Highlights from the 2018 Joining FORCEs Against Hereditary Cancer Conference

Hereditary Cancers: Implications for immune therapies
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Precision medicine is “getting the right drug to the right patient at the right time.” It is best suited to treat the worst, most genetically complicated tumors. The fundamental premise of precision medicine is that like snowflakes, every metastatic tumor is complex and unique. This knowledge, along with other genomic breakthroughs, is changing the way that we treat tumors and cancers.

Genomics and immunotherapy
Genomics and immunotherapy are linked to precision medicine.

Genomics is science that focuses on DNA. The study of the DNA changes that occur in tumor, or somatic mutations, has the potential to change treatment. For example, researchers have successfully developed treatments that target tumor-specific (somatic) mutations.

Cancer immunotherapy targets the immune system. Typically, cancer cells turn off the immune response and hide from detection. This allows them to multiple without being destroyed by the immune system. Immunotherapy drugs reactivate the immune system to recognize and destroy tumors with many mutations.

Tumors with many tumor-specific mutations appear more foreign and abnormal. This is why patients whose tumors have more somatic mutations tend to have a better response to immunotherapy than patients with fewer tumor abnormalities. Researchers used to think that patients with hundreds of mutations would never be successfully treated, but now these patients are the best candidates for effective immunotherapy.

Customized combination therapies (not single agents) are needed to effectively treat the unique and complex nature of tumors. Previously, a patient’s diagnosis was based on their tumor type and origin, with treatment based on the origin of the cancer (e.g., in the breast or pancreas). Precision medicine changes this diagnosis-and-treatment model.

In a study that sequenced the breast cancers of thousands of patients, researchers found that no two tumors were alike. Classically, all patients with HER2+ mutations would have been given the same HER2 agent to treat their tumors. However, with precision medicine, these patients can be more effectively
treated based on the unique genetic features of their individual tumors. It no longer makes sense to treat two very different tumor profiles with the same drug regimen.

The ability to use tumor DNA to know the origin of the mutated cell and to identify the genetic changes that drive it is a medical game changer. In precision medicine, the goal is to develop drugs that affects the tumor’s mutation. Precision medicine targets specific mutations rather than treating a tumor based on where it first originated (such as the breast or colon).

**Microsatellite instability**

Microsatellite instability (MSI) is a disorder that is present in both hereditary and nonhereditary cancers. It is due to defects in the Mismatch Repair (MMR) genes that work to correct mistakes in a person’s DNA—defective MMR genes cannot properly repair damaged DNA.

Tumors with high levels of MSI have many mutations because their DNA repair system is very defective. About 3-4% of cancers have high levels of MSI, and about 16% of MSI-high cancers are due to germline (inherited) mutations in an MMR gene. These cancers are associated with Lynch syndrome. About half of MSI-high tumors respond to immune checkpoint blockade (therapy that helps the body recognize and destroy cancer cells) and the response can be durable. With immunotherapy, these patients can go from end-stage to complete remission.

On May 23, 2017 the FDA approved the immunotherapy drug Keytruda (pembrolizumab) for all solid, MSI-high tumors. This was revolutionary because it was:

- the first therapy approved for all solid tumors (not organ-specific)
- the first approval based on a genomic tumor marker
- the first approval based on retrospective data

Several patient cases were presented illustrating the effectiveness of immunotherapy in patients who originally had very poor prognoses but have since been in partial or complete remission.

**Other research and diagnostic advancements**

- I-PREDICT is a research program for newly diagnosed patients who have a lethal tumor and no curative therapies. (Lethal tumors are defined as having a 50% chance of survival for 2 years.) Patients who qualify for this program are treated with precision medicine.
- Liquid biopsy is another important step forward in cancer diagnostics. It is a noninvasive test of blood or urine test—replacing the need for a surgical tumor biopsy—that identifies a tumor’s genomic abnormalities.