Introduction

The recent accelerated approval of the KRASG12C mutant-selective inhibitor Adagrasib (MRTX849) has ignited considerable interest in the development of approved therapies for KRASG12C mutant NSCLC. However, resistance has already been observed in clinical trials, including the SOS1::KRAS inhibitor BI 1701963. The pan-KRAS SOS1 inhibitor BI 1701963 is the first direct RAS signaling modifier in phase I and II clinical trials.

Published data on acquired KRASG12C resistance

- Deep mutational screening allows prediction of clinically relevant mutations
- Vertical (e.g. SOS1i or SHP2i + KRASG12Ci) and parallel pathway inhibitors (e.g. PI3Ki or mTOR + KRASG12Ci) appear promising
- FGFR1 expression is up-regulated in resistant tumors

On-Target KRASG12C Inhibitor Resistance Profiling

- Sotorasib treatment in patients

Mapping in vivo KRASG12C-induced Resistance

- DUSP6 down-regulation is maintained in KRASG12C-resistant SW837 tumors
- FGFR1 expression is up-regulated in resistant tumors
- Tumor microenvironment changes

Strategy to Overcome KRASG12C Resistance

- In the SW837 (CRC) xenograft, Adagrasib (SOS1i)-induced resistance can be overcome by S256D (1701963) (Adagrasib) combination
- Selectors of CRASG12C inhibitors (e.g. Adagrasib) and overcoming resistance to oncoprotein inhibitors in solid tumors and melanoma: KEY viewpoints

Discussion

- ERK1/2 signaling is strongly associated with resistance mechanisms in both in vitro and in vivo setting
- Compounds that inhibit ERK1/2 signaling or suppress resistance to oncoprotein inhibitors in solid tumors and melanoma: KEY viewpoints
- Key findings and conclusions

On the resistance mechanisms of KRASG12C mutant NSCLC to treatment with Adagrasib (MRTX849): Biologic characterization and resistance profi le

- KRASG12C mutation is an effective target for treatment of NSCLC
- Adagrasib (MRTX849) is a potent and selective inhibitor of KRASG12C
- Resistance to KRASG12C inhibitors is associated with high-level KRASG12C expression
- The pan-KRAS inhibitor BI 1701963 reduces KRASG12C expression and resistance
- Key findings and conclusions