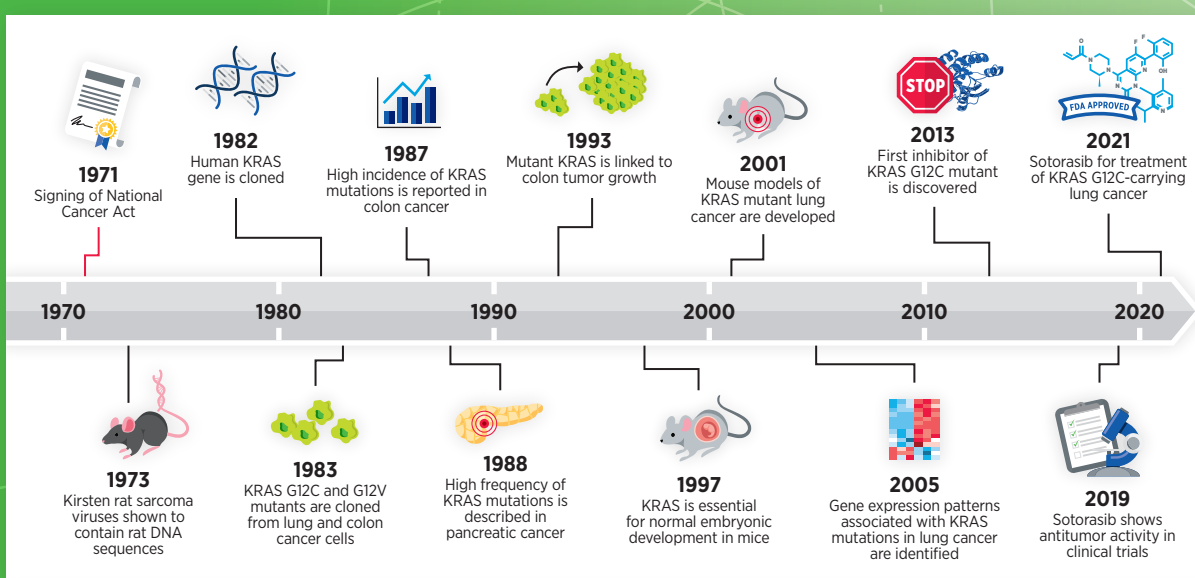


FIGURE 20

NATIONAL CANCER ACT
50 YEARS
 1971-2021

50 YEARS OF MILESTONES IN THE JOURNEY TO TARGET THE UNDRUGGABLE KRAS



Five decades of research led to the development and approval of sotorasib in May 2021. The relationship between RAS genes and lung cancer was first described in 1984, and subsequent discoveries led to the development of direct and indirect inhibitors of KRAS activity. The first clinical trials investigating the efficacy of indirect KRAS inhibitors were carried out in the early 2000s. Since then, many KRAS inhibitors have been developed and tested. Targeting KRAS with small molecular inhibitors has been particularly

challenging because the protein was considered to lack an accessible or “druggable” pocket when present in its three-dimensional form in the cells. With the dawn of precision medicine and availability of deeper insights into the mutational landscape of lung cancer, a renewed enthusiasm and biological and clinical progress have led to the development of sotorasib (Lumakras), which was approved in May 2021 by FDA based on promising results from preclinical and clinical studies.