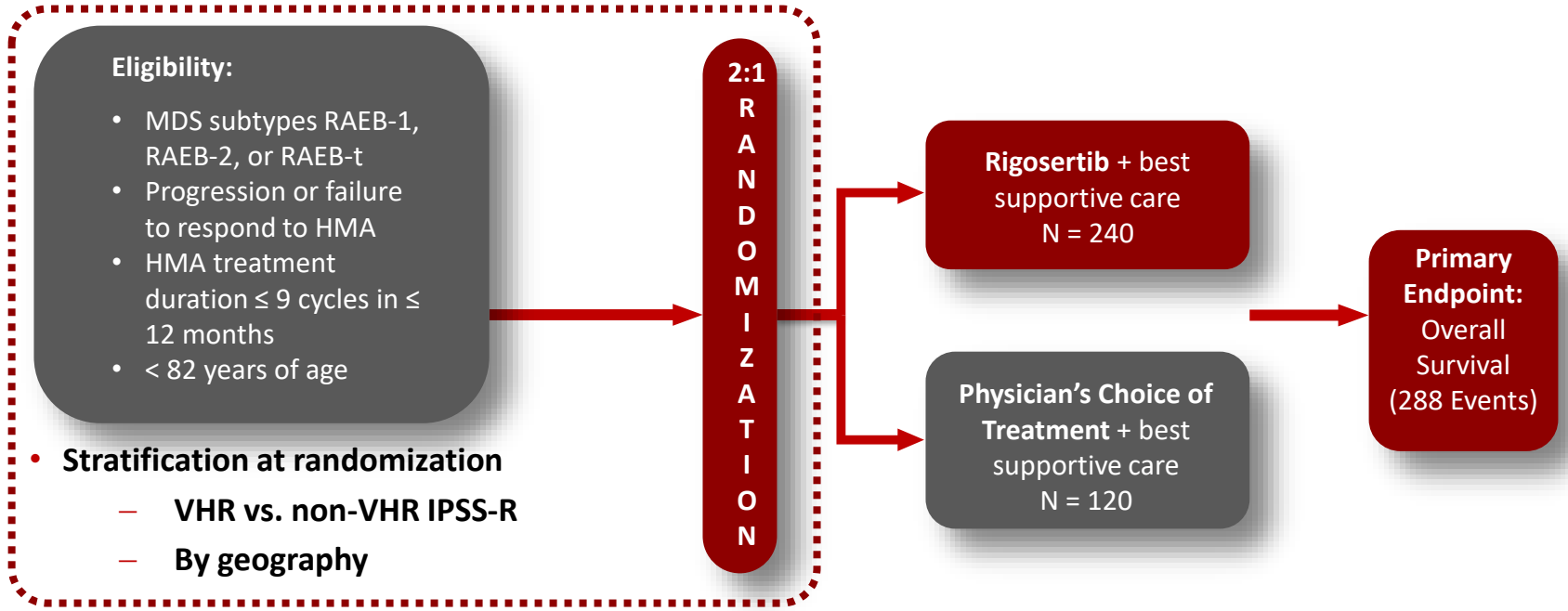
Introduction

- 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 190 patients with HMA failure HR MDS at the time of study entry prior to receiving rigosertib in the INSPIRE study (NCT025622443) 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;

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 which has recently been achieved.
- Key inclusion criteria includes:
  - age < 82 years,
  - RAEB-1, RAEB-2 or RAEB-t and ≥ 1 cytopenia;
  - Higher Risk MDS per IPSS-R Intermediate risk (IR), high risk (HR) and very high risk (VHR);
  - Duration of prior HMA ≤ 9 cycles within 12 months and last dose of HMA ≤ 6 months before enrollment;
  - One of the following:
    - Progression (2006 IWG criteria) at any time after initiation of AZA or DEC treatment ***or***
    - Failure to achieve complete or partial response or HI (according to 2006 IWG) after at least six 4-week cycles of AZA or either four 4-week or four 6-week cycles of DEC ***or***
    - Relapse after initial complete or partial response or HI (according to 2006 IWG criteria) ***or***
    - Intolerance to azacitidine or decitabine;

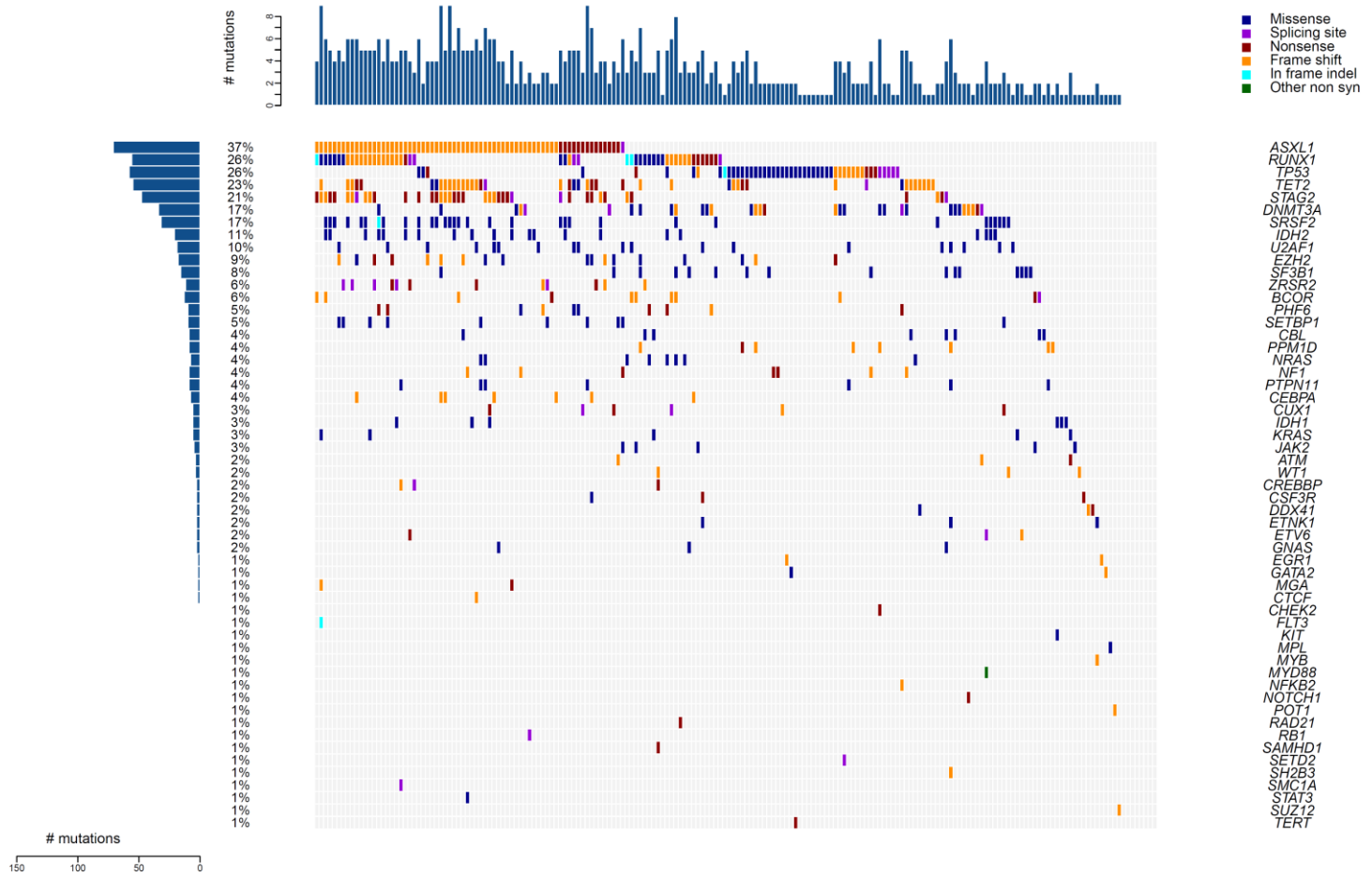
Methodology

- 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; future analyses will report longitudinal assessment while on therapy as well as at the time of disease progression;
- 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: Patient Demographics (N=190)

		Number of patients (%)
Sex	Female	67 (35)
	Male	121 (64)
	Unknown	2 (1)
Race	Asian	22 (12)
	Black	3 (2)
	White	152 (80)
	Other	6 (3)
	Unknown	7 (4)
Age (yr)	Median	73
	Range	54 – 82
ECOG performance Status	0	40 (21)
	1	87 (46)
	2	19 (10)
	Unknown	44 (23)
MDS type	Primary (de novo)	145 (76)
	Secondary	12 (6)
	Unknown	33 (17)
WHO/FAB classification	RAEB-1	50 (26)
	RAEB-2	78 (41)
	RAEB-t	26 (14)
	Unknown	36 (19)
Failure type after the last HMA therapy	Progression	61 (32)
	Failure	59 (31)
	Relapse	29 (15)
	Intolerance	8 (4)
	Unknown	33 (17)
Revised IPSS score	Low	0
	Intermediate	19 (10)
	High	44 (23)
	Very High	93 (49)
	Unknown	34 (18)

Figure 1: Genomic Profiling in Patients with HMA Failure at Baseline for INSPIRE Study



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 190 pts of which 157 pts were randomized and 33 pts were screen failures;
- Median age is 73 years (54-82). IPSS-R scores for the pts randomized were: Intermediate 19 (10%), High 44 (23%) and VHR 93 (49%);
- In total 55 different mutations were identified at baseline prior to pts receiving study treatment with either IV rigosertib or PC and the median number of mutations per pt was 3;
- The most common mutations identified in pts were *ASXL1 37%, TP53 26%, RUNX1 26%, TET2 23%, STAG2 21%, DNMT3A 17%, and SRSF2 17%;*

Figure 2: Pair-wise Analysis of Mutation Co-Occurrence

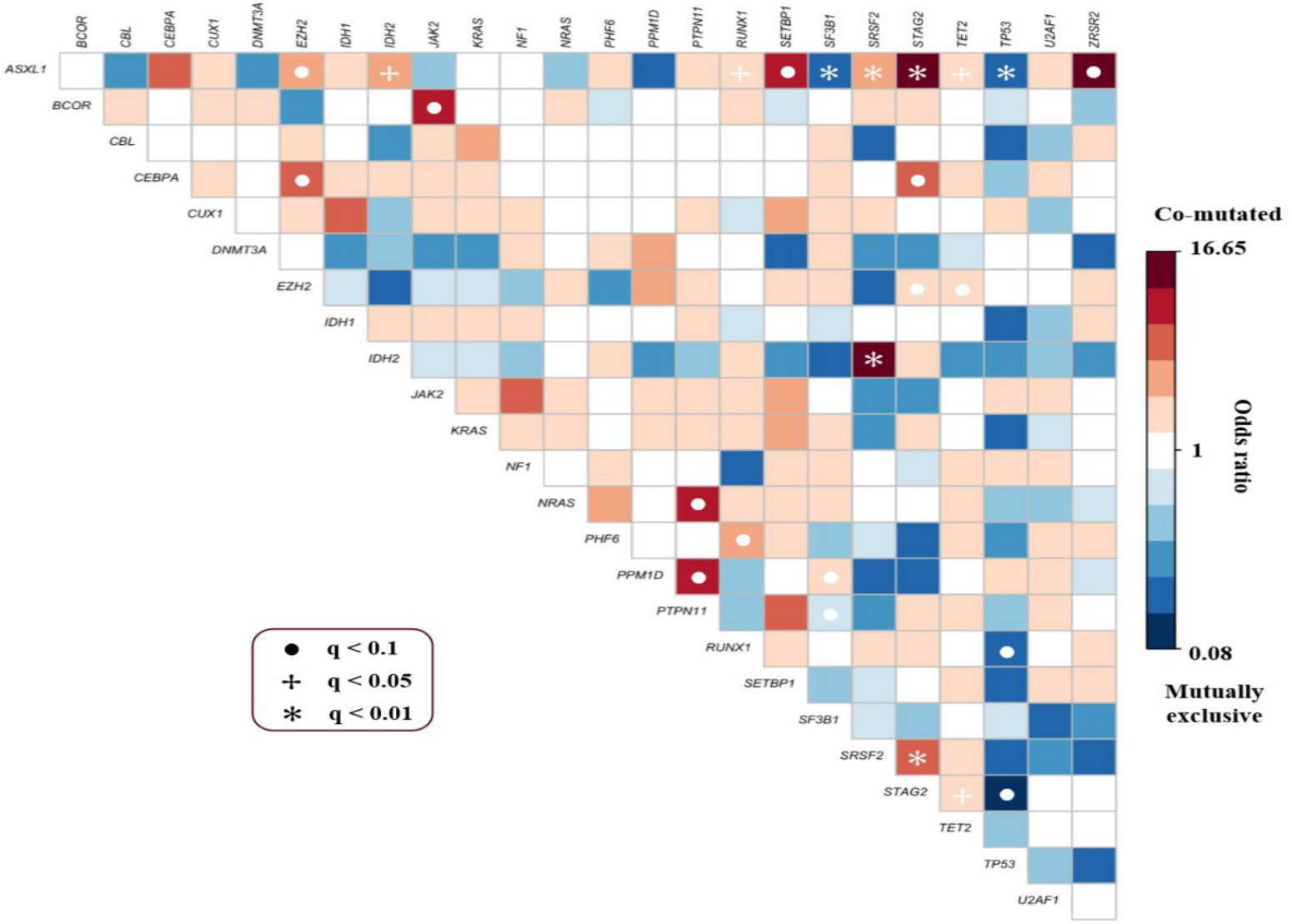


Figure 3: Correlation of Mutation and Baseline Clinical Features

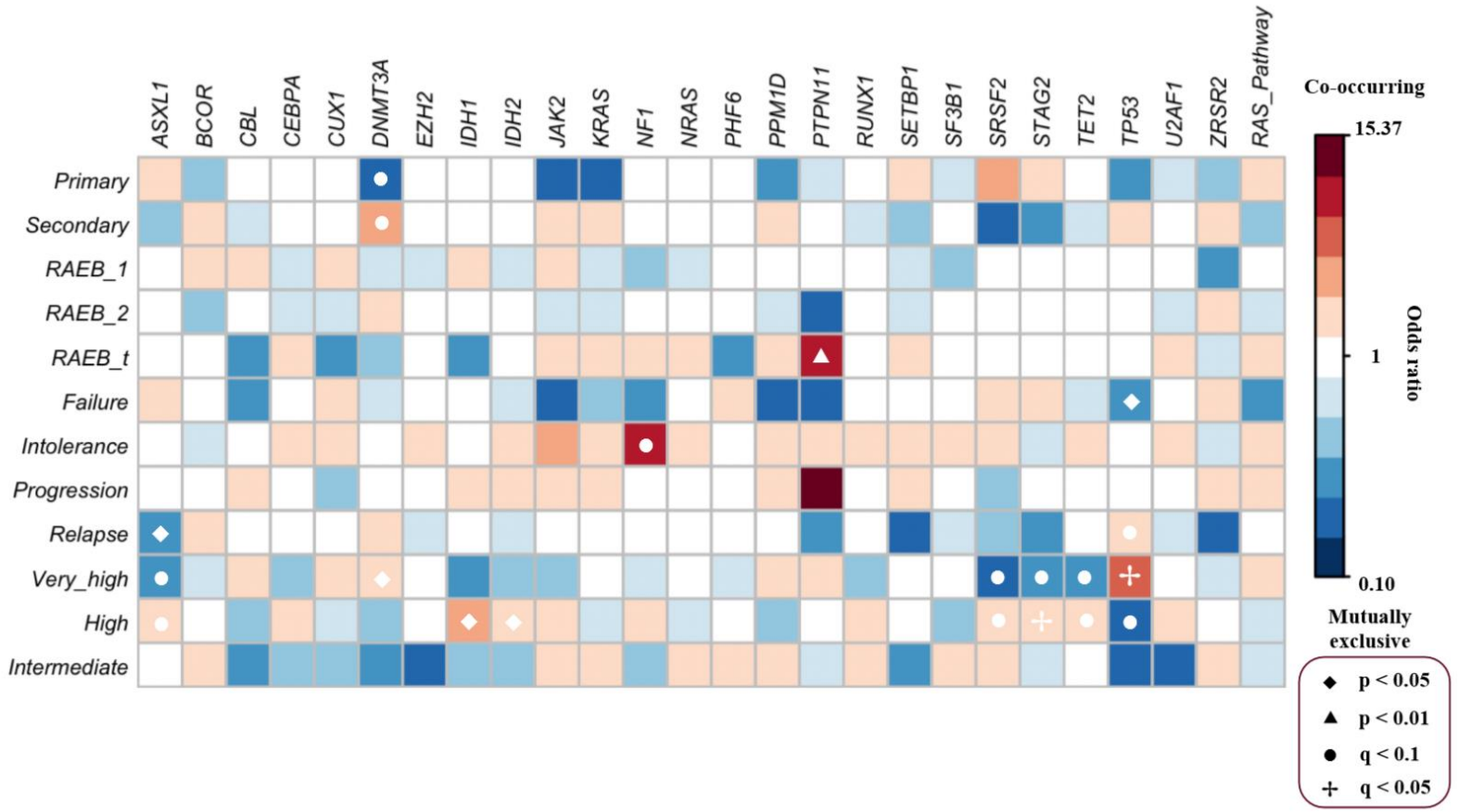
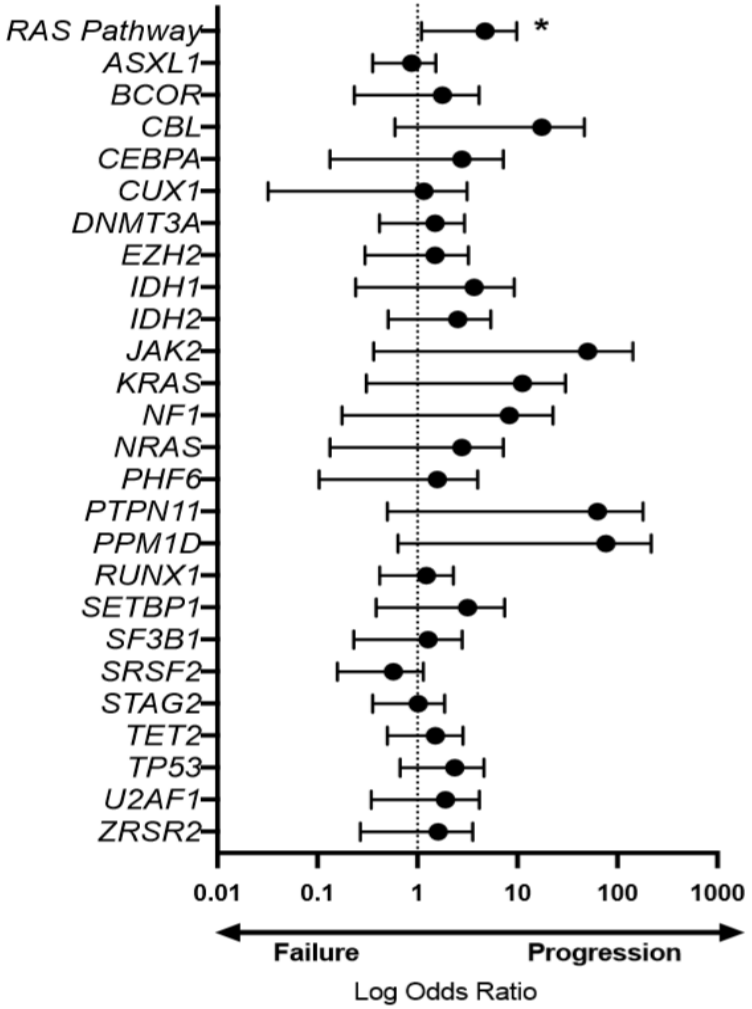


Figure 4: Correlation With Mutations and Types of Failure



RAS pathway includes NRAS, KRAS, CBL, NF1, and PTPN11

Conclusions

- The baseline mutational analyses from the INSPIRE study provides important new insights regarding the genomic profile of patients with HMA failure, especially for the subset categorized as VHR;
- The genomic profile is representative of a cohort enriched for the VHR subset;
- RAS pathway mutations were observed more commonly in patients that progressed on HMA therapy vs patients that failed HMA therapy as defined by IWG 2006 criteria;
- Future genomic analyses of the INSPIRE study will expand the data set and will evaluate correlation of clinical responses with changes in mutational status;
- It is anticipated that these analyses will provide important new insights in the selection of mutations, including but not exclusively the RAS pathway, on the development of leukemic progression in patients with HR MDS following HMA failure and treatment rigosertib.

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* Represents sites that contributed patient samples used in this analysis

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