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Tebentafusp: The First FDA-approved Monoclonal Antibody for Cancer Treatment in 2022

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It has been more than 35 years since the first monoclonal antibody was approved by the US Food and Drug Administration (FDA) in 1986. Since then, antibody engineering has considerably progressed. Today, antibodies are known as a major type of therapeutics with various diagnostic and therapeutic applications. Owing to the developments in the field of antibodies, nowadays, antibodies have high levels of specificity towards their target, resulting in a minimized level of side effects. The global market for therapeutic antibodies was valued at more than US$110 billion in 2018. By 2025, this market value is expected to be almost three times its value in 2018. Such market size growth is mainly due to the FDA approval of various monoclonals to treat different human diseases (such as autoimmune, metabolic, and infectious diseases) and cancers. Until December 2019, 79 therapeutic mAbs were granted approval by the US FDA. From January 1 to February 4, 2022, three antibody products were granted FDA approval for the first time for medical use in the US. Moreover, as of February 4, 2022, 18 investigational antibody therapeutics were in regulatory review for possible approval in either the US or EU. Our previous review article covered monoclonal antibodies approved by the US FDA for cancer treatment in 2020 and 2021 (1). Overall, 13 antibody therapeutics were approved by FDA in 2021 (four of which were for cancer treatment and nine for non-cancer indications). Moreover, only one of the FDA-approved antibody therapeutics in 2022 is for cancer treatment, making *tebentafusp* the only FDA-approved antibody therapeutic (approved on January 25, 2022) in 2022 as of February 10.

Tebentafusp-tebn (also known as *tebentafusp* or *IMCgp100* or by the brand name, *KIMMTRAK*) is a bispecific immunoconjugate developed by Kimmtrak, Immunocore Limited (2). Tebentafusp is a bispecific synthetic protein composed of an HLA-A*02:01-restricted affinity-enhanced T-cell receptor (TCR), specific for the glycoprotein 100 (gp100) peptide YLEPGPVTA, fused to CD3-redirected single-chain variable fragment (scFv). This construct can redirect T cells towards tumor cells positive for gp100 (2). Such constructs are called "immune-mobilizing monoclonal T-cell receptors against cancer (ImmTAC)" (2). ImmTACs are a novel type of T-cell–redirecting bispecific fusion proteins that employ a high-affinity transgenic TCR specific for a particular HLA-presented peptide antigen (2). Upon interaction with their HLA-presented peptide antigen on the surface of their target cells, ImmTACs recruit and trigger the activation of T cells via their anti-CD3 scFv (2). As a result, various types of cytokines and other immune cytolytic mediators are secreted against the target cells.

Uveal melanoma accounts for about 3 - 5% of all melanoma cases diagnosed each year. It is the most common intraocular-related malignancy in adult humans (3, 4). Uveal melanoma originates from melanocytes but has various distinct characteristics compared to cutaneous melanoma (3, 4). Such characteristics include different molecular mediators, metastatic behaviors, and a different tumor-immune microenvironment (3, 4). Near half of the patients with uveal melanoma demonstrate cancer metastasis mainly to the liver leading to a very poor prognosis (with a median overall survival of approximately 12 months) (5, 6). Researchers believe that such a different feature of this neoplasm is the main reason for the poor clinical outcomes (5, 7). Moreover, until early 2022, no effective therapy was available for patients with uveal

melanoma.

The clinical efficacy of tebentafusp was evaluated in the IMCgp100-202 clinical trial (NCT03070392). This was a randomized, open-label, multicenter trial with 378 metastatic uveal melanoma patients (who were all positive for HLA-A*02:01) (2). Moreover, no patient had any prior systemic or localized liver-directed therapy. The patients were randomly selected for the tebentafusp group (which included 252 patients who received tebentafusp administered weekly by intravenous infusion) or the control group (which included 126 patients who received pembrolizumab, ipilimumab, or dacarbazine based on the investigator's choice) in a ratio of 2:1, respectively. The primary endpoint for this study was overall survival (2).

Overall survival at 12 months was 73% and 59% in the tebentafusp and control groups, respectively (2). Another investigated factor was progression-free survival that was significantly higher in the tebentafusp group than in the control group at six months (31% versus 19%) (2). It is essential to mention that the investigators also observed various treatment-related side effects (2). These adverse events included several skin conditions such as a rash (83%), pyrexia (76%), and pruritus (69%), which were mainly due to $gp100^{+}$ melanocytes (2). Moreover, cytokine secretion-related conditions were also observed in patients, which was believed to be due to high-level T cell activation (2). It is essential to mention that the researchers did not observe any treatment-related mortality in this trial (2). There were also several laboratory abnormalities during this study (2). These abnormalities included the declined levels of lymphocyte count, hemoglobin, and phosphate and elevated levels of creatinine, glucose, aspartate aminotransferase (SGPT), and alanine aminotransferase (SGPT) (2).

The patients in the tebentafusp group were administered weekly by intravenous infusion (20 mcg on day 1, 30 mcg on day 8, 68 mcg on day 15, etc. until disease progression or observance of any uncontrollable lethal toxicities). This dosing scheme is the appropriate dosing for tebentafusp administration as recommended by FDA (8).

The development of antibodies to treat various human diseases and cancers with no available effective treatment has significantly progressed in recent years. Nowadays, engineered fusion proteins with monoclonal antibodies used in their constructs are stepping into the therapeutic antibody market more than ever. In recent years, it has been demonstrated that such fusion proteins can be effective and reliable therapeutic approaches for treating patients with various hard-to-treat malignancies. In the discussed clinical trial, the treatment of metastatic uveal melanoma patients with a soluble fusion protein composed of an affinity-enhanced transgenic TCR and CD3-directed bispecific was related to prolonged overall survival in the patients in comparison with the control group. It is worth mentioning that anti-tebentafusp neutralizing antibodies were developed in some patients. It was indicated that these neutralizing antibodies had no significant effect on the tebentafusp concentration or the overall survival of the patients. However, whether these neutralizing antibodies can have adverse effects on tebentafusp in vivo activity has not been elucidated yet.

Footnotes

Authors' Contribution: PS, PS, and AS were contributed to writing and revising the manuscript.

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