Venetoclax in CLL patients who progress after B-cell Receptor inhibitor treatment: a retrospective multi-centre Italian experience

The B-cell receptor signalling inhibitors (BCRi) ibrutinib and idelalisib have changed the treatment paradigm for chronic lymphocytic leukaemia (CLL) patients (Furman *et al*, 2014). These drugs induce high rates of durable responses both in previously untreated and relapsed/refractory patients and are increasingly being used in routine clinical practice. However, a substantial proportion of patients discontinue treatment because of progressive disease (PD) or development of adverse events (AE) (Mato *et al*, 2018). For these patients, available treatment options include switching to another BCRi or treatment with the BCL2 inhibitor, venetoclax (Jones *et al*, 2018; Coutre *et al*, 2018).

To date, the optimal sequence and timing for these two options has not been established. A recent post-hoc subgroup analysis of patients from a phase 2 study of venetoclax following ibrutinib and/or idelalisib treatment reported a lower overall response rate (ORR) and a shorter progression-free survival (PFS) in those patients that had received two compared to one prior BCRi treatment (Wierda *et al*, 2019). In contrast, no difference in ORR or PFS was observed after venetoclax treatment between patients exposed to one or two prior BCRi treatments in another study (Eyre *et al*, 2019), but a difference was seen between patients that had discontinued treatment because of PD *versus* those that had discontinued treatment because of toxicity or another reason.

To further investigate how venetoclax responses are affected by prior BCRi treatment, we conducted a multi-centre retrospective analysis of 76 patients treated at 18 Italian centres. Patients who received at least one dose of venetoclax were included in the analysis. Differences in PFS and overall survival (OS), defined as time elapsed from the start of venetoclax to progression or death, respectively, were analysed using the Kaplan-Meier product limit estimator and the log-rank test. Patients were treated with ibrutinib, idelalisib or venetoclax according to their European Medicines Agency labels.

Of the 76 evaluable patients, 52 had received venetoclax after one BCRi (ibrutinib $n = 37$, idelalisib $n = 15$) and 24 after two BCRi treatments (ibrutinib followed by idelalisib $n = 16$, idelalisib followed by ibrutinib $n = 8$). Both groups of patients had received a median of 4 lines of therapy before initiating venetoclax. The median duration of the first BCRi treatment was 14·5 months (range 1–59) in patients who received only one BCRi and 16 months (range 1–46) in patients who received two BCRi treatments. The median duration of the second BCRi treatment was 7·5 months (range 1–39). The reason for discontinuation was PD in 26 patients from the single BCRi group and 18 from the two BCRi group, whereas an AE was the cause of treatment discontinuation in 14 patients that received a single BCRi and 5 patients that received both drugs. Data regarding the remaining 13 patients were not available.

Comparison of venetoclax treatment outcome between patients that had received one or two prior BCRi treatments showed a higher ORR and complete response (CR) rate in the former group of patients (74% ORR and 23% CR vs. 50% ORR and 5% CR, respectively), but these differences were not significant. However, significant differences between the two groups were observed at 12 months with respect the estimated PFS (78% vs. 35%, $P = 0·011$) and estimated OS (88% vs. 57%, $P = 0·015$), which were both higher in patients that had received only one BCRi treatment (Fig 1A, B).

Comparison of venetoclax treatment outcome according to cause of BCRi discontinuation showed a significantly higher ORR in patients who discontinued BCRi because of an AE compared to patients who discontinued BCRi because of PD (91% vs. 49%, respectively, $P = 0·03$). Moreover, the estimated PFS and OS at 12 months were also significantly higher in patients who discontinued BCRi due to AE compared to PD (PFS 84% vs. 45%, $P = 0·003$; OS 93% vs. 62%, $P = 0·028$) (Fig 1C, D). Importantly, these differences were also observed in subgroup analysis of patients that had received one or two BCRi treatments, although they lost statistical significance because of the smaller number of patients (Fig 1E, F).

Overall, our data are similar to the findings of the studies by Wierda *et al* (2019) and Eyre *et al* (2019), although certain differences exist (Table I). In particular, the ORR was lower in our study compared to that reported by Eyre *et al* (2019) (74% and 50% vs. 85% and 80% in patients that received one or two BCRi treatments, respectively), which could possibly be due to the higher percentage of patients that had discontinued BCRi treatment because of PD in our study (70% vs. 54%, respectively). A higher frequency of PD as a cause for BCRi discontinuation could also explain the lower estimated 12-month PFS and OS in our patients that had received two BCRi treatments compared to those patients with two BCRi treatments reported by Eyre *et al*

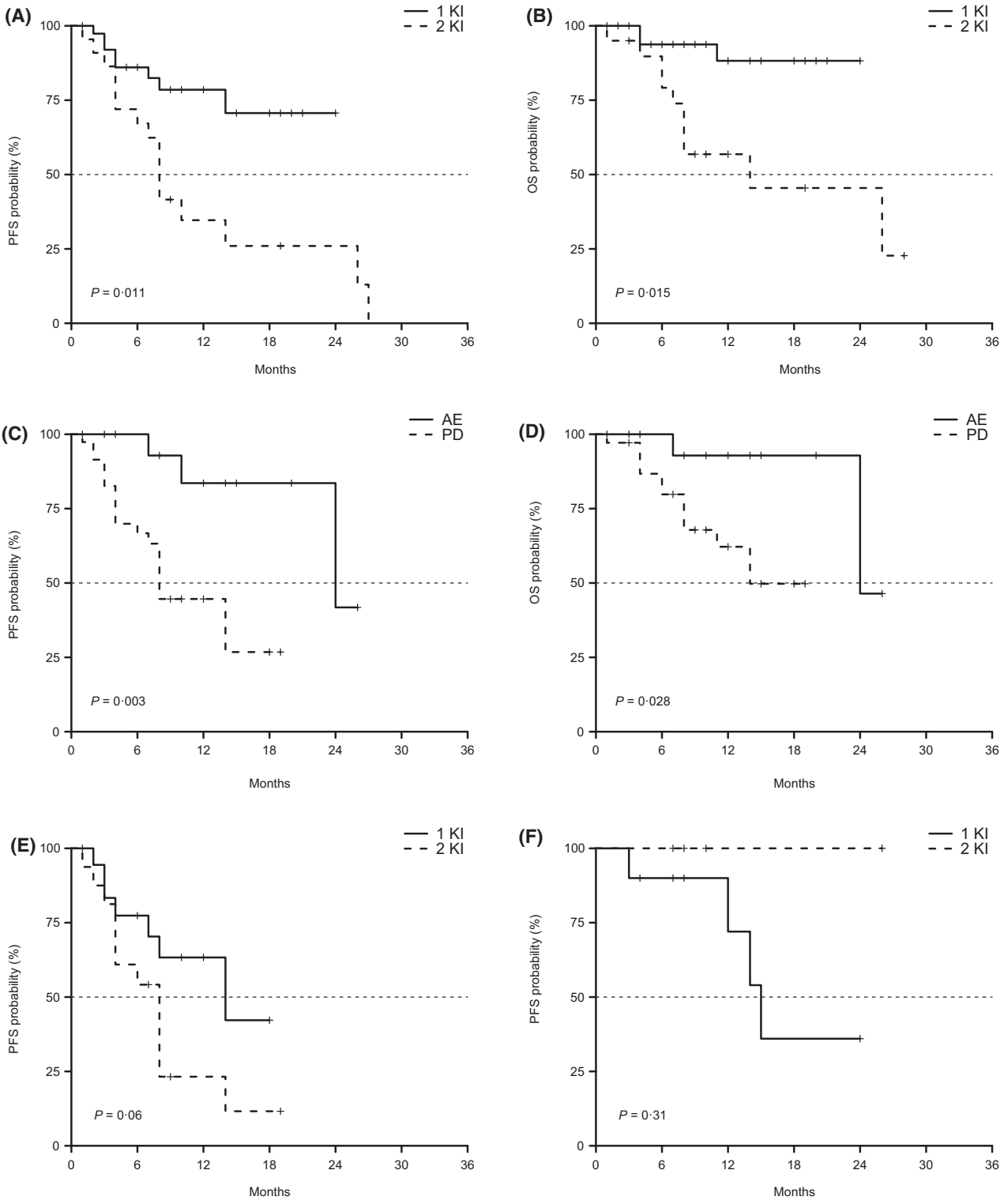

Fig 1. Kaplan-Meier survival curves for patients stratified according to number of prior BCRi treatments or reason for discontinuation of BCRi treatment. (A) PFS in patients that received 1 *versus* 2 BCRi treatments. (B) OS in patients that received 1 *versus* 2 BCRi treatments. (C) PFS according to reason for discontinuation of BCRi treatment. (D) OS according to reason for discontinuation of BCRi treatment. (E) Subgroup analysis of PFS in patients that discontinued BCRi treatment because of PD. (F) Subgroup analysis of PFS in patients that discontinued BCRi treatment because of AE. 1 KI, patients that received 1 prior BCRi treatment; 2 KI, patients that received 2 prior BCRi treatments; AE, adverse events; BCRi, B-cell receptor inhibitor; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

Table I. Outcomes with venetoclax.

	Current study	Wierda *et al* (2019)	Eyre *et al* (2019)
Patients, *n*	76	127	105
Venetoclax response			
ORR after			
1 BCRi	74%	75%	88%
More than 1 BCRi	50%	43%	80%
PFS after			
1 BCRi	78%	82%	65%
More than 1 BCRi	35%	58%	61%
OS after			
1 BCRi	88%	93%	75%
More than 1 BCRi	57%	89%	70%
ORR after BCRi discontinued for			
AE	91%	50%	92%
PD	49%	38%	84%
PFS after BCRi discontinued for			
AE	84%	na	na
PD	45%	na	na
OS after BCRi discontinued for			
AE	93%	na	na
PD	62%	na	na

AE, adverse events; BCRi, B-cell receptor inhibitor; na, not available; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival.

(2019). Despite these differences, both our study and that of Eyre *et al* (2019) observed that patients that discontinued BCRi treatment because of an AE had a significantly higher ORR and longer PFS and OS compared to patients that discontinued BCRi treatment because of PD. The study of Wierda *et al* (2019) also reported a better ORR on venetoclax in patients that discontinued BCRi treatment because of an AE, but did not report an effect on PFS and OS. However, consistent with our data, that study reported a significantly longer PFS and OS in patients that received venetoclax after one compared to two prior BCRi treatments (Table I). Collectively, these findings suggest that both the cause of BCRi discontinuation and the number of prior BCRi treatments can influence the response to venetoclax. Given the particularly short 12-month PFS in patients that received venetoclax because of progression after two BCRi treatments, our data suggest that venetoclax should be administered to all patients that discontinue the first BCRi treatment because of PD, whereas an alternate BCRi should be considered only in patients that discontinue BCRi for an AE.

Author contributions

Conception and design of the study: II, FM, LL. Collection and assembly of data: II, FM, LL. Data collection: FM, AF, FRM, LS, LT, GDP, GR, GMR, AI, SC, MC, PS, RB, LL, MG, GDA, AT, LS, AC, RF all were involved in collection of data. Data analysis and interpretation: FA and AP performed the statistical analysis. Manuscript writing: DE and LL wrote the manuscript, which all authors critically reviewed. Final approval of manuscript: All authors were involved in research design, or the acquisition, analysis or interpretation of data, critically revising the manuscript and the final approval.

Idanna Innocenti[1,*]
Francesca Morelli[2,*]
Francesco Autore[1]
Alfonso Piciocchi[3]
Annamaria Frustaci[4]
Francesca R. Mauro[5]
Luana Schiattone[6]
Livio Trentin[7]
Giovanni Del Poeta[8]
Gianluigi Reda[9]
Gian M. Rigolin[10]
Adalberto Ibatici[11]
Stefania Ciolli[12]
Marta Coscia[13]
Paolo Sportoletti[14]
Roberta Murru[15]
Luciano Levato[16]
Massimo Gentile[17]
Giovanni D'Arena[18]
Dimitar G. Efremov[19]
Alessandra Tedeschi[4]
Lydia Scarfò[6]
Antonio Cuneo[10]
Robin Foà[5]
Luca Laurenti [1,2]

[1]Institute of Haematology, Fondazione Policlinico Universitario A. Gemelli IRCCS, [2]Institute of Haematology, Università Cattolica del Sacro Cuore, [3]Italian Group for Adult Haematological Diseases (GIMEMA), Data Centre, Roma, [4]Haematology, Niguarda Cancer Centre, ASST Grande Ospedale Metropolitano Niguarda, Milano, [5]Haematology, Department of Translational and Precision Medicine, Sapienza University, Roma, [6]Division of Experimental Oncology, IRCCS Istituto Scientifico San Raffaele and Università Vita-Salute San Raffaele, Milano, [7]Haematology and Clinical Immunology, Department of Medicine, Padova, [8]Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Roma, [9]IRCCS Ca' Granda - Università degli Studi, Milano, [10]Haematology section - University of Ferrara, Ferrara, [11]Division of Haematology and Bone Marrow Transplant, IRCCS San Martino-IST, Genova, [12]Haematology Unit, Careggi Hospital, Firenze, [13]Division of Haematology, A.O.U. Città della Salute e della Scienza di Torino and Department of Molecular Biotechnology and Health Sciences, University of Torino, Turin, [14]Haematology and Clinical Immunology, University of Perugia, Perugia, [15]Haematology and Stem Cell Transplantation Unit, Ospedale Oncologico A. Businco, AO Brotzu, Cagliari, [16]Haematology Unit, A. Pugliese Hospital, Azienda Ospedaliera Pugliese Ciaccio, Catanzaro, [17]Haematology Section, Cosenza Hospital, Cosenza, [18]Haematology and Stem cell Transplantation Unit, IRCCSCROB, Referral Cancer Center of Basilicata, Rionero in Vulture and [19]Molecular Haematology, International Centre for Genetic Engineering and Biotechnology, Trieste, Italy.
E-mail: luca.laurenti@unicatt.it

*These authors have contributed equally to the work.

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A novel dimeric CXCR4 antagonist synergizes with chemotherapy in acute myeloid leukaemia by mobilizing leukaemic cells from their associated bone marrow niches

Acute myeloid leukaemia (AML) is a haematological malignancy characterized by the uncontrolled proliferation of haematopoietic stem/progenitor cells. The effectiveness of chemotherapy in the treatment of AML is limited by drug resistance and relapse because the bone marrow microenvironment protects AML cells against chemotherapeutic drugs (Meads *et al*, 2008). The bone marrow stromal cells (BMSCs) secrete SDF-1α (also termed CXCL12), which can activate C-X-C chemokine receptor type 4 (CXCR4) on the surface of AML cells to facilitate the trafficking and retention of AML cells in the bone marrow and promote their growth and anti-apoptotic responses (Burger & Burkle, 2007). Drugs targeting the CXCR4/SDF-1α axis can interrupt the interaction between AML cells and the bone marrow microenvironment. HC4319 is a novel dimeric ligand with high affinity for CXCR4 that was developed by our laboratories to prevent