Inotuzumab ozogamicin in clinical development for acute lymphoblastic leukemia and non-Hodgkin lymphoma

Amandeep Aujla¹, Ravijot Aujla² and Delong Liu¹,³*

Abstract

B cell acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL) frequently express CD19, CD20 and CD22 on the cell surfaces. Immunotherapeutic agents including antibodies and chimeric antigen receptor T cells are widely studied in clinical trials. Several antibody-drug conjugates (ADC) have been approved for clinical use (gemtuzumab ozogamicin in acute myeloid leukemia and brentuximab vedotin in Hodgkin lymphoma as well as CD30+ anaplastic large cell lymphoma). Inotuzumab ozogamicin (INO), a CD22 antibody conjugated with calicheamicin is one of the newest ADCs. INO has been approved for treatment of relapsed/refractory B cell precursor ALL. Multiple ongoing trials are evaluating its role in the relapsed/refractory B cell NHL. This review summarized recent development in INO applications for ALL and NHL.

Keywords: Acute lymphoblastic leukemia, CD22, Inotuzumab ozogamicin, Non-Hodgkin lymphoma, Antibody-drug conjugate, ADC

Introduction

The prognosis of adults with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL) is still very poor [1–5]. With the increasing use of next-generation sequencing (NGS) and molecular biomarkers, early diagnosis and targeted therapy become possible [6–10]. It appears that NGS-based minimal residual disease (MRD) monitoring may better predict MRD relapse and lead to earlier intervention [11]. B cell ALL and NHL frequently express CD19, CD20 and CD22 on the cell surfaces. Monoclonal antibodies (MoAb) against CD20 have been widely used for the treatment of multiple lymphoid malignancies [12–14]. Immunotherapy with bispecific antibodies such as blinatumomab against CD19 is being studied in multiple types of B cell malignancies [15–23]. Immune checkpoint inhibitors have also been approved for treatment of Hodgkin lymphoma [24]. Chimeric antigen receptor (CAR) T cells are also being widely studied in clinical trials [25–31]. CD19 is the most commonly targeted surface marker in CAR T trials [32–37]. CD20, CD22, and CD30 are also targeted antigens of CAR T cells in ALL and lymphoma trials [26]. Tisagenlecleucel has been approved for R/R B ALL and diffuse large B cell lymphoma (DLBCL) [36, 38–42]. In addition, axicabtagene ciloleucel has been approved for R/R DLBCL [43, 44].

In addition to the above immunotherapeutic agents, conjugation of cytotoxic agents with monoclonal antibodies is an evolving field with the development of multiple targeted cytotoxic agents called antibody-drug conjugates (ADC) [45]. These are being used and studied with targets across different malignancies (e.g. trastuzumab emtansine in breast cancer, gemtuzumab ozogamicin in acute myeloid leukemia and brentuximab vedotin in Hodgkin lymphoma as well as CD30+ anaplastic large cell lymphoma) [46–52]. Inotuzumab ozogamicin (INO), a CD22 MoAb conjugated with calicheamicin is one of the newest ADCs in clinical application [53, 54]. INO has been approved for treatment of R/R B cell precursor ALL [55–63]. Multiple ongoing trials are evaluating its role in the R/R B cell NHL. This review summarized recent development in INO applications for B cell ALL and NHL.
CD22 expression and function
CD22 is an inhibitory component of the B-cell receptor (BCR) complex expressed exclusively in pre-B, immature and mature B cells but is lost upon differentiation to plasma cells [64–66]. It mediates negative impact on BCR signaling pathway by dephosphorylating the associated cascade components via protein tyrosine phosphatases [67–69] (Fig. 1).

CD22 positivity in lymphoid malignancies
CD22 expression increases progressively along the pathway of B cell maturation. Raponi et al. reported CD22 expression among different subtypes of ALL as 83% of Pro-B, 96.4% of common B cell, 91.9% of Pre-B and 100% of the mature B cell ALL [70]. In mature B cell lymphoma, its expression has been reported as 95% in chronic lymphocytic leukemia, 89% in diffuse large B-cell lymphoma, 98% in follicular lymphoma, 96% in lymphoplasmacytic lymphoma and 100% in hairy cell, mantle cell, marginal zone, splenic marginal zone lymphomas and monoclonal B-lymphocytosis [71]. Hence CD22 can serve as a good target for therapy of B cell malignancies.

Inotuzumab ozogamicin: CD22 antibody-drug conjugate
Structure and function
Inotuzumab is a humanized IgG4 monoclonal antibody that binds CD22. It is conjugated via an acid labile linker to the cytotoxic chemotherapy, calicheamicin (N-acetylated-γ-calicheamicin dimethyl hydrazide). Calicheamicin is a potent cytotoxic antibiotic that binds DNA in the minor groove and causes double-strand DNA breaks leading to cell death [72]. Binding of drug to CD22 receptor leads to its endocytosis and cytotoxic chemotherapy is released in acidic lysosomal environment with degradation of the linker. CD22 receptor is then recycled back to the surface and may play a role in augmented efficacy [73, 74].

Preclinical studies
CD22 monoclonal antibody (MoAb) with or without conjugation to calicheamicin has similar affinity to CD22 receptors on human B-lymphoma cells [73]. In vitro studies showed enhancement of cytotoxic potency of calicheamicin by 1.5 to 39-fold when conjugated to CD22 MoAb against CD22+ B-lymphoma cell lines. INO

---

![Fig. 1 CD22 structure and signaling pathway. CD22 molecule is a transmembrane protein from SIGLEC (Sialic acid-binding immunoglobulin-type lectins) family. It has three parts: (i) V-type Ig domain with sia-binding site, (ii) C1-type Ig domain, (iii) C2-type Ig domain. The CD22 intracellular region contains ITIMs (Immunoreceptor tyrosine-based inhibitory motifs). The tyrosine residues of the ITIMs become phosphorylated with the ligand binding, which leads to activation of SHP-1 (Src homology region 2 domain-containing phosphatase-1), SHP-2 (Src homology region 2 domain-containing phosphatase-2), SHIP-1 (Src homology region 2 domain-containing inositol 5′-polyphosphatase-1). These phosphatases act as negative regulators for down-streaming signaling from B-cell receptors.](image-url)
(CMC-544) was noted to inhibit the growth of CD22+ human B-cell lymphomas grafted subcutaneously into the mice in a dose dependent manner. Half-life of CMC-544 is 35 h and was noted to be similar in both tumor bearing and non-tumor bearing mice. However AUC (area under curve) of serum levels in tumor bearing mice was noted to be 37% lower, suggesting absorption by targeted tumor tissue [73]. Similar preclinical studies in mice with ALL cells and subcutaneous xenografts also showed that INO not only inhibited the growth of ALL xenografts but also prevented engraftment of ALL cells and development of disseminated disease in SCID (severe combined immune deficiency) mice [75, 76]. These results were also replicated in pediatric B-ALL cells with additional findings that efficacy (inducing apoptosis) is not dependent on CD22 expression and receptor saturation, in contrast to gemtuzumab ozogamicin [77]. High expression of CD22 was reported to accelerate the response in comparison to low CD22 expression cell lines.

**Clinical trials of inotuzumab ozogamicin in ALL**

Phase 1 dose finding study for Inotuzumab ozogamicin (INO) in CD22-positive R/R ALL was done with 1.2, 1.6, or 1.8 mg/m2 doses per cycle on days 1, 8, and 15 over a 28-day cycle [78]. The recommended phase 2 dose (RP2D) was determined to be 1.8 mg/m2 (Table 1).

The safety and efficacy of INO were further assessed in phase 2 expansion cohort. INO was given as 0.8 mg/m2 on day 1; 0.5 mg/m2 on days 8 and 15; The dosage was lowered to 1.6 mg/m2 per cycle after complete remission (CR) or CR with incomplete marrow recovery (CRI). CR/CRI was achieved in 69% (CR 29%) with RP2D and MRD negativity was reported in 75% of this population (CR/CRI). Median progression free survival (PFS) in all treated populations was 3.9 months and median overall survival (OS) of 7.4 months. Twenty-four out of 72 (33%) patients in total proceeded to allogeneic stem cell transplant (AlloSCT) and most of the patients were given fludarabine and/or total body irradiation (TBI) based conditioning regimen except one patient who received dual alkylator conditioning (cyclophosphamide, thiotepa, and fludarabine). Among these, 12 deaths occurred (2 died due to relapse/progressive disease; 7 died ≤100 days due to sepsis, graft-versus-host disease, venoocclusive disease and respiratory failure). Four patients developed venoocclusive disease (VOD), none of whom had received pre-study AlloSCT (Two patients experienced VOD during therapy or follow-up without AlloSCT and two developed VOD after AlloSCT) [78].

INO has been approved by FDA for treatment of adults with R/R B-cell precursor ALL based on results of INO-VATE trial [63]. This phase 3 trial compared INO given as 0.8 mg/m2 on day (D)1 followed by 0.5 mg/m2 on D8 and D15 (total 1.8 mg/m2 every 4 weeks) against standard chemotherapy in Ph-positive or Ph-negative refractory or relapsed B-ALL. Chemotherapy regimens included FLAG (Fludarabine, cytarabine and Granulocyte stimulating factor), cytarabine with mitoxantrone or cytarabine alone. This phase 3 study demonstrated that single agent INO led to a significantly higher CR rate than that in the chemotherapy group (80.7% vs. 29.4%; p < 0.001), and a longer CR duration (4.6 vs. 3.1 months; p = 0.03).

Veno-occlusive disease (VOD) with liver function abnormality and weight gain was a major adverse event. Therefore, careful planning for INO therapy prior to AlloSCT is important to minimize VOD complications. It is generally advised that length of INO therapy should be limited. Longer spacing from end of INO therapy to AlloSCT is also being studied, such as adding blinatumomab as consolidation prior to AlloSCT [79, 80].

INO has also been studied in a phase 2 trial in combination with chemotherapy for R/R Philadelphia chromosome-negative ALL [55]. It was combined with mini-Hyper-CVD regimen (miniHCVD) (cyclophosphamide 150 mg/m2 every 12 h on days 1–3, dexamethasone 20 mg/day on days 1–4 and 11–14, and vincristine 2 mg flat dose on days 1 and 8, alternating with methotrexate 250 mg/m2 on day 1 and cytarabine 0.5 g/m2 every 12 h on days 2 and 3 [55, 56]. INO was administered on day 3 of cycles 1 through 4. INO was given as 1.3 mg/m2 for cycle 1 followed by 1 mg/m2 for cycles 2 to 4 (the details of the schedules and doses were summarized in the tables of the reference [81]). Investigators started ursodiol 300 mg three times daily as VOD prophylaxis later as protocol amendment. Maintenance therapy was given as per POMP regimen (for details of the regimen, see references [55, 59, 81]). ORR was 78% (59% CR) with MRD negative rates of 52% (at time of morphological response) and 82% (at 3 months). OS rate at 1 year was 46% (mOS of 11 months), mOS was noted to be higher in patients treated as first salvage regimen (mOS approaching 17 months) compared to those receiving as second salvage regimen. VOD was observed in 6/26 (23%) patients who underwent subsequent AlloSCT and 3/33 (9%) in those who did not receive AlloSCT. All VOD cases had received clofarabine based conditioning regimens with or without busulfan. For patients who are candidates for AlloSCT, treatment with INO should be limited to 2 cycles of induction or the fewest number of cycles required to achieve a CR/CRI (if CR/CRI not achieved after 2 cycles) [55, 79, 80].

**Clinical trials of inotuzumab ozogamicin in NHL**

Preclinical Studies confirmed the potency and dose-dependent cytotoxicity of INO on CD22 positive B-lymphoma cell lines and anti-tumor efficacy in mouse
Table 1 Clinical trials of inotuzumab ozogamicin (INO)

| Reference | Phase | Disease | Intervention INO + | ORR (CR) | mPFS | mOS | Significant toxicities |
|-----------|-------|---------|-------------------|----------|------|-----|-----------------------|
| [55]      | 2     | R/R Ph-Negative CD22 positive ALL | Mini-Hyper-CVD with INO and Rituximab | ORR was 78% (59% CR) MTD negative rates of 52% (at time of morphological response) and 82% (at 3 months), | Median DFS of 8 months. | 11 months | VOD (15%); prolonged thrombocytopenia (81%); 95% suffered hepatotoxicity (20% with grade 3 or higher) |
| [63]      | 3     | Refractory or Relapsed ALL | 0.8 mg/m2 (D1), 0.5 mg/m2 (D8), 0.5 mg/m2 (D15) | CR + CRI 80.7% (CR 35.8%) | 5 months | 7.7 months | Grade 3 or more thrombocytopenia, hepatotoxicity and VOD (11%) |
| [78]      | 1/2   | R/R ALL | 1.8 mg/m2 weekly | 69% CR/CRI (29% CR) | – | – | cytopenias and liver toxicity |
| [84]      | 1     | R/R FL (100%) | Single agent | CR: 54% ORR: 85% | – | – | No DLTs. MTD of 1.8 mg/m2 confirmed in Japanese population. |
| [85]      | 1/2   | CD20 and CD22 positive B-NHL. Relapsed follicular lymphoma (35%), Relapsed diffuse large B-cell lymphoma (39%), or refractory aggressive NHL (25%) | Dose escalation (0.8, 1.3 and 1.8 mg/m2) study in combination with Rituximab 375 mg/m2 MTD of determined to be 1.8 mg/m2. | FL: 87% (62%) DLBCL: 74% (50%) Refractory: 20% | FL: NR (2 year PFS rate of 68%) FLBCL: 17.1 months Refractory: 8.8 months | Grade 3 to 4 thrombocytopenia (31%) and neutropenia (22%), SAEs of Pneumonia (4%), Sepsis (3%) and liver dysfunction (4%). No VOD. |
| [86]      | 1     | B-NHL (CD20 and CD22-positive, B-cell NHL which has progressed after 1 or 2 prior therapies) | 1.8 mg/m2, IV on day 2 of each 28 day cycle; up to 8 cycles + R 375 mg/m2, IV on day 1 of each 28 day cycle; up to 8 cycles | 80% (60%) | 14.4 months | 24.5 months | 1 death due to neutropenic pneumonia in INO-CVP arm. (13/48) 27% discontinued therapy in INO-CVP arm due to adverse effects |
| [87]      | 1     | CD22 positive NHL with at least 1 prior treatment | INO (0.8 mg/m2) + RCVP | 84% (24%) | – | – | 90% SAEs, with thrombocytopenia, neutropenia, elevated liver enzymes and hypophosphatemia |
| [88]      | 1/2   | CD22 positive NHL with at least 1 prior treatment; DLBCL (38%) FL (25%) MCL (24%) Refractory (42%) | INO (0.8 mg/m2) + R-GDP | Phase 1: 53% (20%); Phase 2 dose (RP2D): 50% (14%) | 6 m: 58% 12 m: 37% 24 m: 24% | 6 m:81% 12 m: 61% 24 m: 55% | Grade 3 or more thrombocytopenia (75%); neutropenia (62%). One patient with grade 3 VOD. |

Abbreviations: R/R refractory /relapsed, CVD cyclophosphamide vincristine dexamethasone, m month, ORR overall response rate, CR complete remission, PFS progression free survival, OS overall survival, DFS relapse free survival, VOD veno-occlusive disease, NHL non-Hodgkin lymphoma, NR not reached, MTD minimal residual disease, MTD maximal tolerated dose, SAE serious adverse event, DLBCL diffuse large B cell lymphoma, FL follicular lymphoma, MCL mantle cell lymphoma, RP2D recommended phase 2 dose, GDP gemcitabine dexamethasone cisplatin

models with B-cell lymphomas [72, 73]. When combined with rituximab, additive anti-tumor activity with superior efficacy was achieved in vitro on human B-Lymphoma cell lines [82].

Phase 1 studies of INO monotherapy determined maximum tolerated dose (MTD) of 1.8 mg/m2 every 4 weeks in humans with grade 3 or higher thrombocytopenia and neutropenia as the dose-limiting toxicities (DLT). VOD was reported in patients post autologous stem-cell transplant setting and those with prior history of VOD like syndrome [83, 84]. Phase 1/2 study of INO in combination with rituximab (375 mg/m2) every 4 weeks determined MTD of 1.8 mg/m2 every 4 weeks and showed ORR of 87, 74 and 20% in relapsed follicular lymphoma (FL), relapsed DLBCL and refractory B-NHL respectively. 68% of relapsed FL remained progression free at 2 years with median PFS of 17.1 months in relapsed DLBCL and 1.9 months in refractory disease [85]. Thrombocytopenia (56%; 31% grade 3 or higher) and neutropenia (34%; 22% grade 3 or higher) were the most common adverse events requiring dose modification. Serious adverse events included pneumonia (4%), sepsis (3%) and liver dysfunction (4%).
Similar phase 1 study with the combination of rituximab (375 mg/m²) and standard dose INO (1.8 mg/m²) every 4 weeks was studied in the Japanese population [86]. Nine out of 10 patients experienced grade 3 or higher adverse events including thrombocytopenia, neutropenia, elevated liver enzymes and hypophosphatemia; 5 out of 10 patients discontinued treatment because of these adverse events. Overall response rate (ORR) was reported at 80% (CR 60%).

INO in reduced dose of 0.8 mg/m² once every 3 weeks has also been studied in combination with rituximab-based chemo-immunotherapy regimens. Phase 1 study of INO in combination with R-CVP (Rituximab, Cyclophosphamide, Vincristine and Prednisone) determined 0.8 mg/m² as MTD with DLT of reversible grade 4 neutropenia [87]. ORR of 84% (CR 24%) was reported in MTD cohort along with median PFS of 14.4 months and median OS of 24.5 months (aggressive NHL; NR in indolent NHL).

Another phase 1 study of INO (0.8 mg/m² every 3 weeks) in combination with R-GDP (Rituximab, Gemcitabine, Dexamethasone, Cisplatin) reported ORR of 53% (CR 20%) in refractory/relapsed B-cell NHL with major toxicities of grade 3 or higher thrombocytopenia (75%), neutropenia (62%) and one case of VOD [88] (Table 1).

Veno-occlusive disease associated with inotuzumab ozogamicin

VOD as seen with gemtuzumab ozogamicin has been reported with the use of INO in the setting of autologous or allogeneic transplant [55–57, 59, 63, 73, 85]. A retrospective study of 26 patients with refractory ALL received INO followed by AlloSCT. Conditioning regimens consisted of cyclophosphamide, clofarabine, fludarabine, melphalan, thiota and total body irradiation [89]. Five patients suffered fatal hepatic VOD at a median of 23 days after SCT. In particular, patients who received conditioning with double-alkylating agents (e.g., high-dose busulfan and cyclophosphamide) may be at especially higher risk of VOD [90]. Splitting INO dosage appears to be useful to minimize VOD [55, 56]. Incorporation of blinatumomab as consolidation in the miniHCVD -INO-blinatumomab regimen increases the time between INO and AlloSCT [55, 56, 59, 81]. This may further decrease the VOD risk.

**Table 2 Ongoing trials of inotuzumab ozogamicin (INO)**

| Reference | Phase | Disease | Intervention | Recruitment |
|-----------|-------|---------|--------------|-------------|
| NCT03441061 | 2 | B-ALL with positive MRD | INO | Recruiting |
| NCT03677596 | 4 | R/R B-ALL | Investigating lower dose level (1.2 mg/m²/cycle) for those with higher risk for liver toxicity or VOD. | Not yet recruiting |
| NCT03460522 | 2 | Precursor B-cell ALL in 56–74 years old | INO induction followed by conventional chemotherapy | Recruiting |
| NCT02311998 | 1/2 | Ph + B-ALL and MCL-blast phase | Bosutinib plus INO | Recruiting |
| NCT01925131 | 1 | Acute leukemia of ambiguous lineage, Recurrent Ph + B-ALL, Recurrent Burkitt Lymphoma | INO plus CVP (cyclophosphamide, Vincristine, Prednisone) | Recruiting |
| NCT03798142 | 1/2 | Ph negative B-ALL | INO followed by Blinatumomab | Recruiting |
| NCT03851081 | 1/2 | r/r B-ALL | INO plus Vincristine (liposomal) | Not yet recruiting |
| NCT01664910 | 1/2 | Conditioning regimen for HSCT | INO plus Rituximab, Bendamustine and Fludarabine | Recruiting |
| NCT03249870 | 2 | Ph negative B-ALL in 55 years or older | INO plus CVP induction | Recruiting |
| NCT03610438 | 2 | ALL with positive MRD prior to HSCT | INO | Not yet recruiting |
| NCT03856216 | 2 | Allogeneic SCT | Pre and Post HSCT INO | Not yet recruiting |
| NCT01371630 | 1/2 | Untreated ALL in 60 years and older | INO plus combination chemotherapy | Not yet recruiting |
| NCT03150693 | 3 | Newly diagnosed B-ALL in 18–39 years old | INO plus chemotherapy | Recruiting |
| NCT03094611 | 2 | R/R ALL | Lower dose INO | Recruiting |
| NCT03488225 | 2 | ALL | INO plus HyperCVAD | Recruiting |
| NCT01679119 | 2 | DLBCL | INO plus R-CVP versus Gem-R-CVP | Recruiting |
| NCT02981628 | 2 | B-ALL in 1–21 years old | INO | Recruiting |
| NCT03628053 | 3 | ALL | Tisagenlecleucel versus Blinatumomab or Inotuzumab | Not yet recruiting |

**Abbreviations:** R/R refractory/relapsed, CVAD cyclophosphamide vincristine Adriamycin dexamethasone, NHL non-Hodgkin lymphoma, DLBCL diffuse large B cell lymphoma, ALL acute lymphoblastic leukemia, Gem gemcitabine, R rituximab, CVP cyclophosphamide vincristine prednisone, VOD veno-occlusive disease
Conclusion

Single agent inotuzumab ozogamicin has shown higher response rates and longer duration of remission in direct comparison against intensive chemotherapies for R/R B cell ALL. Incorporation of INO into miniHCVD regimen appears to be effective with less toxicity. Although results from NHL trials have not been as encouraging, further studies are still ongoing (Table 2).

Abbreviations

CAR: Chimeric antigen receptor; DLBCL: Diffuse large B cell lymphoma; INO: Inotuzumab ozogamicin

Acknowledgements

DL is a professor of medicine in the Department of Medicine, New York Medical College and Westchester Medical Center, Valhalla, NY, USA.

Funding

The study is partly supported by the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

Availability of data and materials

The material supporting the conclusion of this review has been included within the article.

Authors’ contributions

DL and AA designed the study and drafted the manuscript. All authors participated in the revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This is not applicable for this review.

Consent for publication

This is not applicable for this review.

Competing interests

The authors declare that they have no competing interests.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

1Department of Medicine, New York Medical College and Westchester Medical Center, Valhalla, NY 10595, USA. 2Punjab Institute of Medical Sciences, Jalandhar, Punjab 144006, India. 3Department of Oncology, The First affiliated hospital of Zhengzhou University, Zhengzhou, China.

Received: 18 February 2019 Accepted: 27 March 2019

Published online: 11 April 2019

References

1. Abou Dalle I, Jabbour E, Short NJ, Ravandi F. Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. Curr Treat Options in Oncol. 2019;20(1):34.

2. Frey NV, Luger SM. How I treat adults with relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia. Blood. 2015;126(5):589–96.

3. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. N Engl J Med. 2015;373(16):1541–52.

4. Jabbour E, Pui CH, Kantarjian H. Progress and innovations in the Management of Adult Acute Lymphoblastic Leukemia. JAMA Oncol. 2018;4(10):1413–20.

5. Zugmaier G, Goekbuget N, Viardot A, Stelljes M, Neumann S, Horst HA, Reichle A, Marks R, Faal C, Buehgemann M, Holland C, Schmidt M, Mergen N, Goebeler M-E, Einsele H, Bargou RC, Topp MS. Long-term survival in adult patients with relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL) who achieved minimal residual disease (MRD) response following anti-CD19 BIOTM Blinatumomab. Blood. 2014;124(21):2287.

6. Byrd JC, Furman RR, Couteé SE, Flinn IW, Burger JA, Blum KA, Grant B, Shanan JP, Coleman M, Wierda WG, Jones JA, Zhao W, Heerema NA, Johnson AJ, Sukbuntherng J, Chang BY, Clow F, Hedrick E, Buggy JJ, James DF, O’Brien S. Targeting BTK with Bruton’s tyrosine kinase inhibitor therapy in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369(1):32–42.

7. Byrd JC, Harrington B, O’Brien S, Jones JA, Schuh A, Devereux S, Chaves J, Wierda WG, Avant FN, Brown JR, Hillmenn P, Stephens DM, Giaha P, Barrientos JC, Pagel JM, Voyajch, Johnson D, Huang J, Wang X, Kaptein A, Lannuzzi BJ, Covey T, Fandis M, McGeery J, Hamdy A, Rothbaum W, Iznazri D, Diaco T, Johnson AJ, Furman RR. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374(4):323–32.

8. Cortes JE, Apperly JF, DeAngelo DJ, Deininger MW, Kota VK, Roussel P, Gambacorti-Passeroni C. Management of adverse events associated with Bruton’s tyrosine kinase inhibitor treatment of chronic-phase chronic myeloid leukemia: expert panel review. J Hematol Oncol. 2018;11(1):143.

9. Rossiari F, Minutolo F, Orucuolo E. Past, present, and future of Bcr-Abl inhibitors: from chemical development to clinical efficacy. J Hematol Oncol. 2018;11(1):84.

10. Jastaniah W, Elman N, Abdalla K, Al-Azmi AA, Elqami AM, Alkasar A, Daghistani M, Felimban S. Early vs late MRD response and risk-based treatment intensification of childhood acute lymphoblastic leukemia: a prospective pilot study from Saudi Arabia. Exp Hematol. 2018;71(1):29.

11. Cheng S, Inghirami G, Cheng S, Tam W. Simple deep sequencing-based post-remission MRD surveillance predicts clinical relapse in B-ALL. J Hematol Oncol. 2018;11(1):105.

12. Ribrag V, Koscielny S, Bosq J, Leguay T, Casassonis O, Forrester L-M, Recher C, Ghesquieres H, Morschhauser F, Girault S, Gouill SL, J德拉-Urribi M, Mariette C, Cornillon J, Cartron G, Verge V, Chassagne-Clemont D, Cobert H, Coffiller B, Lamy T, Tilly H, Salles G. Rituximab and dose-dense chemotherapy for adults with Burkitt’s lymphoma: a randomised, controlled, open-label, phase 3 trial. Lancet. 2016;387(10036):2402–11.

13. Thomas DA, Faderl S, O’Brien S, Bueso-Ramos C, Cortes J, Garcia-Manero G, Giles FJ, Verstovsek S, Wierda WG, Pierce SA, Shan J, Brandt M, Hagemeister FB, Keating M, Cabanillas F, Kantarjian H. Chemoinmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer. 2006;106(7):1569–80.

14. Thomas DA, O’Brien S, Faderl S, Garcia-Manero G, Ferrajoli A, Wierda W, Ravandi F, Verstovsek S, Jorgensen JL, Bueso-Ramos C, Andreff M, Pierce S, Garris R, Keating MJ, Cortes J, Kantarjian HM. Chemoinmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. J Clin Oncol. 2010;28(24):3880–9.

15. King AC, Pappacena J, Tallman MS, Park JH, Geyer MB. Blinatumomab administered concurrently with Oral tyrosine kinase inhibitor therapy is a well-tolerated consolidation strategy and eradicates measurable residual disease in adults with Philadelphia chromosome positive acute lymphoblastic leukemia. Blood. 2018;132(Suppl 1):1414.

16. Koprijnik J, Marcotulli D, Jones E, Perry G, Kuo Y-H, Gagnon J, Aviador M, Stanislauks G, Mccluskey J. Blinatumumab induces responses in Extramedullary B-cell acute lymphoid leukemia (B-ALL) and lymphoid blast crisis chronic myelogenous leukemia (CML), and rarely results in CD19 negative relapse. Blood. 2018;132(Suppl 1):2703.

17. von Stackelberg A, Locatelli F, Zugmaier G, Handgretinger R, Trippett TM, Fielding AK, Giebel S, Haddad V, Hoelzer D, Holland C, Ifrah N, Katz A, Coiffier B, Lamy T, Tilly H, Salles G. Rituximab and dose-dense chemotherapy for adults with Burkitt’s lymphoma: a randomised, controlled, open-label, phase 3 trial. Lancet. 2016;387(10036):2402–11.

18. Garris R, Keating MJ, Cortes J, Kantarjian HM. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer. 2006;106(7):1569–80.

19. Sanford M. Blinatumomab: first global approval. Drugs. 2015;75(3):321–7.

20. Li Z, Song W, Rubinstein M, Liu D. Recent updates in cancer immunotherapy: a comprehensive review and perspective of the 2018
Kantarjian H, Jabbour E. Incorporating immunotherapy into the treatment strategies of B-cell adult acute lymphoblastic leukemia: the role of Blinatumomab and Inotuzumab Ozogamicin. Am Soc Clin Oncol Educ Book. 2018;38:574–8.

Kantarjian H, Ravandi F, Short NJ, Huang X, Jain N, Sasaki K, Daver N, Permararaj N, Khoury JD, Jorgensen J, Alvarado Y, Konopleva M, Garcia-Manero G, Kadja T, Yilmaz M, Bortakur G, Burger J, Kornblau S, Wierda W, DiNardo C, Ferrajoli A, Jacob J, Garris R, O'Brien S, Jabbour E. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukemia: a single-arm, phase 2 study. Lancet Oncol. 2018;19(12):240–8.

Kantarjian HM, Yu J, Jabbour EJ, Bhattacharya H, Yan E, Cappelleri JC, Marks DJ. Patient-reported outcomes from a phase 3 randomized controlled trial of inotuzumab ozogamicin versus standard therapy for relapsed/refractory acute lymphoblastic leukemia. Cancer. 2018;124(10):2151–60.

Sasaki K, Kantarjian HM, Ravandi F, Short NJ, Kebriaei P, Huang X, Ryting ME, Jain N, Konopleva MY, Garcia-Manero G, Champlin RE, Kadja TM, Cortes JE, Estrov Z, Takashahi K, Mace M, Houli M, Nanaiz P, Jacob J, Garris R, Jabbour EJ. Sequential Combination of Low-Intensity Chemotherapy (Mini-hyper-CVAD) Plus Inotuzumab Ozogamicin with or without Blinatumomab in Patients with Relapsed/Refractory Pharyngeal Chromosome-Negative Acute Lymphoblastic Leukemia (ALL): A Phase 2 Trial. Blood. 2018;132(Suppl 1):S53.

Short NJ, Jabbour EJ, Ravandi F, Huang X, Jain N, Sasaki K, Permararaj N, Daver NG, Khoury JD, Jorgensen JU, Alvarado Y, Konopleva MY, Garcia-Manero G, Kadja TM, Yilmaz M, Borthakur G, Burger JA, Kornblau SM, Wierda WG, CD DN, Ferrajoli A, Nanaiz P, Jacob J, Garris R, O'Brien SM, Kantarjian HM. Chemoinmunotherapy with Inotuzumab Ozogamicin Combined with Mini-Hyper-CVAD, with or without Blinatumomab, for Newly Diagnosed Older Patients with Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: Results from a Phase II Study. Blood. 2018;132(Suppl 1):36.

Kantarjian HM, DeAngelio DJ, Stelljes M, Martelli G, Lipton RB, Stock W, Kebriaei P, O'Brien S, Wang K, Wang T, Paccagnella ML, Sleigh B, Vandendries E, Advocat S. Inotuzumab Ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med. 2016;375(8):740–53.

Ereño-Orbea J, Icard T, Cui H, Mabhab-Jafari MT, Bentebrék S, Guarné A, Rubinstein JL, Julien JP. Molecular basis of human CD22 function and therapeutic targeting. Nat Commun. 2017;8(1):764.

Stamenkovic I, Seed B. The B-cell antigen CD22 mediates monocyte and erythrocyte adhesion. Nature. 1990;345(6270):74.

Rubinstein JL, Julien J-P. Molecular basis of human CD22 function and activity: insights into a unique immunoglobulin superfamily molecule. Annu Rev Immunol. 2002;20:641–70.

Kantarjian HM, Advani AS, Kalland DR, Armellino DC, Boghaert ER, Hamann PR, Khan A, Zeh H, O'Brien S, Jabbour EJ, Zhang H, Sallan SE, Kantarjian HM, Advani AS. Inotuzumab ozogamicin in adults with relapsed or refractory acute lymphoblastic leukemia: a phase 1/2 study. Blood. 2017;13(15):1167–80.

Kantarjian H, Jabbour H, Jain N, O'Brien S, Jabbour E. Role of inotuzumab ozogamicin in the treatment of relapsed/refractory acute lymphoblastic leukemia. Immunotherapy. 2016;8(2):135–43.

Kantarjian HM, DeAngelio DJ, Advani AS, Stelljes M, Kebriaei P, Cassidy RD, Merchant AA, Fujishima N, Uchida T, Calabchio M, Ejduk AA, O'Brien SM, Jabbour EJ, Zhang H, Sleight B, Vandendries E, Marks DI. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukemia: results from the open-label, randomised, phase 3 INO-VATE study. Lancet Haematol. 2017;4(8):e387–98.

Liu D, Zhao J, Song Y, Luo X, Yang T. Clinical trial update on biscoptic antibodies, antibody-drug conjugates, and antibody-containing regimens for acute lymphoblastic leukemia. J Hematol Oncol. 2019;12(1):15.

DiJoseph JF, Dougher MM, Armellino DC, Evans DY, Damle NK. Therapeutic potential of CD22-specific antibody-targeted chemotherapy using inotuzumab ozogamicin (CMC-544) for the treatment of acute lymphoblastic leukemia. Leukemia. 2007;21:2240.

de Vries JF, Zwaan CM, De Bie M, Voerman JS, den Boel MJ, van Dongen JIM, van der Velden VHJ. The novel calcineurin-conjugated CD22 antibody inotuzumab ozogamicin (CMC-544) effectively kills primary pediatric acute lymphoblastic leukemia cells. Leukemia. 2011;26:255.

DeAngelio DJ, Stock W, Stein AS, Shustov A, Lipton RB, Schiffer CA, Vandendries E, Liu A, Ananthakrishnan R, Boni J, Laird AD, Fostvedt L, Kantarjian HM, Advani AS. Inotuzumab ozogamicin in adults with relapsed or refractory CD22-positive acute lymphoblastic leukemia: a phase 1II study. Blood. 2017;13(15):1167–80.

George B, Kantarjian H, Jabbour E, Jain N. Role of inotuzumab ozogamicin in the treatment of relapsed/refractory acute lymphoblastic leukemia. Immunotherapy. 2016;8(2):135–43.
patients with advanced acute lymphoblastic leukemia after salvage therapy with Inotuzumab Ozogamicin. Clin Lymphoma, Myeloma Leuk. 2013;13(3): 296–301.

90. Dalle J-H, Giralt SA. Hepatic Veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. Biol Blood Marrow Transplant. 2016;22(3):400–9.