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Introduction

- **Independent drug action (IDA)** assumes the response of a patient to a **combination therapy** is determined by the response to **the more effective** drug, with **no drug interaction** (additivity, synergy, antagonism) ¹

- IDA hypothesis at **individual-level** (treatment effect, E):

$$E_{A+B} = \max(E_A, E_B)$$

- **Model-based meta-analysis (MBMA)** integrates aggregate data from multiple trials to evaluate treatment effects

- IDA hypothesis at **population-level** (response rate, P):

$$P_{A+B} = P_A + P_B - P_A \cdot P_B$$

Aims

- To evaluate the IDA hypothesis within the MBMA framework to predict combination therapy outcomes
- To assess its performance by comparing predicted outcomes with observed clinical trial results

Methods

Data source

- Digitized progression-free survival (PFS) curves in non-small cell lung cancer from CODEx databases ²
- Combination drug doses were equal to monotherapy doses

Table 1 Summary of trial data

# Treatments	24
# Trials	256
# Study arms	315
# Patients	49427

Analysis strategy assuming IDA

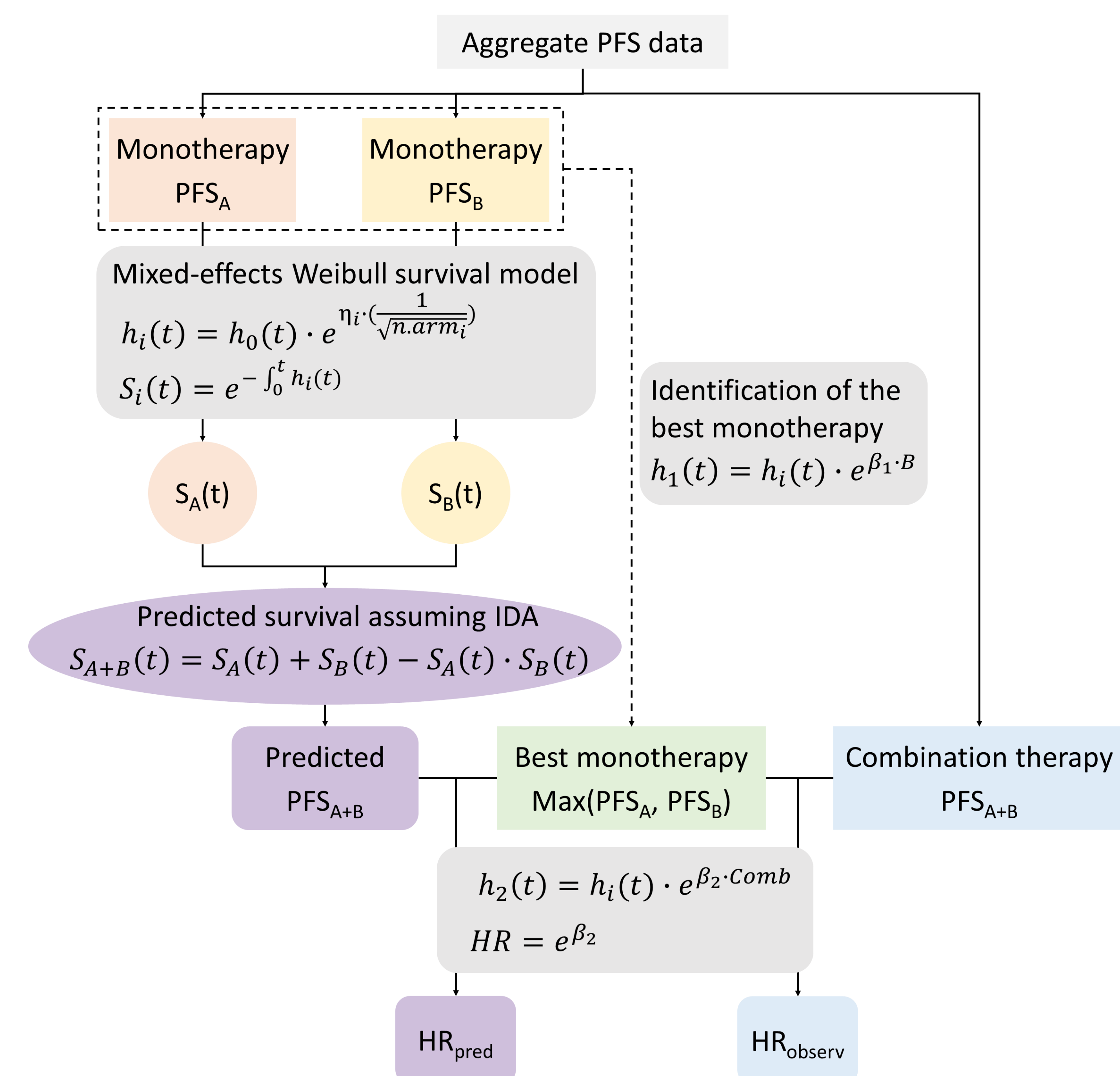


Figure 1 Analysis strategy assuming IDA. $h_0(t)$, the basic Weibull hazard function, $h_0(t) = \lambda^\gamma \gamma t^{\gamma-1}$. η_i : between study variability (BSV). $n.arm_i$: Number of patients per study arm i . B , binary indicator for monotherapy B . $Comb$, binary indicator for combination therapy. HR , hazard ratio.

- References
1. Palmer & Sorger. Cell. (2017); 171:1678–1691.
 2. <https://codex.certara.com/>

Results

Overview of observed and predicted PFS

- The model predicted PFS assuming IDA aligned closely with observed data in most combination therapies (9/16)

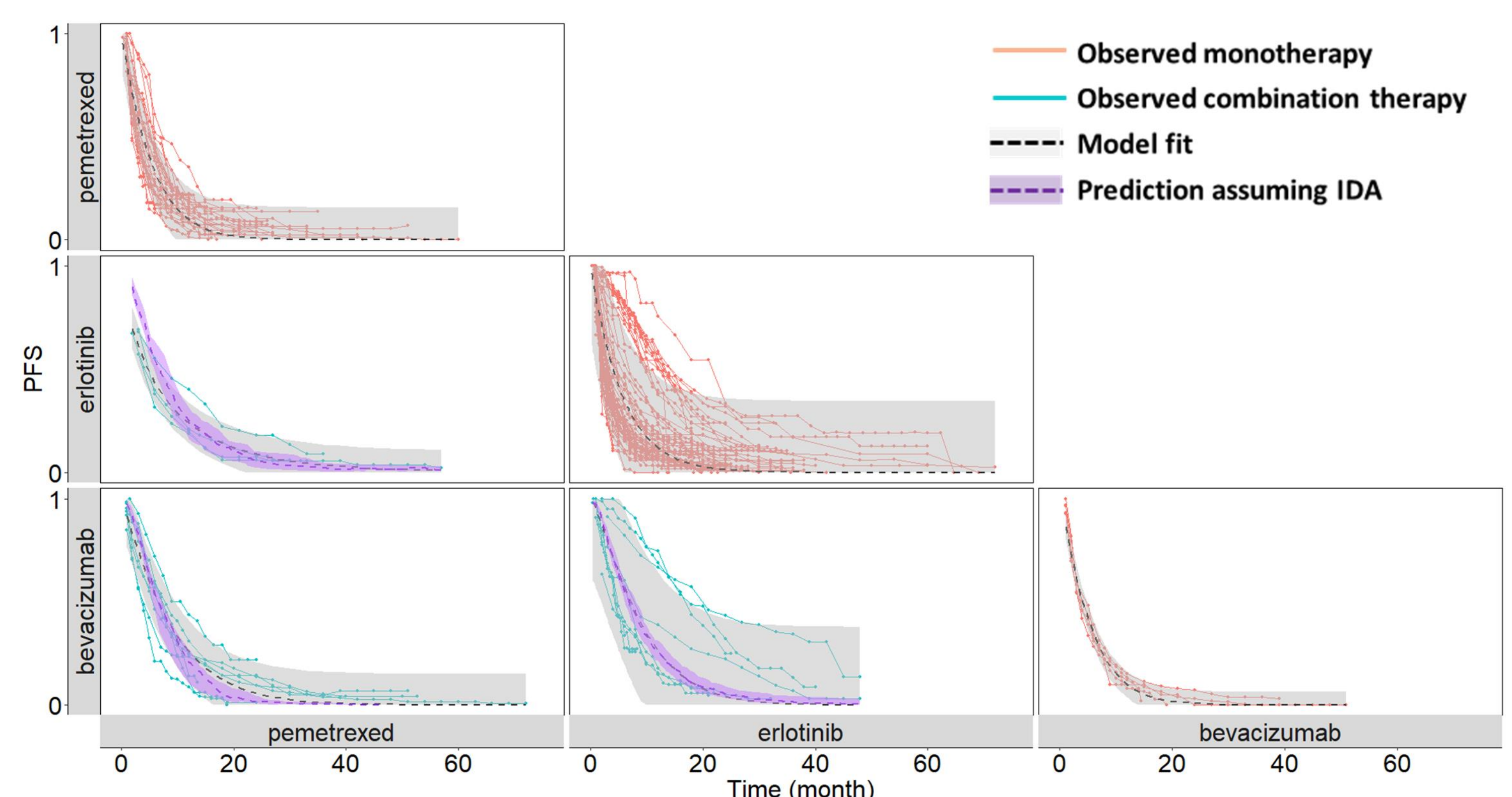


Figure 2 Overview of observed and predicted PFS. Due to space constraints and clarity considerations, only combination therapy of three drugs are shown here involving chemotherapy, target therapy and monoclonal antibody, respectively.

HR of combination therapy over the best monotherapy

- $HR_{pred} < HR_{observ} < 1$ for most combinations (9/16), suggesting that assuming IDA is likely sufficient to predict combination treatment effect in most cases
- Models assuming IDA were not able to adequately capture the PFS for several combination therapies (4/16), especially concerning erlotinib and chemotherapy
- $HR_{observ} < HR_{pred}$ for three combinations of pembrolizumab and chemotherapy, suggesting potential synergy or additivity

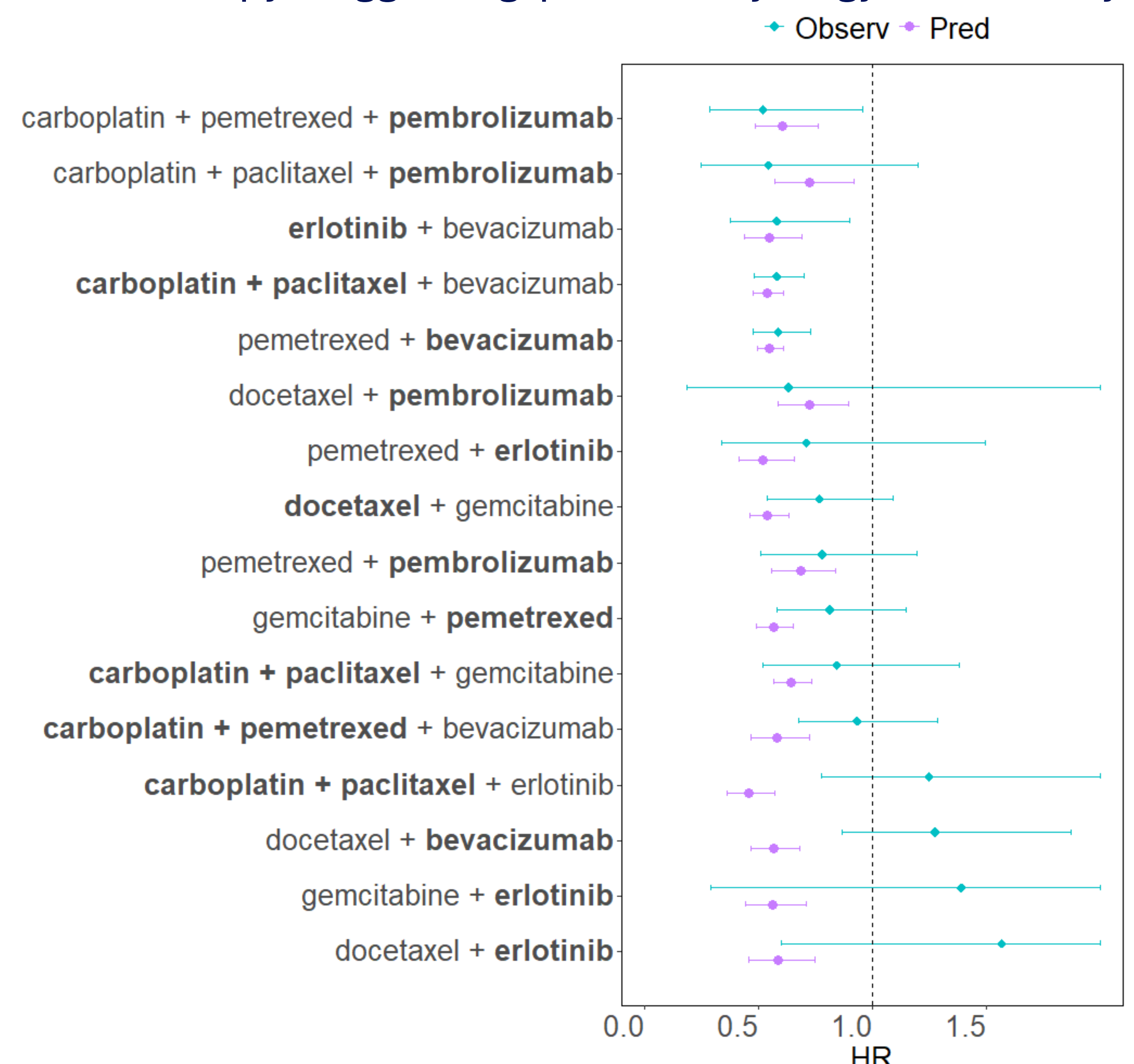


Figure 3 Hazard ratio (HR) of observed and predicted combination therapy over the best monotherapy. Drugs with bold names are the best monotherapy in each combination. The wide confidence intervals (CIs) across 1 were associated with combination therapies with limited study and sample size.

Conclusions

- Assuming IDA in MBMA may be sufficient for predicting combination treatment effect using monotherapy trial data
- For particular combinations (e.g. erlotinib, pembrolizumab), further investigation in interaction effects may be warranted