We have demonstrated by immunoblotting that CLL cells treated with ribosomal subunit S235/236, pERKT202/Y204 and pAKKT308 (BI anti-Ig only) chemokine production, indicating that cerdulatinib may inhibit BCR-induced calcium flux at 1 μM, using anti-IgM or IL-4 and CD40L to mimic signals from the lymph node environment in vitro. Cerdulatinib was able to overcome BCR- and microenvironmental-mediated signalling and is in phase I clinical trials for several leukaemia/lymphomas including CLL.

These BCR-induced signals were inhibited by cerdulatinib in a dose (Figure 1C-D) induced phosphorylation (p) of pAKTS473, S6KT389, pS6 and pERKT202/Y204. These BCR-induced signals were inhibited by cerdulatinib in a dose dependent manner and most strongly between 0.3-1 μM. These results are consistent and comparable to idelalisib and ibrutinib [4]. Cerdulatinib (produced by Portola Pharmaceuticals) is a novel dual SYK/JAK inhibitor which has the potential to overcome the resistance mechanisms described previously and is in phase I clinical trials for several leukaemia/lymphomas including CLL.

We used BI anti-IgM or IL-4 and CD40L to mimic signals from the lymph node environment in vitro. Cerdulatinib was able to overcome BCR- and IL-4/CD40L promoted survival of CLL cells (Figure 5A-B). Bi-anti-IgM and IL-4/CD40L treatment induced expression of anti-apoptotic proteins MCL-1 and BCL-XL, shown by immunoblotting in a representative sample (Figure 5C-D) in line with previously published data. Simultaneous inhibition of SYK and JAK by cerdulatinib decreased MCL-1 and BCL-XL protein expression but had no discernible effect on Bcl-2 protein expression.

Conclusions
Cerdulatinib is a novel dual SYK/JAK inhibitor which is able to overcome BCR- and microenvironmental-mediated signalling and is currently in clinical trials for CLL.

References

Figure 1. Cerdulatinib inhibits BCR mediated signalling

Figure 2. Cerdulatinib suppresses chemokine secretion

Figure 3. Cerdulatinib inhibits IL-4 induced signalling and abrogates IL-4 increased IgM expression

Figure 4. Cerdulatinib induces apoptosis in CLL cells in a time and concentration dependent manner

Figure 5. Cerdulatinib is synergistic with ABT-199 in the presence of IL-4/CD40L

Figure 6. Cerdulatinib induces apoptosis irrespective of microenvironmental support

Since we showed that cerdulatinib could inhibit MCL-1 and BCL-XL expression induced by IL-4/CD40L and anti-IgM ligation, but not BCL-2, we investigated whether cerdulatinib would synergise with venetoclax in vitro to augment CLL cell killing. CLL cells were stimulated with IL-4/CD40L for 6 hours then treated with cerdulatinib or ABT-199, alone or in combination. In the presence of CD40L/IL-4, the combination of cerdulatinib with ABT-199 further enhanced apoptosis, indicating synergistic effects (Figure 6A). Synergistic interactions between cerdulatinib and ABT-199 were evaluated as indicated (Figure 6B). Points below the diagonal line represent synergistic interactions, above the line are additive.

Figure 7. Cerdulatinib is synergistic with ABT-199 in the presence of IL-4/CD40L.