# Evaluation of dosing of E7820 in humans from preclinical and clinical data using a biomarker

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## Introduction

**E7820**:

- novel, oral anti-cancer agent
- inhibits angiogenesis by inhibition of mRNA expression of $\alpha_2$-integrin[1]
- has shown to inhibit tumor growth in preclinical experiments[2] and is now being tested in phase I and II.

**Aims**:

- Develop a PK-PD model from preclinical experiments, describing changes in $\alpha_2$-integrin expression levels and tumor growth inhibition in response to treatment with E7820.
- Investigate what integrin inhibition levels are correlated with tumor stasis
- Investigate whether these target levels are achieved in patients using tolerable doses

## Preclinical data

**Tumor growth experiments**:

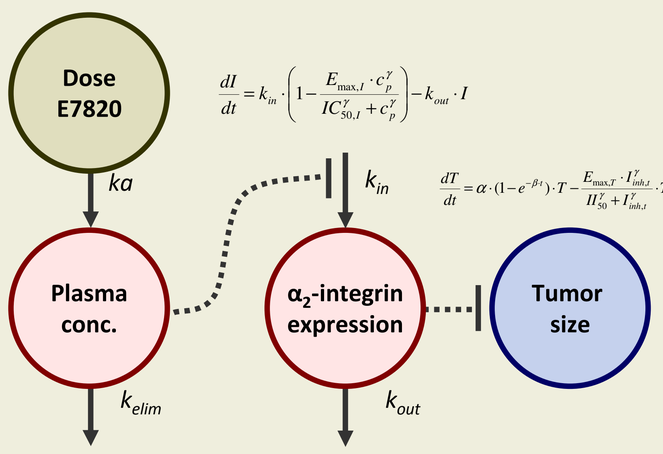
- xenografted mice, 5 dose levels
- pancreatic KP-1 tumor
- doses 0–200 mg/kg, during 21 days
- $\alpha_2$-Integrin levels were measured on platelets by FACS, tumor size using a caliper.

**PK-PD modeling**:

NONMEM VI, visual predictive checks constructed to judge model fit. Base model shown below. Several models for tumor growth inhibition were investigated.

## PK-PD model

Pharmacokinetics Pharmacodynamics




## Key findings

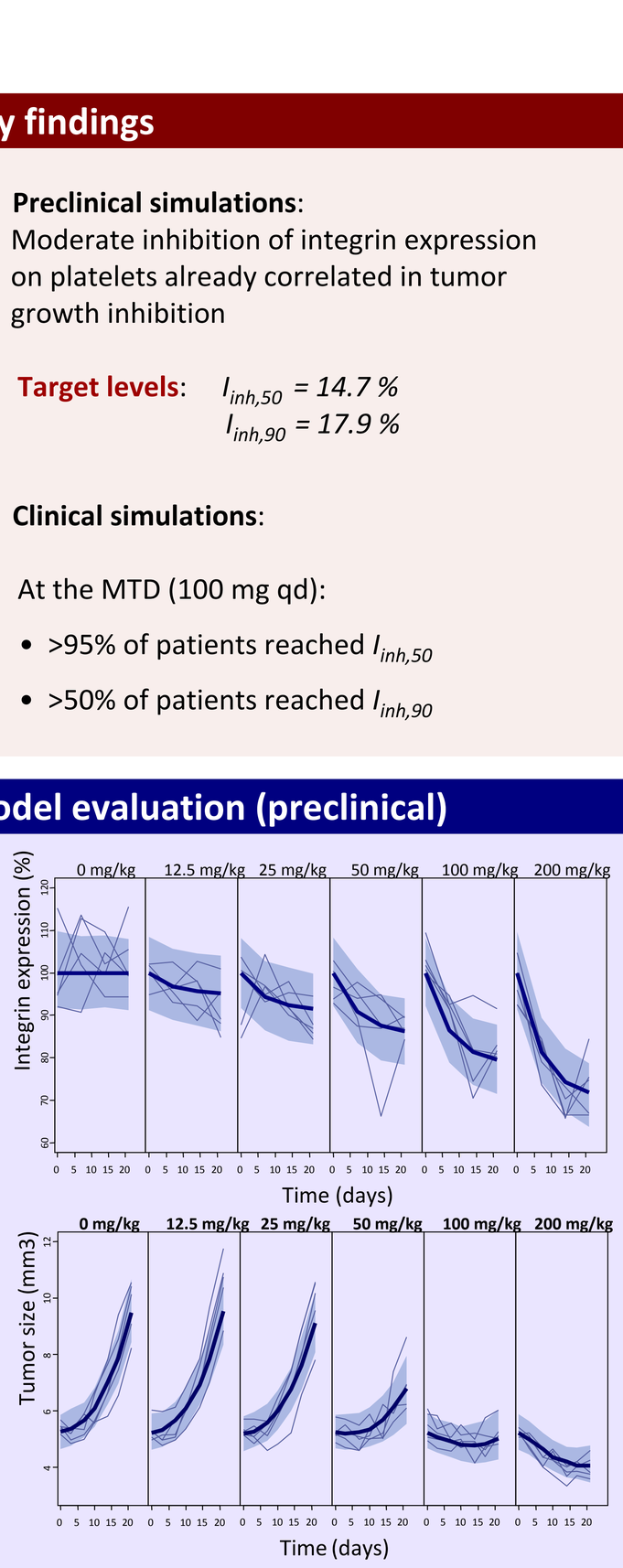
- **Preclinical simulations**:
  Moderate inhibition of integrin expression on platelets already correlated in tumor growth inhibition

  **Target levels**: $I_{inh,50} = 14.7\ \%$
  $I_{inh,90} = 17.9\ \%$

- **Clinical simulations**:

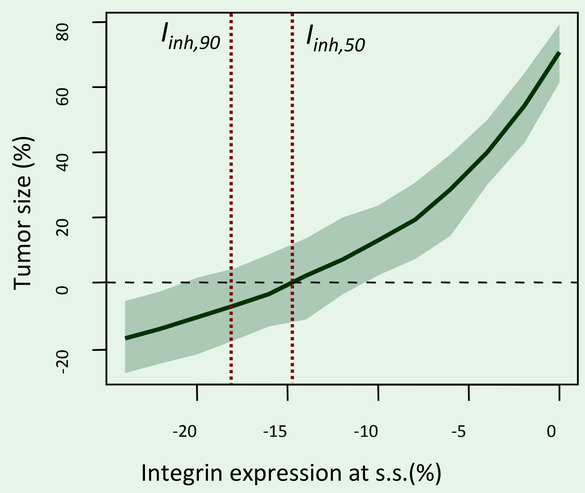
  At the MTD (100 mg qd):
  - >95% of patients reached $I_{inh,50}$
  - >50% of patients reached $I_{inh,90}$

## Model evaluation (preclinical)




*Observed and model predicted integrin expression (upper) and tumor growth inhibition (lower) at dose range*

## Model simulations (preclinical)




*Simulated $\alpha_2$-integrin expression and tumor growth inhibition over dose range*

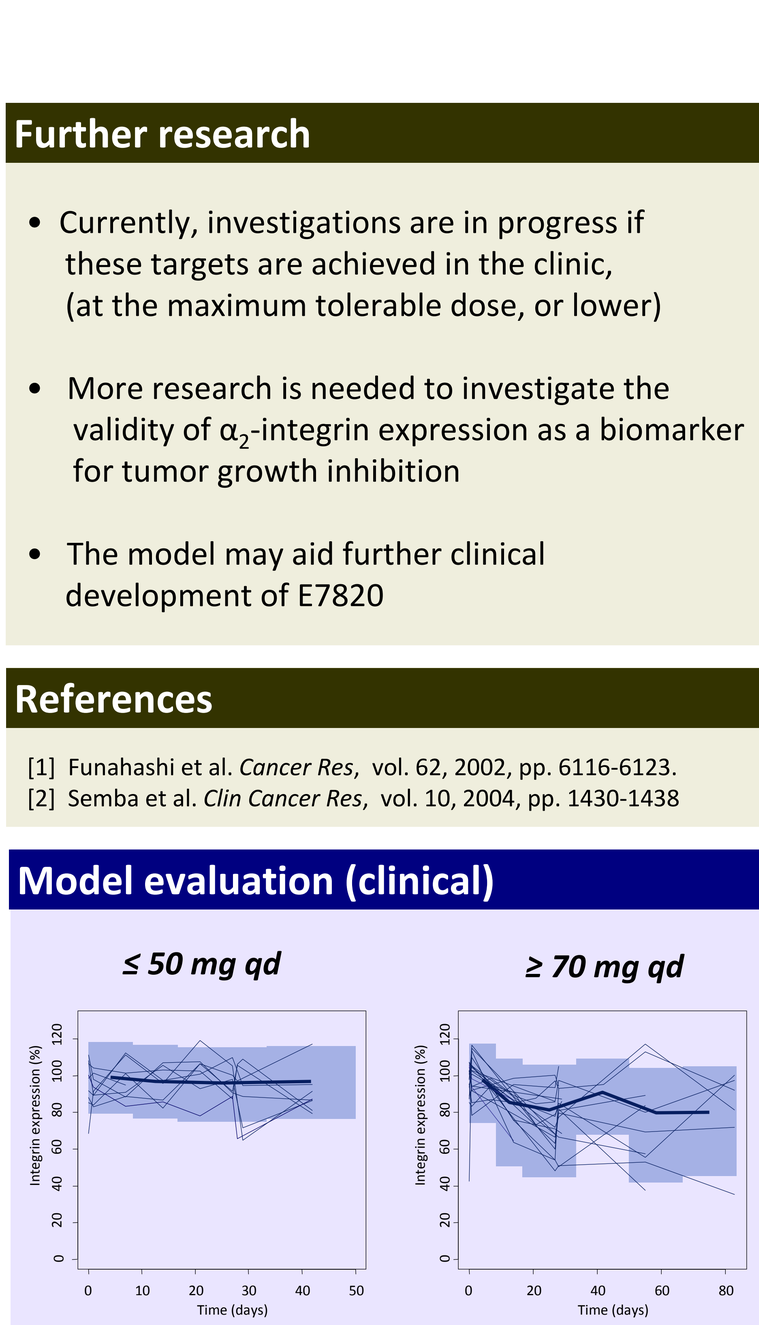
## Further research

- Currently, investigations are in progress if these targets are achieved in the clinic, (at the maximum tolerable dose, or lower)
- More research is needed to investigate the validity of $\alpha_2$-integrin expression as a biomarker for tumor growth inhibition
- The model may aid further clinical development of E7820

## References

[1] Funahashi et al. *Cancer Res*, vol. 62, 2002, pp. 6116-6123.
[2] Semba et al. *Clin Cancer Res*, vol. 10, 2004, pp. 1430-1438

## Model evaluation (clinical)

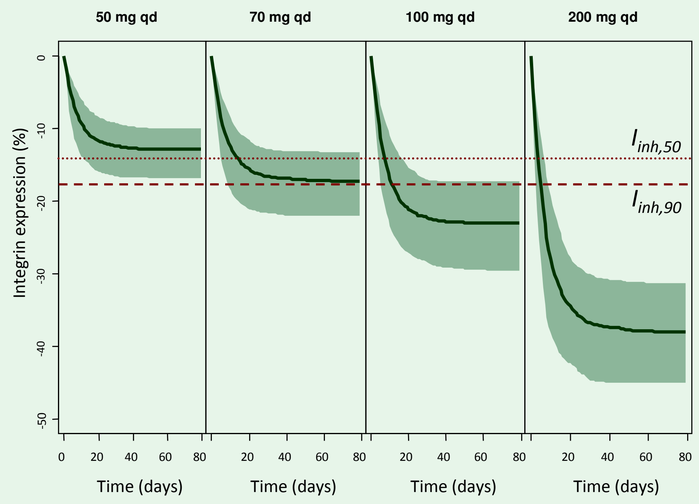



*VPCs (90% PI) of the PK-PD model for $\alpha_2$-integrin expression on platelets in patients, for low and high dose levels.*

## Model simulations (clinical)

**Table 1**. Expected relative integrin expression inhibition at steady state, obtained from simulations of clinical dosing regimens.

| Dosing regimen | Expected $I_{int,av}$ at $t$ = 21 (CI 95%) |
|---|---|
| 50 mg qd | 12.8% (9.1% – 17.7%) |
| 70 mg qd | 17.2% (11.9% – 23.3%) |
| 100 mg qd | 23.0% (16.5% – 30.2%) |
| 200 mg qd | 37.8% (29.1% – 48.0%) |




*Expected $\alpha_2$-integrin expression profiles (relative to baseline, without residual variability) during four continuous dosing regimens (qd). Grey areas indicate the 90% model prediction intervals.*