Exposure-Response (ER) Analyses to Support the Recommended Dose of Varegacestat (VAR) for Patients With Desmoid Tumors (DT)

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BACKGROUND

- VAR is an investigational once daily (QD), oral gamma secretase inhibitor (GSI) that is in development for the treatment of DT.
- Recently reported outcomes in the RINGSIDE study met primary and all key secondary endpoints with a manageable safety profile (Gounder MM, et al (2026) *J Clin Oncol* **44**, Abs #11506).
- This analysis aimed to characterize the relationship between VAR plasma exposure and selected efficacy endpoints in patients with progressing desmoid tumors (DTs) and safety endpoints in patients with advanced solid tumors (ASTs) and DTs. The analysis also investigated the effects of selected covariates on ER model parameters to support dosage recommendations.

METHODS

- Incidence of efficacy and safety endpoints was assessed across a pool of patients with DT and solid tumors in Phase 1 to Phase 3 studies treated across a dose range of 0.3 to 2 mg QD, as well as 2, 4, and 8 mg twice weekly (BIW). Ovarian toxicity (OT) and serious adverse events (SAEs) were also assessed.

Modeling Approach	Efficacy Endpoints	Safety Endpoints
Logistic regression	•ORR	•Grade 2+ TEAEs: hypophosphatemia, ALT elevation, fatigue, diarrhea, and nausea/vomiting •TESAEs
Cox PH	•PFS	•Time to First Onset: •Grade 2+ rash •Ovarian toxicity
Nonlinear mixed-effects (TGI Model)	•Tumor Volume (TTV) •Tumor Size (SLD)	

Exposure Metrics for both analysis were: $C_{avg,0\text{-}t}$, $mC_{avg,0\text{-}t}$, $C_{avg,ss}$, $C_{max,ss}$, $C_{min,ss}$.

DATA DISPOSITION

- Efficacy analysis included 198 participants from Ph2/3 RINGSIDE study (DT):
  - 42 participants treated with VAR from Part A.
  - 79 treated with VAR and 77 treated with placebo from Part B.
- Safety analysis included 157 participants treated with VAR:
  - 36 from Ph1 Study CA002001 (solid tumors).
  - Ph2/3 RINGSIDE study (DT), 42 from Part A and 79 from Part B.

DOSE STRATIFICATION FOR ER ANALYSIS

Dose Levels	N	CA002-001	RINGSIDE Part A	RINGSIDE Part B
0.3 mg QD	2	2 (100.0)	0 (0.0)	0 (0.0)
0.6 mg QD	2	2 (100.0)	0 (0.0)	0 (0.0)
1.2 mg QD	99	6 (6.1)	14 (14.1)	79 (79.8)
1.5 mg QD	7	7 (100.0)	0 (0.0)	0 (0.0)
2 mg QD	7	7 (100.0)	0 (0.0)	0 (0.0)
2 mg BIW	16	2 (12.5)	14 (87.5)	0 (0.0)
4 mg BIW	16	2 (12.5)	14 (87.5)	0 (0.0)
8 mg BIW	8	8 (100.0)	0 (0.0)	0 (0.0)
All Data	157	36 (22.9)	42 (26.8)	79 (50.3)

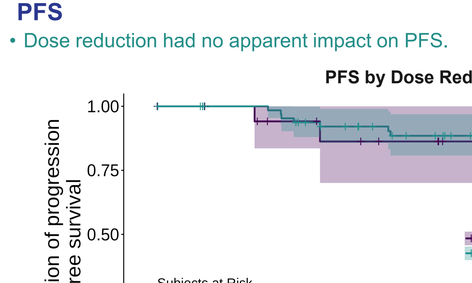
Covariate	Efficacy Population: Treatment Group N = 121	Efficacy Population: Placebo Group N = 77	Safety Population: Treatment Group N = 157
Sex			
Male	37 (30.6%)	29 (37.7%)	54 (34.4%)
Female	84 (69.4%)	48 (62.3%)	103 (65.6%)
Baseline ECOG score			
0	93 (76.9%)	61 (79.2%)	103 (65.6%)
1	28 (23.1%)	16 (20.8%)	53 (33.8%)
Age (years) Median (min-max)	40 (18-72)	39 (20-69)	45 (18-84)

EXPOSURE-EFFICACY RELATIONSHIP

Total Tumor Volume (TTV)/Sum of Longest Diameter (SLD)

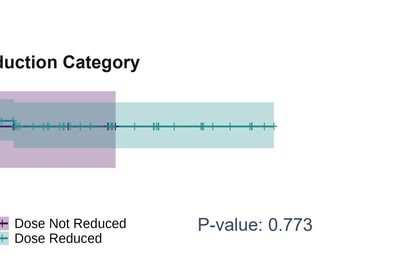
- No impact of dose reductions on TTV/SLD.
- At 1.2 mg QD, TGI models predicted greater target attainment at Week 48 compared to 0.9 mg QD.

Observed TTV over Time by Dose Reduction Category



Starting dose of 1.2 mg QD. Presented in median percent change from baseline.

Observed SLD over Time by Dose Reduction Category



Starting dose of 1.2 mg QD. Presented in median percent change from baseline.

ORR

- Trend toward increase in ORR with higher VAR C_{avg}, however not statistically significant (p = 0.0818).
- Trend toward decreasing ORR with lower starting dose compared to 1.2 mg QD.

ORR vs. VAR exposure

Model-Simulated ORR vs. VAR Starting Dose

PFS

- Dose reduction had no apparent impact on PFS.

PFS by Dose Reduction Category

KEY SAFETY OUTCOMES ACROSS POOLED ANALYSIS of Ph2/3 RINGSIDE + Ph1 CA002001

- Most frequently occurring Grade 2+ TEAEs: rash, diarrhea, nausea/vomiting, fatigue and hypophosphatemia.

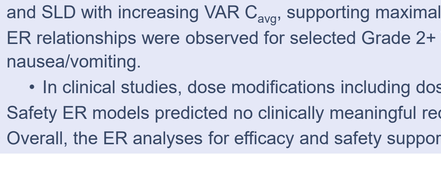
AE of Interest	Treatment-emergent serious adverse events (TESAEs)	Grade 2+ hypophosphatemia	Grade 2+ fatigue	Grade 2+ nausea/vomiting	Grade 2+ diarrhea	Ovarian toxicity[a]	Grade 2+ rash	Grade 2+ ALT elevation
Incidence (%)	49 (31.2)	47 (29.9)	43 (27.4)	31 (19.7)	59 (37.6)	32 (50.0)	58 (36.9)	9 (5.7)

Note: Safety analysis population count was (N = 157) for all endpoints except ovarian toxicity (N = 64).
[a]Ovarian toxicity included amenorrhea, premature menopause, menopause, and ovarian failure; and all were Grade 2.

EXPOSURE-SAFETY RELATIONSHIP

- Identified statistically significant (p < 0.05) ER relationships for VAR C_{avg} and the endpoints TESAEs, Grade 2+ TEAEs: nausea/vomiting, fatigue, diarrhea, hypophosphatemia and rash. No statistically significant relationship was observed between VAR exposure and Grade 2+ ALT elevation and ovarian toxicity.
- Model predictions did not indicate a clinically meaningful reduction in the incidence of AEs at reduced starting doses compared to 1.2 mg QD.

Grade 2+ Nausea/Vomiting vs. VAR Exposure



Grade 2+ Fatigue vs. VAR Exposure

Grade 2+ Diarrhea vs. VAR Exposure

Model Predictions of Logistic Regression Safety Endpoints Using Starting Doses of 0.6, 0.9, and 1.2 mg QD VAR

CONCLUSIONS

- Although exposure was not a statistically significant predictor of PFS and ORR, increasing trends were observed in ORR, TTV, and SLD with increasing VAR C_{avg}, supporting maximal efficacy at 1.2 mg QD.
- ER relationships were observed for selected Grade 2+ TEAEs; including rash, fatigue, diarrhea, hypophosphatemia, and nausea/vomiting.
  - In clinical studies, dose modifications including dose reductions, were effective in managing these AEs.
- Safety ER models predicted no clinically meaningful reduction in AE rates at reduced starting doses of 0.9 or 0.6 mg QD.
- Overall, the ER analyses for efficacy and safety support 1.2 mg QD as the recommended dose.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ASTs = advanced solid tumors; BIW = twice weekly; $C_{avg,0\text{-}t}$: average concentration from first dose (time 0) to the time of safety assessment, AE occurrence or censoring (t); $C_{avg,ss}$: steady-state average concentration; $C_{max,ss}$: steady-state maximum concentration; $C_{min,ss}$: steady-state minimum concentration; DTs = desmoid tumors; ECOG = Eastern Cooperative Oncology Group; ER = exposure-response; GSI = gamma-secretase inhibitor; Gr2+ = Grade 2+; Max = maximum; $mC_{avg,0\text{-}t}$: modified average concentration from first dose (time 0) to the time of safety assessment, AE occurrence or T_{max}, where T_{max} is the maximum observed time-to-event across all patients with events; Min = minimum; N = number of participants; ORR = objective response rate; OT = ovarian toxicity; PCFB = percent change from baseline; PFS = progression-free survival; Ph = Phase; QD = once daily; SAEs = serious adverse events; SLD = sum of longest diameter; TEAEs = treatment-emergent adverse events; TESAEs = treatment-emergent serious adverse events; TGI = tumor growth inhibition; TTV = total tumor volume; VAR = Varegacestat

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