Author's response to reviews

Title: Single Arm NCRI Feasibility Study of CHOP in Combination with Ofatumumab in Induction and Maintenance for Patients with Newly Diagnosed Richter's Syndrome

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Author's response to reviews: see over
Dear Dr Crow

Many thanks for your reply to myself and Dr Anna Schuh with regard to the BMC Cancer manuscript

MS: 1726363839126243 “”Single Arm NCRI Feasibility Study of CHOP in Combination with Ofatumumab in Induction and Maintenance for Patients with Newly Diagnosed Richter‘s Syndrome”.

We are very grateful for the reviewer’s comments on the manuscript. To address your first point, the main reason to include the phrase ‘feasibility’ within the title of the article is that it was one of the key outcome measures of the study. The literature in Richter’s Syndrome has shown that it is extremely difficult to perform clinical trials in this disease because of the nature of the patient cohort, and the rarity of the disorder. This study is the first ever national UK study in this disorder and therefore will be of great interest to the UK readership particularly because we are displaying a proof of principle that it is possible to perform studies with this group of patients.

That said, I am happy to alter “Feasibility” with “phase II” within the study title and I have changed this within the altered manuscript. I will now address the comments made by both reviewers.

Reviewer: Preetesh N Jain

Discretionary Revisions – Whilst accelerated phase CLL is an interesting phenomena, it is not relevant to the paper here as this is a phase II clinical trial with the pre-defined inclusion criteria for the study including patients with biopsy proven Richter’s Syndrome (DLBCL) only.

Major Compulsory Revisions – as mentioned in your email, we have disregarded comments:

1 (no figures or tables)
2 (no results for a protocol paper)
3 “Explain whether a combination of O-hyperCVAD could be better than O-CHOP?”

The authors feel strongly that hyperCVAD is too toxic for the demographic of patients with Richter’s Syndrome (they are typically elderly, with pre-treated CLL and are not as fit as patients with de novo DLBCL). As a result of this, one of the aims of the study was to combine ofatumumab with combination chemotherapy that has efficacy; but that was relatively non-toxic in this difficult-to-treat patient group. The authors feel that this is already clearly addressed in the study background section, which includes the rationale:

“Moreover, these regimens are toxic and inappropriate for many patients with R5.” Line 93-94. The papers that used HYPER-CVAD are referenced within the paper.

4. Whether the dose of ofatumumab chosen is based on pharmacokinetics? 1000 or 2000 mg/m2

The authors provide a section from the CHOP-OR protocol to explain the rationale behind using the 1000mg dose:

“The proposed individual ofatumumab dose in this study, 1000 mg, was selected based on available pre-clinical and clinical data. Preclinical data suggest that ofatumumab plasma concentrations >10 ug/mL are sufficient to suppress peripheral B-cell recovery in cynomolgus monkeys as well as suppress tumor cell growth in Daudi tumor-bearing SCID mice. Pharmacokinetic data from the Phase I/II study in 33 patients with relapsed or refractory CLL (Study Hx-CD20-402) were analysed using a two-compartment model with a decrease in clearance after the first dose and assuming a constant rate infusion using a nonlinear mixed-effects modelling approach (NONMEM). The resulting model was used to simulate concentration-time data for 500 subjects receiving ofatumumab at 300 mg at Day 1 and 1000 mg at Day 8 during the first 28-day cycle, then 1000 mg on Day 1 of each subsequent 28-day cycle for a total of six cycles. Based on the simulations, the probability of maintaining plasma ofatumumab concentrations >10 ug/mL was approximately 90% or greater by the end of the second cycle, throughout the remainder of the dosing period, and for 4 weeks after the last dose; the probability of Cp >10 μg/mL was approximately 80% at 8 weeks after the last dose. Thus, the proposed dosing
schedule is expected to achieve prolonged maintenance of plasma concentrations >10 ug/mL in a high proportion of patients with CLL. A currently ongoing open-label Phase II study of ofatumumab, fludarabine, and cyclophosphamide in patients with previously untreated CLL administers ofatumumab dose of 1000 mg every four weeks for six cycles (Study Hx-CD20-407). Although, no efficacy results are available currently, no major safety issues have been observed to date (Ofatumumab Investigator Brochure, 2009).

The authors will add a short sentence with a reference to highlight the rationale for 1000mg dosing. (Line 189-190)

5 Authors should discuss data from R-CHOP in Richter’s and compare with O-CHOP.

This abstract that is eluded to was not available when the study was designed. No results for the protocol paper are available to date and it is outside of the remit of a protocol paper to discuss a true comparison at present. The paper with the abstract results in was formally published this year (2014). I will now make reference to it within the paper. Lines 95-97.

6. The paper (following this abstract) is now referenced within the protocol paper (Lines 97)

7. Explain whether the pts who achieve CR will be considered for SCT after maint or before maint.? Whether the characteristics of prior CLL determine their treatment decision?

8. Clonality with prior CLL - will it affect the treatment decision?

See comment lines 125-127 and lines 276-277 addressing these comments

Reviewer: Bertrand Coiffier

This is a proposal for a phase II study in Richter syndrome. The rational to use ofatumumab is very low considering that in DLBCL ofatumumab has a response rate below 10%. Why not using rituximab? Or doing a randomized phase II? The role of ofatumumab in the future is near zero. When this study will be finished, the drug might have disappeared.

During all the paper the study/regimen is called CHOP-OR or CHOP-O. What is the meaning of this “R”? Is rituximab added in some patients?

The authors thanks the reviewer for their comments. Firstly, we are concerned that the reviewer may consider this a proposal for a study rather than one that is ongoing, recruiting patients and promises to be the largest phase II study ever performed in Richter’s syndrome. This is a national UK study that has received complete backing by the UK CLL community. As outlined within the paper, the rationale for Ofatumumab is clearly described in lines 100-109:

“Ofatumumab is a fully humanised monoclonal IgG anti-CD20 antibody. It specifically and powerfully targets a unique CD20 epitope on B cells. When compared with rituximab, it binds with increased affinity and has a longer dissociation time, both of which improves its complement-mediated cellular cytotoxicity (Barth et al., 2012; Teeling et al., 2006). As a result, ofatumumab has a greater potential to induce B cell apoptosis independently of p53 than rituximab, and has been shown to be efficacious and non-toxic in relapsed B-CLL refractory to fludarabine and alemtuzumab; a group that commonly possess TP53 mutations and/or deletions (Wierda et al., 2010). Given the high incidence of TP53 disruption in patients with DLBCL-RS (Chigrinova et al., 2013) and that patients characteristically relapse early after initial response to induction, it was felt that ofatumumab as induction (alongside CHOP) and maintenance therapy would represent both a pragmatic and biologically-sound treatment for patients with RS within this phase II clinical trial”

The paper that the reviewer refers to using Ofatumumab as a single agent in relapsed, refractory DLBCL was published recently and therefore considerably after the study was designed (Coiffier et al., 2013). The authors would also like to stress that its use as a single agent in the context referred to in the reviewer’s comments is different from its use within our study.
To perform a randomised phase II study would require a large multinational study. The authors felt that a phase II single arm study focused partially on the feasibility of recruitment was the first and most important study to prove that could be performed.

The study is called “CHOP-OR” because it represents another option to CHOP. i.e. “CHOP or ...”

We apologise for any confusion over the phrase CHOP-OR, however we also believe that this does not represent a reason to accept or reject a paper, particularly when it is clear that this is a non-randomised phase II study. The statement with regard to whether or not ofatumumab is still an active and useful agent is very subjective and there are many clinicians that still disagree with this. It is possible that this statement largely comes from data that has been published in more recent times with ofatumumab compared to novel molecular inhibitors in CLL (Byrd et al., 2013) and not in the context of Richter’s Syndrome. To the authors knowledge there is no other clinical data available using Ofatumumab in Richter’s Syndrome.

The authors do hope these are adequate answers to the questions. The authors would also like to stress that the trial is relatively near to completion is highly likely to a.) be the largest prospective Richter’s study and b.) prove the feasibility of such studies. As a result we do feel that this is likely to have an important impact in the field of haemato-oncology.

With Kindest Regards,

Dr Toby Eyre & Dr Anna Schuh.

References


