IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Diaz et al.		
U.S. Patent No.:	11,591,393	Attorney Docket No.:	52261-0005IP1
Issue Date:	February 28, 2023		
Appl. Serial No.:	17/465,101		
Filing Date:	September 2, 2021		
Title:	CHECKPOINT BLOCKADE AND MICROSATELLITE INSTABILITY		

DECLARATION OF DR. DUNG LE

I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 10/4/2024

By: Dung Le Digitally signed by Dung Le Date: 2024.10.04 11:39:22 -04'00'

Dung Le, M.D.

JHU 2130
Merck Sharp v. Johns Hopkins
IPR2024-00240

I, Dr. Dung Le, declare as follows:

1. I am one of the inventors of United States Patent No. 11,591,393, which is entitled "Checkpoint Blockade and Microsatellite Instability" (the "'393 Patent").

2. I am employed by the Johns Hopkins School of Medicine. I am not otherwise being paid for the time I spent on this matter.

3. I am a professor of oncology at the Johns Hopkins University School of Medicine and a member of the Johns Hopkins Bloomberg-Kimmel Cancer Center. I completed my residency in 2004 and my fellowship in oncology in 2007, both at Johns Hopkins. My research interests include novel approaches to treating patients with gastrointestinal cancer. I have served as the principal investigator (PI) on many clinical trials focused on testing immunotherapy in patients with gastrointestinal cancers. As relevant here, I served as the national principal investigator on two studies on the use of the anti-programmed death-1 (PD1) drug pembrolizumab to treat cancers with mismatch repair deficiency. These studies were referred to by Merck in its applications to FDA as KEYNOTE-016 and KEYNOTE-164. I was also a participant in additional clinical trials of pembrolizumab including KEYNOTE-158 (cohort K) and KEYNOTE-177, a Phase III randomized study that tested pembrolizumab as a first-line therapy for

colorectal cancer (CRC). These studies led to multiple FDA approvals of pembrolizumab for the treatment of MSI-H cancers.

4. I understand that Merck has challenged the validity of the claims of the ’393 patent and related patents as part of a dispute before the United States Patent and Trademark Office.

5. I have been asked by the Johns Hopkins University (“JHU”) to submit this declaration to provide certain facts that I have personal knowledge of relating to: (1) my team’s June 10, 2013 submission of information related to clinical trial NCT01876511 to ClinicalTrials.gov; (2) the presentations and publications relating to our subsequent clinical study of pembrolizumab in patients with MSI-H/dMMR and microsatellite stable (“MSS”)/MMR proficient cancers; and (3) the impact that our invention has had and continues to have on the care of cancer patients.

6. NCT01876511 was entitled, “Phase 2 Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors.” EX1005 (ClinicalTrials.gov, NCT01876511). In compliance with NIH regulations, our team first submitted information for this clinical trial for posting on ClinicalTrials.gov on June 10, 2013. *Id.*

7. MK-3475 was the reference name used by Merck for the checkpoint inhibitor drug pembrolizumab at the time NCT01876511 was first submitted.

Merck now sells pembrolizumab under the brand name Keytruda. These three names are interchangeable, but I will generally use pembrolizumab.

8. On and before June 10, 2013, my understanding is that pembrolizumab had not been approved by the United States Food and Drug Administration ("FDA") for the treatment of any disease.

9. Hopkins researchers had, for several years before the NCT01876511 submission, been studying a different checkpoint inhibitor drug, nivolumab,[1] in the treatment of various types of cancer, including colorectal cancer. While nivolumab was effective in treating some types of cancer, the data from the study of nivolumab demonstrated that it was generally ineffective for the treatment of colorectal cancers, yielding no response in 32 of 33 colorectal cancer patients. EX1013 (Topalian); EX2024 (Brahmer). Based on this data, CRC patients were not understood to be good candidates for anti-PD-1 therapy.

10. In those earlier studies, there was, however, one anomalous patient who experienced complete remission when treated with nivolumab. My colleagues, Drs. Topalian and Pardoll, as well as other JHU researchers involved in those studies could not explain the patient's remarkable response to nivolumab. In discussions with our cancer genetics colleagues, Drs. Vogelstein, Kinzler,

[1] Nivolumab is now sold by Bristol Meyers Squibb, under the brand name Opdivo. *See* EX2088.

Papadopoulos and Diaz, the notion that the patient could be microsatellite instability high ("MSI-H") was suggested. When we tested this patient, we learned that he was indeed MSI-H. These revelations led to our hypothesis that MSI-H might serve as a biomarker to identify patients who would respond well to treatment with anti-PD-1 therapies. The clinical trial that followed the submission of NCT01876511 was performed by the JHU team in part to investigate whether MSI-H could be used as biomarker to identify patients who would be likely to respond to treatment with anti-PD-1 therapy and should therefore receive the treatment. We hypothesized that MSI-H patients would benefit from treatment with these drugs and patients who were MSS would be unlikely to benefit from these drugs.

11. My team and I designed a study with three experimental arms that would test our hypothesis in (A) MSI-H colorectal cancer patients, (B) MSS colorectal cancer patients, and (C) MSI-H non-colorectal cancer patients. The study was designed to comply with JHU Institutional Review Board (IRB) requirements. Each of the arms of the study is referred to as an "experimental" arm because patients in each arm would be treated with an investigational drug for which there was no FDA approval. The study was designed without a control arm, in which patients would have been treated with the standard of care treatment at the time, to use as a comparison for the treatment arms. We appreciated that as a

small study without a control arm, the results of our study would have to be extraordinarily strong to be of value.

12. If our hypothesis was correct, we would see substantially more patients in the MSI-H CRC arm respond to treatment with pembrolizumab than in the MSS CRC arm. If our hypothesis was wrong, we would see no responders in either arm (as in the prior nivolumab studies) or a similar number of responders in both arms. If our hypothesis was wrong, we likely would have concluded that the anomalous response previously seen in the one colorectal patient was not tied to his MSI-H status.

13. We proposed the study to Merck in a Letter of Intent in December 2012. My team and I also prepared a draft protocol for the underlying study and shared it with Merck in February of 2013. Merck's clinical research team accepted our proposal with minor edits to dosing and patient scan timing that were in line with dosing/scan regimens then being used by Merck in other trials.

14. My team filed an Investigational New Drug (IND) application with FDA for our proposed clinical trial. Dr. Luis Diaz was the IND holder. As the IND holder, Dr. Diaz was responsible for the overall conduct of the study and for reporting our results to FDA. Before we submitted NCT01876511, we also obtained consent from Merck to cross reference Merck's IND for pembrolizumab.

15. I was the lead principal investigator responsible for all sites in NCT01876511 and was responsible for the day-to-day running of the study.

16. My understanding was that our proposed trial of pembrolizumab could not proceed without our study first being registered on ClinicalTrials.gov. By June of 2013, I had worked on several dozen human clinical studies and had served as the principal investigator on approximately 10 human clinical studies. Before beginning work on any of these studies, I understood that approval by the JHU Institutional Review Board (IRB) and the posting of a compliant clinical trial submission on ClinicalTrials.gov were prerequisites. In addition, Merck required that JHU and I, as the Principal Investigator, register NCT01876511 on the ClinicalTrials.gov website prior to shipment of pembrolizumab for use in the study. EX2131 (IICT Agreement), Section 9.F).

17. Our June 10, 2013 submission to ClinicalTrials.gov (EX1005) describes our experimental plan to test the hypothesis that MSI-H might be an effective biomarker to identify cancer patients likely to be responsive to treatment with pembrolizumab.

18. It is my understanding that Federal regulations require that ClinicalTrials.gov submissions include certain details about a planned human clinical study, including a description of the study, conditions to be treated, the study design including the number of arms and interventions, study outcomes to be

measured, and study eligibility. I understand that these details must also be regularly updated until the study is complete. As required by the terms of our contract with Merck and our understanding of the applicable regulations, we updated the NCT01876511 submission with protocol amendments and clinical study data 28 times over the years between 2013 and 2020.

19. I was not paid to prepare the trial protocol or to register the clinical trial (NCT01876511) on ClinicalTrials.gov. My team and I were not paid by Merck or any other company to conduct our initial study. In fact, Merck did not provide any financial support for the initial phase of our study. Instead, Merck supplied us with sufficient pembrolizumab to conduct our study. With support from the non-profit organization Swim Across America and other philanthropic sources, we were able to conduct our study and provide treatment to the enrolled patients free of charge, which is common in oncology clinical trials. We also did not expect to benefit directly from any future sales of pembrolizumab because JHU is an academic research institution that does not sell pharmaceutical products.

20. For some drugs, efficacy data can be collected in animal models prior to performing a human clinical trial. Unfortunately, before conducting our human clinical trial, we could not obtain data on the efficacy of pembrolizumab in human patients with MSI-H cancers using animal models. There were then and still are no animal models that accurately represent the response of human MSI-H cancers to

checkpoint inhibitors. Unlike other drugs, immunotherapies such as anti-PD-1 drugs like pembrolizumab target the human immune system, and at the time the effect of such drugs on these types of cancer in the human body could not be modeled in animals. Even today, the effect of drugs such as pembrolizumab on human cancer are best studied in humans. In these circumstances, by necessity, the clinic is the experiment.

21. To evaluate whether our MSI-H hypothesis was correct, our only option was to conduct a human clinical trial. And before we could conduct a human clinical trial, we had to first register our clinical trial (NCT01876511) on ClinicalTrials.gov by submitting our experimental plan.

22. As of June 10, 2013, the date that our original submission was posted on ClinicalTrials.gov, we were not yet recruiting patients for the clinical trial. EX1005 (ClinicalTrials.gov, NCT01876511), 3. We received IRB approval for the clinical trial on July 3, 2013, and our clinical trial number was activated on August 27, 2013, after which we were allowed to begin recruiting patients.

23. While our hypothesis made sense to me, I have been involved with many human clinical studies investigating hypotheses that seemed meritorious, including some which had supporting animal data, only to find the hypotheses were not born out by clinical testing. In fact, I am aware of several clinical studies conducted by Merck on pembrolizumab that failed.

24. For example, just after JHU's clinical study was initiated, Merck began its own study on the use of pembrolizumab to treat colorectal cancer patients, using the biomarker PD-L1[2] to identify patients for treatment with pembrolizumab. EX2132 (December PLoS One 2017 Article, "Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma," hereinafter "O'Neil"). In this study, posted to ClinicalTrials.gov on February 3, 2014 as NCT02054806 (EX2080 (NCT02054806 study record)), all but one patient with PD-L1 positive colorectal cancer experienced disease progression after treatment pembrolizumab. That one patient experienced a partial response. EX2132 (O'Neil), 1. Thus, even though using the PD-L1 biomarker seemed like a promising approach, Merck's clinical testing showed that it did not work. This is the unfortunate reality of cancer research—promising hypotheses rarely result in successful clinical trials. One noteworthy point from Merck's trial is that the lone patient who responded was determined to be MSI-H. The clinical study authors concluded that this result "warrant[ed] further evaluation in [the MSI-H] patient population," (EX2132 (O'Neil), 2) based on our on-going study of MSI-H in CRC patients.

[2] PD-L1 is a ligand of the PD-1 receptor and PD-L1 overexpression in tumors was thought to potentially enable tumor cells to block antitumor immune responses. (EX2132 (O'Neil), 1).

25. More recently, several clinical trials involving pembrolizumab (Keytruda) also failed. EX2078, 1 (April 2023 Wall Street Journal article, "Merck Keeps Striking Out on Expanding Its Cancer-Drug Juggernaut"); *see also* EX2076 (December 2023 article, "Merck suffers bad week as 3 Keytruda combination trials fail"); EX2079 (May 2024 article, "Merck's trial of Keytruda regimen fails to meet primary endpoint"); EX2077 (August 2024 article, "Merck's Keytruda flunks pivotal studies in early-stage lung and skin cancers")

26. When we began our study, my team was hopeful that our hypothesis would be supported by the clinical data but appreciated that there was a significant possibility that it would not. After all, the basis for our study was a single patient who went into complete remission when treated with a different drug, while thirty-two other CRC patients showed little to no response to that drug. We certainly did not expect the outcome of our study to be as positive as it was.

27. Before our study and before the FDA approved pembrolizumab for the treatment of MSI-H cancers, the reality of treating colorectal cancer patients in the 2013 timeframe was that it was always palliative. With the treatments then available, the best we as oncologists could do was to extend the patient's life by approximately 2-3 years and manage the patient's symptoms. As was common for most cancers in this timeframe, our clinical options were limited. If the patient's tumor was operable, typically, we would remove it surgically and engage in some

level of post-operative treatment and monitoring. For tumors where surgery was not an option and for metastatic disease, we treated our patients with chemotherapy drugs and/or radiation therapy. The results of these therapies might last several months, and then we would need to try a different therapy when the tumor inevitably progressed. We would continue this cycle until we ran out of treatment options. These therapies were often very hard on our patients, and our patients often experienced substantial side effects and fatigue that needed to be managed. Patients would often need to take a break from therapy to manage the fatigue and other side effects, even as their cancer progressed.

28. Fortunately, our study showed that our hypothesis was correct. The data we obtained from our initial small study were, in fact, far better than we could have hoped for or expected. Anecdotally, our patients felt better almost immediately after beginning therapy. During our regular check-ins with patients, we saw our patients' tumors shrinking rapidly. Tissue biopsies did not show signs of residual tumors. In our preliminary results published on May 30, 2015, we reported objective response rate and immune-related progression-free survival rate of 40% and 78%, respectively, for mismatch repair‑deficient colorectal cancers and 0% and 11%, respectively, for mismatch repair‑proficient colorectal cancers. EX1031 (NEJM Article). In CRC patients, we also saw CEA (carcinoembryonic

antigen) levels decrease dramatically after the initial dose of pembrolizumab. These CEA levels correlated with the progression-free survival (PFS) and objective response measurements we obtained months later.

29. As we have continued to track our study patients, we have seen that their responses are durable lasting years and even after discontinuing pembrolizumab therapy. The current 5-year OS for MSI-H CRC patients treated in the study is 57.5%.

30. These outcomes were extraordinary and to my knowledge had not been seen previously in a clinical trial of a cancer drug. For comparison, other therapies for CRC in clinical trials at this time were showing response rates on the order of 1%. EX2113 (Grothey CORRECT Trial Lancet 2013).

31. Importantly, the patients in our study had failed on prior cancer therapies and were often in hospice care or otherwise close to the end of their lives. To see these patients respond so dramatically was indeed miraculous. To that point in my career as a cancer researcher and physician treating cancer patients, I had not seen such remarkable responses to any treatment. This was an incredibly rewarding time for me as a doctor. For our study patients who came to us with bleak prognoses, the results were miraculous. In many cases, these patients are living normal, cancer-free lives.

32. As the principal investigator for our study, I and the staff at JHU retained control over the ClinialTrials.gov submissions during our study. I also maintained control and oversaw the subsequent study itself, the relevant activities of the collaborating researchers, the recruitment and enrollment of patients, the collection and analysis of the data and the ultimate publication of our preliminary results. All of my collaborators and the clinical study centers were under strict confidentiality obligations and were not free to publish their results separately.

33. Records of the clinical study were maintained under strict confidentiality until we published the anonymized clinical data. I was assisted in maintaining the clinical data by Dr. Jennifer Uram, a regulatory specialist at JHU.

34. The Merck personnel involved with our study, to my observations, did not initially act as though they expected it to be successful and certainly not as successful as it was. We discussed prior studies showing that checkpoint inhibitors were not effective against colorectal cancer, so the Merck employees' muted optimism was somewhat expected. Once we reported our initial data to Merck, however, the Merck team became more focused on what we were doing and there was a much greater urgency shown by Merck for the conduct of our work. While Merck had not agreed to provide financial support for our initial small study, after seeing our preliminary results, Merck agreed to provide our team funding to enroll additional patients and to collect additional data.

35. The initial results from our study were so significant that Merck sought and received breakthrough therapy designations, first for unresectable or metastatic MSI-H colorectal and then for non-colorectal cancer. EX2062 (Merck BTD 11/2/2015 Press Release for CRC Responsive CC Brief); EX2133 (Merck BTD 11/28/2016 Press Release for Non-CRC). Receiving breakthrough designation substantially accelerated the approval process. This designation is rarely given by FDA, which needs to see compelling data to do so. In our case, once granted, Merck consulted with our team on how to compile the trial data so as to expedite approval. From my interactions with Merck at the time, I understood that FDA had also suggested and urged them to pursue a tissue-agnostic indication.

36. Merck ultimately used the JHU-generated data to support its application to FDA for approval of its first MSI-H indication for tissue-agnostic solid tumors in May 2017. In my experience for a large pharmaceutical company to rely on university generated data is unusual. Generally, when a company applies for FDA approval of an indication that came out of an investigator-initiated clinical trial, such as our clinical trial, the company will run its own sponsored clinical trial to replicate the investigator-initiated trial and generate its own data to support the approval. In this case, however, in the interest of expediting the approval process, Merck used the JHU-generated KEYNOTE-016 data to support its FDA application, and as noted on the Keytruda label, the KEYNOTE 016

patients make up a substantial percentage of the total patients cited by Merck in support of the MSI-H indication. EX2124 (May 2017 Label at Section 14.6). Another substantial portion of patients were taken from KEYNOTE-164, which was Merck's company sponsored trial of pembrolizumab for the treatment of MSI-H cancer patients that was initiated on May 29, 2015, the day before I presented the preliminary results of KEYNOTE-016 at ASCO. *Id.*

37. Relying on JHU-generated data from KEYNOTE-016 was not an easy matter. The JHU team, including myself, invested significant time and effort working with Merck to correctly format the JHU-generated data such that it could be incorporated into Merck's FDA application. I understand that Merck deviated from the normal practice in this instance because it was motivated to get approval for the MSI-H indications for pembrolizumab as quickly as possible.

38. Ultimately, on May 23, 2017, FDA granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. EX2205 (Merck Accelerated Approval Ltr.).

39. In its press release, FDA noted "[t]his is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated." EX2004 (2017 FDA Approval News Release), 1. Dr. Richard Pazdur, acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research and director of the FDA's Oncology Center for Excellence, commented that "This is an important first for the cancer community." *Id.* He continued, "Until now, the FDA has approved cancer treatments based on where in the body the cancer started—for example, lung or breast cancers. We have now approved a cancer treatment based on a tumor's biomarker without regard to the tumor's original location." *Id.* *Id.* That FDA granted this expedited, first of its kind, approval with such fanfare is indicative of the paradigm shift in cancer therapy represented by our invention.

40. Merck too was very public about the FDA approval and the significant advance to cancer treatment that it represented. Merck's president, Dr. Roger M. Perlmutter, issued a press release in May of 2017 acknowledging and thanking JHU for its significant contribution: "This is a remarkable time in the field of oncology and we are thankful to the researchers, especially the scientists and clinicians at Johns Hopkins University ***for their important scientific work***[.]" EX2060 (May 25, 2017 Merck Press Release), 2.

41. Shortly after Dr. Permutter made his comments about the approval of Merck's first MSI-H indication, Merck donated $3 million to Swim Across America—the philanthropic organization that funded our initial MSI clinical trial. EX2134 (October 12, 2017 Merck Press Release). Swim Across America is known to support high-risk, high-reward research like the research that led to Merck's MSI-H approvals for pembrolizumab.

42. The response of the clinical oncology community to our study and its results was also very positive. I was chosen to give my presentation entitled "PD-1 Blockade in Tumors with Mismatch Repair Deficiency" at ASCO as a late-breaking abstract. I delivered my presentation to a standing room only crowd of my fellow clinicians in a huge conference hall at ASCO. My understanding is that ASCO keynote presentations are reserved for breakthrough and transformative discoveries in our field. I do not believe that our study would have been selected for oral presentation as a late breaking abstract if it told the attendees something they already knew or that would have been obvious to them. When I revealed our data to the audience, you could hear a pin drop in this huge room.

43. What made the presentation of our study all the more remarkable is that ASCO chose to treat it as a "late breaking" abstract. "Late breaking" abstracts are typically reserved for presentations concerning the bigger Phase 3 drug trials

that tend to include practice changing data. In my experience, it is unusual for a small, Phase 2 clinical trial to receive "late breaking" status.

44. One other distinguishing feature of "late breaking" abstracts is that unlike most of the research that is presented at the conference, ASCO does not release "late breaking" abstracts before the conference. Instead, it treats these presentations somewhat like movie premieres, with fanfare and press conferences the day before the conference to build excitement about the discoveries that will be announced. Accordingly, ASCO representatives asked us not to report our data before my planned talk, but also asked me to describe our study at a high-level at a press conference the day before I presented the data. EX2135 (2015 ASCO Post). All of this required careful coordination with the New England Journal of Medicine, which published our paper, "PD-1 Blockade in Tumors with Mismatch-Repair Deficiency" (EX1031) later on the same day that I gave my presentation. The New England Journal editors told us that they, too, wanted the publication of our results to be breaking news.

45. Typically, presentations at ASCO of clinical trial results of a company's drug are prepared by the company with input, even when they are presented by a non-company researcher. However, I prepared the slides that I presented at ASCO in 2015 describing the results of our clinical trial of Keytruda.

It was our data and our study. While my slides were reviewed and approved by Merck, they were not prepared by Merck employees.

46. I view the treatment given to our study by the ASCO reviewers and New England Journal of Medicine editors as demonstrating their view that our discovery of treating cancer patients with checkpoint inhibitors in response to determining the patient's MSI-H status was a new and important advance in cancer therapy. In the more than nine years since its publication, the NEJM article has been cited more than 9,800 times according to Google Scholar.

47. After I gave my presentation at ASCO, I was interviewed by Dr. Axel Grothey of the Mayo Clinic. EX2136 (Dung Le video). Dr. Grothey observed, "We have for a long time thought of, you know, how do we get immune checkpoint inhibitors into colon cancer because the initial data, initial trials, were not necessarily that intriguing. Everyone is excited about PD-1, PD-L1 antibodies, it works in so many different tumors. In colorectal cancer, this important malignancy, seemed to be left out. And, in addition, we did not have a real biomarker to figure out who are these patients. And then came along your study and all of the sudden we know so much more." *Id*.

48. After I gave my presentation at the ASCO meeting, I gave a similar presentation at the Society for Immunotherapy of Cancer (SITC) in November of 2015, which included updated data on more patients and longer follow up times.

The audience at SITC was a mix of clinical oncologists and research scientists involved in the use of immunotherapies in cancer, and they had a similarly excited reaction to the data I presented. Dr. Diaz gave a similar presentation at the same meeting, which was also well-received.

49. I was also asked by ASCO representatives to present our clinical study results again at the ASCO GI (gastrointestinal) Cancers Symposium in January 2016. I remember that during this presentation, an audience member stood up during the question-and-answer session and expressed his view that it was too early for me to be presenting our data. I took this comment to mean that the audience member thought we needed more data before declaring an association between responsiveness to checkpoint inhibitors and a patient's MSI-H status. That this person, very likely a clinician, would stand up in front of his peers and make such a comment suggested to me that at least he did not believe our discovery was old or obvious.

50. On July 28, 2017, our paper entitled "Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade" was published in the journal Science. EX2118 (July 2017 Article titled "Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade"). This paper presented an expanded study of the efficacy of PD-1 blockade in patients with advanced mismatch repair-deficient cancers across 12 different tumor types. We concluded that our data

supported "the hypothesis that the large proportion of mutant neoantigens in mismatch repair-deficient cancers made them sensitive to immune checkpoint blockade regardless of the cancers' tissue of origin." *Id.* This data showed that 53% of the patients studied showed objective radiographic response and 21% of the patients experienced complete response to checkpoint blockade. *Id.* Our 2017 Science paper has been cited more than 6,200 times according to Google Scholar.

51. The results we saw during our clinical trials were so dramatic, that before first line use of Keytruda in MSI-H patients was approved by FDA in 2020, many doctors were anxious to qualify their MSI-H patients for second line use of checkpoint inhibitors. These MSI-H patients were treated with a short course of chemotherapy, and if that proved unsuccessful, quickly shifted to treatment with Keytruda.

52. Now that our research and multiple follow-on studies have established the link between the MSI-H/dMMR biomarker and successful treatment with checkpoint inhibitors, including Keytruda, and with FDA's approvals, anti-PD-1 therapy has become the standard of care for MSI-H cancer patients.