CLINICAL UPDATE ON K-RAS TARGETED THERAPY IN GASTROINTESTINAL CANCERS

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SELECTED HIGHLIGHTS

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KEY MESSAGES

- *KRAS*-mutant pancreatic and colorectal cancer is common and remains very difficult to target
- Direct inhibition of K-Ras has been demonstrated in preclinical studies, but the path to the clinic is likely to be long
- Targeting signalling pathways downstream of Ras has been largely unsuccessful
- Combining MEK inhibitors with novel targeted agents may improve efficacy
- Immunotherapy has shown clinical promise in *KRAS*-mutant gastrointestinal cancers

BACKGROUND

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- Ras proteins are small guanosine triphosphatases (GTPases) with a key role in regulating cell proliferation and survival[1]
- The *RAS* gene has three isoforms: *HRAS*, *NRAS* and *KRAS*.[2] Activating *KRAS* mutations occur in 57% of pancreatic and 33% of colon cancers (COSMIC database).[2]
- *KRAS* mutations are associated with non-response to anti-epidermal growth factor receptor therapy in colorectal cancer (CRC)[3]
- Efforts to develop a drug targeting aberrant Ras function have been notably unsuccessful, but insights into the structure, function, and signaling of K-Ras have led to renewed optimism[4]
- **This review highlights progress in the development of new agents directly or indirectly targeting K-Ras in CRC and pancreatic cancer**. The next slide depicts the wide-ranging strategies under investigation.

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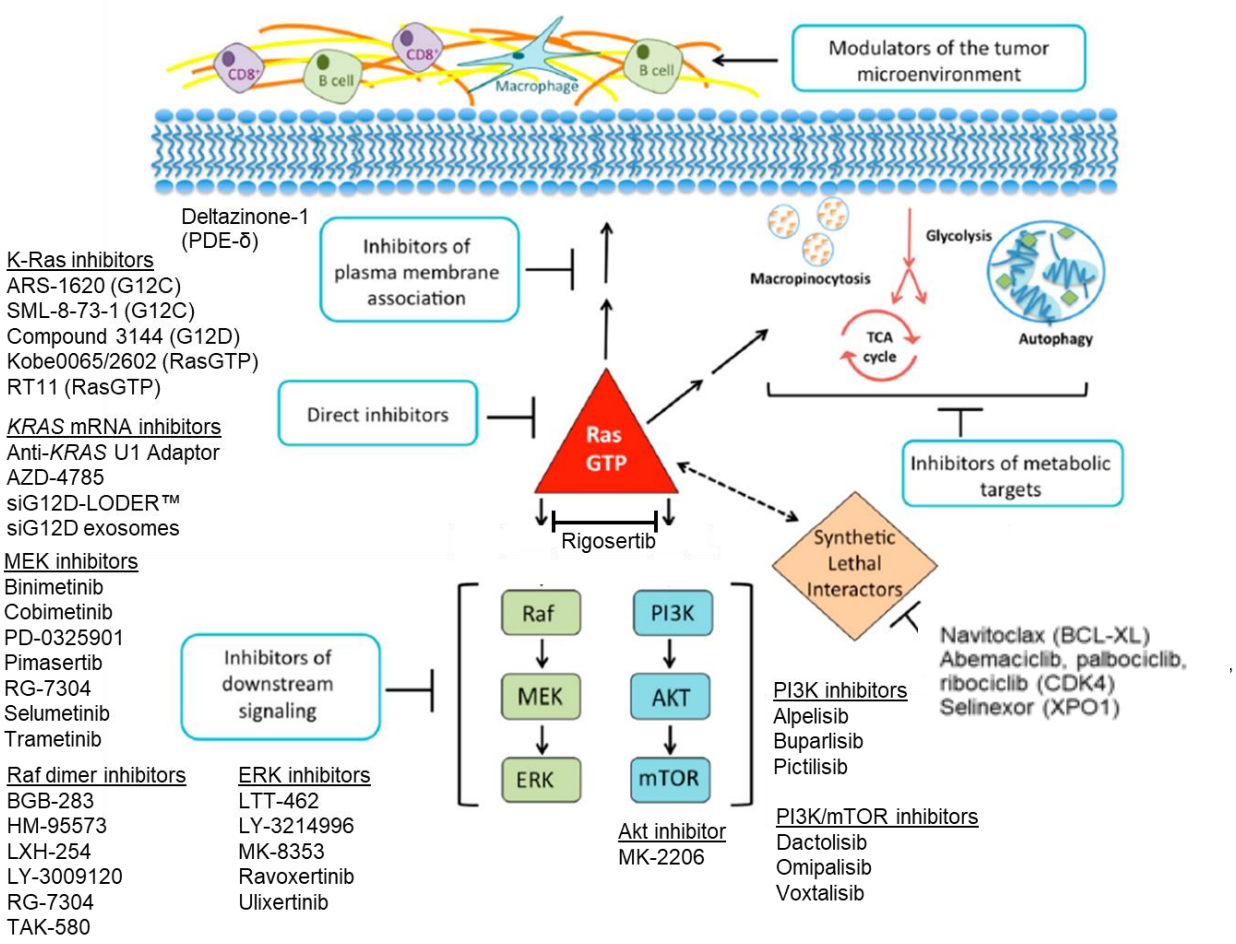
STRATEGIES FOR TARGETING K-RAS



TARGETING THE MAPK PATHWAY: RAF, MEK and ERK

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- **RAF**: Selective B-Raf inhibitors (e.g. vemurafenib) can stimulate the growth of *RAS*-mutant tumors,[1,2] but pan-Raf inhibitors may have potential in *KRAS*-mutant CRC[3]
  - Phase 1: BGB-283, HM-95573, LY-3009120, LXH-254, TAK-580
- **MEK**: Resistance to MEK inhibitors limits their use as monotherapy.[4] Numerous trials are testing strategies for combined inhibition:
  - Dual MAPK targets (e.g. MEK + C-Raf)
  - Inhibition of MEK plus growth factor receptors, PI3K signaling molecules or novel targets
- **ERK:** Phase 1 trials are investigating ulixertinib in pancreatic cancer and LY-3214996 in *RAS*-mutant CRC and pancreatic cancer

MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase

1. Oberholzer PA, et al. J Clin Oncol. 2012;30(3):316-21; 2. Callahan MK, et al. N Engl J Med. 2012;367(24):2316-21;
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TARGETING THE PI3K PATHWAY

- Agents targeting **PI3K**, **Akt** and/or **mTOR** have been largely disappointing, perhaps due to resistance mechanisms[1,2]
  - These may include negative feedback loops, compensatory networks and cross-talk between signaling pathways[1]
- Preclinical studies provide support for **dual inhibition of the MAPK and PI3K pathways** in *KRAS*-mutant CRC and pancreatic cancer,[3,4] but early clinical results are not promising[5-9]
  - Pancreatic cancer patients randomized to the MEK inhibitor selumetinib plus the Akt inhibitor MK-2206 had significantly worse overall survival versus patients randomized to chemotherapy (median 3.9 vs 6.7 months)[9]

mTOR, mammalian target of rapamycin

1. Sartore-Bianchi A, et al. Ann Oncol. 2016 Sep;27(9):1746-53; 2. Brown JS, Banerji U. Pharmacol Ther. 2017;172:101-15; 3. Temraz S, et al. Int J Mol Sci. 2015;16(9):22976-88; 4. Ning C, et al. Oncotarget. 2017;8(27):44295-311; 5. Heist RS, et al. Annals of Oncology. 2014;25(Suppl_4):iv146–iv7;
6. Grilley-Olson JE, et al. Invest New Drugs. 2016;34(6):740-9; 7. Do K, et al. Invest New Drugs. 2015;33(3):720-8; 8. Tolcher AW, et al. Clin Cancer Res. 2015;21(4):739-48; 9. Chung V, et al. JAMA Oncol. 2017;3(4):516-22.

IMMUNOTHERAPY

- Peptides derived from mutant K-Ras have the potential to be used as 'neoantigen' targets for immunotherapy, a strategy that has been actively pursued in pancreatic cancer[1]
- Commercially developed **Ras peptide vaccines** include GI 4000 (phase 2 trial completed),[2,3] TG01[4,5] and TG02
  - Promising long-term survival and immune response was reported in patients vaccinated after pancreatic cancer resection[2-4]
- **Adoptive T-cell therapy** using Ras-specific lymphocytes resulted in a clinically meaningful response in a patient with metastatic CRC[6]

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NOVEL APPROACHES

- **MEK inhibitors** combined with new targeted agents
  - **Cyclin-dependent kinase inhibitors**: preclinical activity against *KRAS*-mutant CRC and pancreatic tumors;[1-3] clinical trial of trametinib plus ribociclib initiated
  - **Navitoclax** (anti-apoptotic protein BCL-XL inhibitor): significant preclinical efficacy;[4] clinical trial of trametinib plus navitoclax in *KRAS*-mutant CRC and pancreatic cancer ongoing
- **Targeting integrin signaling** demonstrated preclinical activity against pancreatic cancer xenografts in mice[5,6]
- **Targeting nuclear export**
  - Selinexor, an exportin-1 (XPO1) inhibitor, showed synergistic activity with gemcitabine in a mouse pancreatic cancer model[7]
  - Clinical trials are now evaluating selinexor combined with chemotherapy in mCRC and pancreatic cancer

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