Tepotinib exposure-response analyses of safety and efficacy in patients with solid tumors

Paul Paik,[1] Sofia Friberg Hietala,[2] Joakim Nyberg,[2] Orestis Papasouliotis,[3] Richard Anziano,[2] Karin Berghoff,[4] Andreas Johne,[4] Pascal Girard,[3] Rainer Strotmann,[4] Wenyuan Xiong[3]

1. Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA (paikp@mskcc.org); 2. Pharmetheus AB, Uppsala, Sweden; 3. Merck, Lausanne, Switzerland ; 4. Merck KGaA, Darmstadt, Germany

CONCLUSIONS

- **No association of tepotinib exposure with safety or efficacy was observed**
- **A flat exposure-response relationship was observed for OR and DOR within the observed exposure range after administration of 500 mg tepotinib once daily in patients with advanced NSCLC harboring *MET* exon 14 skipping**
- **No apparent association between edema, serum lipase, amylase, aspartate aminotransferase, alanine aminotransferase, and tepotinib exposure was identified within the observed exposure range at 500 mg daily dose**
- **The exposure-response analyses confirm that 500 mg once daily is an appropriate dose for tepotinib to be used in the clinical setting**

INTRODUCTION

- Tepotinib is an oral, highly selective MET tyrosine kinase inhibitor that blocks MET-mediated signaling pathways involved in tumorigenesis[1]
- In the Phase II VISION study (NCT02864992), tepotinib has shown efficacy across treatment lines in patients with advanced NSCLC with *MET* exon 14 skipping
  - ORR by IRC was 46.5–50.0% and 55.6–61.7% by INV; onset of response was mostly within 6 weeks with a long median DOR of up to 15.7 months (data cut-off January 1, 2020)[2]
  - Updated efficacy outcomes including subgroup analysis from the VISION study (data cut-off July 1, 2020) are presented in Poster 1283P[3]
- In the absence of a maximum tolerated dose, the biologically active dose of tepotinib 500 mg once daily was defined using a translational modeling approach that integrated non-clinical PK and PD data,[4] non-clinical efficacy data and clinical PK and PD data
- The approved dose of tepotinib in patients with advanced NSCLC and *MET* exon 14 skipping is 500 mg once daily; a dose reduction to 250 mg once daily is recommended for the management of adverse events
- The objective of this analysis was to evaluate the relationship between tepotinib exposure and the efficacy and safety endpoints in patients with solid tumors and confirm the dose recommendations

METHODS

Exposure-efficacy analysis

- Analysis population: data from VISION Cohort A (NSCLC patients with *MET*ex14 skipping receiving tepotinib 500 mg once daily; n=146 patients evaluable for OR with ≥2 post-baseline assessments as of data cut-off January 1, 2020)
- The potential influence of tepotinib exposure on efficacy endpoints, ORR (by IRC or INV) and DOR, were explored graphically by analyzing these outcomes within each $AUC_{T,SS}$ quartile; potential effects of exposure on OR were also evaluated by logisitic regression in a full fixed-effects model covariate analysis
- Exposure metric: $AUC_{T,SS}$ derived from a population PK model

Exposure-safety analysis

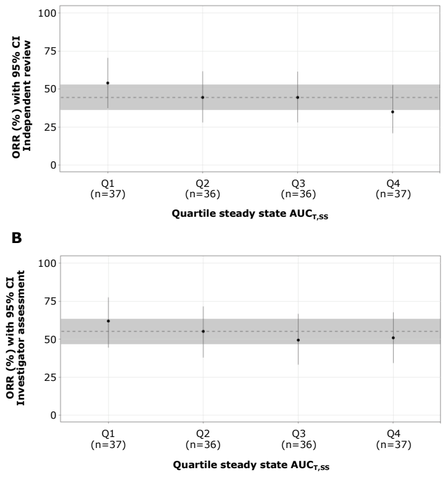
- Analysis population: data from patients (n=499) receiving tepotinib 30 mg to 1,400 mg once daily as monotherapy from five completed Phase I/II studies and one ongoing Phase II study:
  - NCT01014936, advanced solid tumors; NCT03021642, healthy volunteers; NCT01832506, solid tumors; NCT01988493, hepatocellular carcinoma; NCT02115373, hepatocellular carcinoma; NCT02864992 (VISION), NSCLC
- Safety endpoints: safety and laboratory endpoints related to identified potential risks were explored graphically within each AUC_{24h} quartile, including edema (TTE and maximum severity grade), AST, and ALT concentrations, and serum lipase/amylase levels
  - The occurrence of edema was analyzed using a TTE model, in which the base model was described by a constant hazard (exponential distribution) and the impact of covariates was evaluated using the stepwise covariate model building procedure
- Exposure metric: AUC_{24h} derived from a population PK model

RESULTS

Exposure-efficacy analysis

- Graphical analysis did not show increasing response rate with increasing exposure, with 95% confidence intervals largely overlapping across exposure quartiles (**Figure 1**)
- Multivariate logistic regression model-based analyses of the datasets also did not find a consistent effect of tepotinib exposure

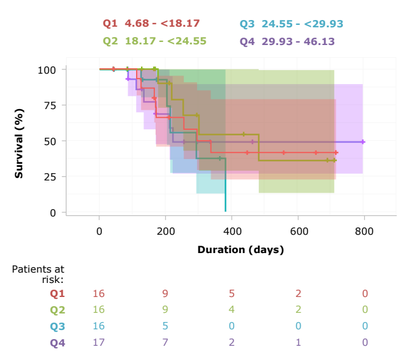
Figure 1. ORR by $AUC_{T,SS}$ quartile as assessed by (A) IRC and (B) INV



Lines represent Clopper–Pearson 95% CI, points are observed ORR per quartile, dashed lines represent overall ORR and shaded areas the 95% CI. Quartile ranges: Q1, 4.68-<19.67; Q2, 19.67-<25.29, Q3, 25.29-<31.76, Q4, 31.76-51.06 µg*h/ml.

- Increasing tepotinib exposure ($AUC_{T,SS}$) was not associated with an increased DOR (**Figure 2**)

Figure 2. KM plots of DOR based on IRC, stratified by tepotinib $AUC_{T,SS}$ quartile (µg*h/ml)



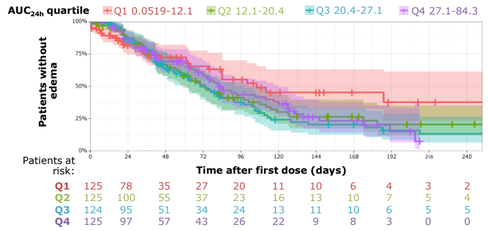
The lines represent the KM estimate and the corresponding shaded area the 95% CI.

Exposure-safety analysis

Time to first edema event

- Graphical analysis and model-based TTE analysis indicated no apparent association between edema risk and tepotinib exposure (**Figure 3**)
  - Edema risk may have reached a plateau at a very low exposure level
- Advanced age was associated with increased risk of edema, independent of tepotinib exposure
  - Median HR at 75 years of age was 1.3 (90% CI: 1.2, 1.5), relative to a 66-year-old patient

Figure 3. KM plots of time to first edema event stratified by AUC_{24h} quartile (µg*h/ml) on the day of edema event or censoring



The lines represent the KM estimate and the corresponding shaded area the 95% CI.

Maximum edema grade

- The distribution of exposure was similar across the maximum severity grade of peripheral edema events
  - The lack of association between exposure and maximum severity grade was consistent across exposure metrics (**Figure 4**)

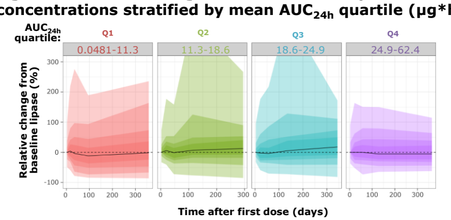
Figure 4. Boxplot of tepotinib AUC_{24h} (µg*h/ml) by edema severity grade (maximum severity per patient)

Study NCT01014936 was excluded in this analysis as peripheral edema was at the time not recognized as a potential tepotinib-associated adverse event; similar results were obtained when these data were included in the analysis.

Serum lipase

- There was no pronounced trend in serum lipase concentration over time
- There is no indication of a correlation between tepotinib exposure and lipase concentration (**Figure 5**)

Figure 5. Relative change from baseline in lipase concentrations stratified by mean AUC_{24h} quartile (µg*h/ml)

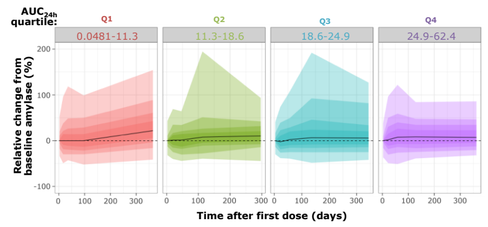


Solid lines represent the median, shaded areas encompass the 40-60-80-95% observed intervals. Time is binned in 5 intervals with an equal number of observations in each bin.

Serum amylase

- Graphical analysis suggested a trend towards increase in amylase concentration over time
  - The median relative change from baseline was less than 25% across all studies
- The increases did not appear to be associated with tepotinib exposure levels (**Figure 6**)

Figure 6. Relative change from baseline in amylase concentrations stratified by mean AUC_{24h} quartile (µg*h/ml)

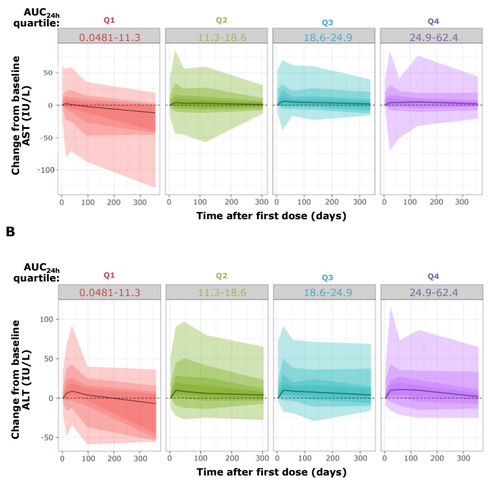


Solid lines represent the median, shaded areas encompass the 40-60-80-95% observed intervals. Time is binned in 5 intervals with an equal number of observations in each bin.

Transaminases

- There was a trend towards a transient increase in the median observed AST and ALT concentrations over time
- There was no clear correlation between tepotinib exposure and the maximum changes from baseline (**Figure 7**)

Figure 7. Change from baseline (A) AST (B) ALT concentrations stratified by mean AUC_{24h} quartile (µg*h/ml)



Solid lines represent the median, shaded areas encompass the 40-60-80-95% observed intervals. Time is binned in 5 intervals with an equal number of observations in each bin.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC_{24h}, area under the curve over 24h; $AUC_{T,SS}$, area under the curve at steady state; DOR, duration of response; HR, hazard ratio; INV, investigator assessment; IRC, independent review committee; KM, Kaplan–Meier; MET, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer; OR, objective response; ORR, objective response rate; PD, pharmacodynamics; PK, pharmacokinetics; TTE, time to event.

References: 1. Bladt F, et al. Clin Cancer Res. 2013;19:2941–51; 2. Paik P, et al. N Engl J Med. 2020; doi: 10.1056/NEJMoa2004407; 3. Mazieres J, et al. Presented at ESMO 2020. Poster 1283P; 4. Falchook GS. Clin Cancer Res. 2020;26(6):1237–46.

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