

Mechanistic Joint Modeling for Longitudinal and Time-to-Event Data in Oncology Drug Development, Recent Advances, and Toward Personalized Medicine

Session Chairs:

Diansong Zhou (AstraZeneca)

Jenny Sheng (BMS)

4:45 PM – 6:15 PM March 23rd

ASCPT, Orlando FL

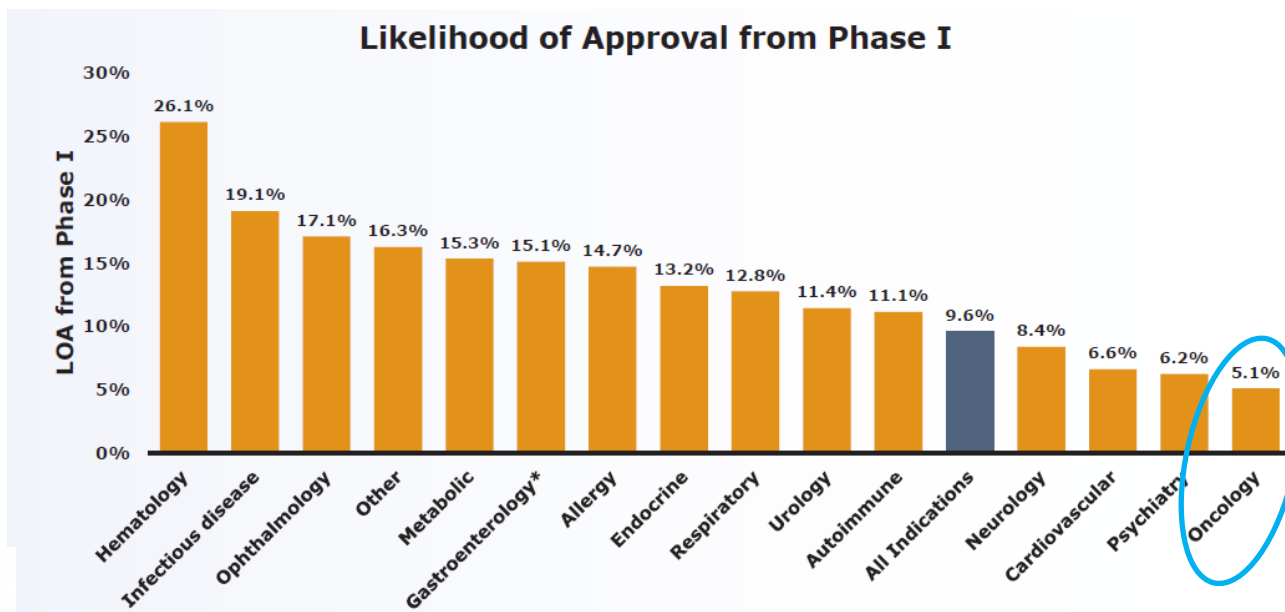


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Background

- Cancer is the second leading cause of death globally and in the US, and was responsible for 8.8 million deaths in 2015.
- Oncology success rate is the lowest across all therapeutic area (5.1%, data from 2006-2015).
- The use of model-based drug development is the community interest and advocated by regulatory (FDA).



Traditional 2- stage Sequential Approach

1. Longitudinal model

Longitudinal tumor size (biomarker) data
+
Longitudinal covariates

2. Event modeling

Progression free survival (PFS),
Overall survival (OS)

Tumor growth rate, time to growth,
response at 6, 8 weeks, etc.

Elucidation of Relationship Between Tumor Size and Survival in Non-Small-Cell Lung Cancer Patients Can Aid Early Decision Making in Clinical Drug Development

Y Wang¹, C Sung^{1,2}, C Dartois¹, R Ramchandani², BP Booth², E Rock³ and J Gobburu¹

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 86 NUMBER 2 | AUGUST 2009

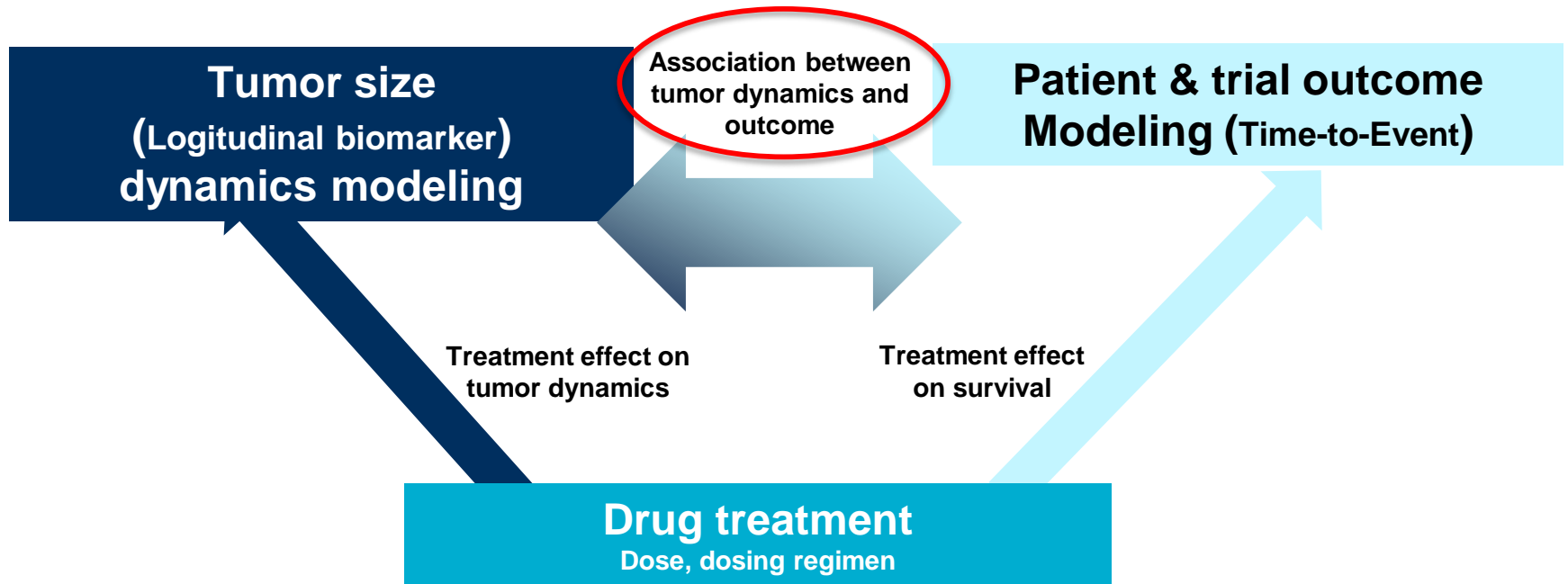
Exploratory Modeling and Simulation to Support Development of Motesanib in Asian Patients With Non-Small Cell Lung Cancer Based on MONET1 Study Results

L Claret¹, R Bruno¹, J-F Lu², Y-N Sun² and C-P Hsu²

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 95 NUMBER 4 | APRIL 2014



Joint Modeling of Tumor Size Dynamics, Biomarkers and Other Baseline Covariates to Improve Prediction of Outcome



Available joint modeling software and packages

- R packages:
 - JM
 - JMBayes
 - JoinerR
 - Lcmm (*latent class mixed models*)
- R/Stan:
 - RstanArm
- SAS:
 - JMFit
- Stata:
 - Stjm
- Monolix - SAEM
- NONMEM



Joint Modelling in Applications in Oncology in Recent Years

Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 560–568; doi:10.1002/psp4.12209
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ORIGINAL ARTICLE

Exposure–Response Analysis of Necitumumab Efficacy in Squamous Non-Small Cell Lung Cancer Patients

E Chigutsa¹, AJ Long¹ JE Wallin^{2*}

BIOMETRICS

Using the SAEM Algorithm for Mechanistic Joint Models Characterizing the Relationship between Nonlinear PSA Kinetics and Survival in Prostate Cancer Patients

Solène Desmée,^{1,2,*} France Mentré,^{1,2} Christine Veyrat-Follet,³ Bernard Sébastien,⁴ and Jérémie Guedj^{1,2}

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Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 373–382; doi:10.1002/psp4.12193
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ORIGINAL ARTICLE

A Pharmacometric Framework for Axitinib Exposure, Efficacy, and Safety in Metastatic Renal Cell Carcinoma Patients

E Schindler¹, MA Amantea², MO Karlsson¹ and LE Friberg^{1*}

The AAPS Journal, Vol. 17, No. 3, May 2015 (© 2015)
DOI: 10.1208/s12248-015-9745-5

Research Article

Nonlinear Mixed-Effect Models for Prostate-Specific Antigen Kinetics and Link with Survival in the Context of Metastatic Prostate Cancer: a Comparison by Simulation of Two-Stage and Joint Approaches

Solène Desmée,^{1,2,4} France Mentré,^{1,2} Christine Veyrat-Follet,³ and Jérémie Guedj^{1,2}

MAIN PAPER

Pharmaceutical
Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.1629

Published online 15 July 2014 in Wiley Online Library

Joint modeling tumor burden and time to event data in oncology trials

Ye Shen,^{a*} Aparna Anderson,^b Ritwik Sinha,^c and Yang Li^d

Research Article

Statistics
in Medicine

Received 20 May 2013,

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Published online 20 July 2014 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.6269

Assessing model fit in joint models of longitudinal and survival data with applications to cancer clinical trials

Danjie Zhang,^a Ming-Hui Chen,^a Joseph G. Ibrahim,^{b,*†}
Mark E. Boye,^c Ping Wang^d and Wei Shen^c



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Objectives of this workshop

- To provide a current clinical and scientific understanding of joint modeling and its applications in oncology clinical development
- Clinical development strategy
 - Early prediction of trial outcome: e.g. pick best combination
 - Trial optimisation
- Dose and schedule optimisation
- Product differentiation
 - Use public data on SoCs etc. to benchmark for target product profile
- Personalised medicine
 - Patient inclusion criteria for next trials



Speakers

France Mentre (INSERM)

Mechanistic joint models characterizing the relationship between nonlinear prostate specific antigen kinetics and survival in prostate cancer patients

Ye Shen (University of Georgia)

Joint modeling tumor burden and time to event data in oncology trials, theoretical consideration and application in non-small cell lung cancer study

Nidal Al-Huniti (AstraZeneca)

Dynamic predictions of progression free survival and overall survival in non-small cell lung cancer using tumor sizes: a longitudinal joint modeling approach for Gefitinib



Dr. France Mentre

- Dr. France Mentré is Professor of Biostatistics in the School of Medicine of University Paris Diderot (Paris 7).
- She heads an INSERM research team on Biostatistical Modelling and Pharmacometrics in treatment of Infectious Diseases. She has worked on development and application of methods for nonlinear mixed-effects models in pharmacokinetics and pharmacodynamics for more than 30 years.
- She is leading the development of the software PFIM for optimal design in pharmacometrics. She worked in the application of these models to understand the variability in the response to anti-infective agents.
- She has published more than 240 articles in biostatistics, pharmacometrics, clinical pharmacology or medical research.
- She received in 2013 the USCF/ISoP Lewis B. Sheiner Lecturer Award and in 2016 the Honorary Fellowship Award of the American College of Clinical Pharmacology. She is one of the founder of the Special Interest Group on Statistics and Pharmacometrics of ASA and ISOP.



Dr. Ye Shen

- Dr. Ye Shen is currently an Associate Professor of Biostatistics in the College of Public Health at the University of Georgia.
- Dr. Ye Shen obtained his BS and MS from Fudan University in China and a PhD in Biostatistics from Yale University.
- Dr. Shen's research interests include joint modeling of longitudinal and event data, spatial statistics, missing data analysis, and robust methods in clinical trial. Along the lines of these topics he has published methodological papers on journals such as *Biometrika*, *Statistics in Medicine*, and *Pharmaceutical Statistics*, as well as collaborative works on high-quality scientific and medical journals including *Nature*, *JAMA Internal Medicine*, and *Lancet Respiratory Medicine*, etc. In addition, Dr. Shen currently serves as an Associate Editor for *Frontiers in Pharmacology*.



Dr. Nidal Al-Huniti

- Dr. Nidal Al-Huniti is currently an Executive Director in Quantitative Clinical Pharmacology at AstraZeneca. He is also an oncology pharmacology co-lead.
- Nidal leads a group of PhD-level scientists responsible for applying theoretical and applied statistical and mathematical approaches in clinical pharmacology to guide the clinical drug development in the areas of oncology, antibiotics and neurosciences, ranging from first time in human to post-marketing activities.
- His contributions have been primarily in the areas of clinical pharmacology and modeling and simulation strategy and execution. He has had many publications in the modeling and simulation applications.
- His interest in joint modeling especially in oncology started 2 years ago. His great interest and leadership has led to multiple posters and several manuscripts.

