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PI3K inhibitors as promising cancer therapeutics: Lessons learned and approaches to clinical trial design

Raoudha Soufi-Mahjoubi

Novartis Pharmaceuticals Corporation, USA

Activation of the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway in cancer is associated with tumor growth, progression, and the development of resistance to anticancer therapy. PI3K is therefore a promising target for drug development. Various PI3K inhibitors are currently under evaluation in clinical trials, including the pan-PI3K inhibitor buparlisib (BKM120) and the PI3K α -specific inhibitor alpelisib (BYL719). Early clinical studies with these compounds indicated the safety profiles were manageable, with mostly on-target adverse events, such as hyperglycemia. Early signs of clinical activity were also observed. However, consistent with preclinical models suggesting PI3K inhibition can overcome resistance to other anticancer drugs, the greatest opportunities for these compounds appear to be in combination, particularly with endocrine and other targeted therapies. Buparlisib is currently being evaluated in various combinations in Phase III studies in breast cancer, including BELLE-2 and BELLE-3, and Phase II studies in other indications. Alpelisib is being evaluated in combination in Phase II studies in breast cancer and head and neck cancer, among other indications. As these compounds advance through clinical development, several questions remain. In particular, which PI3K inhibitor is likely to be most effective in which tumor type, and what biomarker will predict the patient population most likely to benefit from PI3K inhibitor therapy? Novartis is employing a flexible approach to biomarker-driven study design to address these questions and maximise the benefits of clinical studies with buparlisib and alpelisib. An overview of the Novartis PI3K inhibitor program utilising these approaches in different cancers will be described.

Biography

Raoudha Soufi-Mahjoubi MD is Senior Medical Director of US Oncology at Novartis Pharmaceutical Corporation. She obtained her medical degree from Faculté de Médecine, Tunis and specialized in Medical Oncology at Université René Descartes, Paris. She has academic experience in medical oncology, and has 18 years of experience in the pharmaceutical industry with a strong expertise in clinical research and drug development in oncology.

raoudha.mahjoubi@novartis.com