Sarcoma–The standard-bearer in cancer discovery

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Abstract

Sarcoma is a rare tumor type that occurs most frequently in connective tissue. Despite its uncommon occurrence, sarcoma research has provided the means for groundbreaking research that has advanced our understanding of general cancer mechanisms. It is through sarcoma research that the pioneering efforts of cancer immunotherapy were explored, that we understand the inherent genetic nature of cancer mutations, and that we appreciate the subclassification of general cancer types to make more accurate prognoses. This review explores the brief history of sarcoma research and what sarcomas can still teach us about the future of cancer research, especially in regard to novel immunotherapy targets, the role of epigenetics in disease progression and chemoresistance, and the benefits of more focused clinical trials.

Keywords

Sarcoma; Immunotherapy; Epigenetics; Mutational burden; Chemoresistance

1. Sarcoma–the standard-bearer

In battle, the standard-bearer honorarily carries the flag, which represents the nobility and purpose of continuing the fight. In the war on cancer many advances have been made that surround the more common cancers such as breast cancer, prostate cancer, colon cancer, and lung cancer. However, there are these rare tumors of mesenchymal origin, sarcomas, which have disproportionately advanced the front lines of our understanding of cancer mechanisms. It is because of sarcoma research that we even know what oncogenes and tumor suppressor genes are. It is because of sarcomas that we appreciate that there are many subclassifications under a given umbrella of disease that can indicate different prognostic information. Even in the proliferating field of cancer immunotherapy, the first applications were performed 126 years ago in sarcoma patients. What can sarcoma research teach us in the future about cancer mechanisms and therapies? How can a focus on this rare and often
overlooked cancer advance the army of cancer researchers into new and promising research? First we will review where we are and what sarcoma research has taught us in the past.

2. Sarcoma research—the present, past & future

In the recent 2017 cancer progress report (www.cancerprogressreport.org), produced by the American Association for Cancer Research, there is reason for optimism as progress against cancer is evident. Since the 1990s, the cancer death rate among adults and children in the United States has decreased 25 and 35%, respectively. Despite these positive trends, cancer remains the second leading cause of death in the United States and a sobering global health concern. The predictions for the future rise in new cancer cases per year is projected to be 35% more in the United States and 60% more worldwide by the year 2030. More needs to be done to accomplish the goals of the cancer moonshot initiative and win the war on cancer.

Many recent advances in cancer therapy have come through basic science research efforts that strive to understand the mechanisms that drive cancer and uncover its unique vulnerabilities. Targeted therapies designed to attack the Achilles heel of specific cancers are demonstrating promising results with fewer side effects than traditional chemotherapies (Camidge, 2014; Baudino, 2015; Sawyers, 2004). To emphasize this point in shifting the approach to more targeted and personalized therapies, in the past 12 months the FDA has approved 16 new anticancer therapeutics, each designed and approved for a cancer with a specific molecular indication (Table 1).

In spite of these advances in therapeutics, there are cancer subtypes that suffer from dismal outcomes due to a lack of response to current therapies. Even among and common and treatable cancer types, certain patients do not respond because the cancer has advanced and metastasized beyond the point of a curative treatment by the time the patient presents to the healthcare system (Miller et al., 2016). There remain significant gaps in knowledge about these disparities between the biology of individual cancer cases; why some tumors respond and others do not. Vulnerabilities specific to advanced and metastatic cancers are yet poorly understood. Possibly by studying the rare cases and exceptions, we can come to understand the mechanisms that are currently enigmatic and preventing the next major advancement in cancer care.

Outliers teach us what we don’t know and lead us to new questions and discoveries. In medical oncology, each sarcoma patient is an outlier. Sarcomas make up about 1% of all cancers and with over 70 different subtypes of sarcoma it is unusual to have a high volume of patients with any single sarcoma type, even at the largest cancer centers (Bridge, 2014; Demetri et al., 2010). However, through sarcomas we have learned fundamental truths about all cancers: (1) the relationship between the immune system and cancer and the idea that it may be harnessed to target cancer, (2) the conceptual discovery of oncogenes and tumor suppressor genes, (3) personalized medicine, treating subsets of cancer as unique diseases.

Are there still lessons that can be learned from studying this outlier, a sometimes overlooked disease, that can teach us about general cancer mechanisms and the barriers that prevent
further therapeutic success? We think the answer is yes. It is not unprecedented for sarcoma to lead the way in groundbreaking cancer research.

2.1. History of groundbreaking sarcoma research

Cancer immunotherapy is arguably one of the most promising new therapeutic avenues in oncology. Despite the recent advancements of immune checkpoint inhibitors as evidenced by the 3 recently approved PD-L1 inhibitors and 2 PD-1 inhibitors in the past year (Table 1), the first attempts to harness the body’s immune system to fight cancer was conducted in the 1890s. It was not for another 120 years that the first cancer vaccine and the first immune checkpoint inhibitor were approved by the FDA. In the last six years, numerous other vaccines and immune checkpoint modulators have been pushed through preclinical and clinical testing to receive FDA approval.

The father of immunotherapy is considered to be Dr. William Coley. He observed spontaneous remissions of rare sarcomas in patients that simultaneously developed erysipelas. In 1891, Dr. Coley injected streptococcal organisms, also called Coley’s Toxins, into patients with the hypothesis that a mounted immune response to the bacteria would also attack the tumor. The ensuing immune response from the infection resulted in the shrinking of some tumors deemed inoperable. These responses were especially evident in bone and soft-tissue sarcomas. Over 1000 patients were treated with Coley’s Toxins over a forty year span (McCarthy, 2006).

While these studies did not earn Dr. Coley a Nobel Prize, others have made revolutionary discoveries in cancer by studying sarcomas and for their efforts they have been awarded the Nobel Prize. The discovery of an oncogenic retrovirus led to the fundamental tenet of cancer initiation that overexpression of genes can transform cells to become cancerous. This was performed by Dr. Peyton Rous in the early 1900s in which he demonstrated cell-free extracts from a chicken tumor could promote sarcomas in a healthy chicken by transmission of the retrovirus carrying the oncogene src (Weiss and Vogt, 2011).

Another cancer biology breakthrough occurred in sarcoma research in 1976 when Michael Bishop and Harold Varmus published a paper which concluded that the oncogenes in Rous sarcoma virus (RSV), which could infect cells to cause sarcomagenesis, were in fact of cellular, not viral origin (Stehelin et al., 1976). The gene that led to sarcomagenesis had originated in normal cells. They hypothesized that RSV had taken up the gene during replication and had carried it afterwards. The impact of this and subsequent papers published by Bishop and Varmus was to show that the root of many cancers lay in the mutation of genes already found within a healthy cell (Varmus et al., 1989; Bister, 2015). This discovery has shifted much of modern cancer research towards discovery of the mechanisms by which normal cells and cancer cells regulate expression of various oncogenes of cellular origin and away from a sole focus on viral and external carcinogenic causes.

With the idea that genetic mutations cause cancer, the most important cancer gene discovery was made while studying sarcoma. Li-Fraumeni syndrome, named after doctors Frederick Li and Joseph Fraumeni, Jr. who first reported the syndrome in 1969, is an autosomal dominant disorder that greatly increases the risk of developing several cancers (Li and
Fraumeni, 1969). A common diagnosis in patients with Li-Fraumeni syndrome includes rhabdomyosarcoma, a rare childhood cancer developing in skeletal muscle tissue. After identifying multiple rhabdomyosarcoma patients with other cases of childhood sarcoma within their close families, Li and Fraumeni hypothesized a hereditary cause to explain the familial link, as more than one occurrence of these diseases within one family was statistically unlikely. In a research study published in 1990, the doctors examined DNA samples from five Li-Fraumeni syndrome carrying families, ultimately finding an autosomal dominant inheritance of the mutated TP53 gene, which is translated into the p53 tumor suppressor protein (Malkin et al., 1990). This research provided a strong link between p53 and tumor suppressing function and represents the most commonly mutated gene across all cancers.

Sarcomas are a collection of genetically distinct diseases that are parsed into two subcategories of being sarcoma of the soft-tissue or the bone (Bridge, 2014; Demetri et al., 2010). Among these classifications, molecular genetic testing often accompanies a diagnosis to further subtype the sarcoma. Soft-tissue sarcomas, for example can be divided into two major genetic categories: 1) sarcomas with identifiable gene abnormalities (i.e. chromosomal translocations or point mutations), and 2) sarcomas with unknown gene mutations. This latter group typically harbors complex genetic alterations that likely result from an unstable genome. Soft-tissue sarcomas with identifiable gene mutations can be subtyped even further to the specific translocation or point mutation that provides useful diagnostic and prognostic information (Demetri et al., 2010). With the completion of the human genome project, many efforts have been implemented to sequence and subcharacterize cancer. Breast cancer is a quintessential example of a complex group of diagnostic entities that were once considered a single disease, until they were divided into ER/PR +/-, HER2 +/-, triple negative, claudin low or high. One of the most cited works in cancer research, “Molecular portraits of human breast tumours,” (Perou et al., 2000) underlines this point. However, decades before this publication, soft-tissue sarcoma was already being subdivided and characterized to help physicians understand and predict the behavior of specific types of sarcoma (Russell et al., 1977; Brennan et al., 1991).

What is left to learn about cancer that sarcomas can teach us? Has cancer become so individual that the study of general oncogenic mechanisms has become moot? We believe that sarcoma still can teach us about general cancer mechanisms that can help us delineate the epigenetic processes that regulate transformation, metastasis, and resistance. Due to the genetic simplicity of several sarcomas driven by balanced chromosomal translocations (Jones et al., 2016; Chalmers et al., 2017), the noise of chromosomal instability and multiplied passenger mutations is reduced and epigenetic control in cancer can be brought into focus. Touching upon the field of immunotherapy, unique relationships between immune cells and the tumor microenvironment can come to light. For example in synovial sarcoma there is a correlation between metastatic sarcoma cells and immune cells of the myeloid lineage that does not involve the suppression of T-cells (Barrott et al., 2016). We also predict that sarcomas can be the standard-bearer in understanding mechanisms of drug resistance that revolve around the generation of cancer stem cells through epigenetic means to reverse differentiation. Also sarcoma can teach the rest of the cancer world the benefits of running smaller, more focused clinical trials.
2.2. Genetic simplicity

The high mutational burden common in certain cancers can muddy the interpretation of individual events as either drivers of or passengers to oncogenesis. Multiplied genetic and genomic complexities make the discernment of epigenetic drivers of oncogenesis even more difficult (Chalmers et al., 2017). In order to understand epigenetic contributions to oncogenic progression, a genetically simple cancer is preferable. Many sarcomas driven by a balanced chromosomal translocation arise in pediatric patients with few somatic passenger mutations that have accumulated randomly over time. It has been shown that tumor mutational burden increases 2.4-fold over an 80 year span (Chalmers et al., 2017). Some examples of soft-tissue sarcomas with low mutational burden are listed in Table 2. In a study where 100,000 tumors representing 168 different tumor types were sequenced for mutational burden defined as the median number of mutations per megabase, it was found that sarcomas trended on the lower end, with the first soft-tissue sarcoma appearing at 70 on the list out of 168 tumors with a median tumor mutation burden of 3.3/Mb (study median 2.7, study range 0.8–47.3) (Chalmers et al., 2017).

In studying these genetically simple sarcomas, epigenetic methods that promote transformation and progression can be more clearly defined and pathways elucidated. Malignant rhabdoid tumor (MRT) is an aggressive sarcomatous cancer with a very low mutational burden (Lawrence et al., 2013), and not surprisingly has provided some of the greatest insights in epigenetics and oncogenesis. The primary mutation in MRT is the loss of SMARCB1 (also known as SNF5, INI1, and BAF47), which is a core subunit of the SWI/SNF chromatin remodeling complex. The SWI/SNF complex facilitates the unwinding of heterochromatin through an ATP-dependent manner. These complexes are impaired in their targeting to DNA when SMARCB1 is absent resulting in a loss of the complex at enhancers that maintain differentiation and remaining at super-enhancers that promote survival (Wang et al., 2017). These studies have demonstrated how crucial epigenetic integrity is at enhancer regions and may point to universal epigenetic means of reversing the state of differentiation, which is often associated with malignant disease.

A sarcoma that is genomically stable and involves an alteration of the SWI/SNF complex is synovial sarcoma (Jones et al., 2016). It is characterized by a balanced chromosomal translocation involving the SS18 gene on chromosome 18 and SSX genes on the X chromosome. SS18 is also a stable member of the SWI/SNF complex and when the fusion protein SS18-SSX (either SSX1, SSX2, or SSX4) is present, it competes with native SS18 and expels SMARCB1 from the complex (Kadoch and Crabtree, 2013). It is unknown what the genome-wide consequences are for the SWI/SNF complex containing the fusion SS18-SSX. Some postulate that it will act similarly to SWI/SNF complexes that lack SMARCB1 and target superenhancers because of the expulsion mechanism that has been described. However, other biochemical evidence suggest alternative functions for the fusion that involve recruitment of polycomb group repressor complexes (Su et al., 2012), which could explain the epigenetic reprogramming that is necessary to reverse differentiation. Not only can we learn about oncogenic transformation that is regulated by epigenetics by studying synovial sarcoma, but cell fate switching mechanisms. One of the hallmarks of synovial sarcoma is the presence of glandular epithelial structures intermingled with spindle-shaped...
mesenchymal cells (Jones et al., 2016; Sapi et al., 1990). Despite representing distinct germ layers, these cells originate from the same clonal progenitor cell and bifurcate throughout progression most likely through epigenetic means. The process of switching fates between epithelial to mesenchymal characteristics, and vice versa, is thought to be important in the dissemination and metastasis of many carcinomas (Thiery and Sleeman, 2006; Micalizzi et al., 2010).

2.3. Immunotherapy in sarcoma

The prevailing hypothesis in immunotherapy is that the greater number of novel cancer antigens correlates with a greater response to the therapies. These novel cancer antigens are usually a byproduct of high mutational burdens, so in the case of sarcomas that have low mutational burdens (Chalmers et al., 2017), is it desirable to pursue the expanding arsenal of immunotherapies? Because of the promising effects seen in other cancers, the risk-reward ratio was low enough to pursue various immunotherapies in sarcomas with low mutational burdens. The initial attempts to block immune checkpoints using Ipi-limumab, a CTLA-4 inhibitor, did not show promising results in a clinical trial treating patients with synovial sarcoma (Maki et al., 2013). However, new clinical trials that focus on recruitment of patients with metastatic sarcomas have shown response to autologous T-cells in combination with cyclophosphamide and interleukin-2 (Mackall et al., 2008). It is thought that the mutational burden increases in sarcomas as they progress and become metastatic (Przybyl et al., 2014). This information can provide a reference for when immunotherapy should be pursued based on the mutational burden.

Even though multiple cancer antigens improves the likelihood of the immune system recognizing the sarcoma as foreign, all it takes is one antigen that is highly immunogenic. NY-ESO-1 is a cancer testes antigen that is uniquely expressed in synovial sarcomas and myxoid round cell liposarcomas at > 80% (Pollack et al., 2012; Lai et al., 2012). This provides a target for the development of cancer vaccines and training T-cells to recognize and clear NY-ESO-1-expressing cells. This strategy has been adopted by many clinicians and although the studies are on-going, they are demonstrating some positive results and progression through the different phases of clinical trial testing (Mitsis et al., 2016). Many of the checkpoint inhibitor strategies rely on a strong presence of T-cells in the tumor microenvironment that have been shut down and require reactivation by blocking the inhibitory signal. These inhibitory signals can come from the tumors themselves, but most of the inhibition comes from tumor recruitment of myeloid derived suppressor cells (MDSCs) (Liu and Zeng, 2012). Many cancers have a significant correlation between an increase in MDSCs and progression of the disease towards becoming metastatic (Diaz-Montero et al., 2009). Is this correlation primarily influenced by the inhibition of T-cells or could the MDSCs be performing alternative functions that promote metastasis? It has been shown in synovial sarcoma that there is an enhancement of metastasis with an increased presence of macrophages and neutrophils despite the paucity of T-cells in metastatic and non-metastatic disease (Barrott et al., 2016). In researching these interactions, we can understand the biology of how MDSCs are promoting metastasis outside the realm of immune system suppression, which could open other avenues of immunotherapy that could impact many other cancers outside sarcoma.
2.4. Drug resistant mechanisms

While immunotherapy is advancing into sarcoma, surgery, radiation, and adjuvant chemotherapy still remain the dominant means to treat sarcoma patients (Demetri et al., 2010). While responses are seen to varying degrees, resistance is a frequent occurrence during the course of treatment. And it is even more evident in metastatic sarcomas (Reed and Altiok, 2011). The advantage of studying resistance in sarcomas is that the baseline genetic complexity is lower than most other cancers. Understanding the changes that take place during the transformation to a resistant tumor should be easier to tease apart. The other advantage in studying genetically simple tumors to understand mechanisms of resistance is that the in vivo models recapitulate the human disease and serious studies of resistance must be conducted in an in vivo model. Because of the amenable genetics of mice, we can perform minimal genetic mutations to achieve the desired sarcoma phenotype, and most of the time this is sufficient to generate sarcomas that mimic human pathophysiology. Models of synovial sarcoma and alveolar soft part sarcoma are a few examples where the introduction of a single human transgene faithfully generates the sarcoma in mice and the partial responses to chemotherapy and resistance are similar to what is observed in clinical practice (Barrott et al., 2016; Goodwin et al., 2014; Haldar et al., 2007; Barrott et al., 2017). Mechanisms of resistance are associated with the presence of cancer stem cells (Eyler and Rich, 2008). The accrual of these resistant cells within a population of tumor cells is likely due to the epigenetic reversal of the state of differentiation (Easwaran et al., 2014). Thus having genetically simple sarcomas to understand the mechanisms of resistance is beneficial not only from the perspective of identifying accompanying driver gene mutations, but the epigenetic means to switch a cell’s fate from differentiated to more pluripotent.

2.5. Clinical trials in sarcoma

Multisite randomized controlled trials are the gold standard in clinical trials; however, in sarcomas it is especially difficult to achieve the numbers suggested by statistics to support such a trial. Under standard clinical trial design, the effort to achieve high patient enrollment can adversely affect the trial outcome by introducing a high number of false negative results (Matthews, 1995). The idea then is to have a more focused patient enrollment. One way to circumvent this enrollment problem is to design a basket trial in which any disease with a given mutation can be included in the trial. This allows rare sarcomas with a shared mutation to be included with lung, breast, and other more common cancers (Redig and Janne, 2015). In the past, the approach at performing clinical trials with sarcoma was to identify all soft-tissue sarcomas under one umbrella. This lead to more patient accrual, but a lack of effective treatments for all soft-tissue sarcomas that progressed through standard chemotherapy. Physicians and scientists who now design clinical trials for soft-tissue sarcomas appreciate the different subtypes and guide the patient enrollment to be more selective. Gastrointestinal stromal tumors (GIST) with KIT mutations are a prime example of a soft-tissue sarcoma that benefited from a more focused patient enrollment in the clinical trial that tested Imatinib (Gleevec) (Verweij et al., 2004; Learn et al., 2010). Umbrella clinical trials for soft-tissue sarcoma can still be beneficial if adaptive measures are built into the study that can detect failures earlier and redirect the patient to a more effective treatment. While such measures
are being implemented across several cancer types, the area that sarcoma is leading the way in clinical trials is the collaborative nature of performing these trials involving sarcomas. Out of necessity, one site cannot reside in a silo and conduct its own clinical trials. Multiple sites must be integrated into the clinical trial. Not only must the physicians and scientists be in sync across various sites, but the patients also need to interconnect globally and for many subtypes of sarcomas these patient support groups exist to make the patient feel less isolated and more informed.

3. Concluding remarks

It is by working together as physicians, scientists and patients that we can make the next advancement in the war on cancer. We believe that sarcoma can lead the way in many aspects that have stymied the progress of research and therapeutics. Cancer has not become so individualized that general oncogenic mechanisms are to be disregarded. It is in studying the outliers that we can increase our understanding. As the heterogeneity of cancer becomes more complex, let’s look to the genetically simple sarcomas to better understand epigenetic mechanisms that drive transformation, progression, and resistance. Let’s use sarcoma as a model to develop more targets in the field of immunotherapy and design more efficient and economical clinical trials to approve these drugs. Let’s look to the standard-bearer, sarcoma, to push the boundaries and carry the flag of our success forward as it has in the past in battling this deadly disease.

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| Generic name   | Trade name | Molecular target | Approved indication  |
|----------------|------------|------------------|---------------------|
| Regorafenib    | Stivarga   | VEGFR2; TIE2      | Liver cancer        |
| Brigatinib     | Alunbrig   | ALK; EGFR         | Lung cancer         |
| Ibrutinib      | Imbruvica  | BTK               | Lymphoma            |
| Midostaurin    | Rydapt     | FLT3; KIT         | Leukemia            |
| Olaratumab     | Lartruvo   | PDGFRn            | Soft-tissue sarcoma |
| Ribociclib     | Kisqali    | CDK4/6            | Breast cancer       |
| Dabrafenib     | Tafinlar   | BRAF              | Lung cancer         |
| Trametinib     | Mekinist   | MEK1/2            | Lung cancer         |
| Neratinib      | Nerlynx    | HER2/EGFR         | Breast cancer       |
| Niraparib      | Zejula     | PARP1/2           | Ovarian cancer      |
| Rucaparib      | Rubraca    | PARP1/2           | Ovarian cancer      |
| Atezolizumab   | Tecentriq  | PD-L1             | Lung cancer         |
| Avelumab       | Bavencio   | PD-L1             | Bladder cancer, skin cancer |
| Durvalumab     | Infinzi    | PD-L1             | Bladder cancer      |
| Nivolumab      | Opdivo     | PD-1              | Head and neck cancer, bladder cancer |
| Pembrolizumab  | Keytruda   | PD-1              | Head and neck cancer, bladder cancer, lymphoma |
Table 2

Mutational burden in sarcomas.

| Sarcoma                                           | Translocation/Mutation | Median mutations/ Mb |
|---------------------------------------------------|------------------------|----------------------|
| soft tissue angiosarcoma                          | unknown                | 3.3                  |
| uterus sarcoma                                    | JAZF1/JJAZ; YWHAE/FAM22| 2.6                  |
| soft tissue rhabdomyosarcoma (nos)                | TP53                   | 2.5                  |
| soft tissue leiomyosarcoma                        | TP53; ATRX             | 2.5                  |
| soft tissue sarcoma undifferentiated              | KRAS; PIK3CA; SMARCB1  | 2.5                  |
| bone osteosarcoma                                 | TP53; RB1              | 2.5                  |
| soft tissue sarcoma (nos)                         | TP53                   | 2.5                  |
| soft tissue rhabdomyosarcoma embryonal           | BRAF; CTNNB1; FGFR4; KRAS| 2.5                |
| soft tissue malignant peripheral nerve sheath tumor (mpNST) | NF1                  | 2.5                  |
| unknown primary gist                              | KIT; PDGFRα            | 2.5                  |
| uterus leiomyosarcoma                             | TP53; ATRX; MED12      | 2.5                  |
| soft tissue myxofibrosarcoma                      | NF1; TP53              | 2.2                  |
| small intestine gist                              | KIT                    | 1.8                  |
| stomach gist                                      | PDGFRα; KIT            | 1.8                  |
| soft tissue chondrosarcoma                        | COL2A1; TP53; IDH1     | 1.7                  |
| soft tissue solitary fibrous tumor                | NAB2/STAT6             | 1.7                  |
| soft tissue fibrosarcoma                          | ETV6/NTRK3             | 1.7                  |
| uterus endometrial stromal sarcoma                | JAZF1/SUZ12; YWHAE/FAM22; ZCH7/BCOR; PFH1/JAZF1; PFH1/EPC1; PFH1/MEAF6 | 1.7 |
| bone chondrosarcoma                               | TFG/NR4A3; TCF12/NR4A3; AF15/NR4A3; EWSR1/NR4A3 | 1.7 |
| soft tissue Ewing sarcoma                         | EWSR1/FLI1; EWSR1/ERG; EWSR1/E1AF; EWSR1/ETV1; EWSR1/FEV | 1.7 |
| soft tissue liposarcoma                           | FUS/DDIT3; EWSR1/DDIT3 | 1.7                  |
| soft tissue desmoplastic small round cell tumor   | EWSR1/WT1              | 1.7                  |
| soft tissue synovial sarcoma                      | SS18/SSX1; SS18/SSX2; SS18/SSX4 | 1.7       |
| soft tissue rhabdomyosarcoma alveolar             | PAX7/FOXO1; PAX3/FOXO1 | 1.7                  |
| bone chordoma                                     | T (Brachyury)          | 1.3                  |
| soft tissue fibromatosis                          | CTNNB1; APC            | 0.9                  |
| malignant rhabdoid tumor                          | SMARCB1                | 0.2                  |

NOS = not otherwise specified.