Exposure-Response assessment in oncology is complicated by many factors, e.g. dose delay/reduction. In addition, for monoclonal antibodies (mAbs) exposure is usually confounded by key prognostic factors for the disease. There are multiple exposure-response (ER) methodologies, such as direct or indirect (e.g., via tumor growth inhibition (TGI)) ER for progression free survival (PFS) and overall survival (OS). Here, we compare different aspects of multiple direct ER methods, with a case example in oncology.

**OBJECTIVES**

1. **Comparison of Direct ER methods using an oncology Phase 3 study**
   - **Method:** This method is naïve to covariates which means that confounding factors e.g., patient disease may impact the interpretation of the ER.
   - **Method:** Makes no assumptions about the hazard function between groups.
2. **Cox proportional hazards (CPH) analysis with covariate adjustment by exposure quartiles or as a continuous function.**
   - **Adjust** for confounding covariates but makes a strong assumption about the effect across exposure range.
   - **Using** conventional tools, exposure as continuous function assumes linear or log-linear ER relationship but allows simulation of other doses at the same regimen (e.g., 3-weekly).
   - **Covariate** screening is stepwise backward (at α = 0.05) from the set identified from a univariate screen at α = 0.1.
   - **Residuals** of exposure vs. Martingale residuals are used to assess fit of continuous forms of the ER response.
3. **Case matching (CM) using Propensity scores by exposure quartiles**
   - **Optimal** matching based on Propensity scores 2,3 due to their ability to easily deal with mixed variable types [4].
   - **Balance** between comparator groups was assessed by standardized differences.
   - **Correlation** structure was preserved by testing pairwise interaction of covariates between comparator groups.
4. **Parametric survival modeling (PS) with covariate adjustment**
   - **Longitudinal** exposure (plasma compartment or effect compartment) drives the Hazard function.
   - **Allows** for flexible forms of the ER function.
   - **Account for** dosing history (e.g., dose reduction/delay).
   - **Adjust** for confounding covariates but makes an assumption about the effect across exposure range.
   - **Allows** simulation including extrapolation to other dosing regimens.

**RESULTS**

**ER assessment using standard methods by exposure quartiles**

- **Kaplan-Meier (KM)** estimates by exposure quartiles (AUROC, Cmin)
  - **Adjust** for confounding covariates [1].
  - **Optimal** matching based on Propensity scores 2,3 due to their ability to easily deal with mixed variable types [4].
  - **Balance** between comparator groups was assessed by standardized differences.
  - **Correlation** structure was preserved by testing pairwise interaction of covariates between comparator groups.

**CONCLUSION**

- **ER** in oncology is complicated by many factors, including limitations in estimation arising from the need to evaluate integrated hazard functions and with large molecule treatments, exposure confounding with key prognostic covariates.
- **Models** should be developed with both the goal of effect assessment and simulation for dose optimization.
- **Non-parametric** representations of exposure help to assess the true shape with and without the presence of covariates but are limited with respect to simulation.
- **Causal** inference approaches can greatly reduce dependence upon modeling assumptions for assessing exposure.
- We propose a M&S strategy that is fit for purpose and provides a clear strategy for dose optimization if indicated, and addresses regulatory review questions.

**REFERENCES**