**11514** **Poster Discussion Session**

## Tumor volume and T2 hyperintensity changes from DeFi: A phase 3, randomized, controlled trial of nirogacestat in patients with desmoid tumors.

*Thierry Alcindor, Bernd Kasper, Mrinal M. Gounder, Ravin Ratan, Winette T.A. Van Der Graaf, Breelyn A. Wilky, Richard F. Riedel, Noah Federman, Agnese Peruzzi, Stephanie Moody, Allison Lim, Brad Tumminello, Shivaani Kummar, Patrick Schöffski; McGill University Health Center, Montréal, QC, Canada; Universität Heidelberg, Mannheim Cancer Center (MCC), Sarkom Zentrum, Mannheim, Germany; Memorial Sloan Kettering Cancer Center, New York, NY; University of Texas MD Anderson Cancer Center, Houston, TX; Netherlands Cancer Institute, Amsterdam, Netherlands; University of Colorado Anschutz Medical Campus, Aurora, CO; Duke Cancer Institute, Durham, NC; David Geffen School of Medicine UCLA, Los Angeles, CA; Medpace Inc, Cincinnati, OH; PharPoint Research, Durham, NC; SpringWorks Therapeutics, Stamford, CT; Division of Hematology & Medical Oncology, Oregon Health and Science University, Portland, OR; University Hospitals Leuven, Leuven, Belgium*

**Background:** MRI tumor volume or T2 signal intensity changes may represent novel imaging techniques that could have a prognostic or predictive value for assessing response in desmoid tumors (DT). For example, hyperintense areas on T2-weighted images have been associated with active fibroblastic proliferation and ≥90% hyperintensity is associated with DT disease progression, whereas iso- or hypo-intense areas are associated with inactive sites of disease. In DeFi (NCT03785964), the novel gamma secretase inhibitor nirogacestat (n=70 patients) significantly improved the primary endpoint of PFS compared with placebo (n=72 patients; hazard ratio, 0.29 [95% CI, 0.15, 0.55; $P<0.001$]) and significantly improved the secondary endpoint of ORR per blinded, independent central review (41% vs 8%; $P<0.001$). Complete responses were achieved in 7% with nirogacestat and 0% with placebo. Here, we present an exploratory analysis of MRI tumor volume and T2 signal intensity changes in DeFi. **Methods:** Eligible adults had histologically confirmed DT that had progressed ≥20% per RECIST v1.1 within 12 months of screening. Patients were randomized 1:1 to receive nirogacestat 150 mg or placebo twice daily taken continuously in 28-day cycles. Volumetric MRI and T2 hyperintensity of the largest target tumor were evaluated at screening and every 6 cycles during the double-blind phase. MRI T2 signal intensity is represented as the ratio of hyperintensity in total tumor volume to muscle background. A blinded, independent, central radiologist reviewed all MRI scans. **Results:** Nirogacestat treatment led to more substantial reductions versus placebo in tumor volume and T2 hyperintensity ratio (Table). At baseline, similar proportions of patients in each arm had a T2 hyperintensity ratio ≥90% (95% vs 97%). This ratio changed from ≥90% at baseline to <90% at any time after baseline in 34% of patients in the nirogacestat arm and 15% of those on placebo. **Conclusions:** In DeFi, nirogacestat demonstrated substantial reduction of tumor volume and T2 hyperintensity of the largest target tumors by MRI compared with placebo in adults with DT. These results are consistent with the significant improvement in ORR achieved with nirogacestat. These data suggest that volumetric MRI and T2 hyperintensity might provide additional information in the evaluation of treatment response in DT. The prognostic or predictive value of these imaging techniques in DT should be further studied. Clinical trial information: NCT03785964. Research Sponsor: SpringWorks Therapeutics.

**MRI tumor volume and T2 hyperintensity of the largest tumor.**

| Best % change from baseline at any time post-treatment | Median | Interquartile range (Q1, Q3) | Range (min, max) | *P* value |
|---|---|---|---|---|
| **Tumor volume** | | | | |
| **Nirogacestat (n=61)** | –58.9 | –84.7, –8.9 | –100.0, 172.5 | P<0.0001 |
| **Placebo (n=61)** | 13.8 | –26.1, 58.6 | –97.8, 339.0 | |
| **T2 hyperintensity ratio** | | | | |
| **Nirogacestat (n=53)** | –55.1 | –73.5, –20.8 | –100.0, 517.2 | P=0.0001 |
| **Placebo (n=60)** | –19.8 | –42.9, 6.2 | –88.6, 441.7 | |