

Darren Feldman, MD
Advancing Treatment for Germ Cell Tumors

Darren Feldman, MD, is a medical oncologist who specializes in treating patients with genitourinary cancers. Within the Genitourinary Oncology Service at Memorial Sloan Kettering Cancer Center (MSK), Dr. Feldman is the Section Head for Germ Cell Tumors (GCTs), which are the primary focus of his research, and also leads the stem cell transplantation program for solid tumors.

GCTs are responsible for over 95% of cases of testicular cancer and are the most common cancers diagnosed in men ages 15 to 40. GCTs occasionally arise in areas around the thoracic or abdominal cavities, even if there is no evidence of cancer in or near the testicle. Fortunately, most patients are cured initially with first-line chemotherapy, or with a secondary (salvage) treatment if they experience relapse. But for people who experience additional relapse or recurrence, GCTs can become life-threatening.

Dr. Feldman, who is also President of Quality Assurance in the Department of Medicine at MSK, leads local, national, and international clinical trials to treat GCT. He is a recognized expert and regularly collaborates with MSK physician-researchers, including **David Solit, MD**, Geoffrey Beene Chair and Director of the Marie-Josée and Henry R. Kravis Center for Molecular Oncology, which is part of MSK's Human Oncology and Pathogenesis Program, and medical oncologist **Zsofia Stadler, MD**, of the Genetics Service.

Dr. Solit has expertise in genitourinary cancers, including studying the molecular features that drive cancer and determining or developing treatments that target them. Dr. Stadler specializes in the discovery of novel cancer-susceptibility genes, particularly in gastrointestinal cancers, and the development of new approaches to cancer screening and prevention in high-risk families. Dr. Feldman, in his work with Dr. Solit and Dr. Stadler, harnesses MSK's global leadership in cancer biology and genetics to develop new therapies that promise effective treatment for patients with advanced, difficult-to-cure GCTs.

When GCTs advance following salvage treatment, they are considered incurable because of inadequate treatment options. In an analysis of 90 patients with relapsed/refractory GCTs treated at MSK, the average survival time was just four months. These people are young and in the prime of their lives, magnifying the devastation when a patient succumbs to the disease. A death from GCT results in the greatest number of average life years lost from any adult malignancy. New and improved therapies are urgently needed to change the treatment paradigm for patients with relapsed/refractory GCTs.

Clinical Trials Lead to New Findings

Dr. Feldman recently led a national, multicenter, randomized phase 2 clinical study comparing two chemotherapy regimens in people with challenging GCTs.

The first treatment, known as TIP, is a novel regimen using paclitaxel (Taxol®), ifosfamide (Ifex®), and cisplatin (Platinol®). TIP was initially developed at MSK for patients with a GCT whose cancer recurred after treatment with a regimen known as BEP. BEP uses the chemotherapies bleomycin (Blenoxane®), etoposide (Etopophos®), and cisplatin.

TIP's success as a second-line treatment in the above study led Dr. Feldman to then test TIP as an initial treatment for people with high-risk GCTs. After observing highly encouraging early results with first-line TIP, Dr. Feldman initiated the above-mentioned phase 2 clinical trial comparing the efficacy of TIP and BEP.

The Right Therapy at the Right Time

While Dr. Feldman reported no significant difference in outcomes between BEP and TIP, he is currently analyzing correlative data such as tumor biomarker decline rates and tumor genetics to identify certain features that predict success with one regimen versus the other. Measuring the levels of these markers, which are substances in blood, urine, or body tissues that may be elevated by cancer, can help diagnose GCTs, evaluate response to treatment, and monitor possible relapse among people who have achieved remission.

Leveraging the important information on prognostic factors learned from the TIP vs. BEP study, Dr. Feldman has designed a new study that will use tumor marker data and tumor genetics to determine which patients may benefit from switching from one chemotherapy combination to another in the middle of treatment. This international study will be conducted in more than 10 countries in North America, Europe, and Australia and will be led by Dr. Feldman at MSK. The hope is to establish a new standard of care for first-line chemotherapy among patients with advanced GCT who are predicted to have poor outcomes with standard BEP.

In addition, Dr. Feldman is leading an international trial, taking place in 13 countries including the United States, multiple European nations, and Australia, that seeks to determine the optimal second-line chemotherapy regimen for patients with GCTs whose cancer progresses after first-line treatment. The trial is comparing TIP to a different regimen called TI-CE, which was also developed at MSK. TI-CE consists of high-dose chemotherapy followed by autologous stem cell transplantation. Autologous transplants use patients' own healthy blood stem cells to replace their diseased or damaged bone marrow. This large clinical study of more than 400 patients aims to set the global standard of care for second-line treatment of advanced GCT. The trial recently completed accrual, and results are anxiously awaited. Further, Dr. Feldman included in the trial protocol planned collection of tumor and blood specimens for evaluation of genomic and protein factors that predict for outcome to TIP and TI-CE. The specimens collected from this study will represent the largest biobank of cisplatin-resistant GCT samples in the world and offer potential for important discoveries.

Introducing the High-Impact Potential of Immunotherapy to People With GCTs

Cancer cells are masters at evading the human immune system. Immunotherapies called checkpoint inhibitors block specific proteins that have shut down a person's immune response

to cancer. By inhibiting these proteins, the drugs help release the brakes on the immune system, allowing it to launch a fierce attack on cancer cells.

People with GCTs that have progressed following high-dose chemotherapy and autologous stem cell transplantation may benefit from immunotherapy, which was pioneered by MSK.

Dr. Feldman and MSK medical oncologist **Samuel Funt, MD**, recently completed a trial investigating a novel combination of two immunotherapies in patients with incurable GCTs. The trial focused on two common protein targets, PD-L1 and CTLA-4, that prevent the immune system from recognizing and destroying cancer cells. Dr. Feldman and Dr. Funt are seeking to evaluate the effectiveness and safety of combining durvalumab (Imfinzi®), a PD-L1 protein inhibitor, and tremelimumab, a CTLA-4 protein blocker, to create what is known as an immune checkpoint blockade (ICB).

ICB has been a transformative advance in cancer therapy, resulting in long-lasting responses in people with a variety of cancers. ICB blocks the activity of the immune checkpoint molecules PD-1/PD-L1 and CTLA-4, facilitating activation of the immune system against cancer. The results of this study are still being analyzed, but Dr. Feldman and Dr. Funt did observe some activity of the regimen, including one patient who achieved and remains in a prolonged remission.

Understanding Variations in Immunotherapy Treatment Response

Modern immunotherapy has the ability to eliminate cancer in some people, but not in everyone. Dr. Funt and Dr. Feldman need to identify why some people with GCTs, such as the patient with the extraordinary response mentioned above, benefit from ICB while others do not.

Understanding the mechanisms of response and resistance to ICB will help Dr. Feldman and Dr. Funt design their next immunotherapy study to improve upon the existing results and more selectively target those patients most likely to benefit.

Philanthropy will help support this work by funding the genetic sequencing and studying of tumor samples and other relevant data from patients. Dr. Funt and Dr. Feldman will study different cells, such as white blood cells, as well as the characteristics of each person's immune system. The data they generate promises to help guide effective, immunotherapy-based treatments for people with relapsed/refractory GCTs.

Understanding Chemotherapy Resistance

Dr. Feldman's research over the past few years has deepened our understanding of GCT molecular features that predict whether the tumor will be sensitive or resistant to standard chemotherapy. He has analyzed the genetic makeup of tumors from more than 500 patients with GCTs using the MSK-IMPACT® assay, a breakthrough technology developed at MSK that detects genetic mutations in cancers from the most common to the rarest, and identified two genes associated with resistance to the chemotherapy drug cisplatin. This is the largest group of people with GCTs to ever undergo this type of molecular testing. In addition, Dr. Feldman, Dr. Solit, and colleagues recently performed a matched pair analysis comparing the genomic features of tumor taken from the originating site (testis or mediastinum) with that from a

metastasis within the same patients. Surprisingly, this study demonstrated a large difference in the genomic alterations of the primary tumor and the metastasis within the same patient. This heterogeneity may explain why patients with GCT have not responded well to therapies targeting specific genomic alterations in prior clinical trials.

In Development: A Novel Blood Marker Test

The traditional GCT markers, alpha-fetoprotein and human chorionic gonadotropin, are elevated in just roughly 50% of all people with GCTs. In people where these markers are not elevated, physicians are dependent on less sensitive, more time-consuming, and potentially more toxic imaging methods such as CT scans and chest X-rays to achieve the same objectives.

Dr. Feldman and colleagues have been working over the past years to develop novel, potentially more sensitive and specific blood tumor marker tests, called microRNA 371a-3p and microRNA 372-3p, to monitor GCT disease status in people whose traditional markers are not elevated. His team includes Dr. Funt; **Fei Ye, PhD**, Director of Assay Development in the Department of Pathology and Laboratory Medicine; and **Joel Sheinfeld, MD**, and **Richard Matulewicz, MD, MSCI, MS**, both urologists in the Department of Surgery. Their goal: an MSK test for research and clinical purposes with a host of potential applications. These include but are not limited to GCT diagnosis, evaluation of response during treatment and for minimal residual disease (microscopic residual GCT not able to be detected by imaging) after completion of treatment, determination of who needs surgery after treatment, and surveillance for recurrence. Dr. Feldman, Dr. Ye, and colleagues recently obtained approval for the MSK MicroRNA Assay (MMA) by the New York State Department of Health, the first approval of its kind in the United States. However, they still need to demonstrate the utility of the assay in specific clinical scenarios such as those listed above in order to introduce the test into standard clinical practice. Philanthropic funding will be key to these efforts.

Dr. Feldman and Dr. Funt have additional research projects underway. These include:

1. Elucidating the genetic alterations that lead to the development of GCT. More than 500 MSK patients with GCTs have enrolled in our DNA registry, which can determine if there are any common genetic features that predispose people to develop these tumors.
2. Increasing our understanding of the serious late side effects of GCT treatment, which can include cardiovascular disease and other cancers.
3. Learning what causes GCT to transform into other types of cancer, such as adenocarcinomas and sarcomas.
4. Working toward enrolling patients in additional trials evaluating novel agents and combinations that hold promise for the treatment of GCT.