Characterizing Exposure Response of Biologics: Challenges and Opportunities—Regulatory Perspective

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

Outline

- Challenges in exposure-response analysis for biologics
- Opportunities in methodology development
- Summary

Challenges

- Lack of dose-response data
- Exposure-response analysis based on one dose level data
- Response data: time-to-event data (survival, progression-free survival, etc.)
- Patients regrouped based on observed/predicted exposure: randomization broken

Two Cases

Trastuzumab (Herceptin)

- Regimen approved for HER2-overexpressing breast cancer (8mg/kg followed by 6mg/kg q3w) was selected as the Phase 3 regimen for metastatic HER2-overexpressing gastric cancer
- Indication: metastatic HER2-overexpressing gastric cancer

Ado-Trastuzumab Emtansine (T-DM1)

- Trastuzumab linked to a small cytotoxic (microtubule inhibitor) molecule emtansine (DM1)
- Rationale for dosing regimen:
  - Phase 1 MTD=3.6 mg/kg q3w based on thrombocytopenia (grade 4)
  - Multiple phase 2 trials with 3.6 mg/kg q3w
  - One phase 3 trial comparing T-DM1 3.6 mg/kg IV q3w with lapatinib+capecitabine
- Indication: HER2-positive, metastatic breast cancer

Phase 3 Clinical Trial

	Herceptin	T-DM1
Control	Cisplatin+capecitabine/ 5-Fluorouracil (FC)	Lapatinib +Capecitabine (LC)
Active	Trastuzumab + FC (H+FC)	Ado-Trastuzumab Emtansine (T-DM1)

- **Open-label, parallel, 1:1 randomization**
- **Primary endpoint*: overall survival**

***: For T-DM1, progression-free survival (PFS) and OS are co-primary efficacy endpoints**

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103792s5327lbl.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125427Orig1s000StatR.pdf

Efficacy Results

Herceptin

	FC+H (N=298)	FC (N=296)
No. Death (%)	221 (74.2)	227 (76.7%)
Median (95% CI mos)	13.1 (11.9, 15.1)	11.7 (10.3, 13.0)
Hazard ratio (95% CI)	0.80 (0.67, 0.97)	

T-DM1

	T-DM1 (N=495)	LC (N=496)
No. Death (%)	149 (30.1%)	182 (36.7)
Median OS (month)	30.9	25.1
Hazard ratio (95% CI)	0.682 (0.548, 0.849)	

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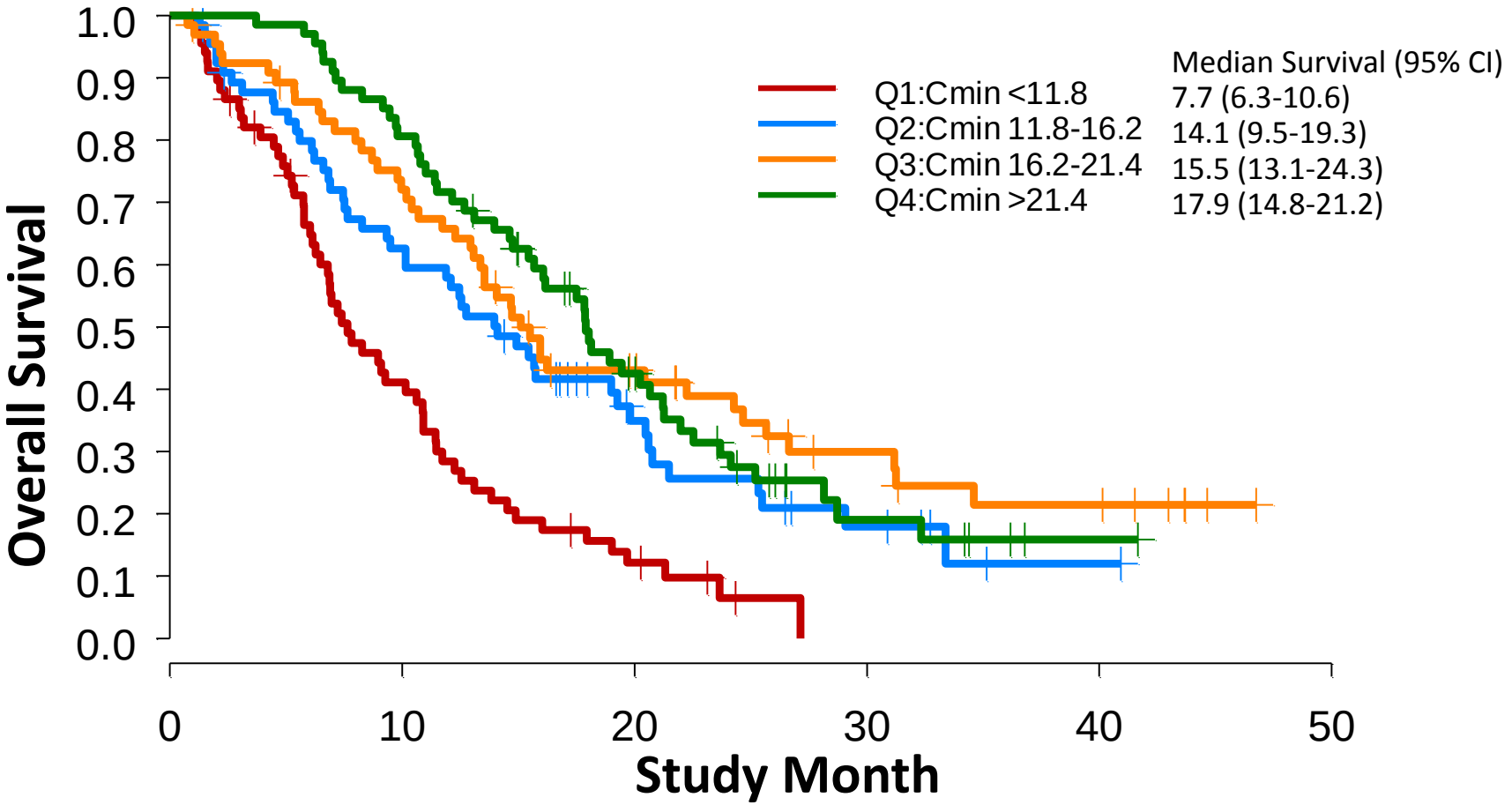
Exposure-Survival for Herceptin

Patients with Cmin <12 µg/mL Had 7-10 Months Shorter Median OS



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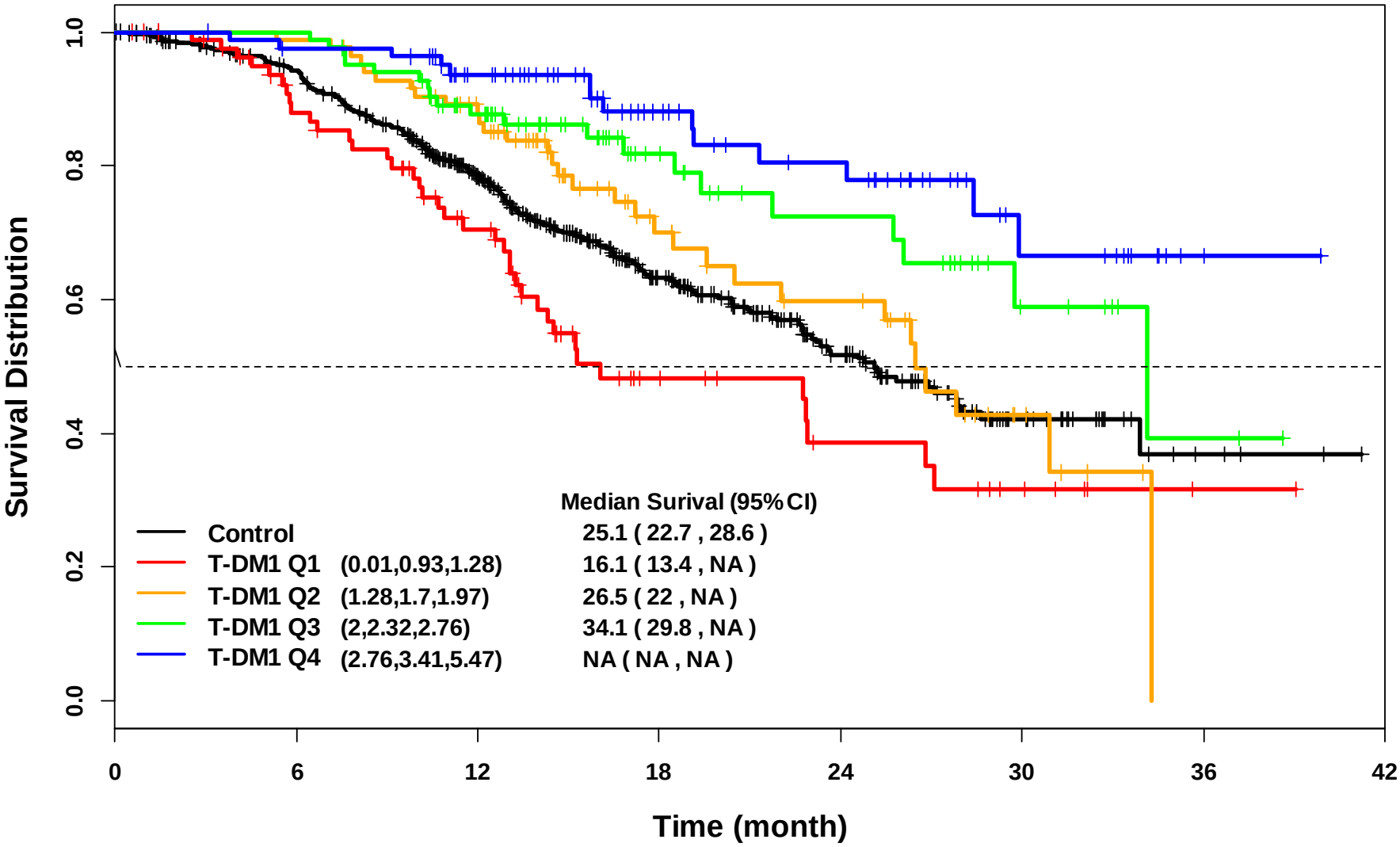
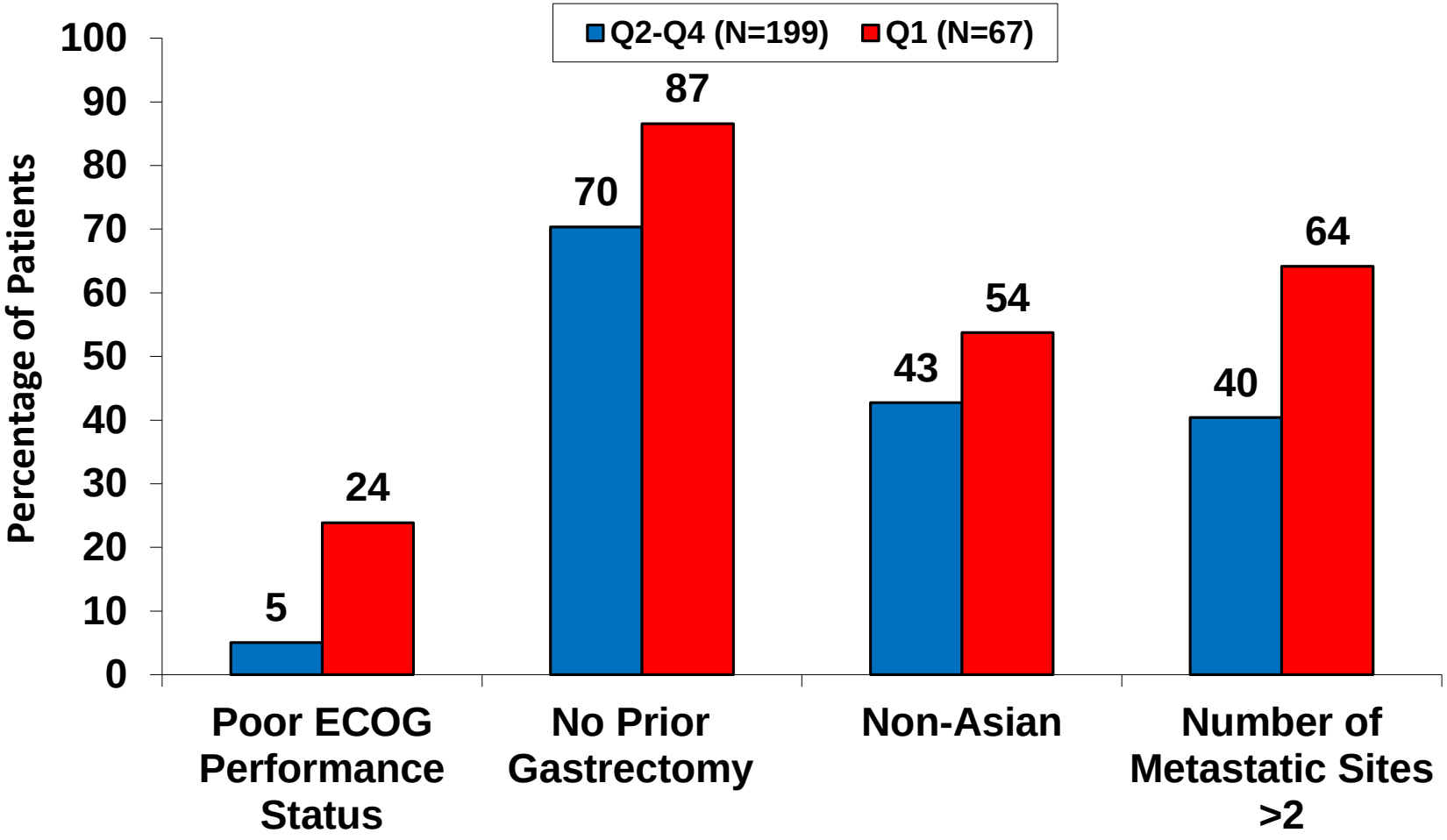
Exposure-Survival for T-DM1



Wang, J. *et al*. Exposure-response relationship of T-DM1: insight into dose optimization for patients with HER2-positive metastatic breast cancer. *Clin Pharmacol Ther. 2014 May;95(5):558-64*

Confounding Risk Factors for Survival (Herceptin Case)



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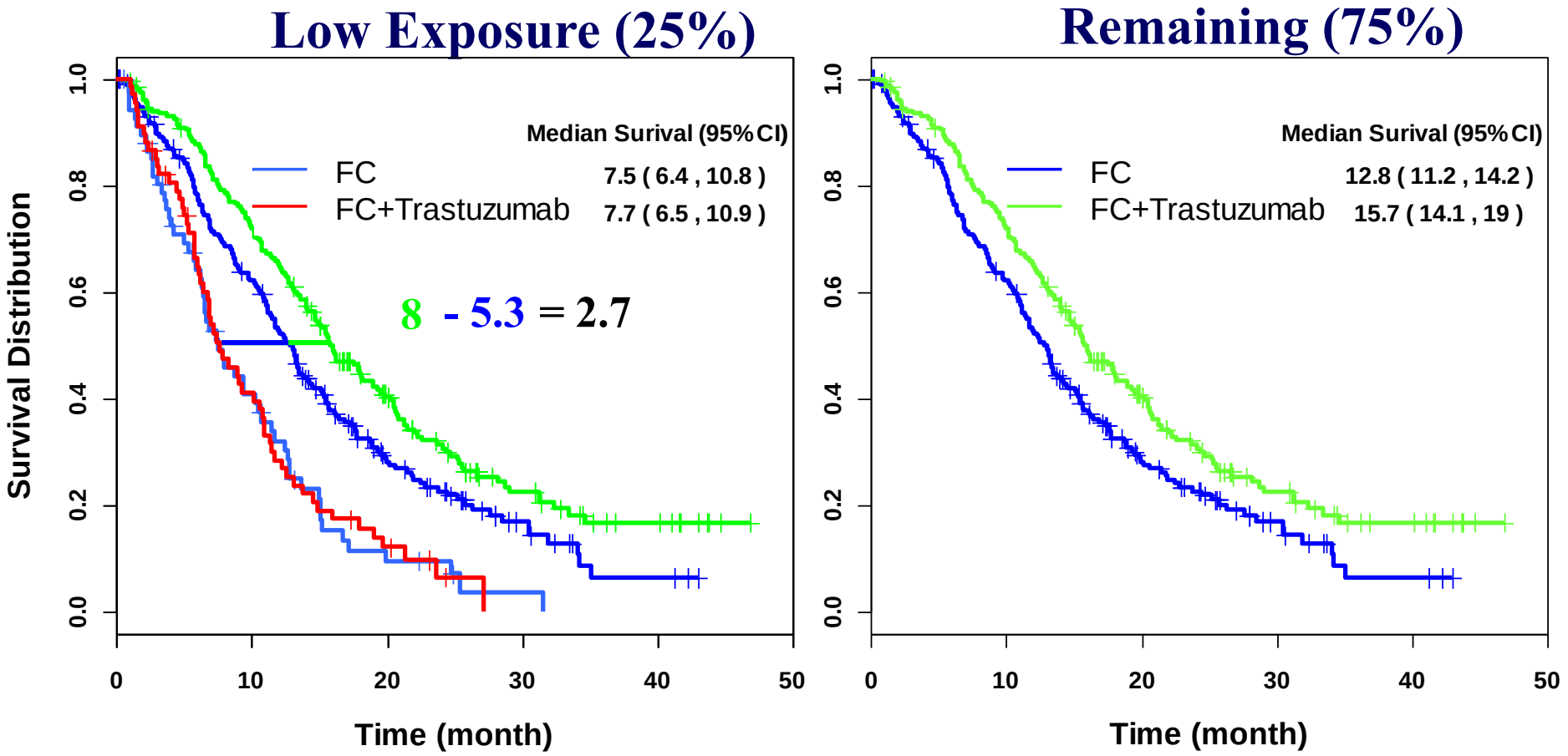
No Survival Benefit in Low Exposure Patients Compared to Matched Control



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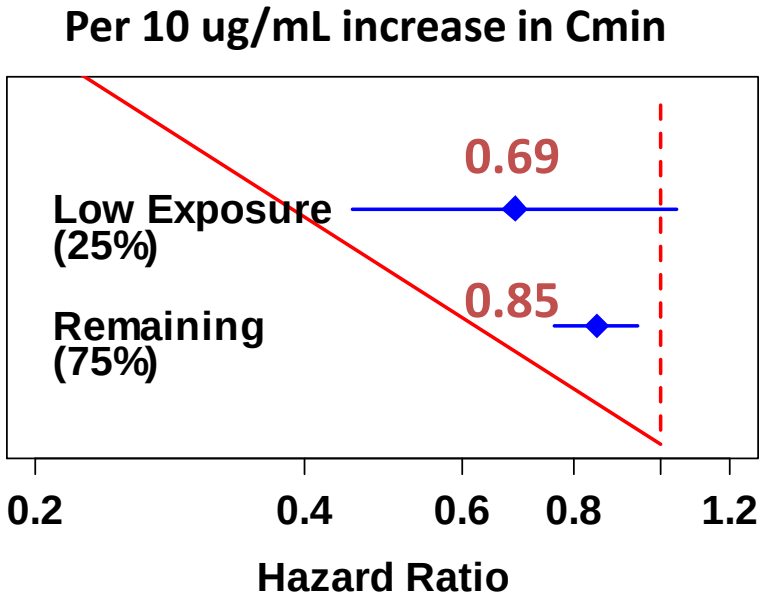
Reason for Lack of Benefit in Selected Subgroup (Matched)

- Low trastuzumab exposure (Cmin <12 ug/mL)
  - Implication: higher dose may work
- Low exposure (high risk) patients may be non-responders?
  - Implication: higher dose may not work

Support for Higher Dose



- All patients are sensitive to higher trastuzumab exposure
- Low exposure (high risk) patients may be more sensitive to higher trastuzumab exposure

Multivariate Cox Regression for T-DM1

Comparison	HR (95% CI)*	P-value
TDM1 Q1 vs. Control	0.97 (0.65, 1.46)	0.89
TDM1 Q2 vs. Control	0.68 (0.44, 1.05)	0.080
TDM1 Q3 vs. Control	0.40 (0.22, 0.72)	0.0024
TDM1 Q4 vs. Control	0.35 (0.20, 0.63)	0.0005

*: After adjusting for covariates: Eastern Cooperative Oncology Group (ECOG), number of disease sites, prior anthracycline use, prior transtuzumab treatment, visceral disease, measurable disease, HER2 shed antigen and tumor burden

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Regulatory Action

- **Herceptin:**
  - **Exposure-response (ER) and case-control analyses provided the rationale for post marketing requirement (PMR) study for a higher dose**
  - **Trial design (dose selection, patient population and effect size assumption) for PMR study was based on ER and case-control analyses**
- **T-DM1:**
  - **Postmarketing commitment to conduct exposure-response analyses for PFS, final overall survival, and safety utilizing data from trial BO25734/TDM4997 (TH3RESA)**

Simulation to Compare Two Methods

- Various true exposure-response (ER) relationships were simulated (ECOG score, tumor size at baseline as covariates)
- Both multivariate regression analysis and the case-control analysis were applied to estimate the hazard ratio (HR) between two regimens within each quartile (Q1 to Q4 defined by exposure)
- Comparison of two methods:
  - Bias in HR estimates
  - Exposure-HR relationship across quartiles

Liu, J; Wang, Y; Zhao, L; Assessment of Exposure-Response (E-R) and Case-Control (C-C) Analyses in Oncology using Simulation Based Approach, 2015 American Conference of Pharmacometrics)

Scenarios Simulated

#	Scenarios	Underlying models
1	Multivariate Cox model	$h(t) = h_0(t) \times exp(0.7 \times ECOG + 0.07 \times Tumor\ size - 0.012 \times C_{trough})$
2	Parametric model + linear concentration effect	$h(t) = 0.065 \times exp(0.7 \times ECOG + 0.07 \times Tumor\ size - 0.012 \times C_{trough})$
3	Parametric model + non-linear concentration effect (normal saturation)	$h(t) = 0.060 \times exp(0.625 \times ECOG + 0.085 \times Tumor\ size - 0.01 \times \frac{60 \times C_{trough}}{30 + C_{trough}})$
4	Parametric model + non-linear concentration effect (fast saturation)	$h(t) = 0.054 \times exp(0.675 \times ECOG + 0.104 \times Tumor\ size - 0.005 \times \frac{60 \times C_{trough}}{0.1 + C_{trough}})$
5	Parametric model + linear concentration effect + an interaction term	$h(t) = 0.055 \times exp(0.75 \times ECOG + 0.07 \times Tumor\ size - 0.012 \times C_{trough} + 0.01 \times ECOG \times C_{trough})$
6	Parametric model + non-linear concentration effect (normal saturation) + an interaction term	$h(t) = 0.054 \times exp(0.64 \times ECOG + 0.085 \times Tumor\ size - 0.014 \times \frac{60 \times (1 - ECOG) \times C_{trough}}{30 + C_{trough}})$
7	Parametric model + non-linear concentration effect (fast saturation) + an interaction term	$h(t) = 0.054 \times exp(0.64 \times ECOG + 0.085 \times Tumor\ size - 0.008 \times \frac{60 \times (1 - ECOG) \times C_{trough}}{0.1 + C_{trough}})$

$h_0(t)$, an unspecified baseline hazard function; ECOG, Eastern Cooperative Oncology Group; C_{trough}, drug trough concentration

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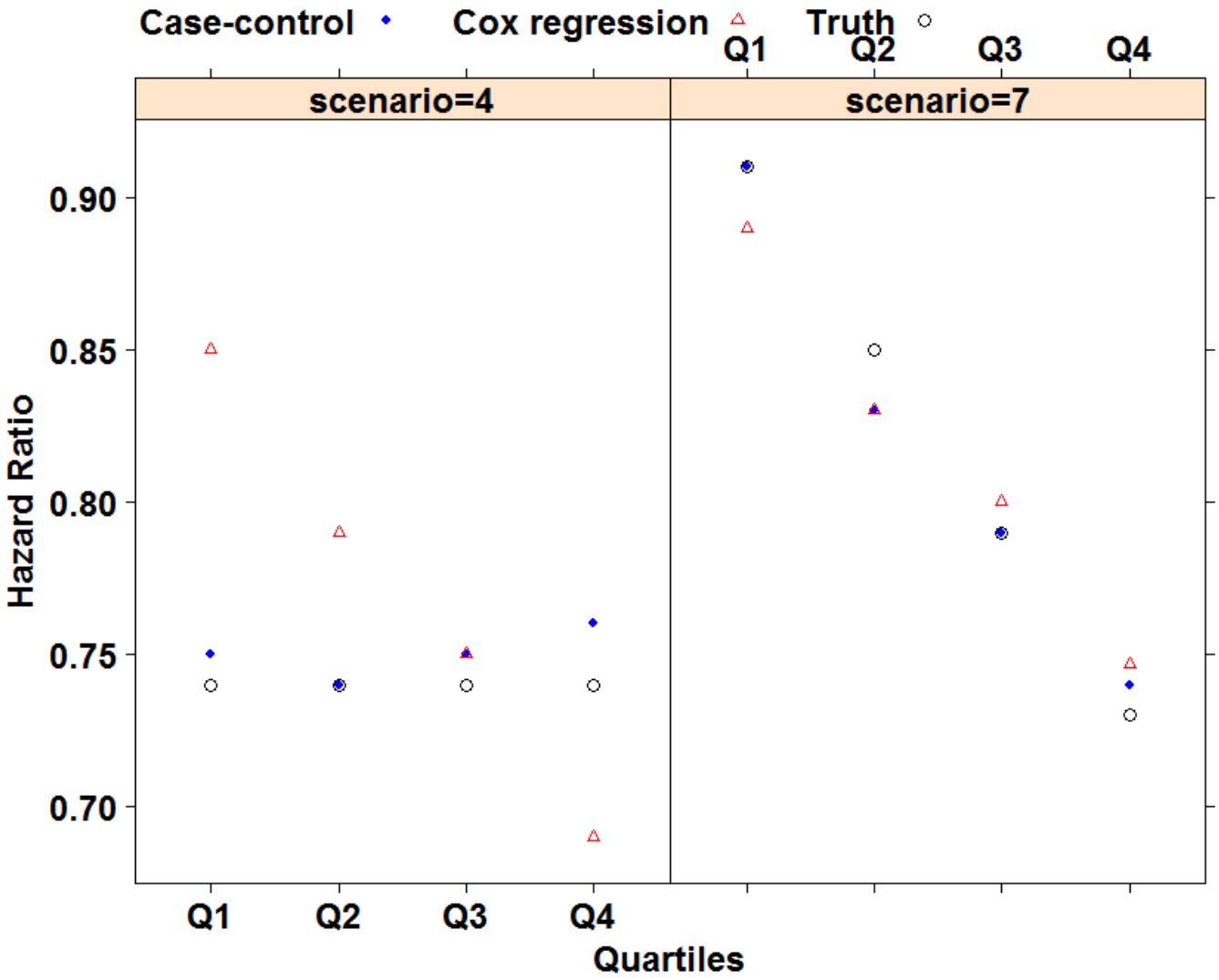
Results for Two Scenarios
(Flat Exposure-Response)



Comparison of Two Methods

- For all investigated scenarios, case-control analysis led to unbiased estimation of hazard ratio (HR) between Q1, Q2, Q3, Q4 and their corresponding matched control groups
- The apparent relationship between HR and the median exposure across the four quartiles reflects the true E-R relationship when there is no interaction between concentration and confounding risk factors.
- When interaction exists, the difference in HR across the four quartiles is the combined effects of exposure and difference in distributions of risk factors across quartiles.
- The apparent exposure-HR relationship across quartiles overestimated the E-R relationship under scenarios 5, 6 and 7 (more severe patients with less sensitivity or smaller Emax)

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Summary

- Exposure-response analyses are routinely used in regulatory review to assess the appropriateness of the proposed dosing regimen
- Risk factors for overall survival have been found to be associated with drug exposure (higher the risk, lower the exposure), leading to confounded steep exposure-survival relationship
- Rigorous analyses should be conducted to adjust for the confounding factors
- The number of risk factors typically precludes the test of all possible interactions in a multivariate regression analysis
- The apparent exposure-HR relationship from matched subgroups should not be automatically treated as exposure-response relationship

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