**Lenalidomide, dexamethasone and alemtuzumab or ofatumumab in high-risk chronic lymphocytic leukaemia: final results of the NCRI CLL210 trial**

Andrew R Pettitt1,2, Richard Jackson1, Silvia Cicconi1, Fotis Polydoros1, Christina Yap3, James Dodd1, Matthew Bickerstaff1, Michael Stackpoole1, Umair T Khan1,2, Stacey Carruthers1, Melanie Oates1, Ke Lin1,4,Sarah E. Coupland1,4, Geetha Menon1,4, Nagesh Kalakonda1,4, Helen McCarthy5, Adrian Bloor6, Anna Schuh7, Andrew Duncombe8, Claire Dearden9, Christopher Fegan10, Ben Kennedy11, Renata Walewska5, Scott Marshall12, Christopher P Fox13 and Peter Hillmen14

1 University of Liverpool, Liverpool, UK

2 Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, UK

3 University of Birmingham, Birmingham, UK

4 Royal Liverpool & Broadgreen University Hospitals NHS Trust, Liverpool, UK

5 The Royal Bournemouth Hospital, Bournemouth, UK

6 The Christie NHS Foundation Trust, Manchester, UK

7 Churchill Hospital, Oxford, UK

8 Southampton General Hospital, Southampton, UK

9 Royal Marsden NHS Foundation Trust, Sutton, UK

10 University Hospital of Wales, Cardiff, UK

11 Leicester Royal Infirmary, Leicester, UK

12 City Hospitals Sunderland NHS Trust, Sunderland, UK

13 Nottingham University Hospitals NHS Trust, Nottingham, UK

14 University of Leeds, Leeds, UK

**Running heads (shortened title):** Lenalidomide combination therapy in high-risk CLL

(50 characters allowed)

**Corresponding author:** Professor Andrew R Pettitt, email: arp@liv.ac.uk

**Word count**

Main text: 1500

**Trial registration:**

EudraCT No: 2010-019575-29

ISRCTN No: ISRCTN40303610

**Acknowledgements:**

We are grateful to Cancer Research UK for endorsing the study, to the NIHR for supporting local trial delivery, and to industry partners for funding trial co-ordination (Celgene, Chugai) and providing (Celgene, GSK/Novartis) or subsidising (Baxter, Chugai) investigational medical products.

Therapeutic response in chronic lymphocytic leukaemia (CLL) is variable, with deletion or inactivating mutation of the TP53 gene on chromosome 17p13 being strongly associated with chemotherapy resistance and short survival1, 2. The UK CLL206 and German/French CLL2O trials 3, 4demonstrated the effectiveness of combining the anti-CD52 monoclonal antibody alemtuzumab with high-dose methylprednisolone (HDMP) or dexamethasone in high-risk CLL,1, 2 and these p53-independent drug combinations became the standard of care for such patients in many centres prior to the advent of novel agents such as ibrutinib, idelalisib and venetoclax.3 The CLL210 trial was developed to evaluate the potential benefit of adding the cereblon-targeting drug lenalidomide to the alemtuzumab/ glucocorticoid backbone. Lenalidomide was of interest owing to its established activity in 17p-deleted CLL coupled with its potential to act in synergy with the other two drugs in a p53-independent manner.4, 5 During the course of the study, alemtuzumab became unavailable and was replaced by the anti-CD20 monoclonal antibody ofatumumab, which has a reported efficacy similar to that of alemtuzumab.6 Although the study showed that both regimens had therapeutic activity, the predefined co-primary endpoints for efficacy and toxicity were not met.

CLL210 was designed as a single-arm phase II trial with a randomisation to lenalidomide maintenance vs placebo for patients who responded to the induction phase. were defined b deletion,not responding to

he study t. Supportive care included aciclovir, pneumocytistis jiroveci prophylaxis, CMV PCR surveillance and G-CSF supportpinging

weretolerability absence of andThe criteria for considering the study treatment to be of potential or definite interest were set at a CR rate of more than 10% or 20%, respectively, and an intolerance rate of less than 50% or 30%, respectively. Minimal residual disease (MRD) was assessed centrally by 4-colour flow cytometry with a sensitivity of 10-4. 7

10111, 212341356, 74, 1489

Sixty-four patients were registered from 21 UK sites between 6 February 2012 and 8 October 2015. Sixteen patients were recruited to the original alemtuzumab protocol until 4 September 2012, after which 48 additional patients were recruited to the revised ofatumumab protocol from 13 September 2013. Baseline features of registered patients are summarised in Table 1 and were broadly as expected. Twenty-nine (45%) patients were treatment-naïve, while the other 35 (55%) had received between one and three lines of prior therapy. Fifty-three (83%) patients had a previously recorded 17p deletion including all 29 treatment-naïve patients and 24/35 (69%) previously treated patients. Patient characteristics were generally well balanced between the alemtuzumab and ofatumumab cohorts.

Within the alemtuzumab cohort, 9/16 patients received all of the planned induction therapy, whereas treatment was terminated prematurely in 7 patients who received a median of 29 (IQR 12, 54) percent of the planned treatment. Within the ofatumumab cohort (excluding one untreated patient who did not start trial treatment due to acute ITP), 24/47 patients received all the planned induction therapy, whereas treatment was terminated prematurely in 23 patients who received a median of 29 (IQR 10, 38) percent of the planned treatment.

Among the 16 patients in the alemtuzumab cohort, the CR/CRi, PR, SD and PD rates were 6%, 69%, 0 and 6%, respectively, while 19% were non-evaluable due to missing data and/or receiving less than 10 weeks of study treatment in the absence of disease progression. Among the 47 patients in the ofatumumab cohort, the CR/CRi, PR, SD and PD rates were 2%, 51%, 9% and 11%, respectively, with 28% being non-evaluable. Consequently, neither regimen met the predefined boundary for being of interest from an efficacy perspective. Of note, the 6% CR rate in the alemtuzumab cohort was substantially lower than the 36% CR rate observed in the CLL2061 trial which employed an 8-fold higher relative glucocorticoid dose.

Kaplan-Meier curves for PFS and OS are shown in Figure 1. Despite the lower-than-expected CR rate in the alemtuzumab cohort, the 2-year PFS rate was surprising good at 58% (95% CI: 27-91%). This compares with ~17% in the CLL206 trial, 12% in the previously treated cohort of CLL2O and 56% in the treatment-naïve cohort of CLL2O (two thirds of whom received alemtuzumab maintenance or HSCT)1, 2 and suggests that adding lenalidomide to alemtuzumab and dexamethasone may prolong PFS without increasing the CR rate. In contrast, the 2-year PFS rate in the ofatumumab cohort of CLL210 was only 30% (95% CI: 18-49%) with a striking difference between previously treated versus treatment-naïve patients (9% and 52%, respectively). 2-year OS rates were higher for the alemtuzumab cohort compared to the ofatumumab one (79% vs 57%).

Our findings revealed interesting differences between the responses induced by the alemtuzumab and ofatumumab regimens. In addition to being more effective in terms of OR rate (75% vs 53%), CR rate (6% vs 2%), 2-year PFS (58% vs 30%), 2-year OS (79% vs 57%), the alemtuzumab regimen produced much higher rates of blood MRD negativity (37% vs 0) and morphological bone marrow clearance (50% vs 8% of responders). In contrast, the two regimens were comparably effective at clearing nodal and splenic enlargement (25% vs 20% of patients, respectively).

Twenty patients (5 from the alemtuzumab cohort and 15 from the ofatumumab cohort) were randomised to lenalidomide maintenance (11) versus placebo (9). The median duration of lenalidomide maintenance was 6 (IQR 2, 10) months. There was a non-significant trend for superior PFS in the lenalidomide arm compared to the control arm and HSCT group (Figure 1). However, these results should be interpreted with caution owing to the small number of patients in each group and the high post-induction drop-out rate.

ssGrade ≥3 SAEs were reported in 13/16 (81%) patients in the alemtuzumab cohort and 28/47 (60%) patients in the ofatumumab cohort. These included 8 treatment-related grade 5 SAEs, of which 2 were in the alemtuzumab cohort (1 infection and 1 neoplasm) and 6 in the ofatumumab cohort (4 infections, 1 haematoma and 1 visceral arterial ischaemia). The intolerance rate was 0.67 (95% CI: 0.51-0.80) for the alemtuzumab cohort and 0.38 (95% CI: 0.30-0.46) for the ofatumumab cohort. Consequently, neither regimen met the predefined boundary for being of interest from a tolerability perspective.

Neither of the two regimens evaluated in CLL210 compare favourably with newer drugs such as ibrutinib, idelalisib and venetoclax when applied as monotherapy to a similar patient population. For example, ibrutinib produced a 2-year PFS rate of 85% in a retrospective study of 108 patients with treatment-naïve 17p-deleted CLL8 and 65% in a combined analysis of 230 patients with a 17p deletion who were recruited into 3 prospective clinical trials of relapsed/refractory CLL.9 Similarly, the 2-year PFS rate among 46 patients with a 17p deletion or TP53 mutation who were recruited into a prospective clinical trial of idelalisib in relapsed/refractory CLL was ~43%,10 while the 2-year PFS for venetoclax in the pivotal study of 158 patients with predominantly relapsed/refractory 17p-deleted CLL was 54% .11

192021228232421252616152718

In summary, although the NCRI CLL210 trial showed that lenalidomide and dexamethasone combined with either alemtuzumab of ofatumumab is feasible and active in high-risk CLL, the study did not meet the pre-specified dual primary endpoints. Furthermore, interest in glucocorticoid/ antibody combinations has now been eclipsed by the emergence of highly effective and well-tolerated novel agents that target Bcl-2 or components of the B-cell receptor signalling pathway. 2616152718

References

1. Pettitt AR, Jackson R, Carruthers S, et al. Alemtuzumab in combination with methylprednisolone is a highly effective induction regimen for patients with chronic lymphocytic leukemia and deletion of TP53: final results of the national cancer research institute CLL206 trial. J Clin Oncol. 2012 May 10;30(14):1647-1655.

2. Stilgenbauer S, Cymbalista F, Leblond V, et al. Alemtuzumab Combined with Dexamethasone, Followed By Alemtuzumab Maintenance or Allo-SCT in “ultra High-risk” CLL: Final Results from the CLL2O Phase II Study. Blood. 2014;124(21):1991-1991.

3. Oscier D, Dearden C, Eren E, et al. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. Br J Haematol. 2012 Dec;159(5):541-564.

4. Arumainathan A, Kalakonda N, Pettitt AR. Lenalidomide can be highly effective in chronic lymphocytic leukaemia despite T-cell depletion and deletion of chromosome 17p. Eur J Haematol. 2011 Oct;87(4):372-375.

5. Riches JC, Gribben JG. Mechanistic and Clinical Aspects of Lenalidomide Treatment for Chronic Lymphocytic Leukemia. Curr Cancer Drug Targets. 2016;16(8):689-700.

6. Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol. 2010 Apr 1;28(10):1749-1755.

7. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008 Jun 15;111(12):5446-5456.

8. Mato AR, Roeker LE, Allan JN, et al. Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial. Am J Hematol. 2018 Nov;93(11):1394-1401.

9. Jones J, Mato A, Coutre S, et al. Evaluation of 230 patients with relapsed/refractory deletion 17p chronic lymphocytic leukaemia treated with ibrutinib from 3 clinical trials. Br J Haematol. 2018 Aug;182(4):504-512.

10. Sharman JP, Coutre SE, Furman RR, et al. Final Results of a Randomized, Phase III Study of Rituximab With or Without Idelalisib Followed by Open-Label Idelalisib in Patients With Relapsed Chronic Lymphocytic Leukemia. J Clin Oncol. 2019 Jun 1;37(16):1391-1402.

11. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial. J Clin Oncol. 2018 Jul 1;36(19):1973-1980.

**Tables**

**Table 1. Pre-treatment characteristics.**

|  |  |  |  |
| --- | --- | --- | --- |
|   | **Ofatumumab** **(N=48)** | **Alemtuzumab** **(N=16)** | **Total** **(N=64)** |
| Age *[median (IQR)]* | 66 (59, 70) | 68 (57, 74) | 66 (59, 70) |
| Gender *[n (%)]*  |   |   |   |
| Female | 15 (31%) | 3 (19%) | 18 (28%) |
| Male | 33 (69%) | 13 (81%) | 46 (72%) |
| Binet stage *[n (%)]*ABCUnknown | 10 (21%)12 (25%)25 (52%)1 (2%) | 7 (44%)4 (25%)5 (31%)0 (0%) | 17 (27%)16 (25%)30 (47%)1 (1%) |
| IGHV Status\*MutatedUnmutatedOther\*\* | 13 (27%)29 (60%)6 (13%) | 2 (12%)11 (69%)3 (19%) | 15 (23%)40 (63%)9 (14%) |
| WHO performance status *[n (%)]* |   |   |   |
| 0 | 25 (52%) | 9 (56%) | 34 (53%) |
| 1 | 17 (35%) | 7 (44%) | 24 (38%) |
| 2 | 6 (13%) | 0 (0%) | 6 (9%) |
| CIRS Total Score\*\*\* *[median (IQR)]* | 2 (0, 4) | 2 (1, 4) | 2 (1, 4) |
| CIRS Severity Index *[median (IQR)]* | 1 (0, 2) | 1 (1, 2) | 1 (1, 2) |
| Previous Treatment *[n (%)]* |   |   |   |
| No | 21 (44%) | 8 (50%) | 29 (45%) |
| Yes | 27 (56%) | 8 (50%) | 35 (55%) |
| TP53 defect\*\*\*\* *[n (%)]* |   |   |   |
| No | 8 (17%) | 3 (19%) | 11 (17%) |
| Yes | 40 (83%) | 13 (81%) | 53 (83%) |

\* IGHV, immunoglobulin heavy-chain variable region. IGHV genes showing >98% homology to the germline DNA were classed as unmutated and the remainder as mutated.

\*\* Other – six patients had no clonal heavy-chain variable region identified and 3 patients had insufficient sample to assess for IGHV status

\*\*\* CIRS score did not include points for having CLL.

\*\*\*\*Previously documented TP53 defects were confirmed in pre-treatment blood samples from 47/53 (89%) patients and consisted of 17p deletion and TP53 mutation (33 patients), 17p deletion only (8 patients) or TP53 mutation only (6 patients).

**Table 2. Summary of all grade ≥3 adverse events (reported as either SAEs or non-serious AEs) occurring with a frequency of >1%.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Toxicity** | **Induction phase** | **Post-induction phase** | **Total events** |
| **Alemtuzumab group (n=16)** | **Ofatumumab group (n=47)** | **Lenalidomide arm (n=11)** | **Control arm** **(n=9)** | **Not randomised** **(n=18)** |
| Lung infection | 8 | 13 | 3 | 3 | 3 | 30 |
| Neutropenia | 4 | 15 |  3 |   | 2 | 24 |
| Sepsis | 13 | 1 |   |   | 3 | 17 |
| Infection, other | 2 | 5 | 1 | 1 | 2 | 11 |
| Febrile neutropenia | 1 | 4 | 1 |   | 3 | 9 |
| Neoplasms, other |   | 2 | 6 |   | 1 | 9 |
| Anaemia | 2 | 3 |   | 1 | 2 | 8 |
| Hyperglycaemia | 3 | 3 |   |   | 1 | 7 |
| Hypophosphataemia |   | 4 | 2 |   |   | 6 |
| Thrombocytopenia | 2 | 3 |   |   |   | 5 |
| Upper respiratory infection |   | 4 |   |   | 1 | 5 |
| Vomiting | 1 | 3 |   |   |   | 4 |
| General, other | 3 | 1 |   |   |   | 4 |
| Infusion related reaction |   | 4 |   |   |   | 4 |
| Bronchial infection | 1 | 1 | 1 | 1 |   | 4 |
| Infective enterocolitis  | 1 | 1 |   |   | 2 | 4 |
| Hyponatraemia | 1 |   | 2 |   | 1 | 4 |
| Hypercalcaemia |   | 4 |   |   |   | 4 |
| Hypokalaemia |   | 1 | 2 |   | 1 | 4 |
| Maculopapular rash | 1 | 1 | 1 |   | 1 | 4 |
| Thromboembolic event |   | 4 |   |   |   | 4 |
| Localised oedema | 1 |   |   | 1 | 1 | 3 |
| Laryngitis | 2 | 1 |   |   |   | 3 |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |

Figure & Legend



Figure 1. Kaplan-Meier plots showing: A) progression-free survival of the alemtuzumab and ofatumumab cohorts from study registration; B) overall survival of the alemtuzumab and ofatumumab cohorts from study registration; C) progression-free survival of patients who were randomised to lenalidomide maintenance or no further treatment or received a haematopoietic stem-cell transplant; D) overall survival of patients who were randomised to lenalidomide maintenance or no further treatment or received a haematopoietic stem-cell transplant.