Dear Editor,

Acute lymphoblastic leukemia (ALL) in infants differs from ALL in older children [1] leading to a poor prognosis [2]. We present a 10-week-old infant diagnosed with immature ALL with myeloid markers in a foreign university hospital. After induction therapy according to LAL/SHOP protocol, 10% leukemic cells were detected in the bone marrow. Treatment was changed to fludarabine, cytarabine, and granulocyte colony-stimulating factor with doxorubicin. Afterwards, still 5% leukemic cells were detected in the bone marrow, so the bispecific T cell engager antibody blinatumomab was given. Due to increasing leukemic cells during the infusion, antibody therapy was stopped and clofarabine, cyclophosphamide, and etoposide were administered. Unfortunately, 31% leukemic cells were identified thereafter. Because of chemotherapy-refractory leukemia, a palliative oral treatment with mercaptopurine was started. However, palliative situation was not accepted by the parents and the infant was admitted to our hospital.

Genomic DNA was isolated from leukemic cells for molecular characterization. A MLL-MLLT3/AF9 rearrangement was detected and used as a marker for minimal residual disease (MRD). For further molecular characterization, targeted deep next-generation sequencing was performed for a panel of 54 leukemia-associated genes [3]. Interestingly, no mutation was found.

Since the CD33 antigen was strongly expressed in the first immunophenotyping, we administered the anti-CD33 monoclonal antibody gemtuzumab ozogamicin (GO) twice, two weeks apart (6 mg/m²), being well investigated in children with AML [4]. As CD38+ leukemic cells with loss of CD33 and CD22 were detected after GO infusion, the anti-CD38 antibody daratumumab was given alternatingly twice, two weeks apart (16 mg/kg). Daratumumab is established in multiple myeloma therapy [5] and showed promising results in preclinical examinations in T-ALL [6]. However, it has never been used in infants. Because reappearing leukemic cells were positive for CD22 and negative for CD33 and CD38 (Table 1), we administered a third antibody, the anti-CD22 monoclonal antibody inotuzumab ozogamicin (0.8 mg/m²) being used in adult ALL, but not yet in infants [7]. Afterwards, we observed a severe tumor lysis syndrome with no measureable leukocytes, indicating that this might be the most effective antibody. Before transplantation, the MRD diagnostics showed only results of 1.0 when blasts could be detected or could not be performed because of absent measureable leukocytes. Although expression of CD19 was identified, we refused to administer the CD19 antibody blinatumomab because of being refractory in first treatment as described above. Shortly after therapy with inotuzumab, allogeneic bone marrow transplantation from an unrelated donor was performed using a special conditioning regimen consisting of thymoglobulin, busulfan, fludarabine, and clofarabine as an additional antileukemic treatment especially in infant ALL with MLL rearrangement [8]. The patient finally recovered completely. A complete molecular remission could be observed in all follow-up bone marrow samples. Currently, 21 months after transplantation, the patient is in a very good physical condition with normal development according to age.

A combination of three different monoclonal antibodies according to the immunophenotype of the leukemic cells can effectively eliminate leukemic cells in chemotherapy-refractory leukemia and serve as bridging to transplant to induce a complete molecular remission afterwards even in infants.
Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the parents of the child included in this study.

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References

1. Pieters R (2003) Biology and treatment of infant leukemias. Humana Press
2. Pieters R, DeLorenzo P, Ancliffe P et al (2018) Outcome of infants younger than 1 year with acute lymphoblastic leukemia treated with the Interfant-06 Protocol; results from an international randomized study. ASH Abstract 655
3. Rinke J, Schäfer V, Schmidt M, Ziemann J, Kohlmann A, Hochhaus A, Ernst T (2013 Aug) Genotyping of 25 leukemia-associated genes in a single work flow by next-generation sequencing technology with low amounts of input template DNA. Clin Chem 59(8):1238–1250
4. Aplenc R, Alonzo TA, Gerbing RB, Lange BJ,Hurwitcz CA, Wells RJ, Bernstein I, Buckley P, Krimmel K, Smith FO, Sievers EL, Arceci RJ, Children’s Oncology Group (2008) Safety and efficacy of gemtuzumab ozogamicin in combination with chemotherapy for pediatric acute myeloid leukemia: a report from the Children’s Oncology Group. J Clin Oncol 26:3290–3295
5. Touzeau C, Moreau P (2017 Jul) Daratumumab for the treatment of multiple myeloma. Expert Opin Biol Ther 17(7):887–893
6. Bride KL, Vincent TL, Im SY, Aplenc R, Barrett DM, Carroll WL, Carson R, Dai Y, Devidas M, Dunsmore KP, Fuller T, Glisovic-Aplenc T, Horton TM, Hunger SP, Loh ML, Maude SL, Raetz EA, Winter SS, Grupp SA, Hermiston ML, Wood BL, Teachey DT (2018 Mar 1) Preclinical efficacy of daratumumab in T-cell acute lymphoblastic leukemia. Blood. 131(9):995–999
7. Lamb YN (2017 Sep) Inotuzumab ozogamicin: first global approval. Drugs. 77(14):1603–1610
8. Stumpel DJ, Schneider P, Pieters R, Stam RW (2015 Sep) The potential of elotuzumab in MLL-rearranged infant acute lymphoblastic leukemia. Eur J Cancer 51(14):2008–2021

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Table 1 Immunophenotyping of leukemic cells before and after antibody therapy

| Time point                                      | Immunophenotyping          |
|------------------------------------------------|----------------------------|
| Initial diagnostics                            | CD33, CD19, CD22, CD79a, CD38, CD10 |
| After 1st gemtuzumab administration            | CD38, CD19                 |
| After 2nd gemtuzumab and 2nd daratumumab admin | CD22, CD19, CD10           |