

Comparison of Phase I combination therapy designs by clinical trial simulations to evaluate early tumor shrinkage

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INTRODUCTION

- In oncology, there is a growing interest in the use of combination therapies in early clinical trials, but most of the time only monotherapy data from each agent and no data from combination agents are available at early stage to evaluate trial design performances and optimize them
- Literature evidence suggests that early tumor shrinkage (ETS) is a good predictor of overall survival^{1,2}

OBJECTIVE

- To compare several designs for the combination of drug M with cetuximab (C) in the treatment of solid tumors by clinical trial simulations, notably in terms of type I error and power to detect the superiority of the combination C+M vs. C alone, based on ETS at week 8

METHODS

Model and simulations settings

- Longitudinal tumor sizes for the combination of C and M are simulated under a tumor growth inhibition (TGI) model, the parameters used (Table 1) were reported in a previous cetuximab analysis³

Table 1: TGI model parameters

Parameter	Value
PD Parameters	
TS0 (mm)	100
KS (week ⁻¹)	0.001*
KDSoC (week ⁻¹)	0.015*
KDC	0.00025
KDM	0.00025
KR (week ⁻¹)	0.2*
ω^2_{TS0}	0.5
ω^2_{KDSoC}	1.5*
ω^2_{KDC}	1.5
ω^2_{KDM}	1
ω^2_{KR}	1*
Covar (η_{KR}, η_{KD})	1 ($\rho=0.82$)
σ_{prop}	0.15
Synergy Parameters	
INT_CM	2
INT_AUC50_CM	75*
$\omega^2_{INT_CM}$	0.4

μ : fixed effect; ω^2 : variance of random effect
 Exponential random effect model, excepted for INT_CM (additive)
 *: fixed at estimation step

$$\frac{dT_S}{dt} = KS \times T_S - KD \times e^{-KR \times t} \times T_S$$

$$KD = KDSoC + KDC \times AUC_C + KDM \times AUC_M \times \left(1 + \frac{INT_CM \times AUC_C}{INT_AUC50_CM + AUC_C}\right)$$

$$TS(0) = TS0$$

- AUC of cetuximab (AUC_C) and M (AUC_M) are simulated (Table 2) and used as a regressor in the TGI model

$$AUC_C = \frac{Dose_C \times BSA}{CL_C \times (BSA/1.85)^{0.75}} \quad AUC_M = \frac{Dose_M}{CL_M}$$

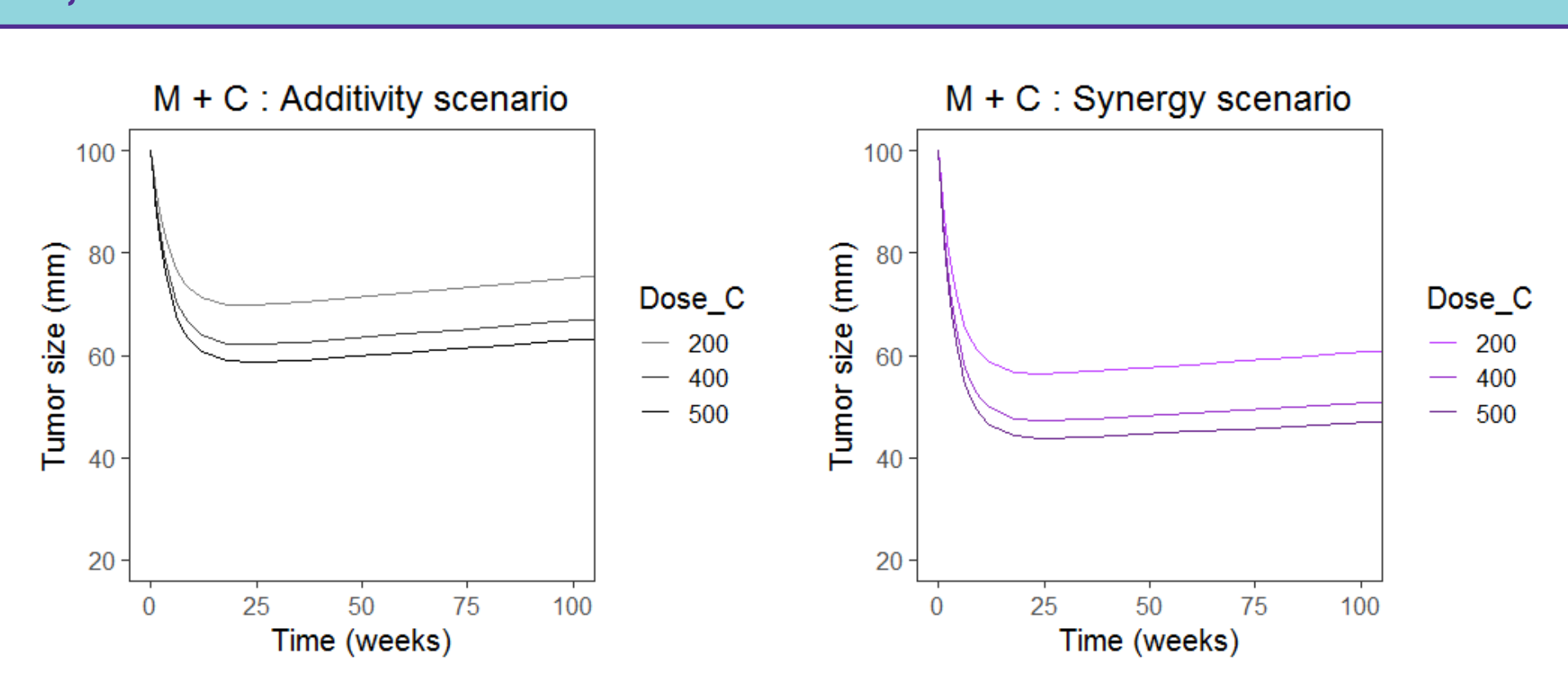
Table 2: PK parameters of C and M

Parameter	Value
PK Parameters	
BSA (m ²)	1.75
CL _C (L.h ⁻¹)	0.023
CL _M (L.h ⁻¹)	0.03
ω^2_{BSA}	0.01
$\omega^2_{CL_C}$	0.0025
$\omega^2_{CL_M}$	0.01

μ : fixed effect; ω^2 : variance of random effect
 Exponential random effect model

- Different scenarios investigated concerning the combination C + M (Figure 1)
 - Under H0, to evaluate type I error, no effect of M (KDM = 0)
 - Under H1, Additivity (INT_CM = 0) / synergy (INT_CM = 2)

Figure 1: Tumor size evolution if additivity (left) or synergy (right) of C and M, for different doses of C



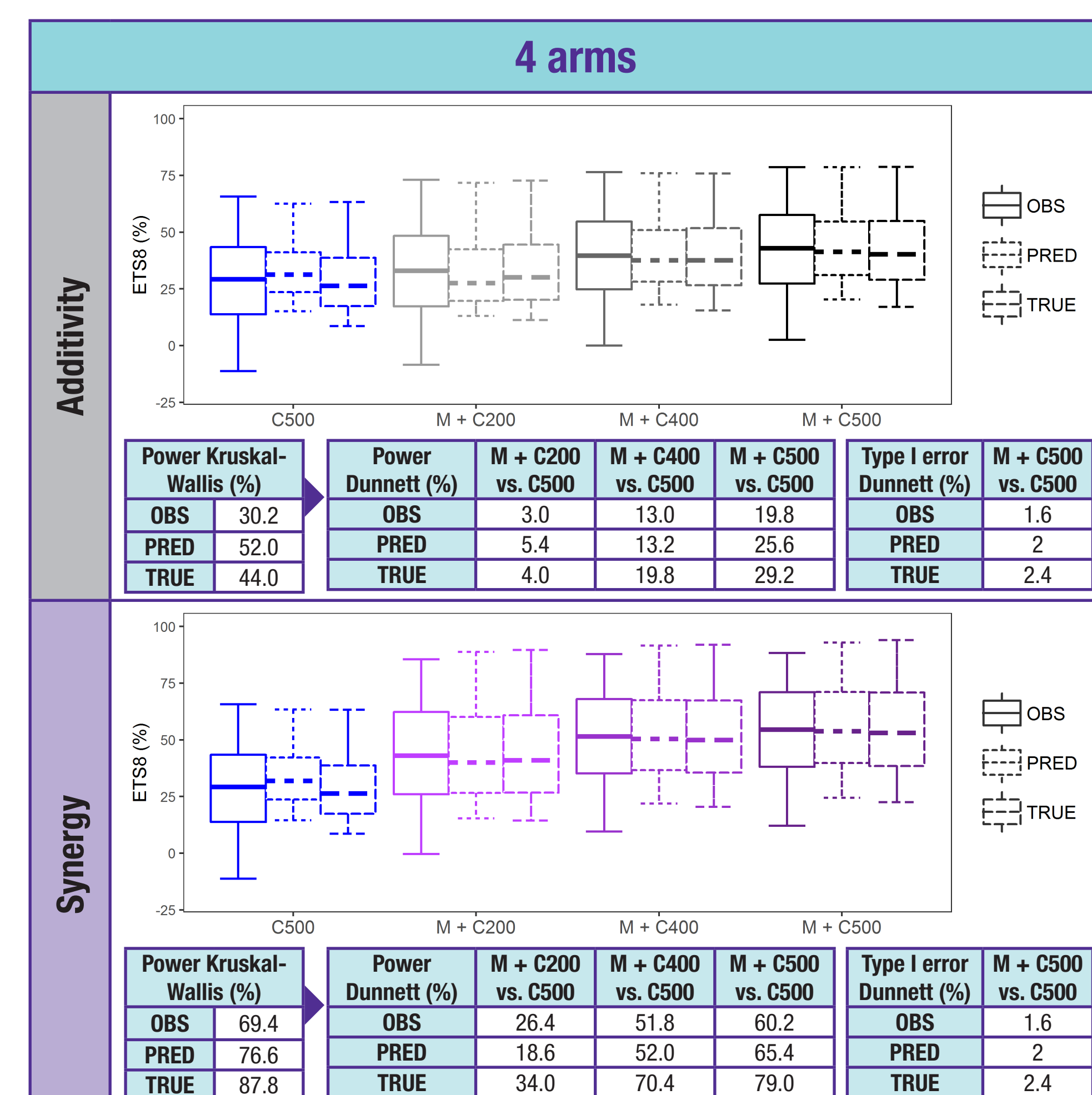
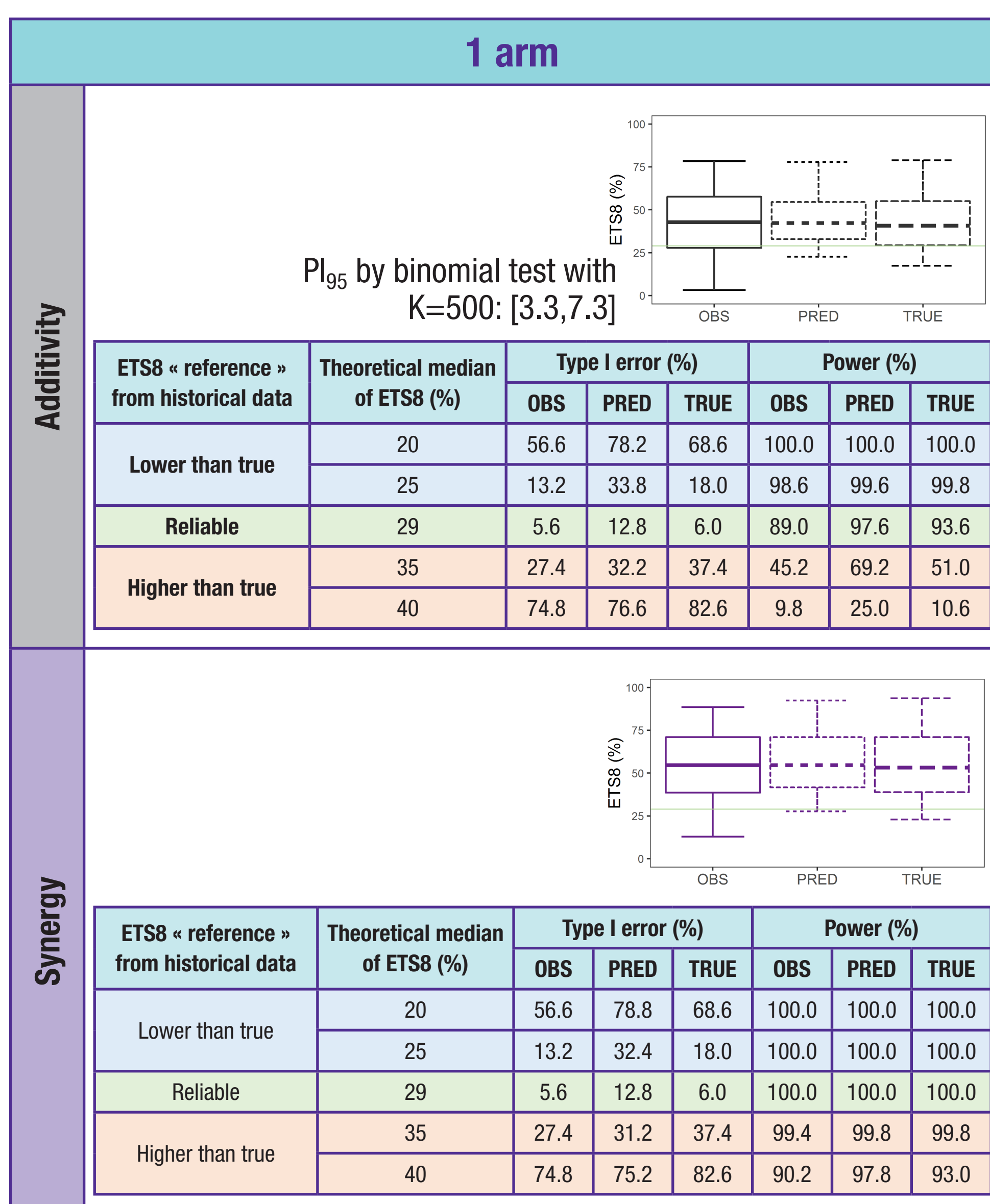
Designs & Analysis

- Tumor size data are simulated for a total of N=60 patients
- Measuring times: before treatment, at week 2, 4, 6 and 8
- Three different designs investigated: 1 arm (historical comparison), 2 arms and 4 arms (with lower doses of C in the combination)
- For each design and each scenario: K=500 simulated datasets
- Parameter estimation using SAEM algorithm in Monolix 2018R2⁴
- Statistical tests (two-sided, $\alpha=5\%$) performed on individual ETS at week 8 (ETS8) using individual observations (OBS), predictions using EBE (PRED) and true values (TRUE)

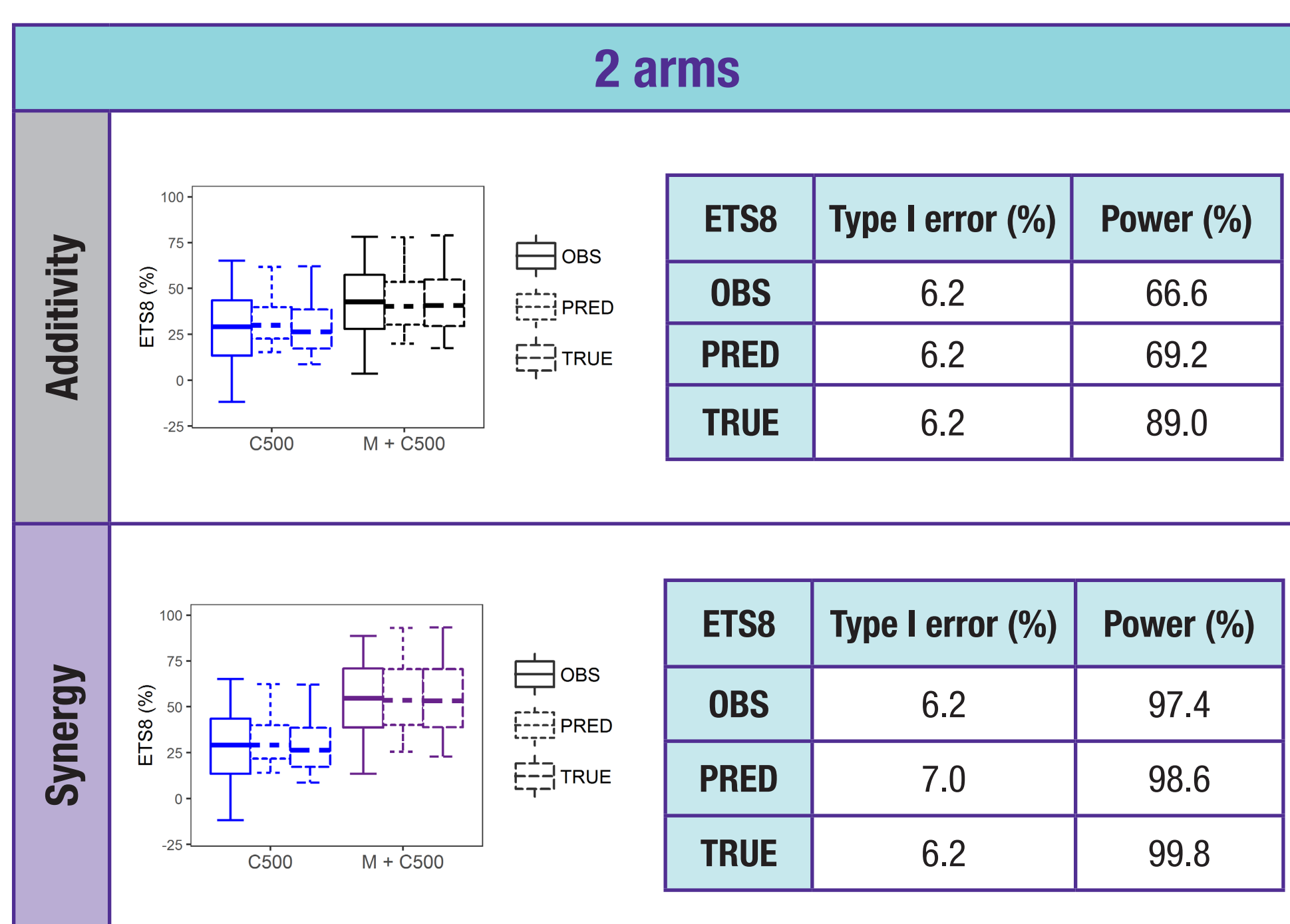
$$ETS8 = \frac{TS(t=0) - TS(t=8)}{TS(t=0)}$$

1 arm		2 arms		4 arms	
C500 + M	60 patients/arm	C500 (reference) C500 + M	30 patients/arm	C500 (reference) C500 + M C400 + M C200 + M	15 patients/arm
One-sample Wilcoxon test ETS8 compared to a «reference» ETS8 value expected under C only (reference obtained by simulation without effect of M)		Two-sample Wilcoxon test Comparison of ETS8 between the 2 arms		Global Kruskal-Wallis test Comparison of ETS8 between the 4 arms. If significant: Dunnnett test Comparison of ETS8 in each combo arm to the reference arm	

RESULTS



- The 1 arm design provides the maximum power, but could lead to a strong inflation of type I error in case of wrong historical reference



- The 2 arm design provides a better control of type I error than 1 arm

CONCLUSIONS

- This work highlights the strengths and weaknesses of different early clinical combination designs in ETS, in the context where we have a fixed dose of one agent and different doses of another
- The 1 arm design demonstrated a better power of tests than 2 or 4 arms, but implies strong assumptions on the historical control, leading to strong inflation of type I error in case of under-estimated reference
- Choosing 2 or 4 arms may depend on the objective of the study: a 2 arm design is preferable to reach a good power of tests, but a 4 arm design allows for better dose selection
- An extension of this work is to perform model-based adaptive two-stage designs^{5,6} using the Fisher Information Matrix to optimize the second stage

ACKNOWLEDGEMENTS

The authors would like to thank Thu Thuy Nguyen who contributed to this project. This work was supported by Merck Healthcare KGaA, Darmstadt, Germany. Disclosures: Pascal Girard, Kosalaram Goteti and Vishnu Dutt Sharma have been employed by Merck/EMD Serono.

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