Poster W-017

Exposure-Response Analysis of Efficacy and Safety for Pexidartinib in Patients With Tenosynovial Giant Cell Tumor (TGCT)

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INTRODUCTION

Background

- Pexidartinib is a novel oral small-molecule inhibitor that selectively targets colony-stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication mutation[1,2]
- Pexidartinib has demonstrated significant tumor response and improvements in function in patients with symptomatic tenosynovial giant cell tumor (TGCT) that is associated with severe morbidity or functional limitations not amenable to improvement with surgery[3]

Objective

- To evaluate the exposure-response relationships for efficacy and safety endpoints to support pexidartinib dose selection in patients with TGCT

METHODS

Data Source and Study Design

- A summary of study subjects, endpoints, and covariates included in the analysis is presented in **Table 1**

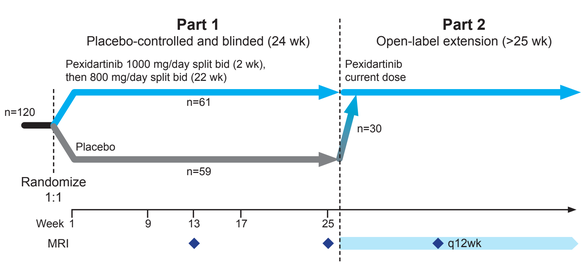
Table 1. Summary of Studies, Endpoints, and Covariates Included in Analysis

Analysis	Studies	N	Endpoints	Covariates Evaluated
Exposure-efficacy	ENLIVEN	113	RECIST at week 25, reported as the sum of the longest tumor diameter[3] TVS response at week 25, reported as tumor volume as a proportion of the maximally distended synovial cavity[3]	Age (years) Body weight (kg) Sex Race (white vs. non-white) Baseline tumor size (mm) Location of investigational site (US vs. ex-US) Joint size (small vs. large) Primary tumor location (upper vs. lower extremity) Study period (1 vs. 2)
PK-PD	PLX108-01 ENLIVEN	141	Longitudinally measured tumor size by RECIST and TVS	Same as above
Exposure-safety	PLX108-01 ENLIVEN	241	ALT >3 × ULN ALT >5 × ULN AST >3 × ULN AST >5 × ULN TBIL >2 × ULN TBIL >2 × baseline	Age (years) Body weight (kg) Sex Race (white vs. non-white) Tumor type (TGCT vs. non-TGCT) Identifier for ENLIVEN placebo crossover patients Baseline lab value for the corresponding endpoint

ALT = alanine aminotransferase, AST = aspartate aminotransferase, PD = pharmacodynamic, PK = pharmacokinetic, RECIST = Response Evaluation Criteria in Solid Tumors, TBIL = total bilirubin, TGCT = tenosynovial giant cell tumor, TVS = tumor volume score, ULN = upper limit of normal.

- Phase 1 Study PLX108-01:
  - First-in-human study evaluating safety, pharmacokinetics (PK), and pharmacodynamics (PD) in patients with TGCT and other solid tumors
  - Pexidartinib was given at 200 mg/day to 1200 mg/day
- Phase 3 Study ENLIVEN (**Figure 1**):
  - Two-part study evaluating efficacy and safety in patients with TGCT
  - Part 1: double-blind, placebo-controlled phase; pexidartinib was given at 1000 mg/day for 2 weeks, followed by 800 mg/day
  - Part 2: open-label extension phase; pexidartinib was given at 800 mg/day

Figure 1. ENLIVEN Study Design



Modeling Approach

- PK-PD modeling of longitudinally measured tumor size
  - Non-linear mixed effect modeling incorporating tumor growth and the magnitude and time of onset of drug effect

$$Y_{ij} = Y_{0,i}\left(1 - E_{max} \times \left(1 - e^{-k_{drug} \times Cavg_{ij}}\right)\left(1 - e^{-k_{onset} \times TAFD_{ij}}\right)\right) + \theta_i \times time$$

    where $Y_{0,i}$ is the baseline tumor size, θ_i is tumor natural growth rate in subject i, $Cavg_{ij}$ is average concentration up to tumor measurement time j in subject i, and TAFD is time after first dose. k_{drug} and k_{onset} refer to rate constant of exposure effect and onset effect respectively
  - Models were developed using NONMEM Version 7.4. The first-order conditional estimation with interaction (FOCEI) method was used for all model runs
  - Covariate effects were assessed on baseline tumor size first, then on drug effect and onset effect, by inspection of covariate relationships with inter-individual random effects
- Exposure-response analysis of tumor response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) or tumor volume score (TVS)
  - Proportional odds logistic regression models with potentially non-linear effects of exposure (e.g., sigmoidal E_{max} relationships), where response variables were ordered as non-response (Y = 0), partial response (Y = 1), and complete response (Y = 2):

$$logit[P(Y_i \le j)] = \alpha_j + \frac{E_{max} \times AUC_i^{\gamma}}{EC_{50}^{\gamma} + AUC_i^{\gamma}}, \text{for } j = 0,1$$

    where $AUCi$ is the average daily area under the concentration-time curve up to 25 weeks of dosing for subject i
  - Models were fit in a Bayesian paradigm using Stan.[4] Weakly informative prior distributions were used for model parameters:

$$P(Y = j|E_{max}, EC_{50}, \gamma) = P(Y \le j) - P(Y < j)$$
$$E_{max} \sim N(0,5),\ EC_{50} \sim scale \times N^{+}(0,5),\ \gamma \sim N^{+}(0,3)$$

  - Covariates evaluation included the following steps:
    1. Study period (1 vs. 2) was added first as a covariate on E_{max}, using non-informative $N\ (0,5)$ prior distributions
    2. A full model with all covariates was fitted, using the regularized horseshoe prior for covariate effect coefficient.[5] Covariate effects for which the 50% central credible interval excluded the null value were selected
    3. A reduced full model was fitted with covariates identified above, using non-informative $N\ (0,5)$ prior distributions
    4. A final model was selected including covariates for which the 90% central credible interval excluded the null value
- Exposure-response analysis of liver enzyme elevations
  - Piecewise-exponential time-to-first-event models with hazards assumed to be constant over time intervals of 0-4 weeks, 4-8 weeks, 8-12 weeks, and 12-80 weeks. Linear and non-linear drug effects were evaluated:

$$log(t) = \alpha_k + slope \times Cavg_{ik}, \qquad t \in I_k, k = 1,2,3,4,5$$

$$log(t) = \alpha_k + slope \times log(Cavg_{ik} + 0.01), \quad t \in I_k, k = 1,2,3,4,5$$

$$log(t) = \alpha_k + \frac{E_{max} \times Cavg_{ik}^{\gamma}}{EC_{50}^{\gamma} + Cavg_{ik}^{\gamma}}, \qquad t \in I_k, k = 1,2,3,4,5$$

    where $Cavg_{ik}$ is the average concentration for subject i in interval I_k, $I_1 = [0,2)$, $I_2 = [2,4)$, $I_3 = [4,8)$, $I_4 = [8,12)$, and $I_5 = [12,80)$ weeks
  - Models were fit in a Bayesian paradigm using Stan.[4] Weakly informative prior distributions were used for model parameters:

$$\alpha_k \sim N(-3,5),\ slope \sim N(0,2),\ E_{max} \sim N(0,5),\ EC_{50} \sim N^{+}(0,5),\ \gamma \sim N^{+}(0,3)$$

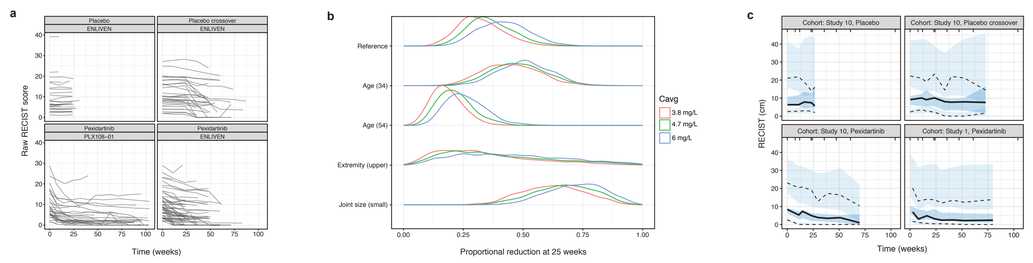
  - Covariate effects were evaluated on baseline hazard or exposure-response relationship, using a full model approach. Non-informative $N\ (0,5)$ prior distributions were used for all covariate effect parameters
- All model qualification was performed using simulation-based predictive checks

RESULTS

- **Exposure-efficacy**
  - Tumor size remained unchanged over 24 weeks in placebo-treated patients; pexidartinib effect was apparent with higher average daily AUC associated with greater reduction in the tumor size. Final model included joint extremity, joint size, and age as covariates on baseline tumor size, drug effect, and onset effect, where joint size had greatest effect (**Figure 2 a-c**)
  - A significant treatment effect with shallow exposure-response relationship was observed for RECIST-based overall response rate (ORR); joint size was identified as a statistically significant covariate on E_{max} (**Figure 3 a-c**)
  - Similar modeling findings were obtained for TVS-based response
- **Exposure-safety**
  - Clinical observation from the ENLIVEN study suggested a lower rate of hepatic adverse effects (30.0% vs. 41.0%) in the crossover subjects who received pexidartinib 800 mg/day, as compared to subjects who received 1000 mg/day for 14 days followed by 800 mg/day
  - Adjusting for potentially prognostic covariates on baseline hazard, a statistically significant exposure-response relationship was estimated for alanine aminotransferase (ALT) >3 × upper limit of normal (ULN) (**Figure 4 a-c**)
  - Significant exposure-response relationships were also estimated for ALT >5 ×ULN, aspartate aminotransferase (AST) >3 × ULN and AST >5 × ULN. An exposure-response relationship for total bilirubin (TBIL) (>2 × ULN or >2 × baseline) was not identified possibly because of low frequency of such events
- **Population simulations**
  - Predicted ORR at week 25 increased as the daily dose increased from 400 mg/day to 800 mg/day, but with no discernable difference between two dose regimens of 800 mg/day versus 1000 mg/day for 14 days followed by 800 mg/day (**Table 2**)
  - Incidence of AST and ALT elevations was predicted to be lower for the 600 mg/day and 400 mg/day regimens (**Table 2**)

RESULTS (CONT)

Figure 2. Longitudinal RECIST-Based Tumor Size PK-PD Modeling: (a) Observed Data, (b) Forest Plot for Covariate Effects, and (c) Visual Predictive Check



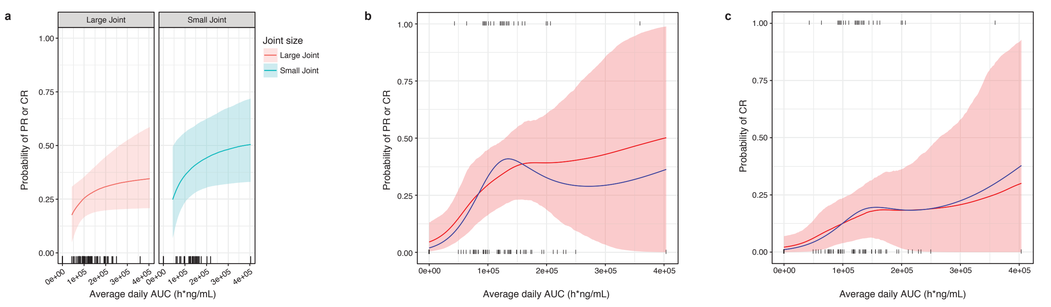
Each line represents the observed tumor size measured over time in individual subject.

For each of the covariates in the final model (age, joint extremity, and joint size), the density represents the conditional mean drug effect at 25 weeks of onset of the drug. Reference is the 44-year-old patient presenting with a tumor in the lower extremity in a large joint.

Observed median RECIST score (cm) is shown as the solid black line, and the observed 5th and 95th percentiles are shown as dashed lines. Shaded regions show the 95% CIs around each quantile of interest (the median and the 90% prediction interval). Binning intervals are shown with the rug across the top of the image. No parameter uncertainty was included in simulations.

PD = pharmacodynamic, PK = pharmacokinetic, RECIST = Response Evaluation Criteria in Solid Tumors.

Figure 3. Logistic Regression of RECIST-Based Response: (a) Probability of PR or CR From Final Model Stratified by Joint Size, (b) Posterior Predictive Check for Probability of PR or CR, and (c) Posterior Predictive Check for Probability of CR



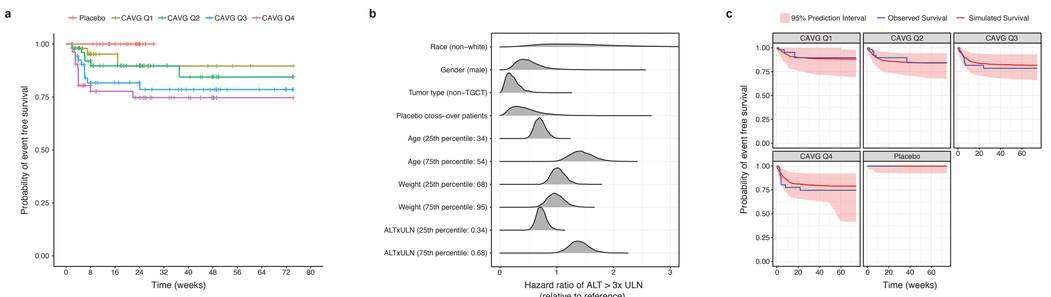
Colored ribbon is 90% credible interval. Vertical bars indicate observed individual exposure values.

Blue line represents smoothed observed proportion. Red line represents posterior predictive median. Red ribbon is the 90% posterior prediction interval. Vertical bars are observed individual data points.

Blue line represents smoothed observed proportion. Red line represents posterior predictive median. Red ribbon is the 90% posterior prediction interval. Vertical bars are observed individual data points.

AUC = area under the plasma concentration-time curve, CR = complete response, PR, partial response, RECIST = Response Evaluation Criteria in Solid Tumors.

Figure 4. Time-to-Event Modeling of ALT >3 × ULN: (a) Kaplan-Meier Plot, (b) Forest Plot of Covariate Effects, and (c) Visual Predictive Check



Reference individual is a 44-year-old, 80-kg, white female with baseline ALT/ULN of 0.48 in ENLIVEN who did not cross over from placebo.

ALT = alanine aminotransferase, CAVG = average concentration during first 2 weeks, TGCT = tenosynovial giant cell tumor, ULN = upper limit of normal. Q1, Q2, Q3 and Q4 refer to quartiles 1, 2, 3 and 4 of CAVG, where Q1 has lowest CAVG and Q4 has highest CAVG.

Table 2. Model-Predicted Event Rate at Different Doses (Median and 90% CrI)

	RECIST-Based ORR	TVS-Based ORR	ALT >3 × ULN	AST >3 × ULN
400 mg/day	0.25 (0.15, 0.36)	0.47 (0.33, 0.59)	0.18 (0.12, 0.24)	0.18 (0.13, 0.25)
600 mg/day	0.29 (0.20, 0.38)	0.54 (0.45, 0.63)	0.20 (0.14, 0.27)	0.20 (0.14, 0.27)
800 mg/day	0.32 (0.23, 0.42)	0.57 (0.47, 0.66)	0.22 (0.15, 0.29)	0.22 (0.16, 0.30)
1000/800 mg/day	0.32 (0.23, 0.42)	0.57 (0.47, 0.66)	0.22 (0.15, 0.30)	0.23 (0.16, 0.30)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CrI = credible interval, ORR = overall response rate, RECIST = Response Evaluation Criteria in Solid Tumors, TVS = tumor volume score, ULN = upper limit of normal.

CONCLUSION

- Analysis results, together with clinical efficacy and safety data, supported the recommendation of pexidartinib 800 mg/day without a loading dose for patients with TGCT

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