Daratumumab with or without chemotherapy in relapsed and refractory acute lymphoblastic leukemia. A retrospective observational Campus ALL study

The anti-CD38 antibody daratumumab, currently approved for the treatment of patients with multiple myeloma, is also being explored for patients with acute lymphoblastic leukemia (ALL), whose blasts commonly express high levels of CD38. Patients with relapsed or refractory (R/R) disease, as well as those with positive measurable residual disease (MRD) have consistently shown unfavorable outcomes and, especially for T-lineage ALL, therapeutic options beyond first-line treatment remain limited. Preclinical studies have demonstrated that daratumumab has significant activity in human xenograft models of ALL, both as a single agent and in combination with chemotherapy. However, the clinical experience is so far very limited. A few case reports have suggested that daratumumab has anti-leukemic activity in R/R and MRD-positive ALL cases, but the small numbers of patients and the positive-outcome bias, due to the propensity to publish mainly positive results, prevent any robust conclusions on the clinical impact of this drug in ALL.

We hereby report a retrospective, observational study performed in patients with R/R or MRD-positive ALL who received daratumumab in Italy in order to provide further information on the safety and efficacy of this drug in a real-life context. In this study we included adult and pediatric patients with R/R or MRD-positive T- or B-lineage ALL or lymphoblastic lymphoma, who received at least one dose of daratumumab between December 2018 and December 2020 at 17 Italian hematology centers. Data were retrospectively collected in an anonymous database. This study was performed in the context of the Campus ALL national framework and in agreement with the Declaration of Helsinki. Patients received daratumumab either off-label or in the context of a compassionate use program, kindly supported by Janssen-Cilag Spa.

Daratumumab was administered at the approved schedule for multiple myeloma (i.e., 16 mg/kg weekly for 8 doses, then every 2 weeks for 8 doses, then monthly until disease progression), either alone or in combination with chemotherapy. The co-primary endpoints were overall response rate and overall survival of patients after daratumumab. Additional endpoints were safety and bridge to allogeneic hematopoietic cell transplant (HCT) after daratumumab. Complete response was defined as a bone marrow blast count <5% without evidence of extramedullary manifestations, partial response was defined as a bone marrow blast count ≥5% and <25% with a reduction of leukemic involvement of at least 50%. For lymphoblastic lymphoma, the Lugano criteria were applied. MRD was monitored either by flow cytometry and/or by real-time quantitative polymerase chain reaction in centralized laboratories. The overall response rate was defined as the proportion of patients who obtained a partial response, a complete response or, only for patients who were MRD positive, MRD negativity. Any systemic anti-neoplastic treatment started at diagnosis or with R/R disease counted as a line of therapy. Any systemic anti-neoplastic treatment started at diagnosis or with R/R disease counted as a line of therapy.

Survival was estimated using the Kaplan-Meier method and overall survival was calculated from the date of the first daratumumab infusion to the date of death or the last follow-up. The association of baseline variables with response was explored using the Fisher exact, χ² or Mann-Whitney test, as appropriate. The cut-off date for this analysis was March 31, 2021 and data were analyzed with STATA 12.1 software (Stata Corporation, College Station, TX, USA).

We included 20 patients (85% males) in the study. Thirteen had T-ALL, four had B-ALL, one had mixed phenotype acute leukemia and two had lymphoblastic lymphoma (B-lineage in 1, T-lineage in the other); 11 patients were treated front-line according to the GIMEMA LAL1913 intensive pediatric-like protocol. The patients’ characteristics are summarized in Table 1.

Daratumumab was administered at a median time of 13 months after diagnosis and patients had received a median of three prior lines of therapy. The median age of the patients at the start of daratumumab treatment was 35 years (range, 8-73) and three patients were below the age of 18. Nine patients had already undergone an allogeneic HCT, with a median time from transplantation to daratumumab treatment of 6 months (range, 2-20). At the start of daratumumab treatment, 80% of patients had a bone marrow relapse, either isolated or with concomi-

| Table 1. Patients’ characteristics. |
|-------------------------------------|
| Variable                          | N. or median | % or range |
| Male sex                          | 17           | 85         |
| Type of ALL                       | 18           | 80         |
| T                                 | 13           | 65         |
| ETP                               | 4            | 20         |
| B                                 | 4            | 20         |
| MPAL                              | 1            | 5          |
| Type of LBL                       | 2            | 10         |
| T                                 | 1            | 5          |
| B                                 | 1            | 5          |
| Firstline treatment               |              |            |
| LAL-1913                          | 11           | 55         |
| Hyper-CVAD                        | 3            | 15         |
| AIEOP-BFM                         | 4            | 20         |
| Others (EWALL, BPM)               | 2            | 10         |
| Allo-HCT before daratumumab       | 9            | 45         |
| Lines of treatment before         | 3            | 1 - 4      |
| daratumumab                       |              |            |
| Age at daratumumab start, years   | 35           | 8 - 73     |
| Below 18 years                    | 3            | 15         |
| Disease status at daratumumab     |              |            |
| start                              |              |            |
| Isolated BM relapse               | 8            | 40         |
| Extramedullary and BM             | 8            | 40         |
| Extramedullary and MRD positivity | 2            | 10         |
| Extramedullary only               | 1            | 5          |
| CR, MRD-positive                  | 1            | 5          |
| Disease characteristics at         |              |            |
| daratumumab start                 |              |            |
| White blood cells, x10⁹/L          | 3.34         | 0.1 - 39   |
| Platelets, x10⁹/L                 | 34           | 1 - 233    |
| Peripheral blood blasts, %        | 14           | 0 - 98     |
| Bone marrow blasts, %             | 45           | 0 - 100    |
| ECOG at daratumumab start         | 2            | 0 - 4      |
| Concomitant chemotherapy           | 9            | 45         |
| Time from diagnosis to            | 13           | 7 - 28     |
| daratumumab, months               |              |            |

ALL: acute lymphoblastic leukemia; ETP: early-T-precursor; MPAL: mixed phenotype acute leukemia; LBL: lymphoblastic lymphoma; alloHCT: allogeneic hematopoietic cell transplant; BM: bone marrow; MRD: measurable residual disease; CR: complete response; ECOG: performance status according to the Eastern Cooperative Oncology Group scale.
tant extramedullary disease. Extramedullary sites involved were the lymph nodes in four patients, the central nervous system in three, the mediastinum in two, the breast in one and the gut in one. The median performance status according to the Eastern Cooperative Oncology Group (ECOG) was 2. Daratumumab was administered alone in 11 cases (in 1 case after a short dexamethasone pre-phase), while nine patients received concomitant chemotherapy (Online Supplementary Table S1).

The overall response rate was 20%, with two patients achieving a MRD-negative complete response, one a complete response with persistent MRD and one a partial response (Table 2). Patients responded after two to six infusions of daratumumab and the median time to response was 4 weeks. Three of the four responses were observed in patients with T-ALL, who were treated with daratumumab as a single agent. Two patients (both with T-ALL) were alive at the last follow-up, one patient died after relapse and one died of treatment-related complications after allogeneic HCT. The characteristics of the responding patients are summarized in Online Supplementary Table S2. Four patients (2 responders, 2 refractory) proceeded to allogeneic HCT after daratumumab.

Next, we explored the potential factors associated with response. Patients with a bone marrow hematologic relapse \( (P=0.013) \), lower platelet count \( (P=0.019) \) and higher circulating blast percentage \( (P=0.034) \) were less likely to respond, while those with a better ECOG performance status \( (P=0.019) \) and who had received fewer prior lines of therapy \( (P=0.022) \) responded better (Table 3). Consistently, bone marrow MRD positivity, with or without extramedullary involvement, was associated with a better overall response rate, without however the difference reaching statistical significance \( (P=0.088) \).

Finally, we evaluated the potential association of CD38 expression on lymphoblasts with response. Among the 18 evaluable cases, CD38 positivity and mean fluorescence intensity did not differ significantly between responders and non-responders (median 96.5% vs. 95.6%, \( P=0.9 \) and 16,800 vs. 12,800; \( P=0.51 \), respectively).

At the last follow-up, all but one patient had stopped treatment and two patients remained alive and in complete remission. The median overall survival of the whole cohort was 4 weeks, with a 3-month overall survival rate of 25% (Online Supplementary Figure S1). No unexpected toxicities were observed and there was only one grade 2 infusion reaction.

### Table 2. Outcome after daratumumab treatment.

| Outcome after daratumumab | N. or median | % or range |
|---------------------------|--------------|------------|
| Response to daratumumab   |              |            |
| Responders                | 4 (20)       |            |
| CR, MRD-negative          | 2 (10)       |            |
| CR, MRD-positive          | 1 (5)        |            |
| PR                        | 1 (5)        |            |
| Non-responders            | 16 (80)      |            |
| Stable disease            | 2 (10)       |            |
| Progressive disease       | 12 (60)      |            |
| Not evaluable             | 2 (10)       |            |
| Allo-HCT post-daratumumab | 4 (20)       |            |
| in CR/PR                  | 2 (10)       |            |
| Treatment duration, weeks | 2 (10-120)   |            |
| Discontinued treatment    | 19 (95%)     |            |

CR: complete remission; MRD: measurable residual disease; PR: partial remission; Allo-HCT: allogeneic hematopoietic cell transplant.

To our knowledge, this is the largest series of ALL patients treated with daratumumab reported so far and further underlines the potential activity of this drug in R/R and MRD-positive cases.

While the advent of monoclonal antibodies and chimeric antigen receptor T-cell therapy is progressively changing the therapeutic scenario in B-lineage ALL, the approved treatment options for R/R and MRD-positive T-ALL remain unsatisfactory, as highlighted by the large prevalence of T-lineage diseases in our cohort (14/20 total patients). Nalernabine has been confirmed to be active in this setting,13 but responses are short-lived and half of the patients are resistant to the drug. More recently, the AKR1C activated prodrug OBI342413 and the BCL-2 inhibitor venetoclax have been tested in R/R T-ALL, and the combination of venetoclax and navitoclax with chemotherapy appears particularly promising.14 However, data on these new agents are still immature and new therapeutic approaches are urgently needed.

Following preclinical data and a few positive case reports, daratumumab has started to be used in patients with advanced ALL without other therapeutic options, but data from unselected cohorts are lacking. In our series, in which we included all patients who received at

### Table 3. Predictors of response to daratumumab.

| Variable* | Number (%) or median (range) | \( P=\) |
|-----------|-----------------------------|--------|
| Sex       | Responders | Non-responders |        |
| Male      | 4 (23.5) | 13 (76.5) |          |
| Female    | 0 (0)    | 3 (100)   |          |
| Age, years | 34 (25 - 45) | 35.5 (8 - 73) | 0.92 |
| T-lineage | 3 (21.4) | 11 (78.6) |          |
| B-lineage | 1 (20)   | 4 (80)    |          |
| Lymphoblastic lymphoma | 1 (50) | 1 (50) | 0.37 |
| Extramedullary disease | 2 (18.2) | 9 (81.8) | 0.008 |
| BM MRD° | 2 (66.7) | 33.7) |          |
| BM relapse | 1 (6.2)   | 15 (93.8) | 0.013 |
| Previous allo-HCT | 2 (22.2) | 7 (77.8) | 1 |
| Previous lines of treatment | 1 | 0.222 |
| White blood cells, x10⁹/L | 3.36 (3.4 - 4.3) | 4.66 (0.1 - 39.4) | 0.91 |
| Hemoglobin, g/dL | 10 (10 - 11) | 9.5 (8 - 13) | 0.25 |
| Platelets, x10⁹/L | 151 (70 - 233) | 27 (1 - 199) | 0.019 |
| PB blasts, % | 0 (0 - 0) | 24 (0 - 98) | 0.034 |
| BM blasts, % | 2 (0 - 78) | 50 (1 - 100) | 0.099 |
| ECOG score | | 0.019 |
| Concomitant chemo | 1 (11.1) | 8 (88.9) | 0.37 |

* Disease status and patients’ characteristics evaluated at the time of starting daratumumab therapy. \(^1\) Includes the patient in complete remission with isolated measurable residual disease positivity and those with extramedullary relapse and measurable residual disease positivity in the bone marrow. Bold values denote statistical significance at the \( P<0.05 \) level.
least one dose of the drug, we observed a relatively low overall response rate of 20% and limited survival. However, most patients were heavily pre-treated, with a poor ECOG performance status and a high disease burden. Indeed, several of these patients would be excluded from any clinical trial. Responses were obtained rapidly, after two to six infusions of the drug, either alone or in combination with chemotherapy, and interestingly also in cases with extramedullary disease. Although limited by the small numbers, we could analyze potential predictive factors of response to daratumumab. We observed that patients with a high ALL burden (i.e., those with a bone marrow hematologic relapse and circulating blasts) were unlikely to benefit from the treatment, while daratumumab proved to be effective in patients with a good performance status and less advanced disease. These findings are in agreement with the current literature, with positive case reports mostly describing patients treated for MRD positivity or with low disease burden and in good clinical conditions. Indeed, a better selection of patients, as well as earlier use of the compound (e.g., in MRD-positive cases) appear crucial to obtain meaningful results. We also evaluated CD38 expression on lymphoblasts before the start of daratumumab therapy and found no significant association with response. Sample investigation was not centralized and so this exploratory analysis was limited by the heterogeneity of antibodies and analytical techniques employed by different flow cytometry laboratories.

We observed a patient who responded to daratumumab despite high disease burden, but in this case the antibody was used in combination with chemotherapy. Recently, a case report outlined the feasibility of this approach,15 which is currently being tested in a clinical trial evaluating daratumumab in combination with chemotherapy in younger ALL patients (NCT03384654). This strategy might be the best option in the presence of a full-blown relapse, but the best chemotherapy regimen to combine with daratumumab remains to be defined. Combinations with innovative drugs with promising activity in ALL, such as venetoclax or bortezomib,16 could also be tested following the experience in multiple myeloma,17 as these patients are often chemorefractory.

We could confirm the safety of daratumumab in the setting of ALL, with a lower than expected rate of infection reactions compared to those occurring in multiple myeloma and no unexpected toxicities. Although limited by its retrospective nature and the heterogeneity of the patients, our study provided data that could help to design new clinical trials aimed at testing daratumumab in ALL and to selecting patients who may benefit more from its use.

In conclusion, our data confirm the potential activity and safety of daratumumab in R/R and MRD-positive ALL, and suggest that this compound should be possibly used earlier, rather than after several lines of salvage treatment. Further studies are needed to clarify whether daratumumab could be another game-changer in this disease.

Marco Cerrano, Massimiliano Bonifacio, Matteo Oliva, Antonio Curti, Michele Malagola, Michele Dargenio, Anna Maria Scattolin, Cristina Papayanniudis, Fabio Forgieri, Carmela Garetti, Ilaria Tanasi, Patrizia Zappasodi, Roberta La Starza, Nicola Stefano Fracchiolla, Patrizia Chiusolo, Luisa Giaccone, Maria Ilaria Del Principe, Fabio Giglio, Matriz Defina, Claudio Favre, Carmelo Rizzari, Barbara Castella, Giovanni Pizzolo, Felicetto Ferrara, Sabrina Chiaretti and Robin Foa

1Divisione di Ematologia, Dipartimento di Oncologia, AOUMC; 2UOC di Ematologia, Azienda Ospedaliero Universitaria Integrata di Verona, Verona; 3Dipartimento di Medicina, Sezione di Ematologia, Università di Verona, Verona; 4Dipartimento di Biotecnologie Moleculari e Scienze per la Salute, Università di Torino, Torino; 5IRCCS Azienda Ospedaliero Universitaria di Bologna, Istituto di Ematologia “Severilou”, Bologna; 6Università di Brescia, Unità Operativa di Ematologia e Centro Trapianti, ASST Spedali Civili di Brescia, Brescia; 7Unità Operativa di Ematologia e Trapianto, Ospedale Vito Fazzi, Lecce; 8Unità Operativa di Ematologia e Trapianto, Ospedale dell’Angelo, Mestre; 9Unità Operativa Complessa di Ematologia, Azienda Ospedaliero Universitaria di Modena, Modena; 10UO Ematologia ed Immunologia Clinica, Azienda Ospedaliero Università Padova, Padova; 11Unità Operativa di Ematologia, Fondazione IRCCS Policlinico San Matteo, Pavia; 12Unità Operativa di Ematologia e Trapianto, AOU Ospedale S. Maria della Misericordia, Perugia; 13UOC Ematologia Fondazione IRCCS Ca’ Granda - Ospedale Maggiore Policlinico, Milano; 14Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma; 15Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma; 16Unità di Trapianto Allogengico di Cellule Stamminali, Dipartimento di Oncologia, A.O.U. Città della Salute e della Scienza, Torino; 17Ematologia, Dipartimento di Biomedicina e Prevenzione, Università di Roma Tor Vergata, Roma; 18Unità Operativa di Ematologia e Trapianto di Malloko Osseo, IRCCS Ospedale San Raffaele, Milano; 19Unità Operativa Complessa di Ematologia, AOUS, Università di Siena, Siena; 20Unità Operativa di Oncologia ed Ematologia Pediatrica, Ospedale Pediatrico Meyer, Firenze; 21Unità Operativa di Ematologia Pediatrica, Università di Milano-Bicocca, Fondazione MBBM, Monza; 22Laboratorio Analisi, AO S. Croce e Carle, Canzo; 23UOC di Ematologia, AORN Cardarelli, Napoli; 24Ematologia, Dipartimento di Medicina Transazionale e di Precisione, Università Sapienza, Roma, Italy

Correspondence: MARCO CERRANO - cerranomarco@gmail.com

ROBIN FOÀ - rfoa@bce.uniroma1.it

doi:10.3324/haematol.2021.279851

Received: September 6, 2021.
Accepted: January 4, 2022.
Pre-published: January 13, 2022.

Disclosures: no conflicts of interest to disclose

Contributions: MC, MB, SC and RF designed the study. MC assembled and analyzed the data. MO collected data and contributed to their analysis. BC analyzed flow cytometry data. MC, MB, SC and RF drafted the manuscript. All authors contributed to data collection, revised the manuscript, and accepted its final version.

Acknowledgements: we thank Janssen-Cilag Spa Italy for providing daratumumab for compassionate use.

Funding: the work was partly supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC), Metastases Special Program, N° 21498, Milan, Italy (to RF).

References

1. Leong S, Inglott S, Papaleondopoulou F, et al. CD1a is rarely expressed in pediatric or adult relapsed/refractory T-ALL: implications for immunotherapy. Blood Adv. 2021;4(19):4665-4668.
2. Bride KL, Vincent TL, Im S-Y, et al. Preclinical efficacy of daratumumab in T-cell acute lymphoblastic leukemia. Blood. 2018;131(9):995-999.
3. Vogiatzi E, Winterberg D, Lens K, et al. Daratumumab eradicates minimal residual disease in a preclinical model of pediatric T-cell acute lymphoblastic leukemia. Blood. 2019;134(2):713-716.
4. Naik J, Tbernali M, de Jong-Korlaar R, et al. CD38 as a therapeutic target for adult acute myeloid leukemia and T-cell acute lymphoblastic leukemia. Haematologica. 2019;104(3):e100-e103.
5. Ofran Y, Ringelstein-Harlev S, Slouzkey I, et al. Daratumumab for eradication of minimal residual disease in high-risk advanced relapse of T-cell/CD19/CD22-negative acute lymphoblastic leukemia. Leukemia. 2020;34(1):293-295.
6. Mirgh S, Ahmed R, Agrawal N, et al. Will daratumumab be the next game changer in early thymic precursor-acute lymphoblastic leukaemia? Br J Haematol. 2019;187(2):e33-e35.
7. Canzel C, Khant M, Dukain C, Rowe JM. Daratumumab for relapsed/refractory Philadelphia-positive acute lymphoblastic leukaemia. Haematologica. 2018;113(10):e489-e490.
8. Zhang Y, Xue S, Liu F, Wang J. Daratumumab for quick and sustained remission in post-transplant relapsed/refractory acute lymphoblastic leukaemia. Leuk Res. 2020;91:106332.
9. Cerrano M, Castella B, Lia G, et al. Immuno-modulatory and clinical effects of daratumumab in T-cell acute lymphoblastic leukaemia. Br J Haematol. 2020;191(1):e28-e32.
10. Ruhayel SD, Valvi S. Daratumumab in T-cell acute lymphoblastic leukaemia: a case report and review of the literature. Pediatr Blood Cancer. 2021;68(5):e28229.
11. Chiaretti S, Messina M, Della Starza I, et al. Philadelphia-like acute lymphoblastic leukemia is associated with minimal residual disease persistence and poor outcome. First report of the minimal residual disease-oriented GIMEMA LAL1913. Haematologica. 2021;106(6):1559-1568.
12. Candoni A, Lazzarotto D, Ferrara F, et al. Nelarabine as salvage therapy and bridge to allogeneic stem cell transplant in 118 adult patients with relapsed/refractory T-cell acute lymphoblastic leukemia/lymphoma. A CAMPUS ALL study. Am J Hematol. 2020;95(12):1466-1472.
13. Evans K, Duan J, Fritchard T, et al. OBI-3424, a novel AKR1C3-activated prodrug, exhibits potent efficacy against preclinical models of T-ALL. Clin Cancer Res. 2019;25(14):4495-4503.
14. Pullarkat VA, Lacayo NJ, Jabbour E, et al. Venetoclax and navitoclax in combination with chemotherapy in patients with relapsed or refractory acute lymphoblastic leukemia and lymphoblastic lymphoma. Cancer Discov. 2021;11(6):1440-1453.
15. Fulcher J, Berardi P, Christou G, Villeneuve PJA, Bredeson C, Sabloff M. Nelarabine-containing regimen followed by daratumumab as an effective salvage therapy and bridge to allogeneic hematopoietic stem cell transplantation for primary refractory early T-cell precursor lymphoblastic leukaemia. Leuk Lymphoma. 2021;62(9):2295-2297.
16. Kaspers GJL, Niewerth D, Wilhelm BA, et al. An effective modestly intensive re-induction regimen with bortezomib in relapsed or refractory paediatric acute lymphoblastic leukaemia. Br J Haematol, 2018;181(4):525-527.
17. Bahlis NJ, Baz R, Harrison SJ, et al. Phase I study of venetoclax plus daratumumab and dexamethasone, with or without bortezomib, in patients with relapsed or refractory multiple myeloma with and without t(11,14). J Clin Oncol. 2021;39(52):3602-3612.