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EDITORIAL

Tumor Type-Agnostic Treatment and the Future of Cancer Therapy

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It is fascinating to see how the science of cancer therapy has evolved. We first classified tumors as "solid" or "liquid" and created the specialties of oncology and hematology to later discover that the shape of the tumors has nothing to do with their etiology, so we ended up combining both specialties. Next, we proceeded to classify cancers according to the organ they grow in, thinking that the origin of the tumors is what causes their biological behaviors, and could guide us in understanding and fighting them properly. After so many years taking this approach, with both tremendous successes and deep disappointments, we are now beginning to appreciate that there is much more complexity to cancer biology than simply the tissue that tumors arise from.

Molecular mechanisms (DNA mutations, translocations, deletions, fusions, etc.) are responsible for the origin and behavior of most tumors. We are starting to change the focus of cancer therapy from organ-specific treatments to molecular marker-specific approaches. This has very recently become a reality when in May 2017 the US Food and Drug Administration (FDA) granted accelerated approval for the anti-PD-1 immune checkpoint inhibitor pembrolizumab in adult and pediatric patients with locally advanced or metastatic solid tumors that are mismatch-repair deficient (dMMR) or microsatellite instability-high (MSI-H), who have progressed after prior treatment and who have no satisfactory alternative treatment options [1]. This "tissue-agnostic" approval has created a new paradigm in oncology.

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In the current issue, Kummar and Lassen [2] present a very comprehensive review of NTRK gene aberrations as one example of success in using this tumor site-agnostic approach. The authors review the diagnostic and treatment strategies that are being implemented to deal with NTRK-fusion genes and the diseases that they cause.

NTRK genes encode for the Trk-family of tyrosine kinases: TrkA, TrkB, and TrkC (encoded by NTRK1, NTRK2, and NTRK3). Normally, these proteins are involved in the development of the nervous system [3]. However, Trks are also present in solid tumors as fusion proteins responsible for the growth of cancer cells, and these oncogenic fusions are associated with poor survival in lung cancers and other tumor types [4]. As seen with several other oncogenes (e.g., ALK, BRAF, ROS1, and others.), NTRK-fusions are present in several different tumors (so far, they are actionable in 17 tumor types). These genomic alterations are becoming a prime example for why the tumor site-agnostic approach might be the new paradigm in fighting cancer [5].

Despite this promise, there are still many challenges that lie ahead. For the molecular diagnosis of these genetic aberrations, fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), reverse-transcriptase polymerase chain reaction (RT-PCR), and next generation sequencing (NGS) of DNA or RNA (or cfDNA), are all possible options. Each of these approaches has strengths and weaknesses, but we also have to play this in the context of the workup for other genetic abnormalities, and keep in mind that in many instances tumor tissue specimens are limited. As an example, in lung cancer we currently perform FISH for ALK and ROS1 translocations, and adding three more FISH tests for each of the NTRKs (and maybe one more for RET fusions) will markedly increase the cost of workup for these patients. Furthermore, the gene fusion partner, which might become relevant in the future, will not be identified by this technique. RT-PCR is a very sensitive assay, but we would need a lot of primers to cover all known NTRK genetic abnormalities (there are more than 60 NTRK fusions documented to date). Is the solution to develop improved IHC methods, like we are doing for ALK, and hopefully will one day have for ROS1 and NTRK

oncogenes? Or should we try to establish NGS as the standard of care, to detect a large panel of possible genetic alterations, followed by a more limited follow up, for example when we look for TKI-resistant ALK variants? Nonetheless, for those who are not fans of NGS, we can say that at the moment, several NTRK 1–3 introns are not well covered by currently available NGS panels. Should we do whole genome NGS to find all possible alterations while significantly increasing the cost of the diagnostic workup? These are some of the questions that remain while we increase the accuracy of available diagnostic techniques and make them more cost effective.

For the treatment of NTRK-rearranged tumors, we are fortunate to already have clinical data available from phase I studies with two agents, entrectenib and larotrectenib, with acceptable toxicities regardless of tumor type, patient age, and fusion type [5, 6], and more data is coming from other agents in development, including CEP-701, ARRRY-470, DS-6051b, and TPX-0005 [7–10]. While NTRK-fusions are not very frequent in most cancers (less than 1%), in common tumors like lung cancer, where this year we can expect more than 235,000 new patients in the US alone, this 1% becomes an important group of patients who will benefit from such novel targeted agents.

Other tumor site-agnostic genetic abnormalities that can be targeted include BRAF mutations, and dMMR or MSI-H. To date, immunotherapy has become a panacea for almost all tumor types, especially after the US FDA granted a tumor type-agnostic approval to pembrolizumab, as mentioned before [1]. This indication covers patients with solid tumors that are dMMR or MSI-H, have progressed following prior treatment, and who have no satisfactory alternative treatment options, as well as patients with colorectal cancer who have progressed following treatment with certain chemotherapy drugs.

MSI involves the gain or loss of nucleotides from DNA elements composed of repeating motifs, which occur as alleles of variable lengths, called microsatellite tracts [11]. MSI can result from inherited mutations or originate somatically. Tumors are classified as dMMR if they have somatic or germ line mutations in MMR genes (Lynch syndrome results from inherited mutations of known MMR genes). MSI can also be the result of certain epigenetic changes or altered microRNA pathways affecting MMR proteins [12]. Although MSI is most commonly found in colon and endometrial cancers, it has also been detected in as many as 24 cancer types, suggesting that MSI is a generalized cancer phenotype [13, 14]. Noteworthy, the genomes of dMMR tumors contain a high number of somatic mutations, and hence make them more susceptible to immune checkpoint blockade regardless of their tissue of origin.

In many tumors, immune checkpoint ligands on tumor cells and immune cells interact with their cognate receptors on effector T-cells, inhibiting an adaptive immune response to the cancer cells. Once this interaction is blocked by checkpoint inhibitors, it uncovers a subset of tumors which are highly responsive to an endogenous immune response [15]. This immunologic attack can translate into a potent and durable anti-tumor effect, but can also exert severe autoimmune adverse events [16]. How to identify and enrich tumors that respond to checkpoint inhibition is an area under intense investigation. Predictive biomarkers include PD-L1 expression, tumor mutation burden (TMB), lymphocytic infiltrates, RNA expression signature, and mutation-associated neoantigens (MANA). The latter is a biomarker that we may use across tumor types [17]. dMMR cancers are predicted to contain a large number of MANAs, and hence be recognized by the immune system [18].

In their prospective study, Le et al. used pembrolizumab in dMMR cancers across different tumor types. All patients (n = 86) had received at least one prior therapy, had evidence of progressive disease prior to enrollment, and had dMMR assessed by either PCR or IHC [19]. Twelve different cancer types were enrolled in the study. Objective radiographic responses were noted in 53% of patients (52% of patients with colorectal cancer and 54% of patients with cancers originating in other organs), with 21% achieving a complete response (CR). Disease control was attained in 77% of the 86 patients. At the time of publication, neither median progression-free survival (PFS) nor overall survival (OS) had been reached and the study was ongoing. Eleven patients achieved a CR and were taken off therapy after two years of treatment. No evidence of cancer recurrence has been observed in these patients with a median time off therapy of 8.3 months. In terms of toxicity, treatment-related adverse events were manageable, and resembled those reported in other studies using pembrolizumab.

Other tumors are being driven by BRAF genetic abnormalities, which present another tumor site-agnostic target. Mutations in the *BRAF* gene were first identified and implicated in human cancers in 2002 [20]. Constitutively activating *BRAF* mutations have been reported in 7–15% of all human cancers, with melanoma having one of the highest incidences (40–70%) [21]. Other tumor types with a high prevalence of $BRAF^{V600}$ mutations include hairy cell leukemia, multiple myeloma, papillary thyroid cancer, histiocytic conditions (e.g., Erdheim-Chester disease and Langerhans cell histiocytosis), serous ovarian cancer, non-small cell lung cancer, and colorectal cancer [22–28]. The oncogenic $BRAF^{V600}$ driver mutation is often associated with an aggressive phenotype, and shorter disease-free survival (DFS) and OS than wild type BRAF [29]. We now have highly active therapies targeting this mutation in melanoma patients, such as the BRAF TKIs dabrafenib, vemurafenib, and encorafenib, and combinations of BRAF inhibitors and MEK inhibitors [30–32]. Thus, there is an increased interest in the evaluation of these treatments in solid tumors with $BRAF^{V600}$ mutations other than melanoma. The combination of dabrafenib and the

MEK inhibitor trametinib was approved for BRAF mutated NSCLC in June 2017. This approval was based on results from a multicenter, open-label trial, which sequentially enrolled 93 patients who had received previous systemic treatment for advanced NSCLC (Cohort B, $n = 57$) or were treatment-naïve (Cohort C, $n = 36$) [33]. The response rate was 63% for cohort B and 61% for cohort C. Interestingly, monotherapy with dabrafenib in 78 patients with previously treated *BRAF* mutant NSCLC, yielded a response rate of 27%. Although this is a great activity for previously treated NSCLC, the addition of a MEK inhibitor (trametinib) was necessary to achieve a significant higher response rate. Cohn et al. in 2017 published their results of a multicenter, national screening study for $BRAF^{V600}$ mutations, which confirmed previously reported incidences of this driver oncogene, and will allow the identification and possible enrollment of patients into the VE-BASKET study [34].

In conclusion, we can say that several actionable somatic cancer gene aberrations (NTRK, dMMR, MSI-H, BRAF) are present in several different tumor types, validating the concept of site-agnostic tumor therapy. The "organ-based" or "tumor site-based" clinical models that we have used to guide therapy before have not been adequate to predict tumor response or resistance and need to change. The new generation of oncology trials of tumor type-agnostic drugs bring hope to find new pathways of drug discovery and development.

Compliance with Ethical Standards

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