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Panel: Multiple Myeloma

Attention:
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Peptide-drug conjugates (PDC) enable selective delivery of cytotoxic payloads to target cells, which results in improved efficacy, reduced systemic toxicity and improved pharmacokinetics (PK)/pharmacodynamics (PD) compared with traditional chemotherapy. PDCs also allow for higher drug loading and enhanced tissue penetration capacity, and the peptides are modified more easily than an antibody that is used for antibody-drug conjugates (ADCs).[1]

Melphalan flufenamide (also known as melflufen in clinical development) is a lipophilic PDC that delivers an alkylator payload into tumor cells. Chemically, melflufen is an ethyl ester of a dipeptide consisting of melphalan and para-fluoro-L-phenylalanine. The peptide-conjugated structure of melphalan flufenamide is very lipophilic, allowing it to diffuse readily across the lipid bilayer membrane of the cell. Once inside the cell, overexpressed aminopeptidases cleave the peptide bond, rapidly releasing hydrophilic melphalan, which has reduced ability to diffuse back across the lipid bilayer membrane, becoming entrapped within the cell. This results in a high intracellular accumulation of melphalan, which enters the nucleus, causing DNA strand breaks and apoptosis. Melflufen is 50-100-fold more potent than melphalan in myeloma cells.[2]

PEPAXTO® (melphalan flufenamide) received US FDA Approval on February 26, 2021. The approved indication in combination with dexamethasone is for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody (i.e., triple-class refractory multiple myeloma).[3]

Need for new treatments for triple-class relapsed/refractory multiple myeloma (RRMM)
All patients with multiple myeloma become refractory to the available therapies, including proteasome inhibitors (PIs), immunomodulatory agents (IMiDs), and monoclonal antibodies (MAbs). With each subsequent relapse, patients with RRMM typically have worse outcomes, including lower response rates, shorter progression-free survival (PFS) and overall survival, and decreased treatment duration.[4,5] Triple-class refractory (TCR) multiple myeloma is characterized by poor survival outcomes.

There is little consensus regarding a preferred treatment paradigm for these patients. Current approaches include conventional chemotherapy, salvage autologous stem cell transplantation, and recycling previous regimens that were previously effective but non-curative, and may offer some efficacy due to clonal evolution.[6]

Need for treatments for extramedullary disease (EMD)

Ten to 30% of patients with relapsed/refractory multiple myeloma have clonal plasma cell spread to tissues outside the bone marrow at the time of diagnosis. These patients can present with disease in liver, skin, CNS, kidneys, lymph nodes, pancreas or as pleural effusion. EMD has a more aggressive phenotype, is more treatment-resistant, and has a poor prognosis.[7-9] There have not been any prospective therapeutic studies specifically dedicated to EMD. As a result, there is no specific treatment strategy that is recommended over any other and patients with EMD are usually treated with the same therapies used for multiple myeloma found in bone marrow.[7,9] The HORIZON study, which evaluated the efficacy and safety of melflufen is summarized below. It included 157 patients and 55 of these patients had extramedullary disease and a subpopulation analysis was done on these patients with EMD.[10,11]

Specific changes requested to NCCN guidelines:

We respectfully request that the NCCN Multiple Myeloma Guidelines Panel kindly consider listing PEPAXTO® (melphalan flufenamide) as a preferred treatment in combination with dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody. The request is based on the HORIZON phase 2, single-arm, open-label multicenter study that evaluated the efficacy and safety of melflufen plus dexamethasone in heavily pretreated patients, primarily with triple-class refractory MM, including a large subset with EMD, and 59% refractory to prior alkylator therapy.[10] These data have been submitted to the FDA and the application was approved on February 26, 2021 under accelerated approval, a designation intended for treatments which offer a meaningful advantage over available therapy, and received a priority review designation, an acknowledgement that this treatment has the potential to offer a significant improvement in safety or efficacy.

Rationale for the use of melphalan flufenamide for RRMM:

In support of the proposed change request, I wanted to highlight components in the HORIZON study. At the data cut off on January 14, 2020, of the 157 patients in the intent-to-treat (ITT) population, 76% were triple-refractory and 80% were refractory to ≥1 anti-CD38 mAb, and 55 patients (35%) had EMD.[10,11] The study included patients with a median age of 65 years, an ECOG PS≤2 and a median of 5 lines of prior therapy (range: 2 to 12).[10] Patients received treatment with a 28-day cycle of melflufen (40 mg IV on Day 1) + dexamethasone (40 mg on Days 1, 8, 15, 22; dose-reduced to 20 mg for patients ≥75 years). Treatment continued until disease progression or unacceptable toxicity.[10]

Efficacy Profile:

The primary endpoint of overall response rate (ORR) in the ITT population (N=157) was 29% and the clinical benefit rate (CBR) was 45%. In the triple-class refractory patients (n=119), the ORR was 26% and the CBR was 39%.[10] In a subgroup of patients with EMD (n=55), which is a subset of the triple-class refractory patients, the ORR was 24%. The median DOR was 5.5 months in both the ITT population, and the EMD subgroup and 4.4 months for the triple-class refractory patients.[10,11]

The response rate in patients with EMD was as follows:[11,12]

- Patients with EMD: ORR was 24% (n=55)
- 49% (n=27) of EMD patients had soft tissue plasmacytoma and 51% (n=28) of patients with EMD had bone-related plasmacytoma (49%)
- Patients with bone-related EMD: ORR was 25% (n=28)
- Patients with soft-tissue EMD: ORR was 22% (n=27)
- Patients with CNS EMD: ORR was 0% (n=5)

The median progression-free survival (PFS) and overall survival (OS) in the ITT population was 4.2, and 11.6, respectively. The median PFS and OS in the triple-class refractory population was 3.9, and 11.2 months, respectively.[10] The median PFS and OS in the EMD population was 2.9, 6.5 months, respectively.[11] Among patients with a response (≥PR), median PFS was 8.5 months (95% CI, 5.4-13.4) in the ITT population (n=46), 8.5 months (95% CI, 5.3-13.4) in the triple-class—refractory population (n=31), and 17.3 months (95% CI, 5.3-not evaluable) in the EMD subgroup (n=13).[10,11]

HORIZON Subgroup Efficacy Analysis

A subgroup analysis of R/R multiple myeloma patients showed good efficacy in patients with high-risk cytogenetics, elderly patients (≤75 years of age, and patients exposed to and refractory to prior alkylator therapy).

- Patients with high-risk (HR) cytogenetics including gain(1q), del(17p), t(4:14),and t(14:16)was done. The ORR was 20% in the HR cytogenetic group and 35% in the standard-risk cytogenetic group. Median DoR was 6.7 months in responding patients with HR cytogenetics. Median PFS and OS was 3.1 months and 11.5 months, respectively, in patients with HR cytogenetics.[13]
- In elderly patients (N=25), the ORR was 32%. In responding patients, the DoR was not reached. The media PFS and median OS in the elderly subgroup was 5.6 months and 13.5 months, respectively.[14]
- Of the 157 patients in the Horizon study, 138 had been exposed to prior alkylator therapy and 92 were refractory to alkylators. The ORR in alkylator-refractory patients was 20.7 months and the median DOR was 4.2 months. The median PFS and median OS was 3.7 months and 9.7 months, respectively.[15]

Time to next treatment (TTNT) was part of an exploratory analysis in the HORIZON study:[11]
TTNT was defined as the time from start of melflufen to first subsequent therapy or death (whichever occurred first); patients were followed for ≤2 years after disease progression, and TTNT was

retrospectively reviewed. In the ITT population, median TTNT was 5.8 months and in the triple-class-refractory group, median TTNT was 5.3 months.[10]

In a separate Phase 1/2 study (ANCHOR), patients that were refractory or intolerant to an IMiD and/or proteasome inhibitor were treated with either daratumumab (DARA) or bortezomib (BORT) plus melflufen and dexamethasone. These triplet combinations were well tolerated and had encouraging activity in heavily pretreated RRMM with poor prognostic factors. DARA-melflufen-dex treatment resulted in an ORR of 76% and a median PFS of 14.3 months in patients with an average of 2 (range 1-4) prior lines of therapy. BORT-melflufen-dex treatment resulted in an ORR of 67% , and a CBR of 83% in a small number of patients. [16,17]

Safety Profile

In the HORIZON study, the ITT population (n=157) patients were included as part of the safety analysis. Overall, 100% patients experienced any-grade AEs and 89% patients had grade 3/4 AEs. The safety profile consisted primarily of hematologic adverse events that are well-known to physicians and were clinically manageable with dose modifications and supportive care. The most common grade 3/4 hematologic AEs were neutropenia (79%), thrombocytopenia (76%), and anemia (42%).[10] Grade 3/4 thrombocytopenia with concurrent grade 3/4 bleeding events occurred in 3% of patients (1 was grade 4) and grade 3/4 neutropenia with concurrent grade 3/4 infections occurred in 11% of patients (1 was grade 4).[10] AEs led to melflufen dose reductions in 27% of patients and dose delays in 61% of patients.[10]

There were very few non-hematologic events in this heavily pretreated population. The most common nonhematologic grade 3/4 AE was pneumonia (10%). Gastrointestinal events were mostly grade 1/2 and did not result in treatment discontinuation. [10]

The following references are submitted to assist the committee in their review:

1. Ma L, Wang C, He Z, et al. *Peptide-drug conjugate: A novel drug design approach*. Curr Medicinal Chem, 2017; 24: 3373-3396
2. Wickstrom M, Nygren P, Larsson R, et al. *Melflufen – a peptidase-potentiated alkylating agent in clinical trials*. Oncotarget. 2017 Jun 8;8(39):66641-66655. PubMed PMID: 29029544.
3. Pepaxto®. Package Insert. Oncopeptides Inc. USA 2021 (registered).
4. Szabo AG, Iversen KF, Möller S, Plesner T. *The clinical course of multiple myeloma in the era of novel agents: A retrospective, single-center, real-world study*. Clin Hematol International. 2019;1:220-228.
5. Gandhi UH, Cornell RF, Lakshman A, et al. *Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy.* Leukemia. 2019;33(9):2266-2275.
6. Mikhael J. *Treatment options for triple-class refractory multiple myeloma*. Clin Lymph, Myeloma Leuk. 2019; 20(1):1-7
7. Touzeau C, Moreau P. *How I treat extramedullary myeloma*. Blood 2016; 127(8):971-976.
8. Sevcikova S, Minarik J, Stork M, et al. *Extramedullary disease in multiple myeloma–controversies and future directions*. Blood Rev. 2019; 36:32-39

9. Jagosky MH, Usmani SZ. *Extramedullary disease in multiple myeloma*. Curr Hematol Malig Reports 2020 (eub). Doi.org/10.1007/s11899-020-00568-3
10. Richardson PG, Oriol A, Larocca A, et al. *Melflufen and dexamethasone in heavily pretreated relapsed and refractory multiple myeloma*. J Clin Oncol. 2020; doi.org/10.1200/JCO.20.02259
11. Richardson PG, Mateos M-V, Oriol A, et al. *HORIZON (OP-106): Melflufen Plus Dexamethasone (dex) in 55 Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM) with Extramedullary Disease (EMD)—Subgroup Analysis*. Amer Soc Hematol 2020b, abstract #3214
12. Richardson PG, Mateos MV, Rodriguez-Otero P, et al. *Activity of melflufen in RR MM patients with extramedullary disease in the phase 2 HORIZON Study (OP-106): Promising results in a high-risk population*. Presented at IMW September 12-15, 2019; Boston, MA.
13. Mateos M-V, Oriol A, Larocca A, et al. *HORIZON (OP-106): Melflufen Plus Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma with High-Risk Cytogenetics—Subgroup Analysis*. Amer Soc Hematol 2020, abstract #3237.
14. Larocca A, Richardson PG, Oriol A, et al. *HORIZON (OP-106): Melflufen Plus Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma—Age Subgroup Analysis of Elderly Patients*. Amer Soc Hematol 2020, abstract #2293.
15. Rodrigues-Otero P, Mateos M-V, Oriol A, et al. *HORIZON (OP-106): Melflufen Plus Dexamethasone (dex) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM) Exposed to Prior Alkylator Therapy—Subgroup Analysis*. Amer Soc Hematol 2020, abstract 2321
16. Ocio EM, Efebera YA, Hajek R, et al. *ANCHOR (OP-104): Melflufen Plus Dexamethasone (dex) and Daratumumab (dara) or Bortezomib (BTZ) in Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to an IMiD and/or a Proteasome Inhibitor (PI) - Updated Efficacy and Safety*. Amer Soc Hematol 2020, abstract #417.
17. Oriol A, Larocca A, Leleu X, et al. *Melflufen for relapsed and refractory multiple myeloma*. Expert Opin Invest Drugs 2020

We appreciate your review and consideration of this submission.

Sincerely,

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