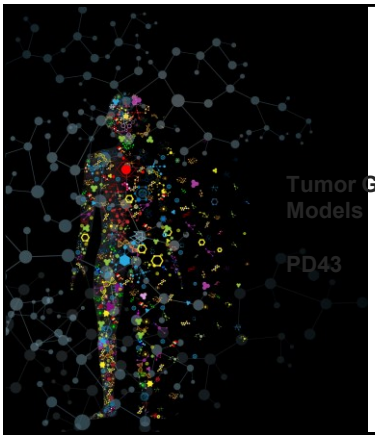
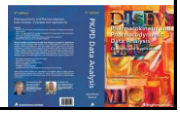


CERTARA

Tumor Growth Inhibition Models

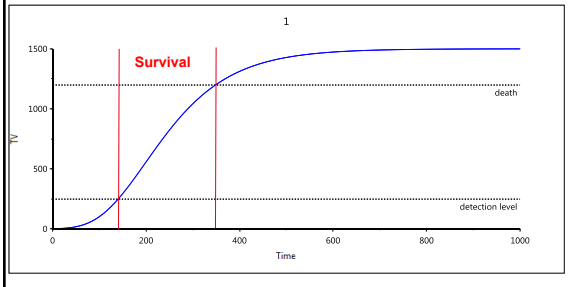
PD43



Overview

- Tumor Growth Modeling
- Preclinical models
  - Xenografts
  - Modeling Strategy
  - Models of Tumor Growth/Kill
    - Gompertz
    - Simeoni
    - Jumbe
- Demo
- Summary
- Q&A
- New PML Library
  - NONMEM-2-PML

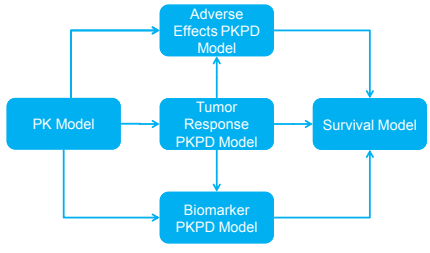
Tumor Growth Modeling: Survival



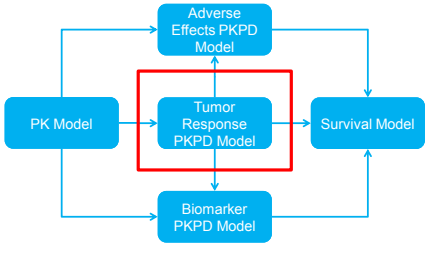
Gompertz: $TV = TV_0 \cdot e^{\frac{A}{\alpha}(1-e^{-\alpha \cdot t})}$

TV_0: Initial Tumor Volume
A: initial growth rate constant
α: deceleration rate constant

Tumor Growth Modeling: Clinical Scenario



Focus of our Session: Tumor Response PKPD



Preclinical Scenario: Xenografts

- Xenograft models are in vivo models to establish antitumor activity of compounds in drug discovery process
  - Human tumor fragments are subcutaneously implanted into the flank of nude or severe combined immunodeficient mice
  - Xenograft mice develop human solid tumors
  - Once the tumors have reached a predefined size (~100-300 mm^3), the mice are randomized to different treatment groups (one placebo group)
  - Doses are given and tumor size is measured over a period of time
- Tumor dimensions are measured with caliper
  - Tumor volume estimated from length and width

Preclinical Models: Typical Modeling Strategy

- Pharmacokinetics
  - Only Satellite PK measurements in study
  - PK part is frozen in PK/PD model
- Tumor dynamics is modeled in two stages
  - Tumor aggressiveness and resistance estimated on control group
  - Drug induced decay estimated on all treatment groups
    - Rank order compounds on antitumor potency
    - Sensitivity analysis performed on PD parameters
- Simulations
  - Testing of new dose levels and regimens
  - Eventually scale to first dose in human

CERTARA

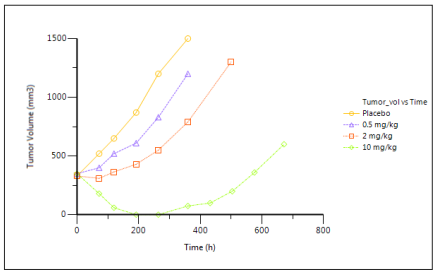
Models of Tumor Growth/Kill: Objective

- Characterize tumor growth/kill using three different models:
  - Gompertz - TGI
  - Simeoni
  - PD43: Jumbe
- Find estimates for:
  - Tumor growth rate
  - Tumor kill rate

CERTARA

PK32: Exploratory Data Analysis

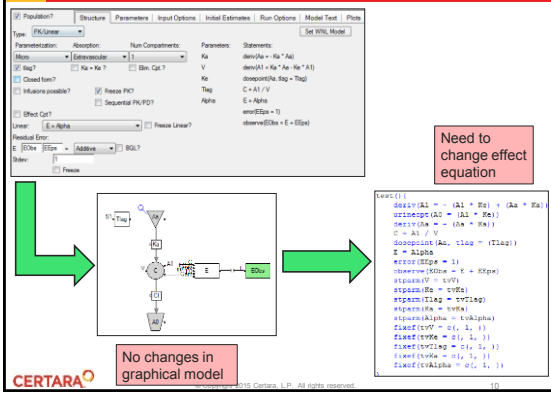
- Linear plot of tumor volume versus time



Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

CERTARA

Building Gompertz Model: Built-in Options



CERTARA

Building Gompertz Model - textual

$$\frac{dE}{dt} = E \cdot \left(\alpha - \beta \cdot ln\left(\frac{E}{E_0}\right)\right)$$ Gompertz model

$$decay = \gamma \cdot C(t) \cdot E$$ Drug induced decay

$$\frac{dE}{dt} = E \cdot \left(\alpha - \beta \cdot ln\left(\frac{E}{E_0}\right)\right) - \gamma \cdot C(t) \cdot E$$ combined model

```
test({
  ## PK Model ##
  deriv(Aa = - Ka * Aa)
  deriv(A1 = Ka * Aa - Ke * A1)
  C = A1 / V
  dosepoint(Aa, tlag=Tlag, idosevar = AmDose)

  ## Tumor Growth Inhibition Model ##
  EFfect(EEps = E + 1
  observe(EObs = E + EEps)

  ## Initialize tumor
  sequence(E=E0)

  ## fixed effects for the PK model - all parameters frozen ##
  fixef(Ka(freeze) = c(, 4.0488, ))
  fixef(V(freeze) = c(, 2.561, ))
  fixef(Ke(freeze) = c(, 0.1439, ))
  fixef(Tlag(freeze) = c(, 0.8454, ))

  ## fixed effects for the Tumor Growth Inhibition Model ##
  fixef(E0 = c(, 350,))          # Initial Tumor Volume
  fixef(a = c(, 0.005,))         # growth rate constant
  fixef(b = c(, 0.15,))          # decelleration rate constant
  fixef(g = c(, 0.001,))         # drug decay rate constant
}
```

Gompertz model
drug induced decay

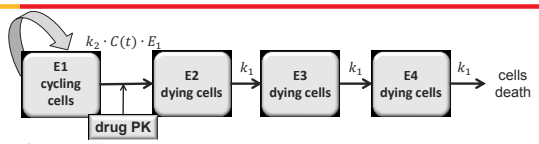
CERTARA

Simeoni Model

- Empirical models (e.g. Gompertz) are only describing tumor growth/kill
  - Expect parameter change upon dose level or regimen changes
- Mechanistic models consider systems biology
  - Different cell populations
  - Cell-cycle kinetics
  - Biochemical processes
    - But require a lot of assumptions and/or experimental observations
- Simeoni model as compromise of a semi-mechanistic model
  - Less assumptions
  - Requires only typical preclinical data
    - PK
    - Tumor growth curves

CERTARA

Simeoni Model



$$\frac{dE_1}{dt} = \frac{\lambda_0 \cdot E_1}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} - E\right)^{\psi}\right]^{\frac{1}{\psi}}} - k_2 \cdot C(t) \cdot E_1$$

$$\frac{dE_2}{dt} = k_2 \cdot C(t) \cdot E_1 - k_1 \cdot E_2$$

$$\frac{dE_3}{dt} = k_1 \cdot (E_2 - E_3)$$

$$\frac{dE_4}{dt} = k_1 \cdot (E_3 - E_4)$$

$$E = E_1 + E_2 + E_3 + E_4$$

CERTARA

 13

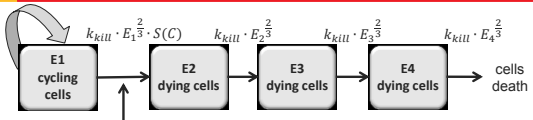
Simeoni Model in PML

```
test(){
    ## PK Model ##
    deriv(Aa = - Ka * Aa)
    deriv(A1 = Ka * Aa - Ke * A1)
    C = A1 / V
    dosepoint(Aa, tlag=Tlag, idosevar = AaDose)

    ## PD Model
    psi = 20                                    # exponent to switch between exponential and linear growth
    E = E1 + E2 + E3 + E4                       # tumor volume is sum of tumor volumes from all compartments
    Inh = (1 + (lambda0*E/lambda1)^psi)^(1/psi) # inhibition function - denominator part
    deriv(E1 = (lambda0 * E1 / Inh) - k2 * C * E1)  # de for compartment of proliferating cells
    deriv(E2 = k2 * C * E1 - k1 * E2)           # de for first transit compartment of damaged cells
    deriv(E3 = k1 * (E2 - E3))                  # de for second transit compartment
    deriv(E4 = k1 * (E3 - E4))                  # de for third transit compartment
    sequence(E1= E0)                            # initialize tumor
    error(EPS = 1)                              # residual error initially set to 1
    observe(EObs = E + EPS)                     # additive residual error model for effect

    ## secondary parameters
    secondary(Eth=lambda1/lambda0)                      # threshold tumor volume
    secondary(Ct=lambda0/k2)                            # threshold concentration for tumor eradication
    deriv(AUC=C)                                        # calculating drug exposure (AUC)
    TKI=(k2*AUC)/lambda0                                # time efficacy index

    ## fixed effects for PK model - all frozen ##
    fixef(Ka(freeze) = c(, 4.0488, ))
    fixef(V(freeze) = c(, 2.561, ))
    fixef(Ke(freeze) = c(, 0.1439, ))
    fixef(Tlag(freeze) = c(, 0.8454, ))

    ## fixed effects for PD model ##
    fixef(lambda0 = c(0, 0.5, ))                # first-order rate constant of tumor growth
    fixef(lambda1 = c(0,3, ))                   # zero-order rate constant of tumor growth
    fixef(E0 = c(0,340,))                       # tumor volume at inoculation time
    fixef(k1 = c(0,0.05,))                      # transit rate constant
    fixef(k2 = c(0,0.2,))                       # decay rate constant
}
```

CERTARA

 14

PD43: Jumbe Model



$$\frac{dE_1}{dt} = k_{growth} \cdot E_1^{\frac{2}{3}} - k_{kill} \cdot E_1^{\frac{2}{3}} \cdot S(C) \qquad S(C) = k_{kill,max} \cdot \frac{C^n}{KC_{50}{}^n + C^n}$$

$$\frac{dE_2}{dt} = k_{kill} \cdot E_1^{\frac{2}{3}} \cdot S(C) - k_{kill} \cdot E_2^{\frac{2}{3}}$$

$$\frac{dE_3}{dt} = k_{kill} \cdot (E_2^{\frac{2}{3}} - E_3^{\frac{2}{3}})$$

$$\frac{dE_4}{dt} = k_{kill} \cdot (E_3^{\frac{2}{3}} - E_4^{\frac{2}{3}})$$

$$E = E_1 + E_2 + E_3 + E_4$$

CERTARA

 15

PD43: Jumbe Model in PML

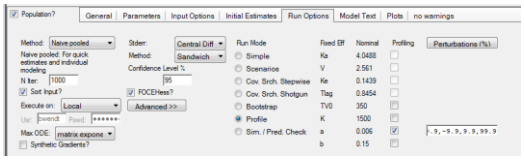
```
test(){
    ## PK Model ##
    deriv(Aa = - Ka * Aa)
    deriv(A1 = Ka * Aa - Ke * A1)
    Cp = A1 / V
    dosepoint(Aa, tlag=Tlag)

    ## PD Model ##
    Inh = Kmax * (Cp / ( KC50 + Cp))        # inhibition using Hill equation
    E1=max(E1,0)                            # Effect should be positive or 0
    E2=max(E2,0)
    E3=max(E3,0)
    E4=max(E4,0)
    deriv(E1 = (Kgrow - Inh * Kkill) * E1^(2/3))            # de for compartment of proliferating cells
    deriv(E2 = (Inh * Kkill * E1^(2/3) - Kkill * E2^(2/3)))  # de for first transit compartment of damaged cells
    deriv(E3 = (Kkill * E2^(2/3) - Kkill * E3^(2/3)))       # de for second transit compartment
    deriv(E4 = (Kkill * E3^(2/3) - Kkill * E4^(2/3)))       # de for third transit compartment
    E = E1 + E2 + E3 + E4                   # tumor volume is sum of tumor volumes from all compartments
    sequence(E1 = E0)                       # initialize tumor
    error(EPS = 1)                          # residual error initially set to 1
    observe(EObs = E + EPS)                 # additive residual error model for effect

    ## fixed effects for PK Model - all frozen
    fixef(Ka(freeze) = c(, 4.0488, ))
    fixef(V(freeze) = c(, 2.561, ))
    fixef(Ke(freeze) = c(, 0.1439, ))
    fixef(Tlag(freeze) = c(, 0.8454, ))

    ## fixed effects for PD Model ##
    fixef(Kgrow = c(, 0.01, ))                  # growth rate constant
    fixef(Kkill = c(, 0.1, ))                   # killing rate
    fixef(Kmax = c(, 5, ))                      # scaling parameter for Kkill
    fixef(KC50 = c(, 300, ))                    # concentration at half-maximal killing rate
    fixef(E0 = c(, 350, ))                      # initial tumor volume

    ## secondary parameters ##
    secondary(TSC = Kgrow * KC50/(Kkill * Kmax - Kgrow))    # tumor static serum drug level
}
```

CERTARA

 16

Initial Estimates for either model

- Use Initial Estimates Tab
- You can derive initial estimates from sensitivity analysis:
  - Switch to Population mode
  - Go to Run Options Tab
  - Select Profile as Run Mode:



- Enter Perturbations (%), e.g. -99.9, -99, -9, 9, 99, 999

Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

CERTARA

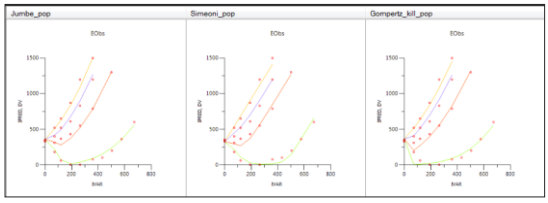
 17

Demo

CERTARA

 18

PD43: Results



	Name	RatCode	LogLik	-2LL	AIC	BIC	nParm	nObs	nSub	EpsShrinkage	Condition
1	Jumbe_pop	3	-149.25937	298.51394	310.51394	318.71771	6	29	4	0	36254.517
2	Simeoni_pop	1	-154.09726	308.19452	320.19452	328.39829	6	29	4	0	
3	Gompertz_kill_pop	3	-159.61319	319.22638	329.22638	336.06286	5	29	4	0	3319460.4

PD43: Results

	Name		
	Gompertz_kill	Simeoni	Jumbe
Parameter	Estimate		
E0	361.828	324.308	357.601
a	0.005		
lambda0		0.018	
Kgrow			0.036
g	0.191		
k2		0.339	
Kmax			14.142
k1		0.030	
Kkill			0.172
stdev0	59.440	49.144	41.587
b	0.002		
lambda1		3.021	
KC50			1.605

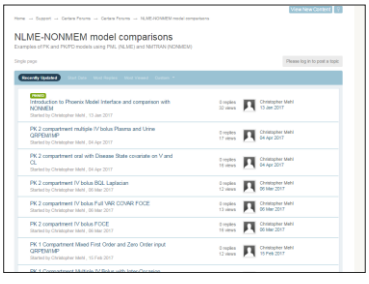
- Initial Tumor Volume
- Exponential growth rate constant
- Drug-induced decay rate constant
- Transit rate constant
- Residual error

PK43: Summary

- Tumor Growth/Kill Models
  - Gompertz
    - Classic equation
    - Empirical
      - Single growth phase: exponential
      - Drug effects the total tumor volume
      - Drug induced decay expressed by proportional factor
  - Simeoni
    - Widely used
    - Semi-mechanistic
      - Two different growth phases: exponential and linear
      - Differentiates proliferating cells from dying ones
      - Drug induced decay expressed by proportional factor
  - Jumbe
    - Semi-mechanistic
      - Single growth phase: exponential
      - Differentiates proliferating cells from dying ones
      - Drug induced decay expressed with saturable function

New PML Library: NONMEM-2-PML

- https://support.certara.com/forums/forum/35-nlme-nonmem-model-comparisons/



New PML Library: NONMEM-2-PML

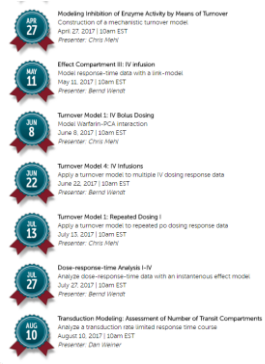
Coming up…

Modeling PK/PD Systems with Distributed Delays
Speaker(s): Wojciech Krzyzanski
Date: May 16, 2017
Time: 11 am EST
Duration: 1 hour

Modeling Inhibition of Enzyme Activity by Means of Turnover
Construction of a mechanistic turnover model
April 27, 2017 | 10am EST
Presenter: Chris Mehl

CERTARA

Coming up…



CERTARA