RESEARCH LETTER

blood advances

TO THE EDITOR:

Real-world experience of combined treatment with azacitidine and romidepsin in patients with peripheral T-cell lymphoma

Matko Kalac,[1,2] Salvia Jain,[3] Constantine S. Tam,[4] Zhengrui Xiao,[5] Francesca Montanari,[6] Jennifer Kanakry,[7] Bryan D. Huber,[8] Mendel Goldfinger,[5] Owen A. O'Connor,[9] and Enrica Marchi[9]

[1]Department of Hematology and Oncology, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Department of Hematology and Oncology, University of California, Irvine, CA; [3]Department of Medicine, Massachusetts General Hospital, Boston, MA; [4]Alfred Hospital and Central Clinical School, Monash University, Melbourne, VIC, Australia; [5]Department of Medicine, Albert Einstein College of Medicine, New York, NY; [6]Department of Hematology, Yale University Cancer Center, Greenwich, CT; [7]Experimental Transplantation & Immunotherapy Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; [8]Blood and Marrow Transplant/Acute Leukemia Program, Intermountain Medical Group, Salt Lake City, UT; and [9]Division of Hematology and Oncology, University of Virginia Cancer Center, Charlottesville, VA

Patients with peripheral T-cell lymphoma (PTCL) have been reported to have poor outcomes, particularly in relapsed or refractory (R/R) setting, in which median progression free survival (PFS) is only 3.1 months from first relapse.[1] Our preclinical work has suggested that combination of epigenetic therapies may exhibit a unique mechanism of action in lymphoma models.[2-4] A phase 1 study of oral azacitidine and romidepsin (aza/romi) demonstrated higher efficacy in patients with PTCL than in patients with B-cell lymphomas, with a markedly longer PFS in the former.[5] A phase 2 study of aza/romi in patients with PTCL demonstrated an overall response rate (ORR) and complete response rate (CRR) of 61% and 48%, respectively, with an ORR and CRR of 80% and 67% in patients with PTCL of T–follicular helper (TFH) cell phenotype origin.[6] Although the biological basis for this is yet to be clarified, the recognition that many PTCLs are driven by gross epigenetic dysregulation has been suggested.[7-9] Oral azacitidine is not widely available outside the United States, leading many clinicians who have deployed aza/romi regimen globally, to substitute it with subcutaneous (SC) azacitidine. Herein, we report on an international, real-world evidence with aza/romi in patients with PTCL, as a crucial step in confirming the applicability of favorable results observed in clinical trials.[10]

The study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board and performed in accordance with the Declaration of Helsinki. Patients were identified through pharmacy database searches, and data were collected via a retrospective chart review. Diagnoses were made based on the 2016 WHO classification of lymphoid neoplasms. Patients were treated using either a previously reported schedule of oral azacitidine,[6] if available (8 patients), or 1 of the following schedules: (A) azacitidine 75mg/m^2 SC on days from 1 to 7 and romidepsin 14 mg/m^2 on day 1, 8, and 15 of a 28 day cycle (total of 9 patients); (B) azacitidine 75mg/m^2 SC on days from 1 to 5 and romidepsin 14 mg/m^2 on day 8, 15, and 22 of a 35 day cycle (1 patient); or (C) azacitidine 75mg/m^2 SC on days from 1 to 7 and romidepsin from 12 to 14 mg/m^2 on day 8, 15, and 22 of a 28 day cycle (9 patients). To be included in this data set, patients were required to have received 1 cycle of therapy. Responses in all patients were assessed using positron emission tomography/computed tomography.

We retrospectively identified 27 patients who were treated with aza/romi, including 19 patients with angioimmunoblastic lymphoma, 2 with adult T-cell leukemia/lymphoma, 3 with TFH-PTCL, 1 with PTCL-not otherwise specified (NOS), and 2 with composite lymphoma (TFH-PTCL with diffuse large B-cell lymphoma and anaplastic lymphoma kinase negative [ALK-] anaplastic large cell lymphoma [ALCL] with follicular lymphoma [FL]). Their clinical characteristics are presented in Table 1, and detailed information of each patient is presented in supplemental Table 1. Notably, the median age was 65, and the oldest patient treated was aged 78 years; 9 patients had performance status of ≥2, and 2 had second

Submitted 30 November 2022; accepted 6 February 2023; prepublished online on *Blood Advances* First Edition 15 February 2023; final version published online 18 July 2023. https://doi.org/10.1182/bloodadvances.2022009445.

All data are available on request from the corresponding author, Matko Kalac (mkalac@hs.uci.edu).

The full-text version of this article contains a data supplement.

Table 1. Patient characteristics

Median age, y (range)	65, (35-78)
Sex	
Female	9
Male	18
Race	
White	19
Black	6
Asian	2
Ethnicity	
Hispanic	7
Non-Hispanic	20
ECOG PS	
0	5
1	13
2	8
3	1
PTCL subtype	
AITL	19
ATLL	2
TFH-PTCL	3
PTCL-NOS	1
Composite (TFH-PTCL + DLBCL and ALK- ALCL + FL)	2
Stage at romidepsin azacitidine start	
I-II	8
III-IV	19
Median number of previous therapies (range)	1 (0-5)
Treatment-naive	3
Previous therapies	
Anthracycline-based	20
Platinum-based	7
Pralatrexate	3
Anti-CD20	4
Brentuximab	8
Other therapy	7
ASCT	7

AITL, angioimmunoblastic lymphoma; ALK- ALCL, anaplastic lymphoma kinase negative anaplastic large cell lymphoma; ASCT, autologous stem cell transplant; ATLL, adult T-cell leukemia/lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; NOS, not otherwise specified.

malignancies. Twenty of 26 evaluable patients were previously treated with an anthracycline-based therapy, whereas 7 patients received an autologous stem cell transplant before study inclusion. Twelve of the 27 patients had next generation sequencing performed. The most common mutations found were those of *TET2* (29%), *RHOA* (15%), *IDH2* (11%), and *DNMT3A* (7%) (Figure 1A).

Among 26 evaluable patients, the ORR was 76.9%, and the CRR was 53%. The median number of aza/romi cycles was 3 (range, 1-12), and the median follow-up was 8.7 months. The ORR and CRR in patients with angioimmunoblastic lymphoma and TFH-PTCL was 69.5% (16/23) and 60.8% (14/23), respectively. The ORR and CRR in patients who had mutations in *TET2*, *IDH2*, and *DNMT3A* (total of 9 individual patients) were 77.7% (7/9) and 44.4% (4/9), respectively. The overall outcomes and duration of response (DOR) are shown in Figure 1B. Median overall survival was not reached, and median PFS was 13.3 months (Figure 1C,D). Median DOR was not reached (Figure 1E). For patients who did not undergo stem cell transplant, the median PFS was 7.07 months, and the DOR was not reached (supplemental Figure 1A). PFS for patients who underwent stem cell transplant was not reached (supplemental Figure 1B). All 3 patients who were treated with aza/romi as the front-line therapy achieved remission (2 complete remissions and 1 partial remission). Five of 7 patients with primary refractory disease responded to treatment. Median DOR for the last line of treatment before aza/romi was 3.6 months. Interestingly, 8 patients received aza/romi before stem cell transplant (1 autologous and 7 allogeneic), with all patients still in complete remission as of their last disease assessment. One patient died of transplant-related mortality 8 months after his allogeneic stem cell transplant, with no evidence of relapse. Median follow-up duration for patients after transplant was 11.5 months.

Treatment was well-tolerated, but notable adverse effects included nausea, fatigue, rash, neutropenia, and thrombocytopenia (supplemental Table 2). One patient experienced febrile neutropenia, whereas another had pulmonary infiltrates (differential diagnosis included drug toxicity vs infection). Thrombocytopenia was the most common reason for dose reduction of romidepsin (to 12 mg/m^2) or its omission on day 8, 15, or 22.

In this less selected, real-world patient population, the data confirm our earlier observations regarding the treatment merits of aza/romi in patients with PTCL. This patient population includes patients with poor performance status and second malignancies, which would prevent them from participating in clinical studies. Our data also suggest that azacitidine can produce significant responses in combination with romidepsin, which compare favorably with single agent azacitidine.[10,11] We do note that these studies cannot be compared in the absence of a randomized trial and that further research is needed (an ongoing randomized phase 2B trial of aza/romi vs investigator's choice is underway [NCT04747236]). Adverse event profiles noted with aza/romi suggest that hematologic toxicity might be augmented by the combination compared with that by azacitidine alone. These toxicities were, however, manageable and not in excess of conventional chemotherapy. Furthermore, and although based on small numbers, the potential priming effects of the epigenetic treatment in patients before autologous stem cell transplant (ASCT) is similar to that reported by Ma et al and suggest that this novel regimen may have advantages over traditional chemotherapy before transplant.[12] We have to stress that this is a small, retrospective study and, therefore, insufficient on its own to make broader conclusions. It is, however, 1 piece of data that supports the overall activity of this regimen in the patient population with very limited treatment options.

Acknowledgments: The authors thank their patients and their families for the participation in this study. The authors also thank the Translational Orphan Blood Cancer Research Initiative/Scarlet Feather Fund at University of Virginia. O.A.O. is an American

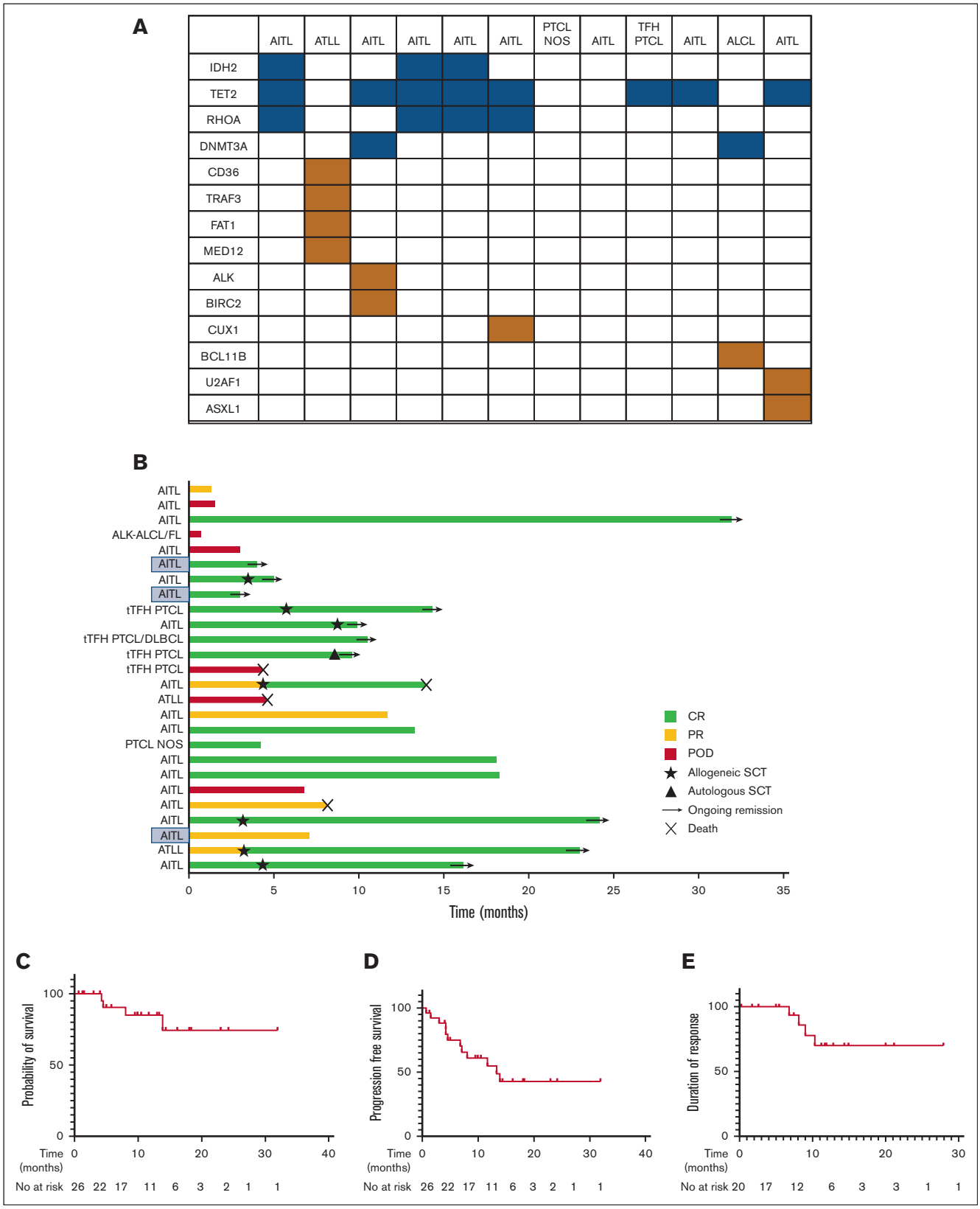

Figure 1. Romidepsin and azacitidine in patients with PTCL treated in a real world setting. (A) Mutations identified in patients who had next generation sequencing (blue squares represent mutations in *RHOA*, *IDH2*, *TET2* and *DNMT3*A, orange squares are other mutations). (B) Outcomes and duration of response in patients treated with romidepsin and azacitidine in a real-world setting. Green lines: complete remission; yellow lines: partial remission; red lines: progression of disease; black star: allogeneic stem cell transplant; black triangle: autologous stem cell transplant; black arrow: ongoing remission; black St. Andrews cross: death. Frontline treated patients are highlighted on the y axis with blue squares. (C) Overall survival. (D) Progression free survival. (E) Duration of response.

Cancer Society research professor. O.A.O. and E.M. are funded by the Office of Orphan Products Development grant RO1 #FD-R-006814-01.

Contribution: M.K. collected and analyzed the data and wrote the manuscript; S.J. collected the data and collaborated on the manuscript preparation; C.S.T., Z.X., F.M., J.K., B.D.H., M.G., and E.M. collected the data and collaborated on the manuscript preparation; and O.A.O. conceived the study and collaborated on data analysis and manuscript preparation.

Conflict-of-interest disclosure: M.K. receives research funding from Janssen and provides consultancy for Seagen, Acrotech Biopharma, Cardinal Health, Guidepoint, and GLG. C.S.T. received honoraria from Janssen, AbbVie and BeiGene, and research funding from Janssen, AbbVie and BeiGene. O.A.O. received honoraria from Astex, Kymera, Dren, and Myeloid Therapeutics. E.M. reports research funding from Merck, Celgene/Bristol Myers Squibb, Astex Pharmaceuticals, and Myeloid Therapeutics and serves in the data safety monitoring committee with Everest Clinical Research for Kyowa Kirin. The remaining authors declare no competing financial interests.

ORCID profiles: M.K., 0000-0003-1238-0760; S.J., 0000-0003-1566-9308; C.S.T., 0000-0002-9759-5017; Z.X., 0000-0001-5586-9668; J.K., 0000-0001-9522-3618.

Correspondence: Matko Kalac, University of California Irvine, Tisch Cancer Institute, 200 S Manchester Ave, Orange, CA 92868; email: mkalac@hs.uci.edu.

References

1. Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *J Clin Oncol*. 2013;31(16):1970-1976.
2. Kalac M, Scotto L, Marchi E, et al. HDAC inhibitors and decitabine are highly synergistic and associated with unique gene-expression and epigenetic profiles in models of DLBCL. *Blood*. 2011;118(20):5506-5516.
3. Marchi E, Zullo KM, Amengual JE, et al. The combination of hypomethylating agents and histone deacetylase inhibitors produce marked synergy in preclinical models of T-cell lymphoma. *Br J Haematol*. 2015;171(2):215-226.
4. Scotto L, Kinahan C, Douglass E, et al. Targeting the T-cell lymphoma epigenome induces cell death, cancer testes antigens, immune-modulatory signaling pathways. *Mol Cancer Ther*. 2021;20(8):1422-1430.
5. O'Connor OA, Falchi L, Lue JK, et al. Oral 5-azacytidine and romidepsin exhibit marked activity in patients with PTCL: a multicenter phase 1 study. *Blood*. 2019;134(17):1395-1405.
6. Falchi L, Ma H, Klein S, et al. Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: a multicenter phase 2 study. *Blood*. 2021;137(16):2161-2170.
7. Couronné L, Bastard C, Bernard OA. TET2 and DNMT3A mutations in human T-cell lymphoma. *N Engl J Med*. 2012;366(1):95-96.
8. Lemonnier F, Couronné L, Parrens M, et al. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. *Blood*. 2012;120(7):1466-1469.
9. Ma H, Marchi E, O'Connor OA. The peripheral T-cell lymphomas: an unusual path to cure. *Lancet Haematol*. 2020;7(10):e765-e771.
10. Yoon SE, Cho J, Kim YJ, Kim SJ, Kim WS. Real-world efficacy of 5-azacytidine as aalvage chemotherapy for angioimmunoblastic T-cell lymphoma. *Clin Lymphoma Myeloma Leuk*. 2022;22(11):e972-e980.
11. Dupuis J, Tsukasaki K, Bachy E, et al. Oral Azacytidine in Patients with Relapsed/Refractory Angioimmunoblastic T-Cell Lymphoma: Final Analysis of the Oracle Phase III Study [abstract]. *Blood*. 2022;140(suppl 1):2310-2312.
12. Ma H, Cheng B, Falchi L, et al. Survival benefit in patients with peripheral T-cell lymphomas after treatments with novel therapies and clinical trials. *Hematol Oncol*. 2020;38(1):51-58.