COSMIC, chemotherapy plus ofatumumab at standard or mega dose in chronic lymphocytic leukaemia, a phase II randomised study

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Chemoimmunotherapy (CIT) comprising cytotoxics and anti-CD20 monoclonal antibodies (mab) has long been the therapeutic mainstay for chronic lymphocytic leukaemias (CLL). The CD20 mabs commonly incorporated into CLL-directed CIT are rituximab, obinutuzumab and ofatumumab (Hillmen *et al*, 2015; Goede *et al*, 2014), however optimal dosing strategies for CD20 mabs remains unknown. Ofatumumab monotherapy has efficacy in CLL and comprises high total doses (22.3g, mega-Of) with dose intense delivery in the first eight weeks of therapy. In contrast, ofatumumab-based CIT regimens utilise lower total doses (6.3g, sOf) but are associated with high response rates (Robak *et al*, 2017; Wierda *et al*, 2010). As therapeutic CIT-induced cytoreduction occurs predominantly in the first two cycles of therapy we hypothesised that a more dose intense ofatumumab-based regimen could maximise CLL cytoreduction. We designed a phase II randomised controlled trial (RCT) in relapsed CLL to test whether high dose ofatumumab based CIT was sufficiently efficacious to be investigated in larger trials.

COSMIC was a phase II RCT for patients with relapsed CLL. Randomisation was between six, 28-day cycles of sOf or megaOf. Ofatumumab was given in combination with investigator's choice of chemotherapy comprising six cycles of either fludarabine and cyclophosphamide (FC) or bendamustine (B). The treatment schedule for sOf-FC/B was FC or B in combination with ofatumumab 300mg day 1 cycle 1, ofatumumab 1000mg day 8 Cycle 1, ofatumumab 1000mg day 1 cycles 2-6. Treatment schedule for megaOf-FC/B was FC or B in combination with ofatumumab 300mg day 1 cycle 1, ofatumumab 2000mg, days 8, 15, 22 cycle 1, ofatumumab 2000mg days 1, 8, 15, 22 cycle 2, ofatumumab 2000mg day 1 cycles 3-6. The primary endpoint was the rate of complete remission (CR) or complete remission with incomplete count recovery (CRi) by International Workshop on CLL (iwCLL) criteria to assess if either of the dose schedules should be tested further (Hallek *et al*, 2008). Secondary objectives included the rate of undetectable minimal residual disease (MRD), overall response rate (ORR), progression free survival (PFS), overall survival (OS) and toxicity. Further information on trial design, treatment, endpoints, patient allocation, and statistics are presented as supplementary information.

The flow of patients is shown as a CONSORT diagram in supplementary figure 1. Between October 2012 and March 2016 62 patients were randomised to either sOf (32) or megaOf (30) from 17 centres within the United Kingdom. 61 participants received at least one dose of study drug (32 sOf and 29 megaOf). Recruitment was slower than predicted with 62 patients randomised as opposed to the planned 82. The decision to stop recruitment in March 2016 was made at the end of the recruitment period and

following a reassessment of study power. With at least 28 assessable patients per arm, the new trial power was 75%.

Patient characteristics are summarized in Supplementary Table 1. Of the 61 participants 72% were male, 54% were under the age of 65 years, 52% had a performance status of 0, 77% had received a prior fludarabine, 79% had a remission of more than 24 months after the most recent line of therapy and 69% of participants had received one prior line of therapy (median 1, range of 1 to 5). Many participants had CLL with adverse prognostic markers with 67% having somatically unmutated immunoglobulin heavy variable genes or the IGVH3-21 gene, 67% had a beta-2 microglobulin greater than 4mg/L, 46% of cases were CD38+ and 26% of cases possessed a chromosome 11q deletion. No participants had a deletion of chromosome 17p in >20% CLL-cells which was an exclusion criteria. *TP53* sequencing was not performed.

Of 32 patients who received sOf, 21 were treated with FC and 11 with B. Of the 29 patients who received megaOf, 17 were treated with FC and 12 with B. Most participants completed allocated therapy with 66% receiving six cycles of treatment. Three or less cycles of therapy were delivered to 16% sOf and 14% megaOf participants.

For the primary endpoint, an intention to treat analysis revealed that 7/32 (22%) sOf and 7/29 (24%) megaOf participants achieved CR/CRi which fell short of the predefined efficacy threshold required to proceed to further study. Patients previously treated with fludarabine had lower rates of CR/CRi than those not exposed to this agent (17% versus 43%). The proportion of patients achieving CR/CRi was similar in patients aged ≤65 and >65 years, in males and females and in those with prior remissions of 6-24 months versus >24 months. Marrow and blood MRD responses revealed 12% and 22% respectively of sOf participants and 21% and 31% megaOf participants were MRD negative at the end of treatment, Table 1.

Figure 1A shows PFS curves with the median PFS for sOf of 18 months and for megaOf of 22 months. Figure 1B shows the OS curves with median OS not reached for sOf while for the megaOf is 50.30 months. Observed toxicities were compatible with those known for FC, B and ofatumumab with no excess infusional reactions in mega-Of treated participants. Full details on safety and toxicity are presented as supplementary information.

Neither sOf or megaOf in combination with FC or B, reached pre-specified endpoints in terms of rates of CR/CRi to warrant further investigation. The PFS and OS outcomes compare favourably with other studies using CIT in relapsed CLL (Iannitto *et al*, 2011; Hillmen *et al*, 2011; Fraser *et al*, 2020). Most

participants in this study had received only one prior CIT regimen and we found that further CIT was deliverable with 66% of participants receiving six cycles of therapy. Targeted agents are now standard of care for CLL; however, our results would support the use of CIT for a minority of patients with long-remissions after frontline CIT, no adverse features and who wish to receive defined duration therapy.

This study does not support the use of dose escalated ofatumumab based CIT in CLL. However, these results do not preclude the existence of such dose response when CD20mabs are combined with targeted agents and further investigation of CD20mab dose with targeted agents may be warranted.

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Author contributions

PH, DH, TM, AR, DA and AB conceived and designed the COSMIC trial. PH, DH, JE, TM, AR, DA, AB, AH and DP are responsible for the Protocol/Patient Information Sheet and analysis of results. DA, JE, DH and PH wrote the manuscript. DA, AB, AN, PS, DT, TM, and PH recruited patients. All authors read and approved the final manuscript.

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Conflicts of interest.

The authors declare no relevant conflicts of interest.

Table legends

Table 1. Clinical and minimal residual disease responses in patients who received at least one dose of drug calculated on an intention to treat basis three months following completion of therapy. [1]Responses for all fludarabine cyclophosphamide (FC) and bendamustine (B) treated patients. [2] Complete remission/complete remission incomplete (CR/CRi). [3]Responses for FC treated patients. [4]Responses for B treated patients. [5]Bone marrow minimal residual disease (MRD) responses assessed three months following completion of therapy calculated following imputation of missing data. [5]95% confidence interval. [6] Standard dose ofatumumab (sOf). [7] Megadose ofatumumab (megaOf).

Figure Legends

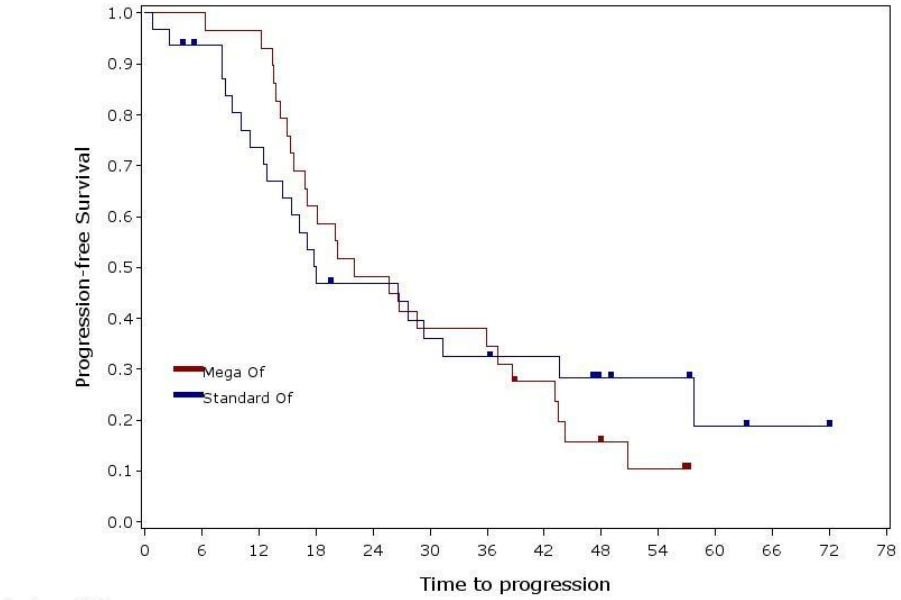
Figure 1A. Kaplan-Meier curves for progression free survival for patients treated with standard dose ofatumumab (standard Of) and mega dose ofatumumab (Mega Of). Progression free survival was calculated at the study reporting date from time of randomisation to the date of progression or death. **Figure 1B**. Kaplan-Meier curves for overall survival for patients treated with standard dose ofatumumab (standard Of) and mega dose ofatumumab (Mega Of). Overall survival was calculated at the study reporting date from the time of randomisation to date of death.

Table 1.

	sOf (n=32)[6]	MegaOf (n=29)[7]	Total (61)
Overall[1]			
Achieved CR/CRi[2]	7 (22%) (95% CI: 7.6%, 36.2%)	7 (24%) (95% CI: 7.5%, 40.7%)	14 (23%) (95% CI: 12.4%, 33.5%)[5]
Did not achieve CR/CRi	22 (69%)	21 (73%)	43 (70%)
Missing	3 (9%)	1 (3%)	4 (7%)
Total	32 (100%)	29 (100%)	61 (100%)
FC[3]			
Achieved CR/CRi	6 (29%)	4 (23%)	10 (26%)
Did not achieve CR/CRi	13 (62%)	13 (77%)	26 (69%)
Missing	2 (9%)	0 (0%)	2 (5%)
Total	21 (100%)	17 (100%)	38 (100%)
B[4]			
Achieved CR/CRi	1 (9%)	3 (25%)	4 (17%)
Did not achieve CR/CRi	9 (82%)	8 (67%)	17 (74%)
Missing	1 (9%)	1 (8%)	2 (9%)
Total	11 (100%)	12 (100%)	23 (100%)
≤65 years			
Achieved a CR/CRi	5 (26.3%)	3 (21.4%)	8 (24.2%)
Did not achieve a CR/CRi	12 (63.2%)	11 (78.6%)	23 (69.7%)
Missing	2 (10.5%)	0 (0.0%)	2 (6.1%)
Total	19 (100%)	14 (100%)	33 (100%)
>65 years			
Achieved a CR/CRi	2 (15.4%)	4 (26.7%)	6 (21.4%)
Did not achieve a CR/CRi	10 (76.9%)	10 (66.7%)	20 (71.4%)
Missing	1 (7.7%)	1 (6.7%)	2 (7.1%)
Total	13 (100%)	15 (100%)	28 (100%)
Male			
Achieved a CR/CRi	4 (19.0%)	6 (26.1%)	10 (22.7%)
Did not achieve a CR/CRi	15 (71.4%)	16 (69.6%)	31 (70.5%)
Missing	2 (9.5%)	1 (4.3%)	3 (6.8%)
Total	21 (100%)	23 (100%)	44 (100%)
Female			

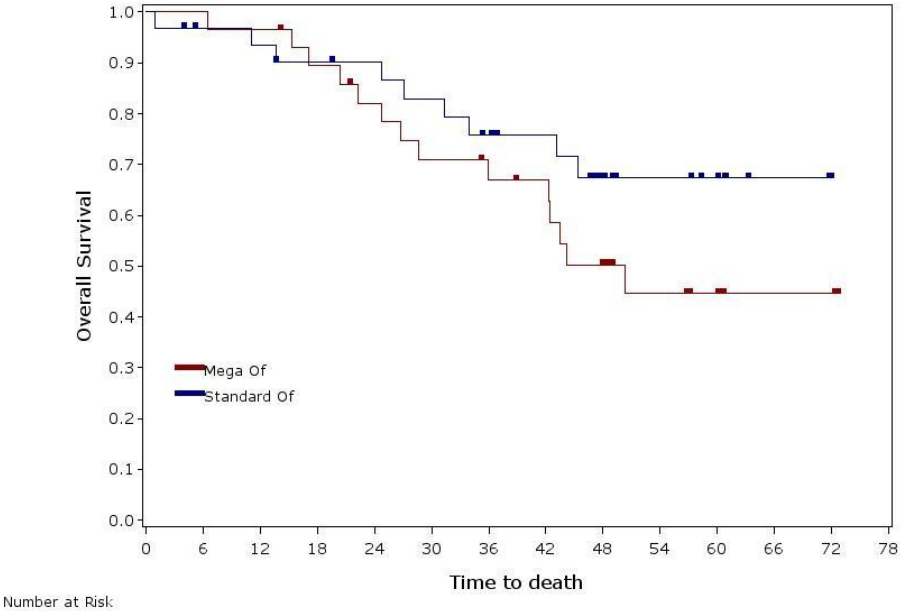
Achieved a CR/CRi	3 (27.3%)	1 (16.7%)	4 (23.5%)
Did not achieve a CR/CRi	7 (63.6%)	5 (83.3%)	12 (70.6%)
Missing	1 (9.1%)	0 (0.0%)	1 (5.9%)
Total	11 (100%)	6 (100%)	17 (100%)
Duration of previous remission, 6-24 months			
Achieved a CR/CRi	2 (28.6%)	1 (16.7%)	3 (23.1%)
Did not achieve a CR/CRi	4 (57.1%)	5 (83.3%)	9 (69.2%)
Missing	1 (14.3%)	0 (0.0%)	1 (7.7%)
Total	7 (100%)	6 (100%)	13 (100%)
Duration of previous remission, >24 months			
Achieved a CR/CRi	5 (20.0%)	6 (26.1%)	11 (22.9%)
Did not achieve a CR/CRi	18 (72.0%)	16 (69.6%)	34 (70.8%)
Missing	2 (8.0%)	1 (4.3%)	3 (6.3%)
Total	25 (100%)	23 (100%)	48 (100%)
Marrow MRD[5]			
MRD negative	4 (12%) (95% CI: 1.0%, 24.0%)	6 (21%) (95% CI: 5.9%, 35.4%)	10 (16%) (95% CI: 7.1%, 25.7%)[5]
MRD positive	28 (88%)	23 (79%)	51 (84%)
Total	32 (100%)	29 (100%)	61 (100%)

Figure 1A.



Number at Risk							
Mega Of	29	28	14	10	4	0	
Standard Of	32	22	13	9	5	2	1

Figure 1B.



Number at Risk							
Mega Of	29	28	22	17	12	6	2
Standard Of	32	28	25	20	13	6	1