



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Safety and Preliminary Efficacy of DFV890 in Adult Patients with Myeloid Diseases: A Phase 1b Study

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Background and Significance:

Patients (pts) with myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) have a high unmet medical need, with limited standard-of-care therapeutic approaches, particularly after failure of response to first-line agents, and with allogeneic hematopoietic transplant as the only potential curative option.

Through the production of interleukin (IL)-1 β and IL-18, the NLRP3 inflammasome has been implicated as a major driver of inflammation associated with acute and chronic inflammatory diseases. The NLRP3 pathway is activated in hematopoietic stem and progenitor cells and in the marrow microenvironment in myeloid neoplasms such as MDS and CMML contributing to ineffective hematopoiesis and clonal progression (Hamarsheh 2020; Basiorka 2016). DFV890, a small molecule NLRP3 inhibitor, blocks IL-1 β and IL-18 secretion and pyroptotic cell death in response to a wide variety of NLRP3-dependent danger signals, both in vitro and in vivo. Therefore, DFV890 may disrupt the smoldering inflammation and provide disease-modifying benefits to pts by improving hematopoiesis.

Study Design and Methods:

This is an open-label, phase 1b, multicenter study with a randomized dose-optimization part and a dose-expansion part consisting of two groups evaluating DFV890 in pts with very low, low, or intermediate risk MDS (LR-MDS) per revised International Prognostic Scoring System (IPSS-R) criteria and low or intermediate-1 risk CMML (LR-CMML) per CMML-specific Prognostic Scoring System (CPSS) criteria (NCT05552469).

Eligible pts must be 18 years of age, with an Eastern Cooperative Oncology Group performance status ≤ 2 , candidates for serial bone marrow assessments who are willing to undergo a bone marrow aspirate/biopsy during the trial, and meet one of the following: (a) IPSS-R-defined LR-MDS who failed to respond to or did not tolerate erythropoiesis-stimulating agents (ESAs) or luspatercept or hypomethylating agents (HMAs) and pts with del 5q who failed to respond to or did not tolerate lenalidomide; (b) CPSS-defined LR-CMML who failed to respond to or did not tolerate hydroxyurea or HMAs. Key exclusion criteria include treatment with systemic antineoplastic or any experimental therapies within 28 days (or 5 half-lives, whichever longer); unresolved treatment-related toxicities prior to the first dose of study treatment; previous treatment with agents targeting the NLRP3 inflammasome and the IL-1 pathways; prior use (≤ 1 week or 5 half-lives, whichever is longer) of hematopoietic colony-

stimulating growth factors, thrombopoietin mimetics or ESAs; and concomitant medications, known to modulate cytochrome P450 enzymes.

DFV890 is administered orally twice daily (bid) for a minimum of 24 weeks (6 cycles of treatment [1 cycle=28 days]) until treatment discontinuation. In the dose-optimization part, pts are randomized to receive either low dose or high dose bid and stratified by indications. The recommended dose (RD) determined from this part is further explored in the dose-expansion part to confirm safety and tolerability of DFV890 and explore preliminary efficacy.

The primary objective is to assess safety (incidence and severity of adverse events, and dose-limiting toxicities) and tolerability to then determine the optimal RD for DFV890. Secondary objectives include assessment of DFV890 pharmacokinetics, evaluation of the preliminary efficacy of DFV890 on transfusion burden, and hematologic improvement: time to onset of transfusion independence; duration of response, best overall response, overall response rate, progression-free survival, and time to progression; and reduction in spleen volume (for CMML). Key exploratory objectives include patient perceptions of tolerability as measured by patient-reported outcomes; and determination of genetic characteristics and potential predictive markers of efficacy and/or resistance.

The study is currently enrolling in Singapore, Hong Kong, and the USA with plans to treat approximately 80 pts. The first patient first visit was achieved on May 8, 2023.

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Figure 1. Study Design



BID, twice daily; CMML, chronic myelomonocytic leukemia; LR, lower risk; MDS, myelodysplastic syndrome; RD, recommended dose; SA, single agent.

Figure 1

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