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EDITORIAL

When biomarkers define a drug indication

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1. Introduction

By the end of May 2017, the US FDA-approved the programmed death 1 inhibitor (PD-1) pembrolizumab (Keytruda, MSD) for treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch-repair-deficient (dMMR) solid tumors [1]. What makes this approval exceptional compared to any previous regulatory drug approval is that it was granted solely based on the presence of specific biomarkers and not on a conventionally defined disease indication [2]. The clinical study data that led to this approval comprised of 15 different conventional cancer indications, however, with one common denominator that their tumors were either MSI-H and/or dMMR [3]. Traditionally, oncology drugs have been approved for treatment of specific cancer diseases defined based on histological findings related to certain organs, such as tubular carcinoma of the breast and non-small cell lung cancer (NSCLC). Over the past 20 years, the drug-diagnostic co-development model has played an increasing role for drugs like trastuzumab (Herceptin, Roche/Genentech) and pertuzumab (Perjeta, Roche/Genentech) that have been approved for HER2 positive breast cancer and likewise crizotinib (Xalkori, Pfizer) for ALK or ROS1 positive NSCLC as well as a number of other anticancer drugs [4,5]. However, with the recent approval of pembrolizumab for the treatment of MSI-H and/or dMMR solid tumors, it is the first time that the FDA approves an indication for any anticancer drug based on a site-agnostic indication.

2. MSI-H and dMMR

MSI-H is a condition of genetic hypermutability caused by the loss of MMR activity and resulting in ineffectiveness of the mechanisms responsible for the DNA replication process and postreplicative repair [6,7]. In fact, genomes of cancer diseases deficient in MMR contain higher numbers of somatic mutations [8]. MSI-H tumors are further characterized by lymphocyte infiltration and increased neoantigen, which serve as target for the immune system and simulate the anti-oncogenic response. The high level of lymphocyte infiltration and the strong expression of increased neoantigen results in upregulation of both PD-1 as well as programmed death ligand 1 (PD-L1) [2,9].

Several methodologies are available depending on whether MSI-H or dMMR is being studied [10,11]. Defects in the MSI are measured by poly chain reaction (PCR) amplifying microsatellite repeats, and the Bethesda panel is the most widely used panel. MMR is measured using immunohistochemistry (IHC) staining to detect the absence or loss of a particular protein within the nucleus of the tumor cells. There are pros and cons with regard to the two methods. The IHC laboratory test is much more widely available than the PCR test, but the results will often be affected by the tissue fixation conditions. The MSI analysis requires normal tissue in addition to tumor tissue for comparison, and will also require micro dissection, but often will not be affected by the fixation. In order to compare the two methods, a number of studies have been conducted and the results show a high concordance between the two methods. However, the next generation sequencing (NGS) technology is on the doorstep and companies have started to produce panels and kits allowing massive parallel sequencing of the MMR genes. To the best of my knowledge, no fully validated assay is yet available, but also for this method, it is important that standard panels will be available [10].

How frequent is MSI-H and/or dMMR found across different cancers? It seems like colorectal cancers (CRC) are among the diseases with the highest incidence and here, the range is of 15−25%, but also a disease like endometrial cancer have shown similar high incidence [9,10]. At the other end of the scale we find diseases like prostate cancer, breast cancer, as well as renal cell carcinoma with an incidence of a few percent. Altogether more than 20 different tumor types have shown to exhibit MSI-H and/or dMMR, however, these figures should be taken with some reservation as they are generated based on data from relatively small studies, so the incidences must be even more prevalent as we learn more about the conditions. The figures presented here are mostly taken from patients with primary disease and moving into the metastatic setting, the incidences will normally be somewhat lower and for metastatic CRC it has been estimated as low as 5% [2].

3. Pembrolizumab in patients with MSI-H or dMMR

The approval of pembrolizumab for the treatment of MSI-H and/or dMMR solid tumors was not based on a single study but generated on data from a composite of five individual
multicenter, multi-cohort, single-arm trials [2,3]. A total of 149 patients were identified across these five clinical trials, of which 98% of the patients had a metastatic disease. The major efficacy outcome was antitumor activity measured as objective response rate (ORR) according to RECIST 1.1. More than half of the patients had a conventional diagnosis of CRC and the remaining group (39.6%) consisted of 14 different diagnoses with endometrial, biliary, and gastroesophageal cancer being the most frequent. Of these 149 cancer patients, 47 had dMMR identified by IHC, 60 had MSI-H assessed by PCR, and 42 used both tests. The ORR for the CRC group was 39.9% (95% CI, 31.7–47.9) with more than 78% of the patients responding after 6 months. Data from a recent article published in New England Journal of Medicine show that the overall response rates was similar irrespective of whether the patients belonged to the CRC group or the none-CRC group [2]. A couple of other recent studies with pembrolizumab in the same type of patients have shown similar outcome which adds to the evidence that these tumors are sensitive to treatment with immune checkpoint inhibitors regardless of origin [8,12].

One shortcoming in relation to the approval of pembrolizumab for this new indication was the concomitant lack of a FDA-approved companion diagnostic [2]. The identification of patients with MSH-D or dMMR tumors was performed by local laboratory-developed tests, which is likely to add to an increased test-to-test variability. The FDA explained this unusual exception by the fact of highly unmet medical needs, high response rate, and the known safety profile of pembrolizumab. However, in relation to the post-approval requirements, MSD, producers of pembrolizumab, committed themselves to develop an analytical and clinical validated assay.

Looking at the guidance document issued by FDA in 2014 on IVD Companion Diagnostics Devices, it is clearly stated that an assay must be developed when it is essential for the safe and effective use of a corresponding therapeutic product [13]. Further, it is stated that the FDA will only approve the therapeutic product or new therapeutic indication if a companion diagnostic is approved simultaneously. Such a wording underlines the importance that the FDA attaches to this type of assay and normally, the word essential in the definition for a companion diagnostics device should be taken seriously, but there seems to be exceptions. In fact, the recent example is not the first time such a waiver has been granted. In 2016, when crizotinib was approved for treatment of ROS1 positive NSCLC, a similar waiver was given, and it was only in June 2017 that a companion diagnostic assay was regulatory approved, which was the Oncomine Dx Target Test (Thermo Fisher Scientific) [14].

4. Biomarker-defined drug indications

Over the last few years we have experienced an increasing number of basket trials being initiated where a specific therapy is studied simultaneously for more than one disease and where patients are enrolled based on specific biomarkers rather than tumor site and histology [2,15]. Despite the principle of basket trials are appealing there seems to be challenges. One recent example is vemurafenib (Zelboraf, Roche/Genentech) in patients with BRAF mutation, where it seems to show that advanced melanoma and NSCLC are the only cancer diseases to benefit from this treatment [2,16,17]. Likewise, 20 years of clinical research with trastuzumab has only led to the approval of two indications: breast cancer and metastatic gastroesophageal cancer. Tumor site and histology do matter and not every genetic aberration found in the tumor is targetable regardless of origin. Having said that, it is probably not the last time a drug is being approved for a site-agnostic indication and others may be just around the corner, and that could be the tropomyosin receptor kinase (TRK) inhibitors. Especially in patients harboring NTRK fusions, these drugs have shown clinical activity in patients with metastatic or unresectable solid tumors [18,19]. The target for these molecules is the TRK receptor family comprising of the three transmembrane receptors encoded by NTRK1, NTRK2, and NTRK3. The patients most likely to respond to treatment with a TRK inhibitor are identified by NGS in order to detect fusions involved with NTRK [18]. Despite the compound from Loxo Oncology (larotrectinib) still being in phase 2, it has already shown efficacy across 17 different cancers; so it looks like this could be the next candidate for a new approval of a site-agnostic anticancer drug.

For a site-agnostic drug indication the development of a companion diagnostic assay plays a crucial role and an analytical and clinical validated assay needs to be approved at the same time as the drug. The biomarker(s) are the one(s) that defines the indication and the companion diagnostic is the tool for this purpose [20]. Another important aspect of having a validated assay available relatively early on in the development is in relation to the clinical development of the drug/indication. For the current approval of pembrolizumab, data from 5 different clinical multicenter trials were pulled all using local laboratory-developed assays, so the number of different assays being used in the studies will most likely have to be counted in large numbers [3]. So, a couple of relevant question to ask are; 1) how well are these patients defined with respect to MSH-D and/or dMMR status and 2) how can these data be extrapolated to other similar type of patients? The FDA probably asked these questions, but still they found the advantages outweighed the drawbacks with regard to the approval of pembrolizumab for this new indication. Drug-diagnostic co-development requires detailed planning, and especially for a site-agnostic indication, it is essential that an analytical and clinical validated assay is available at the same time as the drug, which hopefully we will see in the future for this type of drug indications.

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Declaration of interest

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Papers of special note have been highlighted as of considerable interest (†) to readers.
3. The rationale of the US FDA for approval of pembrolizumab for patients with MSI-H or dMMR solid tumors.