Few Drug Approvals in MDS: Lessons and Insights from a Decade of Clinical Trials

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Aside from allogeneic transplantation, the current standard of care approach for higher-risk myelodysplastic syndromes/neoplasms (HR-MDS) remains monotherapy with a hypomethylating agent (HMA) including azacitidine, decitabine, or oral decitabine/cedazuridine. Many attempts using HMA-based combinations have failed to improve upon HMA monotherapy. While promising efficacy was observed in early phase clinical trials with several agents, subsequent randomized phase 3 trials failed to confirm improvements in complete response (CR) rates or overall survival.

In this lecture, I will discuss lessons learned from the recently reported negative trials of azacitidine in combination with eprenetapopt (APR-246), magrolimab, pevonedistat, sabatolimab, tamibarotene, and venetoclax.

First, I will make a case for emphasizing biological classification rather than disease risk status alone to select patients for HR-MDS trials.

Second, I will argue argue that *TP53* inactivated MDS and CMML patients should be treated in dedicated clinical trials. Alternatively, if *TP53* inactivated MDS is included in HR-MDS trials, then randomization stratification by *TP53* inactivation status should be considered.

Third, will make a cae to caution against ignoring signals of excessive toxicity and premature investigational agent discontinuation observed in early phase trials.

Fourth, I will show that the International Working Group (IWG) 2006 response criteria, long used in HR-MDS trials, can both overestimate and underestimate the true therapeutic benefit. Instead, I will advocate for using the IWG 2023 response criteria to better capture clinically meaningful benefits in HR-MDS.

Lastly, I will emphasize the need for the scientific community to access patient-level data and samples from failed phase 3 trials in an efficient and expedited fashion to inform the development of subsequent trials.