A Conversation with Dr. Iman Osman – Developing a Program to Predict irAEs and Therapeutic Outcomes in Immunotherapy.

Dr. Osman is the Associate Dean for Clinical Research Strategy and Director of the Interdisciplinary Melanoma Program at New York University Grossman School of Medicine. She was originally trained as a medical oncologist in Egypt, and later pursued further training in the United States. She completed two fellowships at Memorial Sloan Kettering in molecular pathology and clinical research oncology before joining NYU as an attending physician and independent investigator in the early 2000s. While she continues to see patients once a week, her primary focus is on conducting translational research in melanoma. She leads the Melanoma Research Enterprise at NYU. In 2015 she was appointed to a senior leadership role at NYU where she currently works at a strategic level to promote and strengthen the overall clinical research efforts at NYU.

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Building a Strong Melanoma Research Program at NYU

Dr. Osman's path to melanoma research was serendipitous. After finishing her training at Memorial Sloan Kettering Cancer Center focusing on prostate cancer research under the guidance of a greatly respected oncologist, she was bound to the New York area for family reasons. An offer from NYU's Department of Dermatology was forthcoming, a department with a strong, decades long, melanoma program. She quickly became interested in the disease. Dr. Osman noted, "When I realized how little progress had been made in treatment options over the previous decade, I realized that 'Wow,' if the situation is this bad, we can have a real impact!". With the support of the talented team at NYU, she accepted the challenge of building a strong world-class melanoma program that focuses on patient-centric research to improve patients' treatment outcomes. Despite the significant advances that have been made in basic and clinical melanoma research over the past 10-15 years, there is still a lot of work to be done. Dr. Osman added, "I used to get bored every 2-3 years when I thought I was hitting a plateau, but I'm not bored because we still have a lot of unanswered questions that we need to find solutions for." Melanoma has changed completely in the last 10-15 years from a disease that once metastatic, exhibited very low survivability measured in months to one with greater hope of good long-term survival. In fact, Dr. Osman says, "We have immunotherapy and targeted therapies that work and now an important question is how to predict response and toxicity."

Predicting Therapeutic Outcomes

Predicting outcomes before determining a therapeutic approach is crucial in cancer treatment because it helps clinicians make informed decisions about which treatment approach to take (or not). In the past, when there were limited treatment options, predicting outcomes was not as important because all outcomes were generally poor. However, with the development

of new and varied treatments, it is now essential to know which patients are more likely to respond to a particular therapy, which patients are at risk of toxicity, and which patients may be super-responders. Dr. Osman explains that in certain diseases when you are not expecting response, there is a subset of patients that defies the odds and responds really well. "Often times you think of prediction as prediction of the worst, of prediction of the people who will have recurrence and the prediction of the people who will die. But it is also important to learn from the people who did extremely well."

Initially Dr. Osman's question was who will respond and who will not respond, but then, with the introduction of immunotherapy, the question became who will have toxicity and who will not have toxicity. "So, this is what we are trying to do with the Sengenics immunoprofiling platform. Usually, people look at response and toxicity as two distinct predictions. We are trying to find biomarker signatures that can predict both at the same time.," explains Dr. Osman. "You can add to your decision-making equation whether patients will respond or not and whether they will have toxicity or not."

The identification of molecular targets is already a part of the standard of care in other types of tumors. For instance, in breast cancer, if a patient is estrogen or progesterone receptor positive, we know they will respond to hormone therapy, whereas if they are HER2 negative, they will not respond to Herceptin. Genomic testing is also used to identify mutations such as EGFR, which can determine a patient's likelihood to respond to targeted therapies. However, when it comes to immunotherapy, it's much more complex than that. There is no one protein that can predict response and toxicity. As the field continues to identify biomarker signatures, clinicians can tailor treatments based on a patient's genotype or phenotype, leading to higher treatment success rates and sparing patients from ineffective treatments that also carry the risk of increased toxicity.

Given all of the complexities involved, Dr. Osman notes that developing a predictive tool is a challenging and resource intensive endeavor that requires a deep understanding of the processes involved. Creating a test that can be used in a research lab and publishing a paper is not the same as creating a test that can be used in a clinical setting. "As an oncologist, I was trained to see patients, write grants, and papers, but developing an assay requires a commercial partner and expertise beyond my common sense. There are many technical, feasibility, and reproducibility issues that need to be addressed. Nonetheless, I believe that developing a predictive tool to be used in the clinic is where the real impact is, not just on high impact research papers, but also on people's lives."

Exploring Autoantibodies in Immunotherapy Prediction

Immune checkpoint inhibition was revolutionary for melanoma as well as other types of cancer. Dr. Osman explained that "the idea is that you stimulate the immune system against the tumor, but when you stimulate the immune system, you not only stimulate the immune system that will attack the tumor, you can potentially stimulate the immune system to attack self-antigens, resulting in immune-related adverse events (irAE)."

Dr Osman hypothesized that even before patients start immunotherapy, they could have baseline autoantibodies that predispose them to an autoimmune reaction. These baseline levels of autoantibodies are below clinical detection but not enough to trigger autoimmune disease. However, the baseline levels could enable prediction of subclinical susceptibility to develop immune related adverse events (irAE). When patients are treated with checkpoint inhibitors, the response is unleashed and causes the development of autoimmune toxicity.

Dr. Osman conducted a pilot study on about 20 patient samples, which showed promising results indicating distinct autoantibodies between the groups that did and did not have irAEs. She then increased the sample size to over 130 patients and obtained similar results, which enabled her to win a large grant from the NCI and convince Bristol Myers Squibb (BMS) to partner with her and provide access to a larger pool of patient samples from clinical trials. Dr. Osman notes that obtaining samples from clinical trial patients is beneficial because they are well standardized and minimize a lot of confounding factors.

Dr. Osman says that the original plan was to focus on toxicity, but then in one of their External Advisory Board meetings, one of the members pointed out that they might be missing an opportunity. He asked why they were not looking to see if autoantibodies could predict response to treatment (in this case recurrence). Although it was not included in the original study design, Dr. Osman and her team were able to go back and look at the data and clinical annotations with this in mind. Dr Osman said, "To my surprise, autoantibodies can also predict response to treatment. It was a very clear and very clean result."

One of the questions she is exploring now is 'Why?'. Dr. Osman notes that it is logical to expect autoantibodies to be associated with toxicity, but now wants to understand why autoantibodies are also associated with response. At this point, she decided to explore available autoantibody platforms and did a technology

comparison and reviewed the quality of publications. "I decided to explore how the Sengenics platform could be useful for this application, even if it required re-running some of the samples. This is when I started working with Sengenics."

"We ran a smaller number of samples with Sengenics to test if we could see a signal associated with response and toxicity. From there, we developed a custom array based on our targets of interest and inclusion criteria. Now we are testing the predictive value of the custom array with blinded samples. It's important to note that achieving 100% predictive value is typically not possible but predicting toxicity and response with 80% sensitivity and specificity is considered a successful outcome."

Prediction Methods to Benefit the Entire Patient Population

Dr. Osman and her team are currently working on several research questions. They are examining the validity of the custom array with blinded samples. They want to understand why the autoantibody signature is related to response. They are also addressing the issue of minority populations with regard to response prediction.

"We know that minority populations show higher rates of autoimmune diseases and have different types of toxicity following treatment. Therefore, we are examining how to test these populations and ensure that they are accurately represented in our research. It's essential to understand that it is an incorrect assumption to think that if something works in a white population, it will work for other populations. We need to address these issues to improve patient outcomes," emphasized Dr. Osman. "I believe it is critical to develop predictive models that can be applied to all patients, not just those from the majority population. It is important to recognize that immune responses can vary between different populations and that the assumption that what works for one group will work for another is an oversimplification."

Dr. Osman and her team will be presenting at this year's American Society for Clinical Oncology (ASCO) this coming May 31st to June 4th in Chicago. They will be sharing their study results that examined autoantibody signatures in underrepresented minority populations using the Sengenics immunoprofiling platform. (Determinants of racial disparities in immune related adverse events (irAE) with checkpoint inhibition (ICI) in melanoma. Abstract #9549, Poster Board # 312). This study was conducted with MD Anderson because they had greater access to minority populations receiving immunotherapy. Sera from 35 underrepresented minorities was compared with sera from 190 white patients and significant differences in autoantibodies associated with response and toxicities were observed between the 2 groups.

One of the other topics Dr. Osman has been working on recently is machine learning and artificial intelligence in the context of cancer treatment. "We published a paper where we trained an algorithm to predict who would respond to immunotherapy based on tissue sections stained with H&E (hematoxylin and eosin) prior to treatment. We collaborated with BMS and used tissue sections from a clinical trial. We found that the algorithm was useful in predicting outcomes for more advanced, metastatic disease but not for earlier stages." Dr. Osman and her team will also be presenting this work at ASCO.

Dr. Osman makes the point that machine learning is not a one-size-fits-all solution. "There are limitations to what these algorithms can do, and it takes human intelligence to develop them and to interpret their results. One possibility is that the algorithm requires a certain volume of disease to predict outcomes, and if the volume is too low, it can't make accurate predictions. Alternatively, the algorithm may have its own limitations and will plateau at a certain point."

In wrapping up the discussion, Dr. Osman stated that "ultimately, our goal is to develop tools that can be used by community hospitals and clinics, not just world-class research institutions. To be effective for a broad population, these tools need to be ethnicity-aware, reproducible, and easy to use. Overall, our focus is on developing predictive tools that can benefit everyone, not just a select few."