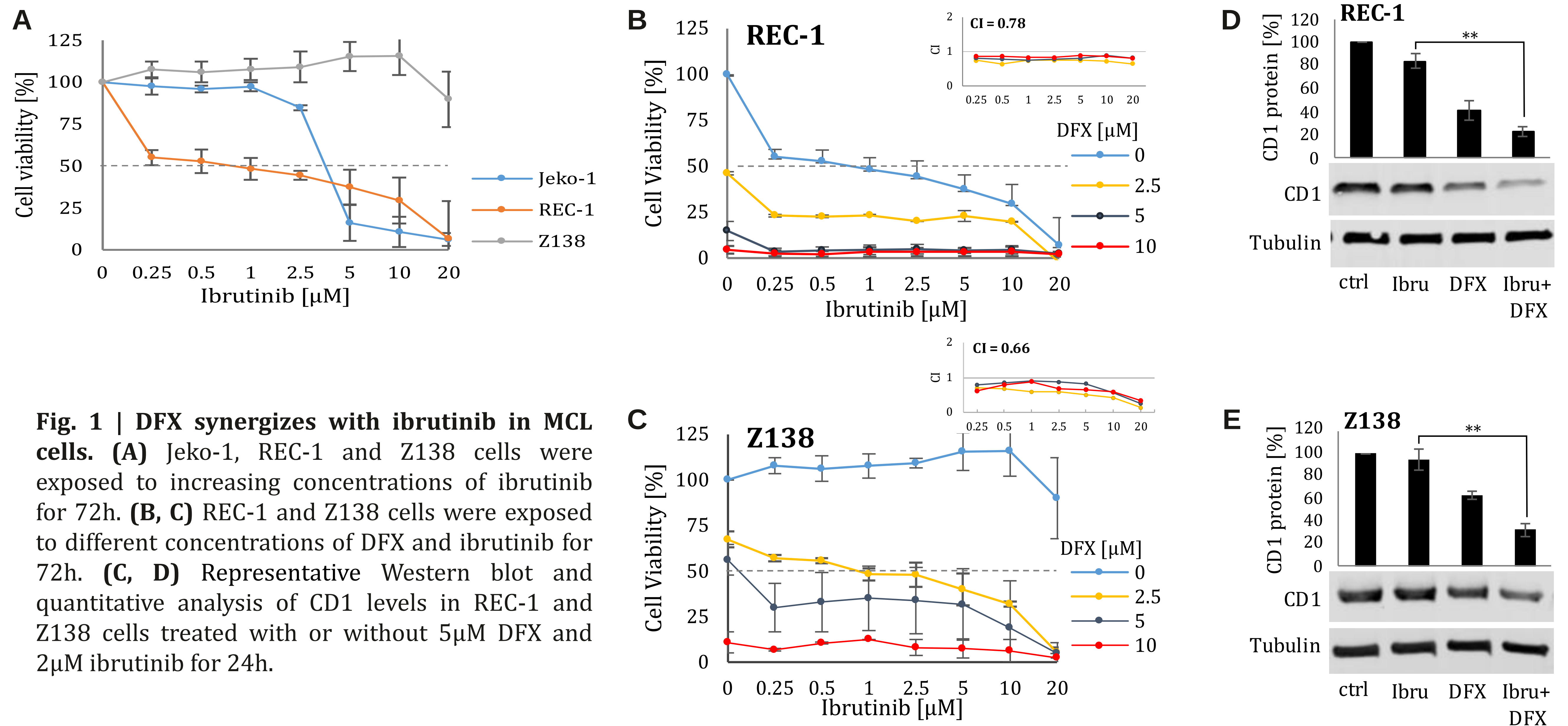


Background

- Ibrutinib resistance is a major clinical obstacle in mantle cell lymphoma (MCL) due to primary- and *de novo*- resistance.
- Deferasirox (DFX) is a clinically approved iron chelator with minor side effects.
- We have previously shown DFX to exert an anti-tumoral effect in MCL cell lines and patient-derived cells.
- We have previously shown DFX to induce ROS levels leading to oxidative stress and DNA damage and to trigger CD1 proteolysis by modulating the PI3K/AKT/GSK3 β pathway.
- Studies show that rationally combined therapies act synergistically and continuously improve median survival of MCL patients.

Results

- Ibrutinib significantly reduced the viability of Jeko-1 and REC-1 cells in a dose-dependent manner, while Z138 cells were resistant to this treatment (Fig. 1A).
- DFX increased the sensitivity of REC-1 cells to ibrutinib (CI = 0.78) (Fig. 1B).
- DFX restored the sensitivity of Z138 cells to ibrutinib, after being completely ibrutinib-resistant (CI = 0.66) (Fig. 1C).
- Ibrutinib treatment reduced CD1 levels to 84.1 $\pm$ 5.1% in the sensitive REC-1 cells and to 94.4 $\pm$ 5.6% in the resistant Z138 cells (Fig. 1D, E).
- DFX-ibrutinib combination reduced CD1 level substantially to 23.1 $\pm$ 2.6% and 32.2 $\pm$ 3% in the REC-1 and in the resistant Z138 cells, respectively (Fig. 1D, E).



Conclusions

- Our findings support the relevance of the DFX-ibrutinib combination treatment in MCL.
- This combination enhances the efficacy of both drugs and restores the anti-proliferative activity of the drugs in resistant MCL cells.
- The efficiency of the drugs correlates with their ability to mediate CD1 degradation.
- An effective synergistic effect of DFX and ibrutinib provides potential, clinically feasible therapeutic options for MCL patients and hopefully, a novel approach to overcome drug-resistance in the more aggressive relapsed/refractory MCL.