

## **Waking Up the Warriors: The Rise of Cancer Immunotherapy**

Malini Gandhi

Class of 2017

[malini.gandhi@yale.edu](mailto:malini.gandhi@yale.edu)

ENGL 121-07: Writing About Medicine and Public Health

Professor Randi Epstein

Summary of Paper Assignment: The assignment for this paper was to delve into any topic in medicine or public health by explaining the science, detailing the history, and incorporating interviews with doctors, researchers, and patients. My paper focuses on the recent rise of cancer immunotherapy, a treatment that harnesses the body's immune system to fight cancer.

Note: The names of the patient and his wife have been changed in this essay to protect their confidentiality.

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**Waking Up the Warriors**  
*The Rise of Cancer Immunotherapy*

Michael Davis first felt that something was wrong when he was walking his dog on the steep, hilly roads of Vancouver. It was winter, and around him the mountains stretched wide. He would time himself on the route – after going to the naval academy as a teenager and learning to fly planes, he had spent his life training for marathons and triathlons, and even now he loved the competition of it all. But as the days grew longer, he found that he was walking slower and slower. When he took long breaths, he felt a pain deep inside. His doctor prescribed him an inhaler, but the pain didn't go away. Thinking he might have a blood clot from travelling, his doctor did a full work-up – but never found a clot. The day Davis received the diagnosis of lung cancer was March 18, 2015. It was not yet spring.

Davis has feathery white hair and deep lines across his forehead; when he smiles, his eyes brighten and his whole face crinkles. He remembers the first thing he and his wife Lisa did after receiving the diagnosis: go online. “The life expectancy stats were terrible,” he said, “It was a shock. You think, other people get cancer, not me. Until it happens.” The cancer had already invaded his pancreas, and there were tiny seeds in his brain. He started on chemotherapy, but after a few months, the tumor loomed as large as ever.

It was then that his doctor suggested he enter a trial for a drug that was the hub of excitement among oncologists: a new therapy that harnesses the body's immune defenses to fight cancer. Doctors call it immunotherapy, as in therapy for your immune system – as opposed to standard chemotherapy, which is chemical treatment to kill cancer cells. Davis hadn't heard of it, but after a few infusions, something remarkable happened. The tumor in his lungs faded to a thin, hovering shadow. The tumor in his pancreas disappeared completely.

Davis doesn't know what will happen now. The cancer still lingers in his lungs. But he says, "Cancer used to be thought of as a terminal disease, and now it is becoming a chronic disease. And this – this immunotherapy – maybe this is the bridge."

It's a bridge whose foundations have been slowly laid for over a century, but only in the past few years has it started to rise and take shape. In less than a decade, cancer immunotherapy has gone from a fringe idea to one of the most promising forms of cancer treatment. The excitement in the medical community is palpable. Just last month, Facebook billionaire Sean Parker pledged \$250 million to support immunotherapy research<sup>1</sup>. Scientists are citing a paradigm shift in how cancer is treated. Yet despite the rising excitement, doctors warn that there is still a ways to go.

In the fall of 1890, a young bone surgeon examined the swollen hand of a girl in his New York City office. A slender, shy man who had grown up among the rows of potatoes on his father's Connecticut farm, William Coley was barely out of medical school when the clear-eyed seventeen-year-old Elizabeth Dashiell came to him with pain in her hand<sup>2</sup>. She turned out to have a sarcoma, a cancer of the bone, and over the next few months, little lumps on her breasts grew to the size of goose eggs. Her body became studded with hundreds of tiny tumors. She vomited up blood<sup>3</sup>. In January of 1891, Dashiell died, Coley by her side. He was twenty-eight-years old and shaken.<sup>4</sup>

Dazed, Coley began to sift through the clinical records at New York City Hospital, searching for sarcoma.<sup>5</sup> It was then that he stumbled across something strange. Tucked into one

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<sup>1</sup> Pollack, Andrew. "Sean Parker, a Facebook and Napster Pioneer, to Start Cancer Immunotherapy Effort." *The New York Times* (April 13, 2016)

<sup>2</sup> Hall, S. *A Commotion in the Blood: Life, Death, and the Immune System*. (New York: Henry Holt, 1997), 22,30.

<sup>3</sup> *Ibid*, 27, 28.

<sup>4</sup> *Ibid*, 29.

<sup>5</sup> *Ibid*.

of files was the case of Fred Stein, a German immigrant who, after a botched surgery failed to remove a growth behind his ear, developed a raging bout of the bacterial infection erysipelas<sup>6</sup>. According to the record, within a few months, something miraculous happened – Stein’s tumor melted away.<sup>7</sup> Mystified, Coley set out in search of this man who had disappeared into the streets of New York over a decade earlier – and, after weeks of trudging through the Lower East Side knocking on tenement house doors, Coley finally found him, black-bearded, a telltale scar snaking behind his ear<sup>8</sup>. His cancer had never come back. Exhilarated and convinced that the infection had cured Stein’s cancer, Coley began injecting his patients with erysipelas bacterial strains<sup>9</sup>. So began the tangled history of cancer immunotherapy.

During his lifetime, Coley would famously inject over 900 cancer patients with an infectious, fever-inducing brew dubbed “Coley’s toxins.”<sup>10</sup> Yet despite some successes, muddled understanding of immunology and cold opposition from doctors who championed newly introduced radiation therapies meant that by the time Coley died, his ideas were widely ridiculed<sup>11</sup>. In 1963, Coley’s toxins were added to the American Cancer Society’s list of “Unproven Methods of Cancer Management” – which included quack therapies like mistletoe.<sup>12</sup>

The dismissal of immunotherapy as a mistletoe-like sham hinged on a central question in tumor immunology that, as Stephen Hall writes in *A Commotion in the Blood*, “works at a boundary as much philosophical as scientific: Where does the Self end and Non-Self begin?”<sup>13</sup> The immune system is designed to root out and attack “foreign” invaders. But they are trained to pass by and hold their swords when encountering “self.” Since cancer cells come from self,

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<sup>6</sup> Ibid, 41

<sup>7</sup> Ibid.

<sup>8</sup> Ibid, 42.

<sup>9</sup> Parish et al. “Cancer immunotherapy: The past, the present and the future.” *Immunology and Cell Biology* (2003) 81, 106.

<sup>10</sup> Ibid.

<sup>11</sup> Hall, 116.

<sup>12</sup> Ibid.

<sup>13</sup> Ibid, 361

immunologists during much of the twentieth century reasoned, naturally, that they must *look* like self.<sup>14</sup> The idea of coaxing the immune system into attacking what looked like one of their own was considered ludicrous and, frankly, impossible. Some early twentieth-century immunologists were particularly snarky: William Woglom wrote in 1929 that, “It would be as difficult to reject the right ear and leave the left intact as it is to immunize against cancer.”<sup>15</sup>

Over the twentieth century, attitudes towards immunotherapy seesawed back and forth as immunologists debated this central question of self and non-self. Then, in the 1980s, two things happened. First, scientists discovered interferon and interleukin-2, powerful molecules that kick immune cells into action. Remarkably, these molecules melted away tumors in some patients.<sup>16,17</sup> Though the therapy was highly toxic, it suggested that revving up the immune system to fight cancer was a possibility.<sup>18</sup>

And second, immunologists realized that tumors might not appear so innocent to the immune system after all. Instead, as Hall writes, tumors “teeter at the very edge between Self and Non-self.”<sup>19</sup> It’s not like cancer is a new, foreign invader – more like the same old self, but in a new outfit. As cancer cells spiral out of control, they express odd-looking proteins that help them proliferate feverishly and invade other tissues<sup>20</sup>. They end up looking like self gone a bit mad – still self, but wearing wonky hats. The immune system is not oblivious – it sees these hats and realizes that it is no longer quite dealing with one of their own.<sup>21</sup> There is a traitor in their midst.

The key to this discovery was a dark-haired German woman working at a post office

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<sup>14</sup> Parish, 106-7.

<sup>15</sup> Woglom, W. H. Immunity to transplantable tumors. *Cancer Res.* 4, 129 (1929).

<sup>16</sup> Kirkwood et al. “Comparison of intramuscular and intravenous recombinant alpha-2 interferon in melanoma and other cancers.” *Ann Intern Med* (1985) 103(1): 32-6.

<sup>17</sup> Rosenberg et al. “Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer.” *New Engl J Med* (1985) 313(23): 1485-92.

<sup>18</sup> Atkins et al. “Cancer immunotherapy: Past progress and future directions.” *Seminars in Oncology* (2015) 42: 4, 518.

<sup>19</sup> Hall, 361.

<sup>20</sup> *Ibid*, 361-2.

<sup>21</sup> *Ibid*.

outside of Frankfurt. Hall calls her “Frau H.”<sup>22</sup> Frau H was dying from melanoma when her doctors, desperate, tried something different. They removed Frau H’s cancer cells and altered them a bit. Then they injected them back. Remarkably, Frau H went into remission – and went back to the post office.<sup>23</sup> Somehow, Frau H’s body was seeing her cancer as something to fight. Her immune cells were spotting some molecule on her tumor – one of the funny-looking hats – that flagged it as a traitor. And they were attacking. Intrigued, the French immunologist Theiry Boon set out to find out what this molecule was. Fourteen years later, he found it: a protein he named MAGE-3.<sup>24</sup> The first “tumor-associated antigen” – what immunologists call the strange “not-quite-self” proteins that lets the immune system sniff cancer cells out – had been discovered. Armed with this finding, researchers set out to make new cancer vaccines, confident that if they immunized patients with these tumor-associated antigens, they would be successful.<sup>25</sup>

But it wouldn’t be so easy. Dr. Mario Sznol, Professor of Oncology at Yale and a specialist in skin cancer, remembers the string of failures in the 1980s and 90s. Sznol is a small man with round wire glasses and wisps of brown hair; he talks slowly and wistfully, articulating each word. His office is impeccably clean, the circular table at the front gleaming. “Almost everything we tried in the late 80s and 90s just didn’t really work,” Sznol said.

What catapulted immunotherapy forward in the past decade was the simple realization that traitors don’t like being found out. It turns out that to avoid getting busted, cancer cells carry around a circus bag of tricks to soothe the anger of their attackers.<sup>26</sup> One of these tumor tricks is a “sleeping spell” of sorts. Special proteins called immune checkpoints normally play important

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<sup>22</sup> Ibid, 350.

<sup>23</sup> Ibid, 352-3.

<sup>24</sup> Ibid, 365.

<sup>25</sup> Atkins, 519.

<sup>26</sup> Mellman et al. “Cancer immunotherapy comes of age.” *Nature* (2011), 480.

roles in the body in toning down hyperactive immune responses.<sup>27</sup> But tumor cells co-opt these proteins to make T cells, a powerful class of immune warriors, go drowsy.<sup>28</sup>

Researchers reasoned that all they had to do was block tumors from putting immune cells to sleep. If immune checkpoints could be inhibited, then the immune system could be woken up to fight cancer. The sleeping spell could be lifted. In 1996, they found something that seemed to work: a drug that blocked the immune checkpoint CTLA-4.<sup>29</sup> This drug showed “remarkable activity” in patients with advanced melanoma, said Sznol. Yet improvement was mostly limited to melanoma, and did not extend to other more common cancers. As Sznol put it, “anti-CTLA-4 was still not a home run – it was kind of a single.”

The home run would come a few years later, when another immune checkpoint axis, PD-1/PD-L1, was discovered. When cancer cells sense an impending attack from T cells, they express a molecule called PD-L1 on their surfaces. PD-L1 engages with a receptor on T cells called PD-1, which dampens T cell activity, putting these warriors to sleep just as they are reaching for their swords.<sup>30</sup> Blocking PD-L1 with a drug could jolt the T cells awake and let them pick up their swords again. In 2010, these drugs entered a large clinical trial – and this is when immunotherapy took off.

When the very first activity began to emerge from this trial, Sznol said it was clear that “this was something very different.” He remembers driving down to New York City and sitting down with two Mederex officials who were producing anti-PD-L1 to warn them that if they didn’t expand the trial so more patients could access the drug, “I’m going to bus my patients down and we’re going to picket your facility.”

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<sup>27</sup> Chen et al. “Oncology Meets Immunology: The Cancer-Immunity Cycle.” *Immunity* (2013) 39(1): 1-10.

<sup>28</sup> Ibid.

<sup>29</sup> Mellman, 484.

<sup>30</sup> Sznol et al. “Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer.” *Clin Cancer Res* (2013), 19(5): 1021-34.

Sznol said he “wasn’t sure if they took me seriously,” but regardless, the trial was expanded – and the results were stunning.

“What we saw is good activity in renal cancer, and in melanoma we saw a 30% response rate, which is the best single agent activity we’d ever seen. But the thing that changed the world was that there was activity in lung cancer,” Sznol said. “For the first time, you could see meaningful activity in a high incidence cancer like lung cancer. That’s when people first started to get excited.”

Dr. Roy Herbst, Chief of Oncology at Smilow Cancer Hospital at Yale-New Haven and a lung cancer specialist, clearly remembers the first lung cancer patients he treated with immunotherapy.

“I remember this one patient, a 68 year old guy who had failed all prior chemo,” Herbst said. “I saw him later after he was treated with immunotherapy and he was walking around, completely fine. It was incredible. I had been doing cancer research for a long time, and I had never seen anything like this. I said to myself then that we have a miracle on our hands.”

Sznol, too, realized that this was something significant.

“I remember the day I presented the initial clinical trial data was a Tuesday morning, and I thought my God, this is the best phase one data we’ve ever seen, if I present this data my phone is going to be ringing off the hook,” Sznol said. “So I came in the next day after the presentation and cleared off my schedule, waiting for the phone calls to come, but no one called. I don’t think anyone still quite recognized just how important this was.”

But it didn’t take long. One by one, the anti-PD1/PD-L1 drugs were shown to have activity in almost every major cancer. The excitement skyrocketed. At the first International Cancer Immunotherapy Conference in September 2015, the presentations were standing room



only.<sup>31</sup>

Today, over half of the current cancer clinical trials in the United States involve some form of immunotherapy.<sup>32</sup> ““Everyone had always said that ‘immunotherapy won’t work for lung cancer,’” Herbst said. “Now we are eating our words. Now everyone’s like, ‘of course, I always thought it would work.’” And so, over a century after William Coley found himself face-to-face with a black-bearded, cancer-free man with a scar behind his ear, cancer immunotherapy has risen from the heap of ridiculed therapies to a brightening spotlight.

Yet despite the excitement, immunotherapy is far from a cure-all. Davis remembers when he first started in the immunotherapy trial. At every milestone in his cancer treatment, Davis sends what he calls a “Davisgram” to his family and friends: “it’s like a telegram, a little email to keep everyone up to date on my cancer treatment,” he explains with a laugh, “I’ve gotten some great comments on them.” When he sent out the Davisgram to announce that he was starting immunotherapy, he was hopeful – but also knew enough not to get too optimistic. Since his diagnosis, Davis said that he and his wife Lisa had become “crazy about medical literacy” and decided that, “instead of crying, we’d tackle the problem and challenge the doctors and ask lots of questions” (“Lisa, she’s a smart one,” he said, smiling). And so they knew there was a high chance he may not respond to the immunotherapy at all.

“We knew that it wasn’t a magic bullet,” Davis said. “There are some people that have amazing cures, but those are rare. And there are certainly some people who see their lifespans extended. But for many people, it doesn’t do anything.”

This is one of the biggest problems with cancer immunotherapy right now – it doesn’t

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<sup>31</sup> Gorman, C. “Cancer Immunotherapy: The Cutting Edge Gets Sharper.” *Scientific American*. (2015)

<sup>32</sup> Ibid.

work for everyone. And at this point, it's not entirely clear who will respond and who won't.

Herbst put it bluntly: "Immunotherapy is incredible – we're seeing responses in lung cancer that five years ago we never would have dreamed of. That's the good news. The bad news is that it only works in one out of four. What about the other three?"

Predicting who will respond to immunotherapy is a tricky business – something that Dr. David Rimm, Director of Translational Pathology at Yale, knows well. Rimm's desk is strewn with old copies of *Cell* and hundreds of glass microscope slides tinged with blue. He is a skinny man with a friendly, frank way of speaking.

According to Rimm, the simplest idea for predicting which patients will respond is just to look at how much PD-L1 (that's the molecule tumors use to put immune cells to sleep) is expressed. If tumors aren't casting this sleeping spell to begin with, then drugs that block the sleeping spell won't make a difference – "it isn't rocket science," Rimm said.

Sliding a slice of tumor under the microscope, Rimm points out a web of blue ("those are the tumor cells," he says) and the occasional flush of brown ("that's the PD-L1.") In this sample, the brown is rare and faint, like a breath – Rimm says he would categorize this sample as "less than 1%" in terms PD-L1 expression. "Compare that to this one," he says, and whips another slide under the microscope – this time the brown is bolder, more frequent.

Researchers have been using this very test to measure tumor PD-L1 levels and see if these levels can predict response to immunotherapy. They have had some success.<sup>33,34</sup>

But the test isn't perfect. Dr. Leena Gandhi, Director of Thoracic Oncology at New York University Langone Medical Center, stresses that, "while the PD-L1 expression assay is the best thing we have at present, it's by no means a good predictor." One issue is that PD-L1 expression

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<sup>33</sup> Herbst et al. "Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients." *Nature* (2014) 515.

<sup>34</sup> Garon et al. "Pembrolizumab for the treatment of non-small-cell lung cancer." *The New England Journal of Medicine* (2015) 372:21.

in a tumor is heterogeneous, rampant in some regions of the tumor but absent from others.<sup>35</sup> This means that just looking at a small tumor slice could give a false impression of overall PD-L1 levels. Back under the microscope, Rimm points out a bold patch of brown right next to a stretch of blue. “Look here’s negative staining right next to positive staining,” he says, “If your core biopsy went like this, you might have thought it was negative.” Researchers are trying to improve these tests – but, as Sznol said, “it’s going to be a long slog.”

Why do the tumors of some patients cast this PD-L1 sleeping spell – the strokes of brown under Rimm’s microscope – and others don’t? For some patients, the reason PD-L1 is not expressed could simply be because there are no immune cells in their tumors.<sup>36</sup> If there are no attackers nearby, there is no reason for the tumor to feel threatened and cast a sleeping spell.

According to Sznol, for many patients who do not respond to PD-1/PD-L1 immunotherapy, this could be precisely the problem: “their tumors just don’t have T cells.” If immune cells never reach the tumor in the first place, then drugs meant to awaken them once they get there won’t make a difference. There’s no point in trying to rouse an army to attack a fort if the army never made it to the fort to begin with.

So how can the army be brought to the fort – how can doctors help lure immune cells to tumors? Sznol said a few things could be going wrong in patients with tumors empty of immune cells. Perhaps their tumors are somehow preventing T cells from approaching. Right now, Sznol is experimenting with drugs that help T cells journey to tumors. Or, perhaps their T cells never spotted those “not-quite-self” proteins that mark a tumor as a traitor. So the T cells never came

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<sup>35</sup> McLaughlin et al. “Quantitative Assessment of the Heterogeneity of PD-L1 Expression in Non-Small-Cell Lung Cancer.” *JAMA Oncology* (2016).

<sup>36</sup> Sznol, M. “Blockade of the B7-H1/PD-1 Pathway as a Basis for Combination Anticancer Therapy.” *The Cancer Journal* (2014), 20:4.

over to the tumor because they just didn't know about it. Here, doctors are looking at injecting patients with the "not-quite-self" proteins (a cancer "vaccine"). This strategy could show these "not-quite-self" proteins to T cells, grabbing their attention and drawing them to tumors – a bit like fishing bait.

One idea that has incited conversation – and controversy – among oncologists is that killing cancer cells with chemotherapy could help lure in immune cells to a tumor.<sup>37</sup> Chemotherapy causes cancer cells to burst open and release their contents. Some speculate that this could allow "not-quite-self" tumor proteins to spill out in clouds and attract immune attention – like a whole toppled-over barrel of fishing bait. Ira Mellman, Genentech's vice president of cancer immunology, said that, "chemotherapy may in fact be, to some extent, immunotherapy."<sup>38</sup>

But not everyone is on board with this idea. Gandhi warns that, "while there is a lot of postulation about how chemotherapy could cause cell killing and provoke an immune response, we don't really know that." Sznol came down even more harshly: "there are lots of people in the field who buy into that whole antigen release thing, but I think it's all bullshit. I don't spend any of my time doing that."

Other researchers are trying to bypass the hassle of luring in immune cells to the tumor by hand-delivering T cells specially engineered in the lab to target "not-quite-self" tumor proteins. These sci-fi-like constructs are known as CAR-T cells.<sup>39</sup> Dr. Samuel Katz, a pathologist at Yale, is one of the many researchers working on CAR-T. The technique is promising – but can be dangerous if these killing machines go rogue, provoking too strong an immune response or

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<sup>37</sup> Mellman, 487.

<sup>38</sup> Gorman.

<sup>39</sup> Jackson et al. "Driving CAR T-cells forward." *Nature Reviews Clinical Oncology* (2016)

turning on innocent cells. Sznol dubbed CAR-T cells “little atomic bombs.” But Katz is working to make this therapy safer – and is hopeful that CAR-T cells will prove to be powerful new tools.

In this frenzy of research activity, doctors are excited – but many are wary of becoming too optimistic.

“The danger in the field is that while there is a lot of excitement, as there should be, getting to the next level will be very hard,” Sznol said.

And Gandhi said that the current hype surrounding immunotherapy is sometimes harmful. Due in part to the fanfare accompanying the rise of immunotherapy, she said that both doctors and patients often push forwards with immunotherapy treatment long after it becomes clear that it’s not working. According to Gandhi, there is a persisting misconception in the medical community that it can take longer to see a response to immunotherapy than to other treatments, and so doctors should wait longer before abandoning it. Yet in reality, “the data point exactly in the opposite direction. Most responses to immunotherapy, if they are going to happen, occur right away.”

“This has led to an unfortunate situation where both doctors and patients continue immunotherapy far longer than they should, often to the point where patients are not well enough to receive any other treatment,” Gandhi said. “It’s led to people on their deathbed still wanting to continue immunotherapy, because there’s not a good understanding that it’s not miracle drug.”

And the road to making it a “miracle drug”, Sznol said, will be a difficult one. He said that while a lot of his colleagues are more optimistic, he thinks it will be “very tough.”

“I get asked almost every day what it will take to take this to the next level. I don’t think I know. I could give you a hundred different possibilities, and I don’t know which of those will

sort itself out. We're in this period where we're just doing a lot of trials, and praying that a signal will come out that's so strong that we'll be able to see it. But it may not be that easy," he said.

Looking back on the tides of immunotherapy over the past century, Sznol said he doesn't think this is just another wave of false hope – but whether the progress will plateau here or really take off, he's not sure.

"Anti-PD-L1 is more active than any other therapy that's been developed – this is certainly not a flash in the pan," Sznol said. "But there is still a huge amount of work to be done."

Meanwhile, Davis is waiting on his next CT scan. He had to take a break from the anti-PD-L1 drug for a bit because his lungs became clogged with too much inflammation – a side effect of waking up the immune system. Now, he's taking another drug to dampen the inflammation, but said that it makes him exhausted. "I used to be able to run marathons, but I can't do that anymore. I tried to go for a two-mile walk this morning and just couldn't do it. It's been very discouraging." He said he and Lisa didn't get in much skiing in Vancouver this past winter, "but next winter we will."

Davis said that having cancer is like carrying an elephant with him. "The elephant might be sleeping, and then there's no problem," he said. "But on the other hand, the elephant might be out romping around. Elephants have bodily functions, and you never know when it's going to do it. So you are always carrying this elephant wherever you go – it's there with you, all the time."

Immunotherapy has quieted this elephant down, but it still lumbers silently in his lungs. Davis is not sure if it's going to stay quiet. This week, he'll be meeting with his doctors to see what Plan B is – if there is one – if immunotherapy doesn't work.

“It’s been an interesting journey, and I’ve met a lot of passionate people who think they are really on the cusp of something – this immunotherapy is the first thing that has really shown action like this,” Davis said. Yet “as a cancer patient, I live CT scan to CT scan...And I don’t know what the next day will bring.”

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