# U-DESPA: a Bayesian Utility-based approach for dose-regimen optimization relying on Dose-Exposure-Safety/Pharmacodynamics/Anti-tumor activity relationships modeling for oncology clinical trials

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**Résumé**

With the development of novel therapies such as Molecularly Targeted Agents (MTAs) and immunotherapies, the MTD paradigm that "more is better" does not necessarily hold anymore. In this context, doses and schedules of novel therapies may be inadequately characterized and oncology drug dose-finding approaches should be revised. In January 2023, in the frame of the interdisciplinary Project Optimus, FDA issued a draft guidance requiring new strategies of dose-regimen optimization prior to initiating registration trials in oncology. In this guidance, the dose-regimen optimization is proposed to rely on a quantitative assessment of the relationship between dosage and relevant endpoints. We developed a Bayesian dose-finding design allowing to 1. Directly determine the optimal dose-regimen at the end of the dose escalation phase, or 2. Use of dedicated dose finding cohorts randomizing patients to candidate optimal dose-regimens after safe dose-regimens have been found. This Bayesian dose finding design relies on a dose-exposure model built from pharmacokinetic data using non-linear mixed effect modeling approaches. Three models are also built to assess the relationships between exposure and the probability of different relevant endpoints on safety, pharmacodynamics and anti-tumor activity. These models are then combined to predict the different endpoints for every candidate dose-regimen. A utility function is finally proposed to quantify the trade-off between these three endpoints and to determine the optimal dose-regimen. We perform an extensive simulation study to evaluate the operating characteristics of the method. Based on these outcomes, this approach is planned to be applied on a dose finding clinical trial to support decision on the dose-regimen to be further used for late-stage development.

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