explanations behind the low frequency of AEs and the presumably lower than expected tumoricidal efficacy in the placebo group. The actual doses administered in the various arms are missing in the article. It would be highly useful to have these doses.

Conclusions: As innovators of PLED therapy and founders of PledPharma AB, our most sincere interest is that mangafodipir/calmangafodipir may be available for clinical use as soon as possible. From published preclinical and clinical data [see 4] we are confident that these substances will work in patients. However, to reach that goal demands optimally designed and executed clinical studies. That is particularly important for phase II trials, intended to lay a strong scientific foundation for subsequent pivotal phase III studies. Regrettably, the PLIANT study does not fulfill those demands, and to proceed into phase III studies based on explorative findings seems far from an optimal decision.

Disclosure statement

Jan Olof G. Karlsson and Per Jynge are two of the founders of PledPharma AB. Karlsson and Jynge are inventors on two granted patent families (e.g., US6258828 and US6147094) covering the therapeutic use of mangafodipir, which are owned by GE Healthcare. Karlsson owns shares in PledPharma AB, and is the first inventor on two granted patent families (e.g., US8377969, US8633174, and US9187509) covering the therapeutic use of calmangafodipir, which are owned by PledPharma AB. Karlsson is a former employee of GE Healthcare and PledPharma AB. Jynge is a former scientific advisor to PledPharma AB.

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LETTER TO THE EDITOR

The PLIANT trial gives trustworthy data

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We thank Karlsson and Jynge for their letter [1] to the article published in Acta Oncologica about the results of the placebo-controlled study PLIANT [2], exploring the neuroprotective effects of calmangafodipir in oxaliplatin-treated patients with metastatic colorectal cancer (mCRC), and the possibilities to respond to the issues raised.

1. Writing an article, besides editorials, as an 'editor in own journal' may raise concerns about conflicts of interest. The manuscript handling system used by Acta Oncologica, ScholarOne® automatically blinds all manuscripts when the editor-in-chief is one of the authors. The manuscript is then handled independently by one of the editors. This has been explained to Karlsson and Jynge by the editor in charge of their letter. It cannot be denied that close relationships, as for example, can be the case in research councils when one of the members apply for research support, may result in difficult positions even if the process is strictly regulated with no possibilities to influence the process and decision. The Committee of Publication Ethics, COPE (https://publicationethics.org), has dealt with cases of 'articles from editor in own journal' and given recommendations. These have been followed by the journal. The process with an editor (Professor Olav Dahl, Bergen) independently handling the reviewing process could have been included in the Disclosure Statement. All connections with PledPharma were openly disclosed.

2. Karlsson and Jynge criticize us for not having included three references that in their view would have shed light upon the findings in PLIANT. The first two references, one of which is a case report, were mentioned in a review article by Karlsson et al. [3], presenting the differences between the original substance mangafodipir and the derivative

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calmangafodipir used in the trial. The study by Coriat et al. [4], mentioned in a review article by Karlsson et al. [5], also referred to, is important and present apparently favourable results, but it is a non-randomized phase II study, used mangafodipir and therefore of not immediate interest giving it sufficient priority to be included in the reference list. Our article already included 49 references, above the recommended number in the Instructions to authors.

3. It is true that the number of adverse events, both haematological and oxaliplatin-induced peripheral neuropathy (OIPN), appears lower than has been reported in other studies using a modified FOLFOX6 regimen. But given that the regimen has been followed and considering the caveat that intertrial comparisons are notoriously difficult, there is no clear reason for this possible discrepancy (see also below under point 8 describing the chemotherapy doses given in the study). The study was continuously monitored, but due to a very fast patient recruitment before the planned number of patients had been reached, it was not possible to act earlier. The observed prevalence of symptoms can also vary randomly in small samples.

4. The statistical analysis plan described the change of the primary endpoint from neutropenia to OIPN in 26 February 2015 and it was signed and approved by 1 March 2015, and this decision was based on blinded data. The study was unblinded on 23 March 2015 and topline results for the treatment phase was communicated on 29 March 2015. The dates stated by Karlsson and Jynge are not correct. As stated in the article, even though this could have been written more clear, the study from the patient and investigator perspectives remained blinded until after the 12-month follow-up period was completed.

5. Assessment of the laboratory values for the original primary endpoint, neutropenia was for obvious reasons not done more than one month after the end of chemotherapy. Neither did the physicians record OIPN, initially a secondary endpoint, during follow-up. All data collection of OIPN during follow-up was done using a patient-reported outcome, the Leonard questionnaire, which was also defined as a secondary endpoint. It was not mandatory and some hospitals did not bring their patients in after treatment, once responses and progression had occurred, which limited the number of patients for long-time follow-up assessment. The results of the collected values after 9 and 12 months are thus uncertain, however, it is true they did not reveal any difference between placebo and calmangafodipir. The Leonard scale scores in the 5 μmol/kg group, being the recommended calmangafodipir dose for further testing, remained at the same level or lower, indicating a persistent effect. The coasting phenomenon with OIPN peaking at 3–6 months after end of treatment, seen in the placebo group, is consistent with literature [6]. We have no explanation why the recorded scores in the placebo group at the 9-month follow-up dropped down to the same levels as in the calmangafodipir-treated groups. The International Association for the Study of Pain (IASP) (https://www.iasp-pain.org/Guidelines) recommends that chronic pain is present when the duration is 3 months or longer, why we believe it is appropriate to state that also persistent problems, at least during the first six months after end of treatment, are favourably influenced.

6. It is true that the objective response rates (ORR) first reported orally in June 2015 at the MASCC meeting, primarily presenting phase I data, were lower than when finally reported. The initially reported ORRs were unfortunately reported incorrectly (prior to complete cleaning and final lock of the database) and this was not observed prior to the meeting. The ORRs reported in the publication are confirmed and correct and well in line with what is reported in similar studies. It is not possible to state or rule out that median PFS is lower in the PLIANT study than in other studies. We have discussed the results referring to that the study included also second-line patients, that patients could not have disease that could be resected even if excellent response was seen and that the patients should have indications to be treated with combination chemotherapy, that is, be symptomatic or have rapidly progressing disease and thus not be candidates for single fluoropyrimidine therapy. All these factors are adverse prognostic signs, well explaining that PFS appears lower than reported in other studies, where patients are likely much more selected.

7. As stated in the Statistical Methods section, the purpose of the trial was to elucidate whether calmangafodipir 'appears effective to proceed with further development', which is PledPharma's decision and responsibility. The study was designed to protect the type-I error rate for the primary endpoint using one of the typical dose-finding strategies according to regulatory guidelines, an one-sided test with 90% confidence intervals to reveal the most efficacious active treatment arm with a pre-defined hierarchical test order comparing single or combination of treatment arms versus placebo. For all secondary endpoints, no adjustment for multiplicity was planned, nor performed, and results in those are to be interpreted as exploratory, that is, hypothesis generating, and they were done using a conventional two-sided hypothesis test procedure. The study failed to confirm efficacy in the primary endpoint as it was defined. The manuscript presents a selection of secondary endpoints which has been decided to be important for further clinical development of this drug with regard to a regulatory perspective. All these variables were decided prior to the start of the study, presented in the study protocol and addressed in a detailed statistical analysis plan, SAP. This also included pooling of active treatment arms. This statistical strategy is typical and common practice for randomized clinical trials, and approved by regulators including statistical reviewers on their side. It is not a weakness of the study. Of course, results have not a confirmatory value, but authors never attempted to claim this.

8. A lower than expected frequency of physician-assessed OIPN lowers the possibilities to detect differences, if true, with statistical significance. You could expect a frequency of adverse effects higher than what was seen, but it is an absolute must to report data as they came out. Karlsson and Jynge try to explain the apparently lower frequency of adverse effects by lower doses or lower activity of the drugs. There is no evidence for that neither of these are behind the frequencies. The modified FOLFOX6 is a reference regimen used in multiple trials. The oxaliplatin dose (85 mg/m^2 every fortnight)

is like the original FOLFOX-4 regimen and used in most modifications of that regimen, but not in the 'original' FOLFOX-6 where the dose was 100 mg/m^2 [7]. None of the many variants have been properly compared with each other, although assumed to be similar in activity. In one study in elderly patients with mCRC, the classic LV5FU2, the basis in FOLFOX-4, alone or when combined with irinotecan, resulted in longer overall survival when compared with simplified LV5FU2, used in FOLFOX-6 and all modifications [8]. In the PLIANT trial, all patients except one patient treated with calmangafodipir 5 μmol/kg received the planned dose of 85 mg/m^2 oxaliplatin at the first cycle (the exceptional patient received 100 mg/m^2), and median and interquartile doses at all eight cycles in all groups were the same, or 85 mg/m^2. Mean dose decreased slightly to 81–83 mg/m^2 in the different groups, telling that dose intensity was at a high level, congruent with low toxicity. Delays in the administration of cycles were seen, but was not particularly high (seen in 25–40% of the patients at cycle 8 with a tendency to more delays using calmangafodipir 5 μmol/kg. Commercially available oxaliplatin was used. Similar high dose intensity for 5-fluorouracil was seen. Too low doses of the chemotherapy cannot explain the lower than expected frequency of adverse effects.

Conclusions

Karlsson and Jynge as innovators of the therapy and founders of PledPharma AB may be eager to see that calmangafodipir can be available for clinical use as soon as possible and that they feel confident that it will work in patients. This does not surpass the requirements to conduct studies in the order they should be done with regards to regulatory requirements (phase I followed by phase II, now reported in the publication [2], and finally phase III). The PLIANT study was properly designed and executed, and it could show clinically meaningful gains (about a 40% relative reduction) in prevention of a disabling adverse effect from oxaliplatin, OIPN [9,10]. The primary endpoint, physician assessed OIPN during therapy, could not be met since it did not reach statistical significance. In retrospect, it would have been better to record patient-reported problems after therapy and use these for deriving the primary endpoint; those recordings were statistically significant and clinically meaningful in the PLIANT study, but neither FDA, nor EMA had an interest to include them as primary endpoints in the clinical development program. The coming pivotal studies, being natural steps forward after the outcomes of the exploratory findings in this study, will use a patient-reported outcome after treatment as the primary endpoint. We share the beliefs of Karlsson and Jynge that calmangafodipir will work sufficiently well in patients, but not their opinions of the PLIANT study.

Disclosure statement

Bengt Glimelius, Consulting PledPharma AB, chief-editor of Acta Oncologica. The handling of the letter behind this response and our response has been done by one of the editors of the journal, professor Olav Dahl, Bergen, Norway; Jan Kowalski, Consulting PledPharma AB; Jacques Näsström, Employment, Leadership, Stock, Patent, PledPharma AB.

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