Article:
Morley, N.J. and Marks, D.I. (2016) Inotuzumab ozogamicin in the management of acute lymphoblastic leukaemia. Expert Review of Anticancer Therapy, 16 (2). pp. 159-164. ISSN: 1473-7140

https://doi.org/10.1586/14737140.2016.1131614

Expert Review of Anticancer Therapy

ISSN: 1473-7140 (Print) 1744-8328 (Online) Journal homepage: http://www.tandfonline.com/loi/iery20

Inotuzumab ozogamicin in the management of acute lymphoblastic leukaemia

N.J. Morley & D. Marks

To cite this article: N.J. Morley & D. Marks (2015): Inotuzumab ozogamicin in the management of acute lymphoblastic leukaemia, Expert Review of Anticancer Therapy, DOI: 10.1586/14737140.2016.1131614

To link to this article: http://dx.doi.org/10.1586/14737140.2016.1131614

Accepted author version posted online: 12 Dec 2015.

Publisher: Taylor & Francis

Journal: *Expert Review of Anticancer Therapy*

DOI: 10.1586/14737140.2016.1131614

Inotuzumab ozogamicin in the management of acute lymphoblastic leukaemia

N.J.Morley (1) and D.Marks (2)

(1) Department of Haematology, Sheffield Teaching Hospitals, UK, (2) Adult BMT Unit, Bristol Haematology and Oncology Centre, University Hospitals Bristol NHS Trust, UK

Abstract

Whilst most adult patients with acute lymphoblastic leukaemia will go into remission with standard induction chemotherapy, many will relapse. Response rates to standard salvage chemotherapy regimens are low and the outlook on relapse is very poor and associated with significant morbidity and mortality hence the need for newer targeted approaches. Inotuzumab ozogamicin (previously known as CMC-544) is an antibody-drug conjugate and consists of a monoclonal anti-CD22 antibody bound to calicheamicin. The target, CD22, is widely expressed on acute lymphoblastic leukaemia cells making it a potential therapeutic target. The calicheamicin is delivered intracellularly and causes leukaemia cell apoptosis. Overall response rates of 57% were observed in a Phase II study and the final results of a Phase III randomised controlled trial comparing this drug to the investigator choice 'standard of care' chemotherapy are eagerly awaited. Whilst initial results are promising, there have been concerns regarding liver toxicity and the incidence of veno-occlusive disease of the liver especially in patients who have previously received or go on to allogeneic stem cell transplant.

Keywords

Acute lymphoblastic leukaemia, Inotuzumab Ozogamicin, CD22, Calicheamicin, Veno-occlusive disease of the liver, relapse.

Introduction

Adult Acute Lymphoblastic Leukaemia (ALL) is a relatively rare disorder with an incidence of between 1.0 and 1.7 new cases per year per 100,000 population (1)(2). Initial response to treatment is usually favourable with remission rates from standard induction chemotherapy around 85 to >90% (3) (4) but overall 5 year survival rates are only 40-50%(3) (4). Current issues in the management of adult ALL include treatment related toxicity, selection of patients for allogeneic transplant and most importantly the poor outcome of relapsed disease.

Relapsed or refractory ALL represents a challenging situation with no successful standard of care chemotherapy treatment. Overall survival rates are low between 7% and 24%(5),(6). Conventional chemotherapy regimens used include FLAG (+/-Idarubicin), high dose cytarabine based regimens and Clofarabine based regimens. For those with later relapses (usually 18 to 24 months from diagnosis) standard Induction regimens can be repeated but there are concerns about toxicity arising from cumulative anthracycline doses. Response rates to these treatments are disappointingly low at around 36-48% (6). Ultimately for the patients who are fit enough, where a suitable donor is found the aim is to proceed to allogeneic stem cell transplant (SCT). Survival rates in this setting have been reported between 16-23% with SCT(5) (6) and only 4% following chemotherapy(5). Those patients who relapse after SCT fare significantly worse and again there is no standard therapeutic approach.

The poor response rates to standard chemotherapy approaches in relapsed ALL have led to trials looking for newer targeted approaches especially with monoclonal antibody based treatments or T cell engaging strategies. Blinatumomab is a bi-specific antibody targeting CD19 and CD3. A Phase II study investigating Blinatumomab in patients with relapsed/refractory ALL showed responses (Complete response or complete response with partial haematologic recovery) in 25 out of 36 (69 %) patients(7). The results of a larger Phase III study comparing Blinatumomab to 'standard of care chemotherapy' (The Tower Study)(8) are awaited. Chimeric antigen receptor T cells are T cells which have been genetically modified to express anti-CD19. They have been shown in small numbers of children and adults to produce complete remission rates of 90% in patients with relapsed/refractory ALL (9) However there are concerns around the high incidence of severe cytokine release syndrome necessitating the use of the IL-6 antagonist Tociluzumab in over a quarter of patients. This is also not a uniform technology with a variety of viral vectors and co-stimulatory domains being tested. Inotuzumab is the focus of this review and therefore Blinatumomab and chimeric antigen receptor T cells will not be considered further.

Inotuzumab ozogamicin

Inotuzumab ozogamicin (Previously known as CMC-544) is an antibody drug conjugate and consists of a monoclonal anti-CD22 antibody bound to calicheamicin (10). The target, CD22, is a member of the immunoglobulin superfamily and is found on mature B cells and to a lesser extent immature B cells. It is a particularly promising target because of its widespread expression on B cells. A study of CD22 expression in children and young adults with relapsed or refractory ALL showed expression in all patients and in ≥ 90% of cells in 155 out of 163 (95%) patients. Density of CD22 expression was noted to be lower in patients with MLL gene rearrangement although the significance of this is not known. Levels of soluble CD22 were also noted to be low in both blood and bone marrow(11). However neither the intensity of CD22 antigen expression that constitutes positivity is clear nor the percentage of cells that need to be positive to make those cells a target for the antibody. Antibody bound CD22 is usually internalised rather than shed so the caliceamicin is delivered and released intracellularly (12). Calicheamicin is a product of the bacteria *Micromonospora echinospora* and is cytotoxic. Calicheamicin binds to DNA causing dsDNA breaks leading to cell death (10). It would therefore appear to be a potentially effective treatment for malignant B cell disorders.

Dosing

A Phase I dose escalation study of Inotuzumab given every 3-4 weeks in 79 patients with relapsed B cell lymphoma was performed to investigate the maximum tolerated dose (MTD) and safety. An MTD of 1.8mg/2 was suggested (13). During this study the interval of dose administration was increased from three to four weeks to allow time for platelet count recovery. There has also been a suggestion that lower doses given more frequently may be more effective and associated with less toxicity and so Inotuzumab at a dose of 0.8mg/m2 on day 1 and 0.5mg/m2 on Day 8 and Day 15 has also been used (14).

Inotuzumab levels have also been studied and found to correlate with response. (15) In a Phase II study Inotuzumab levels at 3 hours post infusion >100ng/mL CR was seen in 8/9 patients (89%) compared with 5 of 15 (33%) with levels less than 100ng/mL (p=0.008). The reason for differing post infusion levels in patients is not known.

Toxicity

Inotuzumab is usually given as an intravenous infusion over 1 hour with premedication consisting of oral paracetamol, intravenous antihistamine and corticosteroid to reduce the incidence of infusion related events. Despite this there is a reported incidence of drug related fever, Grade 1-2 in 40% of patients and Grade 3 or 4 in 20% of patients (15). Drug related hypotension is also seen but is usually milder with 24% of patients experiencing grade 1 to 2 reactions (15).

Initial safety data from 79 patients treated for relapsed non-Hodgkin's Lymphoma in a Phase I dose escalation study of Inotuzumab given every 3-4 weeks showed that the most common adverse event (AE) in patients receiving the MTD was low platelets with nearly 90% of patients experiencing any grade and >30% severe (Grade 3 or 4) thrombocytopaenia. Neutropaenia and transaminitis was also seen but to a lesser extent. One patient had veno-occlusive disease of the liver (VOD) (but had been noted to had a previous VOD like illness, had had a previous autologous transplant and previous radiotherapy involving the liver). (13). Further studies in patients with ALL have shown similar results (14,15). Provisional data published in abstract form from the Phase 3 study showedGrade>/=3 hepatobiliary in 9% and any grade VOD in 15/109 patients (16). When used in elderly patients with ALL in combination with low intensity chemotherapy (mini-hyper-CVAD) high numbers of Grade ≥ 3 toxicities were seen, especially infections (88%), thrombocytopaenia (76%) and increased bilirubin (24%) (17). However it is not possible to determine whether this increased toxicity is due to patient age or concurrent chemotherapy. It is likely that it is a combination of both.

Results of Inotuzumab in Acute Lymphoblastic Leukaemia

A Phase II study performed at the MD Anderson Cancer Centre explored the use of Inotuzumab Ozogamicin in 49 adults and children with relapsed and refractory ALL(15). The median age was 36 years (range 6-80 years) and patients had to have CD22 expression of at least 20% as assessed by flow cytometry to be eligible. For 13 patients this was the first salvage regimen, 24 second and 12 ≥ 3rd salvage regimen. Responding patients were permitted to proceed to allogeneic transplant. Inotuzumab ozogamicin was given at a dose of 1.8mg/m2 as an intravenous infusion over 1 hour at an interval of 3-4 weeks. Pre-medication was with oral paracetamol and intravenous antihistamine and corticosteroid. Patients with stable or progressive disease (who were CD20 positive) were also given Rituximab (9 out of 49 patients). A maximum of 4 cycles of Inotuzumab was given. The overall response rate was 57% with 28 out of 49 patients responding. 19/49 (39%) of patients had resistant disease. Patients who were Philadelphia chromosome positive were less likely to respond although the difference in response rates was not statistically significant. Minimal residual disease (MRD) by flow cytometry was assessed in 27 patients achieving CR/CRp (For definitions see Table 1), and was negative in 17 (63%) patients. The median overall survival in this study was 5.1 months. Attaining MRD negativity was not associated with improved survival.

Twenty two patients proceeded to allogeneic transplant (19 in remission 3 with active disease) with a variety of conditioning regimens (most commonly Busulfan + clofarabine in 8). 5 of 23 (23%) had clinical evidence of veno-occlusive disease (2 biopsy proven), 4 of whom died. There were also five deaths from infection. The duration of complete response was short including the 22 patients who underwent SCT (median survival 5.2 months). Of those transplanted 9 were still alive and free from relapse at the time of publication however longer term follow-up will be required to see if those remissions are durable.

Significant adverse events included myelosuppression and related events (especially bacterial infections and pneumonia). Grade 1-4 drug related fever was seen in 29 (59%) patients and was severe (Grade 3 to 4) in 9. Minor elevation of liver enzymes were also commonly seen 27 (55%) grade 1-2 but were less commonly severe (1 patient, grade 3). Mild (Grade 1or 2) bilirubin increases were seen in 12 (24%) patients and 2 (4%) patients had a more significant (Grade 3) rise.

A further 41 patients were studied in addition to the 49 described above but were treated with a weekly schedule of Inotuzumab at a dose of 0.8mg/m2 on day 1 and 0.5mg/m2 on Day 8 and Day 15 (14). Again this was a group of patients with heavily pre-treated relapsed/refractory ALL. Overall 17 (19%) experienced a CR, 27 (30%) CRp and 8 (9%) CRi giving an overall response rate of 58%. Response rates were similar in both the weekly and single dose groups. Negative MRD by flow cytometry was seen in 36 of 50 responding patients. 34 (38%) patients had resistant disease. The median overall survival was 6.2 months (5.0 months with single dose schedule and 7.3 months with weekly dose schedule). The median duration of remission was 7 months. Toxicity was reduced in the weekly group with less fever, hypotension and liver function abnormalities.

Inotuzumab has also been studied in combination with reduced intensity chemotherapy (mini hyper CVD) in patients aged >60yrs with newly diagnosed ALL. Preliminary results from 33 patients were published in Abstract at EHA 2015

with 29/30 evaluable patients attaining CR or CR with incomplete platelet recovery (17). There were significant levels of Grade 3 or 4 toxicities mainly infective and haematologic. Grade 2 VOD was seen in 2 (7%) patients. Historical comparison to Hyper CVAD+/- Rituximab suggested improved overall survival rates with 2 year survival rates of 78% compared with 38%.

The MD Anderson Cancer Centre reported retrospectively on the use of Inotuzumab in patients under 18 years of age who were refractory to conventional salvage chemotherapy for relapsed ALL. The dose used was initially 1.3mg/m2 and subsequently 1.8mg/m2 per cycle up to a maximum of 8 cycles. Initially the dose was given every 3 weeks but later as a weekly divided dose. Five patients were treated with no response seen in two. The other three patients had a CR (two with incomplete platelet recovery). Three patients proceeded to transplant, one of whom developed VOD having received busulphan and clofarabine conditioning (18).

Global Phase III Clinical Trial of Inotuzumab

This is an open-label, randomized phase III study of Inotuzumab Ozogamicin compared to a pre-defined investigator's choice in adult patients with relapsed or refractory CD22-positive Acute Lymphoblastic Leukemia (ALL)(19). Standard of care chemotherapy (SOC) options included FLAG, High dose cytarabine or cytarabine and Mitoxantrone based chemotherapy. Provisional results were presented as a Late Breaking Abstract at the European Haematology Association Annual Meeting 2015 (16). Inotuzumab was given at a dose of 1.8mg/m2 per cycle at three or four week intervals up to a maximum of 6 cycles. The two primary endpoints were complete remission +/- incomplete haematologic recovery and overall survival. In total 326 patients were entered. An analysis of the first 218 patients randomised showed a significant improvement in CR/CRi rates of 80.7% compared with 33.3% ($p<0.0001$). Improved rates of minimal residual disease (MRD) negativity in those with CR/CRi were also seen 78.4% versus 28.1% ($p<0.0001$). More patients in the Inotuzumab arm proceeded to transplant, 48 compared with 20 in the SOC arm. However whilst response rates were improved including MRD negativity duration of remission was short in both arms (4.6 months versus 3.1 months $p=0.0169$).
Grade ≥3 hepatobiliary toxicity was seen in 9% vs 3% and VOD was seen in 13 patients compared with 1 patient in the standard of care arm. 5 of the veno-occlusive disease cases happened during treatment and 10 after subsequent transplant. 2 fatalities due to VOD were reported. Further results including comparison of survival in the 2 groups are keenly awaited and are expected to be available early in 2016.

Potential Interaction with transplant

Kebriaei et al from the MD Anderson reported the outcome of 26 patients transplanted between September 2010 and October 2011 following achieving complete remission with Inotuzumab given for primary refractory or multiply relapsed ALL. Conditioning regimens included cyclophopsphamide or etoposide + TBI, clofarabine and busulphan and fludarabine melphalan +/-Thiotepa. In 85% of patients the regimen was considered to be myeloablative. 9 patients were considered to have high risk cytogenetics and patients had previously received a median of three lines of salvage chemotherapy.The results showed an Event Free Survival (EFS) of 30% at 6 months and 22% at 1 year with an OS of 20% at 1 year (20). Further follow up is required to determine if these patients will be cured.
Five patients had fatal VOD at a median of 23 days post SCT following a variety of conditioning regimens. Diffuse alveolar haemorrhage seen in 4 patients. The non relapse mortality was 60% at 1 year indicating that toxicity is an issue. Disease recurrence accounted for 8 deaths (20)
Clearly this is a very high risk group of patients but the excessive toxicity dose raise the issue of the problem of veno-occlusive disease of the liver in patients who have received Inotuzumab. Baseline VOD rates are thought to range between 0-30% of all patients depending on the use of TBI, intensity and hepatotoxic components of the preparative regimen and previous liver toxicity.

The VOD issue

Veno-occlusive disease is a clinically diagnosed syndrome characterised by jaundice, tender hepatomegaly and weight gain due to fluid retention. The precipitating events appear to be sinusoidal endothelial cell and hepatocyte injury resulting from chemotherapy and radiotherapy usually as part of stem cell transplant conditioning regime. As a result of this, micro-thromboses form in the hepatic venules and sinusoids contributing to obstruction of portal flow, portal hypertension and ascites. Fibrosis of venule walls and sinusoids may occur in some patients and appear to be an important determinant of outcome. Known risk factors include previous SCT, conditioning regimens using Busulphan or Total Body Irradiation (TBI) and previous liver injury. Obtaining a liver biopsy in suspected patients isn't always feasible for clinical reasons but histological changes seen include centrilobular necrosis and hepatic congestion. It is a potentially fatal complication in patients receiving SCT but has also been seen in patients receiving treatment for acute leukaemia/high risk MDS but who have not been transplanted.

Data from a related calicheamicin containing drug

Mylotarg® or Gemtuzumab Ozogamicin (GO) is a monoclonal anti CD33 antibody conjugated to calicheamicin and so may provide insight and experience into this issue with Inotuzumab. This is a drug used in the treatment of acute myeloid leukaemia (AML). It too has been observed to be associated with transaminitis, raised bilirubin levels and VOD. The mechanism of VOD in patients receiving GO is not fully understood,

Giles et al studied the incidence of VOD in 119 patients receiving Myelotarg based regimens but not SCT for high risk MDS and AML. VOD was diagnosed clinically using the Seattle and Baltimore criteria. 14/119 (12%) of patients developed VOD. VOD was also considered to be the main cause of death in 5 of these patients (21).

The Research on Adverse Drug Events and Reports reviewed the incidence of VOD and suggested a rate of 9% in patients receiving GO who did not receive a transplant and that this was increased when followed by SCT and was especially high when GO was administered within 3/12 of allo SCT (22).

In a retrospective study from the Dana-Farber Cancer Institute 62 patients with MDS/AML receiving Allo SCT were assessed for VOD using the Baltimore clinical criteria. 14 of these patients had received GO prior to SCT. 13/62 patients were diagnosed with VOD. 9/14 (64%) had GO exposure and 4/48 (8%) were without prior GO exposure indicating that patients receiving GO prior to SCT are at increased risk of developing VOD (23).
However concerns regarding GO and liver toxicity / VOD are not always consistent between studies. The United Kngdom Medical Research Council AML15 Trial contained 1113 patients with AML randomised to received GO in induction alongside either DA3+10 or FLAG-Ida chemotherapy and again in consolidation phase 948 patients were randomised to receive GO or not alongside MACE or Ara-C 1.5g/m2 or 3.0g/m2. In this study GO was used at a dose of 3mg/m2 on Day 1. It showed no excess of non-haematologic toxicity in induction and no increase in liver toxicity overall or in patients proceeding to SCT within 120 days (24). This raises the issue of whether hepatic toxicity/VOD is a dose effect.

Strategies to avoid this potentially fatal complication might include careful selection of patients avoiding those who have previously had liver injury, the use of prophylactic defibrotide (although this is unproven therapy) and the use of conditioning regimens which are known to have a reduced risk of VOD.

Expert commentary and five year view

With overall response rates of 57-80% this is a drug with clear evidence of efficacy in patients with relapsed Acute Lymphoblastic Leukaemia and in 5 years is likely to be a standard of care treatment for relapsed ALL in adults. The question arises as to how it can be best used both safely and appropriately. If used in relapsed disease where the intention is to proceed to allogeneic stem cell transplant then its use might be restricted by the risk of VOD. Further information regarding this risk will be helpful and consideration will have to be given to careful patient selection, close monitoring for VOD and prompt treatment of what potentially is a fatal complication. Another consideration

will be the choice of dosing schedule with a suggestion that with a weekly dosing schedule the toxicity is reduced without compromising the efficacy. Its use in molecular failure is more uncertain as the data for Blinatumomab are better defined. Other possible uses are in patients with primary refractory disease and those who relapse post allogeneic transplant but again there will be concerns in these two difficult groups of patients about the risk of VOD and also the durability of responses. This drug will also need to be compared with Blinatumamab and chimeric antigen receptor T cells in terms of efficacy and toxicity as all three have evidence of efficacy but concerns regarding toxicity. It will also need to be tested in the paediatric population.

Consideration will also have to be given to how best to incorporate this drug into frontline clinical trials in newly diagnosed patients. Although the limited data available in the elderly is encouraging concerns regarding haematologic, infective and liver toxicity when given alongside chemotherapy are present in this setting.

Current clinical trials investigating Inotuzumab in ALL include; a Phase I/II studying 2 different doses of Inotuzumab in combination with chemotherapy as frontline treatment in the elderly (25), a Phase 1/2 study in combination with Bosutinib in patients with Philadelphia chromosome positive ALL and CML in lymphoid blast crisis (26), a Phase I study in combination with CVP (cyclophosphamide, vincristine and prednisone) for patients with relapsed/refractory CD22 positive Acute Leukaemia (27) and a study investigating Inotuzumab in combination with Fludarabine and Bendamustine for CD22 positive malignancies prior to allogeneic transplant (28). The results of these studies are awaited with interest.

Key issues

- Most adult patients with ALL will go into remission with standard induction chemotherapy but many will relapse.
- Response rates to standard salvage chemotherapy regimens are low and the outlook in relapse is very poor and associated with significant morbidity and mortality hence the need for newer targeted approaches.
- Inotuzumab ozogamicin (Previously known as CMC-544) is an antibody drug conjugate and consists of a monoclonal anti-CD22 antibody bound to calicheamicin.
- The target, CD22, is widely expressed on Acute Lymphoblastic Leukaemia cells making it a potential therapeutic target.
- Overall response rates of 57% were seen in a Phase II study and final results of a Phase III randomised controlled trial comparing this drug to investigator choice 'standard of care' chemotherapy are awaited.
- Whilst initial results are promising there have been concerns regarding liver toxicity and the incidence of veno-occlusive disease of the liver especially in patients who have previously received or go on to allogeneic stem cell transplant.
- This drug is likely to become a standard of care treatment for relapsed ALL in adults
- Future studies investigating the role of this drug in the front line setting are needed.

Financial and competing interests disclosure

NJ Morley has served on the advisory boards for Roche and Amgen. D Marks has served on the advisory boards and consulted for Pfizer and Amgen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

1. Acute lymphoblastic leukaemia (ALL) incidence trends over time. Available at: www.cancerresearchuk.org/ [Last accessed 9 December 2015]

2. SEER Stat Fact Sheets: Acute Lymphocytic Leukemia (ALL). Available at www.seer.cancer.gov/statfacts/html/alyl.html [Last accessed 9 December 2015]

3. Rowe JM, Buck G, Burnett AK, Chopra R, Wiernik PH, Richards SM, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 2005;106(12):3760–7.

4. Larson R a, Dodge RK, Burns CP, Lee EJ, Stone RM, Schulman P, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood. 1995;85(8):2025–37.

5. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood 2007;109(3):944–50.

6. Gökbuget N, Stanze D, Beck J, Diedrich H, Horst H-A, Hüttmann A, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. Blood; 2012;120(10):2032–41.

7. Topp MS, Gokbuget N, Zugmaier G, Klappers P, Stelljes M, Neumann S, et al. Phase II Trial of the Anti-CD19 Bispecific T Cell-Engager Blinatumomab Shows Hematologic and Molecular Remissions in Patients With Relapsed or Refractory B-Precursor Acute Lymphoblastic Leukemia. J Clin Oncol. 2014;32(36):4134–40.

8. Phase 3 Trial of Blinatumomab vs Investigator's Choice of Chemotherapy in Patients With Relapsed or Refractory ALL, NCT020131. Available from: www.clinicaltrials.gov [Last accessed 9 December 2015]

9. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. NEJM 2014;371:1507-17.

10. Pfizer. Inotuzumab ozogamicin Fact Sheet. 2012. Available at: www.pfizer.com/files/news/asco/inotuzumab_fact_sheet.pdf [Last accessed 9 December 2015].

11. Shah NN, Stevenson MS, Yuan CM, Richards K, Delbrook C, Kreitman RJ, et al. Characterization of CD22

expression in acute lymphoblastic leukemia. Pediatr Blood Cancer 2015;62(6):964–9.

12. DiJoseph JF, Dougher MM, Kalyandrug LB, Armellino DC, Boghaert ER, Hamann PR, et al. Antitumor efficacy of a combination of CMC-544 (inotuzumab ozogamicin), a CD22-targeted cytotoxic immunoconjugate of calicheamicin, and rituximab against non-Hodgkin's B-cell lymphoma. Clin Cancer Res. 2006;12(1):242–9.

13. Advani A, Coiffier B, Czuczman MS, Dreyling M, Foran J, Gine E, et al. Safety, pharmacokinetics, and preliminary clinical activity of inotuzumab ozogamicin, a novel immunoconjugate for the treatment of B-cell non-Hodgkin's lymphoma: results of a phase I study. J Clin Oncol 2010;28(12):2085–93.

14. Kantarjian H, Thomas D, Jorgensen J. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. Cancer 2013;119(15):2728–36.

15. Kantarjian H, Thomas D, Jorgensen J, Jabbour E, Kebriaei P, Rytting M, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Oncol 2012;13(4):403–11.

16. DeAngelo DJ et al. Efficacy and Safety of Inotuzumab Ozogamicin vs Standard of care in salvage 1 or 2 patients with Acute Lymphblastic Leukaemia: an ongoing Global Phase 3 Study. Haematologica. 2015;100(S1):LB2073.

17. Jabbour E et al. Inotuzumab Ozogamicin in combination with low intensity chemotherapy (mini-hyper-CVAD) for the front line therapy in elderly patients (>60 years) with acute lymphoblastic leukaemia. Haematologica. 2015;100(S1):S114.

18. Rytting M, Triche L, Thomas D. Initial experience with CMC544 (inotuzumab ozogamicin) in pediatric patients with relapsed B cell acute lymphoblastic leukemia. Pediatr blood 2014;544:369–72.

19. A Study Of Inotuzumab Ozogamicin Versus Investigator's Choice Of Chemotherapy In Patients With Relapsed Or Refractory Acute Lymphoblastic Leukemia. NCT01564784. Available from: www.clinicaltrials.gov [Last accessed 9 December 2015]

20. Kebriaei P, Wilhelm K, Ravandi F, Brandt M, de Lima M, Ciurea S, et al. Feasibility of allografting in patients with advanced acute lymphoblastic leukemia after salvage therapy with inotuzumab ozogamicin. Clin Lymphoma Myeloma Leuk 2013;13(3):296–301.

21. Giles F, Kantarjian H, Kornblau S. Mylotarg^{TM}(gemtuzumab ozogamicin) therapy is associated with hepatic venoocclusive disease in patients who have not received stem cell transplantation. Cancer 2001;406–13.

22. McKoy JM, Angelotta C, Bennett CL, Tallman MS, Wadleigh M, Evens AM, et al. Gemtuzumab ozogamicin-associated sinusoidal obstructive syndrome (SOS): An overview from the research on adverse drug events and reports (RADAR) project. Leuk Res 2007;31(5):599–604.

23. Wadleigh M, Richardson P, Zahrieh D. Prior gemtuzumab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell. Blood

2003;102(5):1578–82.

24. Burnett AK, Hills RK, Milligan D, Kjeldsen L, Kell J, Russell NH, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. J Clin Oncol 2011;29(4):369–77.

25. Inotuzumab Ozogamycin in Elderly Acute Lymphoblastic Leukemia (ALL), NCT01371630. Available from: www.clinicaltrials.gov [Last accessed 2015 Oct 19]

26. Phase I/II Study of Bosutinib in Combination With Inotuzumab Ozogamicin in CD22-positive Philadelphia-Chromosome (PC) Positive Acute Lymphoblastic Leukemia (ALL) and Chronic Myeloid Leukemia (CML) NCT02311998. Available at www.clinicaltrials.gov [Last accessed 19 Oct 2015]

27. Inotuzumab Ozogamicin and Combination Chemotherapy in Treating Patients With Relapsed or Refractory Acute Leukemia, NCT01925131.. Available from: www.clinicaltrials.gov [Last accessed 19 Oct 2015]

28. CMC-544 and Allogeneic Transplantation for CD22 Positive-Lymphoid Malignancies, NCT01664910. Available at: www.clinicaltrials.gov [Last accessed 19 Oct 2015]

Table 1 Response Criteria

CR	Complete Remission Attainment of bone marrow blasts <5% with recovery of platelets to >/= 100 x10 9/L and neutrophils to >/= 1.0 x10 9/L
CRi	Complete remission with incomplete haematologic recovery. Same as CR but with platelets to </= 100 x10 9/L and neutrophils to </= 1.0 x10 9/L
CRp	Complete remission with incomplete platelet count recovery. Same as CR but with platelets to >/= 100 x10 9/