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Letters to the Editor

Authors' reply: Perspective: The approval and withdrawal of melphalan flufenamide (melflufen): Implications for the state of the FDA

With interest we read the paper by Dr Olivier and Dr Prasad on the accelerated approval of melphalan flufenamide (hereinafter referred to as melflufen) [1]. The authors make several unjustified claims which we would like to address to clarify potential misunderstandings. First, it is stated that in the OCEAN trial [2] the combination of pomalidomide/-dexamethasone is a suboptimal treatment in the control arm. At the time of initiation of the study in 2017 this was the most used regimen in patients who had received two to four prior lines of treatment. For this reason, EMA approved pomalidomide/dexamethasone as the control arm. Triplets were not yet widely approved. This is also shown by the readout of multiple studies in relapsed refractory multiple myeloma over the last two years; studies which recruited patients in the same time period as OCEAN [3–5]. This is further substantiated by the ongoing DREAMM-3 trial, which also uses pomalidomide/dexamethasone as a comparator, but only expects to have its primary readout late in 2022 [6]. In addition, the authors seem to be not aware that until today pomalidomide/dexamethasone is often used in both the United States as well as Europe during this stage of the disease; the IntrinsiQ prescription tracking database still shows that pomalidomide/dexamethasone is the most commonly prescribed treatment regimen for myeloma patients after 2 prior lines of therapy in the US [7]. Also, OCEAN included patients who were lenalidomide-refractory. These patients pose a real clinical challenge in the real world [8]: the OCEAN trial very well defined this patient population in a clinical trial setting with a head-to-head trial design against one of the most often used regimens. Although the median progression free survival (PFS) gain of 2 months may seem modest, this represents a 40% increase of median PFS. We therefore strongly disagree with the authors on the relevance of the comparator arm as well as the meaningfulness of the PFS gain, which was the primary endpoint for which the study was powered.

The second point the authors raise is the difference between melflufen and melphalan. Again, the authors make some misleading claims; although the molecular structure has similarities, the drugs properties are very different. Also, in OCEAN it is clearly shown that melflufen works in alkylator refractory patients, notably with a twofold increase in both PFS and OS when compared to pomalidomide. This was true not only for patients refractory to bendamustin and cyclophosphamide but also standard dose melphalan [1]. In addition, there is an abundance of preclinical evidence showing both molecules have different modes of action at the molecular level, including the circumvention of P53 induced apoptosis and other important mechanisms [9].

Regarding point 3 and 4 we wish to comment the following: the authors apparently do not appreciate the challenges the lenalidomide refractory patient poses in clinical practise: these patients often have very limited treatment options and new drugs are clearly needed. Melflufen has a unique mode of action and has shown to lead to significant responses in the pivotal phase II HORIZON study [10]. It would be unethical to not approve a new compound in an area with such a large unmet need, when available data also suggests benefit to the same extent as Selinexor [11] or Belantamab [12], two drugs with challenging side-effect profiles, while safety is clearly less of a problem with melflufen. Although the confirmatory phase III study OCEAN did not show an OS benefit, we wish to state that it is unjustified to state that melflufen is a detrimental drug. While the non-significant and non-mature overall survival (OS) hazard ratio of 1.10 should be carefully investigated, we, nor the regulatory authorities, have so far identified a toxicological safety signal, but rather a very different behaviour across large relevant patient subgroups with both statistically superior and inferior OS results across subgroups, for example the age spectrum. A highly unexpected heterogeneity in OS in a phase 3 study warrants further examination. While younger transplanted patients seem to do very well on pomalidomide, elderly non-transplanted patients (which is the most relevant patient category in real-world clinical practise) do significantly better on melflufen. We encourage the authors to carefully analyse the subgroup data on OS which were published in the supplement. In this respect the manufacturer has recently rescinded its voluntary withdrawal from the drug in the US market [13] to agree with the FDA on the benefit/risk profile of the drug in different patient populations. In addition, the European Medicines Agency (EMA)'s CHMP has recently issued a unanimous positive opinion for full approval of melflufen in Europe in patients with triple-class-refractory (TCR) disease. Based on the subgroup data, patients with a time to progression of less than 3 years after an autologous stem cell transplant should not be treated with melflufen.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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