Computational Analysis of Genomic Abnormalities from a Phase 3 Trial of Rigosertib in Higher-risk MDS - Simulation of a Predictive Signature for Clinical Response

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BACKGROUND

Although hypomethylating agents (HMAs) are the first line of treatment in higher risk-myelodysplastic syndromes (HR-MDS), failure to respond or progression is universal. There is no FDA approved second line therapy.[1] RIG (RIG) is a novel therapy currently in phase III development for a subgroup of HR-MDS patients who fail to respond to HMA therapy. Currently in phase III development in HR-MDS, RIG acts as a Ras mimetic to inhibit cellular signaling pathways by binding to the Ras-binding domain found in Ras effector proteins.[2]

This study used computational biology modeling (CBM) to map biological pathways to retrospectively identify characteristics of HR-MDS patients who achieve greater clinical benefit (response and/or survival) with RIG treatment from the Rig Phase III ONTIME trial. This model can be customized per a patient's genomics and analyzed virtually for response to drugs and other therapies, effects of genetic aberrations, and other outcomes of interest.

OBJECTIVES

- Utilizing computational biology modeling (CBM) technology to identify and elucidate biomarkers and mechanisms correlating to better outcomes to RIG treatment in HR-MDS patients.
- Correlating CBM results incorporating personalized genomics and cytogenetics for the prediction of clinical outcomes.
- This model can be customized per a patient's genomics and analyzed virtually for response to drugs and other therapies, effects of genetic aberrations, and other outcomes of interest.

METHODS

General HR-MDS Model Creation

A generalized disease model of HR-MDS was created based on key pathways and processes involved in HR-MDS pathogenesis from peer-reviewed scientific literature, experimental data, and genotyping.

Creation of Individualized HR-MDS Models

Genomic and cytogenetic information used in this virtual study were gathered from 54 patients deemed adequate for CBM from the ONTIME (NCT0124500), an open-label, randomized controlled trial. Genomic aberrations were interpreted for phenotypic implications (ie. gain of function versus loss of function) using PubMed to create 54 customized, individualized HR-MDS models.

RIG Digital Drug Model

A digital drug model for of RIG was created for CBM by programming RIG mechanism of action and effects on specific protein targets and pathways determined from published literature.

Virtual Clinical Trial

Using the digital drug model of RIG, virtual applications of RIG were applied to each patient's disease ~~in~~ via computer simulation.

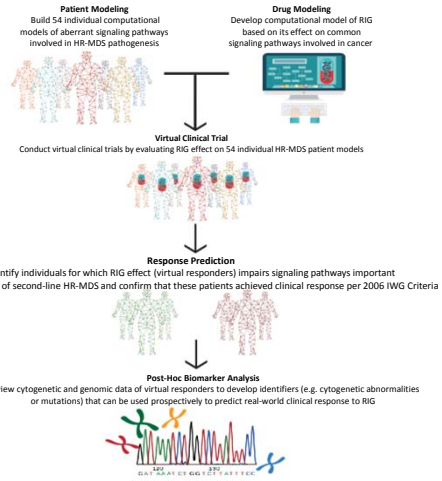
Response Prediction

The efficacy of RIG in the genetically varying individual patient models was measured as a function of disease inhibition score – the degree to which crucial cancer signaling pathways were repressed. Through extensive retrospective and prospective simulation prediction analysis of over 250 MDS patients and FDA approved agents (including lenalidomide [n=136] and HMAs [n=211]), a disease inhibition score of 20% was established as the threshold indicative of response.

This threshold has been validated in past and current studies[5, 6, 7,8]. Patients with a disease inhibition score of ≥20% were classified as virtual responders and those <20% were classified as virtual non-responders (defined by 2006 IWG criteria) during treatment with RIG in the ONTIME trial.

Post-Hoc Biomarker Analysis

Post-hoc analyses of virtual responders and virtual non-responders were performed to determine all unique cytogenetic and genomic identifiers between the two groups. Genomic DNA was isolated from single microscopic slides from HR-MDS patients and subjected to sequence analysis of a "myeloid panel" comprising of 24 selected loci known to be frequently mutated in MDS and acute myeloid leukemia. Standardized cytogenetic investigations were performed.[2]



RESULTS

Virtual Clinical Trial and Response Prediction

	Responder	Non-Responder
Virtual Response Definitions	Disease inhibition score ≥20%	Disease inhibition score <20%
Clinical Response Definitions	Complete Response (mCR) or Partial Response (mPR) per 2006 IWG Criteria	Stable Disease (SD) or Progressive Disease (PD) per 2006 IWG Criteria

Table 1: Definition of response criteria.

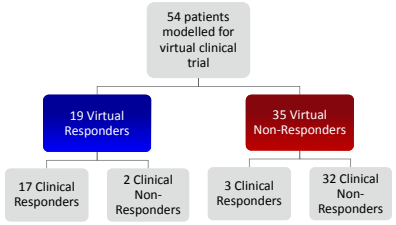


Figure 1: Identification of responders and non-responders by CBM.

	Sample Size	Median Disease Inhibition Score
Virtual Responder	19	32.27
Virtual Non-responder	35	3.84

Table 2: Disease inhibition score for virtual responders and non-responders.

CBM Correlation Statistics		
PPV	NPV	Accuracy
85%	94.12%	90.74%

Table 3: Correlation statistics for virtual and clinical response.

Post-Hoc Biomarker Analysis

Responder/Non-Responder Rules	Sample Size	Median Disease Inhibition Score	P-value	
			Responder	Non-responder
All patients	54	7.52	0.565	0.547
Trisomy 8	17	29.65	0.395	0.776
Trisomy 21	5	58.96	0.056	0.994
Trisomy 21 or Trisomy 8	22	29.65	0.115	0.948
Trisomy 21 or Trisomy 8 without Del 3 or Del 5 or Del 7or Del 14 or Del 16	15	29.65	0.003	0.999
All other cytogenetics	32	5.78	0.925	0.147

Table 4: Post-hoc analysis of cytogenetic abnormalities for virtual responders and non-responders.

- **Are the results of the virtual clinical trials supported by outcomes data from the ONTIME trial of RIG?**

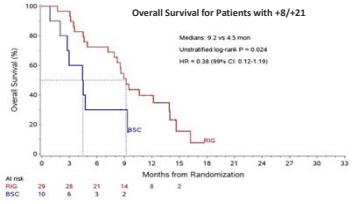


Figure 2: Kaplan-Meier curve representing +8/+21patients from ONTIME trial.

- **Is there biological plausibility for better activity of RIG in cytogenically-defined subgroups?**
  - RIG effect in trisomy 8 considered to be related to gain-of-function in three genes present on chromosome 8 – *MYC*, *FNTA* and *KAT6A*
    - *MYC*, *FNTA* and *KAT6A* genes involved in proliferation and viability that are targeted by RIG mechanism of action
  - RIG effect in trisomy 21 considered to be related to gain-of-function in two genes on chromosome 21 – *GART* and *TIAM1*
    - *GART* and *TIAM1* involved in proliferation and viability that are targeted by RIG mechanism of action
  - Lack of RIG effect in del(5q) is thought to be related to deletion of genes implicated in the RAS signaling pathway, namely *HMGCR* (encodes rate limiting enzyme for prenylation of RAS)[3] and *RASA1* (negative RAS regulator)[4]

CONCLUSION

- Retrospectively identified HR-MDS patients that have a marrow blast count reduction from treatment with IV RIG.
- Independently confirmed previous observations that HR-MDS patients with trisomy 8 achieve survival benefit with RIG.
- Discovered a new cytogenetic identifier – trisomy 21 – as a positive predictor of benefit for HR-MDS patients treated with RIG
- Correlated cytogenetic abnormalities with molecular mechanism of action for RIG, thus establishing biological plausibility for activity in these well-defined patient subgroups
- The results of this study reinforce the clinical strategy for targeting the highest-risk MDS patients for treatment with RIG and also support a role for CBM in the prospective identification of individuals most likely to respond to novel therapeutic modalities.

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