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## All in the family: back-to-back kinase inhibitors for the treatment of chronic lymphocytic leukemia

Meghan C. Thompson, Lindsey E. Roeker and Anthony R. Mato

Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

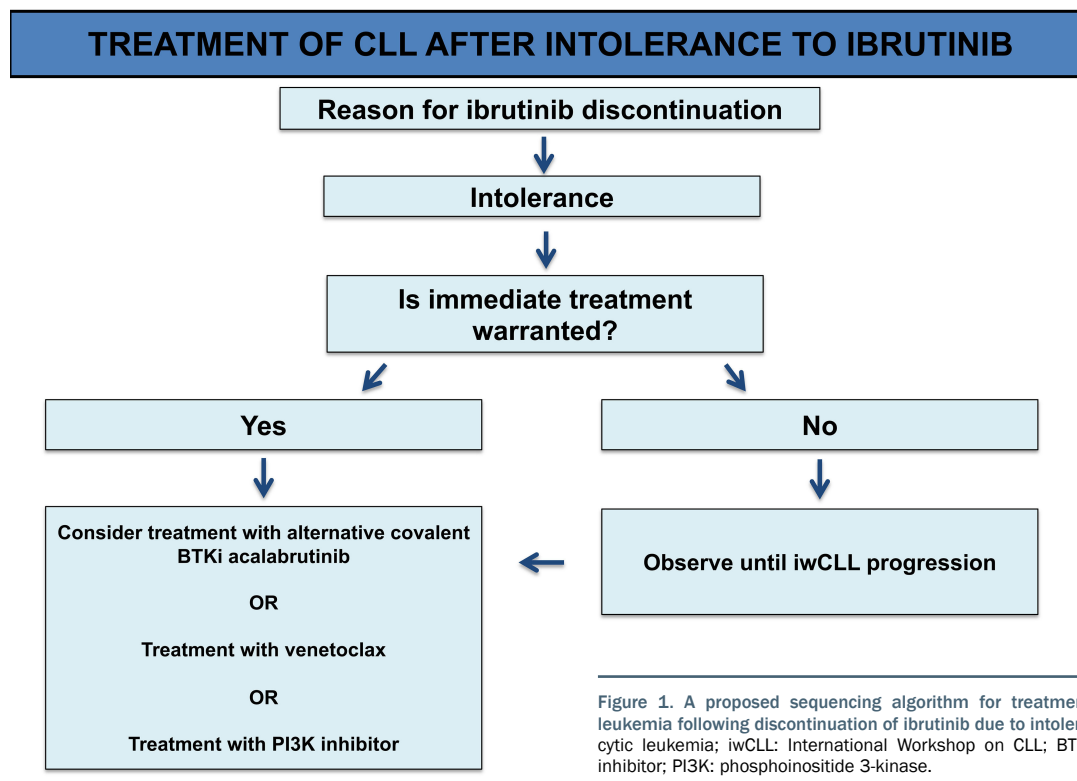
E-mail: ANTHONY R. MATO - [matoa@mskcc.org](mailto:matoa@mskcc.org)

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In this issue of *Haematologica*, Rogers *et al.* address a key sequencing question in the management of chronic lymphocytic leukemia (CLL) by reporting the results of the largest prospective clinical trial evaluating acalabrutinib for the treatment of CLL following intolerance to ibrutinib.<sup>1</sup> While the Bruton tyrosine kinase (BTK) inhibitor ibrutinib has led to a paradigmatic shift in the treatment of CLL away from chemoimmunotherapy, high rates of ibrutinib discontinuation remain a major problem.

Real-world evidence and long-term follow-up from clinical trials of ibrutinib have established that drug intolerance due to toxicity, rather than progressive CLL, is the most common reason for discontinuation of ibrutinib treatment.<sup>2,4</sup> Real-world data from 616 CLL patients treated with ibrutinib in clinical practice documented that 41% of patients discontinued ibrutinib (median follow-

up 17 months), and more than half of all discontinuations were due to toxicity.<sup>2</sup> Real-world evidence from the UK documents high rates of ibrutinib discontinuation due to reasons other than disease progression (17.5%).<sup>3</sup> Furthermore, similar patterns have emerged with longer follow-up data from clinical trials, with more patients discontinuing ibrutinib due to toxicity than because of CLL progression. At 5 years of follow-up of the RESONATE-2 trial of ibrutinib for initial treatment of CLL, 41% of patients had discontinued ibrutinib therapy, with a 21% discontinuation rate due to adverse events including atrial fibrillation.<sup>4</sup> Furthermore, in a pooled analysis of CLL patients treated with ibrutinib on three randomized phase III studies, 11% of patients permanently discontinued ibrutinib due to adverse events and 13% of patients required dose reductions due to adverse events, highlighting the significant impact of adverse events while on



treatment with ibrutinib.<sup>5</sup> These studies clearly established that intolerance to ibrutinib is a common scenario encountered in clinical practice, which may limit the clinical benefit of this drug that has been largely studied as a continuous therapy.

Given the clinical efficacy of BTK inhibition in CLL, for patients who discontinue a BTK inhibitor due to intolerance, an important question is whether treatment with an alternative kinase inhibitor is an acceptable treatment option. This is particularly relevant given the development of more selective BTK inhibitors with fewer off-target effects. Newer BTK inhibitors include approved therapies such as acalabrutinib, as well as emerging covalent and non-covalent BTK inhibitors in clinical development (zanubrutinib, LOXO-305, ARQ-351).

Previously, Awan *et al.* addressed this key question by conducting a small cohort study of acalabrutinib treatment for patients who discontinued ibrutinib due to intolerance (defined by the investigator's discretion).<sup>6</sup> In this study of 33 patients, the efficacy of acalabrutinib following ibrutinib was high (overall response rate 76%) with only 9% of patients discontinuing acalabrutinib due to an adverse event.<sup>6</sup> However, this study examined only a small number of patients and lacked an objective definition of ibrutinib intolerance.

The study by Rogers *et al.* is the first prospectively designed study to answer this important sequencing question.<sup>1</sup> Intolerance was defined as discontinuation of ibrutinib due to either persistent/recurrent grade 2 adverse events despite dose modification or interruption or persistent grade 3/4 adverse events. Sixty patients with relapsed and/or refractory CLL were treated with acalabrutinib (median number of prior therapies 2) with a

prior median duration of ibrutinib therapy of 5.7 months. Overall, the approach was well-tolerated, with the most common adverse events being diarrhea (53%), headache (42%) and contusion (40%). Only 40% of patients had ibrutinib-related intolerance adverse events, and 67% of events were lower grade with acalabrutinib than with ibrutinib; only one adverse event (increased levels of liver enzymes) occurred at a higher grade with acalabrutinib treatment than with ibrutinib treatment. Notably, more patients discontinued acalabrutinib because of CLL progression (23%) than because of adverse events (17%). Acalabrutinib following discontinuation of ibrutinib for intolerance was efficacious, with an overall response rate of 73% and a 24-month estimated progression-free survival of 72% (median follow-up, 35 months). It should be noted that the majority (94%) of patients with available pre-treatment sequencing data did not have *BTK* or *PLCG2* mutations prior to initiating treatment with acalabrutinib.<sup>1</sup>

In addition to the work presented by Rogers *et al.*, two additional recent studies have also shown that treatment of CLL with an alternative kinase inhibitor following ibrutinib intolerance is safe and efficacious.<sup>7,8</sup> A phase II study examined the phosphoinositide 3-kinase (PI3K) inhibitor umbralisib in 51 patients with relapsed/refractory CLL who were intolerant to prior BTK inhibition (n=44) or PI3K inhibition (n=7) and showed a median progression-free survival of 23.5 months, with the majority (58%) of patients remaining on umbralisib for longer than on their prior kinase inhibitor therapy.<sup>7</sup> Additionally, LOXO-305 (pirtobrutinib), a novel, highly selective, non-covalent BTK inhibitor showed a favorable safety profile in 170 patients with CLL/small lymphocytic leukemia, of

whom 86% had received prior treatment with a BTK inhibitor, with 33% discontinuing the prior BTK inhibitor due to reasons other than progressive CLL.<sup>8</sup> Furthermore, LOXO-305 had promising efficacy in this heavily pre-treated population with an overall response rate of 62% in 121 efficacy-evaluable patients with CLL/small lymphocytic leukemia who had previously been treated with a BTK inhibitor.<sup>8</sup>

Taken together, these studies challenge the traditional sequencing paradigm of switching drug classes in the setting of CLL therapy discontinuation for intolerance. In Figure 1, we propose a sequencing algorithm incorporating the new data from Rogers *et al.* While venetoclax is an acceptable option in the setting of intolerance to BTK inhibitors,<sup>9</sup> CLL remains an incurable, chronic disease and there is a strong scientific rationale for maximizing clinical benefit from each drug class prior to exposing patients to the selective pressures of another therapeutic class. In the case of the common problem of intolerance to ibrutinib it is best to keep the solution “all in the (BTK inhibitor) family.”

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### Contributions

MCT and ARM drafted the manuscript. MCT, LER and ARM provided feedback and edited the manuscript.

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## Do we need more genome wide association studies?

Stephan Menzel

Red Cell Research Unit, King's College London, London, UK

E-mail: STEPHAN MENZEL - [stephan.menzel@kcl.ac.uk](mailto:stephan.menzel@kcl.ac.uk)

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Much of the individual biological traits we have, of what we look like, of our physical and mental abilities, of our risk to suffer from the non-communicable diseases that will ultimately end our lives, is encoded in the genetic ‘background’, consisting of millions of single-nucleotide polymorphisms (SNP) and other common sequence variants that each have minute functional effects on regulatory sequences within our genome.

Genome-wide association studies (GWAS) are the tool of choice to make the connection between common-variant genotype data, collected either through genome sequencing or with genotyping arrays (‘chips’), and human phenotype. In its simplest form, GWAS compare the frequency for each of thousands or millions of

common genetic variants between groups of patients and controls, thus identifying genetic risk factors for the diseases studied this way.

There are limits to what the traditional GWAS approach can achieve. Suffocating type-I error rates arising from the analysis of millions of genetic variants make it necessary to assemble very large groups of patients and controls, but even then, only the strongest genetic risk factors can be identified with meaningful certainty. Even so, finding this initial set of genetic factors has significantly enhanced our understanding of pathways leading to common disease or shaping health-relevant physiological traits. With the majority of disease risk factors still hidden, however, it is presently impossible to assemble enough genetic information to