penetrance rate is high (conferring approximately 80% lifetime risk of CRC). These proteins form specific heterodimers, for example, MutSα (MSH2-MSH6) functions in DNA mismatch/damage recognition, and MutLα (MLH1-PMS2) functions as an endonuclease, and in the termination of mismatch-provoked excision.[6] Per CAP Colon and Rectum Protocol (Version: ColonRectum 3.4.0.0), MMR deficiency is prognostic for patient outcome, as a screening tool for HNPCC/Lynch syndrome, and as a predictive marker of response/resistance to specific chemotherapy.[7] Detecting MMR deficiency by IHC remains the first-line screening test in all newly diagnosed CRC or endometrial cancer cases; it directs the course of additional molecular diagnostic testing.[3,4,8] This patient showed loss in expression of MSH2 and MSH6 proteins. Per CAP guidelines, the next steps entailed sequencing germline *MSH2*—if this was found negative, then evaluation of *EPCAM* deletion, methylation of *MSH2* promoter, and sequencing of germline *MSH6* should follow.[7] However, these were not carried out in the index case.

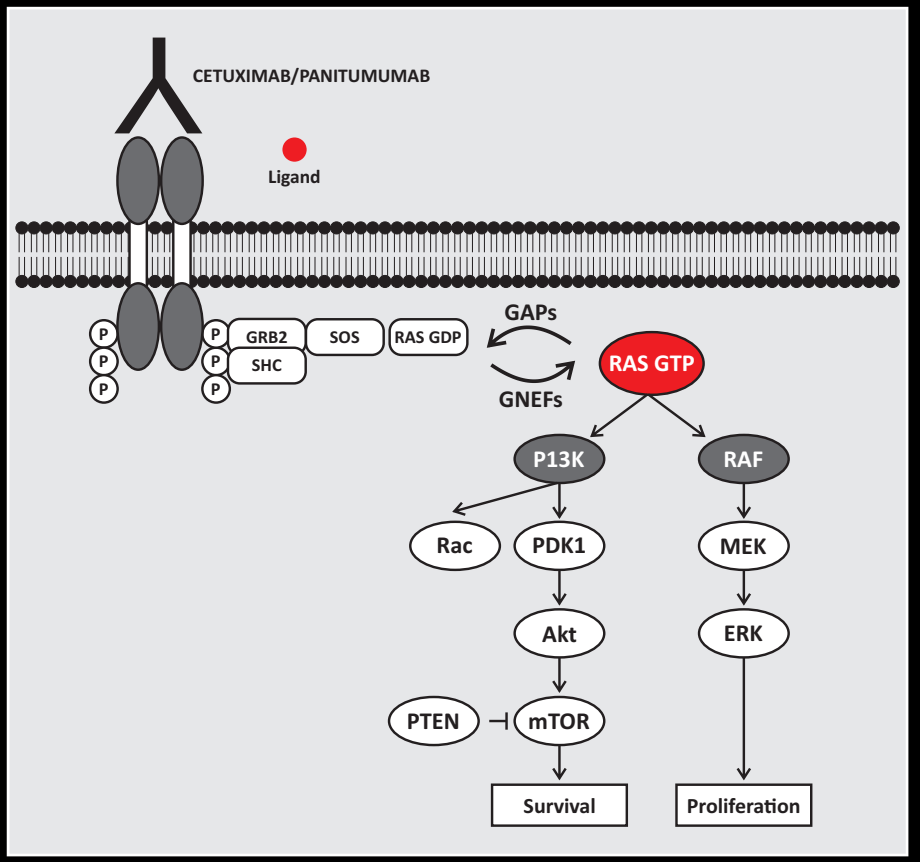

Figure 6: EGFR signaling pathways in CRC [Modified from Normanno et al. Nat Rev Clin Oncol, 2009]. Ligand binding to EGFR leads to activation of downstream pathways, including MAPK pathway (RAS-RAF-MEK-ERK) and the PI3K pathway (PI3K-AKT-mTOR). Both these pathways are critical in regulating cellular processes in cancer. EGFR MoAb prevent ligand binding and, therefore, downstream activation of these pathways. GAP = guanosine triphosphatase-activating proteins; GDP = guanosine diphosphate; GEF = guanine exchange factors; GTP = guanosine triphosphate; Cetuximab/Panitumumab = anti-EGFR monoclonal antibodies

Aberrations in several genes, and signaling pathways have been implicated in CRC. The epidermal growth-factor receptor (EGFR) pathway remains a cornerstone in CRC pathogenesis.[9] The three *RAS* isoforms *[KRAS, NRAS,* and *HRAS]* encode small GTPases, which shuttle between inactive guanosine diphosphate (GDP)-bound and active guanosine triphosphate (GTP)-bound forms.[10] They function in transducing signals from EGFR to downstream effectors including the PI3K-AKT-mTOR pathway, and RAS-RAF-MEK-ERK pathway. The RAS proteins play pivotal role in regulating cellular growth, survival, differentiation, migration, adhesion, and cytoskeletal integrity. Activating mutations in RAS proteins