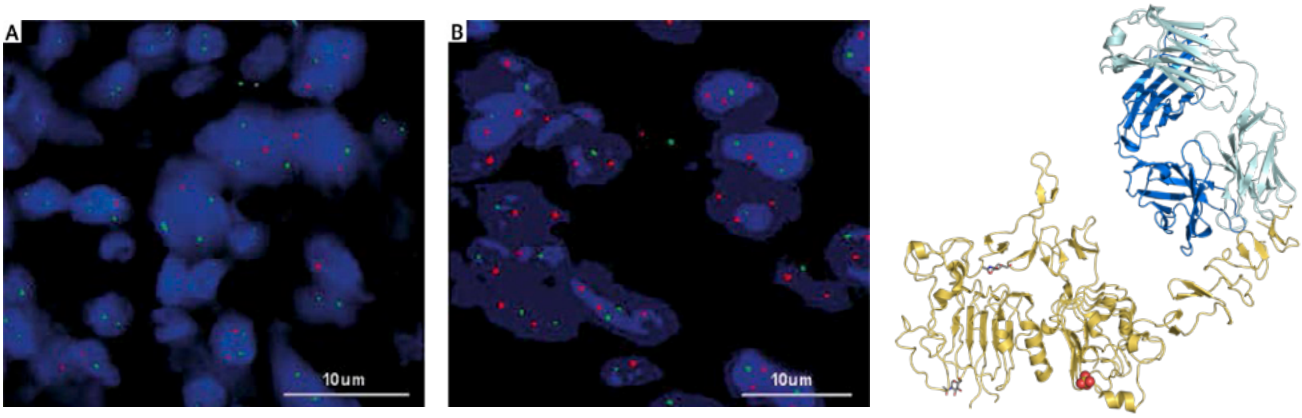
Using Champions' Patient-Derived Xenograft (PDX) Models for Preclinical Validation of HER2-Specific Small Molecule Inhibitors

HER2/neu (encoded by ERBB2 in humans) is a member of the HER/EGFR family of tyrosine kinase receptors that facilitates the translation of extracellular signals into cellular outputs such as growth and proliferation. A single unit glycoprotein receptor, HER2 broadly consists of an extracellular ligand-binding domain, transmembrane domain, and an intracellular kinase domain[1,2]. Interestingly, the signaling capacity of HER2, rather than being contingent on ligand binding and stimulation, appears to rely on its ability to form heterodimers with the other family members EGFR, HER3, and HER4[1,2]. This atypical function has led some to describe HER2 as a co-receptor and master coordinator of HER family signaling. Dimerization consequently leads to intracellular signal transduction through a number of pathways including MAPK and PIK3CA/AKT[2].



The HER2 gene amplification detected by FISH. A ratio of HER2 (red): CEP17 (green) < 2.0 was considered non-amplified (E, negative) and ratios ≥ 2.0 were considered amplified (F, positive).*M. Chen et al. Contemporary oncology 18. 95-9. 10.5114/wo.2014.41383.*

Overexpression of HER2, typically but not always, occurs via whole gene amplifications of HER2 and leads to constitutive homo- and hetero-dimerization at the cell surface and downstream signaling activation[3]. Constitutive HER2 signaling can also occur, though less commonly, through the acquisition of gain-of-function mutations[4]. HER2 alterations have been identified in numerous cancer types, including breast, gastric, colorectal, and NSCLC and such prominence has made HER2 an attractive target for therapeutic intervention. A number of agents have been developed to blockade HER2 oncogenic signaling in breast cancer, including the biologics trastuzumab and trastuzumab-emtansine, and small molecule tyrosine kinase inhibitors (TKIs) such as lapatinib and neratinib[3]. Nevertheless, currently-available HER2 TKIs tend to be promiscuous in their activity, inhibiting other HER/EGFR family members with near equipotency, which increases the potential for side effects and adverse events[5]. These barriers reduce the clinical effectiveness of HER2 TKIs, often times requiring intermittent or modified dosing regimens to circumvent the associated tolerability concerns. It is within this landscape that a biotech company in the Pacific Northwest began developing a HER2-specific, orally bioavailable TKI, tucatinib[5].

Tucatinib was developed as a reversible, ATP-competitive inhibitor in a similar vein to lapatinib and neratinib. In contrast to those molecules, however, tucatinib has at least a 50-fold selectivity for HER2 over EGFR and HER4 in kinase and biomedical assays (data not shown)[5]. This selectivity also manifested in vitro, with tucatinib preferentially inhibiting a cell line expressing HER2 and minimal EGFR (BT-474) compared to a cell line showing the converse expression profile (A431) (Figure 1A). Growth of a cell line xenograft of BT-474 was also arrested by treatment with tucatinib (Figure 1B). It was at this juncture the biotech company requested Champions Oncology to evaluate tucatinib using our extensive bank of patient-derived TumorGraft® models, recognizing that this platform is more reflective of the clinical, morphological, and molecular profile of human cancers.

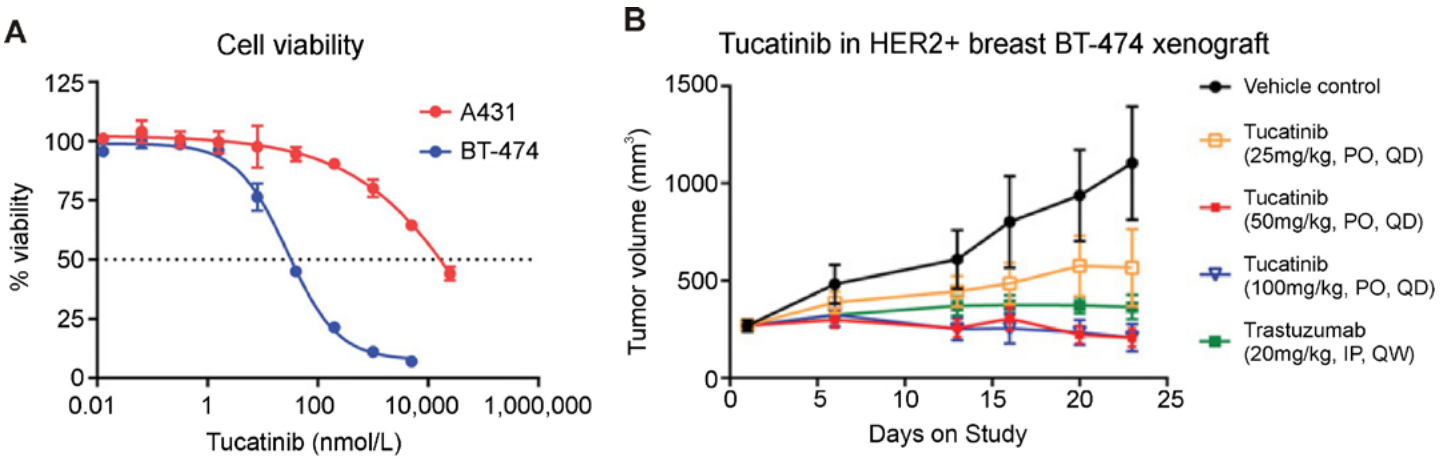


Figure 1.

In cooperation with analysts at Champions Oncology, the company selected a panel of HER2-amplified breast models, as well as additional HER2-amplified models from our colorectal and esophageal cohorts for indication expansion (HER2 copy number range by whole exome sequencing; 34-85 copies/cell) (Figure 2).

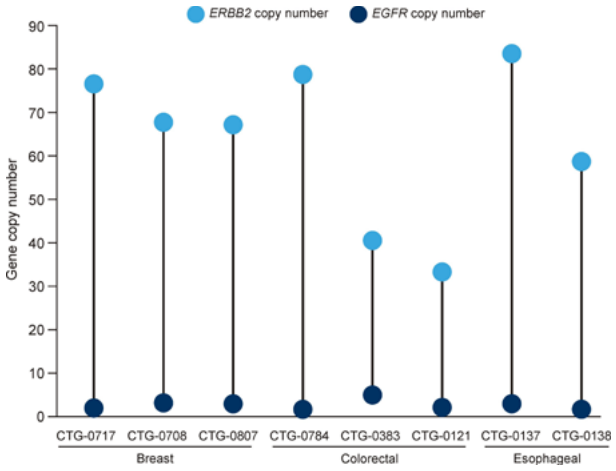
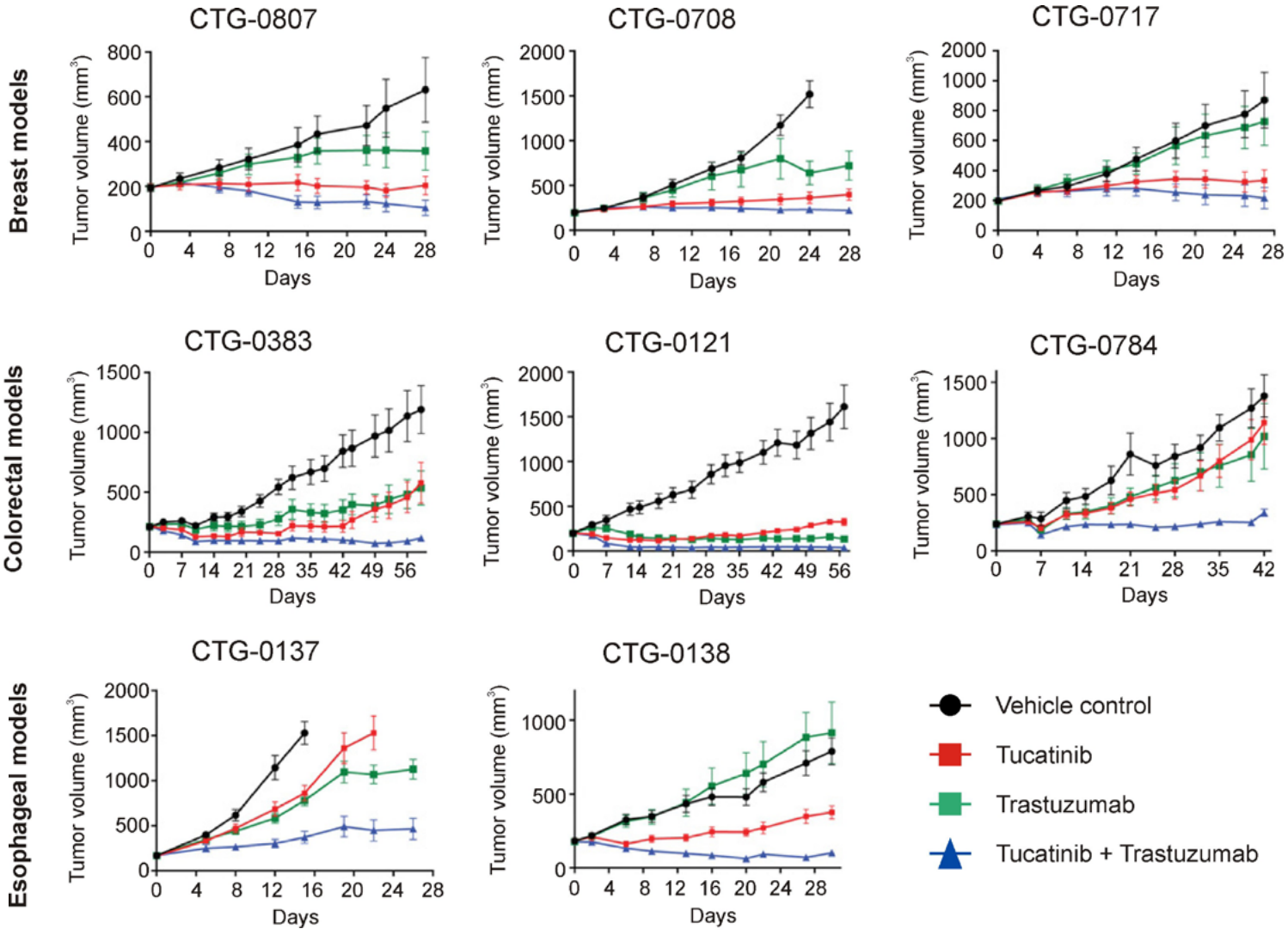


Figure 2.

Moreover, many of the models were strongly positive (+3) for HER2 by IHC (data not shown). These models were screened against tucatinib, both as a single agent and in combination with the HER2-targeted biologic, trastuzumab (Figure 3). Tucatinib was generally effective as a monotherapy, slowing growth or inducing some level of regression in all TumorGraft® models, with its inhibitory activity as effective if not more so than the commonly employed standard-of-care HER2 inhibitor, trastuzumab. The combination of tucatinib with trastuzumab proved to have an even greater inhibitory effect, with sustained tumor regression observed to some degree in virtually every model, with CTG-0137 the lone exception, where, rather than regression, tumor stasis was induced after a short time of slowed growth.



This study exemplifies why deployment of highly characterized TumorGraft® models within drug development pipelines is central to accurately gauging therapeutic efficacy in clinically-relevant settings. The data from these studies indicates that tucatinib has activity as a monotherapy across different tumor types carrying HER2 gene amplifications but is even more effective when combined with other HER2-targeting agents. This critically important data is imperative to informing the design of subsequent clinical trials to ensure the most relevant populations of patients are enrolled, which provides the greatest opportunity for success.

References

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