CLINICAL UPDATE ON K-RAS TARGETED THERAPY IN GASTROINTESTINAL CANCERS

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SELECTED HIGHLIGHTS

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Please note:

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• 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

• Ras proteins are small guanosine triphosphatases (GTPases) with a key role in regulating cell proliferation and survival\(^1\)
• The \textit{RAS} gene has three isoforms: \textit{HRAS}, \textit{NRAS} and \textit{KRAS}.\(^2\) Activating \textit{KRAS} mutations occur in 57\% of pancreatic and 33\% of colon cancers (COSMIC database).\(^2\)
• \textit{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.

STRATEGIES FOR TARGETING K-RAS

K-Ras inhibitors
ARS-1620 (G12C)
SML-8-73-1 (G12C)
Compound 3144 (G12D)
Kobe0065/2602 (RasGTP)
RT11 (RasGTP)

KRAS mRNA inhibitors
Anti-KRAS U1 Adaptor
AZD-4785
siG12D-LODER™
siG12D exosomes

MEK inhibitors
Binimetinib
Cobimetinib
PD-0325901
Pimasertib
RG-7304
Selumetinib
Trametinib

Raf dimer inhibitors
BGB-283
HM-95573
LXH-254
LY-3009120
RG-7304
TAK-580

ERK inhibitors
ERK inhibitors

PI3K inhibitors
Alpelisib
Buparlisib
Pic替lisib

PI3K/mTOR inhibitors
Dactolisib
Omisalisib
Voxalisib

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TARGETING THE MAPK PATHWAY: RAF, MEK and ERK

- **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

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

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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\textsuperscript{1}
- Commercially developed \textbf{Ras peptide vaccines} include GI 4000 (phase 2 trial completed),\textsuperscript{2,3} TG01\textsuperscript{4,5} and TG02
  - Promising long-term survival and immune response was reported in patients vaccinated after pancreatic cancer resection\textsuperscript{2-4}
- \textbf{Adoptive T-cell therapy} using Ras-specific lymphocytes resulted in a clinically meaningful response in a patient with metastatic CRC\textsuperscript{6}

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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