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POSTER ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

First Report on the Effects of Lisaftoclax (APG-2575) in Combination with Novel Therapeutic Regimens in Patients with Relapsed or Refractory Multiple Myeloma (R/R MM) or Immunoglobulin Light-Chain (Amyloid Light-Chain [AL]) Amyloidosis

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Background
R/R MM is an incurable condition, with virtually inevitable relapse. AL amyloidosis is a rare disease that may cause serious illness and even death. Lisaftoclax is a novel, potent, selective BCL-2 inhibitor under clinical development for treatment of patients with hematologic malignancies or solid tumors, and has shown clinical antitumor benefits. In a previous study on chronic lymphocytic leukemia, lisaftoclax was shown to require only a short (daily vs weekly) dose ramp-up to mitigate tumor lysis syndrome and was associated with a low incidence of adverse events (AEs) (Ailawadhi et al. *J Clin Oncol* 2021;39:abstract 7502; Davids et al. *Blood* 2022;140[suppl 1]:2326-2328).

Methods
This multicenter study evaluated lisaftoclax combined with pomalidomide and dexamethasone (Arms A and C) or daratumumab, lenalidomide, and dexamethasone (Arm B) in patients with R/R MM (Arm A and B) or R/R amyloidosis (Arm C). Eligible patients had an ECOG performance status ≤ 2; ≥ 1 prior line of therapy; and adequate organ function. Patients with R/R amyloidosis also needed confirmed symptomatic organ involvement, in addition to purpura and/or carpal tunnel syndrome. Lisaftoclax was administered orally daily (QD) at 5 dose levels (400, 600, 800, 1,000, and 1,200 mg) without ramp-up in repeated 28-day cycles. Pomalidomide, daratumumab, and lenalidomide were administered per label use. Dexamethasone 40 mg (20 mg for patients aged > 75 years) was administered on Days 1, 8, 15, and 22 of 28-day cycles. Study objectives were safety and efficacy assessments of the combination treatments.

Results
As of July 3, 2023, a total of 30 patients were enrolled: 22 in Arm A at dose levels of 400 (n = 3), 600 (n = 4), 800 (n = 3), 1,000 (n = 6), and 1,200 mg (n = 6); 3 in Arm B at 600 mg; and 5 in Arm C at 400 (n = 1) and 600 mg (n = 4). A total of 66.7% of patients were male, and the median (range) age was 70.5 (24-88) years, with 66.7% of patients above the age of 65. The median (range) lines of prior therapies was 4 (1-19), and median (range) time from diagnosis to first dose was 5.2 (1-29) years. The median (range) number of treatment cycles was 4 (1-19). A total of 18 patients were triple-class-exposed, 7 had received pomalidomide, and 3 harbored t(11;14) at baseline. A total of 19 patients reported experiencing any-grade lisaftoclax treatment-related adverse events (TRAEs), including neutropenia or nausea (16.7% each); and thrombocytopenia, leukopenia, abdominal distension, constipation, or diarrhea (6.7% each). Seven patients experienced grade ≥ 3 TRAEs, including neutropenia (10%) and febrile neutropenia, iron deficiency anemia, thrombocytopenia, prolonged electrocardiogram QT interval, and acute kidney injury (3.3% each). Two patients experienced lisaftoclax-related serious AEs, of which 1 was febrile neutropenia and 1 acute kidney injury. In Arm B, 1 patient experienced a dose-limiting toxicity (prolonged QT interval). A total of 12 patients discontinued

treatment because of disease progression (n = 8), an AE (n = 1), noncompliance (n = 1), and investigator/patient decision (n = 2). In Arm A, 21 patients with R/R MM were evaluable, of whom 9 experienced a partial response (PR) and 5 a very good PR (VGPR). The overall response rate (ORR [PR or better]) was 66.7%, with a median (range) time to response of 1.2 (1-3) months. After a median (range) time to response of 1.4 (1-2) months, 2 patients with R/R MM in Arm B achieved a PR (n = 1) or VGPR (n = 1). In Arm C, 3 patients with R/R amyloidosis achieved a hematologic VGPR; the ORR was 60%; the median (range) time to response was 0.9 (1-1) month; and 1 patient experienced organ function improvement.

Conclusion

Lisaftoclax, combined with novel therapeutic regimens, was well tolerated and has demonstrated preliminary antitumor activity in patients with AL amyloidosis or R/R MM. Internal study identifier: APG-2575-MU101; clinical trial registration: NCT04942067.

Disclosures Ailawadhi: *Beigene, BMS, Cellectar, GSK, Janssen, Pfizer, Regeneron, Sanofi, Takeda:* Consultancy; *AbbVie, Amgen, Ascentage, BMS, Cellectar, GSK, Janssen, Pharmacyclics, Sanofi:* Research Funding. **Gibbs:** *Jansen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS:* Honoraria. **Khouri:** *GPCR Therapeutics:* Other: Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events; *Janssen:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events. **Chen:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company. **Guo:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company. **Li:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company. **Ahmad:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company. **Wang:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company. **Yang:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees, Other: Leadership, Patents & Royalties. **Zhai:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company, Other: Leadership (CMO).

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