Before You Invest:

Lessons From What Patient Data Reveals About Drug Programs

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When pre-existing RESISTANCE kills an attractive drug program.

Case Study

The MDM2

$1B+

Invested by multiple companies

A Costly Failure

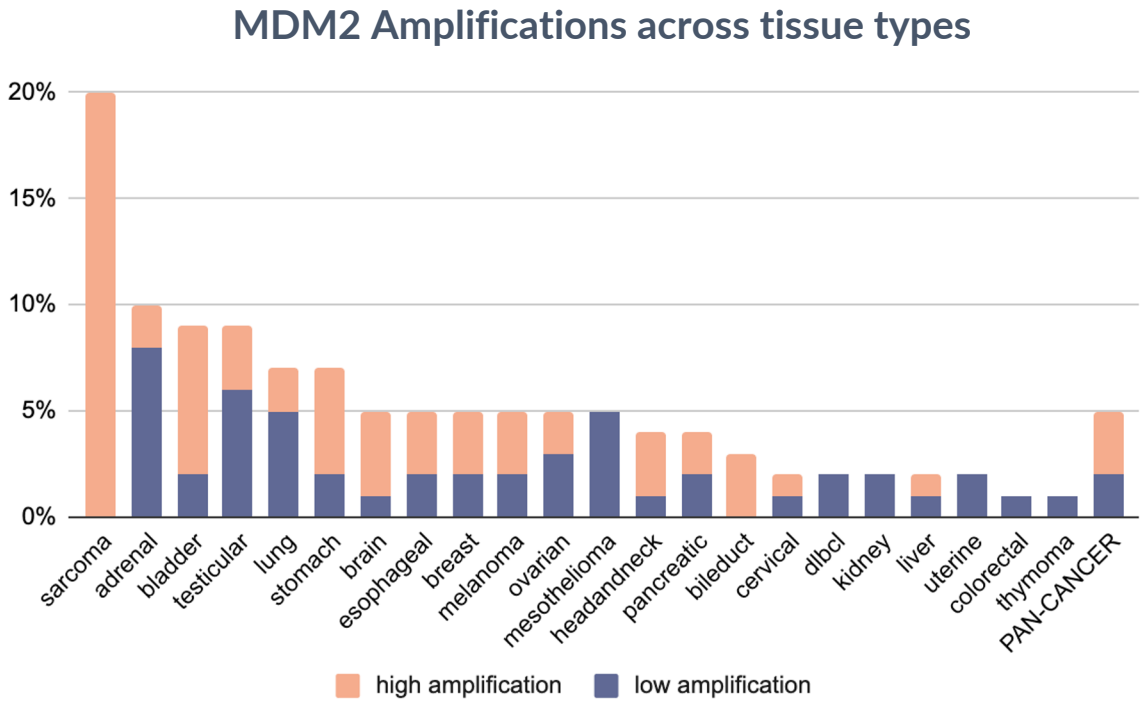
Despite massive investment from multiple companies, clinical trials for MDM2 inhibitors have repeatedly shown minimal benefits for cancer patients.

Strong data from preclinical models was actually validated by patient data. What was missed by the preclinical models was a preexisting resistance that dramatically reduced the response rates.

What the Patient Data Revealed

Patient data uncovered two resistance mechanism present in patient before the treatment even began:

- One resistance mechanism (via MDM4) was known, another (hotspot TP53 mutations) was revealed by patient data.
- Patient data also revealed that MDM2 amplifications are very early events in tumor evolution, providing time for the accumulation of MDM4 or TP53 mutations, which effectively killed the MDM2 programs.
- The resistance mechanisms are virtually impossible to discover in preclinical models, and clinical trials are used to identify them. It doesn't have to be this way.



Consistent with clinical results, data from patients show that Sarcoma is the most likely tissue to deliver clinical benefits. Unfortunately, the two resistance mechanisms reduced the response rates, effectively killing the MDM2i category.

The Take-Home Message:

If resistance exists before treatment, no molecule can fix it

The flaw of preclinical models

Preclinical models simply do not allow for the observation of the true complexity of real tumors, often missing important factors like intrinsic resistance that dramatically reduce clinical response rates.

Patient data opportunity

Data from patients not treated with your inhibitor can reveal the resistance mechanisms. Yes, you will need a sophisticated computational approach, but it can be done before you dose your first patient.

Strategic Recommendations

From Insight to Action

Consult Patient Data for Reliable Outcomes:

Preclinical models are good for some stuff, not the other.

The models are important, but it is equally important to remember what they do not see.

If resistance exists before treatment, no molecule can fix it.

Use patient data to assess PoS and also the commercial potential.

A correct patient selection strategy could save your drug program.

Patient data should be used before your trial begins.

There is a false assumption out there that to discover resistance, you need to run a trial! Not really, as treatment-naive patient data allow detection of the majority of intrinsic resistance mechanisms.

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

Full MDM2 report available at:

https://www.gordion.bio/portfolio-optimization