Pembrolizumab for dMMR/MSI-H tumors marks first tumor agnostic FDA approval

The United States Food and Drug Administration's approval earlier this year of pembrolizumab marks the first tumor agnostic indication for a cancer drug.[1,2] Accelerated approval was granted for the treatment of adult and pediatric patients with any unresectable or metastatic solid tumor that displays mismatch repair deficiencies (dMMR) or high levels of microsatellite instability (MSI-H) and who have progressed after previous treatment and have no satisfactory alternatives. It is also approved specifically for patients with MSI-H or dMMR colorectal cancer (CRC) that has progressed after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Pembrolizumab is a programmed cell death protein-1 (PD-1) receptor inhibitor that blocks the interaction between PD-1 and its ligand, PD-L1, restoring the activity of tumor-infiltrating T cells and boosting the antitumor immune response. It is thought to be particularly effective in dMMR/MSI-H tumors because they have a high mutational load and therefore display an abundance of antigens on their surfaces to provoke an immune response.

Approval for the drug was based on the demonstration of durable responses in 149 patients with MSI-H or dMMR cancers across 5 uncontrolled, multicohort, multicenter, single-arm trials. In all, 90 of the patients had CRC, and the remaining 59 patients had 1 of 14 other cancer types that included endometrial, biliary, gastric or gastroesophageal, pancreatic, and breast cancers.

Patients in these trials received pembrolizumab at 1 of 2 different doses, either 200 mg every 3 weeks or 10 mg/kg every 2 weeks, until unacceptable toxicity or disease progression that was symptomatic, rapidly progressive, required urgent intervention, or coincided with a decline in performance status. Treatment was administered for a maximum of 2 years. Patients with an active autoimmune disease or a medical condition that required immunosuppression were ineligible for treatment in all 5 studies.

The median age of enrolled patients was 55 years; 56% were men; 77% white, 19% Asian, 2% black; 98% had metastatic or unresectable disease; and all had an Eastern Cooperative Oncology Group Performance Status of 0 or 1 (range, 0-5, where 0 denotes full activity and 1, restricted in physically strenuous activity but ambulatory). MSI-H and MMR status were identified prospectively using polymerase chain reaction and immunohistochemical analyses, respectively.

The primary endpoint was objective response rate (ORR), according to Response Evaluation Criteria in Solid Tumors

What's new, what's important

The approval of the PD-1 receptor inhibitor, pembrolizumab, for the treatment of adult and pediatric patients with any unresectable or metastatic solid tumor that displays dMMRs or high levels of MSI-H, marks the first tumor-agnostic indication for a cancer drug. It was also approved for patients with MSI-H or dMMR colorectal cancer that has progressed after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Approval was based on demonstration of durable responses in 149 patients with MSI-H or dMMR cancers who received pembrolizumab at 200 mg every 3 weeks or 10 mg/kg every 2 weeks, until unacceptable toxicity or disease progression. Treatment continued for a maximum of 2 years. The ORR was 36.9% and, among 78% of patients who responded, the responses lasted 6 months or more. There were 11 CRs and 48 partial responses PRs and response rates were similar across tumor types. The most common adverse events included fatigue, pruritus, diarrhea, decreased appetite, and rash, among others.

The prescribing information states that pembroliumab's safety and efficacy have not been established in pediatric patients with MSI-H cancers of the central nervous system. It also carries warnings about immune-mediated toxicities, including pneumonitis, colitis, hepatitis, among others. It should be permanently discontinued with grade 3, 4, or recurrent grade 2 pneumonitis, colitis, nephritis/renal dysfunction, and endocrinopathies, or for AST or ALT levels >5 times ULN or total bilirubin levels >3 times ULN. For patients with liver metastases who begin treatment with grade 2 AST or ALT, treatment should be permanently discontinued on increases of >50%, relative to baseline, lasting more than a week. Patients with reproductive potential should be advised that pembrolizumab can cause fetal harm.

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Mechanism of action: pembrolizumab

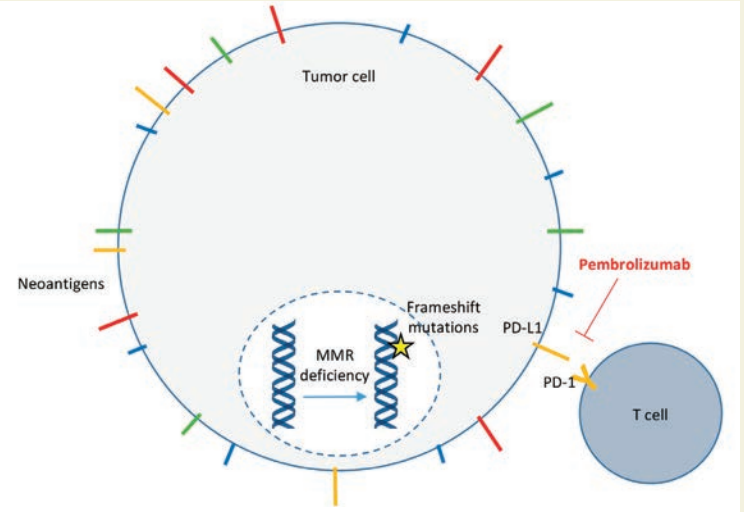
DNA repair defects expose cancer cells to the immune system. Our DNA comes under frequent assault from both environmental stressors and errors during the replication process that can cause structural damage. To counter this threat, cells have developed a complex signaling network that detects and repairs, if possible, the damaged DNA. One of the pathways of DNA repair, the mismatch repair (MMR) system, recognizes and repairs the genetic mismatches that can occur when the DNA is replicated.

When the MMR system is malfunctioning, as it often is in cancerous cells due to hereditary or somatic mutations in the component genes, DNA mismatches go unrepaired, which can lead to the accumulation of mutations in the genome. Defective MMR can also drive the development of microsatellite instability (MSI) – fluctuations in the length of repetitive sequences of DNA within the genome whose function is unknown. The presence of MSI within a tumor is indicative of a defective MMR system.

Tumors that have high levels of MSI (MSI-high) or defects in the MMR system (dMMR) are usually hypermutable, displaying hundreds or thousands of DNA mutations. These can serve as antigens that stimulate the immune system and, accordingly, MSI-high or dMMR tumors often contain lots of infiltrating T cells.

To overcome this increased exposure to the immune system, the molecular mechanisms that tumors have evolved in order to evade the anti-tumor immune response are also upregulated in MSI-high and dMMR tumors. For example, they express high levels of the programmed cell death protein-ligand 1 (PD-L1) on their surface.

PD-L1 activates the programmed cell death protein-1 (PD-1) receptor on the surface of T cells, which initiates a signaling cascade that ultimately leads to the downregulation of T-cell activity. Thus, high levels of PD-L1 on the tumor surface help to dampen down the anti-tumor immune response by inactivating all the T cells that infiltrate the tumor microenvironment.



Defects in the mismatch repair (MMR) system lead to an accumulation of frameshift mutations, which can serve as neoantigens on the surface of a tumor cell that stimulate the immune response. Tumor cells, in turn, boost the expression of immune checkpoint proteins on their surface as a way of overcoming the heightened anti-tumor immune response. The use of checkpoint inhibitors, such as pembrolizumab, which reinstate T cell activity and boost the immune response, is therefore highly effective in these tumor types. Created by Jane de Lartigue, PhD.

Pembrolizumab is an anti-PD1 monoclonal antibody that blocks the interaction between PD-1 and PD-L1 and thus restores the activity of T cells, increasing the ability of the immune system to detect and fight tumors. The efficacy of immune checkpoint inhibitors such as pembrolizumab is greatly enhanced in tumors with a high mutational load that provoke a strong anti-tumor immune response, such as MSI-high and dMMR tumors. The approval of pembrolizumab in MSI-high and dMMR tumors marks the first approval of a cancer drug that is independent of the tumor type.

(RECIST, version 1.1), as assessed by blinded independent central radiologist review, and response duration. The ORR across all five studies was 36.9% and, among 78% of patients who responded, the responses lasted 6 months or more. There were 11 complete responses (CRs) and 48 partial responses (PRs) and response rates were similar across tumor types.

The safety profile was consistent with previously reported safety data for pembrolizumab. The most common adverse events included fatigue, pruritus, diarrhea, decreased appetite, rash, pyrexia, cough, dyspnea, musculoskeletal pain, constipation, and nausea.

The prescribing information includes a "limitation of use" that states that pembroliumab's safety and efficacy haven't been established in pediatric patients with MSI-H cancers of the central nervous system.[3] It also details warnings and precautions about immune-mediated toxicities, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and renal dysfunction, among others.

Patients should be monitored for signs and symptoms of these toxicities and treated appropriately. Treatment should be withheld and corticosteroids should be administered for grade 2 or higher pneumonitis, colitis, hepatitis, and nephritis; and corticosteroids and hormone replacement as clinically indicated for endocrinopathies. It should also be withheld for aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >3-5 times the upper limit of normal (ULN) or total bilirubin levels >1.5-3 times ULN.

Pembrolizumab should be permanently discontinued upon grade 3, 4, or recurrent grade 2 pneumonitis, colitis, nephritis/renal dysfunction, and endocrinopathies or for AST or ALT levels >5 times ULN or total bilirubin levels >3 times ULN. For patients with liver metastases who begin treatment with grade 2 AST or ALT, treatment should be permanently discontinued following increases of more than 50%, relative to baseline, that last for at least 1 week.

Health care providers should also bear in mind that pembrolizumab can, more rarely, cause other immune-mediated toxicities, such as arthritis and exfoliative rash that may require treatment and, based on its mechanism of action, pembrolizumab can also cause fetal harm. Patients with reproductive potential should be advised of the implications. Pembrolizumab is marketed as Keytruda by Merck & Co Inc.

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