RNA Interference is Progressing Toward Commercialization – the Case of Phase 2 in Pancreatic Cancer

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Drugs based on RNA interference (RNAi) are evolved to advanced clinical and approval stages. Following a successful Phase 1 clinical trial, the siG12D-LODER has entered recently to a phase 2 trial in Memorial Sloan Kettering (NY), and, pending interim results will be extended to full confirmatory Phase 2/3 trial. The RNAi-based drug siG12D has demonstrated in-vivo effective targeting of the well-known 'undrugable' oncogene KRAS, and early efficacy evidence in humans. Formulation of siG12D within the polymeric matrix named LODER (LOcal Drug EluteR) resulted in continuous RNAi-drug release over 3-4 months, enabling a permanent drug distribution over the entire tumor. In addition to targeting KRAS, LODER solved the major challenge of impermeability of the tumor microenvironment (TME). Recent findings also suggest that the siG12D-LODER therapy may convert 'immune privilege' conditions in tumors to a 'hot' TME enriched by anti-tumor cytokines. LODER can encourage infiltration of macrophages, NK/NKT-cells and lymphocytes, and improve penetration of mABs. With such a multiple effect on TME the siG12D-LODER potentially can raise the response of solid tumors to immuno-oncology (IO) drugs such as PD-1/PDL-1 and CTLA-4 checkpoint blockers and CAR-T therapies. Specifically, no clear patient response has been observed in the clinical studies in pancreatic tumors designed to assess the efficacy of PD1 and of CTLA-4 blockers. Two Phase 2 clinical studies in pancreatic cancer of siG12D-LODER with concomitant standard chemotherapies or IO drugs are in preparation. RNAi-drugs for additional solid tumor indications, including siHSP90 for prostate cancer, are now in pre-clinical development stages.