

Phase I Clinical Trials: Hypothesis Testing

Faculty Presenter

Keith Flaherty, MD, Director of Termeer Center for Targeted Therapy & Director of Clinical Research, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA

Scholars' Summaries

*Authored by **Joseph M. Caster, MD, PhD**, UNC Hospitals Radiation Oncology, Chapel Hill, NC, USA*

Dr. Keith Flaherty gave an excellent lecture which highlighted the importance of moving early-phase drug trials in academia away from yes/no efficacy studies and into hypothesis-driven studies to address issues of treatment failure or success and the evolution of drug-resistance. He very nicely highlighted his work with BRAF-mutated melanoma. From the beginning, they initially attempted to use sorafenib as a BRAF inhibitor and quickly found that this drug showed very little efficacy (only 2 PRs out of approximately 50 patients). Rather than giving up on the hypothesis, they investigated and discovered that sorafenib was a poor BRAF inhibitor at the concentrations achievable in patients. They obtained much better results by utilizing a novel BRAF inhibitor. He then went on to perform elegantly designed and pre-planned tissue analyses in patients who did not respond to BRAF inhibition and was able to identify several intriguing alterations which appear to identify patients unlikely to respond to BRAF therapy. Further, some of them may be amenable to dual pathway inhibition, and early phase trials in these patients are ongoing. Dr. Engelman highlighted similar experiences with EGFR-mutated NSCLC patients. These sessions very clearly highlighted the utility and importance of moving beyond treating all patients with a single genetic or epigenetic alteration the same (since we know that they are not) and trying to find ways to better identify subsets of patients who are most and least likely to benefit from novel therapies.

*Authored by **Russell W. Jenkins, MD, PhD**, Dana-Farber Cancer Institute, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*

Dr. Keith Flaherty gave an outstanding talk geared towards senior fellows and junior faculty, designed to help us develop a portfolio of clinical trials. He provided a useful framework for thinking rationally and scientifically about such trials, including discussion of focused and testable hypotheses, drug characteristics (including pharmacokinetics and pharmacodynamics), clinical drug activity, variable effect (i.e. intrinsic resistance), and loss of effect (i.e. acquired resistance). Using his extensive expertise and experience with BRAF inhibitors, he walked us through the early stages of development of BRAF inhibitors, emphasizing important lessons regarding the utility of identifying resistance mechanisms by focusing on non-responders and patients who develop resistance on therapy. Additionally, he impressed upon us the importance of thinking about toxicity with single-agent vs. combination therapies and how the toxicity profile can be shifted in combination therapies in such a way as to permit higher doses of both drugs, citing the use of BRAF and MEK inhibitors in melanoma. Dr. Flaherty peppered into his discussion great mentoring and practical teaching points regarding early phase clinical testing and pre-clinical evaluation.

This was a fantastic platform in which to hear the story of how preclinical evidence led to novel clinical agents to solve a specific clinical problem and how lessons learned from clinical trials generated new questions that could be addressed by further preclinical evaluation. A highly practical and engaging session on all levels!

Authored by Go J. Yoshida, MD, PhD, Tokyo Medical and Dental University, Tokyo, Japan

Developing a research design of Phase I clinical trials requires a testable hypothesis. Scientific hypotheses should be evaluated with a repeated number of experiments and analyses. Before oncologists perform first-in-human Phase I clinical trials in healthy people to confirm the safety and pharmacodynamics of a drug, it should be investigated whether or not the chemical works as an “anti-cancer drug” both in vitro and in vivo. In this lecture, Professor Flaherty introduced the example of the investigations before the clinical trial phase I of anti-melanoma agent targeting mutant BRAF.

BRAF mutations are found in 7% of all cancer tissues and in 60% of malignant melanoma patients. As compared with ARAF and CRAF, si-RNA-mediated depletion of mutant BRAF (BRAF inhibition; BRAFi) significantly induces the apoptotic death of malignant melanoma cells. That is why mutant BRAF can be the target molecule for melanoma treatment.

Sorafenib is an orally available multi-kinase inhibitor which inhibits tumor proliferation by targeting multiple kinases including the vascular endothelial growth factor receptors VEGFR1, VEGFR2, VEGFR3, and the platelet-derived growth factor receptor PDGFR; it targets tumor progression by inhibiting FLT3, c-Kit, and BRAF. Since BRAF mutations are frequent in melanoma, sorafenib has been investigated in various Phase I, II, and III clinical trials. The drug is well tolerated with mild to moderate adverse effects, which are mostly limited to cutaneous toxicity, diarrhea, and fatigue. However, sorafenib as a monotherapy or in combination with chemotherapy is of limited use. Median progression-free survival was only 3 months. Two phase III trials combined with chemotherapy failed in vein. The relative activation of ERK and proliferative marker Ki-67 were analyzed in order to assess the biological effect of sorafenib in vivo. Indeed, among 39 patients with metastatic melanoma who received sorafenib, only one patient showed clinical response, and 7 patients exhibited stable disease at 12 weeks. In contrast, PLX4032 is a selective BRAF inhibitor used for BRAF mutant melanoma in vitro and in vivo. PLX4032 optimized formulation achieves preclinical target exposure for tumor regression.

RTK (receptor tyrosine kinase) tends to be up-regulated when MITF expression level is low. Shift in transcriptional state with BRAF/MEK inhibition results in the enrichment of MITF(low)/AXL(high) subpopulation. MITF (low) tumor cells activate both canonical Wnt/beta-catenin and ROR2-dependent non-canonical Wnt signaling pathways. Furthermore, increased oxidative phosphorylation in mitochondria and expression of anti-apoptotic bcl-2 are recognized in tumor cells expressing low amount of MITF. Notably, neural crest stem cells also exhibit much the same genetic expression pattern. It has been recently reported that the deregulation of RNF125, the ubiquitin ligase of EGFR, alters EGFR expression indirectly by controlling JAK1, a newly described RNF125 substrate. In addition to its effect on EGFR, JAK1 expression was also found to regulate other genes, including GAS6/AXL, IL6, KIT, and PDGFR, all of which are implicated in BRAFi (BRAF inhibition) resistance. Targeting multiple pathways is likely to be more efficacious for eradicating tumor cells than targeting EGFR alone. Thus, the effect of JAK inhibition on the regulation of multiple RTKs linked to BRAFi resistance may offer an efficient therapeutic modality. That is why combination therapies targeting both JAK1 and EGFR are expected to be effective against BRAFi-resistant melanoma tissues with de novo low RNF125 expression.

Authored by David B. Zhen, MD, University of Michigan Medical Center, Ann Arbor, MI, USA

Phase I clinical trials not only allow one to study the dosing and safety of drugs but also portend opportunities for the translational investigator to develop interesting questions and ideas for hypothesis testing that then can drive the creation of further clinical research studies. Dr. Keith Flaherty outlined his steps for developing a phase I clinical trial pipeline, which involve finding a testable hypothesis, studying a drug from multiple aspects including assessment of functional/molecular characteristics, biological target effect, and clinical effect, and investigating and understanding the variable effects that may differ from results seen in pre-clinical work conducted on the drug. When conceptualizing this approach as a continuous process, the number of potential interesting research questions and studies is potentially endless. As an example, Dr. Flaherty presented his interesting experience and novel research on the development of BRAF inhibitors for treatment of melanoma, starting from his early work initially evaluating the molecular and clinical effects of sorafenib and continuing with how persistent inquisition led to the eventual production of vemurafenib, which has now become a standard of care of treatment in melanoma. As such, Dr. Flaherty’s presentation as well as the experience gained at STOFF has helped me to expand upon my thought process of clinical trials and better understand how to seek interesting avenues in my own work as I develop a career in translational research.