Pancreatic ductal adenocarcinoma (PDAC) is almost universally fatal. The annual number of deaths equals the number of newly diagnosed cases, despite maximal treatment. The overall 5-year survival rate of <5% has remained stubbornly unchanged over the last 30 years, despite tremendous efforts in preclinical and clinical science. There is unquestionably an urgent need to further improve our understanding of pancreatic cancer biology, treatment response and relapse, and to identify novel therapeutic targets. Rigorous research in the field has uncovered genetic aberrations that occur during PDAC development and progression. In most cases, PDAC is initiated by oncogenic mutant KRAS, which has been shown to drive pancreatic neoplasia. However, all attempts to target KRAS directly have failed in the clinic and KRAS is widely assumed to be undruggable. This has led to intense efforts to identify druggable critical downstream targets and nodes orchestrated by mutationally activated KRAS. This includes context-specific KRAS effector pathways, synthetic lethal interaction partners and KRAS-driven metabolic changes. Here, we review recent advances in oncogenic KRAS signalling and discuss how these might benefit PDAC treatment in the future.