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ONCE WEEKLY SELINEXOR, CARFILZOMIB, AND DEXAMETHASONE (XKD) IN CARFILZOMIB NONREFRACTORY MULTIPLE MYELOMA (MM) PATIENTS

Topic: 14. Myeloma and other monoclonal gammopathies - Clinical

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Background: Exportin 1 (XPO1) mediates the nuclear export and functional inactivation of tumor suppressor proteins (TSPs), is associated with poor prognosis in MM, and contributes to proteasome inhibitor (PI) and immunomodulatory drug (IMiD) resistance. Selinexor (SEL) is a novel, oral, first-in-class selective inhibitor of nuclear export (SINE) compound that blocks XPO1, forcing the nuclear retention and activation of TSPs. SEL in combination with low dose dexamethasone (dex) ± bortezomib (BOR) is FDA approved for previously treated MM. The synergy of SEL with the PI BOR has been confirmed in the phase 3 BOSTON study in MM patients (pts) with 1-3 prior therapies; once weekly (QW) SEL, QW BOR, and dex (XVd) significantly increased progression-free survival (PFS), time to next therapy, and overall response rate (ORR) as compared to standard twice weekly BOR/dex (Vd), despite XVd using 40% less BOR and 25% less dex than standard Vd.

Aims: To determine if the addition of QW SEL to the PI carfilzomib (CAR)-dex (XKd) would be an active and tolerable regimen in pts with heavily pretreated MM.

Methods: In the XKd arm of the multi-arm Phase 1b/2 STOMP study, SEL at 80 or 100 mg QW was evaluated in combination with CAR at 56 or 70 mg/m^2 QW plus dex at 40 mg QW in pts with heavily pretreated MM not refractory to CAR. Study objectives were to determine the maximum tolerated dose and recommended phase 2 dose (RP2D) and assess the safety and activity of the XKd regimen.

Results: As of 4 Jan 2021, 27 pts were enrolled: 18 (67%) were male, median age 71 years (range 50-76), and median of 4 (range 1-8) prior lines of therapy. All 27 pts were previously treated with BOR, 26 (96%) lenalidomide

(LEN), 19 (70%) pomalidomide (POM), 18 (67%) daratumumab (dara). The majority of pts (67%) were triple-class treated (PI, IMiD, and anti-CD38 mAb), and 44% had documented triple-class refractory MM. Nine pts (33%) had MM quad-refractory to BOR, LEN, POM, and dara.

Common hematologic treatment-related adverse events (TRAEs) (total, grade ≥3) included thrombocytopenia (74%, 56%), anemia (59%, 19%), and neutropenia (30%, 7%), typically without concurrent symptoms. Non-hematologic TRAEs included nausea (67%, 4%), fatigue (52%, 7%), and anorexia (52%, 4%). RP2D was identified as SEL 80 mg QW, CAR 56 mg/m^2 QW, and dex 40 mg QW.

As of 3 Feb 2021, ORR was 78% (21/27) with 5 pts reaching CR (19%), 8 VGPR (30%), and 8 PR (30%). Median PFS was 23.7 months. Among 18 pts previously treated with dara, ORR was 67% and median PFS was 23.7 months. In 9 pts with MM refractory to BOR, LEN, POM, and dara, ORR was 67% and 4 pts had VGPR (44%).

Summary/Conclusion: In pts with heavily pretreated MM, weekly XKd is highly active with an ORR of 78% and deep responses (≥VGPR 48%) with an overall PFS of 23 months. All AEs, including grade 3/4 thrombocytopenia, can be managed with appropriate supportive care and dose modifications. These data support further investigation of XKd in pts with previously treated MM including those with prior dara treatment.

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