Before You Invest:

Lessons From What Patient Data Reveals About Drug Programs

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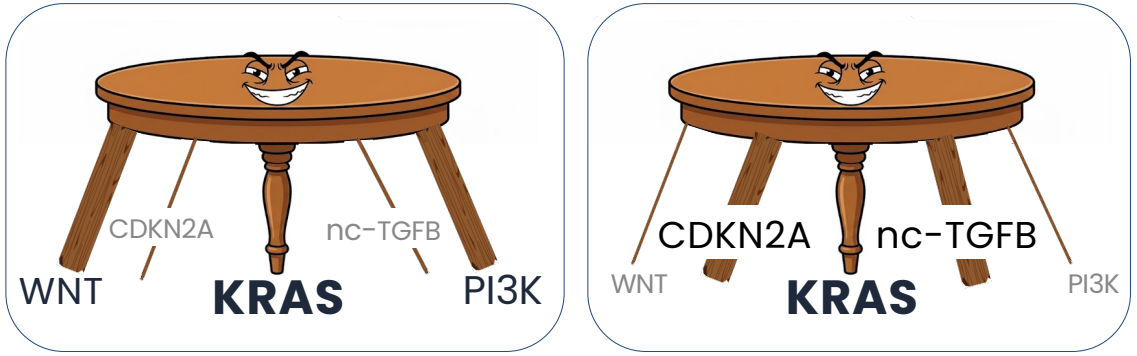
Context Is King



KRAS case study

100+

Assets targeting KRAS are currently in development

KRAS G12C inhibitors: scientific breakthrough, commercial disappointment, clinical mediocrity

The first approval of Sotorasib in 2021 was a game-changer. Yet, KRAS inhibitors suffer from moderate response rates and the rapid emergence of resistance.

In 2024, Sotorasib generated $350M in revenue. Not bad, but the hype was massive, and since 25% of all tumors carry a KRAS mutation, such a number is a disappointment.

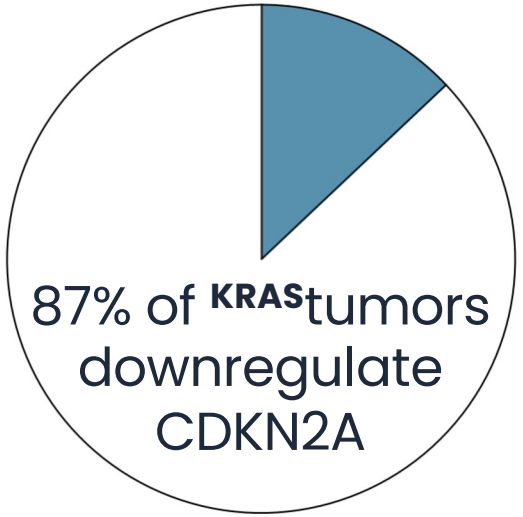
What the Patient Data Revealed

KRAS is one of the most frequently mutated oncogenes.

However, KRAS is not a solo driver.

- Inhibiting solo drivers like HER2 or EGFR translates into high clinical response rates.
- KRAS is always supported by the deregulation of other pathways. To make matters worse, in different tissues, different “support mechanisms” are deregulated.
- The effect of contributing players is very difficult to measure in cell line models. E.g., in pancreatic cancer KRAS mutation is always accompanied by the downregulation of CDKN2A. However, in tissue cultures, CDKN2A appears irrelevant for cell growth!

In pancreatic cancer 100% of KRAS mutations are accompanied by ncTGFbeta activation



ncTGFbeta (non-canonical TGFbeta signalling) is triggered when SMAD4 or TGFBR2 is downregulated and the TGFB1 signalling is redirected to its non-canonical pathway.

The Take-Home Message:

KRAS drug combinations will be tissue-specific

Cancer biology is complex

Gleevec, Herceptin and Tagrisso succeed because they inhibit solo drivers. KRAS therapy will require intelligent combinations that will be tissue-specific.

Patient data opportunity

The pathways supporting KRAS in different tissues are visible in patient data. Just take a look and design the appropriate treatment for your product. This will also assess the size of the commercial opportunity for your product.

Strategic Recommendations

From Insight to Action

Consult Patient Data for Reliable Outcomes:

- **Use patient data, not clinical trials to identify synergistic combinations**
  G12C inhibitors confirmed what patient data shows. Co-deregulated pathways drive intrinsic resistance. Drug combinations are a necessity.

- **Different strategies are required for different tissues.**
  Assess the commercial opportunity for your product in combo settings in different tissues before you enter clinical trials.

- **Patient data should be used before your trial begins.**
  There's a common misconception that clinical trials are required to assess response rates. Treatment-naive patient data can actually identify factors that limit clinical response before any patients are dosed.

Medicines intended to work in patients should be developed with patient data in mind.

For inspirations check:

https://www.gordion.bio/before-you-invest