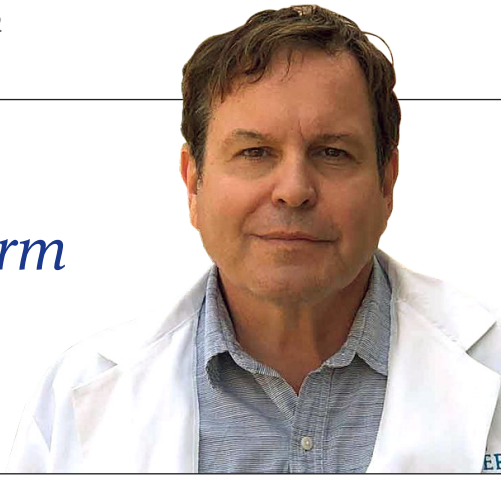
Dr Steven Mamus:
Smart Test Promises to Transform How We Recommend and Administer Immunotherapy



Dr Steven Mamus writes ...

It is very encouraging to see the accelerating number of cancer immunotherapies that I can offer as a treatment option for my patients. Cancer treatment was changed dramatically by the emergence of immune checkpoint inhibitors (ICI) over the last decade. Using this powerful class of drugs, we harness a person's immune system to help find and fight their tumor by re-engaging key mechanisms that tumor cells have shut off to protect themselves. From my perspective as a clinical oncologist, this rapidly shifting landscape means navigating the art of matching the right drug at the right time and dose for each patient, closely monitoring them for side effects of new drugs, and continuously assessing if we need to change treatment plans.

A patient's situation can change very quickly with immunotherapy. We can see rapid, durable improvements in those that respond. In contrast, unfortunately, more than two-thirds of patients do not benefit, with some patients being treated with ICIs for nearly 9 months (more or less) without before seeing any results (good and bad) [1]. Many are also faced with a cascade of treatment-related toxicity that can occur at any time due to the re-engagement of their immune system – what we call immune-related adverse events (irAE) [2]. One of the greatest challenges for us oncologists is striking the right balance between managing response and this toxicity of checkpoint inhibitors.

Interestingly, and confounding this dynamic balancing act, is evidence which is suggesting that patients with strong irAEs are often those who have better odds of achieving a durable response [3]. Permanently stopping or switching a treatment plan due to an irAE may not be in a patient's best interest. In contrast, subjecting a patient who is never going to respond to ICIs to toxicity that can affect almost any organ is also clearly something we strive to minimize.

When determining whether to treat a patient with an ICI, the current standard clinical practice often requires testing a tumor sample obtained by surgery or a needle biopsy. A PD-L1 test may be ordered on the biopsy, which measures the amount of a protein on the cancer cells that keep immune cells at bay. If you have high levels of PD-L1, you may be more likely to benefit from ICIs. Sadly, cancer cells are complex and unpredictable. Despite best efforts, PD-L1 by itself is not able to predict who will benefit from immunotherapy. Another tool is Tumor Mutation Burden (TMB), which measures the extent of DNA mutations in a tumor and acts as a proxy for how readily an engaged immune system may recognize the tumor. Studies have shown

that patients with higher TMB, which can be caused by environmental or biological processes such as smoking or ultraviolet radiation, are sometimes associated with greater response rates following treatment with ICIs. Both PD-L1 and TMB markers look at the molecular signatures of tumor cells. Unfortunately, the data does not support TMB as a good predictor of response. The limited success at predicting who will benefit from an ICI implies that these tumor-based methods alone are imperfect and there is a need for improved predictors. Cancer does not exist in isolation. It is thought that the most successful approaches will need to consider the larger systemic picture, comprising a combination of the tumor, its interaction with its environment, the immune system, and a patient's genome.

EpiSwitch® CiRT *offers a rational approach to starting or stopping immunotherapy*

Oxford BioDynamics, a biotechnology company focused on advancing personalized healthcare, is offering a first-of-its-kind commercial solution that works by capturing a systemic signal combing these components. OBD recently launched its flagship product, the EpiSwitch Checkpoint inhibitor Response Test (CiRT), a test to specifically assess a cancer patient's response to ICIs. EpiSwitch CiRT has demonstrated that it can stratify patients in either a high or low response likelihood category with high accuracy [4]. This promises to add real value – both supporting our decision on whether ICI therapy is appropriate for a patient and giving us a rational approach to stopping and/or restarting therapy at the right time.

The current recommendation is that ICI therapy be temporarily withheld if toxicity exceeds a defined threshold grade, and permanently discontinued if it exceeds a higher threshold. Often there is a fine line between the decision to resume or discontinue. Given our latest suspicions that irAEs and beneficial responses are closely linked, we need tools such as EpiSwitch CiRT to provide evidence supporting whether persevering after an irAE is the right call for an individual patient. Similarly, decisions about changing an ICI therapy will be better supported with knowledge of a patient's continued likelihood of response.

Significantly, EpiSwitch CiRT was validated across several cleared ICI's and over 15 widespread oncological indications [4]. A reliable, universal test would go a long way in simplifying our patient treatment planning. At present, there is a rapid, uncoordinated expansion of ICI therapy options and clinical trials which have increased the responsibility of oncologists to stay on top of the expanding alternatives. There are currently seven cleared ICIs in the United States, and more being evaluated in ongoing clinical trials [6].

Just as exciting is the ability of EpiSwitch CiRT to achieve this without a biopsy but, from a convenient blood sample. This means that the test can be ordered at any point in my patient's journey – from the first diagnosis to during therapy – without an additional invasive procedure disrupting standard clinical practice.

The team at OBD was able to build and validate this blood test by capitalizing on their pioneering process that has already delivered the EpiSwitch CST (COVID Severity Test), a smart blood test for measuring one's individual likelihood of severe illness due to COVID-19 [5]. Over the last decade, OBD has been refining a remarkable technology – their EpiSwitch platform – for reliably

measuring the precise three-dimensional (3D) shape in which a cell's genetic material is folded. It turns out that a genome's 3D shape ("3D genomics") is as important as the genetic code it contains for controlling how your genes and proteins are expressed. Research has shown, including OBD's, that this 3D genomic fingerprint is highly valuable in answering important clinical questions. Beyond predicting drug response in oncology, EpiSwitch has been quietly gaining ground amongst big pharma and clinical researchers for diagnosing and stratifying patients across diverse health conditions such as neurological and autoimmune diseases. The EpiSwitch signature is therefore wholly different from anything measured by incumbent PD-L1 and TMB tests, and can therefore provide us with an additional, independent metric to boost our conviction in therapy choices.

Although we may first use the EpiSwitch CiRT as a complementary test, as it delivers on its promises, CiRT's role in guiding our decisions and navigating how we administer immunotherapy will doubtless grow. So too will our certainty in delivering the best care we can for our patients living with the most uncertain of diseases.

FOLLOW THE LINK TO SEE THE ORIGINAL ARTICLE:
https://biomag1.com/dr-steve-manus-3182/

Editor's Note:

Dr. Steve Manus is a prominent medical oncologist specializing in the treatment of cancer and blood-related disorders. Dr. Mamus serves as Medical Director of Oncology/Hematology at the Cancer Center of Sarasota, which he founded in 2006 to bring patient-centric care and academic medical expertise to patients. Dr. Mamus also played a key part in the development of MD Anderson Cancer Center Orlando, where he served as chief of medical oncology. Dr. Mamus is nationally recognized with a lengthy list of honors as a physician, clinical research expert, and educator, including being named a top physician by Best Doctors in America. He has been an investigator in over 100 clinical trials involving diverse therapies. Dr. Mamus is board certified in Medical Oncology, Hematology, and Internal Medicine and he is a member of the American Medical Association, Florida Medical Association, American Society of Hematology, and the American Society of Clinical Oncology. Dr. Mamus is of Ukrainian descent, was born in Canada, and lives in Sarasota.

References

[1] John Hopkins. Immunotherapy: Precision Medicine in Action (accessed Mar 2022).

[2] Martins F et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol (2019). DOI:10.1038/s41571-019-0218-0

[3] Johnson DB et al. Immune-checkpoint inhibitors: long-term implications of toxicity. Nat Rev Clin Oncol (2022). DOI:10.1038/s41571-022-00600-w

[4] Hunter E et al. Development and validation of blood-based predictive biomarkers for response to PD-(L)-1 checkpoint inhibitors. MedRxiv (2021). DOI:10.1101/2021.12.21.21268094

[5] Oxford BioDynamics. EpiSwitch CST (COVID Severity Test). www.covidseveritytest.com

[6] Upadhaya S et al. Challenges and opportunities in the PD1/PDL1 inhibitor clinical trial landscape. Nat Rev Drug Discov (2022). DOI:10.1038/d41573-022-00030-4