Costing ‘the’ MTD: What Is the Economic and Human Cost of 1-Size-Fits-All Dose Finding in Oncology?

David C. Norris¹,*

¹ Precision Methodologies, LLC; Seattle, WA  david@precisionmethods.guru

Objectives: The ‘DTAT Principle’ [1] holds forth the promise of individualized ‘MTD,’ dose-finding in Phase I oncology studies, to replace the current practice of seeking ‘the’ MTD qua recommended Phase II dose (RP2D). Against the criterion of individualized dosing, how great a cost does the current 1-size-fits-all dosing constraint impose on society?

Methods: The simulated dose titration in [1] is extended to 1000 subjects, yielding an empirical MTD distribution to which a gamma density is fitted. Individual-level efficacy, in terms of the probability of achieving remission, is assumed to be an Emax-type function of dose relative to MTDᵢ, scaled (arbitrarily) to identify MTD, with the LD₅₀ of the individual’s tumor. (Thus, a criterion 50% of the population achieve remission under individualized dosing.) Current practice is modeled such that all patients receive a first-cycle dose at ‘the’ MTD, and those for whom MTDᵢ<MTDₚ experience a ‘dose-limiting toxicity’ (DLT) aborting subsequent cycles. Therapy thus terminated is assumed to confer no benefit. Individuals for whom MTDᵢ≥MTDₚ tolerate a full treatment course, and achieve remission with probability determined by the Emax curve. A closed-form expression is obtained for the population remission rate, and optimized numerically over MTDₚ, as a free parameter.

Results: Simulated MTD follow a gamma distribution with shape parameter α≈1.75. The population remission rate under 1-size-fits-all dosing at optimized MTDₚ proves to be a function of the shape parameter (and thus the CV) of the gamma distribution of MTD, (Figure 1).

Conclusions: The CV of MTD, determines the efficacy lost under one-size-fits-all dosing at ‘the’ MTD. Within plausible ranges for this CV, failure to individualize dosing can waste fully half of a drug’s efficacy. This underscores the importance to all stakeholders of pursuing dose individualization in early-phase oncology studies, since these losses accrue to patients, investors and society as a whole.

References: