Modelling the biomarker-driven tumour growth inhibition by a novel pan-Trk inhibitor ONO-7579 in xenografted mice

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BACKGROUND

Oncogenic rearrangements of neurotrophic tyrosine receptor kinase (NTRK) encode chimeric proteins with constitutive kinase activity, which promote tumour cell growth and survival. Patients with NTRK fusion-positive cancers well responded to treatment with tropomyosin receptor kinase (Trk) inhibitors in clinical studies [1].
ONO-7579 is a highly potent and selective oral pan-Trk inhibitor which selectively inhibits Trk autophosphorylation, associated with the down-stream signalling [2].

Objective

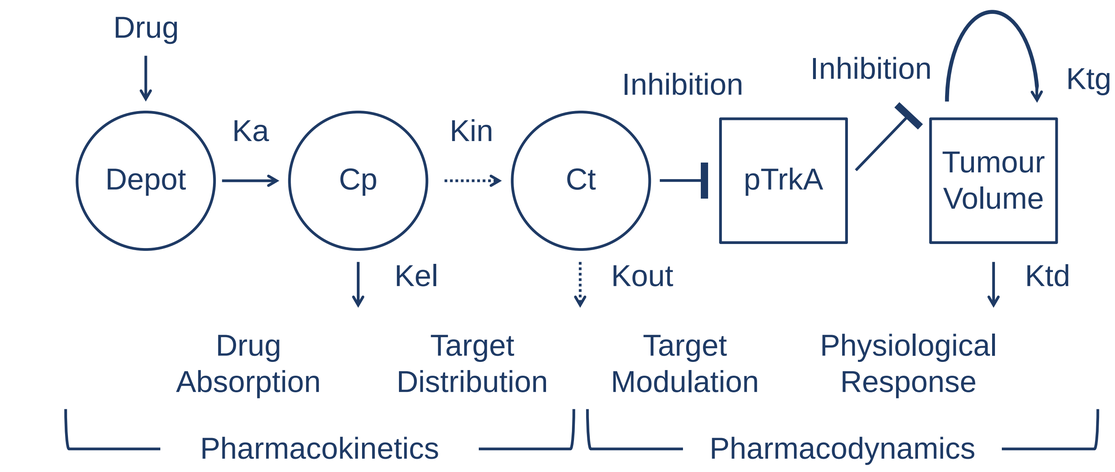
To define relationship between phosphorylated TrkA (pTrKA) and antitumour effect in KM12 xenografted model mice with PK/PD modelling approach in order to contribute to determination of recommended dose with biomarker in early clinical development.

METHODS

Animal studies

- KM12 cells were transplanted subcutaneously into female BALBnu/CrlCrlj mice.
- A single dose of ONO-7579 was orally administered at doses of 0.06 and 0.6 mg/kg to evaluate the time-course of ONO-7579 concentration and pTrkA level in tumour (n=4).
- Repeated doses of ONO-7579 were orally administered once daily for 12 days at doses of 0.06, 0.2, and 0.6 mg/kg to evaluate the time-course of tumour volume (n=8).
- Plasma and tumour concentrations of ONO-7579 and pTrkA level in tumour were obtained from both studies.

PK / PD / Efficacy model analysis



- The resulting data were integrated and plasma PK model, tumour PK model, tumour PK/pTrkA model and pTrkA/tumour volume model were developed in a sequential manner.
- As the final goal, the relationship between pTrkA inhibitory rate and net tumour growth rate (Ktg - Ktd) was predicted.
- All model analyses were performed with NONMEM 7.1.2.

Plasma PK model

A 1-compartment model with first-order absorption was used as a plasma PK model. Where A1 and A2 are the ONO-7579 amounts in the depot and plasma compartments, respectively.

$$\frac{dA1}{dt} = -Ka \cdot A1 \qquad \frac{dA2}{dt} = Ka \cdot A1 - Kel \cdot A2$$

Tumour PK model

Tumour concentrations of ONO-7579 were described with a compartment model which would not influence pharmacokinetics in the central compartment. Where A3 is the ONO-7579 amounts in the tumour compartment.

$$\frac{dA3}{dt} = Kin \cdot A2 - Kout \cdot A3$$

Tumour PK / pTrkA model

The pTrkA responses in the treatment group were expressed as the ratios to control data. The pTrkA was linked to tumour concentrations of ONO-7579, and described with the direct inhibitory Emax model.

$$pTrkA = 100 \cdot \left(1 - \frac{Emax_R \cdot A3^{Hill_R}}{EC50_R{}^{Hill_R} + A3^{Hill_R}}\right)$$

pTrkA / Tumour volume model

In the tumour growth model, a first-order tumour growth rate (Ktg) and a tumour death rate (Ktd) were assumed. Assuming that pharmacological effect would be suppressed according to the tumour pTrk inhibitory rate (100 − pTrkA), the effect was described with a sigmoid Emax model. Temporal specific effect until day 2 (TEMP) was also taken into account as a covariate.

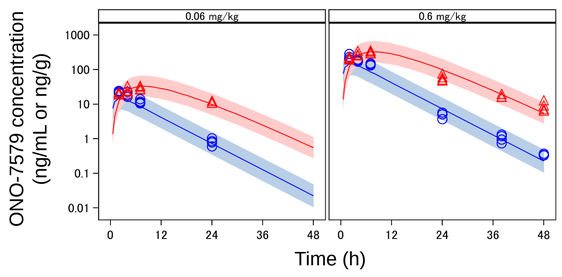
$$\frac{dT}{dt} = Ktg \cdot \left(1 - \frac{Emax_T \cdot (100 - pTrkA)^{Hill_T}}{EC50_T{}^{Hill_T} + (100 - pTrkA)^{Hill_T}}\right) \cdot TEMP \cdot T - Ktd \cdot T$$

RESULTS

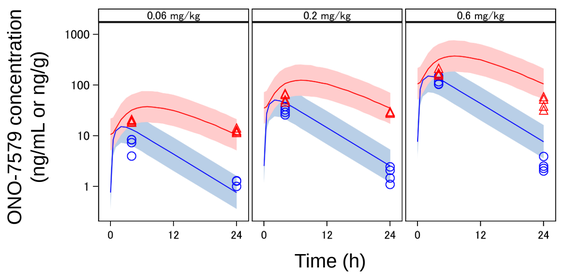
Symbols = observations; Areas = 5th-95th percentiles of model predictions; Lines = median of model predictions

Plasma and tumour PK

- Single administration



- Repeated administration

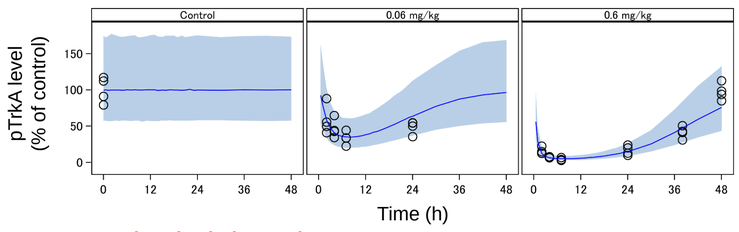


Red = tumour, Blue = plasma

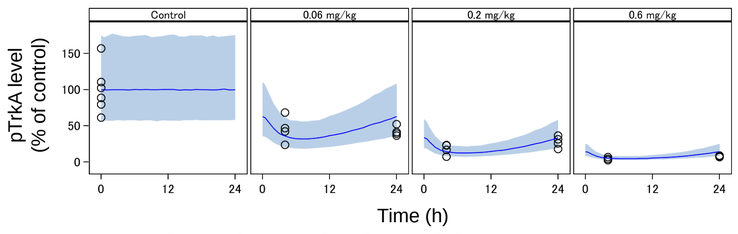
Behavior of ONO-7579 was different between tumour and plasma.
Trough tumour concentration after repeated administration was ≥10 times as high as plasma concentration.

Time-course of pTrk

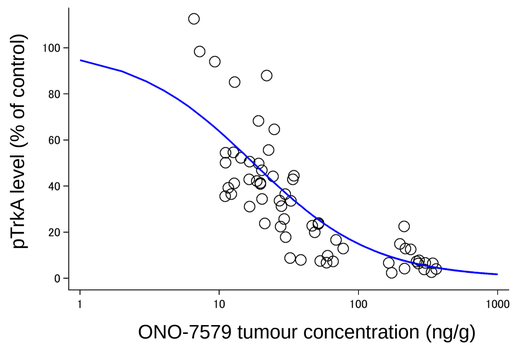
- Single administration



- Repeated administration



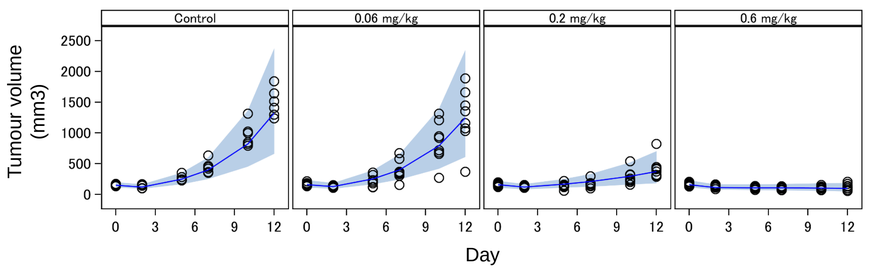
Tumour PK / pTrkA relationship



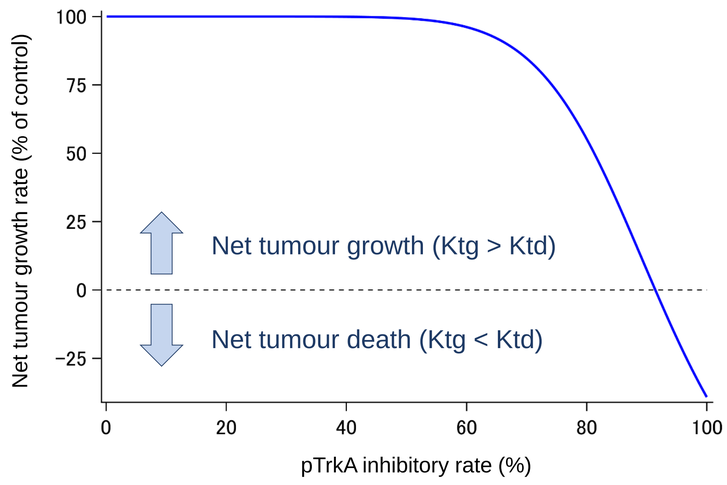
Tumour ONO-7579 and pTrkA were well described with a direct Emax model though a delay in ONO-7579 distribution from plasma to tumour was found.

Time-course of tumour volume

- Repeated administration



pTrkA inhibitory rate / Net tumour growth rate relationship



There was a threshold of pTrk inhibition rate (≥60%) where antitumour effect was exerted.
It turned out that pTrk inhibitory rates ≥ 91.5% were required in order to reduce tumour.

CONCLUSIONS

PK/PD/Efficacy model has identified “switch-like” relationship between pTrkA inhibition rate and antitumour effect in KM12 xenografted model mice, and demonstrated that pTrkA in tumour can be an effective biomarker to consider dosing regimen of ONO-7579 in clinical studies.

REFERENCES

[1] Cocco E., et al., NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol, (2018) 15: 731-747.
[2] Kawamoto M., et al., The novel selective pan-TRK inhibitor ONO-7579 exhibits antitumor efficacy against human gallbladder cancer in vitro. Anticancer Res, (2018) 38: 1979-1986.