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BEFORE YOU INVEST · DRUG PROGRAM INVESTMENT LESSONS

CONTEXT IS KING, BUT WHAT DOES IT ACTUALLY MEAN?

Lessons from what patient data reveals about drug programs

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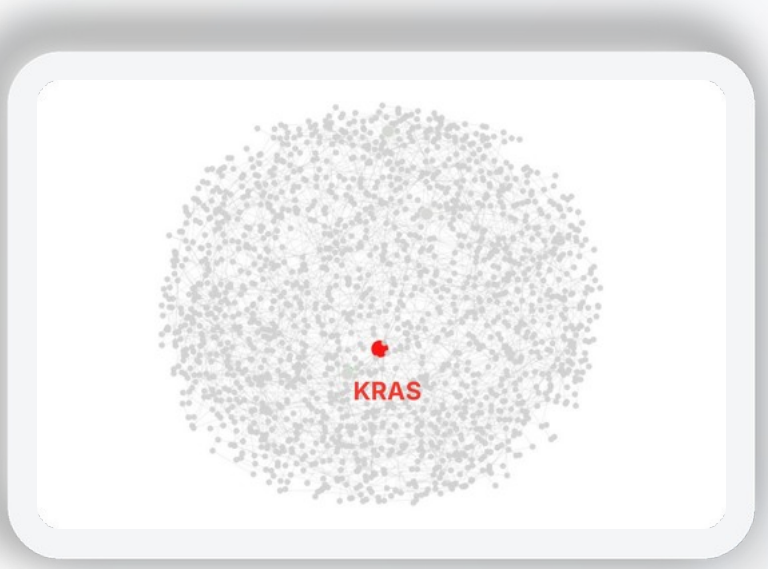
KRAS case study, part 2 · Pancreatic carcinoma

~1,700 genes

are deregulated in every single KRAS tumor



OVERWHELMING, BUT WHAT IF YOU COULD TRANSLATE THIS COMPLEXITY INTO CLINICAL RESPONSE RATES?

The majority of genes are deregulated via DNA mutations, or at the level of transcription, expression, or protein modifications.

Here is shown the complexity of the molecular context in a single patient with a *KRAS* mutation! We all silently sweep under the rug what we cannot comprehend.

But not all gene mutations are created equal. In fact, the majority are irrelevant for tumor survival. RNAseq is noisy, but when superimposed with genetic mutations, it reveals which deregulated genes and pathways are critical for tumor survival.

THREE TIERS OF MUTATIONS

1. **Mutations absolutely required by each KRAS tumor,**
2. **Mutations conditionally important,**
3. **Passenger mutations, irrelevant to the tumor.**

- Tier 1 - These translate into high clinical response rates.
- Tier 2 - These deliver low response rates and small commercial opportunities as small sub-populations respond.

If a Tier 1 mutation affects an oncogene, the job is easy. But how to exploit the vulnerability created by the inactivated tumor suppressor?

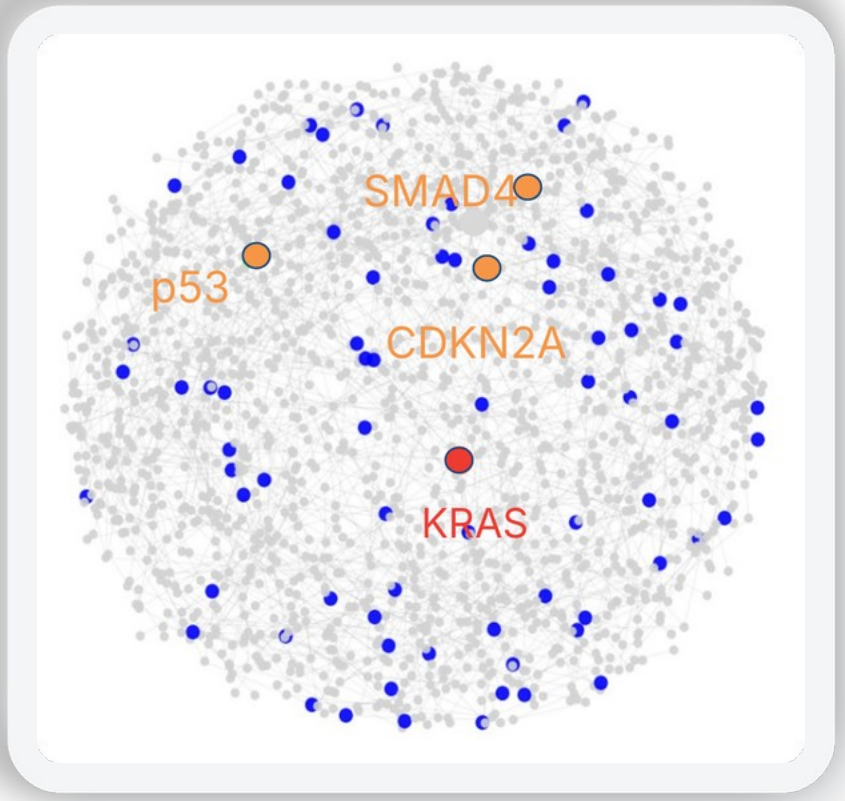


Figure 1. Separating mutations into Tiers is the key to translating cancer genomics into clinical outcomes. Pancreatic KRAS mutated tumor data is presented.

TRANSLATING TIER 1 MUTATIONS INTO CLINICAL RESPONSE RATES

Two therapeutic strategies can be used to eliminate KRAS-driven pancreatic tumors:

Tumor suppressor
Tier 1

Reactivate

Directly:
p53 reactivation (Rezatapopt) is showing some early success in the clinic.
Not applicable to CDKN2A and SMAD4.

Indirectly:
Block MDM2 (downregulates p53), inhibitors are struggling in the clinic.
Histone Deacetylase (HDAC) Inhibitors can upregulate CDKN2A, SMAD4.

Synthetic lethal approach

Synthetic Lethal targets from CRISPR screens → **Yet, no clinically validated** targets from CRISPR screens.

CDKN2A is typically deleted together with MTAP → **PRMT5** as a target for MTAP loss is underperforming in the clinic.

WHAT THE PATIENT DATA REVEALED

Multiple opportunities linked to SMAD4 were discovered.

- Patient data uncovered two strategies for SMAD4 loss: a) block factors downregulating SMAD4, b) block a strong SMAD4 synthetic lethal target.

Drugs that could leverage SMAD4 loss in pancreatic KRAS tumors are already in clinical development for completely different indications!

On top of directly inhibiting KRAS, patient data reveal several opportunities for drug combinations

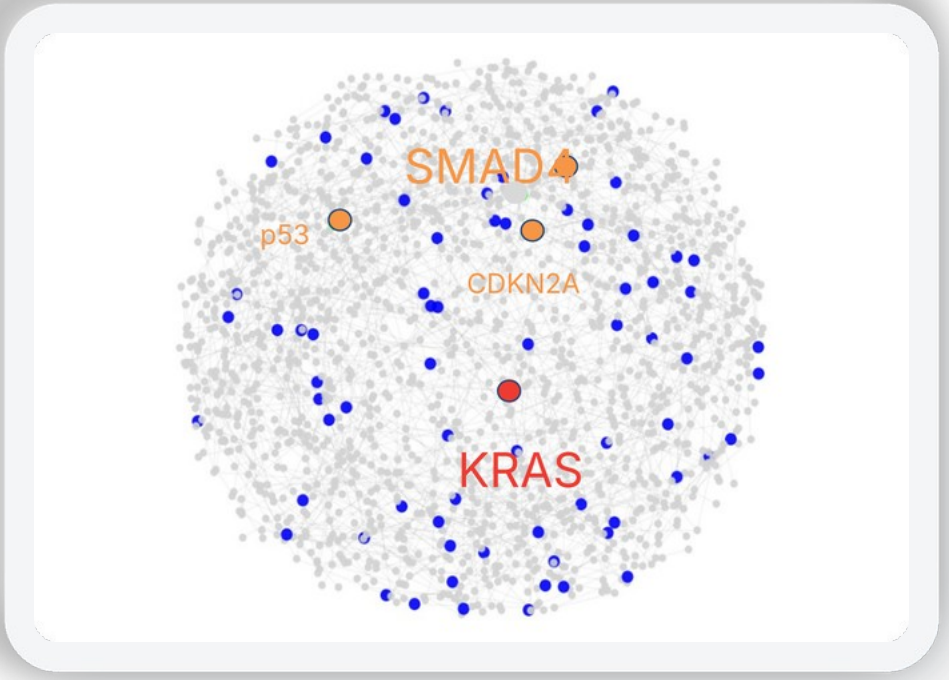


Figure 2. SMAD4 axis offers the biggest differentiation for combination therapies with KRAS inhibitors.

THE TAKE-HOME MESSAGE

KRAS COMBINATIONS WILL TRANSFORM ONCOLOGY AS WE KNOW IT

Cancer biology is complex

Today, this complexity is the reason behind a disappointing 6% success rate of oncology clinical trials. But this **complexity can be turned against cancer**.

Patient data opportunity

In pancreatic cancer, leveraging **SMAD4 dependencies offers unexpected opportunities for drug combinations with KRASi**. Some synergistic drugs are already in late clinical development.

STRATEGIC RECOMMENDATIONS

FROM INSIGHT TO ACTION

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CONSULT PATIENT DATA FOR RELIABLE OUTCOMES

01

Do not bury your head in the sand

The complexity is scary, but it can be comprehended. **Patient data + AI + smart team = breakthrough therapy**

02

Different strategies are required for different tissues.

Each tissue is different. Map all tissues, then prioritize opportunities benefiting the biggest patient population.

03

Patient data should be used before your trial begins.

Cell line models are typically used to design drug combinations. Here, we show that the treatment-naive patient data can identify synergistic drug combinations that will improve clinical response rates and durability.

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

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