Population PK-PD model for E7820 and α_2-integrin expression on platelets in patients with solid tumors and lymphomas

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Introduction

The novel angiogenesis inhibitor E7820 was evaluated in a phase I dose escalation study in patients with malignant solid tumors or lymphomas, the results of which have been reported previously.[1] Its anti-angiogenetic effects are exerted mainly by inhibition of the mRNA expression of α2-integrin. E7820 was administered daily for 28 days, followed by a washout period of 7 days prior to starting subsequent cycles.

Hypothesis: α2-integrin expression on platelets may be a biomarker for tumor growth inhibition in response to treatment with E7820.[2]

Aim: to develop a population PK-PD model for E7820 and its effect on α2-integrin platelet levels.

Methods

Bioanalysis:

- E7820 in plasma/urine by LC/MS/MS.
- **α2-integrin** on platelets by flow cytometry

Dataset:

- PK: 1421 E7820 plasma samples from 37 patients
- PD: 462 α2-integrin level measurements (at 209 unique timepoints) from 29 patients

collected from up to 9 treatment cycles

The population analysis was performed in NONMEM VI. The model building process is summarized in table 1.

After model development, several dosing strategies were evaluated by simulation, for their effect on integrin expression level.

Results

High variability in PD-response was observed, with some patients showing no decrease in PD levels at all (Figure 2, pat.2). In the model this resulted in high IIV in E_{max}.

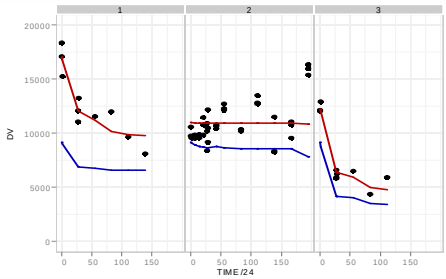

Figure 2. Observed integrin expression levels and model (blue) and individual (red) predictions for three example patients. Pat1&2: 100mg; Pat3: 200 mg.

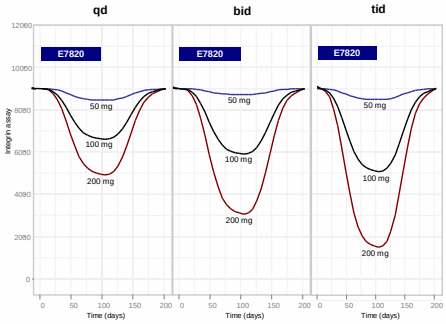

Figure 3. Simulation of different regimens.of E7820: median integrin expression after qd, bid, tid at several dose levels

Simulation studies showed that :

- 50 mg daily resulted in low median response. 100 mg was needed for substantial increase in PD response
- Response increased when E7820 was administered more frequently
- The response obtained by 200 mg QD, was the same as for 100 mg TID
- High variability in response

Model

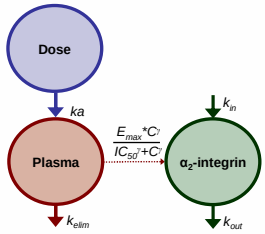

Figure 1. PK-PD model for E7820-α_2-integrin

PK Parameter			RSE	PD Parameter			
CL/F	6.07	mL/hr	(7%)	Baseline	9000	.07	mL/hr
V/F	66.6	L	(8%)	E_{max}	2	.6	L
ka	0.636	hr	(7%)	IC_{50}	900	.636	hr
IIV_{CL}	39.5	%	(12%)	γ	3		
IIV_V	14.7	%	(13%)	IIV Base	30		%
IOV_{MTT}	62.8	%	(15%)	IIV E_{max}	70	.11	%
IOV_N	128	%	(15%)				

Discussion

- The PK-PD relationship that was found, showed high interpatient variability in PD response.
- To serve as a biomarker, expression of α_2-integrin must show correlation with treatment outcome, which has not been demonstrated yet.

Conclusion

A **population PK-PD model** was developed describing:

- disposition of E7820
- effects of exposure on expression of α2-integrin on platelets.

This model was subsequently used for evaluation of different dosing strategies.

For α2-integrin levels on platelets to serve as a **biomarker** for tumor growth inhibition in humans, the relationship between α2-levels on platelets, tumor growth and disease progression should be assessed further.

Modeling process

1. PK model → One compartment, linear elimination, turnover model absorption. No covariates. Negligible renal fraction.
2. PK-PD model → PK fixed. PD: Indirect response, inhibition of input rate. Relationship: sigmoid E_{max}-model. Estimated parameters: baseline, E_{max}, IC_{50}.
3. Test null hypothesis PK-PD relationship? → Confirmed by likelihood ratio test. Sigmoid E_{max} significantly better than linear or E_{max} model.
4. Model improvements? → Delays in response to therapy: no improvement in fit. Development of tolerance to E7820: no improvement in fit
5. Simulate regimes → 50 / 100 / 200 mg daily; qd / bid / td. Effect-measure: median decrease in integrin expression

References

1. Mita M. et al, 2006 ASCO Ann Meeting Proc I, vol 24, no 18S
2. Semba T. et al. Clin Cancer Res, Feb 2004, vol 10, p1430-1438