First to Market

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DISSECTING MODERNA'S MRNA SECOND ACT

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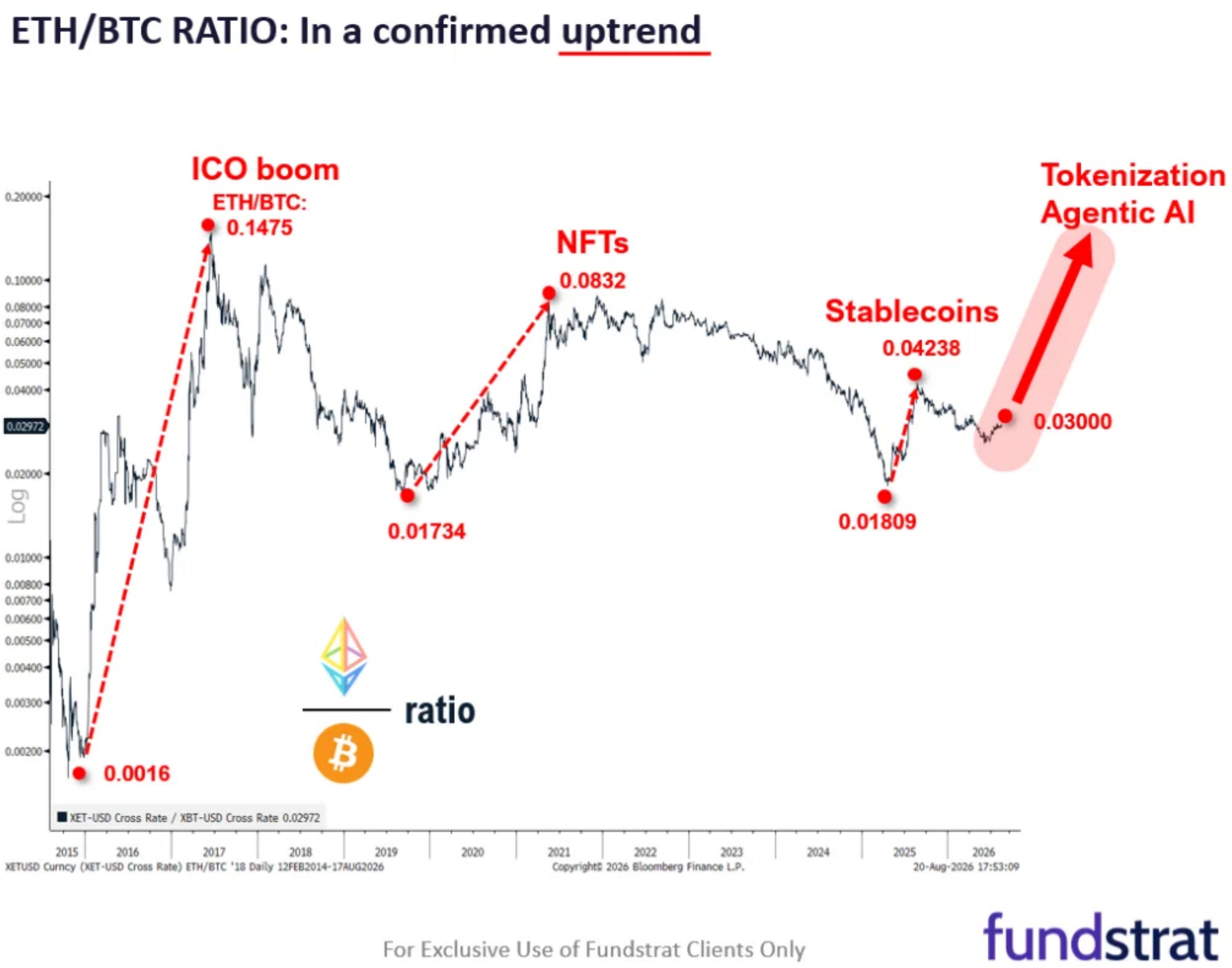
Chart of the Day



Good morning!

One of the bigger market stories this week was the massive surge in Moderna $MRNA shares on Wednesday.

The stock almost tripled (rising 177%) on Wednesday and, after some profit-taking the following day, remained up 111% for the week as of Thursday's close. Such a one-day surge (a $44 billion increase in the company's market cap) is particularly unusual for a company that isn't an AI play or a penny stock, but the news underlying this move makes it obvious what had the market (and likely the general public) so excited.

Moderna announced positive initial results from the Phase III clinical trial of its personalized melanoma vaccine, powered by Moderna's mRNA technology and co-developed with Merck $MRK.

The hope going into the tests was that the vaccine could be administered to those who had developed – and recovered from – melanoma to prevent or significantly reduce the likelihood of further recurrence of melanomas. Recurrence is one of the key mortality risks with this particular type of skin cancer.

As proposed, Moderna's mRNA-based individualized neoantigen therapy, currently called Intismeran, would involve analyzing a patient's existing melanoma to identify gene sequences unique to the cancer cells but not the patient, determining the best gene sequences to target, and then engineering an mRNA vaccine that will teach the patient's immune system to target any cells with those sequences. The treatment would be administered alongside Keytruda, a Merck-developed generalized cancer treatment that circumvents cancer's ability to hide from the immune system by making the system's targeting more aggressive and less discriminating. If it works as intended, this will circumvent both of the problems described above with traditional cancer treatments.

While Moderna's most recent announcement was imprecisely positive, it reported that compared to Keytruda alone, the combination of Intismeran and Keytruda demonstrated "clinically meaningful improvement" in terms of "recurrence-free survival (RFS) and a key secondary endpoint of distant metastasis-free survival

(DMFS)." Detailed Phase III test data will be presented at an unspecified "upcoming international medical meeting," but more limited Phase II results suggested that the "risk of recurrence or death [declined] by 49% [...] in patients with resected high-risk melanoma compared to Keytruda alone" over a three- and five-year period.

What likely has investors excited isn't just due to what this might mean for those with melanoma or their loved ones (112,000 new cases expected in the U.S. this year, according to Moderna). A similar approach could be used in treating other types of cancer. Moderna itself cited non-small cell lung cancer (the most common form of lung cancer), bladder cancer, and renal-cell carcinoma as examples of possible indications for Intismeran.

Here's why the mRNA vaccine is important to oncology: At its core, cancer – any cancer, whether originally detected in one's skin, blood, liver, lung, or elsewhere – is one's own cells mutating (i.e., errors in DNA replication, actually quite a common and generally harmless occurrence) and growing out of control (which is thankfully less common). This has long bedeviled oncological researchers for two reasons.

Firstly, unlike an illness caused by a pathogen like bacteria, cancer is personalized. Something like strep throat tends to be more or less the same from patient to patient, so the same treatment can generally be used for all patients. In contrast, even when two patients have the same type of cancer, the genetic makeup of their respective tumors might well differ significantly. Thus, a treatment that is effective on one patient will not be as effective on the other.

Secondly, because cancer cells are essentially flawed copies of the patient's own healthy cells, the patient's own immune system often does not recognize the cancer cells as foreign and thus will not attack them the way it would a foreign pathogen. What's worse, this similarity with normal healthy cells makes it extremely difficult to find a treatment that will target the cancer cells without also destroying healthy tissue.

Investors are excited because Moderna's announcement signals the possibility of a solution to both problems, though peer review of the trial data will be important to hear and an application for full regulatory approval has yet to be submitted.

It's important to note there are likely limits on this treatment's ability to treat some types of cancers. Some types of cancers (melanomas, for instance) have a higher concentration of mutations (a "mutation burden") that make it easier to identify targets for a customized mRNA treatment. Others – certain pancreatic and prostate cancers, for instance – have a lower mutation burden and thus fewer potential targets. Pancreatic cancer is worth singling out for another challenge for Intismeran. Currently, the timeline to create a personalized treatment is roughly six to eight weeks, and while that is an impressively short timeline, some fast-moving cancers, such as pancreatic cancers, might require a timeline that is even faster.

The question for equity investors is whether the initial, understandable euphoria will last. If it wins full approval, the therapy will still likely be pricier than current state-of-the-art oncology treatments, and manufacturing a bespoke treatment at scale is almost sure to present manufacturing hurdles to overcome. Of course, that could also create some new winners and losers for investors to benefit from.

Although Moderna's mRNA technology first gained widespread attention due to its use in developing a Covid-19 vaccine, a revolutionary advance in oncology treatments have long been among the company's original and primary objectives. It will also remain important to keep an eye out on how Intismeran fares in clinical trials for other types of cancer, currently ongoing.

Share your thoughts

Do you think Moderna $MRNA is still a buy at these levels? Click here to send us your response.

✍Here's what a reader commented ✍

Q: Should insurers be upping their allocations in AI-related private debt instruments?

A: No, insurers have a history of jumping into crowded trades in new hot areas of the market with predictably poor results, and then making the public pay for it in increased premiums and reduced coverage. This happened in the 1980s with their investments in the hot real estate market in the early ‘80s before the Reagan tax reforms pulled the rug from under real estate, resulting in their boycotts of public markets and various “tort reforms” in the states to reduce coverage and limit claim payments Currently, real estate isn’t involved and the collateral is chips and compute which may be even more tenuous than real estate.

Catch up with Fundstrat

The AI bottleneck story is stalling as data center opposition is now resonating with voters. This probably explains why crypto, particularly Ethereum, has been notably outperforming gaining 46% since June 30th.

Technical

Crude has run into its first real area of trading resistance at the downtrend from the April peaks, and a brief pullback from here is likely to be the source of positivity that lifts equities over the next week, ahead of a final push up toward 100 over the next four to six weeks.

Crypto

Crypto continued to rally yesterday despite a more challenging backdrop across traditional markets. Zooming into the price action, I think the composition of the rally is encouraging thus far.

News We're Following

Breaking News

- US buyback pledge draws Japan comparisons and pressures dollar BBG

Markets and economy

- US shoppers tighten budgets, but still find room for treats and splurges REU
- Trump to allow tariff relief for certain ground beef imports BBG
- Bitcoin on track for 20% weekly gain as investor optimism floods back CNBC

Business

- Dutch regulator fines Uber $966 million for automating driver suspensions, document shows REU
- GM ruled U.S. auto sales for 100 years. Now Toyota is closing in WSJ
- Monte dei Paschi launches twin takeover bids to create €70bn Italian bank FT

Politics/U.S.

- Politicians who once championed data centers are now bashing them WSJ
- FBI raids Democrat Swalwell's home in sexual-misconduct investigation, source says REU
- Army plans to phase out drone unit championed by sacked generals HILL
- Trump administration attacks Bar Association’s power to accredit law schools WSJ

Overseas

- Hong Kong's Tiananmen activists convicted in national security trial BBC
- Panama canal to reduce shipping as El Niño strikes vital route GUA
- Swiss Voters Are Set to Reject Stricter Neutrality, Poll Shows BBG

Of Interest

- Gandhi's handwritten notes on life sold for $1.69m at Indian auction BBC
- Three injured after donkey jumps into a van, kicking and biting, in northern Germany AP

Overnight

S&P Futures	+25 ▲ point(s) (+0.33% ▲)
overnight range:	-1 ▼ to +28 ▲ point(s)

APAC

Nikkei	-0.30% ▼
Topix	+0.19% ▲
China SHCOMP	+0.04% ▲
Hang Seng	+1.21% ▲
Korea	+0.88% ▲
Singapore	+0.30% ▲
Australia	-0.27% ▼
India	+0.01% ▲
Taiwan	+0.65% ▲

Europe

Stoxx	50 +0.24% ▲
Stoxx	600 +0.10% ▲
FTSE	100 -0.02% ▼
DAX	+0.25% ▲
CAC	40 -0.01% ▼
Italy	+0.27% ▲
IBEX	+0.64% ▲
Canada	-0.10% ▼
Mexico	+0.55% ▲
Brazil	+0.06% ▲

FX

Dollar Index (DXY)	-0.28% ▼ to 98.617
EUR/USD	+0.22% ▲ to 1.1704
GBP/USD	+0.21% ▲ to 1.3659

GBP/USD	+0.21% ▲ to 1.3659
USD/JPY	+0.28% ▲ to 158.60
USD/CNY	+0.06% ▲ to 6.7208
USD/CNH	+0.08% ▲ to 6.7199
USD/CHF	+0.16% ▲ to 0.7991
USD/CAD	+0.30% ▲ to 1.3749
AUD/USD	+0.66% ▲ to 0.7161

UST Term Structure

2Y-3M Spread narrowed	-0.9bps ▼ to 37.9bps
10Y-2Y Spread narrowed	-0.7bps ▼ to 50.5bps
30Y-10Y Spread widened	0.5bps to 54.6bps

USD HY OaS

All Sectors	+1.4bps ▲ to 310bps
All Sectors ex-Energy	+1.1bps ▲ 301bps
Cons Disc	+2.9bps ▲ to 507bps
Indu	+2.9bps ▲ to 241bps
Tech	-1.3bps ▼ to 206bps
Comm Srvcs	-0.0bps ▼ to 293bps
Materials	+1.0bps ▲ to 271bps
Energy	+0.4bps ▲ to 280bps
Fin Snr	+2.9bps ▲ to 191bps
Fin Sub	+0.5bps ▲ to 286bps
Cons Staples	+1.1bps ▲ to 470bps
Healthcare	+1.1bps ▲ to 319bps

Utes	-0.8bps ▼ to 213bps *

DATE	TIME	DESCRIPTION	ESTIMATE	LAST
8/21	9:45 AM	Aug P S&P Srvcs PMI	54	54.6
8/21	9:45 AM	Aug P S&P Manu PMI	53.9	53.9
8/25	9:00 AM	Jun S&P Cotality CS 20-City m/m	0.1	0.15
8/25	10:00 AM	Aug Conf Board Sentiment	90.2	90.8
8/25	10:00 AM	Jul New Home Sales	620	628
8/25	10:00 AM	Jul New Home Sales m/m	-1.3	1.6
8/26	8:30 AM	Jul PCE m/m	0.1	-0.1
8/26	8:30 AM	Jul Core PCE m/m	0.2	0.13
8/26	8:30 AM	Jul PCE y/y	3.6	3.7
8/26	8:30 AM	Jul Core PCE y/y	3.3	3.28653
8/26	8:30 AM	2Q P GDP QoQ	1.5	1.5
8/26	8:30 AM	Jul P Durable Gds Orders	0.5	0.5

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