Before You Invest:

Lessons From What Patient Data Reveals About Drug Programs

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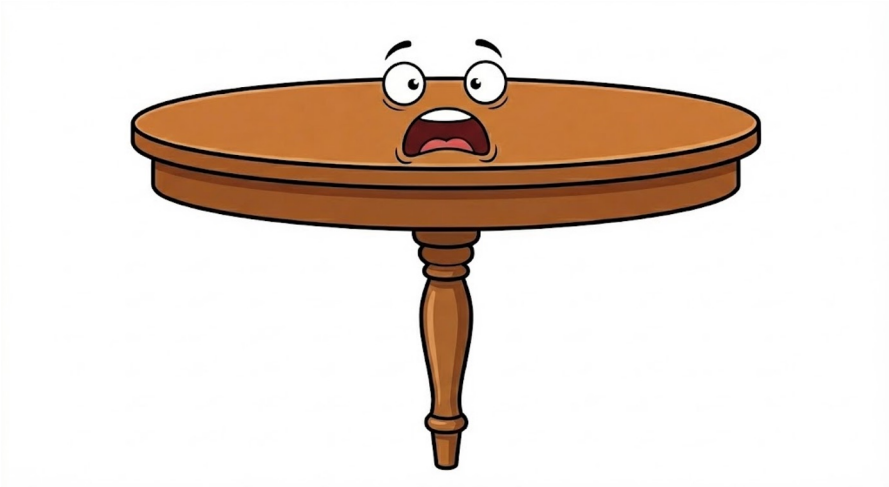
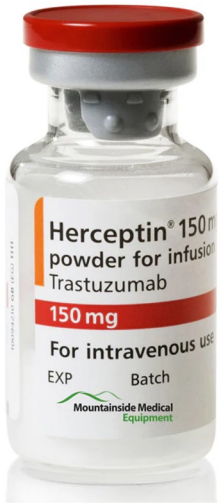
The best target I have ever seen



HER2, the soloist

$100B+

Generated by trastuzumab since approval in 1998



An unexpected success story

HER2 is not the most frequently activated oncogene, nor is it the most highly expressed drug target in cancer.

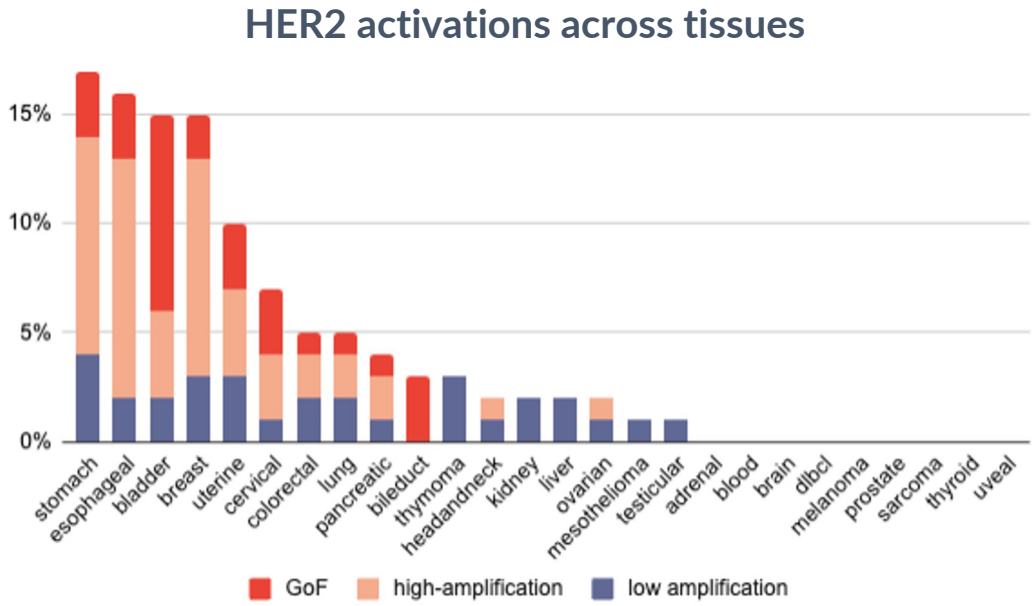
So what went right?

It is the same factor that made Gleevec so wildly successful. HER2 is a solo driver, particularly so in breast cancer.

What the Patient Data Revealed

Patient data uncovered that HER2 is a good drug target.

- HER2 is frequently activated, particularly in breast, stomach, bladder and esophageal tumors.
- Importantly, beyond activating Gain-of-Function mutations, high-level amplifications (>6 additional gene copies) are frequent. These parameters characterize good drug targets.



GoF (Gain-of-Function) mutation; high amplification (≥7 additional HER2 gene copies); low amplification (2-6 additional gene copies).

What the Patient Data Revealed

More importantly, HER2 is a solo driver in breast cancer, but much less so in stomach cancer.

- Clinical response rates to trastuzumab are very high, but why are they stronger in breast cancer than in other tissues?
- Bypass alterations (mutations that can replace HER2 signaling) were less frequent in breast cancer than in tissues with lower response rates.
- Critically important, the bypass alterations clustered together in tissues with lower response rates but not in breast cancer.

Example of alterations that can bypass HER2 in primary tumors

	Gene	Frequency	Clustering
Breast HER2-positive	EGFR	5%	none
	PTEN	20%	
	Gene	**Frequency**	**Clustering**
Stomach HER2-positive	EGFR	15%	strong, found together 4x more likely that expected **p=0.01**
	PTEN	27%	

In gastric cancer, genomic alterations that bypass HER2 signaling are not only more frequent, but they also co-occur within the same tumors.

The Take-Home Message:

Solo-drivers are rare in solid tumors

Cancer biology informs ORR

Gleevec, Herceptin and Tagrisso succeed because they inhibit solo drivers. Solo drivers don't have many co-occurring bypass mutations, but more importantly, the bypass mutations do not cluster together.

Patient data opportunity

Ask a critical question: In my target patient population, what other mutations cluster together? This can inform ORR before clinical trials and, more importantly, guide drug combinations that are key to high ORR and durability.

Strategic Recommendations

From Insight to Action

Consult Patient Data for Reliable Outcomes:

A soloist—or part of a band

Use patient data to determine whether your target is an independent driver or is supported by another player.

Primary tumors predict the ORR and durability of clinical trials

Measure the clustering of mutations in treatment naive tumors.

Patient data reveals which drug combinations to pursue.

Clustered mutations indicate specific combination partners that will dramatically improve the ORR and durability of your asset.

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

For inspirations check:

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