ASCO discussion transcript

Slide 1:

I would like to thank the ASCO education committee for the opportunity to discuss these highly anticipated abstracts today and to talk about the future of immunotherapy in sarcoma – where do we go from here?

Slide 2:

The concept that a link exists between sarcomas and the immune system is not a new concept, but underexplored. – in the 1890s, William coley first reported a patient with complete resolution of his sarcoma, after suffering a severe erisypelas infection. Though his attempts to cure other patients by injecting streptococcus didn't go so well, through the years, investigators have tried cytokines and vaccines, with largely disappointing results. However, Dr. Steven Rosenberg and others began reporting exciting results with adoptive T cell therapy in NY-ESO positive synovial sarcomas. Now, with the sudden explosion of novel immunotherapy approaches and dramatic responses in other cancer types, it's clear that our explorations of the role of the immune system in sarcoma are just beginning.

Slide 3:

In order to discuss the importance of today's abstracts and focus on future directions, let's first review globally our understanding of the immune system. Effective and appropriate immune responses rely on a delicate balance between immune stimulation and inflammation, and timely suppression to protect healthy cells from long term dysregulation and damage. Immune cells exhibit different phenotypes, either pro or anti-inflammatory, and the ratio between these states fluctuates depending on the surrounding microenvironmental cues. These critical signals from the microenvironment include cytokines and expression of various regulatory receptors including immune checkpoint proteins.

Slide 4:

This balance is critical when discussing anti-tumor immunity. Newly transformed cancer cells express various danger signals, including neoantigens or pro-apoptotic signals. Through the process of immunosurveillance, pro-inflammatory immune cells and cytokines generate an attack on the tumor cells, and may lead to elimination prior to detection of a tumor mass. However, if subpopulations of the tumor cells are inherently less immunogenic, those cells may persist through the immune response, leading to a residual tumor that is "immunoedited" – essentially selected for inherently immunoresistant cells that differs from the initial tumor bulk. If the cancer cells evolve additional evasion features and suppresses the ongoing immune response, the tumor will grow and proliferate, escaping the immune response and becoming clinically apparent.

Slide 5:

There are three main mechanisms by which cancer cells may evade the immune system. The tumor cells may lose expression of key immunogenic neoantigens as well as the MHC complex which is required for recognition by cytotoxic T cells. Additionally, the tumor cells may express a variety of suppressive cytokines and checkpoint proteins like PD-L1 that blunt the immune response. As the tumor grows and develops, cytokines like VEGF affect the microenvironment and drive faulty tumor angiogenesis may lead to poor tumor blood flow as well as suppression of immune trafficking. Even if immune cells are

physically able to infiltrate the tumor bed, cytotoxic T cells and macrophages may shift to more suppressive phenotypes through expression of checkpoint proteins, evolution to an anergic or exhausted state, or become T regulatory cells.

Slide 6:

The goal of modern immunotherapy is to combat these escape routes used by the cancer cells and reset the balance to a pro-inflammatory immune environment rather than a suppressive one. Many have described this process like driving a car – for an effective anti-tumor immune response to drive forward, we need the keys, the gas, a roadmap, a lead foot on the accelerator, and a release of the parking brake. Vaccines, utilizing potent, immunogenic tumor antigens or externally derived dendritic cells, aim to boost the initial antigen-presenting phase to the patient's immune system. Adoptive T cell therapy genetically alters the patients own T cells to be specific for cancer cell targets like NY-ESO-1 for synovial sarcoma. This bypasses natural antigen presentation, and ensures at least an initial supply of specific T cells are available. Therapies that affect the tumor microenvironment aim to improve immune cell infiltration into the tumor, and may include chemotherapy, radiation, or potentially anti-VEGF tyrosine kinase inhibitors. Finally, there are over 50 immune cell receptors that regulate activation or suppression of immune responses, and it is these receptors that are the focus of modern drug development, including checkpoint inhibitors, or stimulatory agonists.

Slide 7:

Today's data focuses on only one of these strategies – checkpoint inhibition. we have seen the first data with anti-PD-1 checkpoint inhibitors for sarcoma. As was shown by Dr. Tawbi, there is evidence of tumor responses in about 19% of patients. This is comparable to response rates to monotherapy in other types of solid tumors.

Slide 8:

Importantly, Dr. Tawbi's study met the progression-free rate endpoint over historical controls often used in single arm phase 2 studies, suggesting that pembrolizumab would meet definitions for an active second line regimen for metastatic sarcoma.

Slide 9:

In bone sarcomas, while there still were several significant responders, overall these results did not look as promising. However, RECIST is notoriously inaccurate in bone sarcomas. One wonders whether using adapted radiographic response criteria might suggest additional benefit not only in bone but also soft tissue sarcomas.

Slide 10:

In Dr. George's abstract, we again see a lack of response in leiomyosarcoma, similar to that observed by Dr. Tawbi's group. However, again one exceptional responder was noted, suggesting that histology alone may not reliably determine all potential responders.

Slide 11:

I also wanted to briefly show this abstract from Dr. Rosen's retrospective study of patients receiving nivolumab with or without pazopanib in various sarcomas, which will be presented in the poster session.

Partial responses were observed in osteosarcoma, dedifferentiated chondrosarcoma, and a Ewing sarcoma, with a durable partial response in the chondro patient lasting over 9 months and ongoing. Stable disease was also seen with monotherapy in one patient with LMS, intimal sarcoma, and osteosarcoma.

Slide 12:

In summary, these studies suggest safety and activity for monotherapy in sarcomas which warrants further investigation. It's also important to remember that with checkpoint inhibitor therapy in other types of cancer, benefit can be seen long after the initial therapy, even with a modest response rate. Thus longer follow up is essential to see how these patients ultimately do. While histology-specific expansion cohorts are certainly appealing for UPS and dediff liposarcoma, this would miss the rare responders in other histologies. We know that in sarcoma, patients with the same histology often demonstrate dramatically different responses to chemotherapy or targeted therapy. This appears to also be the case for immunotherapy. Thus a critical need exists for analysis of potential biomarkers in responders, in hopes that later enrollment on these therapies can be stratified by something other than histology alone.

Slide 13:

So what do we know about biomarkers for response to PD-1 therapy from other cancers? The best-characterized biomarker so far appears to be PD-L1 tumor expression. Most tumors that express PD-L1 appear to respond better to PD-1 directed therapy, however there are still some responders even in PD-L1 negative tumors.

Slide 14:

The results reported by Dr. George and Dr. Talmonde confirm previous reports that about 20% of sarcomas will express PD-L1 ligand on tumor cells. However, even in melanoma, PD-L1 expression was not required for response to therapy. There are many issues with using PD-L1 as a biomarker, including differences in staining thresholds and fluctuating expression and heterogeneity within the tumor. The analysis from Dr. Tawbi's study will be helpful to understand more about whether PD-L1 expression is linked to response in sarcomas.

Slide 15:

This makes our third abstract even more exciting, which identifies a new potential prognostic biomarker for sarcoma. IDO1/KYN stimulates suppressive differentiation of T cells, and is highly expressed in sarcomas. KYN positive tumors demonstrated a favorable overall survival and might suggest that altered immunologic milieu within the sarcoma is beneficial in terms of response to therapy. These markers should be included in correlative immunoprofiling for sarcoma patients treated with checkpoint inhibitors, as they could also be a potential predictive biomarker for immunotherapy.

Slide 16:

So how can we prioritize, and really organize our optimization of immunotherapy moving forward? First, are there mechanisms to increase immunogenicity of the tumors, particularly our "QUIET" sarcomas. Data exists in numerous cancers that the use of chemotherapy, radiation, TKIs, and epigenetics may diversify the antigen profile expressed and released in the tumor microenvironment.

Perhaps we are using checkpoint inhibitors too far down the treatment pathway, and better results might be obtained by intensifying the immune response at a time with the highest antigen release from these other strategies. Next, I think it is critical that we try to identify an immunoprofile of responding sarcomas, not necessarily in relation to histology, but more based on biologic basis. Combinations are clearly key, to combat multiple steps in the tumor's immune evasion mechanism. Combination therapies have limited resistance, and the use of upstream with downstream agents has led to improved responses in many other treatment paradigms, like tyrosine kinase inhibitors in melanoma. And finally, in the sarcoma community we need to take advantage of the intense interest in immunotherapy from pharma, government funding strategies, and patients, to begin testing the multitude of new targets, agents, and techniques that are emerging.

Slide 17:

I'm happy to show you that these concepts are already moving forward – this is just a sample of the novel, innovative clnical trials currently ongoing for sarcoma patients. From cutting edge vaccines to adoptive T cell therapy, to exciting combinations of checkpoint inhibitors with TKIs or chemotherapy directed at T regulatory cells, multiple opportunities exist for our sarcoma patients to move forward with immunotherapy.

Slide 18:

So in conclusion, I hope I've convinced you today that checkpoint inhibitors are likely to be effective for a subgroup of patients, and that our priority needs to be to determine what drives this immunoactive phenotype. We need to intensify anti-tumor immunity at multiple points of the cascade, in combinations. And while off-label monotherapy is probably not the way to go, we should push to enroll patients with dediff lipo and UPS in combination clinical trials.

Slide 19:

And my final conclusion along with poor Dr. Coley – there is a future for immunotherapy in sarcomas.