

CONTEXT IS KING

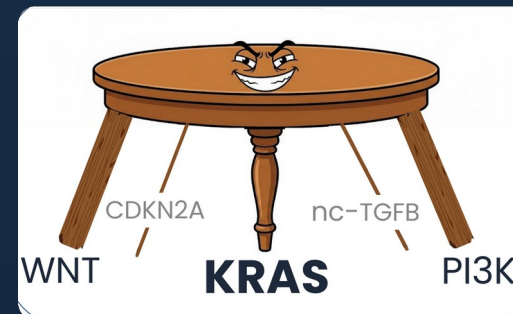
Lessons from what patient data reveals about drug programs



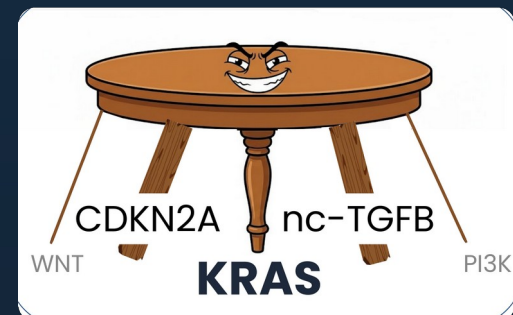
by Pawel Zawadzki, PhD

KRAS case study

Colorectal



Pancreatic



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 ncTGF β activation

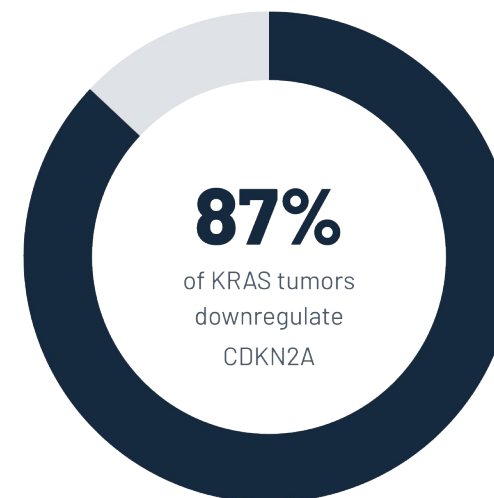


Figure 1. ncTGF β (non-canonical TGF β signalling) is triggered when *SMAD4* or *TGFBR2* is downregulated and the TGF β 1 signalling is redirected to its non-canonical pathway.

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**

01 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.

02 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.

03 Patient data should be used before your trial begins.

There's a common misconception that clinical trials are required to assess response rates. Treatment-naïve 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.**

READ MORE

gordion.bio/before-you-invest · contact@gordion.bio · linkedin.com/company/gordion-bioscience