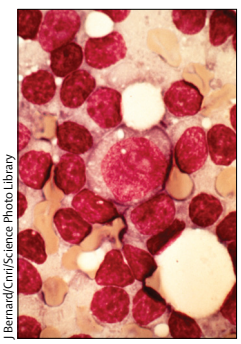
Another treatment option for relapsed or refractory chronic lymphocytic leukaemia



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Most patients with chronic lymphocytic leukaemia relapse after front-line chemoimmunotherapy and a substantial proportion develop adverse genetic abnormalities leading to disease that is refractory to treatment. The introduction of targeted agents, such as the kinase inhibitors ibrutinib and idelalisib and the BCL2 antagonist venetoclax, has substantially improved the outcomes of patients with relapsed or refractory chronic lymphocytic leukaemia.[1–3] These agents induce durable responses in patients with standard as well as high-risk disease features.[4–6]

In *The Lancet Oncology*, Andrew Zelenetz and colleagues[7] report the interim results of a phase 3 randomised controlled trial investigating whether the effectiveness of salvage treatment with the combination of bendamustine and rituximab, a widely used chemoimmunotherapy regimen in patients with relapsed or refractory chronic lymphocytic leukaemia,[8] could be improved by the addition of idelalisib—a first-in-class phosphoinositide-3-kinase δ inhibitor. The primary endpoint of this study was progression-free survival. All patients received up to six cycles of bendamustine plus rituximab and were randomly assigned to receive twice-daily oral idelalisib or matching placebo, administered continuously until disease progression or unacceptable toxicity. The median age of the patients was 63 years, and the median number of previous treatment regimens was two. Most of the 416 enrolled patients (346 [83%]) had unmutated *IGHV* and about a third had either del(17p) or *TP53* mutation.

Patients who received idelalisib in addition to bendamustine plus rituximab had significantly better outcomes compared with those assigned to placebo in terms of the proportion achieving an overall response (70% [145/207] in the idelalisib group *vs* 45% [94/209] in the placebo group), median progression-free survival (20·8 months *vs* 11·1 months), and median overall survival (not reached *vs* 31·6 months). The benefit of idelalisib was consistent across most prespecified high-risk subgroups. Median progression-free survival in patients in the idelalisib group compares favourably to that in patients with relapsed or refractory chronic lymphocytic leukaemia treated with bendamustine plus rituximab in the study by Fischer and colleagues (15·2 months).[8] It should be noted that median progression-free survival in patients with neither del(17p) nor *TP53* mutation who received idelalisib in addition to bendamustine plus rituximab was 24·5 months, whereas it was not reached with ibrutinib combined with bendamustine and rituximab in the HELIOS trial, which excluded patients with del(17p).[9] Additionally, in Zelenetz and colleagues' study, idelalisib was associated with significant clinical activity in patients with either del(17p) or *TP53* mutation, a subset of patients who are resistant to chemotherapy. Findings from studies with other targeted agents show also long response durations in these patients.[7,8]

However, the contribution of bendamustine to the effects of this treatment regimen is unclear, since median progression-free survival in patients assigned to idelalisib combined with bendamustine and rituximab (20·8 months) is similar to that previously reported in frail patients treated with idelalisib combined with rituximab (19·4 months).[3] Similarly, no differences in progression-free or overall survival were reported in patients who received ibrutinib as a single agent or combined with bendamustine and rituximab in a study that combined data from two phase 3 trials in patients with relapsed or refractory chronic lymphocytic leukaemia.[10] Because the addition of chemoimmunotherapy can potentially increase the risk of infection, this issue might be worth investigating.

Moreover, treatment-related toxicity was not a negligible issue in this study. The proportion of patients receiving idelalisib who discontinued treatment because of an adverse event was 28%—twice as high as the proportion in the placebo group. Infections, mostly bacterial, were more common and were more frequently responsible for treatment discontinuation or death in patients in the idelalisib group than in the placebo group. Additionally, the opportunistic infections *Pneumocystis jirovecii* and cytomegalovirus were more frequent in patients treated with idelalisib than in those

who received placebo. However, it should be noted that patients in the idelalisib group continued therapy indefinitely and that prophylaxis for *P jirovecii* and monitoring for cytomegalovirus were not mandatory in this study.

The increased rate of infections recorded this study is similar to that reported in three other studies investigating idelalisib combined with bendamustine and rituximab for the first-line treatment of chronic lymphocytic leukaemia or for the treatment of relapsed indolent non-Hodgkin lymphoma, and idelalisib in combination with rituximab in patients with relapsed indolent non-Hodgkin lymphoma. The currently recommended measures to prevent and monitor infections, cytomegalovirus monitoring, *P jirovecii* prophylaxis, and regular blood tests for granulocyte counts in patients receiving idelalisib, are expected to have a positive effect in reducing the number of infections.

During the past few years, with the introduction of targeted agents, the treatment landscape of chronic lymphocytic leukaemia has evolved rapidly, with favourable consequences for patient outcomes. This study shows that the addition of idelalisib to bendamustine and rituximab can significantly improve outcomes of patients with relapsed or refractory chronic lymphocytic leukaemia compared with bendamustine plus rituximab alone. However, further studies are needed to define the benefit of combining chemoimmunotherapy with kinase inhibitors. Careful selection of patients, better knowledge, management of treatment-related adverse events, and enforcement measures to mitigate the risk of infections might have relevant effects in maximising the therapeutic benefit of idelalisib.

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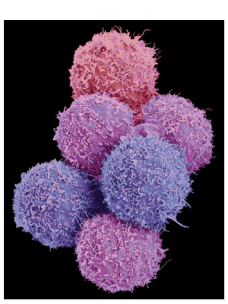
Immune therapy meets precision medicine

Bladder urothelial carcinoma can be a devastating disease and has profound personal and socioeconomic impact. It is the fifth most commonly diagnosed cancer in the USA: nearly 77 000 people were newly diagnosed in 2016, and more than 16 000 individuals died.[1] Bladder urothelial carcinoma also has a high prevalence (over 450 000 in the USA) and tends to recur (in 50–80% of cases depending on disease stage), necessitating intense life-long surveillance. Urothelial carcinoma is, in most high-income countries, one of the most expensive cancers to treat on a per-patient basis.[2] Fortuitously, after decades of inertia because of an almost complete lack of awareness and interest, progress in immune oncology is awakening new hopes and opportunities.

Immune checkpoint inhibitors promise to transform the seemingly unmovable prognosis of patients with metastatic urothelial carcinoma. In 1990, the US Food and Drug Administration approved the first indication for an immunotherapeutic drug—



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