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REVIEW ARTICLE

Confounding factors in exposure–response analyses and mitigation strategies for monoclonal antibodies in oncology

Sonoko Kawakatsu[1,2] | René Bruno[1] | Matts Kågedal[1] | Chunze Li[1] | Sandhya Girish[1] | Amita Joshi[1] | Benjamin Wu[1]

[1]Clinical Pharmacology, Development Sciences, gRED, Genentech/Roche, South San Francisco, CA, USA

[2]Thomas J. Long School of Pharmacy, University of the Pacific, Stockton, CA, USA

Correspondence
Benjamin Wu, Clinical Pharmacology, Development Sciences, gRED, Genentech/Roche, 1 DNA Way, South San Francisco, CA 94080, USA.
Email: wu.benjamin@gene.com

Dose selection and optimization is an important topic in drug development to maximize treatment benefits for all patients. While exposure–response (E-R) analysis is a useful method to inform dose-selection strategy, in oncology, special considerations for prognostic factors are needed due to their potential to confound the E-R analysis for monoclonal antibodies. The current review focuses on 3 different approaches to mitigate the confounding effects for monoclonal antibodies in oncology: (i) Cox-proportional hazards modelling and case-matching; (ii) tumour growth inhibition–overall survival modelling; and (iii) multiple dose level study design. In the presence of confounding effects, studying multiple dose levels may be required to reveal the true E-R relationship. However, it is impractical for pivotal trials in oncology drug development programmes. Therefore, the strengths and weaknesses of the other 2 approaches are considered, and the favourable utility of tumour growth inhibition–overall survival modelling to address confounding in E-R analyses is described. In the broader scope of oncology drug development, this review discusses the downfall of the current emphasis on E-R analyses using data from single dose level trials and proposes that development programmes be designed to study more dose levels in earlier trials.

KEYWORDS

drug development, oncology, pharmacokinetics–pharmacodynamics, statistics and study design

1 | INTRODUCTION

While contemporary drug development in oncology strives to deliver novel therapies to patients rapidly, it is also important to optimize dosing regimens to improve patient-centred care. Doses selected for pivotal trials may be efficacious doses, but not necessarily optimal to minimizing toxicity and maximizing clinical efficacy for all patients. Exposure–response (E-R) analysis is an approach that is used to support dose selection by characterizing the relationship between drug concentrations, efficacy, and safety. A variety of E-R analyses have supported dose labelling of many approved oncology drugs.[1] Among the oncology therapies, however, additional complexity has been observed in characterizing E-R relationships for monoclonal antibodies. Specifically, prognostic factors can impact both pharmacokinetics (PK) and efficacy. This may result in a correlation between exposure and outcome that does not represent a causal E-R relationship and therefore, may not provide a useful basis for dose recommendations. This was exemplified by the HELOISE trial (NCT01450696) of trastuzumab, which was conducted as part of a postmarketing requirement. Following the phase 3 trial ToGA (NCT01041404), trastuzumab was approved in combination with chemotherapy for first-line treatment of HER2-positive advanced

gastric cancer. An E-R analysis, however, found that the patients in the lowest exposure quartile had an overall survival (OS) approximately 8 months shorter than those with higher exposures.[2] This suggested that increasing trastuzumab exposure in this low-exposure subgroup may improve survival benefit, and thus supported the requirement of conducting a postmarketing trial for a higher dose. For this requirement, in the HELOISE trial, a higher trastuzumab dose was compared with the labelled dose in a population with similar prognostic factors as the low-exposure subgroup of the ToGA trial. Despite reliably increasing exposure, the higher dose did not improve OS in patients.[3] This discrepancy between the results of the E-R analysis and the HELOISE trial indicates confounding in E-R analyses of monoclonal antibodies at a single dose level in oncology.

In addition to the potential confounding factors for E-R analyses in oncology, there have been reports of time-dependent changes in the PK that require additional considerations. Monoclonal antibodies that target B-cell receptors, such as rituximab, have been reported to exhibit time-dependent decrease in clearance (CL) owing to target mediated drug disposition.[4–6] Time-dependent PK has also been observed for checkpoint inhibitors nivolumab, pembrolizumab, durvalumab, avelumab and ipilimumab. Across these molecules, the range of CL decrease over time was 17–32%.[7–11] Best overall response was included as a covariate on CL in the time-dependent population PK models of nivolumab and pembrolizumab.[7,9] The time-dependent population PK model of durvalumab included time-varying albumin and tumour size as covariates on CL.[8] While the final models for avelumab and ipilimumab did not incorporate response or time-varying biomarkers as covariates on CL, visual inspection of estimated change in CL over time demonstrated a larger reduction in CL in responders than in nonresponders.[10,11] Overall, the decrease in CL over time in these molecules corresponded to changes in patients' prognoses based on their responses to treatments over time. This observation may be attributed to changes in catabolic degradation of the monoclonal antibodies as a result of changing disease status.[12] The changing drug CL and patient prognostic factors over time could potentially confound E-R analyses.

In this review we will discuss key considerations in interpreting E-R relationships and mitigation strategies to address the confounding effects in E-R analyses in oncology.

2 | E-R ANALYSIS CONSIDERATIONS IN ONCOLOGY

To address confounding factors in E-R analyses for monoclonal antibodies in oncology several key determinants need to be considered. In this review we describe the importance of selecting the appropriate drug exposure metric for E-R analyses and summarize 3 main approaches in oncology to address confounding in E-R analyses: Cox proportional-hazards modelling (CPH) and case-matching analysis; tumour growth inhibition OS (TGI-OS) modelling, and clinical studies with multiple dose levels (Figure 1, Table 1). In addition to describing these approaches we will discuss their strengths and limitations. The current review will focus on E-R analyses for exposure–survival relationships.

2.1 | Selection of drug exposure metric

2.1.1 | Pharmacokinetic parameters

For monoclonal antibodies, particularly those that demonstrate time-dependent PK, the selection of the appropriate exposure metric to use for E-R analyses is critical. An E-R analysis simulation for nivolumab, for example, tested 3 different exposure metrics and resulted in different E-R conclusions. The exposure metrics used were: (i) average concentration at steady state ($Cavg_{ss}$); (ii) average concentration at cycle 1 ($Cavg_{1st\text{-}dose}$); and (iii) trough concentration at cycle 1 ($Cmin_{1st\text{-}dose}$).[13] When $Cavg_{ss}$ was used as the exposure metric there was a steep E-R relationship with a hazards ratio (HR) of 0.92 and 0.14 between quartiles 1 and 4, and the case-matched control arm, respectively. However, when $Cavg_{1st\text{-}dose}$ and $Cmin_{1st\text{-}dose}$ were used the apparent E-R relationship was flat. The flat E-R relationship is consistent with the lack of dose–response relationship derived from the randomized dose-ranging trial for nivolumab.[14] The observed inconsistency in E-R relationship between the different exposure metrics used ($Cavg_{ss}$, $Cavg_{1st\text{-}dose}$ and $Cmin_{1st\text{-}dose}$) can be attributed to the dependence of $Cavg_{ss}$ on concentrations from later post-treatment time points. Patients with improving disease status have reduced drug clearance, so at later time points there is an apparent correlation between exposure and response. Using exposure metrics derived from earlier time points reduces the risk of change in disease status influencing PK, and allows for more accurate assessment of the impact of treatment exposure on clinical response.[15]

In addition to using exposure metrics derived from early time points, consideration should be placed on whether observed or model-derived exposure metrics are used in the E-R analysis. In the E-R analysis for trastuzumab emtansine (T-DM1) the results of CPH were not consistent between model-derived and observed exposure metrics. After adjusting for baseline risk factors in the analyses for both metrics the model-predicted $Cmin_{1st\text{-}dose}$ and area under the curve at cycle 1 ($AUC_{1st\text{-}dose}$) were significantly associated with OS although the observed $Cmin_{1st\text{-}dose}$ and $AUC_{1st\text{-}dose}$ were not.[16] Due to the limited understanding of this discrepancy, a strong recommendation could not be made regarding the selection of observed or model-derived metrics, and it would be prudent for an E-R analysis to examine both. The discrepancy could also be the result of using an inadequate population PK (popPK) model. For trastuzumab, a new popPK model incorporating both linear and nonlinear elimination published in 2019[17] was able to describe the observed data better than the original linear popPK model.[18] As such, should an improved popPK model for T-DM1 becomes available, the E-R relationship for T-DM1 using predicted exposure should be re-assessed. Upon examining both metrics, if either of them is significantly associated with OS, further investigation into the population PK model and E-R analysis is warranted.

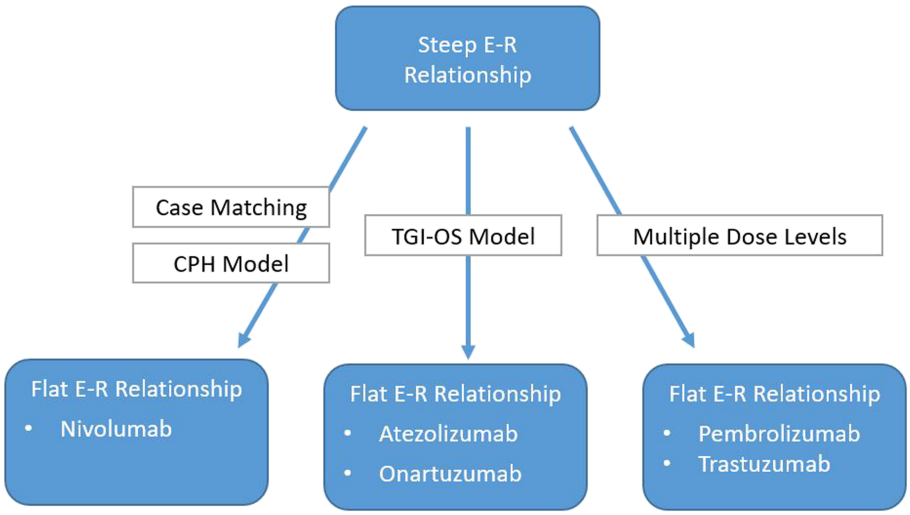

FIGURE 1 Various methods to address potentially confounded positive E-R relationships. Case examples of successful adjustment for confounding factors are listed under each method. E-R, exposure–response; CPH; cox proportional hazard; TGI-OS, tumour growth inhibition–overall survival

TABLE 1 Summary of approaches to address potentially confounded E-R analyses

Approach	Description	Strengths	Limitations
Cox-proportional hazards modelling	Develop a regression model to evaluate the association between hazards/covariates and overall survival	• validate covariates by screening for statistical significance	• requires assumptions about the effect of covariates on the E-R relationship
Case-matching analysis	Build an analysis dataset including patients with similar baseline characteristics between treatment and control arms	• does not require strict assumptions about the effect of covariates on the E-R relationship	• unable to match case to control if limited sample size • if no screening methods are used for statistical significance, selection of covariates can be subjective
Tumour-growth inhibition–OS modelling	Develop a model to describe tumour dynamics, and evaluate this metric as a covariate on OS	• change in tumour size serves as a marker of changing disease status and as an informative predictor of survival • able to separate disease-specific and drug-specific effects on OS	• SLD may not provide adequate information on tumour dynamics • requires ≥1 post-treatment SLD assessment for patients (may not be available for early dropout) • nonexposure-driven TGI models require assumptions and empirical descriptions of tumour shrinkage and growth • new lesions typically not considered
Multiple dose levels	Study multiple dose levels of the drug in a large, randomized groups with balanced baseline characteristics	• dose–response relationship is not confounded by the effect of prognostic factors that confound the E-R relationship • requires no assumptions about E-R relationship	• costly to perform a separate trial or include additional arms • unfeasible in rare populations

CPH, Cox-proportional hazards; E-R, exposure–response; OS, overall survival; SLD, sum of longest diameter

2.1.2 | Assay considerations

The use of free *vs* total PK assays to measure drug exposure and their impact on E-R relationships should be considered. It has been suggested that since free drug concentration is in excess from binding to targets and proteins it is unsuitable for E-R analyses.[19] However, free drug concentration may also reflect active drug in the circulation that can bind to targets, and therefore be relevant in an E-R analysis. It is also thought that because monoclonal antibodies are dosed in excess of target ligands, total concentration would approximate free concentrations, and selection of free *vs* total assay would not impact the E-R analysis.[20] Developing bioanalytical assays to measure free concentrations for monoclonal antibodies also faces numerous technical challenges.[20] As assays are studied and developed further, potential impacts on E-R analyses should be evaluated.

E-R analyses for drugs with multiple analytes such as antibody–drug conjugates (ADCs) involve additional complexities. There is a limited understanding of whether exposure to the cytotoxic drug,

monoclonal antibodies, ADC or other intermediates provides the best correlation for E-R relationships.[21,22] The analyte driving response appears to vary across different ADCs, and this issue should be carefully considered in E-R analyses for ADCs.

2.2 | Selection of adjustment models

2.2.1 | CPH modelling and case matching

CPH modelling is a survival analysis in which a multivariate regression model (*Equation 1)* evaluates the association between covariates (e.g. baseline prognostic factors, exposure measures) and the time until a specific event occurs. The comparison of response between treatment groups is given as an HR, and this ratio is assumed to be constant over time (*Equation 2*). The model allows for estimation of the relationship between exposure and response. Multiple covariates can be evaluated in the model for statistical significance, and it is imperative that they are included to correct for the effects of confounding factors that might otherwise bias the E-R analysis. The structure of the model assumes that the effects of these covariates are time-independent, and also depend upon the value of the covariate and a constant coefficient. This approach has been used to adjust for confounding factors in E-R analyses for T-DM1.[16,23]

$$h(t) = h_0(t) \times exp(b_1X_1 + b_2X_2 + \ldots b_pX_p) \quad (1)$$

where $h(t)$ describes the hazard of an event at time t, determined by a set of covariates (X_1, X_2, ..., X_p); $h_0(t)$ describes the baseline hazard at time t; and the coefficients (b_1, b_2, ..., b_p) describe the relationship between the covariates and the hazard.

$$HR = \frac{h(t)_y}{h(t)_z} = \frac{exp\,(b_1X_{1y} + b_2X_{2y} + \ldots b_pX_{py})}{exp\,(b_1X_{1z} + b_2X_{2z} + \ldots b_pX_{pz})} \quad (2)$$

where *HR* is the ratio of the expected hazards of 2 groups, y and z, and is time-independent. Components of this equation are the same as described for Equation 1.

Case-matching analysis has been widely used in observational studies to adjust for confounding factors. The method was more recently applied to E-R analysis for the first time by Yang *et al*. and has since been used for E-R analyses of multiple oncology biologics such as T-DM1 and nivolumab.[2,13,16] Case-matching analysis adjusts for confounding factors by balancing the distribution of baseline risk factors between the control and treatment groups prior to calculating the HR. Only patients in the control arm that are similar or matched in baseline risk factors to patients in the treatment arm are included in the analysis. The matching process can be optimized with a variety of methods including propensity score matching, Mahalanobis distance matching, and coarsened exact matching.[24–26] In the more commonly used propensity score matching, the score is typically estimated using a linear regression model, and patients with similar scores are matched. Propensity score models can be diverse, as a number of other regression modelling structures can be used to incorporate non-linearity and nonadditivity, and a number of variable selection methods can be explored (e.g. lasso, elastic net).[27–29] The selection of methodology for a given study is an ongoing topic of discussion, and multiple models may be tested for sensitivity. After case-matching, the endpoint can be directly compared between the matched groups by a method of choice (e.g. Kaplan–Meier survival analysis, CPH).

CPH modelling and case-matching address confounding factors in an E-R analysis by accounting for the potential imbalance of baseline covariates in different exposure subgroups. For both approaches to successfully account for confounding in monoclonal antibodies in oncology appropriate covariates that account for imbalances in prognostic factors must be selected. The number of covariates is limited by the increasing potential for over-parameterization of results. In a comparison of response in the Q1 exposure subgroup and the control arm, Li *et al*. used CPH modelling and case-matching.[16] Case-matching analysis demonstrated a greater reduction of the HR. While the case-matching analysis had additional covariates included that could contribute to the reduction of HR the reduction can also be attributed to the limitation of CPH modelling where the structure of the hazards model equation imposes assumptions about the effect of covariates on the E-R relationship.

Case-matching analysis is an appealing alternative to CPH modelling, as it requires no assumptions regarding the relationship between covariates and the E-R relationship. In addition, there is no specific method to select covariates used for matching, and covariates are not screened for significance in the case-matching analysis. The retention of both statistically significant and insignificant covariates may allow for an increased capacity for correction of confounding factors compared to methods that screen for covariates. Covariates that are clinically significant may be statistically insignificant in an analysis due to factors such as small sample size, variability and correlation with other risk factors. Case-matching analysis is limited by the difficulty in matching case to control when using a small study sample or a large number of covariates. If data from an adequate sample size are available, and there is no need for validation of covariates by statistical significance case-matching appears to correct for confounding factors more effectively than CPH modelling.

2.2.2 | TGI-OS modelling

The TGI-OS model is a disease progression model. It is a useful tool in oncology to delineate E-R relationships in the presence of confounding factors. The model is composed of 2 parts: a TGI model that describes tumour dynamics, and a multivariate survival model that incorporates a TGI metric as a covariate on OS. The TGI metric serves as a marker of disease status. TGI-OS modelling mitigates confounding in the E-R analysis by directly evaluating the treatment effect on TGI then separately accounting for the effect of prognostic factors on OS. By mitigating the confounding effects of prognostic factors on the relationship between treatment effect and OS, the TGI-OS model can avoid a false positive E-R relationship.[30–32] The

TGI model structure is typically a simple biexponential model (Equation 3).[33]

$$f(t) = exp(-d \times t) + exp(g \times t) - 1 \quad (3)$$

where *f(t)* is tumour size at time *t*, *d* is the decay rate constant and *g* is the growth rate constant.

In multiple cancer types, the OS is correlated with the tumour dynamics such that the probability of survival decreases with the increase in tumour growth rate (*g* in Equation 3).[33–43] Key determinants for survival are baseline prognostic factors specific for the cancer type and are incorporated in the multivariate TGI-OS models. Drug exposure is evaluated as a covariate in the final multivariate model.[30,31] If it is not significant, this suggests a flat E-R relationship. OS can be simulated for exposure quartiles with normalized prognostic factors to evaluate the presence of an E-R relationship. This approach can remove the confounding effects of imbalanced prognostic factors in different exposure quartiles. Multivariate TGI-OS modelling has successfully evaluated E-R relationships for atezolizumab in multiple indications, and its role in E-R analysis has been increasingly accepted by regulatory agencies.[31]

While TGI-OS modelling allows for the direct separation of treatment effect and disease effects, several limitations must be considered. Nonexposure-driven TGI models while simpler and more flexible than exposure-driven models require assumptions and empirical descriptions of tumour shrinkage and growth. Model building for both exposure and nonexposure-driven models requires 1 or more post-treatment assessments for tumour size, and this may not be feasible in some patients. The incorporation of multiple tumour size assessments in the model, however, makes tumour dynamics a patient-specific explanatory variable and informative predictor of survival. TGI-OS model predictions for treatment effect should be interpreted cautiously when OS may be affected by additional, subsequent treatments that are not accounted for in the model. With the TGI-OS model, it is also difficult to account for the potential appearance of new lesions. Zecchin *et al.* developed a pharmacometric model to incorporate the effect of new lesions on OS in metastatic ovarian cancer, but additional examples and uses of this approach are currently limited.[44,45] Because the TGI-OS model predicts OS based on tumour dynamics, it is more suitable for use in advanced malignancies, where tumour size is typically measured over time.

2.3 | Selection of study design

When an E-R analysis using an adjustment model concludes a positive E-R relationship, it is difficult to discern whether there is a true positive E-R relationship, or there are additional hidden confounders. The only approach that allows for certainty in a positive E-R relationship is to study multiple dose levels of the drug in large, registrational trials. These trials should have randomized groups with balanced baseline characteristics. Studying multiple dose levels allows for the identification of a true E-R relationship because the dose–response relationship is not confounded by the prognostic factors that confound the E-R relationship. However, oncology phase 3 trials typically only study a single dose level, and the exposure range included in the E-R analysis for OS is limited. Including additional arms or performing separate trials to increase this exposure range allows for a more robust E-R analysis. In the previously described case of trastuzumab, the HELOISE trial studying high dose and standard dose trastuzumab revealed that the case-matching analysis conducted for the ToGA study was confounded, and that there appeared to be no causal relationship between exposure and response for trastuzumab in metastatic gastric cancer.[2,3] A similar scenario was observed with pembrolizumab in melanoma and nonsmall-cell lung carcinoma. Pembrolizumab was studied across a 5-fold dose range. Two case-matching analyses were performed for patients receiving 2- and 10-mg/kg dose levels, respectively. In the unmatched analysis, a steep E-R relationship was observed across exposure ranges within each dose level. While case-matching analysis corrected this E-R relationship to a certain degree, it still suggested a positive E-R relationship. When examining hazard ratios across the 2 dose levels, however, the apparent E-R relationship was flat and suggested that higher exposures do not increase OS. The case-matching analysis was unable to fully account for confounders.[46]

Because dose–response relationships are not confounded by the prognostic factors that confound E-R relationships studying multiple dose levels is a robust approach to examine E-R relationships. Unlike statistical approaches discussed in the previous sections, it requires no assumptions about covariates or the structure of the E-R relationship. The major limitation with this approach is the time and cost associated with additional trials or treatment arms. In addition, this approach may not be feasible in rare populations. The utility of studying multiple dose levels may also depend on characteristics of the drug. If a drug has a wide therapeutic window (i.e. monoclonal antibodies), and tested doses appear to be at the top of the dose–response curve studying multiple dose levels in registrational trials may not be necessary. It may be useful if a drug has a narrow therapeutic window and requires quantification of E-R relationships for optimal dose selection. Ultimately, limitations in feasibility motivate sponsors to consider alternative approaches to E-R analyses before studying multiple dose levels.

3 | DISCUSSION

The inability to select an appropriate dose in pivotal trials has been shown to contribute to the declining success rates of drug development programmes.[47,48] A study examining Food and Drug Administration approval packages between 2015 and 2017 found that, in a third of development programmes, no E-R analysis was reported.[49] The expanded use of E-R analysis in more drug development programmes may serve as a solution for declining success rates. E-R analysis is particularly useful in early clinical trials where multiple doses are administered to inform dose selection and optimization. It is often repeated in phase 3 trials given the meaningful sample size for efficacy and safety interpretation. Rather than assuming that 1 dose fits all patients, this

approach identifies whether specific patient subgroups would benefit from alternative doses. A successful example of E-R application was shown for the exposure–survival analysis of ipilimumab. Ipilimumab was originally approved in several countries at a dose of 3 mg/kg for the treatment of advanced melanoma. A phase 2 dose-ranging study, however, suggested improvement in OS with the 10-mg/kg dose.[50] While this study was not statistically powered to detect differences in survival, an E-R analysis pooling data from 4 phase 2 trials demonstrated that OS improved with increasing exposure. In the CPH model results patients in the 5th and 95th percentiles of steady state trough concentration ($Cmin_{ss}$) had an OS HR of 1.52 and 0.552, respectively, relative to patients with median $Cmin_{ss}$.[51] This suggested that OS improved with increased ipilimumab doses. In the postmarketing trial conducted with the 3- and 10-mg/kg doses this relationship was confirmed. Median OS was 15.7 months for the 10-mg/kg dose group, and 11.5 months for the 3-mg/kg dose group (HR 0.84, P = .04).[52] The results of this phase 3 trial are included in the ipilimumab label, and demonstrate that E-R analyses could identify potential survival benefits gained from increased doses and exposures. While the 10 mg/kg dose provided a survival benefit it was also associated with increased treatment-related adverse events. The 3-mg/kg dose was selected as the labelled dose after accounting for efficacy benefit and safety risk.

While the utility of E-R analyses applies across a variety of therapeutic areas, additional considerations are needed for oncology due to the impact of prognostic factors on both exposure and outcome. Performance status, clinical symptoms (dyspnoea, appetite loss, cognitive function), primary tumour site and C-reactive protein concentration are examples of prognostic factors used to predict outcome in clinical settings.[53,54] In oncology, E-R is more than just considering the unidirectional relationship where the dose affects exposure which subsequently affects response. OS is often the primary response endpoint for oncology trials, and its relationship with exposure is confounded by prognostic factors. Recognizing and accounting for the impact of time-varying clinical response and prognostic factors on exposure are critical for accurate E-R interpretations.[55] This relationship is illustrated by the findings for nivolumab, avelumab, durvalumab, pembrolizumab and ipilimumab, where patients with improved post-treatment disease status showed greater time-dependent decreases in drug CL.[7–11] The mechanism is not fully understood, but there is an interaction between clinical response, prognostic factors and exposure. When patients respond to treatment their prognostic factors improve, which in turn decrease the drug CL and increase drug exposure (Figure 2). In an E-R analysis, this could lead to incorrect conclusions that higher drug exposure caused clinical response when in fact the E-R relationship is confounded by the effect of changing prognostic factors on exposure. This may be caused by the unique nature of disease progression in oncology. As a patient's disease status declines clinical changes such as cachexia and inflammation can increase the catabolism and clearance of both endogenous and therapeutic proteins.[56,57] This is supported by the significance of tumour burden and albumin as a covariate on CL in the population PK analyses for nivolumab, avelumab, durvalumab, and pembrolizumab.[8–10,13] Clearance increased with higher tumour burden and lower albumin concentrations. In addition, time-dependent PK was observed for nivolumab in advanced malignancies, but not in patients with resected melanoma.[58] The latter had tumours surgically resected prior to adjuvant treatment with nivolumab and were overall healthier than patients with advanced malignancies. This supports the impact of disease status and prognostic factors on exposure. The hypothesis that clearance is associated with disease status was further evaluated using a machine-learning approach. Data from patients with melanoma and renal cell carcinoma treated with nivolumab were used to develop a model describing the relationship between baseline cytokine features and nivolumab clearance. Model-predicted clearance via cytokine signature was significantly associated with OS across all of the studies, which further supports the hypothesis for the relationship between clearance and disease status.[59,60] Looking prospectively, these collective observations also suggest that the presence of time-dependent PK, and the significance of albumin or tumour burden as a covariate on CL would indicate the risk of a confounded E-R analysis.

A confounded E-R analysis may result in false positive E-R relationships, which may lead to the wrong conclusion that the dose for patients with lower exposure is suboptimal. As seen in the ToGA/HELOISE example, it may lead to the initiation of a new trial in an attempt to rescue patients who failed treatment. Considering these risks 3, mitigation strategies have been discussed in this review: CPH modelling and case matching analysis; TGI-OS modelling; and multiple dose study design. Studying multiple dose levels in randomized, balanced groups appears to be an effective approach that can

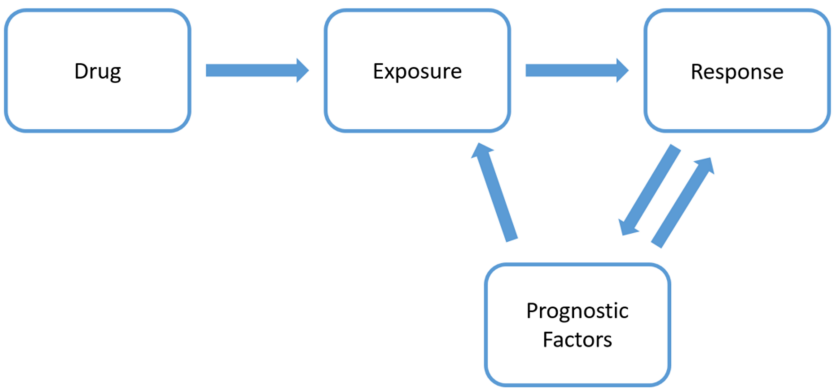

FIGURE 2 Illustration of the relationships between exposure, response and prognostic factors

distinguish with certainty between a true-positive E-R relationship *vs* a false-positive relationship with hidden confounders. This strategy, however, is impractical in most oncology indications, and may offer limited value for monoclonal antibodies with a wide therapeutic window. TGI-OS modelling explicitly separates the drug-specific and disease-specific effect on OS when evaluating the E-R relationship. It also incorporates an estimate of tumour dynamics that serves as an informative biomarker of disease status. CPH modelling and case-matching analysis lack this separation between drug and disease-specific effects. This makes it more challenging to consistently distinguish between exposure- and prognostic factor-driven changes in OS. Case-matching may be preferred over CPH modelling due to the assumptions involved in CPH modelling regarding the relationship between predictors and outcome. While a suggestion of the relative utility of each approach is made here, the unique limitations of each methodology should be considered.

While the effect of changing prognostic factors on exposure and OS can confound exposure–efficacy relationships it does not appear to significantly impact exposure–safety relationships. Among molecules discussed here, it appears that exposure–safety analyses for pembrolizumab, nivolumab, durvalumab and T-DM1 have not faced the same confounding issues as exposure-efficacy analyses.[16,23,61–66] If patients with worsening disease status and prognostic factors are more likely to experience adverse events, and have a decreased drug exposure it could be thought that differences in prognostic factors can confound the exposure-safety relationship. The confounding, however, would contribute to an inverse E-R relationship rather than a positive relationship. In addition, because safety endpoints in E-R analyses are usually drug-related, adverse events rather than disease-related adverse events exposure–safety relationships may be less likely to be influenced by differences in prognostic factors.

Current oncology drug development is rapid and aggressive. Many recent development programmes bypass a dose-ranging phase 2 trial and go directly from phase 1 to phase 3 trials with a single dose level. In some programmes, a phase 2 trial is done, but only with a single dose level or a limited efficacy endpoint. This severely limits the range of exposure data available for an exposure–survival analysis and increases the risk of a confounded E-R analysis. The Food and Drug Administration's E-R Guidance has previously described the risk of characterizing E-R relationships based on data from single dose levels.[67] Sponsors should consider conducting expanded dose-ranging trials early in development programmes to better inform dose selection and potentially avoid the need to study multiple dose levels in late phase trials. Despite the current limitations of E-R analyses, they are required to be included as part of a filing package. The HELOISE trial is an example of the potential risks of confounded E-R analyses. The E-R analysis performed using data from the ToGA trial supported the conduct of the HELOISE trial. No dose–response relationship was observed, however, and patients did not benefit from higher doses of trastuzumab. If the E-R analysis is limited by the range of available exposure data, and could be confounded, any observed E-R relationship should be interpreted with great caution.

Drug development must not only focus on developing novel treatment modalities, but also on selecting the optimal dose for patients. E-R analysis is a useful tool for dose optimization in a variety of therapeutic areas, and also has many applications to support modern drug development. Despite its wide utility, E-R analysis in oncology faces unique challenges when applied to monoclonal antibodies tested at a single dose level. E-R analyses in oncology are susceptible to confounding from unique, disease-related factors. Mitigation strategies presented in the current paper can be employed to account for confounding factors and elucidate the true E-R relationship. In a broader scope, the design of oncology drug development programmes may be structured to more effectively inform dose–response and E-R relationships for dose optimization. Once an E-R analysis is performed, its application in decision-making must be carefully considered based on the methodology and the data used in the analysis. The improvement and effective use of E-R analysis is an effort that must be addressed on multiple fronts of oncology drug development with the common goal of maximizing benefit to the patient and minimizing toxicities.

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The authors except S.K. are all employees of Genentech, Inc., and stockholders of the Roche Group. S.K. has no conflict of interest to declare.

CONTRIBUTORS

S.K. and B.W. wrote the paper with input from all authors. M.K. and C.L. provided significant contributions to the CPH modelling and case-matching section. R.B. provided significant contributions for the TGI-OS modelling section. S.G. and A.J. provided significant contributions to the discussion section. S.K., R.B., M.K., C.L., S.G., A.J. and B.W. reviewed the entirety of the manuscript.

ORCID

Sonoko Kawakatsu https://orcid.org/0000-0001-5202-7975

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