

# Model-informed analysis during NDA/BLA review

## *Insights from two FDA case reviews*

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*Disclaimer: My remarks today do not necessarily reflect the official views of the FDA*

# Take Home Message

- **Analysis on PK and exposure-response relationship facilitates FDA's assessment on efficacy and safety.**
- **Modeling informed analysis can be used to inform trial design in the post-marketing setting.**

# Outline



- **Relevance of model-informed analysis for NDA/BLA review**
  - **Case Study**
    - **Analysis**
      - **Rociletinib**
    - **Design**
      - **Lenvatinib + Everolimus in renal cell carcinoma**
- **Summary**

# Case Study 1: Rociletinib

## Proposed Indication

- Treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, who have progressed on or after EGFR TKI therapy.

## Applicant Proposed dose

- 625 mg PO BID

## Primary Efficacy

- Rociletinib efficacy were primarily assessed under three dose levels from two clinical studies

| Analysis Value      | 500 mg (N=79)      | 625 mg (N=170)     | 750 mg (N=76)      |
|---------------------|--------------------|--------------------|--------------------|
| <b>ORR (95% CI)</b> | 22.8% (14.1, 33.6) | 32.4% (25.4, 39.9) | 32.9% (22.5, 44.6) |

## Adverse Reactions of Special Interest

- *QTc Prolongation, Hyperglycemia, etc.*

*Patients were NOT randomized into different dose cohorts*

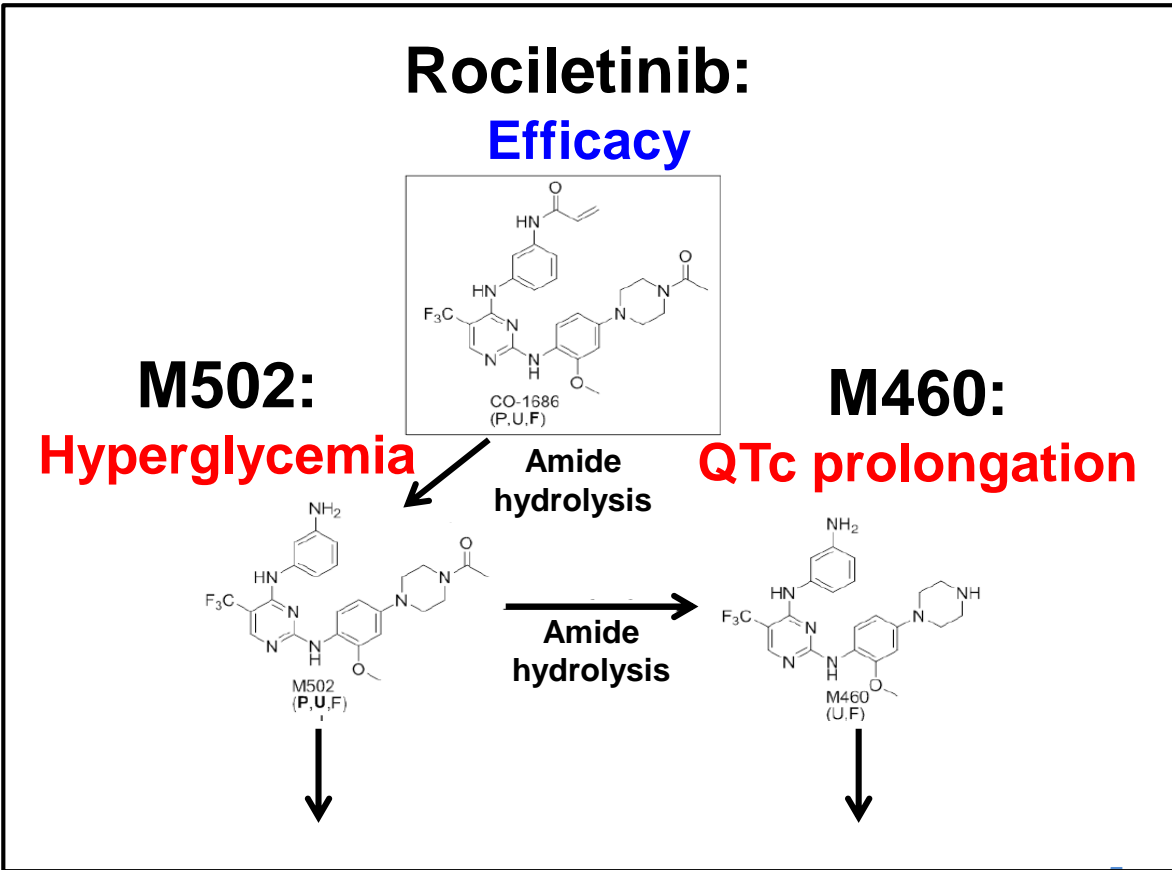
# Rociletinib PK Highlights & Biotransformation Pathway



## Rociletinib PK

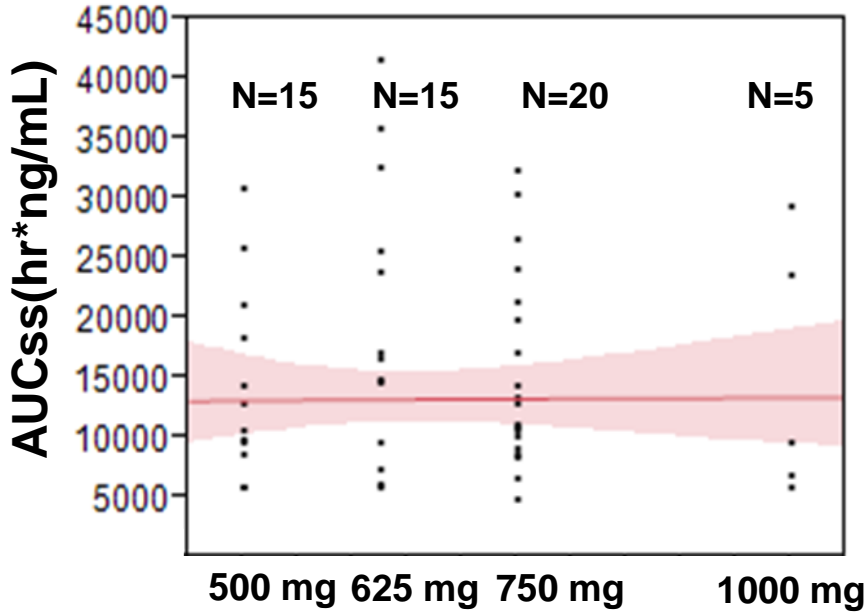
- Highly variable
- No accumulation (3.7 hours half-life)
- **Practically insoluble (<0.1 mg/mL) when pH >2**
- Food effect: high-fat meal increases AUC by 54% (Taken with food)
- Metabolism
  - Mainly by amide hydrolysis and N-acetylation

T<sub>1/2</sub> (M502): 20 hours  
T<sub>1/2</sub> (M460): 51 hours

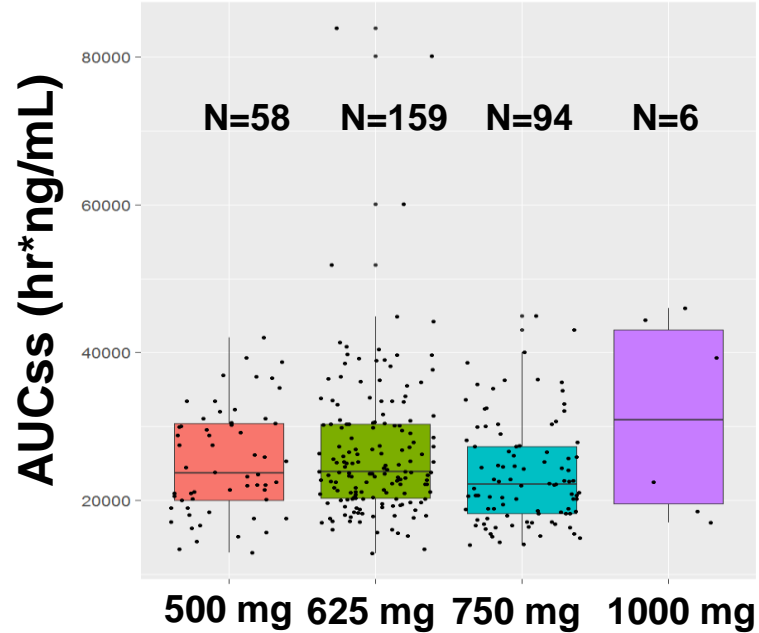


# Similar Rociletinib Exposure from 500 to 1000 mg BID

### Intensive PK

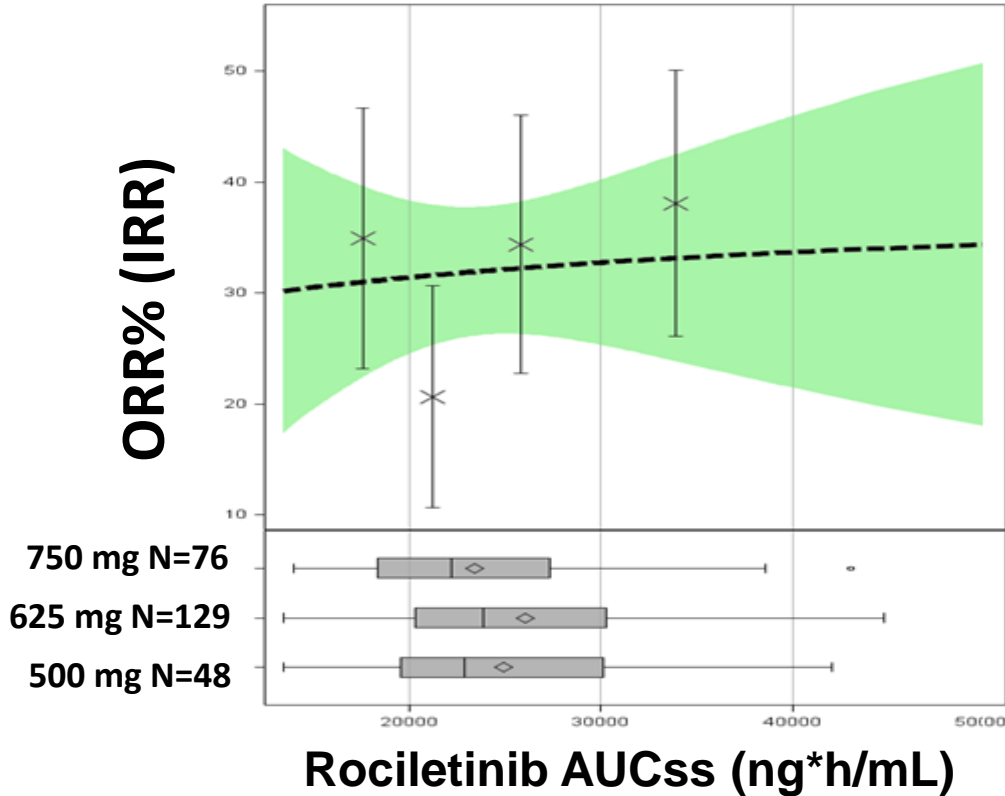


### Population PK



***Dose-Exposure Relationship is flat***

# Flat Exposure-Response Relationship for Efficacy



## From 500 to 750 mg BID

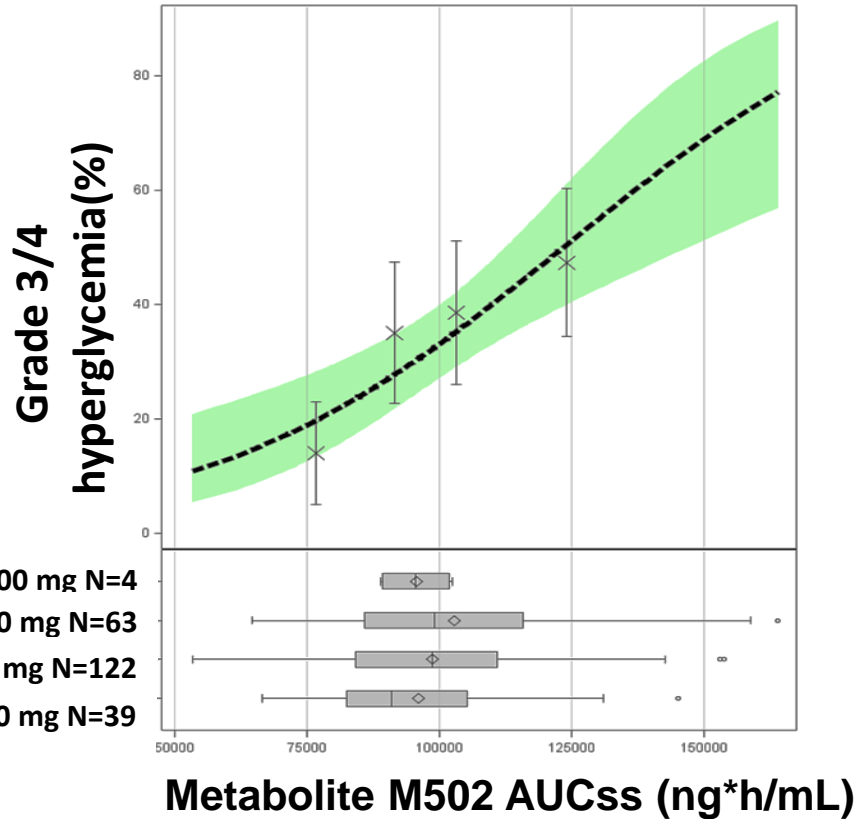
- Rociletinib exposure was comparable
- No E-R relationship for ORR was identified

*No meaningful difference in efficacy would be expected from 500 mg BID to 750 mg BID*

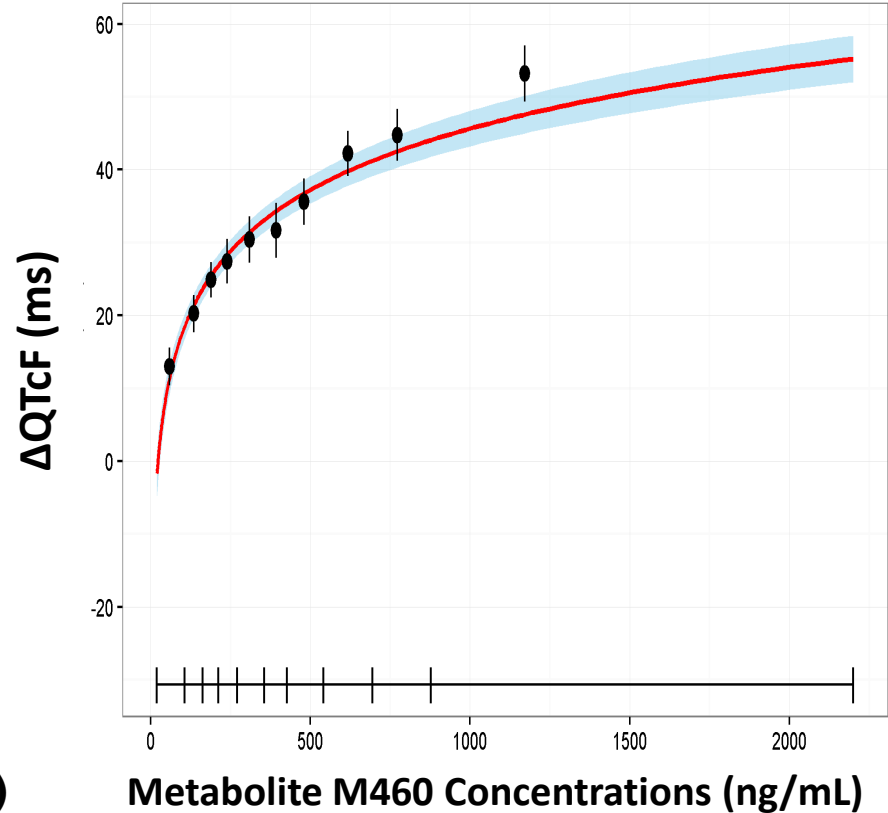
# Steep Exposure-Safety Relationships



## Hyperglycemia



## QTc Prolongation





# Summary of Case 1



- **Dose-exposure relationship is flat from 500 to 1000 mg BID**

**FDA Approach:** Pooling of the efficacy and safety data across several dose groups may provide a reasonable estimate of the true effect of rociletinib on tumor response, and of the drug toxicity.

- **Exposure-efficacy relationship is flat, while exposure-safety relationship is steep**
- **FDA's analysis was discussed and accepted at the advisory committee meeting**

***625 mg BID not adequately supported***

**ODAC vote: 12:1 against approval based on available data**

***FDA issued a complete response letter on this submission.***

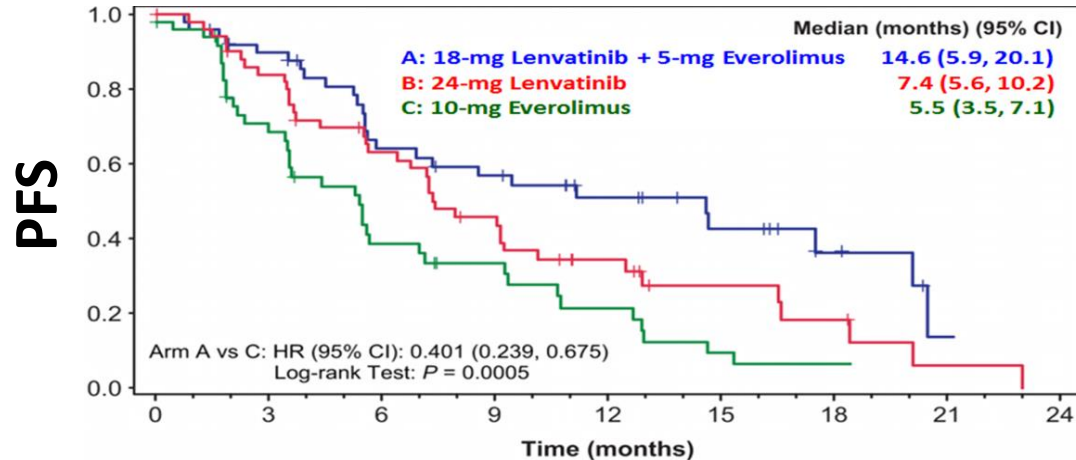
***The applicant terminated the development program.***

# Case Study 2: Lenvatinib for RCC



Tyrosine kinase inhibitor (TKI) for

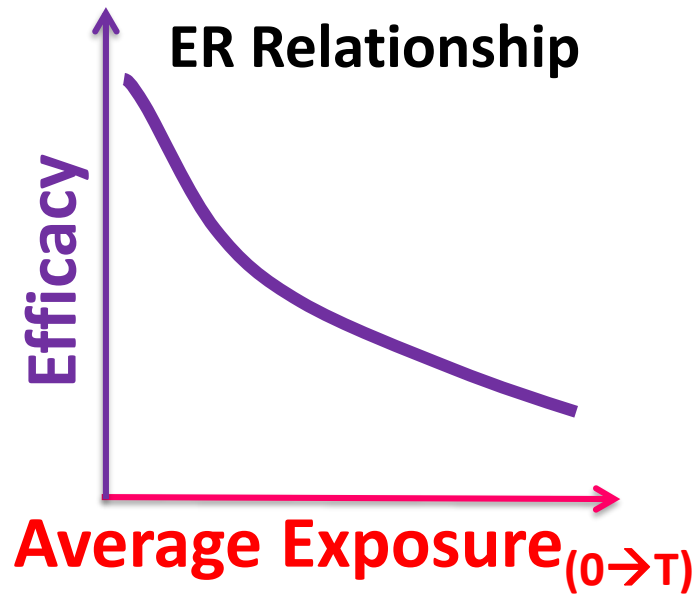
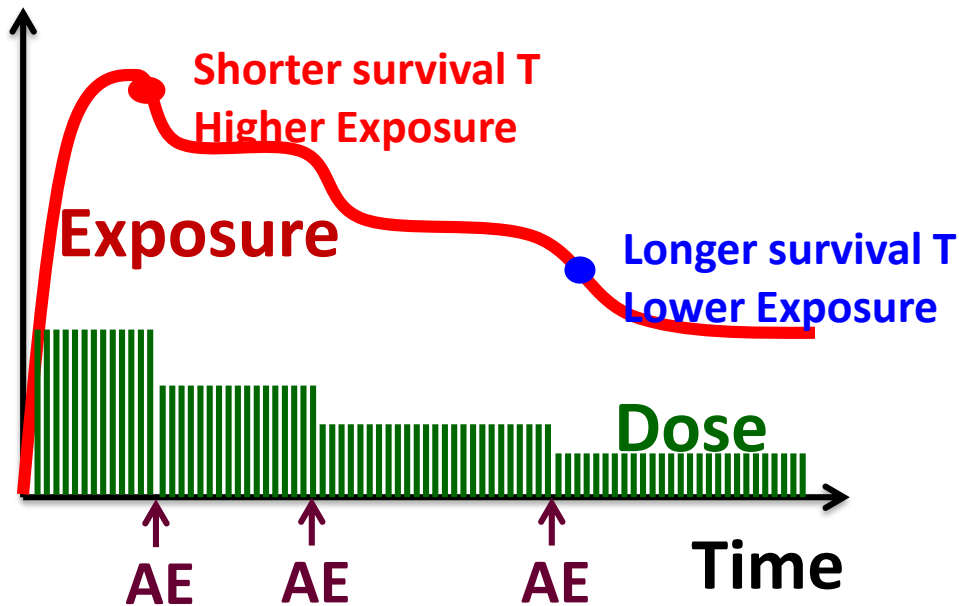
- Differentiated Thyroid Cancer (DTC)
- Advanced Renal Cell Carcinoma (RCC)
  - Approved Dose: 18-mg Lenvatinib + 5-mg Everolimus QD
  - **89%** patients required **dose reduction/interruption**



**PMR To Conduct a Dose Optimization Study**

***Which Dosing Regimen to Study?***

# Dose Adjustment: Challenges for E-R Modeling

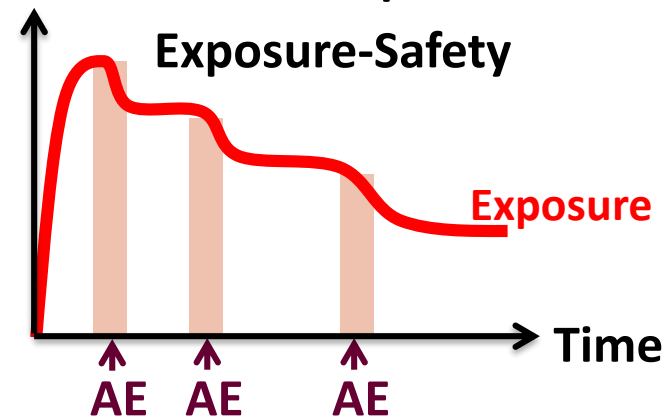
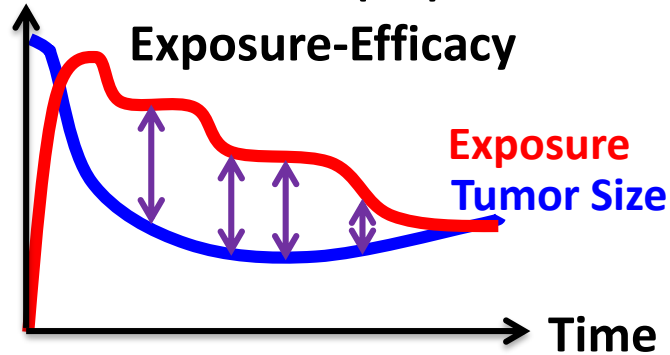


- Exposure not constant over time
- Biased ER relationship

# E-R Analysis incorporating Dose Adjustment



- Time – vary exposure
  - Exposure at each time interval
- Longitudinal tumor size used
  - Capture the varying drug effect over time
- Adverse event (AE) was associated with the concurrent exposure

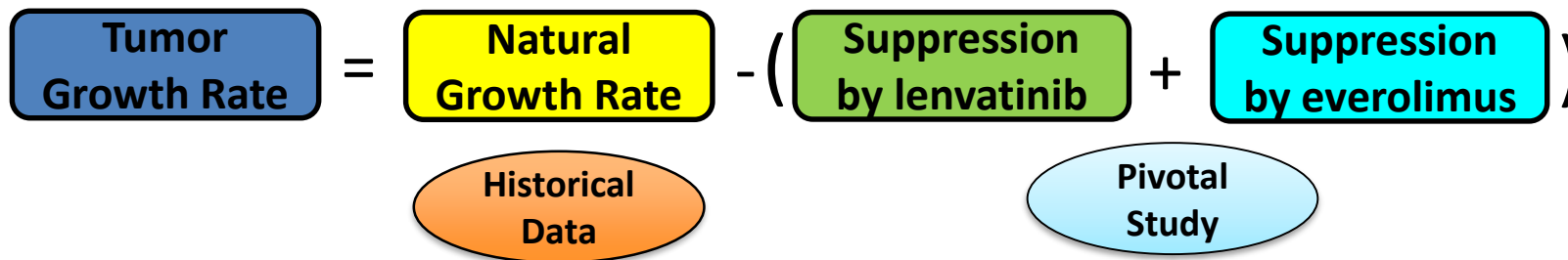


- Dynamically generate dose/exposure profile in the simulation



# E-R Relationship Estimation

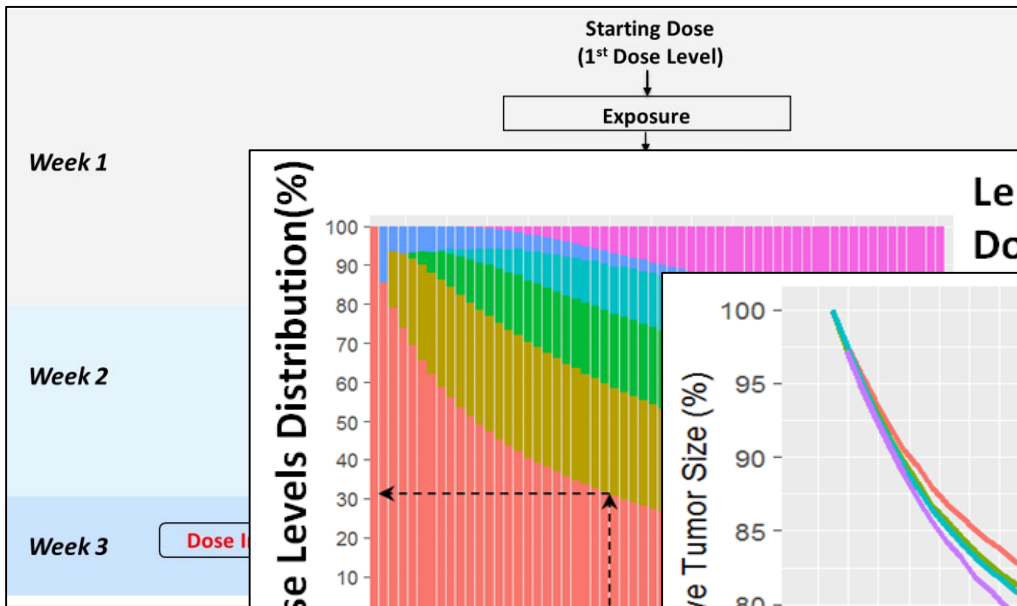
- E-R for Efficacy:
  - An exposure - tumor dynamics model:



- E-R for Safety:
  - An exposure – dosing altering AE model:
    - AE leading to dose adjustment was treated as one repeated event
    - A longitudinal logit mixed effect model for dose-altering AE was developed by sponsor
    - Basis for dosing history generation in the simulation step

# Clinical Trial Simulation:

## Evaluate different dosing regimens



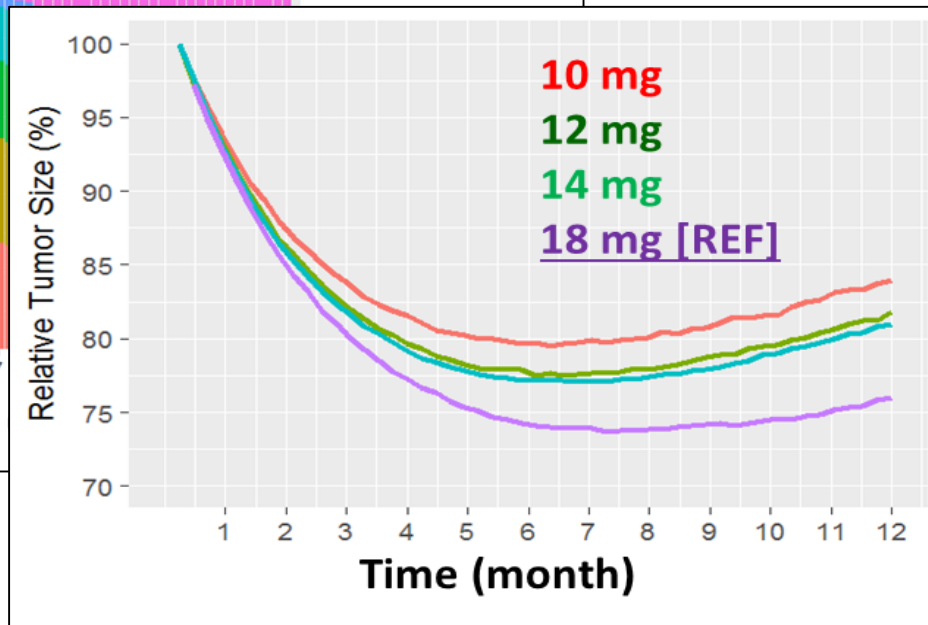
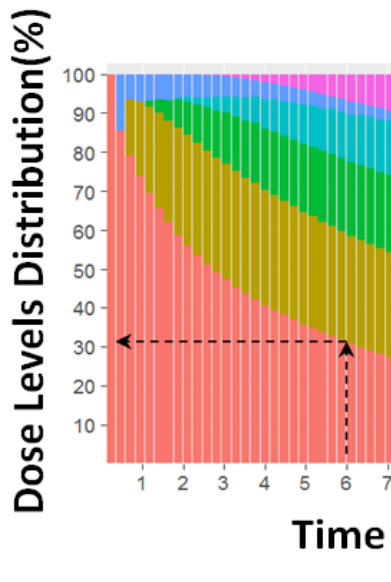
### I. Various candidate dosing regimens

- Rules of dose adjustment were pre-defined

### II. Dosing history generated

- E-R model for safety utilized

Lenvatinib  
Dose Level:

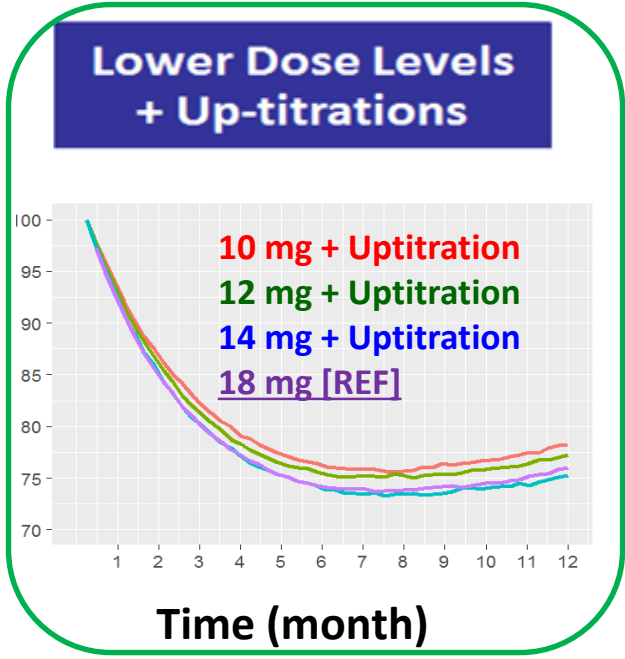
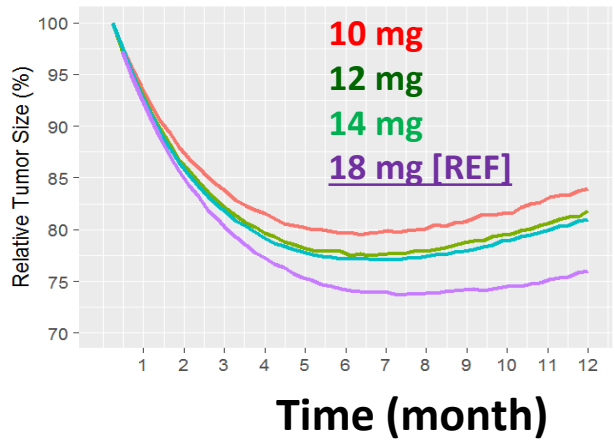


### III. Tumor dynamics generated

- Exposure-tumor model utilized

# Efficacy Profile Prediction

**Lower Dose Levels**



- Tumor dynamics was simulated based on the simulated dosing record
- Lower Starting Doses + Uptitration could provide comparable efficacy

# Regulatory Decisions on Lenvatinib

- **Post-marketing requirement (PMR) issued for dose optimization**
  - Lower starting doses with the option of dose escalation
    - *14 mg Lenvatinib with up-titration + 5 mg everolimus*

## Summary of Case 2

- **Dynamics dose adjustment should be appropriately integrated.**
- **Modeling and simulation can be used to inform the trial design for optimizing the dosing regimen**



## Take Home Message

- **Analysis on PK and exposure-response relationship facilitates FDA's assessment on efficacy and safety.**
- **Modeling informed analysis can be used to inform trial design in the post-marketing setting.**
  - **Frequent dose modification should be appropriately incorporated in exposure-response analysis for dose evaluation.**

# Acknowledgements



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## **Scientists from sponsors**

**THANK YOU**