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616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL DRUG AND CELLULAR THERAPIES

A First in Human Study of VOB560 in Combination with MIK665 in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma, Acute Myeloid Leukemia, or Multiple Myeloma

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Background:

Patients with relapsed and refractory (R/R) acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM) require effective treatment options due to their high mortality rates. The inhibition of 2 anti-apoptotic proteins, B-cell lymphoma 2 (BCL2) and myeloid cell leukemia 1 (MCL1), has shown promise as a therapeutic approach for these cancers. Two novel BH3 mimetics, VOB560 and MIK665, selectively inhibit BCL2 and MCL1, respectively, induce apoptosis in hematological cancer cells and showed efficacy in preclinical models. In combination, VOB560 and MIK665 demonstrated strong synergy and promoted cell death in various hematological cancer models. VOB560 binds to BCL2, disrupting its interaction with pro-apoptotic proteins, causing cell death. MIK665 selectively inhibits MCL1, activating caspases and promoting cell death. Here we report the early clinical findings of the combination of VOB560 and MIK665 from the dose escalation phase in the treatment of hematological malignancies.

Methods:

This was a phase 1b, open-label, multi-center, dose-escalation/-expansion study (NCT04702425) in patients with R/R NHL, AML or MM. In the escalation phase, VOB560 was administered weekly (QW) intravenously (IV) at 25 and 50 mg in combination with MIK665 administered IV at 25 and 50 mg QW. Primary objectives of the dose-escalation phase were to characterize the safety and tolerability of VOB560 in combination with MIK665, and to identify the maximum tolerated dose and/or rec-

ommended doses and regimens for all indications. Secondary objectives were to assess preliminary antitumor activity and pharmacokinetics. Decision was made to halt recruitment in April 2023 for strategic reasons and not to progress further in the expansion phase of the study. This decision was not the consequence of any safety concerns.

Results:

Thirty-seven patients were enrolled in the dose escalation phase. Patients' diagnoses were AML (n=29, 78.4%), MM (n=4, 10.8%), and NHL (n=4, 10.8%). NHL included diffuse large B cell lymphoma (n=3, 8.1%) and follicular lymphoma (n=1, 2.7%). Thirty-six patients permanently discontinued study, due to progressive disease (n=25), physician's decision (n=7), adverse events (AE; n=3) and patient's decision (n=1). Complete remission (CR) was observed in 2 AML patients receiving VOB560 50 mg in combination with MIK665 25 mg QW. One patient relapsed after 7 months, while, the other AML patient, solely on study treatment, was in CR after 18 months. One AML patient showed partial remission. No objective responses were observed in the MM and NHL cohorts.

Five patients experienced dose limiting toxicities (DLTs). DLTs included perimyocarditis (n=1) receiving VOB560 25 mg and MIK665 25 mg, tumor lysis syndrome (TLS, n=1) receiving VOB560 50 mg and MIK665 25 mg, differentiation syndrome (n=1) receiving VOB560 25 mg and MIK665 50 mg, muscle cramp (n=1) receiving VOB560 50 mg and MIK665 50 mg, and decreased ejection fraction (n=1) receiving VOB560 50 mg and MIK665 50 mg. AEs were reported in 37 patients (100%), of which 25 patients (67%) had grade ≥ 3 AEs. Treatment-related AEs (TRAEs) were reported in 23 patients (62.2%). Most frequent TRAEs reported in $\geq 5\%$ of patients were diarrhea and nausea (6 patients each, 16.2%), vomiting, pyrexia and TLS (3 patients each, 8.1%). Anemia, neutropenia, thrombocytopenia, aspartate aminotransferase increased, and infusion-related reaction were reported in 2 patients each (5.4%). Seven patients (18.9%) reported grade ≥ 3 TRAEs. Three patients (8.1%) experienced grade 3 (severe) TLS, while 1 patient (2.7%) each experienced grade 3 (severe) neutropenia, myopericarditis, muscle spasm and differentiation syndrome. No fatal grade 5 serious AE (SAE) was reported. Eighteen patients (48%) experienced SAEs; 6 SAEs were treatment related. These included TLS, hyperphosphatemia, myopericarditis, muscle spasms, leukocytosis, oxygen saturation decreased and differentiation syndrome. Patients who developed troponin increase underwent cardiac MRI, which showed no observable functional or structural changes to the heart.

Conclusions:

Early clinical data of VOB560 in combination with MIK665 reported an acceptable safety profile in patients with hematological malignancies. The observed activity in the AML patients supports the notion that targeting MCL1 and BCL2 is a promising approach in hematological malignancies.

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