1163-92-1421 **Kamrine Poels*** (kpoels@g.harvard.edu), **Adam J Schoenfeld**, **Alex Makhnin**, **Yosef Tobi**, **Yuli Wang**, **Aaron Hata**, **Scott L Weinrich**, **Helena A Yu** and **Franziska Michor**.
Identification of optimal dosing schedules of dacomitinib and osimertinib for a phase I/II trial in advanced EGFR-mutant non-small cell lung cancer.

Despite the clinical success of the third-generation EGFR inhibitor osimertinib as first-line treatment of EGFR-mutant non-small cell lung cancer (NSCLC), resistance predictably arises, and alternative therapies are needed. Dacomitinib, a pan-HER inhibitor, is approved for first-line treatment and results in different acquired EGFR mutations that mediate on-target resistance. A combination of osimertinib and dacomitinib could induce more durable responses by preventing on-target acquired EGFR mutations. We present an integrated computational modeling and experimental approach to identify an optimal dosing schedule for osimertinib and dacomitinib combination therapy. We developed a predictive modeling platform that encompasses tumor heterogeneity and inter-subject pharmacokinetic variability to predict tumor evolution under different dosing schedules, parameterized using in vitro dose-response data. This model was validated using cell line data and used to identify an optimal combination dosing schedule. Our dosing schedule was subsequently confirmed tolerable in an ongoing phase I clinical trial at MSKCC, with some dose modifications, demonstrating that our rational modeling approach can be used to identify appropriate dosing for combination therapy in the clinical setting. (Received September 15, 2020)