haematologica
Journal of the Ferrata Storti Foundation

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Received: July 15, 2026.
Accepted: July 27, 2026.

Citation: Alisson Charmey and Beat C. Bornhauser.
Tripping the switch: p38 inhibition unlocks venetoclax and inotuzumab ozogamicin synergy.
Haematologica. 2026 Aug 20. doi: 10.3324/haematol.2026.301601 [Epub ahead of print]

Tripping the switch: p38 inhibition unlocks venetoclax and inotuzumab ozogamicin synergy

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Disclosures:

No conflict of interest to disclose

Contributions:

AC and BCB wrote the manuscript

Text:

Although childhood B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is fairly well treatable for the majority of patients, disease recurrence and specific adverse genetic profiles continue to drive poor outcomes and represent a persistent therapeutic challenge. This is particularly true for *TCF3:HLF* (17;19)-driven leukemia, a subtype known for its intrinsic resistance to conventional chemotherapy with a 5-year overall survival of <40% and high rate of relapse post-transplantation, highlighting its urgent need for novel therapeutic strategies[1-2]. In this context, the study by Fleischer L. and colleagues arrives at a critical time[3]. While other strategies focus on further refining immunotherapies, such as Blinatumomab and CAR-T cells which are still associated with substantial relapse rates[4], the authors explore the feasibility of using the antibody-drug conjugate Inotuzumab Ozogamicin (InO) and ask whether intracellular stress signaling can be modulated to sensitize leukemic cells.

This work fits naturally into this emerging strategy using InO, a CD22-targeted calicheamicin antibody-drug conjugate (ADC) that has recently shown highly promising results in very high-risk pediatric and relapsed/refractory (r/r) adult BCP-ALL[5-6]. However, its mechanism of action remains only partially understood and effective chemotherapy-sparing combination strategies are still lacking. Previous preclinical studies have shown that InO synergizes with venetoclax (VEN)-based regimens by enhancing DNA damage signaling and mitochondrial apoptosis, but this dual combination has not translated into long-term responses. The addition of dexamethasone reinforces this effect, yet remains insufficient in the *TCF3:HLF* patient-derived xenograft (PDX) models[7], whereas early clinical data in r/r adult B-ALL indicate that this triple combination can achieve durable disease control, outperforming historical standard therapy[8]. This contrast highlights a key point: while InO-VEN combination is active, achieving long-term response in the most aggressive subtypes requires an additional trigger. What has been missing is a clear mechanistic basis to guide such optimization and further boost InO activity in very high-risk settings. This study addresses that gap by bringing p38 signaling to the center of ADC sensitivity and showing that transient modulation of DNA damage response pathways can potentiate both ADC activity and apoptosis-targeting drugs.

One central message of this paper is that BIRB796 treatment, an inhibitor of p38-mediated DNA damage response signaling, enhances the anti-leukemic activity of InO. This effect appears even stronger when apoptosis is further triggered with VEN. Inhibition of p38 in combination with InO increases DNA strand breaks, amplifies H2AX phosphorylation and p53 activity, and enhances mitochondrial priming, ultimately driving apoptosis and cell death in particular when combined with BCL2 inhibition with VEN. Importantly, these effects are not reproduced with the payload alone, indicating that the integrity of the ADC is required for this synergy. These observations also imply a role for p38 as a modulator of ADC processing, potentially by influencing the intra-cellular transport or payload release. This hypothesis is supported by recent findings on the role of p38 in receptor endocytosis, although its impact is clearly context dependent[9]. Together, this suggests that p38 inhibition does not simply add non-specific cytotoxicity but instead reshapes signaling responses and the functional impact of the ADC to increase its therapeutic efficacy in BCP-ALL.

Conceptually, this study extends our understanding of resistance and sensitivity to antibody-drug conjugates. Resistance to ADCs can arise at multiple levels, including reduced target-antigen expression, impaired ADC internalization, insufficient linker cleavage, reduced payload release, and failure to activate downstream apoptotic signaling[10]. The present work identifies stress-response signaling as an additional and potentially targetable layer of control. It suggests that DNA damage pathways can be modulated to increase leukemic cell vulnerability, particularly in very high-risk disease across several patient-derived xenograft models. Even more compelling, the triple combination of InO, VEN, and BIRB796 induces complete remission and durable leukemia-free survival *in vivo* in a *TCF3:HLF* PDX model, a result of high relevance for these refractory leukemias.

Despite its translational appeal, this approach requires careful consideration. The biology of p38 is highly context-dependent, and its inhibition has been reported to have pro-tumoral effects in certain settings, such as skin cancer[11]. Moreover, systemic p38 inhibition has historically been limited by its broad physiological roles and associated toxicities, including hepatotoxicity. The transient nature of p38 inhibition proposed here is therefore particularly attractive, as it may mitigate side effects and was indeed associated with only limited

toxicity in the reported mice model. Because the *in vivo* data of this study relies on a single PDX, it raises questions about general impact. It will be essential to determine if these findings can be applied to other TCF3::HLF xenograft models, to models with distinct mutation landscape in t(17;19)-driven leukemia and to other related high-risk subtypes, such as hypodiploid or MLLr leukemias. In addition, the precise molecular mechanism underlying the synergy between BIRB796 and InO remains incompletely defined, leaving room for further exciting investigations.

Even with these limitations, this study provides a strong biological rationale for transient modulation of p38 signaling in combination with ADC-based therapies. Rather than introducing a new therapeutic class, it suggests a new way to intensify existing treatments by exploiting intracellular stress and apoptotic vulnerabilities. In this sense, this study emerges as a coherent and promising approach for achieving deeper and more durable responses in very high-risk BCP-ALL.

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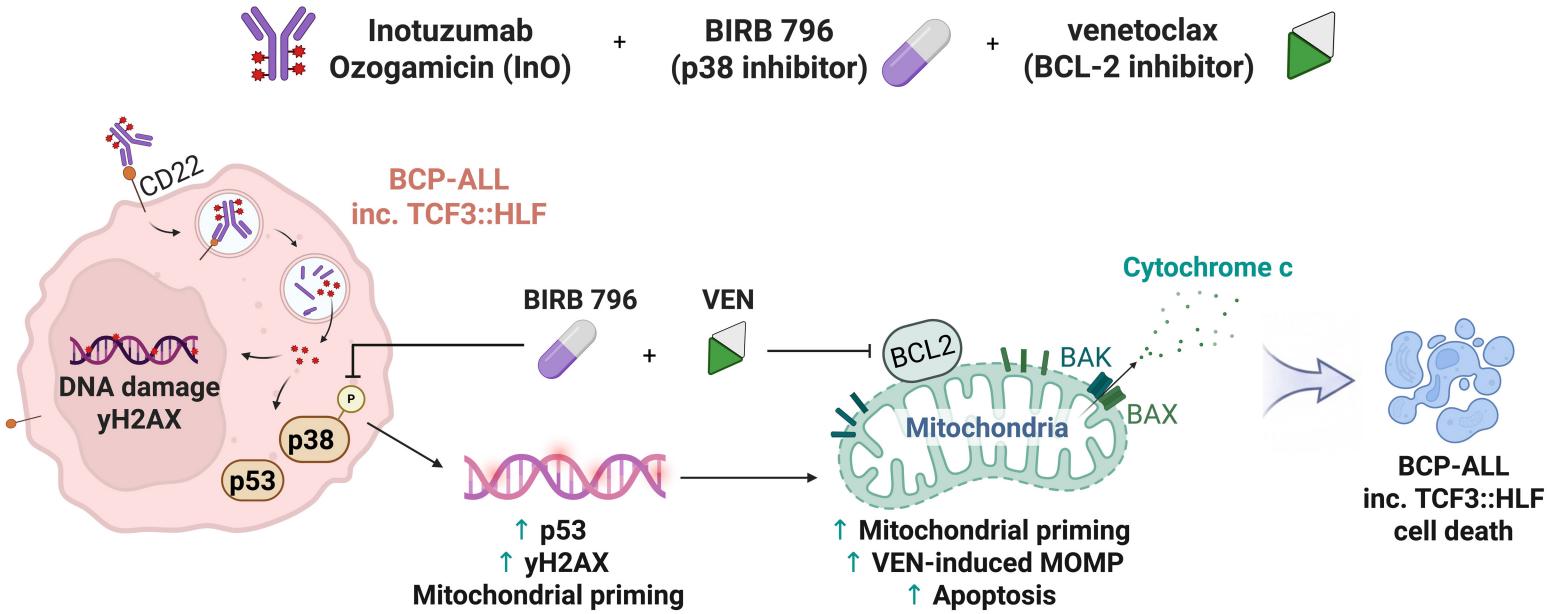
Figure legends:

Fig 1. Synergistic activity of InO, venetoclax and p38 inhibition to exhibit anti-leukemic efficacy in B-cell precursor acute lymphoblastic leukemia.



Control group	InO + BIRB796	InO + VEN	InO + VEN + BIRB796
• Median OS 23 days	• Median OS 83 days • 20% EFS at day 250	• Median OS 70 days • 20% EFS at day 250	• OS of 71% • Relapse-free survival at day 250