Champions TumorGrafts® Guide the Development of a Novel, Selective Dual BRAF/EGFR Inhibitor, CEP-32496

Key Highlights

- CEP-32496 demonstrates overall superiority versus vemurafenib in Champions TumorGrafts that harbor the BRAFV600E mutation as well as other BRAF mutations
- CEP-32496 outperformed single agent SOC in many cases
- Robust anti-tumor activity of CEP-32496 versus vemurafenib in colorectal models
- CEP-32496 also demonstrates activity in several models that have the wild type BRAF gene

In the competitive world of oncology drug development, there is an urgent need to develop more targeted and effective therapies for patients. Personalized oncology is becoming less of a talking point and more of a reality. To support the effective development of oncology drugs in this new environment, Champions Oncology’s predictive patient-derived xenograft (PDX) platform provides the competitive edge necessary to cost effectively bring novel therapeutics to the patients who will benefit most.

Champions TumorGrafts®

Champions Oncology has developed a predictive platform that utilizes the implantation of human tumors into immune-deficient mice. Low-passage TumorGraft models more accurately recapitulate the patient’s tumor by retaining greater histologic and genomic fidelity. Champions TumorGrafts, are clinically and molecularly annotated, as well as profiled for their response to key agents. Champions derives its patient-centric tumor bank from a diverse global population of patients; these patients represent the same population of patients that enroll in industry-sponsored clinical trials.

The TumorGraft platform allows oncology drug developers to screen and test their compounds in a much timelier and cost-effective method. Since Champions TumorGrafts have been proven to predict therapeutic outcomes in patients,1,2,3 the results from testing can be trusted to guide clinical development.

Here, we highlight a case study demonstrating the added value that screening and efficacy evaluation in Champions TumorGrafts has on the development of a novel compound, the dual BRAF-EGFR inhibitor CEP-32496.4,5,6
Mutations in the BRAF gene have been identified in approximately 7% of cancers, including 60–70% of melanomas and 10–16% colorectal cancers. CEP-32496 is an orally active dual inhibitor of wild type and V600E-mutant BRAF kinase and EGFR, as well as other oncogenic protein kinases, including BCR/ABL and RET.

A screening study using a panel of Champions TumorGraft models of both BRAF wild type and mutant colorectal cancer and melanoma was conducted to compare the therapeutic activity of CEP-32496 versus a clinically approved BRAF inhibitor, vemurafenib, as well as two standard of care agents (irinotecan or temozolomide). This screening study demonstrated an overall comparable or superior response (p<0.05) of CEP-32496 compared to vemurafenib in 13 out of 15 Champions TumorGraft models of melanoma. Notably, CEP-32496 displayed robust therapeutic activity (p<0.05) over vemurafenib in seven Champions TumorGraft models of BRAF-mutated colorectal cancer where vemurafenib was ineffective. These results were consistent with the poor clinical response to vemurafenib in BRAF-mutated CRC.

Given the initial encouraging results in colorectal cancer, the anti-tumor activity of CEP-32496 and several standard of care agents for colorectal cancer (irinotecan, oxaliplatin, 5-FU, and cetuximab) were explored further in BRAF-mutated colorectal cancer. In both colorectal models, the combinations used at specific dose ranges achieved significantly improved anti-tumor activity (p<0.05) relative to standard of care agents alone and in many cases vehicle-treated animals with acceptable tolerability profiles.
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Historical Preclinical Response of BRAF Mutated Cancers

In 2011, the approval of vemurafenib in BRAF V600E mutated metastatic melanoma was based on remarkably high response rate of ~80%. Based on vemurafenib's initial success in BRAF V600E mutant melanoma, the compound was tested in BRAF V600E mutant colorectal cancer. The results were remarkably different, with a response rate of only ~5%. It became quite obvious that vemurafenib's significant response in BRAF mutant melanoma was not going to be replicated in BRAF mutant colorectal cancer. This result was disappointing as a compound that seemingly held potential therapeutic value for the treatment of BRAF mutant colorectal cancer patients was no longer a therapeutic option. It has been hypothesized that the key to unlocking the resistance of BRAF mutant colorectal cancer to BRAF inhibitors would be through dual inhibition of EGFR.

TumorGraft Testing Identifies Competitive Advantage for CEP-32496 in BRAF Mutant Colorectal Cancer

BRAF mutant colorectal patients now have another promising therapy in development. CEP-32496 is a dual BRAF-EGFR inhibitor being developed for the treatment of metastatic colorectal cancer as well as metastatic melanoma. The clinical development plan was strongly influenced by the positive comparative results of CEP-32496 against vemurafenib and other standard agents.

By conducting well-designed, expansive Champions TumorGraft studies, the clinical development plans for CEP-32496 could be more effectively and rationally defined to help differentiate it from other BRAF-targeted therapies approved or in clinical trials.

Any Drug, at Any Stage, Can Benefit From Champions TumorGraft Testing

Champions’ knowledgeable and experienced team can help design and conduct the most effective studies to add significant value and efficiency to your oncology compound. We have worked with all large pharmaceutical organizations, as well as big and small biotech, with pipelines of one to 100 compounds. Contact us today to learn more about how we can help identify your path to responsive patients.
References


4Rowbottom MW. et al. Identification of 1-(3-(6,7-Dimethoxyquinazolin-4-yl)oxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl) urea Hydrochloride (CEP-32496), a highly potent and orally efficacious inhibitor of BRAFV600E. J Med Chem. 2012 Feb 9;55(3):1082-105.


