5-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (PQR309), a Potent, Brain-Penetrant, Orally Bioavailable, Pan-Class I PI3K/mTOR Inhibitor as Clinical Candidate in Oncology

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Author(s) Beaufils, Florent; Cmiljanovic, Natasa; Cmiljanovic, Vladimir; Bohnacker, Thomas; Melone, Anna; Marone, Romina; Jackson, Eileen; Zhang, Xuxiao; Sele, Alexander; Borsari, Chiara; Mestan, Jurgen; Hebeisen, Paul; Hillmann, Petra; Giese, Bernd; Zvelebil, Marketa; Fabbro, Doriano; Williams, Roger L.; Rageot, Denise; Wymann, Matthias P.

Author(s) at UniBasel Wymann, Matthias P. ;
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Phosphoinositide 3-kinase (PI3K) is deregulated in a wide variety of human tumors and triggers activation of protein kinase B (PKB/Akt) and mammalian target of rapamycin (mTOR). Here we describe the preclinical characterization of compound 1 (PQR309, bimiralisib), a potent 4,6-dimorpholino-1,3,5-triazine-based pan-class I PI3K inhibitor, which targets mTOR kinase in a balanced fashion at higher concentrations. No off-target interactions were detected for 1 in a wide panel of protein kinase, enzyme, and receptor ligand assays. Moreover, 1 did not bind tubulin, which was observed for the structurally related 4 (BKM120, buparlisib). Compound 1 is orally available, crosses the blood brain barrier, and displayed favorable pharmacokinetic parameters in mice, rats, and dogs. Compound 1 demonstrated efficiency in inhibiting proliferation in tumor cell lines and a rat xenograft model. This, together with the compound's safety profile, identifies 1 as a clinical candidate with a broad application range in oncology, including treatment of brain tumors or CNS metastasis. Compound 1 is currently in phase II clinical trials for advanced solid tumors and refractory lymphoma.

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