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Application of Quantitative Modeling in Oncology Dose Optimization: Opportunities and Challenges

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Outline

- Why are exposure-response analyses important in oncology?
- Why are exposure-response analyses hard in oncology?
- Potential solutions and limitations

Why are exposure-response analyses **important** in oncology?

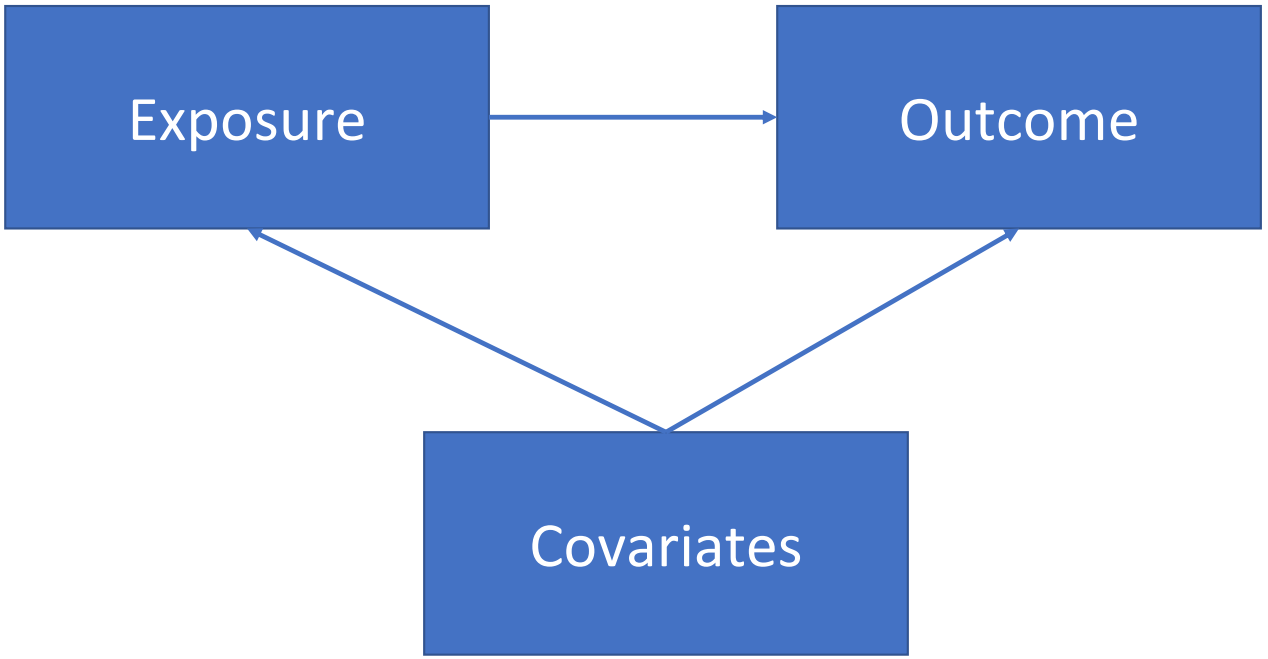
- Modern cancer treatment has substantial differences in dose-response compared to cytotoxic therapies.
- Data ignored in MTD paradigm can be quite informative for dose optimization.
- Optimal dose should also be based on understanding heterogeneity of patient populations.

Why are exposure-response analyses **hard** in oncology?

- Studies are not designed to understand exposure-response
  - Late phase studies often limited to one dose/regimen
  - Sparse PK sampling

- More patient heterogeneity than other disease area

Single dose data is a limitation for exposure-response analysis.



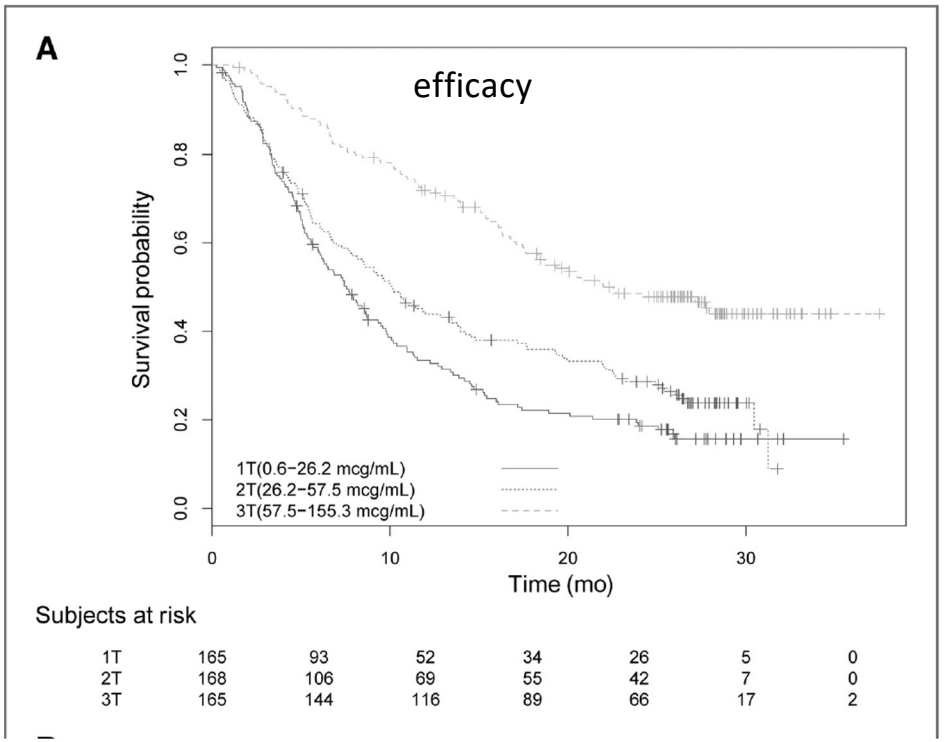
Solution 1: Improved study design

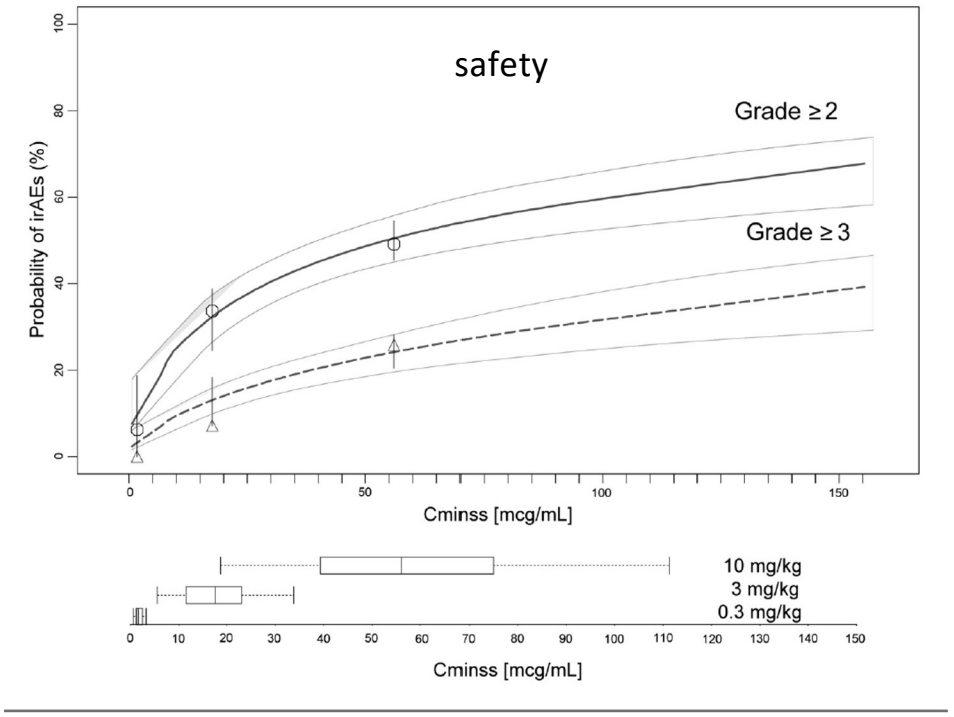
Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study

Phase III Study of Adjuvant Ipilimumab (3 or 10 mg/kg) Versus High-Dose Interferon Alfa-2b for Resected High-Risk Melanoma: North American Intergroup E1609

Multiple doses were tested in late phase studies of ipilimumab.

Both exposure-efficacy and exposure-safety were characterized to inform dose selection.





Solution 2: Quantitative analysis methods

Case study 1:

The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making

The Journal of Clinical Pharmacology
53(2) 160–166

DOI: 10.1177/0091270012445206

Jun Yang, PhD[1], Hong Zhao, PhD[1], Christine Garnett, PharmD[1], Atiqur Rahman, PhD[1], Jogarao V. Gobburu, PhD[1], William Pierce, PharmD[2], Genevieve Schechter, MD[2], Jeffery Summers, MD[2], Patricia Keegan, MD[2], Brian Booth, PhD[1], and Yaning Wang, PhD[1]

Case study 2:

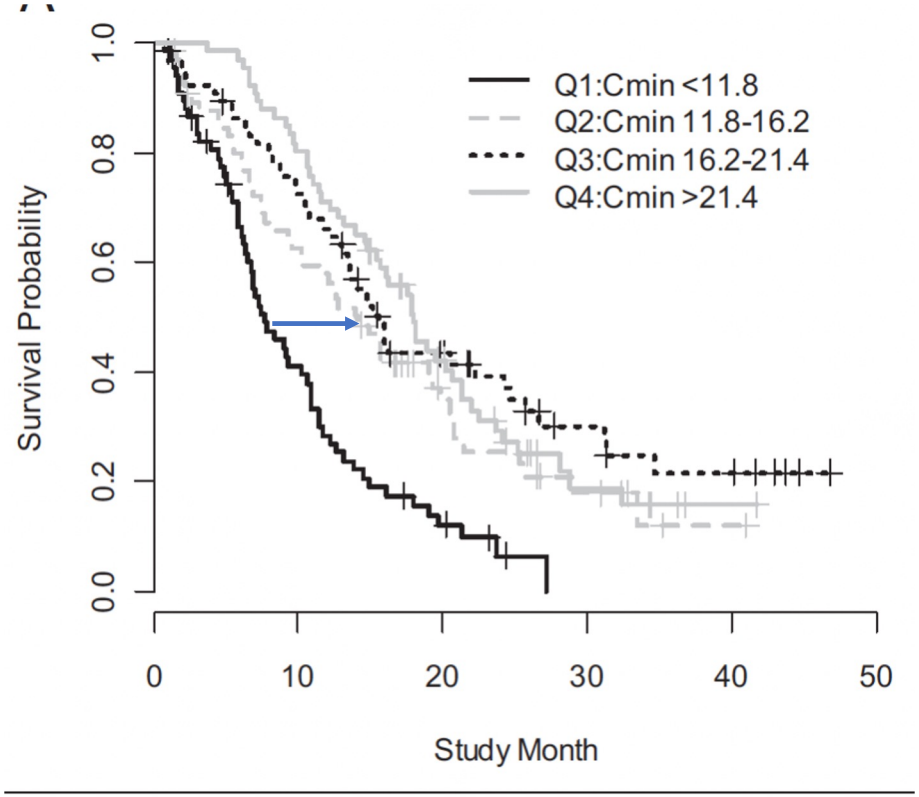
Cancer Chemother Pharmacol (2017) 80:1079–1090
DOI 10.1007/s00280-017-3440-4

ORIGINAL ARTICLE

Exposure–response analyses of trastuzumab emtansine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane

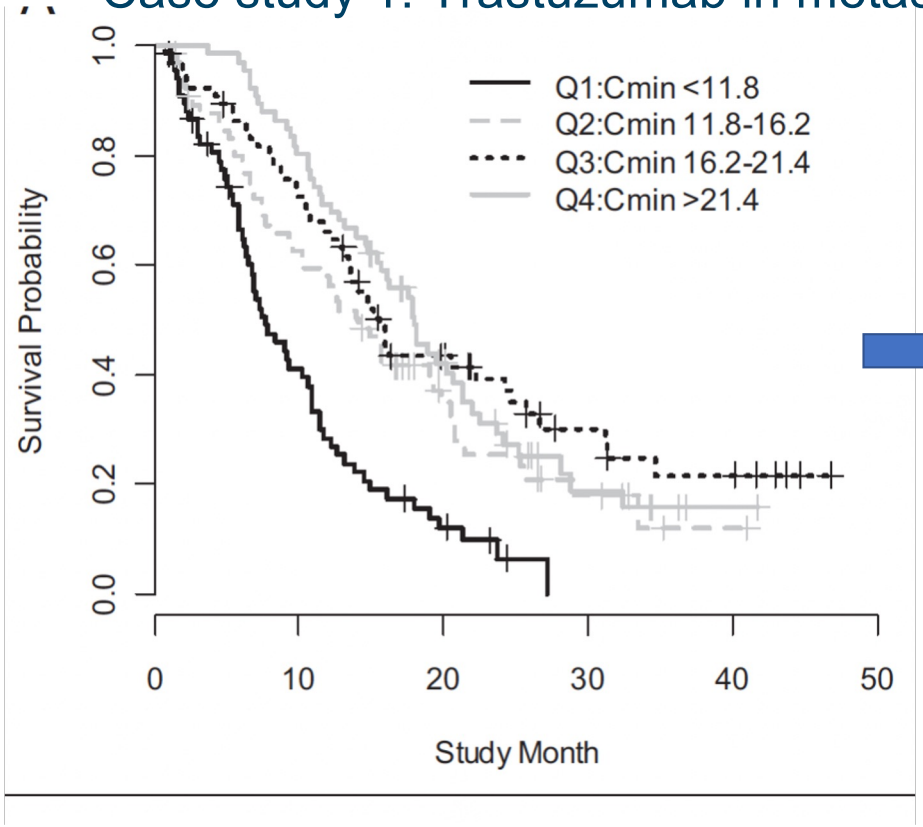
Chunze Li[1] · Bei Wang[1] · Shang-Chiung Chen[1] · Russell Wada[2] · Dan Lu[1] · Xin Wang[1] · Daniel Polhamus[3] · Jonathan French[3] · Shweta Vadhavkar[1] · Alexander Strasak[4] · Melanie Smitt[5] · Amita Joshi[1] · Meghna Samant[6] · Angelica Quartino[1] · Jin Jin[1] · Sandhya Girish[1]

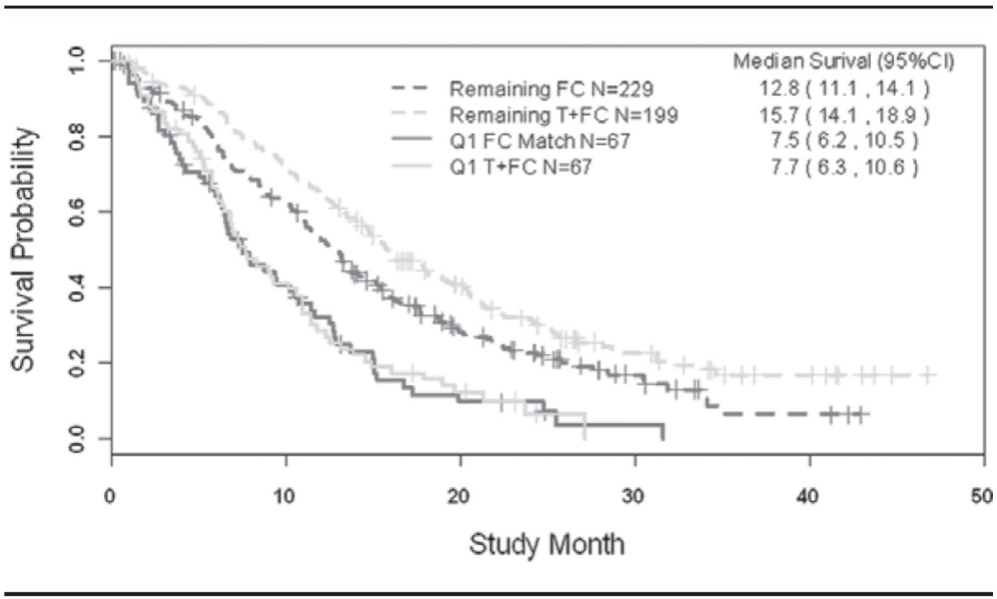
Case study 1: Trastuzumab in metastatic gastric cancer



Could the registrational dose be sub-optimal for some subjects?

Case study 1: Trastuzumab in metastatic gastric cancer





After case-control matching, patients in the Q1 subgroup had similar OS versus FC-treated group (median survival of 7.7 vs. 7.5 months).

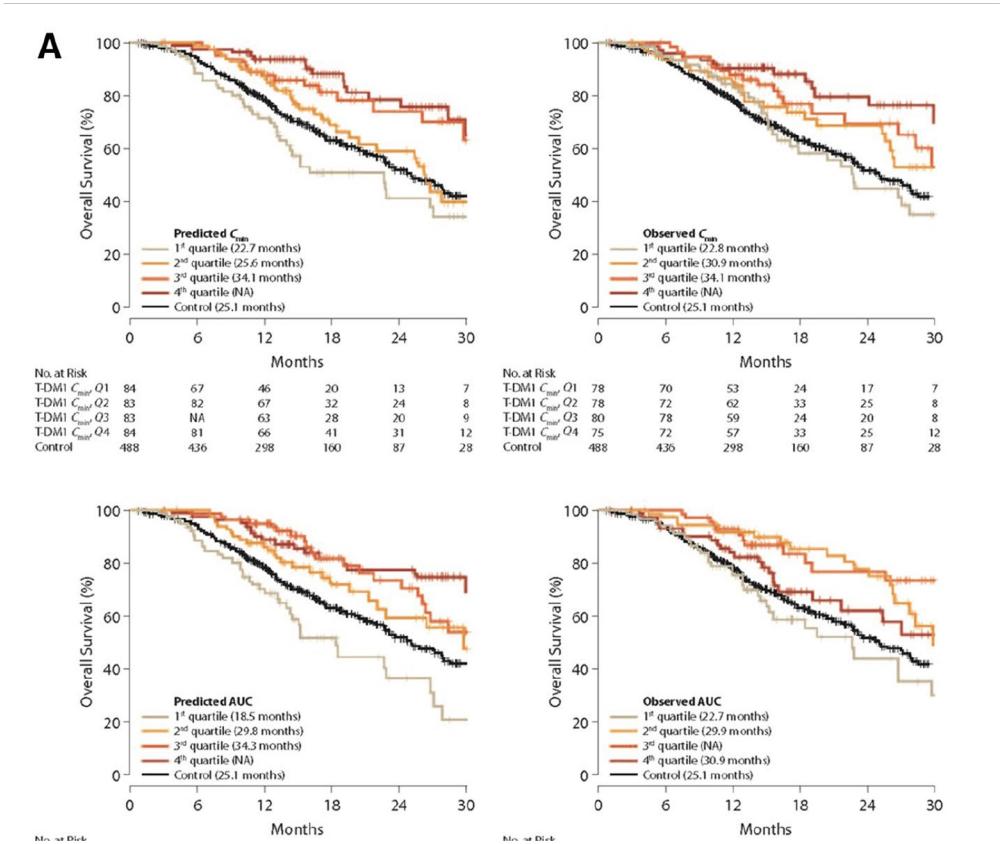
Case study 1: Trastuzumab in metastatic gastric cancer

Key takeaways:

- “ER analyses based on non-randomized exposure groups should always be followed by a thorough check for potential unbalanced distribution of risk factors across different exposure groups.”

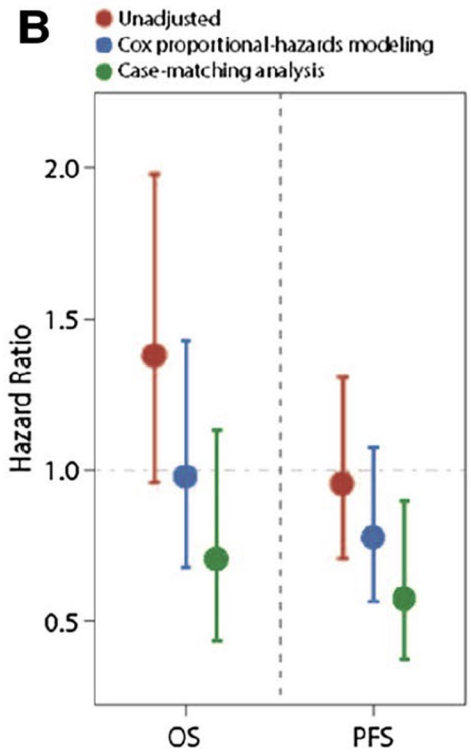
- Such imbalances can be analytically corrected.

Case study 2: Trastuzumab emtansine in HER2-positive advanced breast cancer



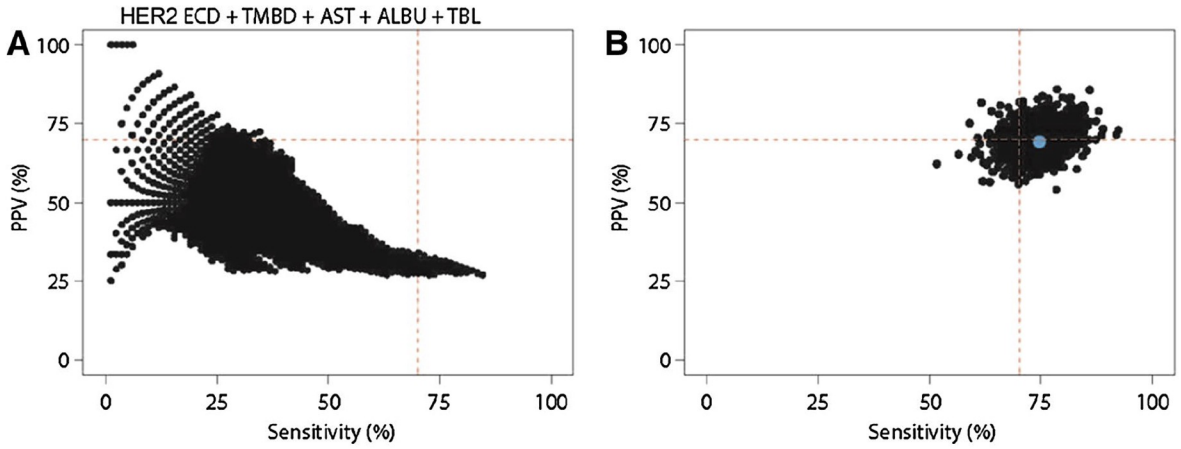
- ER efficacy relationship was inconsistent across exposure metrics.
- These studies were not typically designed for exposure-response analyses.

Case study 2: trastuzumab emtansine in HER2-positive advanced breast cancer



- Apparent exposure–response relationship was seen between Cmin and the OS and PFS.
- After adjusting for baseline risk factors, patients in the Q1 subgroup had similar or better OS and PFS than the control group.

Case study 2: Trastuzumab emtansine in HER2-positive advanced breast cancer



It is not possible to consistently and reliably identify patients with low exposure.

Case study 2: Trastuzumab emtansine in HER2-positive advanced breast cancer

Key takeaways:

- The inconsistencies in the strength of the apparent exposure–response relationships for different exposure metrics suggested a confounding by baseline risk factors.
- The bias that arises from imbalanced comparisons can be analytically mitigated.

Summary

- Despite challenges, there are many successful applications of quantitative modelling in the dosing regimen optimization of oncology drugs

- Improved study design is the most effective solution to these challenges and something we can influence
  - More than one dose/regimen
  - Thoughtful PK sampling design

- Addressing these challenges through modeling is less effective but something we can control
  - Propensity-adjusted analyses
  - Outcome modeling

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- C Li, B. Wang, S. Chen, R. Wada, D. Lu, X. Wang, D. Polhamus, J. French, S. Vadhavkar , A. Strasak, M. Smitt, A. Joshi, M. Samant, A. Quartino, J. Jin, and S. Girish. Exposure–response analyses of trastuzumab emtansine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane. Cancer Chemother Pharmacol (2017) 80:1079–1090

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Questions

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Back Up

Session Description and Objectives

- The traditional paradigm of oncology drug development by taking one (maximum tolerated dose) MTD into late phase testing put many challenges on evidence generation. The promise of FDA's dose optimization initiative Project Optimus offers the hope of a new dawn of Model-Informed Drug Development (MIDD) in Oncology. As such, the pharmacometrics community has been doing and will do more to determine not only the MTD but the best therapeutic dose with optimal benefit-risk. In this webinar, we would like to provide examples of successful applications of quantitative modeling in the dosing regimen optimization of oncology drugs.

- Understanding the need for oncology drug dose optimization;
- Understanding the important guidance provided by Project Optimus;
- Understanding the role of quantitative modeling in supporting dose optimization in oncology;
- Reviewing case studies involving the application of quantitative modelling in supporting oncology drug development.