BCR kinase inhibitors, idelalisib and ibrutinib, are active and effective in Richter syndrome

Richter syndrome (RS) is the transformation of chronic lymphocytic leukaemia (CLL) into an aggressive lymphoma, most commonly diffuse large B cell lymphoma (DLBCL) (Visentin *et al*, 2015, 2017; Mauro *et al*, 2017). Anthracycline- or platinum-based regimes provide complete response (CR) rates of 20–30% in patients with a median survival of 8 months; there are currently no standard salvage approaches for RS (Vitale & Ferrajoli 2016: see Appendix S1). Lenalidomide and B-cell receptor kinase inhibitors (BCRi) have shown remarkable efficacy in non-Hodgkin lymphoma (NHL) and CLL, inducing long-term disease control, durable remissions in heavily treated patients (Buhler *et al*, 2016; Brown *et al*, 2017). Although a few studies investigated the activity of lenalidomide (Czuczman *et al*, 2011) and ibrutinib (Ayers & Mato, 2017) in patients with RS, none have reported the effect of idelalisib.

In this retrospective study, we report on 11 subjects with the DLBCL variant of RS who received 13 different treatments, including lenalidomide (5 patients), ibrutinib (4 patients) and idelalisib (4 patients). Although a longer follow-up is needed, we provide evidence that BCRi, but not lenalidomide, are active and feasible drugs in RS, with an estimated 6-month time to progression (TTP) of 87%, thus opening a new perspective for the management of RS.

Clinical data from 860 patients with CLL referred to the Padua hospital from 1983 to June 2017 were reviewed to identify the occurrence of RS, according to 2008 International Workshop on CLL definition (Hallek *et al*, 2008). This study was approved by ethical committee and was performed in accordance with the Declaration of Helsinki. *IGHV* gene mutational status, cytogenetic and molecular analysis are described in Appendix S1. From December 2015 ibrutinib was prescribed for RS at 420 mg/day (Brown *et al*, 2017) and idelalisib at 150 mg twice daily plus rituximab according to the protocol reported by Furman *et al* (2014). Previously, relapsed RS were managed with lenalidomide 25 mg/day (Czuczman *et al*, 2011).

Computed tomography (CT) and fludeoxyglucose positron emission tomography (FDG PET)/CT scan were performed at screening and after 3, 6 and 12 months of treatment or as needed according to clinical assessment. Responses were assessed according to the 2014 Lugano criteria. The primary endpoint of this study was the 6-month TTP, while secondary endpoints were median overall survival (OS) and overall response rate (ORR). Details on statistical analyses are reported in Appendix S1.

Among the DLBCL-RS followed at Padua University Hospital, 5 received lenalidomide and 8 were treated with BCRi after primary treatment failure. Patient 1 first received lenalidomide at disease progression, then ibrutinib and subsequently idelalisib-rituximab.

Clinical and biological data of our subjects are summarized in Table I, but no significant differences were found. None was classified at low-risk and 7 subjects (54%) harboured *TP53* abnormalities (Table I). All patients received induction chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) and, if suitable, a platinum-based regimen; 8 patients progressed during the last treatment.

The ORRs were 0% and 62.5% (1 CR, 4 partial responses [PR]) for lenalidomide and BCRi, respectively. All patients progressed during lenalidomide, none progressed with idelalisib, and 2 patients treated with ibrutinib progressed after 0.37 (Patient 4) and 13 (Patient 1) months (Fig 1A). Patient 8 developed RS during ibrutinib treatment. He was chemorefractory to both R-CHOP and R-DHAP (rituximab, dexamethasone, high dose cytarabine, cisplatin), but achieved a CR with idelalisib-rituximab, and underwent allogeneic stem cell transplantation (Fig 1A). Representative FDG PET/CT scans performed before and after 6 months of treatment are shown in Figure S1A–C.

After a median follow-up of 6 months from treatment initiation, the median TTP for the patients treated with lenalidomide and BCRi was 2.6 and 13.7 months, and the estimated 6-month TTP was 20% and 87%, respectively (Log-rank test $P = 0.0287$, Fig 1B). Seven patients died during follow-up, 5 of disease progression (4 in lenalidomide and 1 in ibrutinib), 1 of sudden death (probably a fatal cardiac event) in PR, and 1 of pneumonia. The median OS for lenalidomide was 2.6 months while it was not reached with BCRi; the estimated 6-month OS was 20% and 60%, respectively (Log-rank test $P = 0.0426$, Fig 1C). TTP and OS did not differ significantly between ibrutinib and idelalisib (Figure S2). Therapies were well tolerated. We recorded 19 adverse events with lenalidomide, 16 with ibrutinib and 8 with idelalisib (Appendix S1).

RS is characterized by rapid disease progression, limited therapeutic options, particularly after first-line treatment failure, and poor survival. For these reasons some groups are

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Table I. Clinical and biological characteristics of patients.

Variables	All RS patients	Lenalidomide	Ibrutinib	Idelalisib	*P* values
Number of patients	11 (13)*	5	4	4	–
Medium age (years)	65 ± 12	60 ± 14	69 ± 11	68 ± 10	1.0000
Gender (Male/Female)	6/7	2/3	1/3	3/1	0.4857
Time to RS (months)	68.2 ± 44.9	96.1 ± 60.3	47.3 ± 43.6	61.2 ± 30.5	0.3101
Time to new drugs (months)	11.1 ± 8.5	7.2 ± 4.8	12.2 ± 10.1	13.83 ± 10.5	0.9811
Non-GC type†	8 (62%)	3 (60%)	2 (50%)	3 (75%)	0.7648
Median FDG SUV_{max}	13.4 ± 6.2	15.1 ± 6.7	11 ± 4.1	14.4 ± 8.2	0.5782
Largest node (cm)	8.1 ± 4.4	8.3 ± 5.0	8.3 ± 2.6	8.1 ± 6.6	0.6324
Previous therapies (*n*)	2.1 ± 1.3	1.8 ± 0.8	2.0 ± 1.6	2.5 ± 1.7	0.8611
Cycles of platinum-based therapy and/or R-CHOP (*n*)	4 ± 2	4 ± 2	3 ± 3	4 ± 2	0.9598
Response to last treatment					
Disease progression	8 (62%)	3 (60%)	3 (75%)	2 (50%)	0.8133
Stable disease	4 (31%)	2 (40%)	1 (25%)	1 (25%)	
B symptoms	7 (54%)	2 (40%)	3 (75%)	2 (50%)	0.7650
Rossi score					
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.5684
Intermediate	7 (54%)	2 (40%)	2 (50%)	3 (75%)	
High	6 (46%)	3 (60%)	2 (50%)	1 (25%)	
Tsimberidou score					
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.3945
Low-intermediate	2 (15%)	0 (0%)	1 (25%)	1 (25%)	
High-intermediate	7 (54%)	3 (60%)	1 (25%)	3 (75%)	
High	4 (31%)	2 (40%)	2 (50%)	0 (0%)	
TP53 abnormalities‡	6 (46%)	2 (50%)	1 (25%)	3 (75%)	0.5662
NOTCH1 mutation	5 (39%)	2 (40%)	1 (25%)	2 (50%)	0.6376
U-*IGHV*	7 (54%)	2 (40%)	3 (75%)	2 (50%)	0.5684
IGHV4-39	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0000
Clonall related	8 (62%)	3 (60%)	2 (50%)	3 (75%)	0.7648
Treatment duration (months)	5.2 ± 4.3	4.2 ± 4.6	6.4 ± 6.9	5.1 ± 2.3	0.8192
Best response					
Complete response	1 (8%)	0 (0%)	0 (0%)	1 (25%)	0.4481
Partial response	3 (23%)	0 (0%)	1 (25%)	2 (50%)	
Stable disease	5 (39%)	2 (40%)	2 (50%)	1 (25%)	

FDG SUV_{max}, fludeoxyglucose maximum standardized uptake value; GC, germinal centre; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RS, Richter syndrome; U-*IGHV*, unmutated *IGHV* gene.

*11 patients received 13 treatment courses. In particular, Patient 1 received lenalidomide first, then ibrutinib and, at disease progression, idelalisib.

†Non-GC subtype was determined by Hans' algorithm.

‡*TP53* abnormalities include deletion and/or mutation.

investigating new monoclonal antibodies (ublituximab and pemprolizumab) and small molecule inhibitors (selinexor, acalabrutinib and TGR-1202) in the treatment of RS (Ayers & Mato, 2017).

Lenalidomide and BCRi have shown remarkable efficacy in NHL and CLL but only a few reports described their efficacy in RS. Lenalidomide has been evaluated in 11 RS patients; the ORR was 0% and grades 3–4 neutropenia was observed in 48% and pneumonia in 3% of patients (Czuczman *et al*, 2011). Winter *et al* (2017: see Appendix S1) reported a study of 13 ibrutinib-treated RS patients; the ORR was 46% and 1 patient achieved CR and the median TTP and OS was 3.0 and 7.2 months, respectively. Jaglowski *et al* (2015) described their experience with ibrutinib combined with ofatumumab in patients with CLL and RS; of the 3 RS patients, one achieved PR and the other 2 stabilized their disease.

Idelalisib, the first in the class of phosphatidylinositol 3-kinase (PI3K) inhibitors, has never been tested in RS. However, ibrutinib resistance is mediated by a dynamic feedback between neoplastic cells and the tumour microenvironment leading to PI3K/AKT activation. Moreover, *in vitro* inhibition of PI3K has been shown to reverse ibrutinib-resistance and enhance anti-lymphoma activity (Zhao, *et al* 2017: see Appendix S1). These data might explain the activity of idelalisib in 2 (Patients 1, 5) of our ibrutinib-resistant patients and support the investigation of PI3K inhibitors in this setting.

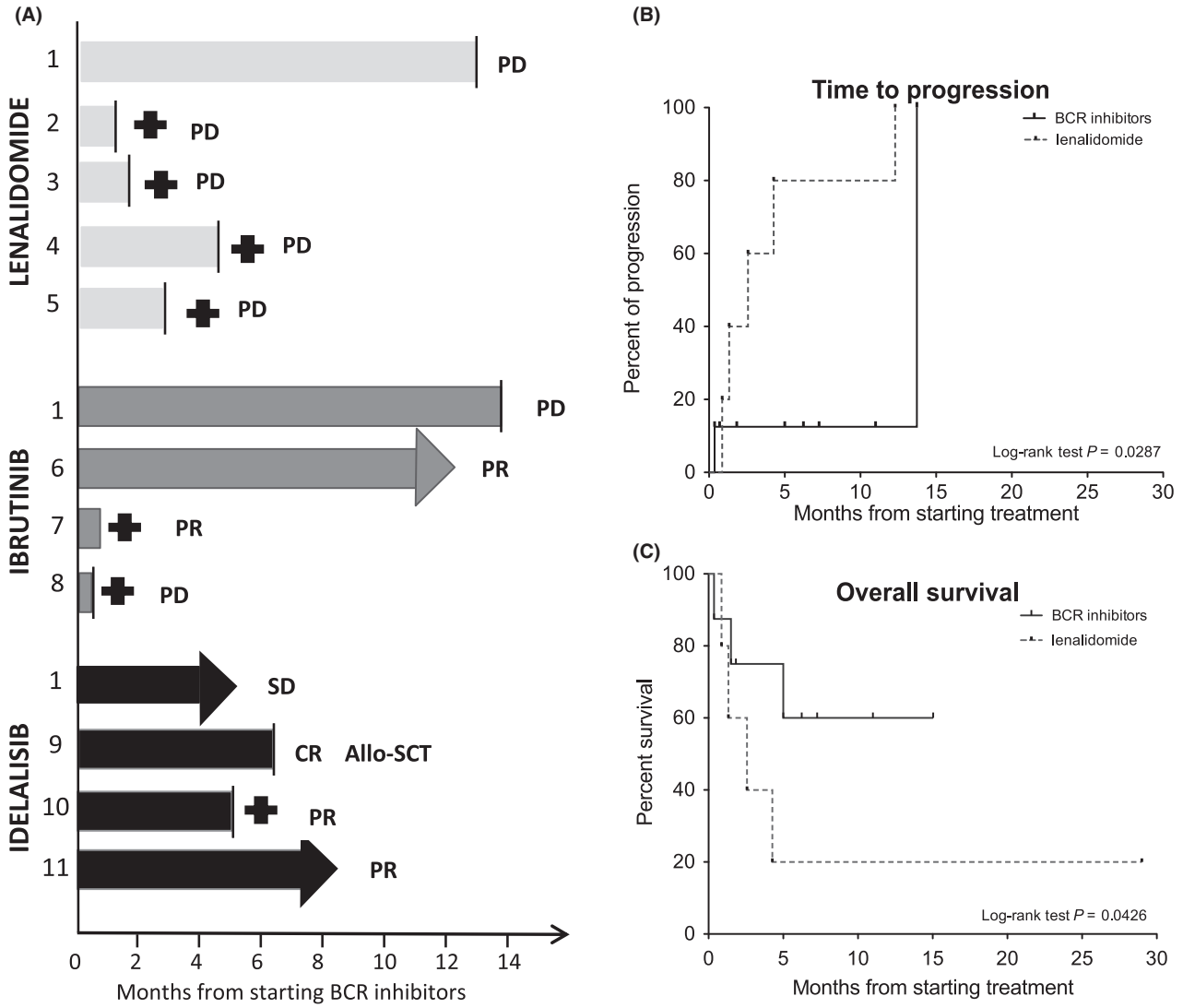

Fig 1. Swimmer and survival plots. (A) Swimming pool plot of patients treated with lendalidomide (top), ibrutinib (middle) and idelalisib (bottom). Head-arrow indicates that the patient is still receiving the drug, | that treatment was stopped and + that the patient has died. (B) Time to progression and (C) overall survival plots. The BCR kinase inhibitors, ibrutinib and idelalisib, produced a significantly delayed progression ($P = 0.0287$) and longer survival ($P = 0.0426$) when compared to lenalidomide. Allo-SCT, allogeneic stem cell transplantation; BCR, B-cell receptor; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

This study provides encouraging evidence that the BCR pathway inhibitors, idelalisib and ibrutinib, are feasible, effective and well-tolerated salvage drugs in RS. In particular, idelalisib has been shown to be an active drug for RS that developed during ibrutinib treatment. Although a longer follow-up is needed, our data indicate that BCR pathway inhibitors may be active in some patients with Richter transformation.

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Authorship contributions

AV designed the study, performed statistical analysis, evaluated the patients and wrote the article; SI, ES, SP, FP provided intellectual input and evaluated the patients; FF performed biological assays and provided intellectual input; MP performed histological assays; LB and MF performed cytogenetic and molecular analyses; SV performed CT scans; MG and MB performed FDG PET-CT scans; FP, GS and LT

evaluated the patients, provided intellectual input and reviewed the article.

Disclosure of conflicts of interest

LT received research founding by Janssen and Gilead. All of the other authors have nothing to disclose.

Andrea Visentin[1,2]
Silvia Imbergamo[1]
Edoardo Scomazzon[1]
Stefano Pravato[1]
Federica Frezzato[1,2]
Laura Bonaldi[3]
Marco Pizzi[4]
Stefania Vio[5]
Michele Gregianin[6]
Marta Burei[7]
Monica Facco[1,2]
Gianpietro Semenzato[1,2]
Francesco Piazza[1,2]
Livio Trentin[1,2]

[1]Haematology and Clinical Immunology Unit, Department of Medicine, University of Padua, [2]Venetian Institute of Molecular Medicine, Centro di Eccellenza per la Ricerca Biomedica Avanzata, [3]Immunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV-IRCSS, [4]General Pathology & Cytopathology Unit, Department of Medicine, University of Padua, [5]Radiology Unit, University Hospital of Padua, Padua, [6]Nuclear Medicine unit, San Giacomo Hospital, Castelfranco Veneto, and [7]Nuclear Medicine unit, Veneto Institute of Oncology IOV-IRCSS, Padua, Italy.
E-mail: livio.trentin@unipd.it

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Representative FDG-PET-CT scans of patients treated with different drugs.

Fig S2. Progression free survival and overall survival curves of patients treated with ibrutinib or idelalisib-rituximab.

Appendix S1. Supplementary methods, results, and references.

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