EX VIVO DRUG SENSITIVITY PROFILING IN MYELODYSPLASTIC SYNDROME (MDS) PATIENTS DEFINES NOVEL DRUG SENSITIVITY PATTERNS FOR PREDICTING CLINICAL THERAPEUTIC OUTCOMES

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Background
Hypomethylating agents (HMAs) remain the standard of care for higher-risk MDS, but limited treatment options exist for patients with HMA-refractory MDS and related myeloid neoplasms.

Aims
To demonstrate the clinical validity and feasibility of using a drug sensitivity screening (DSS) platform to support novel clinical stratification of patients with HMA-refractory myeloid neoplasms.

Methods
We performed drug sensitivity profiling on 60 patient samples in both newly diagnosed and treatment-refractory myeloid neoplasms (46 MDS, 4 CMML, 10 AML). Fresh bone marrow aspirates and/or peripheral blood specimens were RBC-lysed and re-suspended in serum-free media with cytokines. The samples were then plated in 384 well microtiter plates and were screened against a collection of investigational and FDA-approved compounds (up to 76) in triplicate using Notable Labs' automated platform. Specimens were treated for 72 hours and assayed using high-throughput, multi-parametric flow cytometry for both cytotoxicity and differentiation. Following clinical validation of the platform in the 60 primary patients specimens, we conducted a prospective clinical feasibility study enrolling 20 HMA-refractory MDS patients (12 IPSS-R higher risk, 5 lower risk, and 3 MDS/MPN overlap disorders) designed to determine whether DSS could be performed accurately, reproducibly and effectively (upon Tumor Board review) for determining potentially useful drugs within a clinically meaningful turnaround time (≤30 days) sufficient for treatment decision support.

Results
Principal component analysis was performed to explore differential *ex vivo* sensitivity and resistance patterns of the total MDS samples compared to a panel of AML samples. Individual MDS samples clustered according to their *ex vivo* responses, with distinct subgroups enriched for sensitivity to HMAs, HDAC inhibitors, differentiation agents and cytotoxic agents. Additionally, *ex vivo* testing reproduced known mechanisms of action of various drug classes, including cytotoxicity (anthracyclines, antimetabolites, PARP inhibitors) and differentiation (vitamins/steroids and IDH inhibitors).

Clinical parameters, including prior HMA therapy, cytogenetics, prognostic risk category, and mutational profile, contributed to but did not explain all of the variability of *ex vivo* sensitivity patterns. *Ex vivo* drug sensitivity data demonstrated positive and negative predictive values of 85% and 83%, respectively, for clinical response prediction (Fisher’s exact test p-value = 0.0095). In

patients with serial samples, *ex vivo* sensitivity data corresponded to the emergence of clinical resistance.

For the 20 patients with HMA-refractory MDS on the prospective feasibility study, the mean time from enrollment to *ex vivo* trial results was 15.3 days (range 13-24 days) and the mean time to providing treatment recommendations from a biologically focused Tumor Board was 26.8 days (range 20-32 days). Clinical response rate to the next line of therapy was 80% in patients whose next line of therapy overlapped with that recommended by the Tumor Board (n = 6).

Conclusion

Ex vivo therapeutic responses of MDS and AML patient samples recapitulated known clinical and molecular predictors of therapeutic efficacy and provided possible new biologically focused therapeutic options. The accuracy and reproducibility of this platform coupled with the short turnaround time suggests potential utility of this methodology to aid in decision making for novel therapeutic selection in patients with HMA-refractory myeloid neoplasms.