Pharmacokinetic-pharmacodynamic modeling approach to inform the level and duration of HER2 kinase inhibition required to demonstrate the efficacy in subcutaneous xenograft and orthotopic mouse tumor models

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Introduction and Objectives: HER2 is overexpressed in ~25% of metastatic breast cancer patients. HER2 phosphorylation inhibition (pHER2i) in brain provides the opportunity to control brain metastases (BM), improving survival and quality of life over current therapies that control peripheral tumours. An integrated analysis via PK/PD-efficacy modelling of existing HER2 inhibitors would enable the project team to define the lead compound potency, extent/duration of HER2i, and help to predict dose/regimen of an investigational drug to treat BM patients in the clinic.

Methods: PK/PD-efficacy models for pHER2i (Neratinib, Arry-380 and 2 AstraZeneca compounds) were developed using preclinical PK, pHER2i and BT474C1 subcutaneous (SC) and BM mouse xenograft data. PK/PD-efficacy data were sequentially fitted using non-linear mixed-effects modelling implemented in NONMEM V7.2 [1].

Results: Rapid and extensive inhibition was achieved for all compounds in an exposure dependent manner. The pHER2i EC₅₀ for each was derived with Eₘₐₓ fixed to 100%. In SC and BM xenograft models it was found that ~67% pHER2i over 8hr dosing interval required for delivering significant tumour regression, while 45% pHER2i resulted in tumour stasis. Good efficacy was observed in peripheral SC tumor settings for all compounds. However, no efficacy observed with Neratinib and Arry-380 in BM model, which is consistent with the model showing insufficient free brain concentrations and pHER2i.

Conclusion: Correlation between plasma/brain PK, pHER2i and tumour regression established by integrating data for AZ and competitor compounds and this modelling work helped in prioritization of compounds for in vivo testing with benchmarking against compounds in the clinic.