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# 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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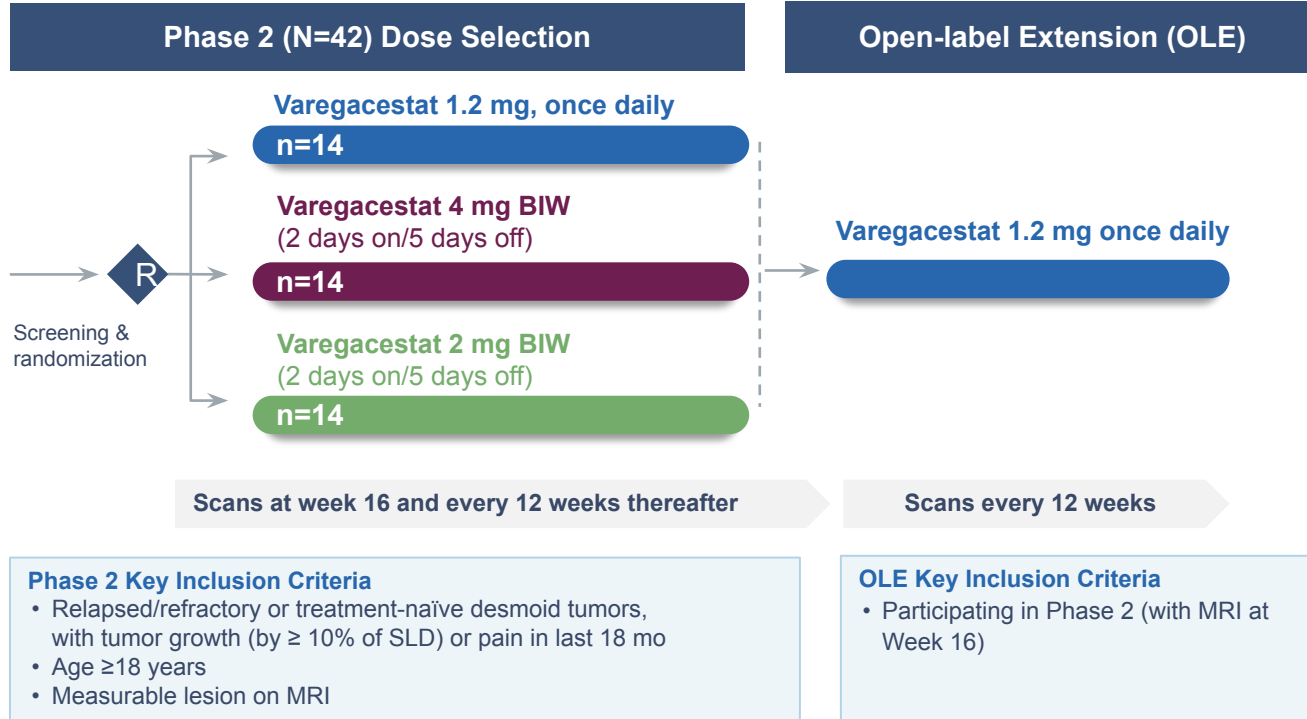
## BACKGROUND

- T2-weighted (T2W) signal intensity and tumor volume on MRI may be more sensitive than RECIST for assessing treatment effect in desmoid tumors (DTs)
- On T2W images, hyperintense areas are associated with active fibroblast proliferation and hypointense areas are associated with loss of tumor cells and an increase in collagenous tissue<sup>1</sup>
- The Phase 2 part of the RINGSIDE study (NCT04871282) demonstrated early and continued MRI-based improvements in DTs with varegacestat (AL102) therapy, and a safety profile consistent with other gamma secretase inhibitors<sup>2</sup>
- We report exploratory analyses of T2W signal intensity, tumor volume and exposure-response (E-R) in the RINGSIDE Phase 2 study

## METHODS

### RINGSIDE Phase 2 Study & Open-Label Extension

Primary Endpoint: Safety  
Secondary Endpoint: Tumor volume reduction at Week 16  
Exploratory Endpoints: ORR by RECIST v1.1 and T2W signal reduction



## Post-hoc Analysis

- Descriptive analysis of T2W signal intensity, tumor volume and RECIST sum of diameters
- Linear correlations of best % changes from baseline on these assessments were evaluated with Pearson correlation coefficient
- A total of 25 responses were observed, of which one PR was unconfirmed
- Exposure-response modeling evaluated time course of drug effect on tumor volume to support selection of 1.2 mg once daily for further study
- Study start: Oct. 6, 2021 | Data cutoff: Jan. 6, 2025
- 42 participants enrolled | 29 (69%) entered the OLE
- Median time on treatment: 23.3 months (range 0.7 – 38.8)
- 12 participants (29%) still on treatment

## Study Population

Characteristics	1.2 mg once daily (n=14)	All doses (N=42)
Age (years), median (min, max)	44.0 (24, 61)	38.5 (19, 72)
Sex, n (%) – Female   Male	11 (78.6)   3 (21.4)	31 (73.8)   11 (26.2)
ECOG Performance Status, n (%) – 0   1	14 (100.0)   0	35 (83.3)   7 (16.7)
Tumor Location at Initial Diagnosis, n (%)		
Intra Abdominal	5 (35.7)	12 (28.6)
Extra Abdominal	9 (64.3)	30 (71.4)
Tumor volume at baseline (cm <sup>3</sup> ), median (min, max)	46.30 (1.4, 244.9)	65.10 (1.4, 1270.3)
Prior Desmoid Tumor Systemic Therapies, n (%)	9 (64.3)	29 (69.0)
Prior Desmoid Tumor Surgeries, n (%)	7 (50.0)	19 (45.2)
Prior Desmoid Tumor Radiation Therapies, n (%)	1 (7.1)	4 (9.5)

Abbreviations: BICR, blinded independent central review | BIW, intermittent dosing 2 days on/5 days off | CR, complete response | ITT, intention to treat | MRI, magnetic resonance imaging | SLD, sum of largest diameters | SD, stable disease | OLE, open-label extension | ORR, objective response rate | PR, partial response | PD, progressive disease | QD, once daily | RECIST, Response Evaluation Criteria in Solid Tumors | T2W, T2-weighted

References: 1. Zanchetta E, et al. Magnetic resonance imaging patterns of tumor response to chemotherapy in desmoid-type fibromatosis. *Cancer Medicine*. 2021;10:4356–4365. | 2. Kasper B, et al. Updated Results of the RINGSIDE Phase 2 Trial and Open-Label Extension of AL102 for Treatment of Desmoid Tumors. Poster at: European Society for Medical Oncology Annual Meeting, Sep.13-17, 2024, Barcelona, Spain.

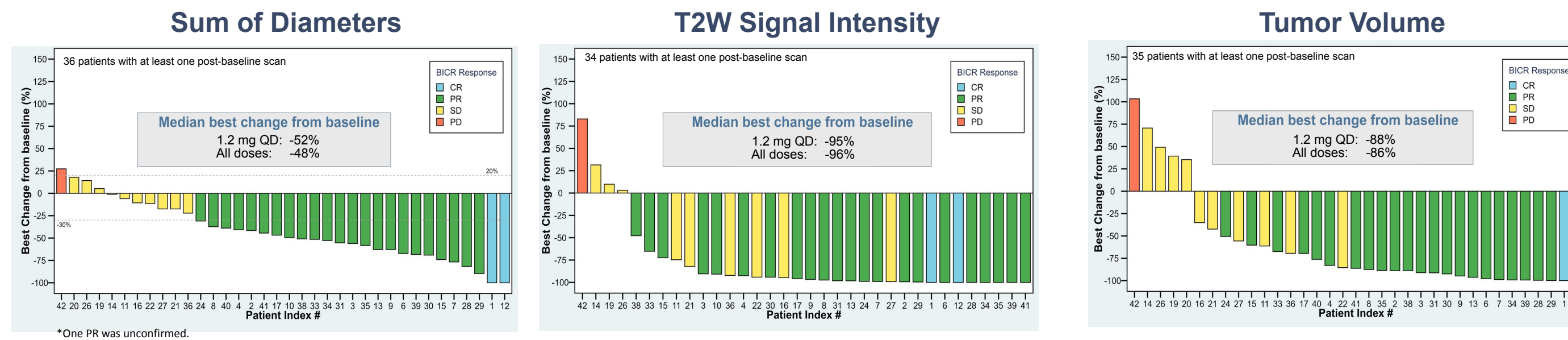
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## RESULTS

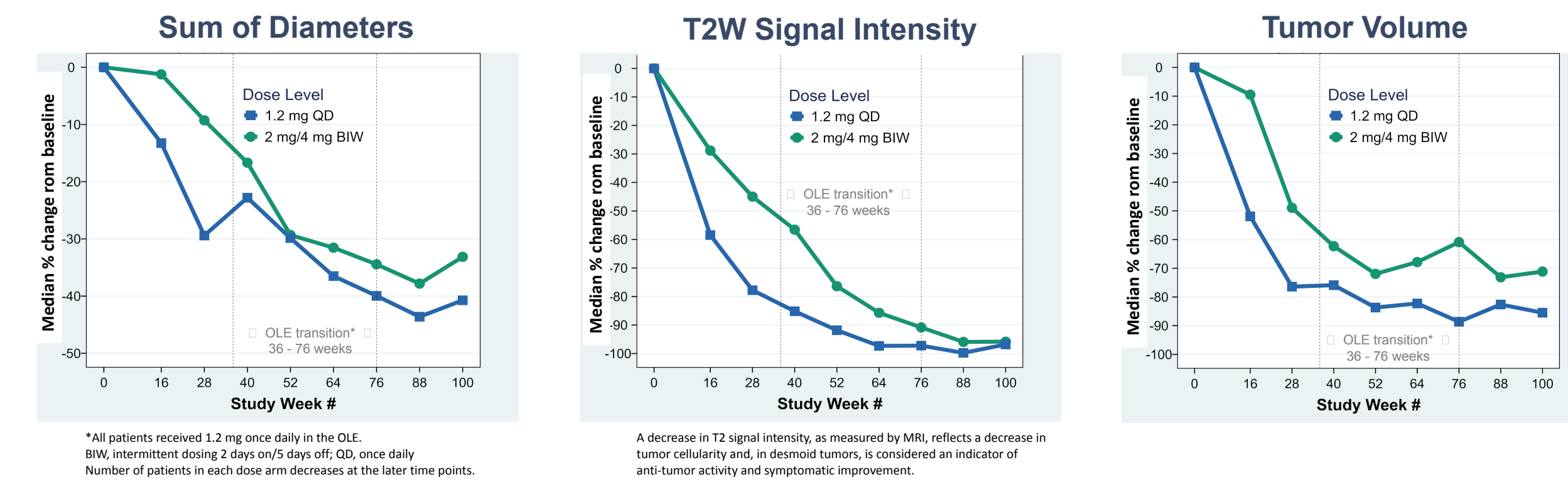
### Best % Change from Baseline by RECIST Response

Color coding by RECIST response\* shows 5-6 additional SD patients that may be responders by T2W and volume assessments



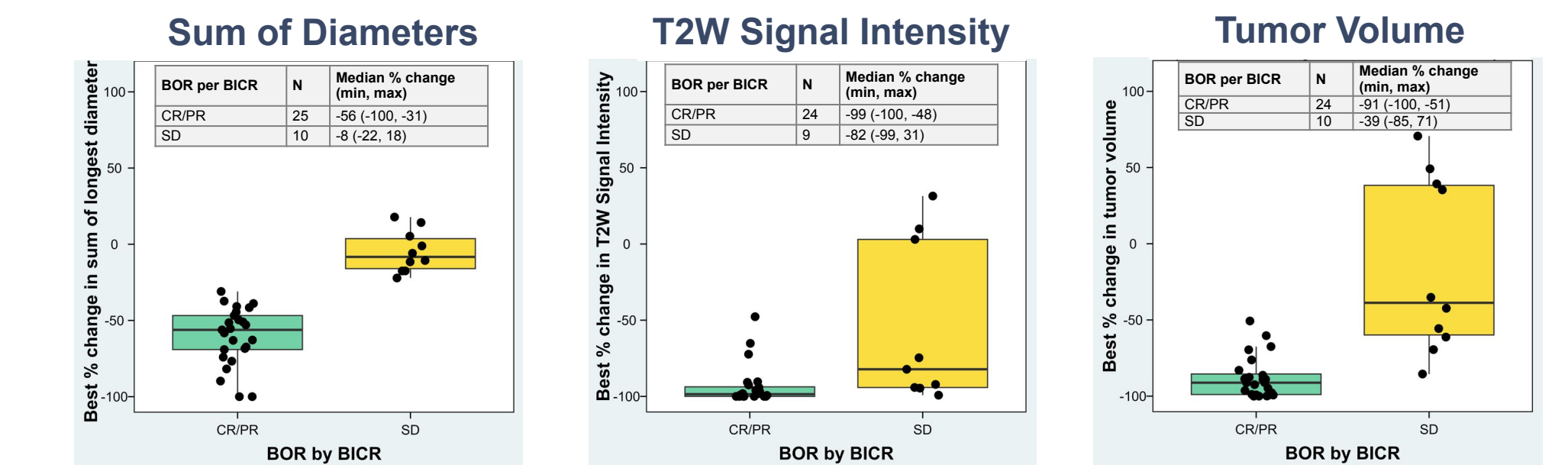
### Median % Changes Over Time

Overall, median % changes at Week 16 were -8% by sum of diameters, -39% by T2W, and -24% by tumor volume



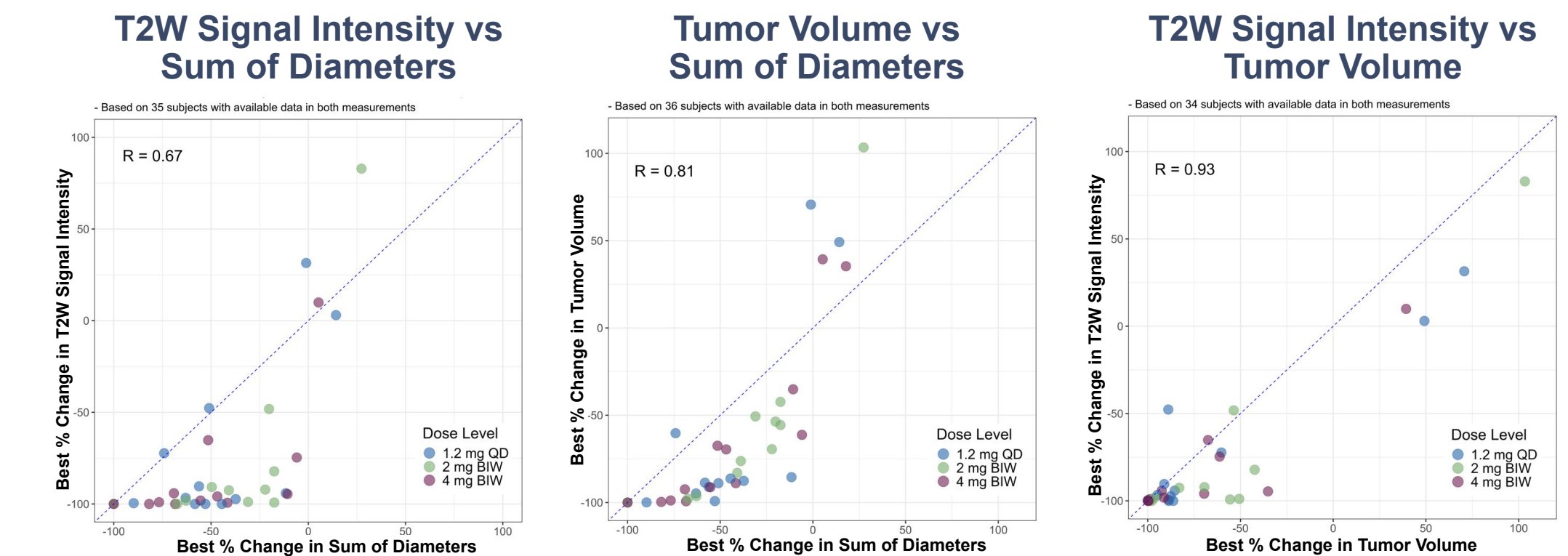
### Median Best % Change in Patients with CR/PR and SD

Increased sensitivity of T2W signal intensity and tumor volume show 5-6 SD patients overlap with RECIST v1.1 responders



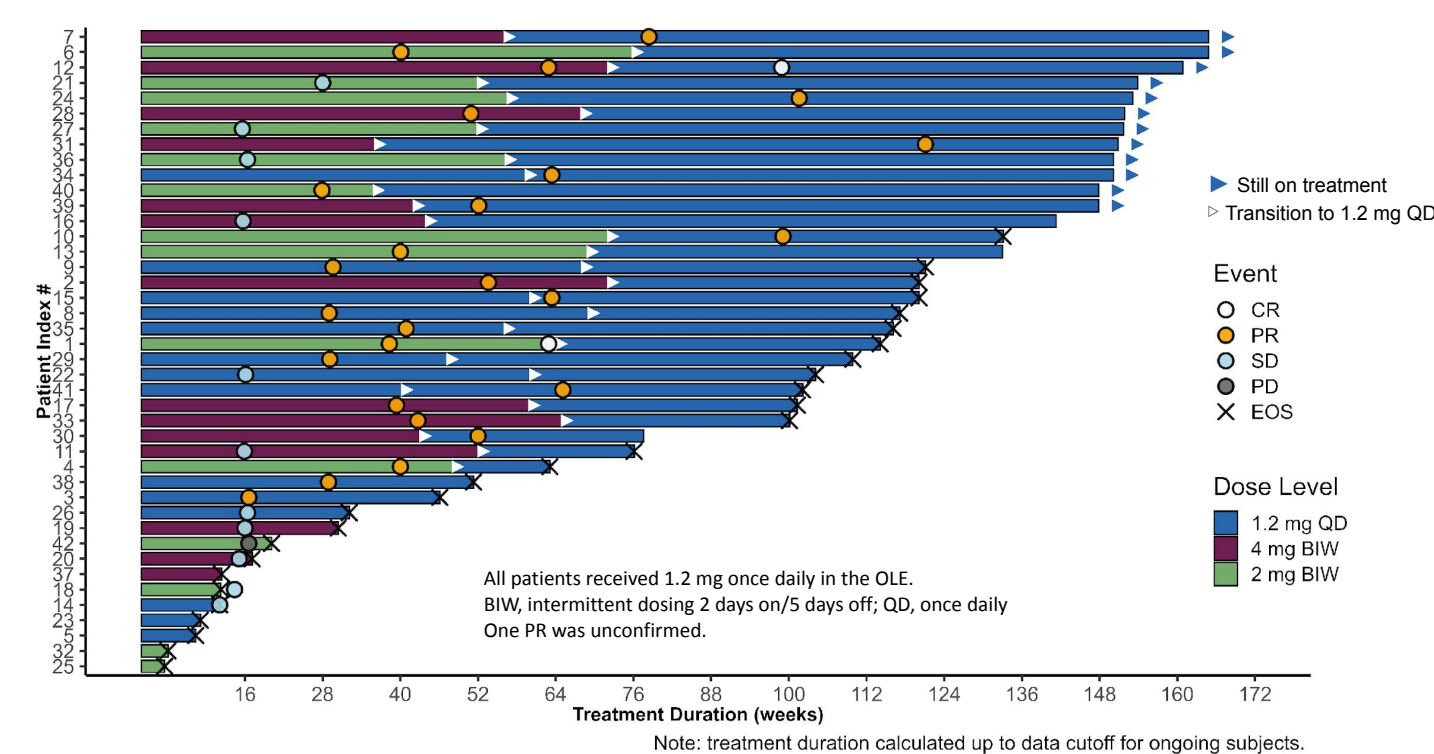
### Best % Change: Correlations Among T2W, Volume, SOD

- T2W and volume demonstrated positive correlation with sum of diameters (R=0.67 and R=0.81, respectively)
- T2W and volume were highly correlated (R=0.93)



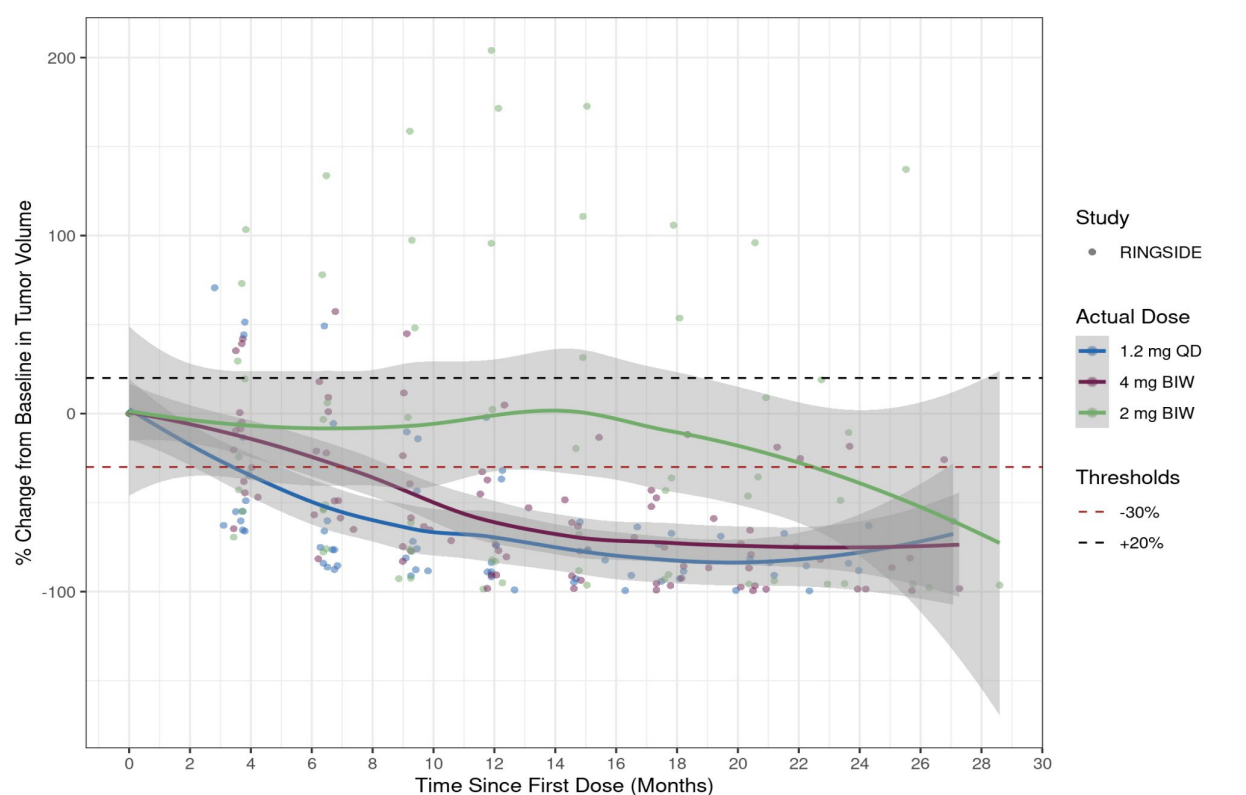
## Treatment Duration and Time to Response

Treatment duration: median 112 weeks | maximum: 165 weeks



## Exposure-Response Analysis

Predicted median time to 30% decrease in tumor volume was 3 months with the 1.2 mg once daily regimen



## CONCLUSIONS

- Substantial early and rapid reductions in T2W signal intensity and tumor volume on MRI preceded subsequent varegacestat responses by RECIST in adults with DT
- These data add to a growing body of work showing T2W signal intensity and tumor volume may play a key 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 patient
- Exploratory exposure-response modelling suggested that 1.2 mg once daily dose achieves earlier and deeper response than the other dose regimens