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Perspective

The approval and withdrawal of melphalan flufenamide (melflufen): Implications for the state of the FDA.

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ABSTRACT

In October 2021, melphalan flufenamide (melflufen) was withdrawn from the US market for the treatment of multiple myeloma. The decision occurred based on results from a phase 3 randomized controlled trial (RCT) which showed numerically inferior overall survival, which previously led the FDA to halt all trials involving this drug. We highlight four issues raised by the approval fate of melflufen. First, the OCEAN trial was designed with a substandard control arm: negative results occurred despite this bias theoretically favoring the experimental arm. Second, a new compound, derived from a well-known drug, is not well fitting the accelerated pathway principles, unless being robustly tested against its parent drug. Third and four, allowing a new compound on the market, while there are known alternatives, and imminent confirmatory data, has the potential to harm patients while bringing earlier market share and profit to the company. While the FDA and the company should be commended for pushing a potentially dangerous product off the US market despite recent approval, yet a re-evaluation of regulatory processes is needed to ensure that cancer patients have timely access to effective medications while being protected against potentially detrimental ones.

On October 25th, 2021, Oncopeptides AB withdrew Pepaxto® (melphalan flufenamide, also called "melflufen") from the US market for the treatment of multiple myeloma. The decision occurred based on results of the OCEAN study, a phase 3 randomized controlled trial (RCT) which showed numerically inferior overall survival with a HR of 1.104. According to a press-release, this decision has been made "after interactions and dialogue with the US Food and Drug Administration (FDA)" [1]. Consequently, the Oncologic Drugs Advisory Committee (ODAC) scheduled for October 28, 2021, discussing this product, has been cancelled [2]. As the company noted: "With the US withdrawal, there is no marketing authorization for melphalan flufenamide anywhere in the world.".

Melflufen had been initially granted accelerated approval on February 26, 2021, based on the HORIZON trial [3]. HORIZON was a multicenter, single-arm trial, enrolling patients with relapsed or refractory multiple myeloma after at least two prior lines of therapy, to receive melphalan flufenamide, in combination with weekly dexamethasone. Approval was limited to a subgroup of patients who had received at least four prior lines of therapy and whose disease was refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD-38 directed monoclonal antibody. This was based on the overall response rate (ORR) results of a subgroup analysis of 97 patients. The ORR was 23.7%, with 0 stringent complete response, 0 complete response, 9 very good partial responses, and 14 partial responses. The median duration of response was 4.2 months (95% CI: 3.2, 7.6).

Since that regulatory decision, the trial results have been published, showing an advantage of melflufen over pomalidomide on the primary endpoint of the trial, being progression-free-survival (PFS).[9] The PFS in the melflufen group was 6.8 months, and 4.9 months in the pomalidomide group (HR=0.79, [95% CI 0.64 – 0.98]; p=0.032). The overall survival (OS) data showed a 5.2 months shorter median OS in the melflufen group (19.8 months) as compared with the pomalidomide group (25.0 months, HR 1.10 [95% CI 0.85–1.44]; p=0.47). It is unfortunate that the overall survival results, that specifically led to the withdrawal of melflufen, were absent from the abstract conclusion: spin in abstracts have been described to mislead clinicians trial's interpretation.[10]

The approval of melflufen and rapid withdrawal within 8 months highlights strengths as well as weaknesses of the current regulatory paradigm for oncology drugs. It also differs from other recent decisions

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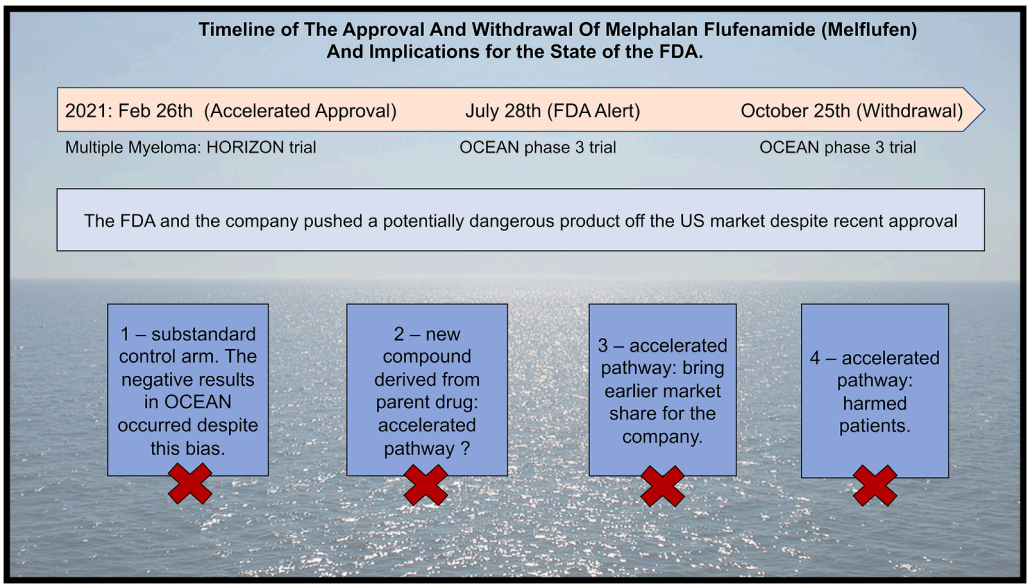

Figure 1. Timeline of The Approval And Withdrawal Of Melphalan Flufenamide (Melflufen) And Implications for the State of the FDA.

to continue marketing authorization for drugs, which have failed their post market studies [4]. Figure 1 illustrates the regulatory fate of melflufen that we will here discuss, with its timeline and implications.

The key strength in the regulatory history of melflufen is that the FDA has showing a willingness to push sponsors to withdraw products that failed to meet post market commitments, even if these products only recently received licensure. Early in 2021, a series of advisory committees voted in 4 of 6 cases to retain products on market, despite failed studies, arguably violating the social contract of accelerated approval. Since this vote, 5 remain on the US market, indicating to companies that post-market commitments may only be enforced weakly. Yet, the action by Oncopeptides AB reaffirms the agency's commitment to enforce the results of post-market trial results.

At the same time, there are 4 weaknesses revealed by melflufen. First, the confirmatory study showed a trend towards excess death despite multiple trial design features that were biased in favor of the melflufen arm. Consider that OCEAN was a randomized phase 3 trial enrolling relapsed or refractory multiple myeloma (RRMM) patients that have received 2 to 4 prior lines of treatment (including a proteasome inhibitor and an immunomodulatory agent (IMID)) and had to be refractory to lenalidomide. Patients were randomized to melflufen and dexamethasone or pomalidomide (another IMID) and dexamethasone. Importantly, daratumumab was not mandatory prior to enrollment.

Substandard control arm has been described as an important issue in the landscape of myeloma trials[5]. The control arm in the OCEAN trial is inferior to the best available standard-of-care in real life patients, which would be a triplet therapy. Patients were selected to be refractory to lenalidomide, and the control arm was the same class of drug (IMID): pomalidomide. Even if some providers would entertain the use of pomalidomide in this setting[6], in the OCEAN trial, patients were specifically selected based on lenalidomide-refractoriness and were not allowed to receive a proteasome inhibitor in combination.

More concerning, patients could enroll the trial without ever having received an anti-CD38 monoclonal antibody, nor being permitted one on study. Daratumumab is an important salvage treatment in advanced lines of RRMM patients, based on several positive randomized trials. From the OCEAN trial report, we know that only 17.6% of enrolled patients were refractory to daratumumab. Also, among all patients, which by definition should have received at least 2 lines of prior therapy, more than half of them (54.5%) previously received 3 or more lines of treatment [9]. The control arm of OCEAN essentially prevented patients to receive a CD38 containing regimen after several lines of treatment, or

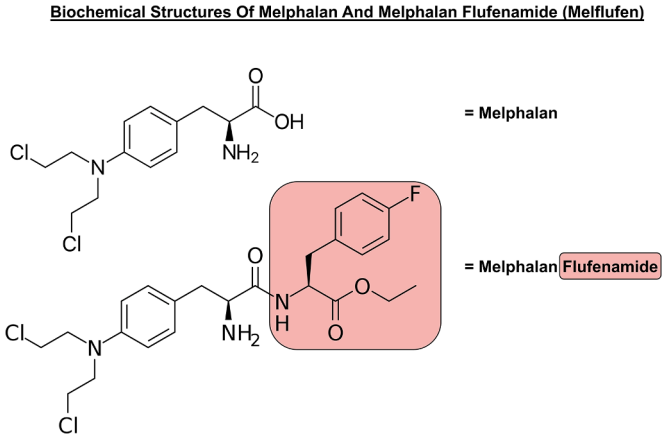

Figure 2. Biochemical Structures Of Melphalan And Melphalan Flufenamide (Melflufen).

delayed it. Despite this, OCEAN was halted because of an excess of mortality in the melflufen arm, after the alert issued on July 28, 2021, by the FDA.

The second weakness raised is that flexible regulatory pathways are being made available to unremarkable, next in class drugs. Melphalan—the parent drug of melflufen—is an alkylating agent, which was first approved in 1964 for palliative treatment of patients with multiple myeloma (MM). Since then, melphalan gained several new indications in MM patients, including in combination with other drugs as conditioning regimens before autologous stem cell transplantation [7].

Biochemically, melflufen is a derivative compound of melphalan, allowing, through lipophilicity and then hydrolysis, rapid cellular uptake and higher release of the metabolite melphalan [7]. Figure 2 shows biochemical structures of melphalan and melflufen, highlighting their similarities. Moreover, other alkylators are routinely used in the care of multiple myeloma, including cyclophosphamide. This raises the question of why the use of the accelerated approval pathway is warranted. Patients already have a number of alternatives, in class treatment options, and could conceivably wait 8 months for the results of randomized data.

Third, melflufen raises the question of who benefits from profits generated during the period of approval. Melflufen net sales between

January and September 2021 were exceeding 15 millions of dollars [11]. Notably, the average cost of melphalan for a MM patient should not exceed 300 - 500 $ during the first months of treatment, and cyclophosphamide costs about 200 – 300 $ a month. Melflufen in contrast costed 19 000 dollars per month. Other drugs withdrawn from market have reported significant revenue. For instance, Lartruvo® (olaratumab) earned 374 millions of dollars. The approval and rapid withdrawal raise the question of whether some portion of these funds should be returned to payers.

Fourth, how much acceleration is needed to tolerate increased uncertainty? The philosophical core of the accelerated approval pathway is that accepting a surrogate endpoint only reasonably likely to predict living longer or living better speeds a drug to market. In the case of melflufen, robust results lagged by 8 months. In the example of nivolumab for small cell lung cancer, confirmatory trials lagged by 8 weeks [8]. Both these products had negative confirmatory trials, but it took more than 2 years after the negative confirmatory results for nivolumab to be withdrawn in small cell lung cancer. If accelerated approvals come with sizable uncertainty, and confirmatory studies are imminent, should they be granted? Melflufen raises the question of whether the acceleration was worth it?

The FDA and company should be commended for pushing a potentially dangerous product off the US market in rapid fashion despite recent approval, yet simultaneously a re-evaluation of regulatory processes is needed to ensure that cancer patients in the US have timely access to effective medications, and be protected against access to medications which may potentially increase their mortality or morbidity.

Authors contribution statement

Authors' contributions: VP and TO contributed to the conception. TO wrote first draft of manuscript and all authors reviewed and revised the manuscript. All authors provided final approval of the manuscript.

Declaration of Competing Interest

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