Using Champions' Patient-Derived Xenograft (PDX) Models for Preclinical Validation of ERK Pathway Inhibitors

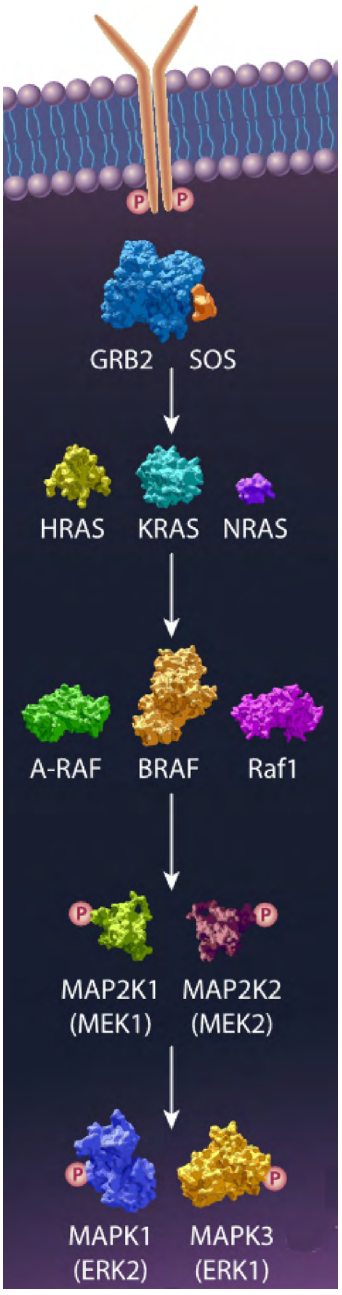

Figure 1.

Cellular responses to external stimuli from molecules such as growth factors, mitogens, cytokines, and the extracellular matrix are governed in part by signal transduction networks. One such network, the ERK pathway, is a central and important signaling pathway that translates extracellular cues from mitogens and growth factors into regulated outputs affecting diverse cellular functions such proliferation, inflammation, metabolism, differentiation, and apoptosis *(Figure 1)*.

De novo genetic abnormalities affecting the canonical RAS/RAF/MEK/ERK axis and leading to downstream ERK activation are prevalent in many human tumors including melanoma, lung, colon, and pancreas. Furthermore, ERK pathway (re)activation is implicated in acquired resistance to a number of different therapies that directly target molecules within the pathway (such as vemurafenib targeting V600-mutated BRAF), as well as other cellular elements upstream such as growth factor receptors and receptor tyrosine kinases[1]. Given that diverse upstream genetic alterations causing deregulation in the ERK pathway are typically channeled through downstream ERK1/2 activity, ERK1/2 is an attractive target for therapeutic intervention.

The competitive landscape for ERK pathway inhibitors continues to grow, with a number of ERK1/2 inhibitors currently in preclinical and clinical development. One being developed by Eli Lilly, LY3214996, is an ATP-competitive ERK1/2 inhibitor with in vitro IC50 values in the 5-200nm range in BRAF- or KRAS-mutated melanoma, colorectal and NSCLC cancer cell lines[2]. Moreover, in vivo xenografts of these same cell lines in athymic nude animals also responded to single agent treatment *(Figure 2)*. At this stage Eli Lilly wished to evaluate LY3214996 in a system more reflective of the morphological and molecular profile of human cancers and worked with data scientists from Champions Oncology to select a BRAF-mutated colorectal cancer patient-derived xenograft (PDX) model from our database of TumorGrafts.

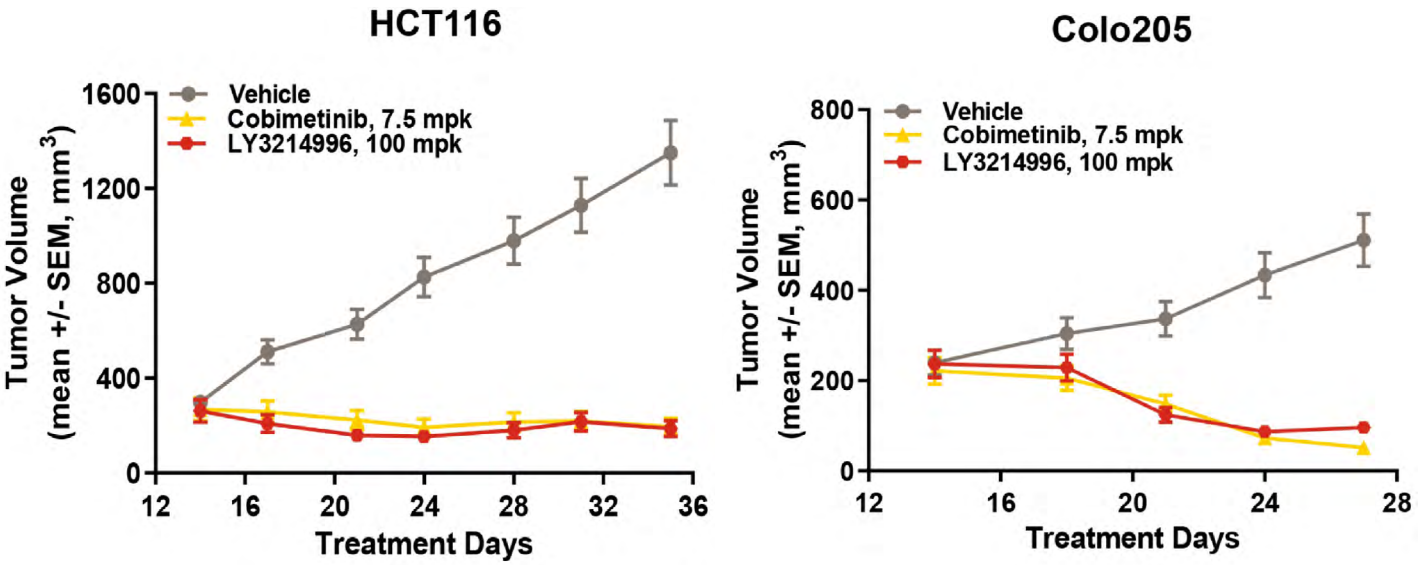

Figure 2. LY3214996 inhibits growth of BRAF- and KRAS-mutated colon cell line xenografts

TumorGraft model CTG-0652 chosen for the study was developed from a moderately differentiated colon adenocarcinoma removed from an 80-year old Hispanic female. Molecular characterization demonstrated the model to be MSI-H through a mutation in MSH6. More importantly for the study, CTG-0652 harbors the archetypal BRAF V600E mutation and is intrinsically resistant to the inhibitor vemurafenib, possibly through upregulation of the receptor tyrosine kinase (RTK) EGFR, which is amplified in this model, leading to strong cell surface expression *(Figure 3)*.

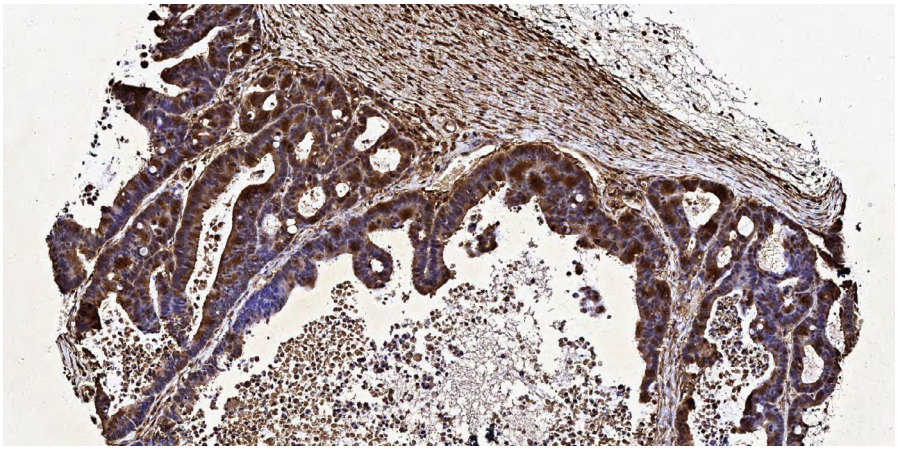

Figure 3. CTG-0652 shows intense membrane expression of EGFR

CTG-0652 reflects a clinical scenario in which BRAF V600E-mutated colorectal cancer patients acquire resistance to frontline BRAF inhibitor therapy (vemurafenib) via upregulation of cell surface RTK expression, a suitable test-bed for screening a novel ERK1/2 inhibitor such as LY3214996. CTG-0652 was confirmed to be resistant to vemurafenib, but responded to single agent treatment with LY3214996, which prevented the normally vigorous growth of the model, with a tumor growth inhibition of 83% observed *(Figure 4)*.

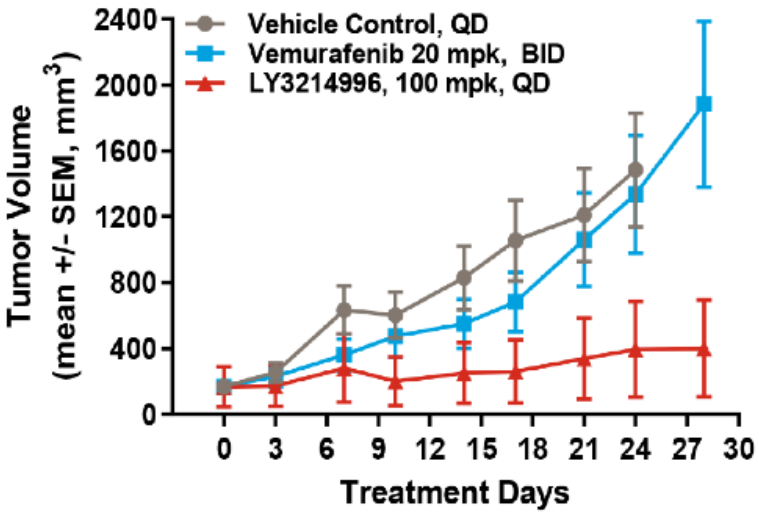

Figure 4. LY3214996 strongly inhibits growth of CTG-0652, a BRAF V600E mutated, vemurafenib-resistant colorectal cancer TumorGraft model.

Eli Lilly was able to run a query based on patient metadata, sequencing, immunohistochemistry, and in vivo drug screening to identify a specific TumorGraft model that mimics the exact kind of clinical scenario for which their drug is being developed. Altogether, the results of this study not only highlight the potential of targeting the ERK pathway as a therapeutic strategy for a variety of tumor types, but also the utility of leveraging extensively characterized TumorGraft models of cancer to determine preclinical efficacy and help make go/no-go decisions on novel oncology agents.

References

1. Luebker SA and Koepsell SA., *Front. Oncol.*, 9: 268. 2019.

2. Bhagwat, SV. et al, *Mol. Cancer Ther.*, 19(2): 325. 2019.