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Author/s:
Gao, MY;Georgiou, A;Lin, VS;Jahja, M;White, CA;Anderson, MA;McCormack, MP;Roberts, AW;Huang, DCS;Thijssen, R

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SHORT REPORT

Haematological Malignancy–Clinical

Potential impact of NOTCH1 activation on venetoclax sensitivity in chronic lymphocytic Leukaemia: In vitro insights and clinical implications

Ming-Yuan Gao[1,2] | **Angela Georgiou**[1] | **Victor S. Lin**[1,2,3,4] | **Michelle Jahja**[1,2] | **Christine A. White**[1,5] | **Mary Ann Anderson**[1,3,4,5] | **Matthew P. McCormack**[6] | **Andrew W. Roberts**[1,3,4,5] | **David C. S. Huang**[1,5] | **Rachel Thijssen**[1,5,7]

[1]The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia

[2]The University of Melbourne, Melbourne, Victoria, Australia

[3]The Royal Melbourne Hospital, Parkville, Victoria, Australia

[4]Department of Clinical Haematology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

[5]Department of Medical Biology, The University of Melbourne, Melbourne, Victoria, Australia

[6]Australian Centre for Blood Diseases, Monash University, Melbourne, Victoria, Australia

[7]Amsterdam UMC location Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

Correspondence
Rachel Thijssen, The Walter and Eliza Hall Institute of Medical Research, Parkville, Vic. 3052, Australia.
Email: r.thijssen@amsterdamumc.nl; thijssen.r@wehi.edu.au

Present address
Matthew P. McCormack, iCamuno Biotherapeutics, Melbourne, Victoria, Australia

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Summary

Despite significant progress in treating chronic lymphocytic leukaemia (CLL), resistance to therapy remains challenging. NOTCH1 activation, common in CLL, confers adverse prognosis. This study explores the impact of NOTCH1 signalling on venetoclax sensitivity in vitro. Although NOTCH1 activation minimally impaired the susceptibility of CLL cells to venetoclax, ex vivo cell competition studies reveal that cells with constitutive NOTCH1 activation outgrew their wild-type counterparts in the presence of ongoing venetoclax exposure. Our findings suggest that while NOTCH1 activation is insufficient to confer venetoclax refractoriness, there is enhanced potential for cells with NOTCH1 activation to escape and thus become fully resistant to venetoclax.

KEYWORDS

apoptosis, bcl-2, chronic lymphocytic leukaemia, co-culture, drug resistance

Outcomes for patients with chronic lymphocytic leukaemia (CLL) have greatly improved since the introduction of targeted therapy with agents such as Bruton Tyrosine Kinase (BTK) inhibitors, novel anti-CD20 monoclonal antibodies, and the BCL2 inhibitor venetoclax. However, resistance to treatment remains a major clinical challenge. *NOTCH1* is one of the most commonly mutated genes in CLL, affecting 6–12% of newly diagnosed cases,[1] with the incidence of *NOTCH1* mutation increasing in relapsed disease.[2] *NOTCH1* mutations frequently co-occur with other poor prognostic markers notably trisomy 12, unmutated *IGHV* and *TP53* deletion or mutation, and have been found to confer an unfavourable prognosis with chemoimmunotherapy as well as, more recently, with targeted agents.[3–5] Clinically,

Andrew W. Roberts, David C. S. Huang and Rachel Thijssen contributed equally to this work.

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NOTCH1 mutations are associated with less favourable outcomes with venetoclax-based therapy for relapsed disease.[5] While overall response and complete response rates are the same as for CLL with unmutated *NOTCH1*, in multivariate analyses, relapse risk is doubled, similar to the increased risk observed with *TP53* aberrations,[5] prompting us to explore further the role of NOTCH1 signalling in venetoclax resistance.

The *NOTCH1* gene encodes a single-pass transmembrane heterodimeric receptor. NOTCH1 signalling is triggered when a ligand from either the Jagged or Delta families (DL1, DL4), expressed on an adjacent cell, binds to the NOTCH1 receptor. This interaction induces two successive proteolytic cleavages, resulting in the release and subsequent nuclear translocation of the intracellular domain (NOTCH1-ICD). NOTCH1-ICD then activates target genes including several members of the hairy/enhancer of split (Hes) family, such as *HES1*.[6,7]

The most common *NOTCH1* mutation in CLL, accounting for 80% of all *NOTCH1* mutations, consists of a 2-bp CT frameshift deletion (c.7541_7542delCT) localized in exon 34. This generates a premature stop codon, deleting the C-terminal PEST domain (Pro2514Argfs*4). The truncated NOTCH protein lacks the critical PEST domain required to target NOTCH1-ICD for proteasomal degradation, thus resulting in prolonged signal activation. In CLL cells, constitutive NOTCH1 signalling promotes survival and proliferation.[8] Beyond mutations in *NOTCH1* resulting in NOTCH1-ICD stabilization and activation, interactions between CLL cells and the tumour environment within the lymph node can also induce NOTCH1 signalling.[9]

To test whether NOTCH1 activation can impact the intrinsic sensitivity of CLL cells to venetoclax, we assessed whether the in vitro sensitivity of CLL cells to venetoclax is altered in the presence of mutated *NOTCH1* or after activation of NOTCH1 signalling.

First, we tested the sensitivity of *NOTCH1*-mutated CLL cells to venetoclax. Primary CLL samples with either wild-type or mutated *NOTCH1* (Table S1) were cultured with increasing doses of venetoclax. All the CLL samples even ones harbouring *NOTCH1*-mutated cells (note the varied variant allele frequencies; VAF), were highly susceptible to venetoclax (Figure S1). There was only a minor suggestion of a difference since *NOTCH1*-mutant containing CLL samples (median IC50 = ca. 5 nM, range = 2.5–8.5 nM) were slightly less sensitive compared with ones that only had wild-type *NOTCH1*- (median IC50 = ca. 2.5 nM, range = 0.8–5.6 nM; $p = 0.08$; Figure 1A).

Considering the variable and low VAFs in the *NOTCH1*-mutated samples, we next investigated the impact of inducing NOTCH1 activation on venetoclax sensitivity in CLL, irrespective of mutation status. The *NOTCH1* mutation in CLL preserves the DNA-binding functions of NOTCH1-ICD.[10] To simulate the effects of *NOTCH1* mutation in CLL and directly activate NOTCH1, we established a co-culture system growing primary CLL cells with bone marrow-derived stromal OP9 cells that express delta-like NOTCH1 ligands (DL1 or DL4), effectively upregulating NOTCH1-ICD. This approach allowed us to model and investigate the direct effects of NOTCH1 activation, akin to *NOTCH1* mutation (Figure 1B).

A series of co-culture experiments were performed to establish the optimal duration for activating NOTCH1 in CLL cells. After 3 days of co-culture with stromal cells expressing DL1 or DL4, NOTCH1 activation was confirmed by NOTCH1-ICD upregulation and HES1 induction (Figure 1C). Interestingly, there was no discernible difference in NOTCH1-ICD upregulation between mutated or wild-type CLL cells. Notably, co-culture alone with OP9 stroma cells, which lack CD154 expression,[11] did not impact venetoclax sensitivity. Furthermore, even with NOTCH1 activation in these primary CLL cells, sensitivity to venetoclax remained unaffected (Figure 1D). Post-NOTCH1 activation, a marginal reduction in venetoclax sensitivity was observed in the *NOTCH1*-mutated CLL cells (Figure S1).

Consistent with prior findings indicating an association between *NOTCH1* mutation and elevated surface expression of CD38,[12] our investigation revealed CD38 upregulation and proliferation of CLL cells in some of the samples following DL1 or DL4 stimulation (Figure 1E,F). However, not all CLL samples exhibited proliferation and CD38 upregulation in response to NOTCH1 activation and these responses did not correlate with the presence of NOTCH1 mutation (Table S1) or baseline NOTCH1 expression (Figure S2C). Irrespective of the NOTCH1 mutational status (as observed in samples CLL335 and CLL367) or the degree of CD38 activation and proliferation induction (exemplified by CLL335 & CLL346), there was no effect on venetoclax sensitivity following co-culture with DL1- or DL4-expressing OP9 stroma cells (Figure 1G).

At first glance, these results appear at odds with clinical observations that time to disease progression is notably shorter with venetoclax in *NOTCH1*-mutated CLL.[5] Interestingly, *NOTCH1* mutations do not alter the initial response of CLL patients to venetoclax. These clinical findings prompted us to evaluate the impact of NOTCH1 activation using an engineered cell-line model as this permitted us to monitor for the gradual emergence of venetoclax resistance. This is not possible with primary CLL cells as their viability is rapidly lost under tissue culture conditions. Since the available CLL cell lines are insensitive to venetoclax (Figure S2), we focussed our efforts on a lymphoid cell-line widely used for venetoclax studies, RS4:11,[13] and established derivatives that overexpress intracellular NOTCH1-ICD (ICN), and hence have downstream pathway activation (Figure 2A). Consistent with observations in primary CLL cells (Figure 1D), NOTCH1-activation in these engineered RS4:11 cells did not alter venetoclax sensitivity in the short-term (24 h) assays (Figure 2B).

However, the RS4:11 cell-line model allowed us to further explore if NOTCH1 activation might confer a growth advantage in cell competition assays, reminiscent of our recent studies demonstrating enrichment for leukaemic cells with *TP53* dysfunction when treated with venetoclax.[13] While RS4:11 cells with NOTCH1 activation expanded

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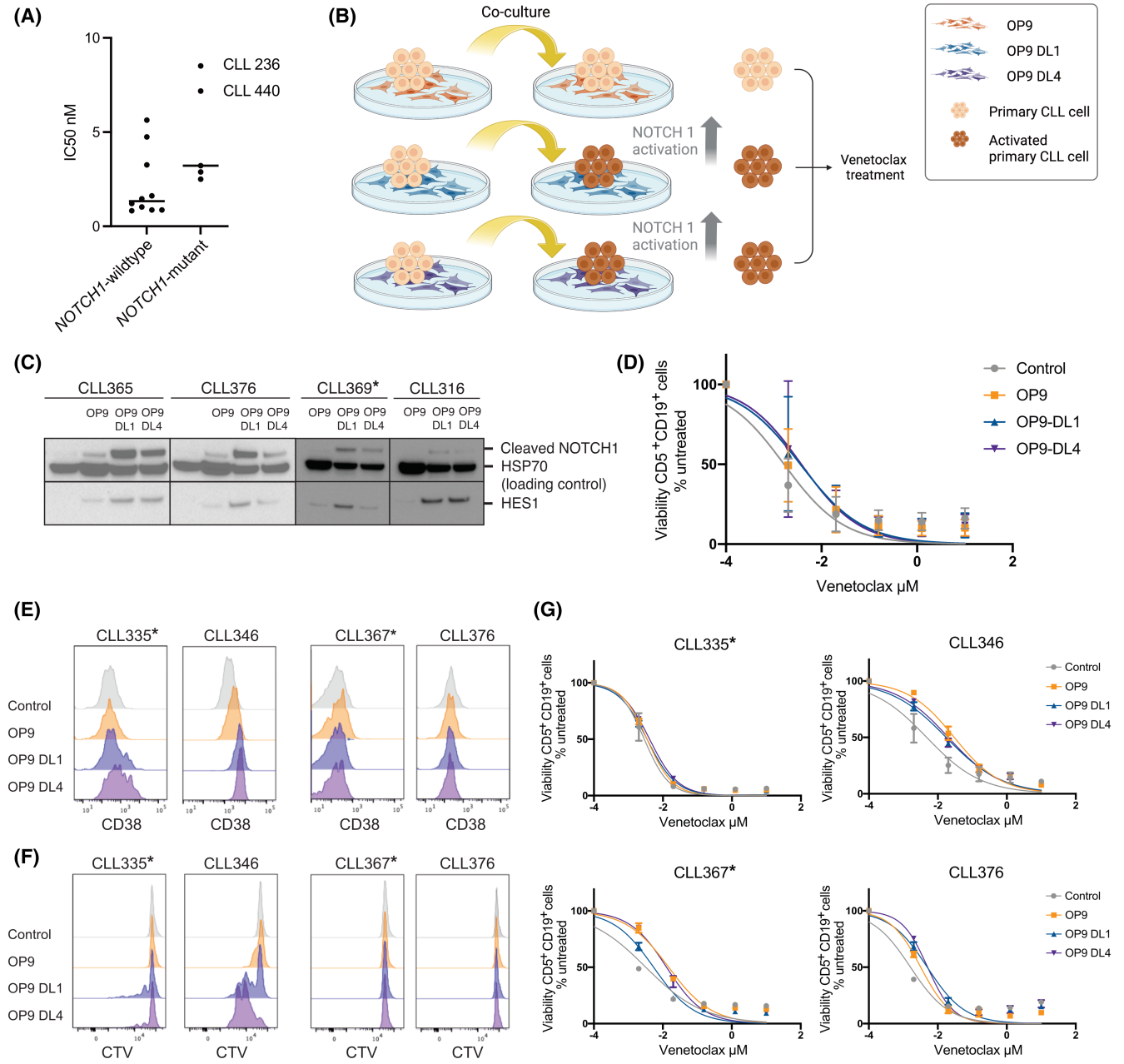


FIGURE 1 Activation of NOTCH1 does not impact short-term venetoclax sensitivity. (A) In vitro sensitivity to venetoclax (0–10 μM for 24 h) of peripheral blood CLL cells (CD5+ CD19+) with either mutated or wild-type *NOTCH1*. IC50 values are indicated and calculated from the nonlinear fitting of cell viability using GraphPad Prism software. IC50 median was 1.5 nM for *NOTCH1*-wild-type samples ($n = 10$) and 3.2 nM for *NOTCH1*-mutated samples ($n = 5$). CLL236 *NOTCH1* mutation 5% VAF, CLL440 *NOTCH1* mutation 50% VAF. A Mann–Whitney *U* test was used to determine statistical significance: no significant difference was detected. (B) Schematic representation demonstrating co-culture model of primary CLL cells and stromal OP9 cells. (C) After 3 days of co-culture with OP9, OP9-DL1, and OP9-DL4 stromal cells, CLL cells were lysed and probed for cleaved NOTCH1 and HES1, with HSP70 as the loading control. Four representative blots of 4 CLL patient samples of a total of 14 samples are shown. *CLL samples with *NOTCH1* mutation. CLL369 *NOTCH1* mutation 40% VAF. (D) CLL samples ($n = 14$) were co-cultured with or without OP9 stromal cells for 3 days. Samples were treated with 0–10 μM venetoclax and the viability of CD5+ CD19+ CLL cells was determined 24 h later by propidium iodide exclusion using FACS. Data were analysed using FlowJo software and plotted using GraphPad Prism software and nonlinear fitting. Data represent means ± SD of 14 samples. (E, F) Cell Trace Violet (CTV)-labelled CLL cells were co-cultured with OP9, OP9-DL1, and OP9-DL4 stromal cells. After 7 days, CD38 protein expression (E) and cell proliferation rate indicated by CTV staining (F) were measured by FACS. *CLL samples with *NOTCH1* mutation. CLL335 *NOTCH1* mutation 30% VAF, CLL367 *NOTCH1* mutation 50% VAF. (G) Primary CLL cells were co-cultured for 7 days and treated with increasing concentrations of venetoclax (0–10 μM) for 24 h. Data represent means ± SD of triplicate measurements in single experiments for viable (PI–) CLL cells (CD5+ CD19+). *CLL samples with *NOTCH1* mutation.

more rapidly when compared with their parental wild-type counterparts, this expansion was significantly enhanced when the cells were treated with clinically relevant doses of venetoclax (VEN IC_{20})[13] (Figure 2C,D). This could be driven by slightly higher BCLxL protein expression in RS4:11 ICN cells at baseline (Figure S3).

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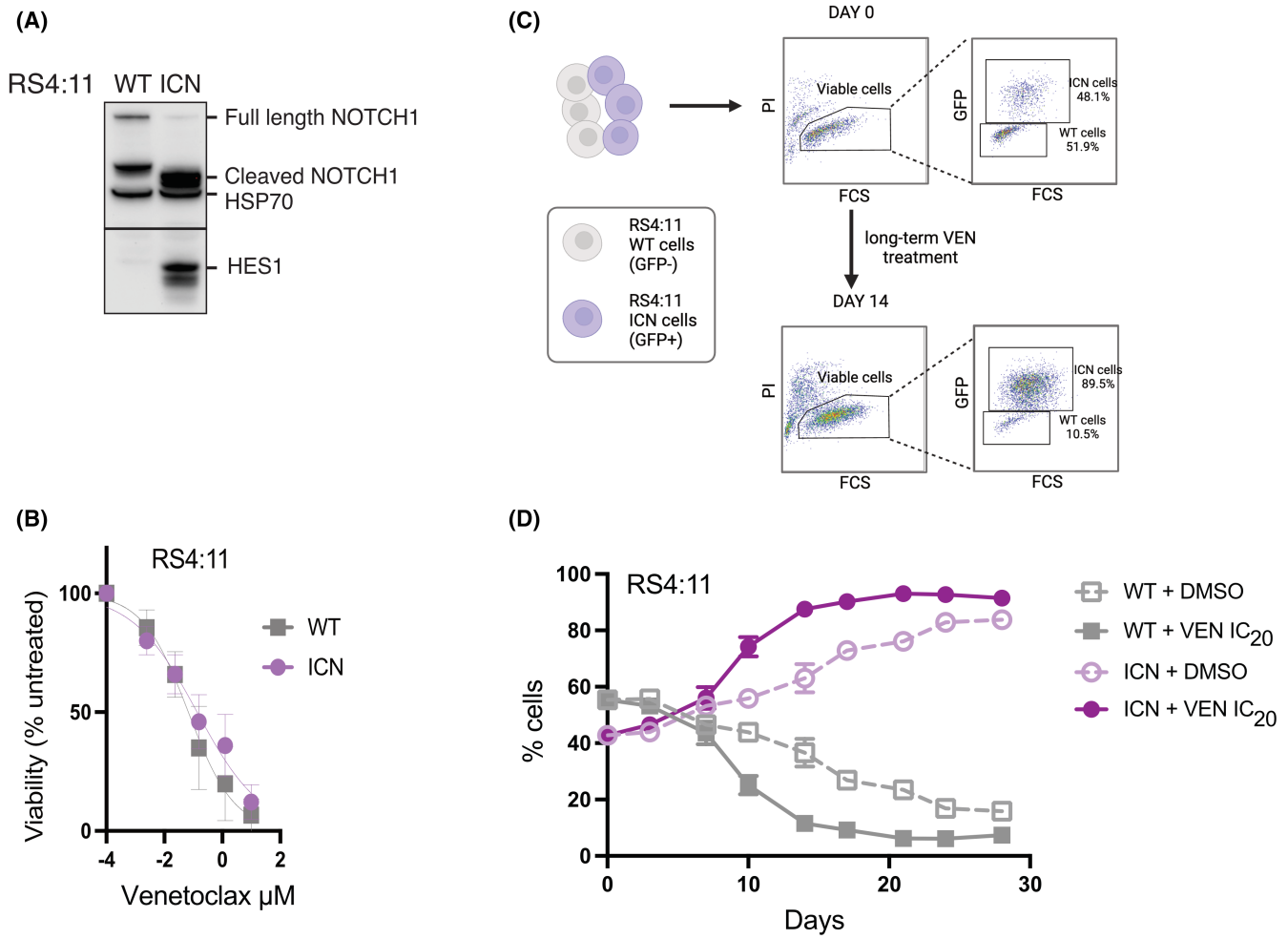


FIGURE 2 Activation of NOTCH1 confers growth advantage under long-term venetoclax pressure. (A) Western blot confirming expression of cleaved NOTCH1 and downstream HES1 (with HSP70 as loading control) in either RS4:11 cells transfected with a vector expressing the intracellular domain of NOTCH1 (ICN) or parental RS4:11 cells (WT). (B) Wild-type (WT) or NOTCH1-activated (ICN) RS4:11 cells were treated with 0–10 μM of venetoclax and their viability was determined 24 h later by CellTiter-Glo assay. Data shown are means ± SD of five independent experiments. (C) Schematic of the in vitro cell competition assay used to evaluate the impact of sub-optimal venetoclax treatment over several weeks on NOTCH1 WT and isogenic NOTCH1-activated clones. Equivalent (50:50) numbers of NOTCH1 WT (GFP–) and NOTCH1-activated ICN (GFP+) cells were seeded and co-cultured in the continued presence of low doses of venetoclax. Cell outgrowth was monitored by flow cytometry to track GFP+ and GFP– cells in viable PI-negative cells. (D) RS4:11 ICN GFP+ (purple) and RS4:11 parental GFP– (grey) cells were seeded in a 50:50 ratio and co-cultured in the continued presence of 10 nM venetoclax (IC_{20}) or DMSO as control. Cell outgrowth was monitored by flow cytometry to track GFP+ and GFP– cells in the viable PI-negative cells. Data shown are means ± SD of three independent experiments.

Overall, this study has provided evidence that direct activation of NOTCH1 signalling is insufficient to confer short-term resistance to venetoclax in primary CLL cells or a leukaemia cell-line in vitro, probably due to higher BAX protein expression together with increased BCLxL expression (Figure S3). However, under long-term venetoclax selection, a marked expansion of NOTCH1-activated cells occurred. Potentially, this sets up a scenario where *NOTCH1* mutated cells can more readily escape and presumably become targets for further genetic changes that allow the acquisition of full resistance. These results indicate that sub-optimal dosing of venetoclax should be avoided in cases of *NOTCH1* mutated CLL. Our study underscores the importance of conducting long-term drug resistance studies in relevant in vitro models.

Although our cell-line model showed that direct in vitro stimulation of NOTCH1 alters the efficacy of venetoclax over time, we have not excluded the potentially important role of the tumour microenvironment and host immune responses in leukaemic cell survival and proliferation.[10] Future investigations should explore how NOTCH1 signalling itself could potentially modify the tumour microenvironment through stromal cell activation, ligand and chemokine expression, and cell survival in response to venetoclax. Such studies are essential for a comprehensive understanding of the role of NOTCH1 signalling in CLL progression and treatment response.

Considering the ongoing combination of venetoclax with a BTK inhibitor, determining whether NOTCH1 activation leads to intrinsic resistance and consequently, a shorter

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progression-free survival is crucial. Instead of relying on an RS4:11 ICN cell-line, we recommend the utilization of the OSU-CLL cell-line to overexpress *NOTCH1* and investigate the impact of venetoclax and ibrutinib over time.[14] Moreover, achieving NOTCH1 ICD overexpression in primary CLL cells through CRISPR-mediated deletion of the PEST domain[15] can provide valuable models for studying acquired resistance to venetoclax and ibrutinib.

AUTHOR CONTRIBUTIONS

M.Y.G., A.W.R., D.C.S.H., and R.T. conceived and designed the study; V.S.L., M.A.A., and A.W.R. were responsible for patient care and recruited patients; M.Y.G., A.G., M.J., and R.T. performed the experiments. M.Y.G., A.G., M.J., V.S.L., and R.T. collected and analysed data; M.Y.G., V.S.L., C.A.W., M.P.M., A.W.R., D.C.S.H., and R.T. helped to interpret the results. M.Y.G. and R.T. wrote the first version of the manuscript; all authors reviewed the data and contributed to the critical revision of the manuscript.

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CONFLICT OF INTEREST STATEMENT

A.G., M.A.A., C.A.W., A.W.R., D.C.S.H. and R.T. are employees of the Walter and Eliza Hall Institute which received milestone and royalty payments related to venetoclax. M.A.A., A.W.R., and D.C.S.H. are recipients of a share in royalty payments paid to the Walter and Eliza Hall Institute of Medical Research. M.A.A. has received honorarium from AbbVie. A.W.R. has received research funding from AbbVie and is the inventor of a venetoclax-related patent.

DATA AVAILABILITY STATEMENT

Any relevant data are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

After written informed consent, peripheral blood samples were obtained from CLL patients (Human Research Ethics Committee approval: Walter and Eliza Hall Institute 05/04).

PATIENT CONSENT STATEMENT

N/A.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

N/A.

CLINICAL TRIAL REGISTRATION (INCLUDING TRIAL NUMBER)

N/A.

ORCID

Rachel Thijssen https://orcid.org/0000-0002-4493-306X

TWITTER

Rachel Thijssen Rachel_thijssen

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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