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Presentation Title: The Discovery of KIN-2787, a solution to the challenges of pan-RAF kinase inhibition.

Abstract: The initial target of BRAF drug discovery programs was the V600E mutation (Class 1), which is an active kinase monomer. Surprisingly, the first generation of "inhibitors" paradoxically activated RAF dimers, resulting in increased pMEK, hyperproliferative toxicities in vivo, and unacceptable single-agent toleration in the clinic. The three marketed RAF inhibitors are only approved in combination with a MEK inhibitor, which serves to counteract the paradoxical activation in normal tissues. Significant drug discovery attention has turned to targeting dimeric BRAF alterations (Class II & III), which have a combined estimated prevalence similar to Class I alterations. However, achieving this inhibition profile with a molecule that has suitable biopharmaceutical properties that can maintain target coverage in the clinic has proven challenging. This presentation will describe the discovery of KIN-2787, which is a highly selective and potent pan-RAF dimer inhibitor with demonstrated anti-tumor efficacy in preclinical models with BRAF Class II, III and NRAS alterations and an encouraging safety profile in toxicology studies.