Biomedicine Hub

Biomed Hub 2017;2(suppl 1):481614 (DOI: 10.1159/000481614)

Received: June 27, 2017
Accepted: September 19, 2017
Published online: November 21, 2017

Commentary

The FDA Changed Everything

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Keywords
Oncologic therapy · Cancer drug approval · Pembrolizumab · TNM staging · Genetic biomarker · Tissue-agnostic cancer drug

Abstract
On May 23, 2017, the FDA approved the first cancer treatment (pembrolizumab) for any solid tumor with a specific genetic biomarker: microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). For the first time in history, a solid cancer treatment was approved based on the genetic makeup of tumor not on the location in the body where the cancer originated, for example lung or breast cancer (TNM staging). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapeutics. All cancer drug approvals in the last 30 years were grounded on TNM staging independent of the therapy type (chemotherapy, monoclonal antibodies, TKI inhibitors, immune therapies or targeted therapies) and despite the huge and fast advances in understanding tumor biology. In fact, the FDA previously approved pembrolizumab taking into consideration the TNM staging, for the treatment of certain patients with metastatic melanoma, metastatic non-small cell lung cancer, recurrent or metastatic head and neck cancer, refractory classical Hodgkin lymphoma, and urothelial carcinoma. The archaic TNM staging will probably be changed under the disruptive wave of molecular biology. The recent FDA approval could be considered the certificate of birth for a truly new dimension of personalized medicine in cancer. We recommend European Union to follow the FDA approach of tissue-agnostic cancer drugs in order to speed up the development of next-generation oncologic therapies and to increase the access of patients to truly personalized medicine.

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On May 23, the FDA approved [1] the first cancer treatment (pembrolizumab) for any solid tumor with a specific genetic biomarker: microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). For the first time in history, a solid cancer treatment was approved based on the genetic makeup of tumor not on the location in the body where the cancer originated, for example lung or breast cancer (TNM staging).

This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.

Pembrolizumab works by targeting the cellular pathway known as PD-1/PD-L1 (proteins found on the body's immune cells and some cancer cells). By blocking this pathway, pembrolizumab may help the body's immune system fight the cancer cells.

MSI-H and dMMR tumors contain abnormalities that affect the proper repair of DNA inside the cell. Tumors with these biomarkers are most commonly found in colorectal, endometrial and gastrointestinal cancers, but also less commonly appear in cancers arising in the breast, prostate, bladder, thyroid gland and other places. Approximately 5% of patients with metastatic colorectal cancer have MSI-H or dMMR tumors.

The TNM staging system for all solid tumors was devised by Pierre Denoix [2] between 1943 and 1952, using the size and extension of the primary tumor, its lymphatic involvement, and the presence of metastases to classify the progression of cancer. In 1987, the Union for International Cancer Control and American Joint Committee on Cancer staging systems were unified into a single staging system.

All cancer drug approvals in the last 30 years were grounded on TNM staging independent of the therapy type (chemotherapy, monoclonal antibodies, TKI inhibitors, immune therapies or targeted therapies) and despite the huge and fast advances in understanding the tumor biology.

In fact, the FDA previously approved pembrolizumab taking into consideration the TNM staging, for the treatment of certain patients with metastatic melanoma, metastatic non-small cell lung cancer, recurrent or metastatic head and neck cancer, refractory classical Hodgkin lymphoma, and urothelial carcinoma.

FDA innovative regulatory approval for pembrolizumab represents a cornerstone for cancer treatment with multiple challenges regarding clinical practice, regulatory framework, market access and reimbursement policy.

A study on 12 cancer types and more than 12,000 tumors published 2 weeks after FDA decision found that the large proportion of mutant neoantigens in MMR-deficient cancers make them sensitive to immune checkpoint blockade (pembrolizumab), regardless of the cancers' tissue of origin [3].

As a consequence, according to the study and FDA approval, before recommending any treatment for a patient with one of the 12 cancer types every doctor should perform the diagnostic test for MSI-H or dMMR in order to identify the patients who might benefit from the therapy with pembrolizumab. In this way, the test must be widely available across countries, performed in high-quality labs, reimbursed by the payers and included in guidelines and protocols usually focused on the TNM staging approach.

From the market access and reimbursement perspective, the challenges are also very important taking into consideration that the HTA systems are designed based on organ-specific approach in the field of cancer drugs.

The era of tissue-agnostic cancer drugs is in its early days, but expectations and promises are high. During ASCO 2017 Annual Meeting, data presented from clinical trials with another drug, larotrectinib [4], suggest that this medicine is likely to become the second approved tissue-agnostic drug by next year. Larotrectinib is a selective inhibitor of tropomyosin receptor kinase (TRK) fusion proteins, which are a product of a genetic abnormality when a *TRK*

gene in a cancer cell fuses with one of many other genes. It is estimated that this abnormality occurs in about 0.5–1% of many common cancers, but in more than 90% of certain rare cancers.

At least 6 other tissue-agnostic cancer drugs presented at ASCO 2017 Annual Meeting are making their way through phase I and II clinical trials. In the fast-moving field of oncology, the molecular biology of the tumor is leading the way over the tissue of origin. Looking into the not so distant future, we have to take into consideration the imminent change of cancer taxonomy based on molecular biology advances. Probably in the future we will no longer discuss only about lung, breast or prostate cancer but we will add details like MSI-H, dMMR or TRK fusion protein in order to be able to provide a better selection of the right drug for the right patient at the right time and from the beginning of the therapy.

The archaic TNM staging will be completely changed under the disruptive wave of molecular biology. The recent FDA approval could be considered the certificate of birth for a truly new dimension of personalized medicine in cancer.

We recommend European Union to follow the FDA approach of tissue-agnostic cancer drugs in order to speed up the development of next-generation oncologic therapies and to increase the access of patients to truly personalized medicine.

Disclosure Statement

The authors declare no conflicts of interest.

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