Poster: PI-062

Exposure-Response Analyses for Vimseltinib in Patients With Tenosynovial Giant Cell Tumor

Binfeng Xia, Chengyue Zhang, Christopher Tait, Amanda Saunders, Frederic J Reu, Qiang Lu

Deciphera Pharmaceuticals, LLC, Waltham, MA, USA

Introduction

- Tenosynovial giant cell tumor (TGCT) is a locally aggressive neoplasm caused by dysregulation of the colony-stimulating factor 1 (*CSF1*) gene leading to overproduction of CSF1[1,2]
  - The disease is not always amenable to surgery, and these patients require systemic therapies[2]
- Vimseltinib is an oral, switch-control tyrosine kinase inhibitor designed to selectively and potently inhibit the CSF1 receptor (CSF1R)[3,4]
  - Vimseltinib was approved in February 2025 by the US Food and Drug Administration (FDA) for the treatment of adult patients with symptomatic TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity[5]
  - In September 2025, vimseltinib was also approved by the European Commission for the treatment of TGCT in a similar patient population[6]
- In the phase 3 MOTION trial (NCT05059262), vimseltinib demonstrated robust antitumor activity versus placebo per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and per Tumor Volume Score (TVS) as well as a favorable safety profile in patients with TGCT not amenable to surgery[7]
- Here, we characterize the exposure-response (E-R) relationship between vimseltinib and 2 key efficacy endpoints in TGCT (objective response rate [ORR] and tumor size dynamics) using data from the pivotal MOTION phase 3 trial

Methods

- The data used for this analysis was derived from the multicenter, randomized, placebo-controlled, phase 3 MOTION trial (NCT05059262; data cutoff: August 22, 2023)[7]
- Pharmacokinetic (PK) metrics were derived for each patient using a previously developed population PK model
- ORR per RECIST v1.1 and per TVS at week 25 were modeled as a binary endpoint using logistic regression models
  - The average vimseltinib concentration during a dosing interval at steady state ($C_{avg,\ ss}$) was selected as an exposure metric
  - The statistical significance for all covariate effects (age, sex, race, main tumor location for tumor size, and tumor type) was tested by a backward deletion procedure to arrive at the final models
- The models for longitudinal tumor size per RECIST v1.1 and TVS were developed based on a published model for TGCT dynamics under treatment with a CSF1R inhibitor (**Equation**)[8]
  - The average concentration up to the time of pharmacodynamic measurement; CSF1R, colony-stimulating factor 1 receptor; E_{max}, maximum effect; k_{drug}, first-order rate constant of exposure effect; k_{growth}, tumor natural growth rate constant; k_{onset}, first-order rate constant of onset effect; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; t, time elapsed since the beginning of the observation period; TAFD, time after first active dose; TS_0, baseline tumor size; Y(t), tumor size per RECIST v1.1 or TVS; TVS, Tumor Volume Score.
  - A stepwise covariate model with adaptive scope reduction was used for the evaluation of covariate-parameter relationships

Equation. Model for TGCT dynamics under treatment with a CSF1R inhibitor[8]

$$Y_t(t) = TS_0 \times [1 - E_{max} \times (1 - e^{-k_{drug} \times C_{av,\ PD}}) \times (1 - e^{-k_{onset} \times TAFD_t(t)})] + k_{growth} \times t$$

$C_{av,\ PD}$, average concentration up to the time of the pharmacodynamic measurement; CSF1R, colony-stimulating factor 1 receptor; E_{max}, maximum effect; k_{drug}, first-order rate constant of exposure effect; k_{growth}, tumor natural growth rate constant; k_{onset}, first-order rate constant of onset effect; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; t, time elapsed since the beginning of the observation period; TAFD, time after first active dose; TS_0, baseline tumor size; Y(t), tumor size per RECIST v1.1 or TVS; TVS, Tumor Volume Score.

Results

- In total, 117 patients from the MOTION trial were included in the E-R analysis (vimseltinib 30 mg twice weekly [BIW], n = 83; placebo, n = 34)

E-R analysis of ORR

- In the ORR per RECIST v1.1 analysis data set at week 25, 40% of patients receiving vimseltinib versus none of those receiving placebo responded to treatment; in the ORR per TVS analysis data set, 67% of patients receiving vimseltinib versus none of those receiving placebo responded to treatment (**Table 1**)

Table 1. ORR by IRR per RECIST v1.1 and TVS at week 25 in E-R population

	RECIST v1.1			TVS		
ORR at week 25, n (%)	Vimseltinib n = 83	Placebo n = 34	Overall N = 117	Vimseltinib n = 83	Placebo n = 34	Overall N = 117
Responder[a]	33 (40)	0	33 (28)	56 (67)	0	56 (48)
Nonresponder[b]	50 (60)	34 (100)	84 (72)	27 (33)	34 (100)	61 (52)

[a]Responders include patients with complete and partial responses. [b]Nonresponders include patients with stable disease or those who were not evaluable.
E-R, exposure-response; IRR, independent radiological review; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TVS, Tumor Volume Score.

- Demographic and baseline clinical characteristics were balanced among analyzed patients receiving vimseltinib vs placebo; most patients were White, and baseline tumor size was comparable between treatment groups (**Table 2**)

Table 2. Baseline patient characteristics in the E-R population

	Vimseltinib n = 83	Placebo n = 34	Overall N = 117
Age, year, median (range)	45 (20–78)	43 (21–66)	44 (20–78)
Sex, female, n (%)	46 (55)	23 (68)	69 (59)
Race, n (%)			
White	59 (71)	20 (59)	79 (68)
Asian	1 (1)	3 (9)	4 (3)
Black or African American	4 (5)	0	4 (3)
Unknown or not reported	19 (23)	11 (32)	30 (26)
Body weight, kg, median (range)	80.0 (46.7–142)	73.4 (43.0–109)	78.0 (43.0–142)
Tumor location, n (%)			
Lower limb	73 (88)	30 (88)	103 (88)
All others	10 (12)	4 (12)	14 (12)
Tumor size per RECIST v1.1, mm, median (range)	63.4 (16.1–246)	57.0 (16.3–156)	62.5 (16.1–246)
TVS, median (range)	6 (1–80)	6.5 (1–100)	6 (1–100)

E-R, exposure-response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TVS, Tumor Volume Score.

- Exposure metrics calculated based on empirical Bayes estimates obtained from the vimseltinib population PK model are presented in **Table 3**

Table 3. Distribution of vimseltinib exposure metrics in E-R population

	Vimseltinib n = 83
$C_{avg,\ ss}$ (ng/mL)	
Mean (SD) [CV%]	642 (239) [37.2]
Median (range)	576 (113–1470)
Geometric mean (geometric CV%) [geometric CI]	598 (41.4) [549–651]
$C_{max,\ ss}$ (ng/mL)	
Mean (SD) [CV%]	856 (286) [33.4]
Median (range)	826 (169–1710)
Geometric mean (geometric CV%) [geometric CI]	808 (37.2) [748–873]
$C_{min,\ ss}$ (ng/mL)	
Mean (SD) [CV%]	491(209) [42.6]
Median (range)	450 (61.2–1250)
Geometric mean (geometric CV%) [geometric CI]	446 (50.0) [403–494]

$C_{avg,\ ss}$, average concentration during a dosing interval at steady state; CI, confidence interval; $C_{max,\ ss}$, maximum plasma drug concentration at steady state; $C_{min,\ ss}$, minimum plasma drug concentration at steady state; CV, coefficient of variation; E-R, exposure-response; SD, standard deviation.

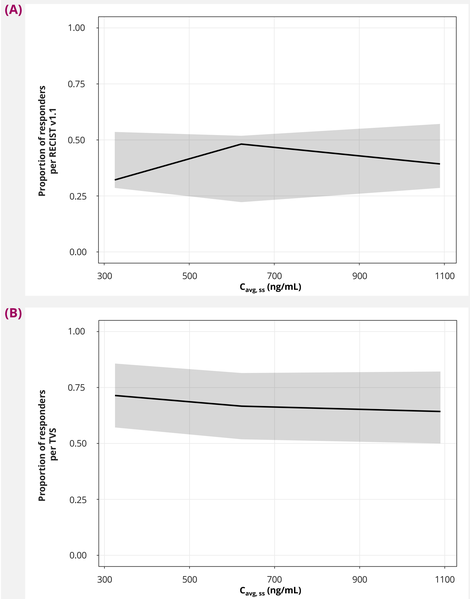
- A covariate effect of baseline tumor size on ORR per RECIST v1.1 was observed, whereas no such covariate effect was identified in the model for ORR per TVS (**Table 4**)
  - There were no covariate effects of age, sex, race, or tumor location for either RECIST v1.1 or TVS
- E-R analyses did not show differences in ORR per RECIST v1.1 and ORR per TVS at different levels of exposure within the evaluated vimseltinib 30 mg BIW dose group (**Figure 1**)

Table 4. Parameter estimates for final E-R model for ORR per RECIST v1.1 and per TVS

Final model for ORR per RECIST v1.1				Final model for ORR per TVS			
Parameter	Estimate	RSE (%)	*P*-value	Parameter	Estimate	RSE (%)	*P*-value
Population values				**Population values**			
Base[a] (probability)	0.405	63.0	0.112	Base[a] (probability)	0.682	32.3	0.00194
$Slope_{Cavg,\ ss}$, LO per ng/mL	-3.34×10^{-5}	3.04×10^{3}	0.974	$Slope_{Cavg,\ ss}$, LO per ng/mL	-4.48×10^{-4}	2.17×10^{2}	0.646
Baseline tumor size effect, LO per mm	−0.0171	41.1	0.0151	Baseline TVS effect, LO	N/A	N/A	N/A
Residual error, sigma	1.14			**Residual error, sigma**	1.14		

RSEs are reported on the LO scale. [a]The base parameter reflects the probability of response for a reference patient with $C_{avg,\ ss}$ of 576 ng/mL and with age: 45 years; tumor size: 63.4 mm (RECIST v1.1) or 6 (TVS); sex: female; race: White or missing; tumor location: lower limb.
$C_{avg,\ ss}$, average concentration during a dosing interval at steady state; E-R, exposure-response; LO, log odds; N/A, not applicable; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RSE, relative standard error; TVS, Tumor Volume Score.

Figure 1. Visual predictive checks for final E-R models for ORR per (A) RECIST v1.1 and per (B) TVS



The thick line corresponds to the observed fractions of responders, and the shaded area corresponds to the associated predicted 90% CI. The x-axis positions are centered between the corresponding tertile boundaries.
$C_{avg,\ ss}$, average concentration during a dosing interval at steady state; CI, confidence interval; E-R, exposure-response; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TVS, Tumor Volume Score.

- At the recommended vimseltinib regimen of 30 mg BIW, ORR per RECIST v1.1 and ORR per TVS at week 25 were predicted to be 41.4% and 68.5%, respectively; no responders were observed with placebo

E-R analysis of longitudinal tumor size

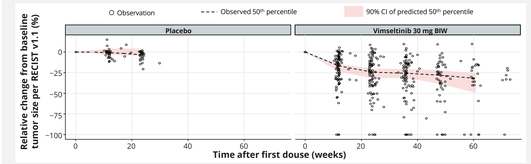
- Baseline characteristics for tumor size per RECIST v1.1 or per TVS for the E-R population are presented in **Table 2**
- The final tumor size per RECIST v1.1 or per TVS models corresponded to a decrease in tumor size with increasing vimseltinib $C_{av,\ PD}$ and time under vimseltinib treatment (**Tables 5, 6 and Figures 2, 3**)
  - Covariate analysis indicated that none of the tested covariates had a statistically significant impact on tumor size per RECIST v1.1 or per TVS

Table 5. Parameter estimates for final E-R model for tumor size per RECIST v1.1

Parameter	Value	RSE (%)	SHR (%)
TS_0, mm	57.3	5.21	
k_{growth}, mm/day	0	(FIX)	
k_{drug}, ng/mL^{-1}	0.00109	17.5	
E_{max}	1.0	(FIX)	
k_{onset}, day^{-1}	0.00783	21.9	
IIV TS_0, CV	0.560	5.97	2.89
IIV k_{drug}, CV	0.999	10.8	21
TS_0–k_{drug}, correlation	−0.339	15.0	
IIV K_{onset}, CV	0.736	14.0	42.2
RUV add., mm	5.13	17.0	23.0

CV, coefficient of variation; E_{max}, maximum effect; E-R, exposure-response; FIX, fixed effect; IIV, inter-indusvial variability; k_{drug}, first-order rate constant of exposure effect; k_{growth}, tumor natural growth rate constant; k_{onset}, first-order rate constant of onset effect; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RSE, relative standard error; RUV add., additive residual unexplained variability; SHR, percentage of shrinkage; TS_0, baseline tumor size.

Figure 2. Visual predictive checks for final E-R model for tumor size per RECIST v1.1



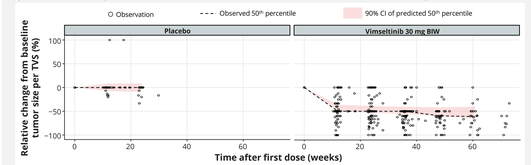
Data are presented on linear scale.
BIW, twice weekly; CI, confidence interval; E-R, exposure-response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Table 6. Parameter estimates for final E-R model for tumor size per TVS

Parameter	Value	RSE (%)	SHR (%)
TS_0	5.91	9.48	
k_{growth}, day^{-1}	0	(FIX)	
k_{drug}, ng/mL^{-1}	0.00109	32.7	
E_{max}	0.546	7.02	
k_{onset}, day^{-1}	0.0272	25.6	
IIV TS_0, CV	1.04	5.78	0.633
IIV E_{max}, SD	1.38	25.0	14
TS_0–E_{max}, correlation	0.160	33.8	
IIV k_{drug}, CV	0.744	37.2	79.8
IIV k_{onset}, CV	0.643	32.7	47.1
RUV prop., CV	0.152	34.2	24.6
RUV add.	0.0920	96.0	24.6

CV, coefficient of variation; E_{max}, maximum effect; FIX, fixed effect; E-R, exposure-response; IIV, inter-indusvial variability; k_{drug}, first-order rate constant of exposure effect; k_{growth}, tumor natural growth rate constant; k_{onset}, first-order rate constant of onset effect; RSE, relative standard error; RUV add., additive residual unexplained variability; RUV prop., proportional residual unexplained variability; SD, standard deviation; SHR, percentage of shrinkage; TS_0, baseline tumor size; TVS, Tumor Volume Score.

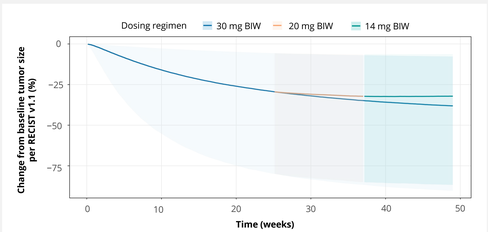
Figure 3. Visual predictive checks for final E-R model for tumor size per TVS



Data are presented on linear scale.
BIW, twice weekly; CI, confidence interval; E-R, exposure-response; TVS, Tumor Volume Score.

- Dose reductions after 24 weeks of treatment with 30 mg vimseltinib BIW appeared to have little impact on the predicted tumor dynamics (**Figure 4**)

Figure 4. Predicted change from baseline tumor size per (A) RECIST v1.1 and (B) TVS versus time with vimseltinib dose reduction from 30 mg BIW, to 20 mg BIW, to 14 mg BIW



The solid line is the median of the simulation, and the shaded region is the 90% prediction interval.
BIW, twice weekly; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TVS, Tumor Volume Score.

CONCLUSIONS

- The E-R relationship of vimseltinib in patients with TGCT reinforces the US FDA–approved regimen of 30 mg BIW
- The E-R relationship between vimseltinib $C_{avg,\ ss}$ and ORR per RECIST v1.1 and TVS at week 25 in patients with TGCT was well characterized by a logistic regression model
- The final models showed good predictive performance for reduction in tumor size over time per RECIST v1.1 and per TVS after treatment with vimseltinib

PRESENTED AT THE 2026 ASCPT ANNUAL MEETING; DENVER, CO, USA; MARCH 4–6, 2026

CORRESPONDING AUTHOR

Binfeng Xia, PhD
binfeng.xia@decipherapharmaceuticals.com

ACKNOWLEDGMENTS

We thank the patients and their families and caregivers, the investigators, and the investigational site staff for the MOTION study. We thank Fanny Gallais and Maarten van Eijk from Pharmetheus for their support in the model development. The MOTION study is sponsored by Deciphera Pharmaceuticals, LLC, a Member of ONO Pharma.
Medical writing support was provided by Marisa Chakhtoura, MSc, PhD, and Alisa Cario, PhD of Red Nucleus, and was funded by Deciphera Pharmaceuticals, LLC.

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DISCLOSURES

All authors are employees of Deciphera Pharmaceuticals, LLC.