Change in T2-Weighted Signal Intensity, Change in Tumor Volume, and Exposure-Response Analysis in the RINGSIDE Phase 2 Study of Varegacestat in Patients with Desmoid Tumors

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Background: T2-weighted signal intensity (T2W) and tumor volume (TV) on MRI may be more sensitive than RECIST for assessing treatment effect in desmoid tumors (DT). On T2W images, hyperintense areas are associated with active fibroblast proliferation and hypointense areas are associated with loss of tumor cells and more collagenous tissue. The RINGSIDE Phase 2 study (NCT04871282) demonstrated early and continued MRI changes in DTs with varegacestat (AL102) therapy. We report exploratory analyses of T2W, TV, and exposure-response (E-R).

Methods: Eligible adults had histologically confirmed DT that had progressed ≥10% unidimensional growth in ≤18 months or DT-related pain requiring non-opioid medication. Participants (pts) were randomized to 3 oral varegacestat doses: 1.2 mg once daily (n=14), 2 mg intermittent (n=14) or 4 mg intermittent (n=14) (intermittent = 2 days on, 5 days off). In the open-label extension (OLE), active pts received 1.2 mg once daily. We performed descriptive analysis of T2W, TV and RECIST sum of diameters (SOD), all of which were evaluated at screening, Week 16 and every 12 weeks thereafter. Linear correlations of best % changes from baseline on these assessments were evaluated with Pearson correlation coefficient. E-R modeling evaluated the time course of drug effect on TV to support selection of 1.2 mg once daily for further study.

Results: As of April 10, 2024, median time on treatment was 23.1 months (range 0.7 – 26.6) and 23 of 42 (55%) enrolled pts were still on treatment. Line graphs of changes from baseline showed rapid and substantial reductions in T2W and TV. By Week 16, the median % changes in T2W, TV and SOD were -39%, -24%, and -8%, respectively. Median best % changes for T2W, TV and SOD were -90%, -84%, and -40%, respectively. Correlations were observed for best % changes in T2W vs SOD (R=0.69), TV vs SOD (R=0.82), and T2W vs TV (R=0.89). In the 23 pts with PR/CR, median best % change was -96% (n=21 evaluable) for T2W and -90% (n=22 evaluable) for TV. In pts with SD, changes in T2W (n=11 evaluable) ranged from +32% to -94%, with a median of -75%, and TV (n=12 evaluable) ranged from +71% to -86%, with a median of +7%. Preliminary E-R analysis predicted median time to 30% decrease in TV of 3 months with the 1.2 mg once daily regimen.

Conclusions: Substantial early and rapid reductions in T2W and TV on MRI preceded eventual RECIST responses in adults with DT treated with varegacestat. These data add to a growing body of work showing T2W and TV may play a role in evaluating treatment response in DT. Future research should evaluate the prognostic or predictive value of these imaging techniques in DT and standardization to allow for use in clinical management of DT patients.

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