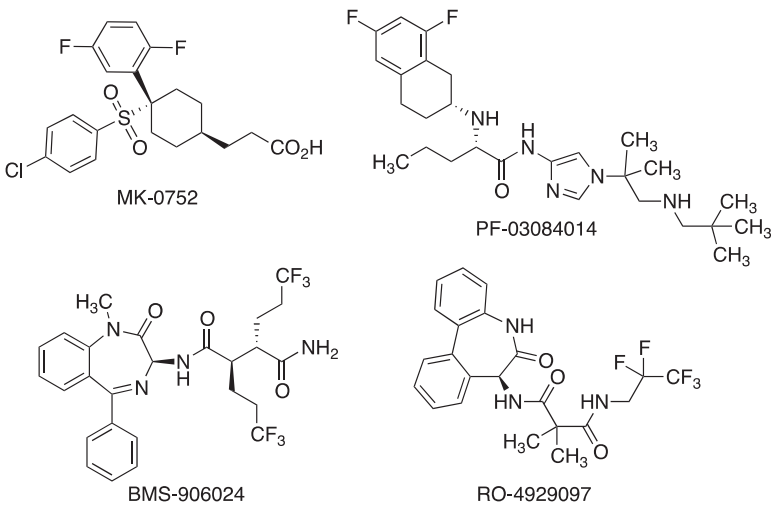
found in more than 50% of patients with this disease. Although a phase I clinical trial in these patients revealed an unfavorable toxicity profile related to inhibition of Notch signaling in the gut there are several ongoing clinical studies involving MK-0752—alone or in combination with tamoxifen, docetaxel, or letrozole—in breast cancer.[126]

Other studies have shown that intermittent doses reduce the toxicity associated with PF-03084014, another selective GSI,[127] and that combination therapies and glucocorticoid treatment increase the antileukemic effects of different pan-Notch inhibitors, ameliorating its intestinal toxicity. The combination of PF-03084014 with docetaxel demonstrated early stage synergistic apoptosis, which provides a strong preclinical rationale for its clinical utility to improve taxane therapy.[128] The benzodiazepine pan-Notch inhibitor BMS-906024[129] is other GSI that has entered clinical trials alone or in combination to treat leukemia and breast, lung, and colon cancers. RO4929097 is another GSI that has entered clinical trials of patients with refractory metastatic or locally advanced solid tumors.[130]



The limitations of GSIs in the clinic have suggested the use of synthetic peptides to block the Notch transcriptional complex directly in the cell nucleus[131] or the use of highly specialized antibodies that block the receptor in an "off" conformation.[132] Several of these antibodies have undergone phase I/II clinical trials, including OMP-59R5, OMP-52 M51, and MEDI0639.

Furthermore, because activation of Notch receptors by the vascular-specific ligand DLL4 (delta-like 4) stimulates the proteolytic cleavage of the Notch intracellular domain, targeting DLL4 provides an alternative way to inhibit the Notch pathway.[133] Demcizumab (OMP-21 M18) is a humanized monoclonal antibody directed against the N-terminal end of DLL4 that received orphan drug status from the FDA in 2014 for the treatment of pancreatic cancer.

7.3 HEDGEHOG SIGNALING/SMO RECEPTOR INHIBITORS

Hedgehog (Hh) signaling has been found to play multiple roles in the proper development of embryonic cells and adult organ homeostasis and repair, and its activation is linked to tumorigenesis of several cancers.[134] Data from many tumors, including glioblastoma, pancreatic adenocarcinoma, breast