**Objectives**:

*Talaromyces marneffei* fungal burden at baseline and early fungicidal activity (EFA, i.e., rate of fungal clearance in log10 colony-forming units [CFUs] per milliliter [mL] of blood) over the first 14 days predicted 24-week mortality in the Itraconazole versus Amphotericin B (AmB) for Talaromycosis (IVAP) trial. However, the evidence showing EFA as a surrogate of mortality to advance the therapeutic agenda in talaromycosis is lacking. Using statistical modeling, we aimed to interrogate whether EFA can reliably predict treatment effects on mortality from the IVAP trial.

**Materials & Methods:**

Among 440 participants in the IVAP trial, we included 286 (139 in the Amphotericin B group and 147 in the Itraconazole group) who had a positive blood fungal count at baseline and at least one additional follow-up fungal count over the first 14 days. As only 95 out of the 286 participants (33.3%) had daily fungal CFUs during the first seven days, we used multiple imputation techniques to generate imputed datasets for sensitivity analysis. We used generalized linear regression to calculate EFA over the first 14 days and investigated the association between EFA and 24-week mortality using Cox proportional hazards models. We then assessed the strength of association between EFA and mortality using trial-level correlation ($R\_{trial}^{2}$), a method widely used as the strongest evidence to quantify whether treatment effects on the primary outcome are captured by the surrogate.

**Results**:

The Cox proportional hazards model showed that for every 0.2 log10 CFUs/mL/day increase in absolute EFA, the hazard of death decreased by 14.7% in the observed dataset (adjusted hazard ratio [aHR] = 0.85; 95% confidence interval [CI]: 0.07 to 1.52; p = 0.03) and decreased by 13.34% in the imputed dataset (aHR = 0.87; 95% CI: 0.02 to 1.45; p = 0.06). Based on the Kaplan-Meier estimates of survival stratified by EFA thresholds (**Figure 1**), we defined and validated an EFA cut-off of $\geq $ 0.3 log10 CFUs/mL/day as a surrogate for survival in predicting treatment effects. The surrogacy analysis showed a low association between EFA and 24-week survival (**Figure 2**). The correlation $R\_{trial}^{2}$ is 0.14 (95% CI: 0.20 to 0.73), which represents that treatment changes in EFA do not yield a precise prediction of treatment-associated changes in survival. As the strength of association varies with different dichotomizations of EFA, we performed an additional analysis using a more conservative dichotomization of EFA $\geq $ 0.5 log10 CFUs/mL/day or less to verify this possibility, which also showed a low trial-level correlation ($R\_{trial}^{2}$ = 0.16; 95% CI: 0.18 to 0.74).

**Conclusions**:

Despite a significant association between EFA and mortality in talaromycosis, there is not enough evidence within the single IVAP trial to support EFA as a surrogate for treatment effects on survival. Our results are not conclusive but underscore the need for more talaromycosis trials with EFA data to enable robust validation, which would allow for the design of more efficient phase II trials and advance the therapeutic agenda for this neglected mycosis.