Orchestrating the KRAS Pathway to Benefit Patients

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Multiple biopharma companies and biotechs are playing in the KRAS space, which is underscored by the fact that at AACR 2022, ~350 presentations were made on the KRAS pathway.

This frenzy of development is an indication that nobody wants to be left behind in the pursuit of a now "druggable" target, especially as some upstream KRAS pathway inhibitors (e.g. SHP2/SOS1) are also a "hot" target with the potential of being the backbone treatment for RASopathy driven tumors.

Within the KRAS mutations, the 1st generation KRASG12C inhibitors, sotorasib and adagrasib, are poised for use in pre-treated NSCLC patients. At the same time, the KRASG12C mutant patients have persisting unmet needs as less than half of the patients respond to these therapies (unlike other targeted therapies in NSCLC) and there is a rapid onset of adaptive resistance.

Next generation KRASG12C inhibitors and several combination approaches are being evaluated to address the gaps with the 1st generation agents

- Upstream targets of KRAS (SHP2, SOS1 etc.)
- Downstream targets of KRAS (MEK, ERK etc.)
- Parallel pathways leading to apoptosis (CDK4/6, MCL-1 etc.)

Of all the KRAS presentations at AACR 2022, we present key highlights on effectively drugging the KRASG12C mutants, and what to expect in the next wave of KRAS pathway inhibitors – other therapeutic nodes on the pathway, combinations, and tumor genotypes. Single agent KRASG12Cis are just the tip of the iceberg of the 'undruggable KRAS' clinical development that will likely intensify with multiple therapeutic interventions emerging with potential to carve out multiple 'personalized' patient segments.

First-in-Class, Sotorasib's Clinical Benefit Validated in Long-Term Follow-Up

Interim outcomes (RR, mDOR) from 124 pre-treated NSCLC patients from CODEBREAK-100 study had led to sotorasib's accelerated approval[1]

- A 2-year analysis, now in 174 patients (~90% had a prior PD-(L)1i, demonstrated slightly better response rates of 41% (vs. earlier 36%), of which CR is ~3% and mDoR of 12.3 months (vs. earlier 10 months)
- mPFS and mOS were also impressive at 6.3 and 12.5 months, respectively
- Additionally, it was effective across PD-L1 expression levels, and also in STK11/LKB1 co-mutation, known to be resistant to immunotherapy
  - Additionally, translational research with ex-vivo treatment of tumors from KRAS-LKB1 mutant NSCLC patients showed enhanced responses to sotorasib combination with AMG 176 (MCL-1 inhibitor) vs. sotorasib alone

More (Effective) KRASG12Ci Treatment Options Lined Up

- **Clinical data on other 1st generation KRASG12Cis that target the KRAS(OFF) state included[2-4]:**
  - Novartis's JDQ443 (does not interact directly w/ H95 in the switch 2 pocket, a recognized route of resistance to adagrasib) demonstrated early signs of clinical activity in 20 NSCLC patients in the KontRASt-01 study, with an ORR of 35% across all doses, and 57% at the recommended dose (n=7), in addition to showing an acceptable safety profile
    - Translational research on combination with TNO155 (SHP2i) enhanced target occupancy and showed similar anti-tumor activity at lower doses vs. monotherapy or other combinations (e.g. MEKi)
  - Inventis Bio's G12Ci, D-1553, also demonstrated compelling data in 32 Chinese NSCLC patients at 41% RR at its RP2D

- **Additionally, combinations are attempting to address resistance seen with 1st generation KRASG12Cis with clinical data awaited, although preclinical evidence was presented[5-8]:**
  - Sotorasib + VS-6766 (RAF/MEKi) – significant inhibition of proliferation of cancer cells bearing acquired resistant mutations to 1st generation KRASG12Ci
  - Sotorasib + ERAS-601 (SHP2i) – tumor regression observed in NSCLC and CRC patient derived xenograft models vs. mono sotorasib
  - Adagrasib + BI 1701963 (SOS1i) – tumor regression in KRASG12Ci resistant animal models
  - Adagrasib + MRTX0902 (SOS1i in IND) – tumor regression in animal models vs. monotherapy

- **Next generation KRASG12Cis targeting KRAS(ON/OFF) states are trying to address the persisting unmet needs of 1st generation KRASG12Cis, as monotherapy and combinations[9-12]:**
  - ERAS-3490 (Erasca), a CNS penetrant G12Ci, has shown significant tumor regression and survival benefit in NSCLC brain metastases model
  - RMC-6291 (Revolution Medicines) displayed enhanced depth and duration of responses than KRASG12C(off) inhibitors in NSCLC preclinical models; synergy was also demonstrated with anti-PD-1 and SOS1 inhibitor combinations
  - GDC6036 (Relay Therapeutics) in combination with GDC-1971, SHP2 inhibitor, demonstrated tumor regression in xenograft models
  - Frontier Medicines' dual targeting of GDP- and GTP-bound KRASG12C inhibitor, is more potent and effective against cells with A59G mutations that render resistance to adagrasib and sotorasib

Hope for Patients with KRAS Addicted Tumors

KRASG12C inhibitors have paved the way for development of additional KRAS inhibitors (targeting allelic variants or multi-KRASi), as they provided significant learnings for drug discovery and development

- Though still in nascent stages of development, other KRAS allelic variants with encouraging translational research presented included:
  - KRASG12D mutations - MRTX1133 (KRASG12Di) + BET degrader (dBET6)[13]
  - KRASG13C mutations - RMC-8839 (KRASG13Ci) + RMC-4550 (SHP2i)[14]
- Multiple approaches to target overall KRAS mutants presented promising preclinical evidence, many of which were SHP2i and/or PD-1 combinations, such as[15-17]:
  - RMC-6236 (multi-RAS) + PD-1i
  - HBI-2376 (SHP2i) + PD-1i
  - ERAS-601 (SHP2i) + ERAS-007 (ERK1/2i)

Although it is very encouraging to see a large artillery of KRAS pathway inhibitors ready to revolutionize the future landscape of KRAS-driven cancers, the scientific evidence needs clinical validation for this class of drugs to be able to create a niche for themselves and be truly transformational for patients.

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