



**Universiteit
Leiden**
The Netherlands

**Outcomes of rare patients with a primary cutaneous CD30(+)
lymphoproliferative disorder developing extracutaneous disease**

Melchers, R.C.; Willemze, R.; Vermaat, J.S.P.; Jansen, P.M.; Daniels, L.A.; Putter, H.; ... ;
Quint, K.D.

Citation

Melchers, R. C., Willemze, R., Vermaat, J. S. P., Jansen, P. M., Daniels, L. A., Putter, H., ...
Quint, K. D. (2020). Outcomes of rare patients with a primary cutaneous CD30(+)
lymphoproliferative disorder developing extracutaneous disease, *135*(10), 769-773.
doi:10.1182/blood.2019002799

Version: Publisher's Version
License: [Leiden University Non-exclusive license](#)
Downloaded from: <https://hdl.handle.net/1887/3181249>

Note: To cite this publication please use the final published version (if applicable).

(I.R.), 031A315 “MessAge” (I.G.), ERA-Net ERACoSysMed JTC-2 project “prediCt” 031L0136A (I.R.), and Bloodwise grant 13020 (R.E.C.).

Authorship

Contribution: R.E.C. and S.C. provided the data; A.G., I.G., and I.R. analyzed the data; A.G., I.G., R.E.C., and I.R. wrote the paper.

Conflict-of-interest disclosure: I.G. received travel and research funding from Bristol-Myers Squibb (BMS). I.R. received honorarium, travel, and research funding from BMS; and honorarium from Janssen-Cilag. R.E.C. received research support and honoraria from Pfizer, Novartis, and BMS, and honoraria from Ariad/Incyte, Abbvie, and Jazz Pharmaceuticals. The remaining authors declare no competing financial interests.

ORCID profiles: A.G., 0000-0003-0378-9601; I.G., 0000-0002-2524-1199; S.C., 0000-0001-5507-6203; R.E.C., 0000-0002-1261-3299; I.R., 0000-0002-6741-0608.

Correspondence: Ingo Roeder, Institute for Medical Informatics and Biometry, Faculty of Medicine Carl Gustav Carus, Technische Universität Dresden, Fetscherstr. 74, D-01307 Dresden, Germany; e-mail: ingo.roeder@tu-dresden.de.

Footnotes

*A.G. and I.G. contributed equally.

†R.E.C. and I.R. contributed equally.

Data of the DESTINY trial are already presented in Clark et al.^{10,11}

The online version of this article contains a data supplement.

REFERENCES

1. Apperley JF. Chronic myeloid leukaemia. *Lancet*. 2015;385(9976):1447-1459.
2. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2016 update on diagnosis, therapy, and monitoring. *Am J Hematol*. 2016;91(2):252-265.

3. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. *J Clin Oncol*. 2016;34(24):2851-2857.
4. Cervantes F, Correa JG, Pérez I, et al; CML Spanish Group (GELMC). Imatinib dose reduction in patients with chronic myeloid leukemia in sustained deep molecular response. *Ann Hematol*. 2017;96(1):81-85.
5. Fassoni AC, Baldow C, Roeder I, Glauche I. Reduced tyrosine kinase inhibitor dose is predicted to be as effective as standard dose in chronic myeloid leukemia: a simulation study based on phase III trial data. *Haematologica*. 2018;103(11):1825-1834.
6. Sauße S, Richter J, Hochhaus A, Mahon FX. The concept of treatment-free remission in chronic myeloid leukemia. *Leukemia*. 2016;30(8):1638-1647.
7. Cortes J, Rea D, Lipton JH. Treatment-free remission with first- and second-generation tyrosine kinase inhibitors. *Am J Hematol*. 2019;94(3):346-357.
8. Rousselot P, Charbonnier A, Cony-Makhoul P, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *J Clin Oncol*. 2014;32(5):424-430.
9. Sausse S, Richter J, Guilhot J, et al; EURO-SKI investigators. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018;19(6):747-757.
10. Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY): an interim analysis of a non-randomised, phase 2 trial. *Lancet Haematol*. 2017;4(7):e310-e316.
11. Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor therapy before complete treatment discontinuation in patients with chronic myeloid leukaemia (DESTINY): a non-randomised, phase 2 trial. *Lancet Haematol*. 2019;6(7):e375-e383.

DOI 10.1182/blood.2019003395

© 2020 by The American Society of Hematology

TO THE EDITOR:

Outcomes of rare patients with a primary cutaneous CD30⁺ lymphoproliferative disorder developing extracutaneous disease

Rutger C. Melchers,¹ Rein Willemze,¹ Joost S. P. Vermaat,² Patty M. Jansen,³ Laurien A. Daniëls,⁴ Hein Putter,⁵ Marcel W. Bekkenk,⁶ Ellen R. M. de Haas,⁷ Barbara Horvath,⁸ Michelle M. van Rossum,⁹ Cornelius J. G. Sanders,¹⁰ Joep C. J. M. Veraart,¹¹ Maarten H. Vermeer,¹ and Koen D. Quint¹

¹Department of Dermatology, ²Department of Haematology, ³Department of Pathology, ⁴Department of Radiotherapy, and ⁵Department of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, The Netherlands; ⁶Department of Dermatology, Academic Medical Centre and Vrije University Medical Centre, Amsterdam, The Netherlands; ⁷Department of Dermatology, Erasmus Medical Centre, Rotterdam, The Netherlands; ⁸Department of Dermatology, University Medical Centre Groningen, Groningen, The Netherlands; ⁹Department of Dermatology, Radboud University Medical Centre, Nijmegen, The Netherlands; ¹⁰Department of Dermatology, University Medical Centre Utrecht, Utrecht, The Netherlands; and ¹¹Department of Dermatology, Maastricht University Medical Centre, The Netherlands

Primary cutaneous CD30-positive lymphoproliferative disorders (pcCD30⁺LPDs) account for ~30% of all cutaneous T-cell lymphomas.^{1,2} This group forms a spectrum, with primary cutaneous anaplastic large cell lymphoma (C-ALCL) on one end,

lymphomatoid papulosis (LyP) on the other, and borderline cases in-between.³ Patients with C-ALCL mainly present with solitary or localized tumors. Patients with LyP present with a waxing and waning eruption of multiple papular and/or nodular skin lesions

that exhibit spontaneous remission of individual lesions. Both conditions have an excellent prognosis with a 10-year disease-specific survival rate of 90% for C-ALCL and almost 100% for LyP.^{1,3} However, a small proportion of patients will develop extracutaneous localizations during follow-up and may require systemic treatment.^{1,3-5} At present, only limited data are available regarding therapeutic management of patients developing extracutaneous disease, and the optimal therapy is unknown.^{3,6-9} Former treatment guidelines suggest anthracycline-based chemotherapy (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone).^{1,3,8,10,11} Unfortunately, information on the efficacy of these therapies is scarce but is essential as a benchmark for novel targeted therapies and for the development of therapeutic algorithms. This knowledge gap motivated us to evaluate current treatment results and prognosis of rare patients with pcCD30⁺LPDs who developed extracutaneous disease.

We identified 313 patients with C-ALCL and 472 patients with LyP who were included in the Dutch registry of cutaneous lymphomas between October 1985 and December 2017. Diagnosis was made by an expert panel of dermatologists and pathologists from the Dutch Cutaneous Lymphoma Group following the clinicopathologic criteria of the World Health Organization–European Organisation for Research and Treatment of Cancer classification.¹ In all patients with C-ALCL, extracutaneous disease was excluded at time of diagnosis by using routine staging procedures (complete blood count, biochemical analysis, and computed tomography scan of chest, abdomen, and neck). Extracutaneous dissemination was defined as the development of histologically proven systemic localizations after diagnosis of C-ALCL/LyP.¹² Follow-up data showed that 51 (6.5%) of 785 patients, including 38 of 313 with C-ALCL (12%) and 13 of 472 with LyP (3%), had developed extracutaneous manifestations. Patients with an anaplastic lymphoma kinase (ALK)-positive C-ALCL (n = 1), insufficient follow-up data (n = 4), or underlying immunodeficiency (n = 3) were excluded. The final study group of 43 patients included 30 patients with C-ALCL and 13 patients with LyP. Response rates (complete response [CR], partial response [PR], or no response or progressive disease [NR]) and patient outcomes were assessed following the European Organisation for Research and Treatment of Cancer, International Society for Cutaneous Lymphomas, and United States Cutaneous Lymphoma Consortium consensus guidelines for primary cutaneous CD30⁺LPDs.¹¹ For the purpose of the study, no distinction was made between different anthracycline-based chemotherapies. This retrospective study was evaluated by the Ethics Committee of the Leiden University Medical Centre and provided with a waiver of consent (G18.118).

The Kaplan-Meier method was used to estimate (5-year) progression-free survival (PFS/PFS5) and overall survival (OS/OS5). Probabilities of (5-year) relapse and (5-year) disease-specific death (DSD/DSD5) over time were calculated with cumulative incidences, taking into account competing risks (any death for relapse, death from unrelated causes for DSD). Comparison between groups was performed by using the log-rank test. A *P* value < .05 was considered significant. All statistical analyses were performed by using SPSS version 23 (IBM SPSS Statistics, IBM Corporation).

The 43 patients with pcCD30⁺LPD who developed histologically proven extracutaneous disease during follow-up included 31 male patients and 12 female patients (male-to-female ratio, ~3:1); the median age at initial diagnosis was 53 years (range, 26-79 years). Clinical characteristics and treatment responses before extracutaneous dissemination are presented in Table 1. After a median follow-up period of 35 months (range, 5-264 months), 32 patients developed nodal involvement, and 11 patients developed both nodal and visceral involvement. Most patients (34 of 43; 79%) were treated with anthracycline-based chemotherapies (detailed information is provided in supplemental Table 1, available on the *BloodWeb* site). Four patients (9%) were treated with radiotherapy (RT), and five patients (12%) received no further therapy, due to patient refusal (n = 1), spontaneous regression (n = 1), or death before treatment initiation (n = 3). Overall, a CR of the extracutaneous manifestations was achieved in 26 (61%) of 43 patients and a PR in 4 (9%) of 43; 13 (30%) of 43 patients had NR. For patients treated with anthracycline-based chemotherapy specifically (n = 34; 79%), a CR was reached in 21 (62%) of 34 patients, a PR in 4 (12%) of 34, and NR in 9 (26%) of 34. All 4 patients treated with RT reached a CR (Table 2).

After treatment of extracutaneous disease, a 48% five-year cumulative incidence of relapse was reported in 26 patients with a CR, including skin-limited (n = 10), systemic (n = 3), and combined cutaneous and systemic (n = 3) relapses. Systemic relapses were only observed in patients with C-ALCL, whereas patients with LyP developed only skin-limited relapses (Table 2). Median time to relapse after extracutaneous treatment was 41 months (range, 4-101 months), and PFS5 was 39%. After a median follow-up period of 81 months (range, 12-360 months), 17 of 43 patients were alive without disease, 4 of 43 were alive with disease, and 19 of 43 had died of lymphoma and 3 of 43 patients had died of other causes. Five-year DSD and OS5 were both 47%.

Interestingly, 13 patients with solitary or localized skin lesions and only involvement of locoregional lymph nodes (T1-2;N1;M0) showed superior response rates and prognosis (11 of 13 [85%] CR, 62% PFS5, and 62% OS5) compared with 30 other patients developing more extensive extracutaneous disease (15 of 30 [50%] CR, 29% PFS5, and 41% OS5) (supplemental Table 2; supplemental Figure 1). In particular, patients with M1 disease showed poor outcomes (2 of 11 [18%] CR, 18% PFS5, and 18% OS5).

Although extracutaneous manifestations occurred more frequently in C-ALCL compared with LyP (11% vs 3%, respectively), the disease course after extracutaneous localizations was comparable (PFS, *P* = .42; DSD, *P* = .77; OS, *P* = .48).

The observed response rates and prognosis of patients with pcCD30⁺LPDs after extracutaneous development are very similar to results reported in ALK-negative systemic ALCL, showing that a similar treatment approach is indicated.¹³⁻¹⁵ Anthracycline-based therapies have been used as first-line treatment in systemic ALCL and have also been suggested as a first option in patients with C-ALCL developing extracutaneous disease. Consistently, in our study, most patients were treated upfront with this modality. Although the majority

Table 1. Clinical characteristics of patients with pcCD30⁺LPDs who developed extracutaneous disease

Characteristic	C-ALCL (n = 30)	LyP (n = 13)	Overall (N = 43)
Sex (male:female)	21:9	10:3	31:12
Age at diagnosis, y			
Median	56	46	53
Range	26-79	31-77	26-79
Initial extent			
Solitary (T1)	16 (54)	0 (0)	16 (37)
Localized (T2)	7 (23)	2 (15)	9 (21)
Generalized (T3)	7 (23)	11 (85)	18 (42)
Initial therapy for cutaneous lesions			
RT	12 (40)	0 (0)	12 (28)
CHOP	5 (17)	0 (0)	5 (12)
MTX	2 (7)	2 (15)	4 (9)
UVB/PUVA	1 (3)	1 (8)	2 (5)
Excision	7 (23)	0 (0)	7 (16)
Expectative	3 (10)	10 (77)	13 (30)
Initial response rates for cutaneous lesions	25 (83)	4 (31)	29 (67)
CR	2 (7)	7 (54)	9 (21)
PR	3 (10)	2 (15)	5 (12)
NR			
Median time to extracutaneous relapse (range), mo	27 (5-264)	60 (7-230)	35 (5-264)
TNM classification: node			
N1	11 (37)	2 (15)	13 (30)
N2	12 (40)	8 (62)	20 (47)
N3	7 (23)	3 (23)	10 (23)
TNM classification: metastases	24 (80)	8 (62)	32 (74)
M0	6 (20)	5 (38)	11 (26)
M1			
Therapy			
Anthracycline-based chemotherapy (+RT/SCT*)	25 (83)	9 (69)	34 (79)
RT	3 (10)	1 (8)	4 (9)
None†	2 (7)	3 (23)	5 (12)
Results			
CR	19 (63)	7 (54)‡	26 (61)
PR	3 (10)	1 (8)	4 (9)
NR	8 (27)	5 (38)	13 (30)
Current status			
Alive without disease	11 (37)	6 (46)	17 (40)
Alive with disease	2 (6)	2 (15)	4 (9)
Died of lymphoma	14 (47)	5 (39)	19 (44)
Died of other cause	3 (10)	0 (0)	3 (7)

Table 1. (continued)

Characteristic	C-ALCL (n = 30)	LyP (n = 13)	Overall (N = 43)
Median follow-up (range), mo	63.5 (12-325)	134 (14-360)	81 (12-360)
5-y PFS, %§	32	54	39
5-y Cumulative incidence of DSD, %§	51	38.5	47
5-y OS, %§	41	61.5	47

PFS was defined as time between date of response to therapy for first extracutaneous lesion(s) and first event (progressive disease following the European Organization of Research and Treatment of Cancer, International Society for Cutaneous Lymphomas, and United States Cutaneous Lymphoma Consortium consensus guidelines for pcCD30⁺LPDs) or death of any cause. Time intervals of cumulative incidence of DSD were determined with time between date of development of extracutaneous disease and date of death from lymphoma or treatment toxicity, and OS was defined as time between date of development of extracutaneous disease to date of death from any cause. Data are presented as N (%) unless otherwise indicated.

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; M0, no evidence of extracutaneous non-lymph node disease; M1, extracutaneous non-lymph node disease present; MTX, methotrexate; N1, involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement; N2, involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement; N3, involvement of central lymph nodes; SCT, stem cell transplantation; UVB/PUVA, ultraviolet B/psoralen and ultraviolet A.

*SCT included autologous SCT as well as allogeneic SCT.

†Spontaneous regression, refused therapy, or death before start of treatment.

‡CR refers to complete remission of extracutaneous localizations.

§After extracutaneous development.

of patients respond to anthracycline-based therapies, ~40% have poor results, which indicates that survival outcomes of these patients need to be improved by optimization of new treatment algorithms (Table 2). Although RT is already suggested as a suitable treatment option in patients with localized lesions and a solitary regional involved lymph node, and we confirmed superior survival in our study, only few patients actually received RT.

Recent studies reported promising results with brentuximab vedotin (BV) as first- and second-line treatment of systemic ALCL.¹⁶⁻²¹ This led to an approval by the US Food and Drug Administration for BV + cyclophosphamide, doxorubicin, and prednisone as a first-line treatment option in systemic ALCL and subsequent incorporation into the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.^{18,22} Several studies also report high response rates of BV (monotherapy) in patients with pcCD30⁺LPDs, including patients with relapsed and extracutaneous C-ALCL.²³⁻²⁵ However, BV is expensive, cumulative neuropathy is a frequent adverse event and long-term effects are still unknown. Furthermore, most BV studies evaluated heterogeneous patient groups, impeding adequate analyses of survival outcomes for specific cutaneous T-cell lymphoma subtypes.

In the current study, we showed that prognosis of patients with a pcCD30⁺LPD who develop extracutaneous localizations corresponds with ALK-negative systemic ALCL and provides a benchmark for novel targeted therapies. Given the therapeutic success in ALK-negative systemic ALCL, BV-based regimens should be considered in patients with a pcCD30⁺LPD who develop extracutaneous localizations. RT may suffice in patients with localized lesions and a solitary regional involved lymph node (supplemental Figure 2).

Table 2. Treatment responses in patients with C-ALCL or LyP developing extracutaneous disease (N = 43)

Therapy	C-ALCL (n = 30)				LyP (n = 13)				Overall (N = 43)					
	N	CR	Relapse skin limited	Systemic relapse	N	CR*	Relapse skin limited (%)	Systemic relapse	N	CR	Relapse (%)	PFS5 (%)	DSD5 (%)	OS5 (%)
Anthracycline-based chemotherapy	25	16/25 (64)	3/16 (19)	6/16 (38)	9	5/9 (56)	3/5 (60)	0/5 (0)	34	21/34 (62)	12/21 (57)	34	46	46
RT	3	3/3 (100)	2/3 (67)	0/3 (0)	1	1/1 (100)	1/1 (100)	0/1 (0)	4	4/4 (100)	3/4 (75)	100	0	100
No therapy	2	0/2 (0)	—	—	3	1/3 (33)	1/1 (100)	0/1 (0)	5	1/5 (20)	1/1 (100)	20	80	20
Total	30	19/30 (63)	5/19 (26)	6/19 (32)	13	7/13 (54)	5/7 (71)	0/7 (0)	43	26/43 (61)	16/26 (62)	39	47	47

Data are presented as n/N (%) unless otherwise indicated.

DSD5, five-year cumulative incidence of DSD.

*CR refers to complete remission of extracutaneous localizations.

Authorship

Contribution: R.C.M., R.W., J.S.P.V., P.M.J., L.A.D., M.H.V., and K.D.Q. designed the research and wrote the paper; M.W.B., E.R.M.d.H., B.H., M.M.v.R., C.J.G.S., and J.C.J.M.V. contributed to the acquisition of the data; H.P. performed and wrote statistical analyses; and all authors contributed to the concept and design of the study and approved the final version of the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: R.C.M., 0000-0001-9811-3932; M.H.V., 0000-0002-5872-4613.

Correspondence: Rutger C. Melchers, Leiden University Medical Centre, Department of Dermatology, B1-Q, Albinusdreef 2, 2333 ZA Leiden, The Netherlands; e-mail: r.c.melchers@lumc.nl.

Footnote

The online version of this article contains a data supplement.

REFERENCES

- Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768-3785.
- Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. 2019; 133(16):1703-1714.
- Bekkenk MW, Geelen FA, van Voorst Vader PC, et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. *Blood*. 2000; 95(12):3653-3661.
- Wieser I, Oh CW, Talpur R, Duvic M. Lymphomatoid papulosis: treatment response and associated lymphomas in a study of 180 patients. *J Am Acad Dermatol*. 2016;74(1):59-67.
- Cordel N, Tressières B, D'Incan M, et al; French Study Group on Cutaneous Lymphoma. Frequency and risk factors for associated lymphomas in patients with lymphomatoid papulosis. *Oncologist*. 2016;21(1):76-83.
- Booken N, Goerdts S, Klemke CD. Clinical spectrum of primary cutaneous CD30-positive anaplastic large cell lymphoma: an analysis of the Mannheim Cutaneous Lymphoma Registry. *J Dtsch Dermatol Ges*. 2012;10(5):331-339.
- Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. *J Am Acad Dermatol*. 2003;49(6):1049-1058.
- Hapgood G, Pickles T, Sehn LH, et al. Outcome of primary cutaneous anaplastic large cell lymphoma: a 20-year British Columbia Cancer Agency experience. *Br J Haematol*. 2017;176(2):234-240.
- Shinohara MM, Shustov A. How I treat primary cutaneous CD30+ lymphoproliferative disorders. *Blood*. 2019;134(6):515-524.
- Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M, Committee EG; ESMO Guidelines Committee. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4):iv30-iv40.
- Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Blood*. 2011;118(15):4024-4035.
- Kim YH, Willemze R, Pimpinelli N, et al; ISCL and the EORTC. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood*. 2007;110(2):479-484.
- Savage KJ, Harris NL, Vose JM, et al; International Peripheral T-Cell Lymphoma Project. ALK- anaplastic large-cell lymphoma is clinically and

- immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood*. 2008;111(12):5496-5504.
14. Gleeson M, Peckitt C, Cunningham D, et al. Outcomes following front-line chemotherapy in peripheral T-cell lymphoma: 10-year experience at The Royal Marsden and The Christie Hospital. *Leuk Lymphoma*. 2018;59(7):1586-1595.
 15. Wang X, Wu J, Zhang M. Advances in the treatment and prognosis of anaplastic lymphoma kinase negative anaplastic large cell lymphoma. *Hematology*. 2019;24(1):440-445.
 16. Donato EM, Fernández-Zaroso M, Hueso JA, de la Rubia J. Brentuximab vedotin in Hodgkin lymphoma and anaplastic large-cell lymphoma: an evidence-based review. *OncoTargets Ther*. 2018;11:4583-4590.
 17. Horwitz S, O'Connor OA, Pro B, et al; ECHELON-2 Study Group. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet*. 2019;393(10168):229-240.
 18. Richardson NC, Kasamon YL, Chen H, et al. FDA approval summary: brentuximab vedotin in first-line treatment of peripheral T-cell lymphoma. *Oncologist*. 2019;24(5):e180-e187.
 19. Garcia S, Loschi M, De Masson A, et al. Brentuximab vedotin as a bridge to allogeneic stem-cell transplantation for refractory or relapsing patients with CD30 positive anaplastic or T-cell non-Hodgkin lymphomas: a study on behalf of the SFGM-TC. *Leuk Lymphoma*. 2019;60(11):2802-2805.
 20. Pro B, Advani R, Brice P, et al. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. *Blood*. 2017;130(25):2709-2717.
 21. Fanale MA, Horwitz SM, Forero-Torres A, et al. Five-year outcomes for frontline brentuximab vedotin with CHP for CD30-expressing peripheral T-cell lymphomas. *Blood*. 2018;131(19):2120-2124.
 22. Horwitz S, Ansell S, Ai WZ, et al. NCCN Guidelines: T-cell lymphomas, version 2.2019. *J Natl Compr Canc Netw*. 2018;
 23. Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a Phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. *J Clin Oncol*. 2015;33(32):3759-3765.
 24. Lewis DJ, Talpur R, Huen AO, Tetzlaff MT, Duvic M. Brentuximab vedotin for patients with refractory lymphomatoid papulosis: an analysis of Phase 2 results. *JAMA Dermatol*. 2017;153(12):1302-1306.
 25. Prince HM, Kim YH, Horwitz SM, et al; ALCANZA study group. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet*. 2017;390(10094):555-566.
- DOI 10.1182/blood.2019002799
© 2020 by The American Society of Hematology

TO THE EDITOR:

Multiple *BCL2* mutations cooccurring with Gly101Val emerge in chronic lymphocytic leukemia progression on venetoclax

Piers Blombery,^{1,3} Ella R. Thompson,^{1,3} Tamia Nguyen,¹ Richard W. Birkinshaw,^{3,4} Jia-nan Gong,^{3,4} Xiangting Chen,¹ Michelle McBean,¹ Rachel Thijssen,^{3,4} Thomas Conway,¹ Mary Ann Anderson,^{2,4} John F. Seymour,^{2,3} David A. Westerman,^{1,3} Peter E. Czabotar,^{3,4} David C. S. Huang,^{3,4} and Andrew W. Roberts^{2,4}

¹Department of Pathology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; ²Clinical Haematology, The Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Parkville, VIC, Australia; ³University of Melbourne, Melbourne, VIC, Australia; and ⁴The Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia

Venetoclax is an oral, highly selective *BCL2* inhibitor approved as monotherapy or in combination with rituximab or obinutuzumab in chronic lymphocytic leukemia (CLL).¹⁻⁴ Despite complete response rates of up to 50%,^{1,4,5} secondary resistance is the most frequent cause of treatment failure.⁶ Resistance mechanisms that have been observed to date in CLL patients treated with venetoclax include (1) early outgrowth of clones with complex karyotype, mutations in *BTG1*, and aberrations of *CDKN2A/B*^{7,8}; (2) the acquisition of a *BCL2* mutation (Gly101Val) that reduces venetoclax binding to *BCL2*^{9,10}; and (3) overexpression of other pro-survival proteins *BCL-XL* and *MCL1*.^{9,11} An important observation in all of these scenarios is the subclonality of the mutation-bearing cells within the resistant CLL tumor compartment.^{9,11} Indeed, the proportion of both the *BCL2* Gly101Val resistance mutation and *MCL1*-overexpressing CLL cells have been reported to vary widely from a minor subclone through to the majority of the tumor compartment.^{9,11} Moreover, different venetoclax resistance mechanisms (including *BCL-XL* overexpression and *BCL2* Gly101Val mutations) have been observed in independent CLL subpopulations within the same patient.⁹ Given the observed subclonality of the *BCL2* Gly101Val mutation in patients to date

and therefore the possibility of additional resistance mechanisms occurring specifically in this subgroup (including a recently described candidate *BCL2* resistance mutation Asp103Tyr¹⁰), we investigated patients with progressive CLL on venetoclax harboring subclonal *BCL2* Gly101Val mutations for the presence of additional acquired *BCL2* resistance mutations to further explain the clinical resistance of the disease in these patients.

Eleven patients with progressive CLL with *BCL2* Gly101Val mutations were identified by sensitive allele-specific droplet digital polymerase chain reaction (ddPCR)⁹ from among a cohort of 67 patients with heavily pretreated relapsed CLL treated with venetoclax on 3 early-phase clinical trials at our institutions.⁸ Seven of these patients were described in the original report of *BCL2* Gly101Val mutations⁹; 4 patients had newly detected Gly101Val mutations in disease progression samples subsequently (supplemental Material, available on the *Blood* Web site). Using sample tumor burden assessed by flow cytometry and variant allele frequency (VAF) quantitation determined by ddPCR, the proportion of the CLL tumor compartment harboring *BCL2*