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DR. ROSENBERG'S ROXBURY MIRACLE

A Cancer Treatment on the Verge of a Breakthrough
The Truffle Pig Makes a High-Conviction Investment

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In the summer of 1956, a 51-year-old man checked into the Veterans Administration hospital in Roxbury, Massachusetts, with acute stomach pain.

Physicians there conducted a laparotomy – a surgical incision into the abdominal cavity to examine the organs and help diagnose the source of his pain. What they found was tantamount to a death sentence: the patient had a tumor in his stomach the size of a large fist that had already spread to his liver and lymph nodes. The surgeons removed as much of the patient's stomach as they could to buy him some time. Then they stitched him up and sent him home to die.

Twelve years later, a young surgeon in training at Harvard Medical School, assigned to the same VA hospital in Roxbury, met a 63-year-old patient coming in to have his gallbladder removed for gallstones. The surgeon checked the patient's medical records. What he found left him dumbfounded: This same man had been diagnosed over a decade earlier with terminal stomach cancer. But when the young surgeon operated to remove the man's gallbladder, all traces of metastatic cancer had completely disappeared.

This case would change the arc of the young surgeon's life… and help give rise to an entirely new field of cancer treatment.

The young surgeon was Dr. Steven Rosenberg – today Chief of Surgery at the prestigious National Cancer Institute ("NCI") and widely regarded as one of the fathers of cancer immunotherapy.

Dr. Rosenberg's journey began in earnest when he searched for an explanation for the miracle patient's spontaneous remission. He identified a crucial clue in the man's medical history.

A few days after his original cancer surgery in 1956, the man had developed a severe infection in his stomach, characterized by virulent pus loaded with alpha streptococcus. Rosenberg knew that other researchers had observed an association between shrinkage of stomach cancer and severe abdominal infection. Furthermore, the medical records showed that his patient's stomach cancer had been densely infiltrated by lymphocytes and other immune cells.

Dr. Rosenberg hypothesized that the man's infection must have super-activated his immune system… and that the patient's own immune system, in turn, had defeated his cancer.

The natural question was: How could other cancer patients' immune systems be super-activated and harnessed to defeat their cancers, too?

Five Decades of Research About to Become Real

Dr. Rosenberg (pictured below) would spend the next five-plus decades doggedly pursuing this question. His research would be published repeatedly in the world's most prestigious scientific journals: *Nature*, *Science*, and *The New England Journal of Medicine* among them. It would garner him a long list of prizes, including the National Medal of Technology and Innovation, awarded by the President to America's preeminent inventors. But Dr. Rosenberg's jewel-in-the-crown therapeutic breakthrough – the harvesting, expansion, and reinfusion of a patient's own Tumor Infiltrating Lymphocytes ("TIL") to fight that patient's cancer – has yet to be approved by the Food and Drug Administration ("FDA"). As a result, it has yet to really reach patients.

The company that has licensed the most foundational pieces of Dr. Rosenberg's work, and with which he himself is most closely associated, is **Iovance Biotherapeutics (Nasdaq: IOVA)**. And in a few weeks, after decades of anticipation, the FDA is due to decide whether to approve Iovance's TIL therapy – which the company has named lifileucel – to treat cancer patients.

In this issue of *Biotech Frontiers*, we'll lay out why we think that Dr. Rosenberg's five and half decades of pioneering work in oncology has not been simply an academic exercise… but instead stands to transform the lives of many cancer patients and reward Iovance shareholders who have funded its development.

As I'll explain, we'll also be betting alongside Iovance's largest shareholder – a legendary biotech investor with a phenomenal track record and a colorful nickname.

To elaborate our investment thesis in Iovance, I'll be relying on the seven-part framework outlined in our Biotech Frontiers Investment Guidebook. Each of these seven factors is highly relevant to a biotech investment's prospects for success. By touching on each, we ensure we haven't missed anything that could upend our thesis.

Let's begin...

I. The Science

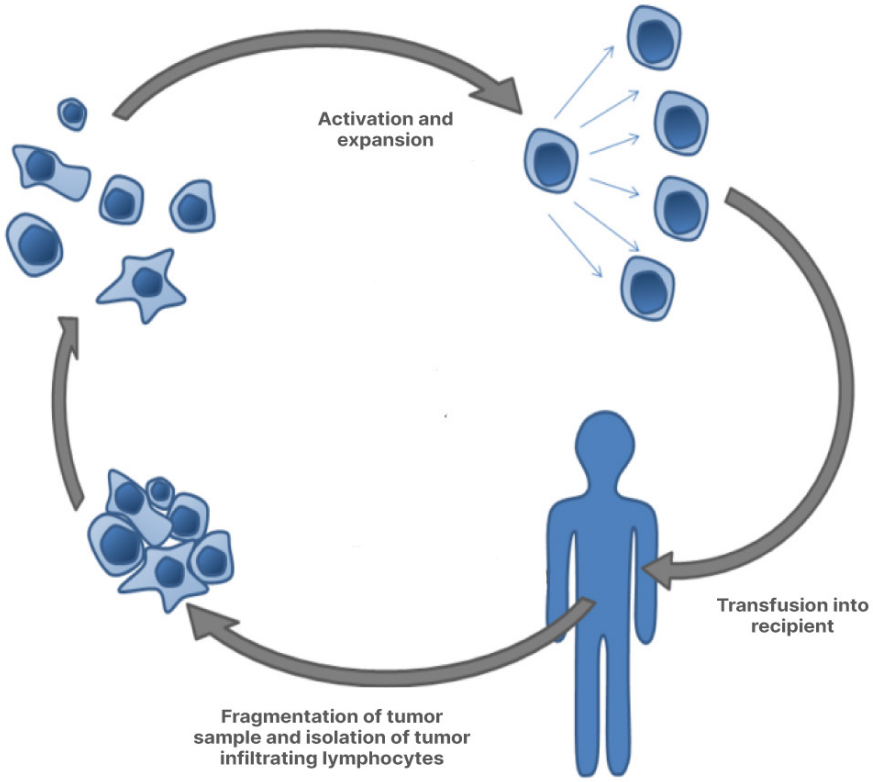
Dr. Steven Rosenberg's career is replete with important discoveries about cancer. But the defining breakthrough with which he's associated is our understanding of how TILs work and how they can be harnessed to fight cancer. Let me explain...

Lymphocytes, commonly known as white blood cells, are the main cellular workhorses of the immune system. We call them lymphocytes because our lymph nodes are their home base. They come in three main kinds: T cells, B cells, and natural-killer ("NK") cells. Each of these kinds of cells plays a distinctive role in the concert of an immune response.

Lymphocytes constantly patrol the body in search of pathogens or abnormal cells. When a solid tumor cancer arises, a small number of these lymphocytes, mainly T cells, are able to recognize the cancer as abnormal and set out to attack it. These T cells actually penetrate the tumor's microenvironment and, at least initially, are able to destroy cancer cells they encounter. The problem is that these "first responder" T cells are outnumbered at the tumor site. In the end, solid tumor cancers have many ways of defeating T-cell effectiveness in those small numbers.

The lymphocytes that have engaged in a "fire fight" with cancer at the tumor site – fighters that Dr. Rosenberg calls Tumor Infiltrating Lymphocytes – are special. Unlike other lymphocytes patrolling the body, TILs know how to recognize and kill the solid tumor with which they've done combat. Dr. Rosenberg asked: What if these special lymphocytes could be extracted, multiplied in a lab, and then reinfused into the patient... so that instead of being outnumbered, they would possess overwhelming numerical superiority?

Following the Path of Tumor Infiltrating Lymphocytes (TILs)



That's exactly how TIL therapy works. When a patient receives TIL therapy, the first step is a biopsy that removes a small sample of the tumor. The patient's own T cells that have penetrated the tumor are then purified from the sample and expanded in laboratory bioreactors.

This expansion step is a breathtaking feat: a small number of T cells from the sample are amplified into an army of 5 billion to 10 billion TILs over a few weeks. The patient receives a bit of carefully orchestrated prep, then the TILs are reinfused. They're given a final boost with a dose of interleukin-2 (IL-2), which helps the reinfused TILs expand even further inside the body. The result is a super-activated army consisting of the patient's own elite T cells that know how to recognize and fight the tumor.

Not every patient who receives TIL therapy experiences a complete cure, as Dr. Rosenberg's miracle patient back in 1968 did with his spontaneous remission. But there is compelling evidence that TIL therapy works.

In Iovance's Phase II trial on patients with advanced, refractory melanoma – the hardest patients to treat because they've failed many other lines of therapy – 5% of TIL recipients achieved a complete response, while 31% achieved a partial response that extended their life in a statistically significant way. (In cancer medicine, a "complete response" means the disappearance of all signs of cancer in response to treatment.) A Phase III trial run by the Netherlands Cancer Institute in Europe on TIL therapy demonstrated even more striking results: In that trial, whose results were published in *The New England Journal of Medicine*, 20% of patients on TIL therapy achieved a complete response.

For patients facing a death sentence, a therapy that can completely cure some and offer significant life extension to others is truly transformative.

But TIL therapy itself, which Iovance developed for the clinic in partnership with the NCI and Dr. Rosenberg's lab, is only one important part of the breakthrough innovation at the company.

The other innovation – equally important – is how to scale TIL therapy so that it can reach tens of thousands of patients… and how to do it quickly enough to make a difference for them.

In the early clinical trials on TILs, T cells extracted from patients were expanded at the tiny number of major academic medical hospitals participating in the trials. As a result, only patients who lived nearby, or who had the financial means to travel for experimental treatment, could participate. Furthermore, these early versions of TIL therapy often required *eight weeks* to amplify the patient's T cells… during which patients with advanced disease would often deteriorate beyond the point that TIL therapy could help them.

One of the boldest, hardest challenges that Iovance took on was how to simultaneously scale and streamline TIL therapy to render it both more accessible and more effective. The company has solved this problem by building two proprietary pieces of infrastructure – one physical, the other virtual. The physical is a custom-built, state-of-the-art manufacturing facility at the Navy Yard in Philadelphia (pictured on the next page). At 136,000 square feet, this cellular manufacturing facility is a feat in and of itself. The second is a network among dozens of cancer hospitals throughout the U.S., with which Iovance has partnered to "distribute" TIL therapy to patients.

In effect – like Federal Express, which disrupted transportation logistics using a similar model – Iovance has built a hub-and-spokes delivery system for TIL therapy, which no other biotech company is close to replicating. Iovance's leading-edge cellular manufacturing site in Philadelphia is the hub. Its group of participating cancer hospitals across America are the spokes. Together, this network enables Iovance to reach cancer patients in most American cities and provide their own bespoke, amplified army of TILs in only 22 days – a remarkable acceleration of the original eight-week timeframe.

II. Sizing the Prize: The Opportunity

"If you're right… you've *got* to get paid." We'll be returning often in *Biotech Frontiers* to the mantra of my late mentor Julian Robertson of Tiger Management – who insisted that the best investments ought to earn 2x, 3x, or even 5x returns. One key way to help us "get paid" is to make sure that when we underwrite a new therapy, its prospective market and its likely share of that market are large enough to leave us a lot of upside relative to the company's current value. We do this by sizing a therapy's total addressable market ("TAM").

By way of reminder, Iovance has called its proprietary TIL therapy lifileucel. Lifileucel's first target market is advanced (or metastatic) melanoma – there are 15,000 new cases annually in the U.S. alone. Iovance hopes that eventually, it will build out sufficient manufacturing capacity to treat at least 10,000 of these patients per year. It's not unrealistic for Iovance to estimate patient demand at that level: about 6,300 patients with metastatic melanoma in the U.S. need second-line therapy each year – that is, after checkpoint inhibitors or targeted therapies fail. Another 4,800 in the U.S. need third- or fourth-line treatment. No other biotech company is close to having a TIL-based therapy approved, and none has built out anything close to Iovance's specialized manufacturing facilities to be able to meet patient demand. So it's safe to say that for some time, Iovance will truly "own" the market it's targeting.

Iovance has not revealed how it intends to price lificeucel. However, many observers have suggested the company will likely price lifileucel comparably to CAR-T therapies – a different modality of cancer treatments that, like lifileucel, are cellular in nature and tailored to the patient's individual immune system. CAR-T therapies, such as Gilead's Yescarta, are priced at $350,000 to $500,000 per year for a patient.

We now have the inputs we need to perform our back-of-the-envelope, market-sizing analysis: Assuming Iovance treats 10,000 patients a year with lifileucel, at a $425,000 midpoint price, annual revenue would be $4.25 billion. Biotech companies with approved therapies are typically valued by the market at 3x to 5x peak sales. Peak sales of $4.25 billion would therefore imply a value for Iovance in the range of $12 billion to $21 billion… or 6x to 10x the company's current $2 billion market cap.

If Julian were here, he would probably remark: "That's enough for us to get paid."

But it's also worth noting that the analysis we've just walked through isn't the "blue sky" scenario. Some 91% of all cancers are solid tumors. Iovance is already advancing Phase III pivotal trials for lifileucel in metastatic non-small-cell lung cancer ("NSCLC") and in cervical cancer. There are many reasons to hope that TIL therapy will be as effective in treating these terrible forms of cancer as it has proven to be in metastatic melanoma. If so, then Iovance's TAM could be much larger than 10,000 patients per year… and its potential blue-sky value higher too.

III. The Capitalization Table

The third factor in our framework is the capitalization table ("Cap Table"). The Cap Table reveals who the company's largest shareholders are, how much they own, and whether they've been adding to or reducing their investments.

We pay special attention to three specific kinds of shareholders:

- **Insiders**, because we can safely assume they know the company better than anyone
- **Smart Money**, because we can piggyback on their proven acumen picking biotech winners
- and **Whales**, because their size can single-handedly drive a stock up (or down)

It's not always the case that all three categories feature prominently in the Cap Table… and if they don't, that's OK. Our job is simply to study the Cap Table carefully and infer what we can from it.

Of the three categories, one speaks to me more powerfully than the others: Smart Money.

The Smart Money are the Warren Buffetts of biotech – the tiny handful of life-sciences hedge funds, venture capitalists, and deep-pocketed family offices that comprise the world's best biotech investors. These firms have demonstrated, often over decades, repeated prescience in identifying home-run biotech successes. By investing alongside them, we're able to leverage their pattern recognition and judgment … for free.

Self-made billionaire Wayne Rothbaum might be the best biotech investor in the world. An early player in Pharmacyclics – the astonishing comeback story we chronicled at the opening of our *Biotech Frontiers Investment Guidebook* – Rothbaum was also the founding investor of Acerta Pharma, a rival to Pharmacyclics in the B-cell lymphoma space that AstraZeneca acquired for $7 billion. One of the most impressive aspects of Rothbaum's investment career is that he's never managed money for others… the billions he's made have not come from charging performance fees on other people's money, but instead from being spectacularly right managing his own.

As investigative reporter Nathan Vardi writes in his riveting book on the Pharmacyclics saga, For Blood and Money – which I highly recommend – Rothbaum has a nickname in biotech circles, given to him by a high-ranking executive at Bayer Pharmaceuticals. The nickname is: the Truffle Pig. Rothbaum had to be told that the nickname was intended as a compliment, not an insult. In Europe, these animals are revered for their exceptional sense of smell, and their ability to spot, deep underground, truffles no human could find.

Rothbaum is Iovance's largest shareholder – he owns 23 million shares, or 9% of the company.

But it gets better… Rothbaum is not only a Smart Money investor, but also a member of Iovance's board – therefore an Insider as well. And while, as an insider, he's not allowed to trade on market-moving, not-yet publicly disclosed developments, Rothbaum is privy to a wealth of information about the company that others may not come across on their own… and that informs his investment judgment.

It's also encouraging that Rothbaum has been continuously increasing his Iovance investment. He joined the Iovance board in 2016 – but made his largest acquisitions of the stock in 2022 and 2023, most recently in September 2023 when he grew his investment by 5 million shares.

The pattern of Rothbaum's investments suggests two things: First, Iovance is a high-conviction investment for him, as he's continually added to his position over time and has made no sales. Second, he believes the stock is cheap, as his biggest purchases came during the 2022 and 2023 biotech bear market, from which IOVA has not significantly recovered. Shares today trade for around $8 – about 85% below the pre-bear market high of $52 per share.

One final noteworthy detail. The world's greatest investors often have a power zone – the epicenter of their circle of competence, the bullseye where their true genius shines brightest. Warren Buffett is an extraordinary investor across the board… but he unquestionably has a power zone in property-and-casualty insurance, the foundation on which Berkshire Hathaway was built.

Wayne Rothbaum's power zone within biotech is oncology, the study of how to treat cancer. Pharmacyclics was a cancer-fighting drug company. Acerta was a cancer-fighting drug company. And Iovance… is a cancer-fighting drug company.

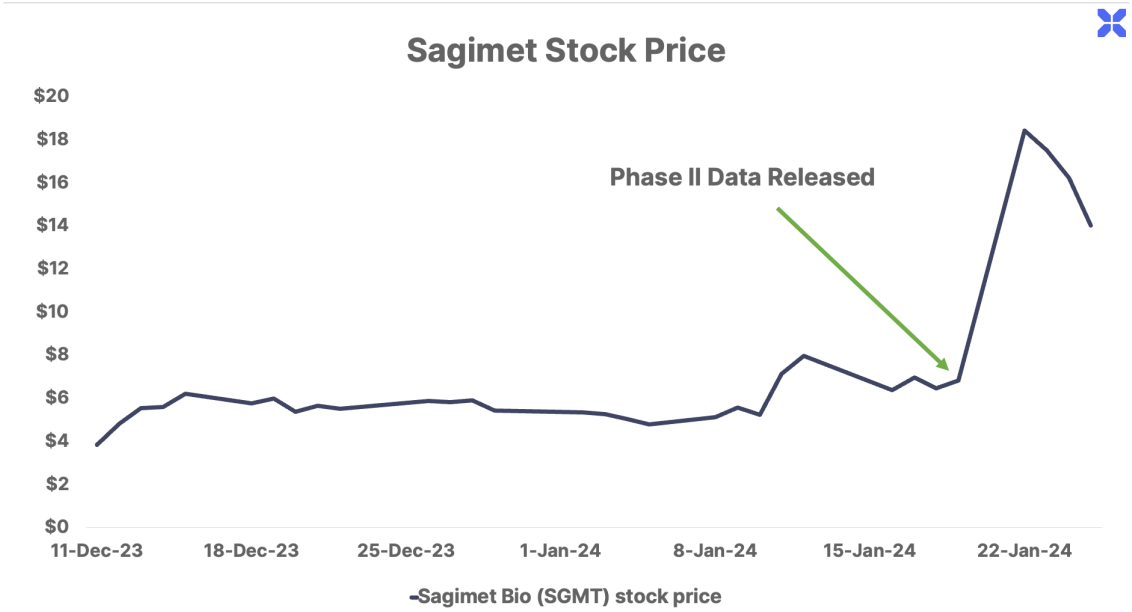
So to sum up: By investing in Iovance, we align ourselves with arguably the world's best biotech investor, in a company where he is the largest shareholder and also a board member… where he's been continuously adding to his position, including with significant recent purchases… and where he is operating within his power zone.

This setup does not guarantee success – but I think it augurs well.

IV. The Catalysts

The fourth factor that matters to us are catalysts – the events such as clinical-trial results, regulatory decisions, and commercial launches that often drive dramatic movements up or down in biotech stocks.

If you are one of *Biotech Frontiers'* inaugural subscribers, you've already witnessed – and I hope participated in – a catalyst-driven success: **Sagimet Bioscience's (Nasdaq: SGMT)** release of its Phase II clinical-trial data in mid-January propelled the stock up more than 200% in the subsequent days, prompting us to recommend selling one half of our position to lock in gains. Not every catalyst will prove to be as potent as Sagimet's Phase II data, and there's always risk that a catalyst can be negative, not positive. But for catalysts, as for the Cap Table, our job is to study this factor carefully and to discern its import for the stock.



Source: Bloomberg

Iovance has two important catalysts on the horizon. The first is the FDA's regulatory decision on whether to approve the company's flagship lifileucel TIL therapy for patients with advanced melanoma. Under a federal law called the Prescription Drug User Fee Act ("PDUFA"), the FDA has fixed deadlines for when it must complete reviews of new therapies. This deadline – the PDUFA date – is exactly 10 months after the agency receives a new drug application… or six months if the FDA designates a new drug for Priority Review. The FDA can and sometimes does re-schedule a drug's PDUFA date if it needs more time to complete its review. However, a scheduled PDUFA date is always an important catalyst.

Iovance's lifileucel, which the FDA has designated for Priority Review, has a PDUFA date of February 24, 2024 – just over two weeks away.

When it comes to binary events such as a regulatory decision to approve a drug, professional investors often perform what's called an expected-value analysis – or an EV tree. My EV tree for Iovance's upcoming lifileucel approval decision looks like this:

The Iovance EV Tree

Event Outcome	Probability	Stock Price	EV Contribution
Approval	80%	$11.00	$8.80
Complete Response Letter	20%	$2.50	$0.50
Expected Value			**$9.30**

Let's translate our EV tree into plain English:

I think there's an 80% probability that the FDA gives lifileucel a green light. In that scenario, I expect Iovance stock to trade up to around $11 per share – roughly 35% above its current level. Conversely, there's about a 20% probability that the FDA issues Iovance a Complete Response Letter ("CRL"). A CRL is the FDA's bureaucratic way of saying: "We're not ready to approve your drug."

CRLs can vary in their significance: some are trivial and can be addressed by a company in a few months or even weeks. Others – such as a request by the FDA for another clinical trial – are devastating setbacks that would require years to remedy. If the FDA issues lifileucel any kind of a CRL, I expect the market to punish IOVA swiftly and harshly, probably sending the stock down to $2.50 per share.

The combined results of these two scenarios suggest an expected value for Iovance stock of $9.30, a modest 15% above current levels. To be clear, we are not buying Iovance with the aim of making 15%. Our aim is to earn a multiple of our investment, and that's exactly what I believe Iovance can make us over a longer time frame. The $9.30 per share expected value simply reflects a probabilistic assessment of what the stock should be worth *today* given our views on the upcoming PDUFA decision. We want that expected value to be positive – i.e., a gain relative to the current price – and it is.

Some readers may ask: If we think there's a 20% chance that the FDA issues a CRL that could send Iovance stock down 70%, why buy the stock now? That's a good question. The answer lies in my belief about what a CRL here would likely mean. It's overwhelmingly likely that a CRL, if it came, would be addressable by Iovance within a short time, probably a few months. The market would likely overreact to a CRL and send the stock down dramatically in the short term, but if the CRL pertained to an easily fixable issue, such as a manufacturing hiccup, I anticipate the stock would recover quickly.

We'll also mitigate the risk of a CRL through our position sizing. As we'll discuss below, I will be recommending we buy a two-thirds-sized position in Iovance, not a full one. If Iovance receives a CRL and trades down violently, we can use the opportunity to add to our position and buy the remaining third at a much lower price.

Let's turn to the second catalyst on the horizon for Iovance: lifileucel's commercial launch. Unlike clinical-trial-data releases and regulatory-approval decisions, commercial launches unfold not in a single day but instead over a period of months – generally the first 12 to 24 months after a drug receives FDA approval.

During this period, the market carefully studies a drug's reception by medical prescribers and payors. The aim is to assess whether a drug will disappoint, meet, or beat commercial expectations. Above all, the market searches for clues about whether a drug is on its way to becoming a blockbuster, commonly understood to be a therapy that generates at least $1 billion per year in sales.

According to *Bloomberg*, the market consensus is that lifileucel will generate about $130 million in sales during its first year, growing to about $225 million in its second year. I think it's likely lifileucel will blow past these expectations, for two reasons.

1. TIL therapy – of which Iovance's lifileucel would be the very first ever approved by the FDA – has been hugely anticipated by the medical community. Dr. Rosenberg began publishing on the promise of TIL therapy back in the 1980s. Nor was Dr. Rosenberg's groundbreaking work on TILs published in obscurity. His work was featured on the covers of *Nature*, *Science*, and *The New England Journal of Medicine* – the most prestigious, widely read scientific journals in the world. As a result, TIL therapy is not a treatment modality that leading oncologists will need to be educated about. They've been waiting for its FDA approval for a long time.

2. The magnitude of the unmet need among patients. Iovance has sought accelerated FDA approval for lifileucel for a very narrow indication: as a treatment for patients with advanced (i.e., metastatic) melanoma who have failed immune checkpoint inhibitors and other targeted therapies. These patients currently have no other treatment options. They've reached the end of the line of what medicine can offer them.

Iovance's decision to seek accelerated approval for this narrow population is strategic. The company knows that by focusing on patients who currently have no options left and therefore no hope, it can apply legitimate pressure on the FDA to tip the scales in favor of approval. Iovance is basically asking: Given lifileucel's convincing clinical-trial results and the 35-year journey TIL therapy has already traveled to get to this point, does the FDA really believe it's doing the public a favor by withholding access to a potentially life-saving therapy from patients who otherwise face certain and imminent death?

But here's the thing: Once the FDA approves lifileucel, even just for the narrow patient population that Iovance has identified, physicians and patients alike will almost certainly use it "off label" for other solid-tumor cancer indications. Why? Because solid-tumor cancers are so often a death sentence and because there's compelling evidence that TIL therapy works. As we saw earlier, robust clinical-trial data has demonstrated that about 30% or more of patients with advanced solid-tumor cancer achieve meaningful positive responses from TIL therapy – with 5% to 20% achieving a complete response.

Results like these mean that once the FDA opens the door for lifileucel just a crack, physicians and patients alike will shove their feet in to pry it open further – even if that means using lifileucel "off label" for indications beyond the narrow scope of what the FDA formally approves at the outset.

To sum up: Iovance offers us two catalysts. The first, the FDA's approval decision, will likely play out within a matter of weeks. The second, lifileucel's commercial launch, will likely unfold over the next one to two years. Together, these catalysts have the potential to propel Iovance's stock much higher.

V. The Balance Sheet

We care about balance sheets because companies that run out of cash fail. But besides avoiding the outright failures, we also seek to steer clear of biotech companies that unnecessarily engage in serial dilution of shareholders, and especially those that have a propensity to raise capital at the wrong times or on the wrong terms.

Conversely, balance-sheet strength is a huge positive for biotech companies. In the first issue of Biotech Frontiers, we visited the extreme side of balance-sheet strength: a group of companies trading at negative enterprise value ("EV") – companies whose net cash positions exceed their market capitalizations.

Iovance does not trade at negative EV, but it does have a solid balance sheet. The company reported $428 million of cash as of its last quarter, which amounts to $1.67 per share, or about 20% of the company's market capitalization.

One important element we need to think about in studying a balance sheet is – where is the company in its life? For example: Is a company already generating healthy streams of cash flow from other products? And does it face any unusual cash needs in the near future?

In Iovance's case, lifileucel is the company's first product… and Iovance does have a big cash crunch coming – for lifileucel's commercial launch if it receives FDA approval.

An analysis by boutique strategy consulting firm Health Care Advances found that single-drug commercial launches for first-in-class therapies typically cost between $260 million and $450 million over the first two years. After that, launch-related expenses usually fall significantly.

lifileucel's commercial launch likely means that Iovance will need to raise capital in the not-distant future.

But I'm not too worried about that adversely affecting our investment, for two reasons.

1. If lifileucel receives FDA approval as I expect, Iovance would be raising capital on the back of positive news, and likely at a higher stock price. We saw Sagimet do the same thing after its terrific Phase II trial results. Biotech companies that achieve an important positive milestone often raise capital on the back of it. That's the right way to do it – in contrast to, say, when a company is close to running out of cash, or has received bad news and is desperate to raise capital with the share price crushed.

2. Iovance benefits from a strong existing investor base. We highlighted Wayne Rothbaum in our discussion of the Cap Table, but the rest of Iovance's Cap Table looks strong as well: the company's top 15 shareholders include Whales such as BlackRock and State Street, as well as other large Smart Money investors such Perceptive Advisors, Millennium Management, and OrbiMed. Having this kind of institutional representation in the Cap Table means that Iovance will likely not struggle to raise capital on fair terms.

There'll be instances in *Biotech Frontiers* when a company's balance sheet is a significant positive driver of our investment recommendation. That's not true for Iovance. But it doesn't have to be a significant positive driver: The main thing we need to assess is whether a company's balance sheet *disqualifies* it from being an attractive investment. Iovance's balance sheet is solid enough to let the company's other compelling strengths shine through.

VI. The Big-Picture Backdrop

Although many casual observers think that biotech investing is entirely about science, insiders know that the biotech sector is one of the most interest-rate sensitive parts of the economy. If you haven't yet grasped the relationship between biotech and interest rates, I would urge you to read (or re-read) Section VI of our Biotech Frontiers Investment Guidebook. We discuss it in detail there.

So in our sixth factor – The Big-Picture Backdrop – we'll widen the aperture and assess how broader conditions in the economy and capital markets may affect interest-rate policy, and in turn our investments.

U.S. economic data in January once again showed surprising strength. The January jobs report revealed that the U.S. labor market added 350,000 positions last month, nearly twice as many as had been expected. Fourth-quarter 2023 GDP, also released in January, likewise beat expectations – coming in at 3.3% annualized. Meanwhile, the most recent data suggests that inflation continues to normalize, with December's reading at 3.4%... still higher than the Fed's 2% target, but significantly below the 8% to 9% range of the year before.

Robust job growth, healthy GDP gains, and falling inflation... all three developments take pressure off the Federal Reserve to cut interest rates. Fed Chair Jerome Powell has recently said as much, telling *60 Minutes* in an interview airing February 4, that while the Fed will likely cut rates in 2024, it's unlikely to do so at its coming March meeting. Instead, Powell explained, there's a consensus at the Federal Open Market Committee ("FOMC") to "wait and see" if inflation continues to trend down before the FOMC cuts.

Is the Fed's patience on rate cuts bad for biotech stocks? In the short term, yes. Biotech investors have been pleading for the Fed to cut rates like a man stranded in the desert begging for a glass of cold water. The Fed's decision to wait on rate cuts may well prompt a sell-off in biotech stocks... or, at a minimum, put a damper on the sector's recent bounce off its all-time lows.

But I am happy about the Fed's rate-cuts patience, for two reasons.

1. It gives us more time to build our *Biotech Frontiers* portfolio, and to be patient in seeking good entry prices for our picks. If Fed rate cuts were coming in March, the biotech sector would be moving explosively higher. It would be incredibly difficult to identify and recommend companies in an environment where biotech stocks were moving up 20%, 30%, or more in a month. For those of you who missed our original basket of 10 biotech stocks trading at or near negative EV, the Fed's rate cut patience is especially good news… as it increases the chances that some of the picks in the portfolio that moved above our "buy up to" prices may come back down.

2. The Fed is right to "wait and see" about rate cuts for the longer-term health of the economy and the markets. So far as investors are concerned, the very worst thing the Fed could do would be to cut rates prematurely, before having compelling evidence that inflation has been wrung out of the system. Such premature rate cuts are exactly what the Fed did in the 1970s, causing inflation to roar back, and turning the 1970s into a train wreck of a decade for stock investors (and for most all Americans, economically speaking). I would much prefer for the Fed to be prudent, even if that means giving up a short-term biotech rally. A biotech rally will come eventually, and when it does, I'd like it to be sustainable.

Bringing this discussion back to Iovance – if Fed Chair Powell had said on *60 Minutes* that the Fed would be cutting rates in March, Iovance stock… along with many other promising biotech stocks… would be 25% to 50% higher. So for this month's pick, the Big-Picture Backdrop is exactly where I'd want it to be.

VII. Expected Value and Risk/Reward

In the final piece of our analysis, we synthesize everything that's come before and distill it into three capsules: a **Premortem statement**, a **Parade statement**, and an **Expected Value Tree** for the proposed investment.

In our **Premortem**, we engage in the following thought experiment: Imagine it's three to five years from now and our investment has not worked out. Why did it fail? By answering this question, we force ourselves to reckon with what could go wrong.

For Iovance, the key risks are regulatory and executional. The regulatory risk is straightforward: the FDA could decide not to approve lifileucel, or to delay its approval significantly. Alternatively, the agency could approve lifileucel but keep Iovance on a very tight leash – for instance, by halting patient access if there are occasional unexpected adverse reactions to TIL therapy. These risks are unlikely, but they undoubtedly exist.

The execution risk centers on Iovance's ability to scale lifileucel to tens of thousands of patients as the company has stated it aims to do. Iovance has built out infrastructure to achieve this aim. But so far, that infrastructure has not been tested in the context of robust patient demand. It remains for Iovance to prove whether it can execute at scale.

A **Parade** statement is the mirror image of a Premortem: We invite ourselves to imagine it's three to five years from now and our investment has been a spectacular success. What went right? Here, too, we are seeking to clarify the likely drivers of our upside so we can reflect on them alongside what could go wrong.

In our upside scenario, three key things go right for Iovance. First, the FDA approves lifileucel, Iovance launches the therapy, and TILs begin to transform patient lives in the thousands – altering perceptions of TIL therapy from a tantalizing promise into a mainstay of cancer treatment. Second, Iovance seizes on its unquestionable scientific and commercial leadership in TIL therapy to press its lead along both dimensions. It continues to innovate next-generations TILs and to expand its manufacturing footprint so it can provide TILs at scale. Third, eventually Big Pharma – my guess would be Roche subsidiary Genentech – decides it must own Iovance and buys the company at a significant premium.

Our **Expected Value Tree** distills everything that's come before into simple arithmetic. We encapsulate our entire investment thesis into a downside scenario, a base case scenario, and an upside scenario. We assign a probability and a stock price to each. And we derive our expected value for the stock based on the sum of these three probability-weighted scenarios and their respective contributions. Here is my Expected Value Tree for Iovance:

Iovance's Downside, Base, and Upside Scenarios

Scenario	Summary	Probability	Stock Price	EV Contribution
Downside Scenario	Regulatory and/ or Commercial Failure	25%	$2	$0.50
Base Case Scenario	Successful Launch and Lifileucel Adoption	50%	$24	$12.00
Upside Scenario	Home Run Success & Iovance Acquired b Big Pharma	25%	$48	$12.00
			Expected Value	$24.50

Astute readers may ask: How does this Expected Value Tree differ from the one we walked through in the Catalysts section? The answer is: that first tree aimed to analyze Iovance's expected value focusing on the immediate, upcoming event of the FDA's regulatory decision. This tree seeks to analyze Iovance's expected value over a three-to-five-year holding period.

As our Expected Value Tree reflects, the risk/reward today in Iovance is very attractive. Accordingly, I recommend that readers **buy Iovance stock up to $9.25 per share**.

There is one important nuance: As mentioned earlier, I would like for us to initiate this position at two-thirds an ordinary position size. To be concrete: Let's imagine that you have $100,000 to invest in stocks, have decided to allocate $50,000 to a biotech portfolio, and are planning for 20 positions in total. That implies $2,500 per investment. I am recommending that you buy two-thirds of your Iovance position (or $1,650 of stock) now, and reserve $850 to add downstream.

The reason we're approaching this recommendation with a staggered entry is to be respectful of the risk associated with the FDA's upcoming regulatory decision. It's likelier than not that the FDA will approve lifileucel. But if it doesn't, and if the stock overreacts to the downside, I'd like us to leave some cash in the bank to add to our investment at a lower price.

Action to Take: Buy Iovance Biotherapeutics (Nasdaq: IOVA) up to $9.25 per share. Please size your investment at two-thirds a full position in your biotech portfolio.

Portfolio Review

BIOTECH FRONTIERS | PORTFOLIO

Company Name	Ticker	Purchase Date	Cost Basis	Closing Price	Market Cap ($m)	Cash ($m)	Debt ($m)	Enterprise Value ($m)	Total Return	Status
VIR BIOTECHNOLOGY	VIR	01-09-2024	$10.18	$9.23	$1,368	$1,685	$128	-$(189)	-9.33%	Buy Under $11.00
LYELL IMMUNOPHARMA	LYEL	01-09-2024	$2.07	$1.71	$526	$607	$65	-$(16)	-17.39%	Buy Under $2.35
NUVATION BIO	NUVB	01-09-2024	$1.51	$1.70	$336	$619	$5	-$(279)	12.58%	Buy Under $1.80
UNIQURE	QURE	01-09-2024	$6.62	$5.47	$323	$658	$165	-$(170)	-17.37%	Buy Under $7.25
SUTRO BIOPHARMA	STRO	01-09-2024	$4.03	$4.77	$209	$355	$38	-$(108)	18.36%	Buy Under $4.10
ATEA PHARMA	AVIR	01-09-2024	$3.45	$4.26	$264	$595	$3	-$(328)	23.48%	Buy Under $3.50
KODIAK SCIENCES	KOD	01-09-2024	$3.16	$5.27	$158	$346	$84	-$(104)	66.77%	Buy Under $3.30
SAGIMET BIO*	SGMT	01-09-2024	$5.56	$6.00	$118	$102	$0	$(16)	7.91%	Buy Under $6.75
ATHIRA PHARMA	ATHA	01-09-2024	$2.87	$3.17	$116	$173	$2	-$(55)	10.45%	Buy Under $3.50
IOVANCE BIOTHERAPEUTICS	IOVA	02-05-2024	$7.92	$8.68	$2,226	$129	$-	$2,097	9.60%	Buy Under $9.25
CHIMERIX	CMRX	02-08-2024	$0.91	$0.91	$81	$129	$-	-$(48)	0.00%	Buy Under $1.05

Closed Positions		Purchase Date	Cost Basis	Sell Price	Total Return	Status
CYTIER THERAPEUTICS	CYT	01-09-2024	$3.05	$3.12	2.30%	Sold February 8, 2024

Disclaimer: this hypothetical portfolio should not be considered investment advice or a recommendation to buy/sell any financial instrument. For informational purposes only. Investors should perform their own due diligence before buying or selling any financial instrument. No express or implied guarantee of accuracy or applicability to real-world trading. Cost basis refers to the closing price the day before a security is recommended.

**Sold 1/2 of Sagimet Bio (SGMT) on January 22, 2024 for a 231.29% gain. Recommended resuming a full position on February 8, 2024, up to $6.75 per share.*

As this month's issue features our first portfolio review, let me share a few words about how I approach this piece of our collaboration.

First, rest assured that I monitor the companies we've recommended in *Biotech Frontiers* daily. When I say "monitor," I don't simply mean digesting the stock-price movements, the news, and developments in the underlying science… all of which I do. I also mean speaking with biotech-industry insiders and proactively seeking color.

Second, I will update you on a company in our portfolio only when there's something important to discuss. I will only write about earnings reports, for example, when one contains a surprise or a noteworthy disclosure that affects our investment thesis. By only writing to you about a company when there's something material for us to talk about, I respect your time… and mine.

So with that context in mind . . . What a remarkable month **Sagimet Biosciences (Nasdaq: SGMT)** has had. The stock took off like a rocket on the back of terrific topline Phase II clinical-trial data on its lead drug candidate Denifanstat, appreciating over 200% in a week, hitting a high of $20 per share. Then the company raised $112.5 million in a secondary offering priced at $12.50 per share, heavily subscribed by large institutions, which prompted the stock to fall back.

Then, on February 6, Big Pharma behemoth Eli Lilly (NYSE: LLY) released successful Phase II data for its drug candidate tirzepatide, which likewise targets NASH – also known as fatty liver disease, which has reached epidemic proportions in the U.S. Eli Lilly's Phase II was not better than Sagimet's. But because it represents competition from a big player, the Lilly release precipitated a further decline in Sagimet's stock – and a parallel collapse in the stocks of several other biotechs focusing on treatments for NASH, including Madrigal Pharmaceuticals (Nasdaq: MDGL), Akero Therapeutics (Nasdaq: AKRO), and 89bio (Nasdaq: ETNB).

After its recent capital raise, Sagimet now has more than $200 million of net cash on its balance sheet. The stock's market capitalization is just about $200 million. So Sagimet is once again trading at a slightly negative EV.

In the meantime, the risk/reward in the stock has become even more attractive than when I first recommended it. The excellent Phase II data for Denifanstat de-risks both the science and the eventual prospects for regulatory approval. The capital raise further de-risks the balance sheet by giving the company a longer financial runway.

In our *Biotech Frontiers Investment Guidebook*, I wrote that biotech is full of surprises. I did not anticipate that Sagimet would explode 200% higher in response to excellent Phase II data. And I also did not anticipate that the stock would collapse after creditable Phase II data from a competitor drug at Lilly.

But we can use these surprises to our benefit. As Sagimet today presents an excellent risk/reward, I recommend the following:

- If you are a *Biotech Frontiers* subscriber who got into Sagimet and sold one-half of your position after we recommended taking profit on gains above 100%, I recommend you now buy back a half-sized position so that you again have a full-sized one.
- If you missed out on our original Sagimet recommendation because the stock was trading above our "buy up to" price, I recommend you now buy a full-sized position.

Action to Take: Buy Sagimet (Nasdaq: SGMT) up to $6.75 per share.

We will be making one other change to the 10-stock basket of negative-EV biotechs that we recommended last month. **Cyteir Therapeutics (Nasdaq: CYT)** is doing what I believe many early-stage biotech stocks that trade at negative EV should do: liquidate, sell its assets, and return cash to shareholders. With Cyteir's stock price currently around $3.12, the stock's liquidation value is substantially higher where the shares trade today. However, we can replace Cyteir with a more compelling negative-EV biotech.

Action to Take: Sell Cyteir Therapeutics (Nasdaq: CYT).

The new member of our 10-stock negative-EV basket is **Chimerix (Nasdaq: CMRX)**, which currently trades at an $80 million market cap with $195 million of cash on its balance sheet, giving the company a negative EV of about $115 million.

Like several other members of our negative-EV basket, Chimerix is a cancer-fighting company. Its lead compound, ONC-201, targets a rare and terrible form of pediatric brain cancer – where it has already shown striking results in a small handful of patients who have received the treatment on a compassionate-use basis. ONC-201 has received three important designations from the FDA: Orphan Drug Designation, Fast Track Designation, and Rare Pediatric Disease Designation.

The last of these means that, if ONC-201 is eventually approved, Chimerix will receive an FDA Priority Review Voucher – effectively, an "express lane pass" that enables any company presenting the voucher to have the FDA review a candidate drug on a significantly expedited timetable. Priority Review Vouchers are typically sold for $100 million. (Indeed, French biotech company Valneva announced it had sold its Priority Review Voucher for $103 million earlier this week.)

I think Chimerix stands a good chance of receiving such a voucher, which by itself would be worth more than the entire current market cap of the company. I'm also encouraged that Chimerix's largest shareholder is RA Capital, one of the most well-respected specialist biotech venture capitalists in the world.

Action to Take: Buy Chimerix (Nasdaq: CMRX) up to $1.05 per share.

That's all for this month. I look forward to updating you around February 24 regarding the FDA's decision on Iovance Biotherapeutics.

Best regards,

Erez