

Ensuring equity in the era of HLA-restricted cancer therapeutics

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ABSTRACT

In January 2022, the US Food and Drug Administration granted regulatory approval to tebentafusp, a bispecific T cell receptor protein that targets melanoma antigen gp100 in the context of the human leucocyte antigen (HLA) A*0201 allele. This approval generated significant excitement, given the relative paucity of effective systemic therapies for advanced uveal melanoma. More broadly, tebentafusp represents the first T cell receptor agent to improve overall survival in any solid tumor.

Although HLA-A*02:01 is the most common allele at this locus overall, its expression varies considerably among ethnic groups. It is most frequently expressed in Europeans, and less commonly in African Americans and people of Asian or Pacific Island ancestry. While uveal melanoma is most common in Caucasian populations, other HLA-restricted cancer therapeutics are being developed for indications with more diverse patient populations, such as cervical cancer.

We advocate for proactive consideration of the populations eligible for each HLA-restricted therapeutic in development to ensure this emerging therapeutic class does not compound long-standing health disparities. As trials may focus on the most prevalent HLA subtypes, it will take the engagement of multiple stakeholders to ensure equitable access to patients of all ethnic backgrounds.

Biologic agents based on the human T cell receptor (TCR) represent an emerging class of immunotherapies that mimic the adaptive immune system's exquisite specificity to target and eliminate cancer cells. While Food and Drug Administration (FDA)-approved chimeric-antigen-receptor T cell therapies (such as the CD19-targeted tisagenlecleucel) are directed at cell surface proteins expressed on cancer cells irrespective of a patient's human leucocyte antigen (HLA) type, TCR-based therapies can target intracellular cancer antigens presented in the context of a specific HLA molecule. As HLA allele frequencies vary across ethnic groups, the clinical benefit of HLA-restricted therapies may be asymmetrically distributed. One of the TCR-based compounds furthest in clinical development is tebentafusp, a soluble TCR targeting the intracellular melanoma lineage-specific antigen gp100.

In 2021, Nathan *et al* reported the results of a phase III randomized trial of tebentafusp compared with investigators' choice of systemic therapy for previously untreated, advanced uveal melanoma in patients that were positive for HLA A*0201.¹ In a preplanned interim analysis of 378 patients, tebentafusp was associated with a significant improvement in the primary endpoint of overall survival compared with investigator's choice therapy (HR 0.51, 95% CI 0.36 to 0.71, $p < 0.0001$). These data have generated significant excitement, given the relative paucity of effective systemic therapies for advanced uveal melanoma and led to tebentafusp's recent approval by the FDA in January 2022. More broadly, tebentafusp represents the first TCR agent to improve overall survival in any solid tumor.

As additional cancer therapies targeting antigens presented by specific HLA alleles are developed, it is important to recognize that HLA allele frequencies vary significantly across different ethnic groups. HLA-A*02:01, the most common allele at this locus overall, is most frequently expressed in Europeans (27.0% allele frequency) and less commonly expressed in African Americans (11.9%) and people of Asian or Pacific Island ancestry (6.5%).² The practical rationale for investigators and trial sponsors to target the largest and most easily recruitable populations is understandable. The age-adjusted incidence of uveal melanoma is indeed considerably higher in the non-Hispanic white population (6.02 per million) compared with that in black (0.31 per million), Asian (0.38 per million), and Hispanic populations (1.67 per million).³ However, the recently published data for tebentafusp and many ongoing trials in other oncology indications give cause for optimism that agents targeting specific HLA-antigen pairs may become relevant to larger and more diverse patient populations across multiple tumor types.

For example, KITE-439 is a TCR-engineered T cell product targeting amino acids 11–19 of the HPV16 E7 protein that was studied in HLA-A*0201+patients with relapsed and refractory HPV 16+tumors



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(NCT03912831)—of note, this is the same HLA allele required for treatment with tebentafusp. As the mortality associated with cervical cancer among black women in the USA is more than twice that among white women (10.1 vs 4.7 per 100,000),⁴ the issue of equitable access to new therapies across diverse HLA subtypes is particularly pressing in this disease. An ongoing trial of HA-1 TCR T cell therapy in several recurrent and refractory hematologic malignancies (NCT03326921) is also limited to patients with the HLA-A*0201 allele. Beyond TCR-based therapies, HLA specificity is relevant to the development of tumor vaccines, several of which are in large randomized phase 3 trials such as the FLAMINGO-01⁵ study in HER2-positive breast cancer (NCT05232916).

Without proactive consideration of the populations eligible for each HLA-restricted therapeutic in development, this emerging therapeutic class has the potential to compound long-standing health disparities. In the USA, African Americans experience the highest death rate and shortest survival of any racial or ethnic group for most cancers.⁶ While unequal exposures to cancer risk factors and unequal access to care across socially constructed races (ie, sequelae of structural racism)⁷ likely account for the majority of these disparities, genetic variation in HLA types across ethnic groups is also a consideration as it relates to immunotherapies. For instance, given the variable representation of different ethnic groups in the US bone marrow donor registry, the success of identifying HLA-matched unrelated donors for allogeneic stem cell transplants is highly correlated with a patient's ancestry. A 2014 analysis of high-resolution HLA data from over 10.7 million adult donors in the National Marrow Donor Program estimated that patients of self-reported white European ancestry had a 75% chance of finding an unrelated HLA-matched adult donor (eight of eight alleles) while the comparable rate for patients of African American ancestry was 19%.⁸

In a 2020 policy statement, the American Society of Clinical Oncology affirmed that 'cancer health equity remains the guiding institutional principle that applies to all its activities across the cancer care continuum.'⁹ As further studies of HLA-restricted agents are conducted, the oncology community should be cognizant of the populations that are by default ineligible for these therapies, especially when these populations overlap with groups that have historically been excluded from medical research and continue to experience significant health inequities.

One potential consideration could be the creation of regulatory incentives (ie, priority review programs) or new public funding opportunities to specifically encourage the development of agents targeting less common HLA subtypes. In addition, clinical investigators and protocol review committees at academic medical centers could proactively monitor the HLA subtypes targeted by their

clinical trial portfolio and actively work to promote inclusivity for all potential trial participants with a variety of agents available for populations with various HLA alleles. While HLA-restricted cancer therapeutics will hopefully provide new treatment options in multiple diseases, it will take the engagement of multiple stakeholders across industry, academia, and regulators to ensure that the development of these agents allows for equitable access to patients of all ethnic backgrounds.

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