Novel PI3kδ inhibitor roginolisib synergizes with venetoclax in hematologic malignancies

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Abstract

The phosphoinositide 3-kinase (PI3K) pathway remains a potent drug target in hematological malignancies despite the challenges that have affected clinical drug development, particularly unpredictable toxicity, and inherent/acquired drug resistance. Herein, we tested the activity of a novel PI3Kδ selective, non-ATP competitive inhibitor, roginolisib (IOA-244), in hematological malignancies including diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL). To identify rational actionable combination partners that can be tested in hematologic malignancies, an unbiased pharmacological screening of 474 compounds was carried out in two lymphoma cell lines. We identified BCL2 blockade with venetoclax as synergistically active with roginolisib, a finding confirmed in a broad panel of lymphoma cell lines, DLBCL cell lines and primary CLL samples. We further demonstrate that the sensitizing effects of roginolisib to venetoclax correlate with suppression of downstream PI3K/AKT pathways and alterations in the expression of the apoptotic proteins BIM, mediated through FOXO1 transactivation, and MCL1, with ubiquitination and degradation mediated through GSK3α/β activation. These findings support proof of concept for roginolisib development in hematological malignancies as a single agent or in combination with venetoclax. A clinical trial of roginolisib with venetoclax and an anti-CD20 antibody is initiating in CLL.

Introduction

The phosphatidylinositol 3-kinases (PI3K) are a family of intracellular signal transducer enzymes that play a significant role in cell proliferation, growth, metabolism, and survival.[1,2] Aberrant expression and signaling through the PI3K pathway significantly contribute to hematological malignancies, making it a focus of drug development, which resulted in fast-track approval for first-generation PI3K inhibitors such as idelalisib, duvelisib, copanlisib, and umbralisib in B-cell malignancies.[3-6] Despite having clinical promise in indolent lymphomas and in chronic lymphocytic leukemia (CLL), severe adverse events limited their continued use. In 2022, the Food and Drug Administration (FDA) raised concerns over their safety, leading to voluntary withdrawals of the lymphoma indications and a recommendation for randomized data for future PI3K inhibitor approvals.[7-10] However, efforts are ongoing to overcome the limitations that were seen with PI3K inhibitors by developing more specific next-generation inhibitors or employing alternative dosing or combination approaches in hematological malignancies.[11-14]

Roginolisib (IOA-244) is a first-in-class non-ATP competitive, selective PI3Kδ inhibitor. Initial structural and biochemical studies identified a unique binding mode, excellent selectivity, excellent pharmacokinetic (PK) properties, and favorable safety profile for roginolisib as compared to idelalisib, parsaclisib, zandelisib and other novel PI3Kδ inhibitors.[15,16] Molecular dynamics studies accompanied by hydrogen/deu-

terium exchange coupled to mass spectrometry (HDX-MS) experiments suggest that the binding mode of roginolisib to PI3Kδ is different compared to the binding mode of idelalisib thereby stabilizing PI3Kδ in an inactive state.[17] These unique features and mechanism of action contribute to the anti-tumor effect and safety profile in pre-clinical studies.[15,18] Additionally, roginolisib shows antitumoral immune modulation by suppressing regulatory T-cell (Treg) proliferation, while having limited antiproliferative effects on $CD4^+$ and $CD8^+$ T cells *in vitro*.[19] These findings are in contrast to idelalisib and duvelisib which show significant immunomodulation of all T cells *in vitro* and in clinical trial samples.[20] These unique immunomodulatory effects of roginolisib improve the therapeutic efficacy of immune checkpoint blockade (ICB) in various syngeneic mouse models by increasing the infiltration of $CD8^+$ T and natural killer (NK) cells and reducing the number of monocytic and granulocytic myeloid-derived suppressor cells (MDSC).[15]

Currently, roginolisib is in the cohort expansion phase of the DIONE-01 trial, a two-part, first-in-human (FiH) dose escalation study evaluating roginolisib in solid tumors and hematologic malignancies[21] (*clinicaltrials gov. Identifier: NCT04328844*). In a phase Ib study, second- and third-line metastatic uveal melanoma (UM) patients had a longer time on roginolisib treatment than prior immunotherapy (17/26 patients) and an improved overall survival compared to historical controls (16 *vs*. 7 months).[22] The mean on-treatment time was 10.7 months (range, 1.5-39.6) as of August 2023, with no dose-limiting toxicities or maximum tolerated dose, no adverse events (AE) of special interest, no serious AE (SAE)/AE-related discontinuations and only one dose modification, which was considered a protocol violation. After selecting 80 mg as the biologically effective dose and recommended phase II dose (RP2D), among 20 UM patients, one demonstrated a partial response (PR) and 18 had stable disease.[23] In total, the safety profile of roginolisib in patients with metastatic solid tumors (N=36 patients) shows <5 % grade 3/4 toxicities with a median treatment duration of 7 months and 30% of patients treated for over 12 months.[22] Given that all prior PI3K inhibitors have additional inhibition against PI3Kα and/or PI3Kγ, and most of them have active metabolites,[15] it is important to understand whether roginolisib, a PI3Kδ inhibitor with high selectivity and specificity, can still have meaningful anti-lymphoma effect. Additionally, identifying actionable combination partners would be important to enhance activity in lymphoid malignancies.

Methods

Cell lines and chronic lymphocytic leukemia sample culture conditions

The cell lines GRANTA519, JVM2, SP49 (mantle cell lymphoma [MCL]); FARAGE, TMD8, SU-DHL-6, U2932 (diffuse large B-cell lymphoma [DLBCL]); MEC1 (CLL); MJ (cutaneous T-cell lymphoma); and YT (NK lymphoma) were cultured in RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum, 100 U/mL penicillin, 0.1 mg/mL streptomycin, 2 mM L-glutamine, plus IL2 2.5 ng/mL in YT. Human cell line identities were confirmed by short tandem repeat DNA fingerprinting using the GenePrint 10 System kit (Promega, Fitchburg, WI, USA). CLL samples were collected from patients enrolled in our CLL tissue bank approved by the Dana-Farber Harvard Cancer Center Institutional Review Board and written informed consent was obtained before sample collection. Mononuclear cells were isolated from peripheral blood samples by Ficoll gradient centrifugation. Additional methods used in this study are described in the *Online Supplementary Appendix*.

Results

Pharmacological screening indicates the synergistic benefit of combining roginolisib with BCL2, MCL1, and histone deacetylase inhibitors in hematological cancer cell lines

To identify potential actionable combination partners for roginolisib, an extensive pharmacological screen of cancer-targeted, approved therapeutics and emerging drugs for lymphoma (N=474 compounds) (*Online Supplementary Table S1A*) as single agents or in combination with roginolisib was carried out in two cell lines selected based on their intermediate sensitivity to single-agent roginolisib and representing a B- and T-cell malignancy.[15] The MCL line SP-53 and the cutaneous T-cell lymphoma (CTCL) line HH were treated with drug combinations for 72 hours as described in the methods. The inhibition of the anti-apoptotic proteins BCL2 and MCL1 and the histone deacetylases (HDAC) appeared the most promising approaches in combination with roginolisib, also considering the potential applications in clinical settings for patients with B- or T-cell malignancies (Figure 1A; *Online Supplementary Table S1B*). Thus, we validated the screening results with wider concentrations of these drugs in the same cell lines and nine additional lymphoma models derived from MCL (GRANTA519, JVM2, SP49), DLBCL (FARAGE, TMD8, SU-DHL-6), CLL (MEC1), CTCL (MJ) and NK cell lymphoma (YT). We tested the BCL2 inhibitors venetoclax and S55746, the MCL1 inhibitor S64315/MIK665 (plus the S63845 compound that was not in the screening library), and the two HDAC inhibitors belinostat and vorinostat (*Online Supplementary Figure S1A-C*). All cell lines benefited from combining roginolisib with venetoclax, with two of nine in the synergistic range and all the others in the additivity range, calculated by HSA score. Seven of nine were synergistic using the combination index, and the others had no benefit from the combination (*Online Supplementary Table S2*; *Online Supplementary Figure S1A*). Similarly, the combination of roginolisib with S55746 showed benefit in all nine cell lines, with three of

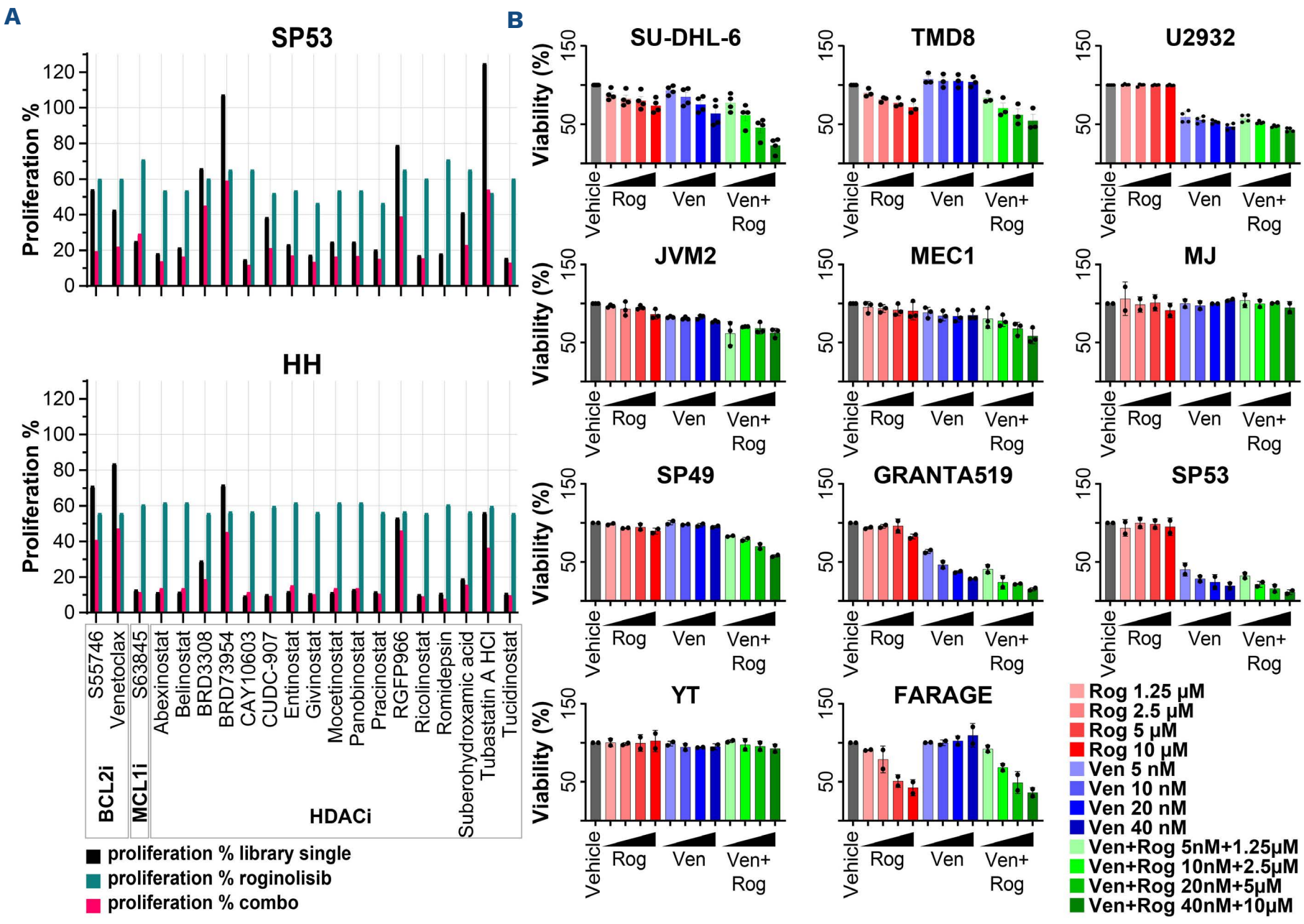

Figure 1. Roginolisib synergizes with the BCL2 inhibitor venetoclax in hematologic malignancies. (A) Bar graphs displaying the proliferation percentage in SP53 (upper graph) and HH (lower graph) cell lines after 72 hours (h) of treatment with 5 μM of BCL2, MCL1, or histone deacetylases (HDAC) inhibitors from the library, alone, with 5 μM of roginolisib (Rog), and in combination. Targets of the compounds (BCL2, MCL1 or HDAC) are shown. (B) Viability by Annexin V-APC/7AAD of cell lines SU-DHL-6, TMD8, FARAGE, U2932, JVM2, SP49, SP53, GRANTA519, MEC1, MJ, and YT following 48 h *in vitro* treatment with increasing concentrations of roginolisib (1.25 μM, 2.5 μM, 5 μM or 10 μM) or venetoclax (ven) (5 nM, 10 nM, 20 nM or 40 nM) alone or in combination (Ven+Rog) in the presence of αIgM and compared with cells treated with dimethyl sulfoxide (DMSO). Data represent ± standard error of the mean from biological replicates. Statistical analysis was done using paired *t* test. Graphs were generated using GraphPad Prism 10.0 software.

nine synergistic and the others additive with HSA score; five of nine were synergistic, one additive and three had no benefit with CI (*Online Supplementary Table S2*; *Online Supplementary Figure S1A*).

The combination of roginolisib with the MCL1 inhibitor S63845 was synergistic in four of nine and additive in all the others, using HSA score. Synergy was found in five of nine and additivity in two of nine by CI (*Online Supplementary Table S2*; *Online Supplementary Figure S1B*). Three of nine combinations with MIK665 had a synergistic HSA score, and all the others showed an additive HSA score; eight of nine showed a synergistic CI, and one had no benefit (*Online Supplementary Table S2*; *Online Supplementary Figure S1B*). Two of nine combinations with the HDAC inhibitor belinostat were synergistic, and all the others were additive by HSA score; five of nine were synergistic, and two of nine were additive by CI (*Online Supplementary Table S2*; *Online Supplementary Figure S1C*). Roginolisib, in combination with vorinostat, was synergistic in one of nine cell lines and additive in all the others, using HSA score; in six of nine cell lines, synergy was found, and additivity in other two cell lines using CI (*Online Supplementary Table S2*; *Online Supplementary Figure S1C*).

Considering the potential for rapidly transferring our findings to the clinical context for patients with B lymphoid tumors, and the beneficial effect observed across all the models studied, we then focused on combining roginolisib with the BCL2 inhibitor venetoclax. To explore the mechanism of combined roginolisib and venetoclax activity, we have analyzed apoptosis using annexin/7AAD in a panel of elev-

en lymphoma cell lines. Cells were treated with increasing concentrations of roginolisib (1.25 to 10 μM) and venetoclax (5 to 40 nM) alone or in combination in the presence of anti-IgM stimulation. DLBCL cell lines SU-DHL-6 and TMD8 showed strong synergistic activity, whereas U2932 did not show synergistic activity. While roginolisib and venetoclax as single agents showed modest cell-killing activity, the combination showed strong synergy in cell killing in the SU-DHL-6 cell line with a median CI of <0.01 in all combinations tested and a median HSA score of 22.9. Although the TMD8 cell line was resistant to venetoclax alone, the combination again showed strong synergy with a median CI <0.32 at all tested combinations and a median HSA score of 12.4. The U2932 and FARAGE cell lines fail to show any synergy in combination in the apoptosis analysis. The MCL cell lines JVM2, SP49 and GRANTA519 showed synergy with the combination, whereas SP53 did not show synergy. The CLL cell line MEC1 also showed synergy with the combination, however the CTCL cell line YT did not show any synergy (*Online Supplementary Table S2*; *Online Supplementary Figure 1B*).

To address whether roginolisib + venetoclax-induced cell death occurs through the activation of the intrinsic apoptotic pathway, we included the pan caspase inhibitor ZVAD in our apoptosis experiments in SU-DHL-6. Both in the single and combination treatment with roginolisib or venetoclax, addition of ZVAD significantly reduced the cell death in SU-DHL-6. In addition, ZVAD reduced the cleavage of PARP and caspase 7 induced by either drug, further validating apoptosis as the main mode of cell death in response to combined roginolisib + venetoclax treatment (*Online Supplementary Figure S2*).

Roginolisib sensitizes lymphoma cell lines to venetoclax by modulating the Bcl-2 family proteins MCL1 and BIM

To investigate the mechanism by which roginolisib sensitizes these lymphoma cell lines to venetoclax, we evaluated changes in the expression of several BCL-2 family proteins that have previously been implicated in venetoclax resistance, including the anti-apoptotic proteins BCL2, BCL_{XL}, MCL1 and A1 and the pro-apoptotic protein BIM and PUMA.[24-26] BCL2, BCL_{XL}, MCL1, BIM, PUMA and A1 levels were evaluated by immunoblotting analysis following 24 hours of treatment with 5 or 10 μM roginolisib or dimethyl sulfoxide (DMSO). Treatment with roginolisib significantly decreased the expression of the anti-apoptotic protein MCL1 in the DLBCL cell lines SU-DHL-6 and TMD8. In addition, a significant upregulation of pro-apoptotic BIM_{EL} was observed with roginolisib treatment in both cell lines tested. However, no significant changes were observed in the levels of BCL2, BCL_{XL}, PUMA and A1 in SU-DHL-6 (Figure 3A, B), whereas a significant increase in BIM_L and BCL2 and a significant downregulation of A1 was also observed in TMD8 (Figure 2A, B). Notably, in the DLBCL cell line U2932, where roginolisib and venetoclax fail to show synergy, no significant changes in the BCL-2 family proteins were observed (*Online Supplementary Figure S3*). Additionally, changes in the BCL-2 family proteins were evaluated in the MCL cell lines SP49, SP53, GRANTA519 and JVM2. No significant change in antiapoptotic MCL1 was detected in these cell lines. Although a modest increase in BIM was observed in JVM2, SP53 and GRANTA519, a significant decrease in BIM_{EL}, and BIM_L counteracted by BCL2 down-regulation was observed in SP49. Pro-apoptotic PUMA was increased in GRANTA519 following roginolisib treatment. The results in

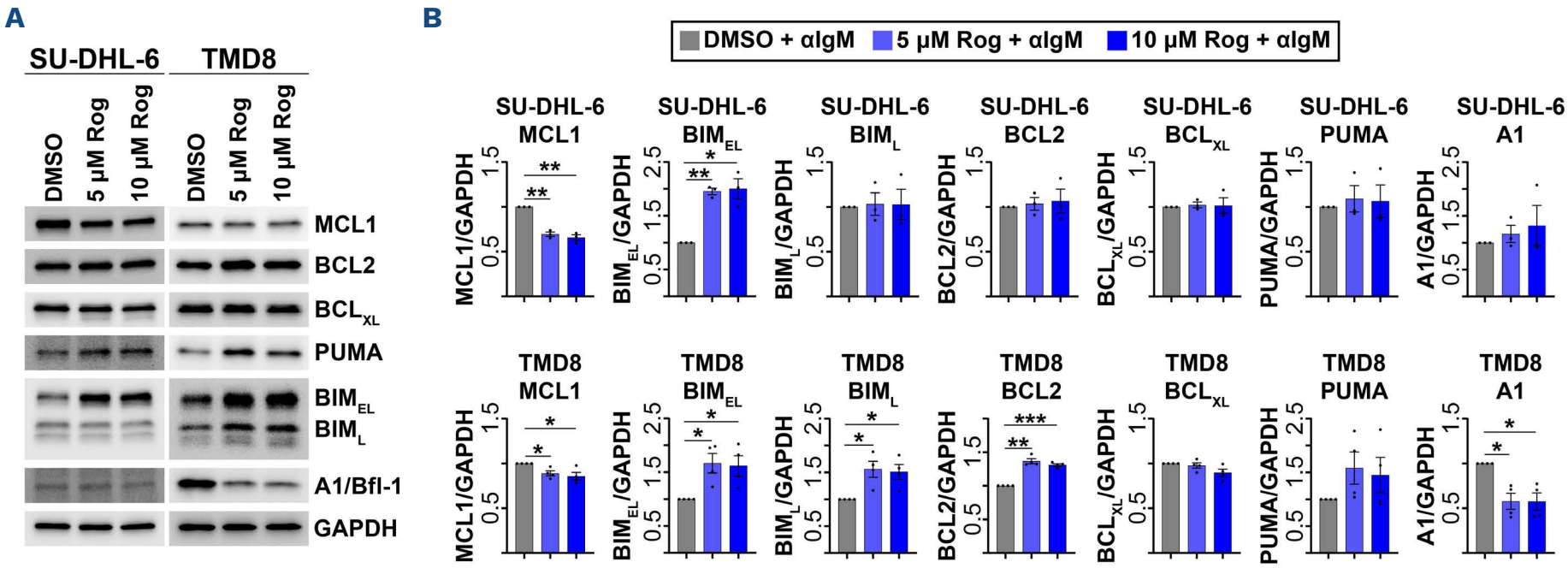

Figure 2. Roginolisib modulates BCL-2 family proteins in diffuse large B-cell lymphoma cell lines. (A) A representative western blot (WB) analysis of BCL-2 family proteins MCL1, BCL2, BCL^{XL}, PUMA, BIM^{EL}, BIM^{L} and A1/Bfl1 and internal control GAPDH in diffuse large B-cell lymphoma (DLBCL) cell lines SU-DHL-6 and TMD8. The levels of proteins were measured following 24 hours (h) of treatment with 5 μM or 10 μM of roginolisib stimulated with αIgM and compared with cells treated with dimethyl sulfoxide (DMSO) stimulated with αIgM. (B) Densitometric quantification and fold changes of each protein from SU-DHL-6 and TMD8 following normalization with GAPDH are shown. Data shown are ± standard error of the mean (SEM) from biological replicates. Statistical analysis was done using paired *t* test. Graphs were generated using GraphPad Prism 10.0 software. *P<0.05; **P<0.01; ***P<0.001.

the MCL cell lines suggest that alternate mechanisms may exist in different lymphoma models (*Online Supplementary Figure S4*).

To provide further evidence that these observed changes in MCL1 and BIM influence the sensitivity to venetoclax after roginolisib, we transfected the SU-DHL-6 cells with both *MCL1* siRNA and *BIM* (BIM_{EL}+BIM_L) mRNA and evaluated cell viability in the presence or absence of increasing concentrations of venetoclax (5-40 nM). Although downregulation of MCL1 and overexpression of BIM significantly reduced the viability of the cells, co-treatment with venetoclax further increased killing in cells transfected with small interfering (si) *siMCL1* + *BIM* mRNA as compared to cells transfected with control RNA (Figure 3A, B) at all venetoclax concentrations tested, suggesting that dynamic changes in MCL1 and BIM levels observed with roginolisib treatment can sensitize cells to venetoclax. A comparison of observed *versus* expected tumor cell survival showed a strong synergistic sensitizing effect in cells with reduced MCL1 and increased BIM levels at all venetoclax concentrations (Figure 3C).

Together these data suggest that the venetoclax-sensitizing anti-proliferative effect of roginolisib is primarily mediated through modulation of the apoptosis pathway by regulating the levels of MCL1 and BIM in DLBCL.

Roginolisib regulates MCL1 and BIM through tumor intrinsic modulation of B-cell receptor downstream kinases in diffuse large B-cell lymphoma cell lines

To decipher the potential mechanism by which roginolisib modulates the expression of MCL1 and BIM, we investigated the tumor intrinsic effect of roginolisib on B-cell receptor (BCR) downstream signaling pathways in SU-DHL-6 and TMD8 cell lines. These pathways included the AKT/FOXO1, ERK axis which has previously been shown to regulate transcription and turnover of BIM[26-29] and the AKT/GSK3α/β axis which has been reported to regulate MCL1 turnover.[30] Cells were treated with increasing concentrations of roginolisib (1.25 to 10 μM) for 1 hour followed by 30-minute stimulation with anti-IgM. As positive controls, other BCR signaling inhibitors, such as the PI3K inhibitors idelalisib and duvelisib or the BTK inhibitor acalabrutinib, were used (5 μM). Changes in phosphorylated levels of AKT, ERK, FOXO1, and GSK3α/β were measured by immunoblot assay and compared to control cells treated with DMSO + anti-IgM. Roginolisib showed a dose-dependent suppression of active phosphorylated AKT and ERK in both SU-DHL-6 and TMD8 cell lines. Similarly, BCR-induced phosphorylation and inactivation of FOXO1 and GSK3α/β were blocked by increasing doses of roginolisib in a dose-dependent manner in both SU-DHL-6 and TMD8. Both the PI3K

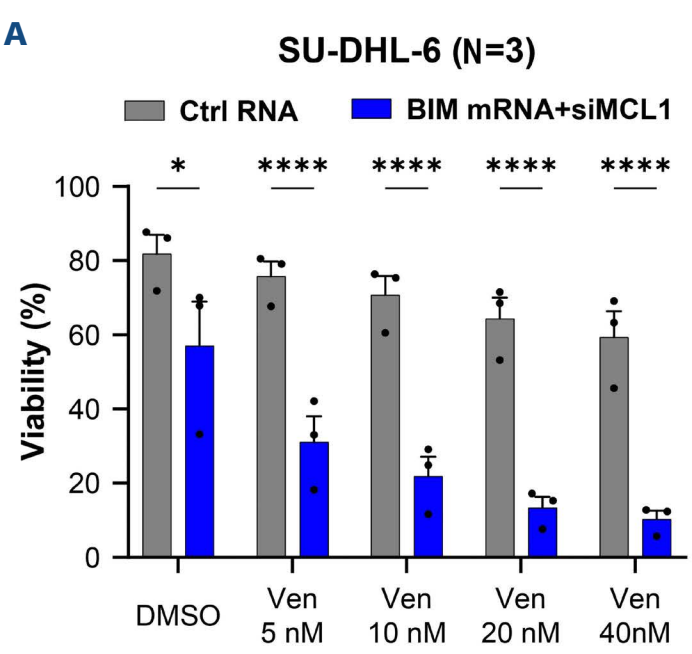

Figure 3. Modulation of MCL1 and BIM sensitizes diffuse large B-cell lymphoma cell line SU-DHL6 to venetoclax. (A) Effect of MCL1 downregulation and BIM overexpression on sensitivity of the diffuse large B-cell lymphoma (DLBCL) cell line SU-DHL-6 to venetoclax (Ven). Viability of SU-DHL-6 cell line was measured by Annexin V-APC/7AAD following 24 hours (h) of nucleofection with small interfering (si)MCL1 + *BIM* mRNA (BIM_{EL} and BIML) or control (ctrl) RNA in cells treated with increasing concentrations of Ven as indicated in the figure (5-40 nM) or dimethyl sulfoxide (DMSO). Each dot represents a biological replicate (N=3). (B) Western blot demonstrating ectopically expressed BIM_{EL} and BIM_L and suppression of *MCL1* following nucleofection with combo RNA (siMCL1 + BIM_{EL} + BIM_L) or control RNA from a representative experiment. (C) Analysis of synergistic or additive effects on the viability of SU-DHL-6 cells treated with varying concentrations of Ven following downregulation of MCL1 plus overexpression of BIM. Each dot represents 4 different concentrations of Ven from 3 replicates. The diagonal XY line represents the situation in which observed survival equals predicted survival. Dots beneath this line indicate synergistic interactions, whereas dots on the XY line represent additive interactions.

inhibitors idelalisib and duvelisib significantly reduced the phosphorylation of AKT, ERK, FOXO1, and GSK3, while the BTK inhibitor acalabrutinib showed only modest activity in suppressing these kinases in these cell lines (Figure 4A, B; *Online Supplementary Figure S5*). Interestingly roginolisib showed modest activity in suppressing the phosphorylation of AKT in the U2932 cell line where there was no observed synergy with the combination, and therefore did not significantly impact the phosphorylation and inactivation of FOXO1 and GSK3α/β (*Online Supplementary Figure S6*), and the subsequent regulation of the BCL-2 family proteins MCL1 and BIM (*Online Supplementary Figure S3*). These findings suggest that roginolisib indeed synergizes with venetoclax primarily by modulating BCL-2 family proteins through inhibition of BCR kinases.

Roginolisib shows tumor intrinsic activity in chronic lymphocytic leukemia patient samples

Given the known activity of PI3K inhibitors and venetoclax in CLL and the synergistic activity of roginolisib with venetoclax in the CLL-like cell line MEC1, we have investigated the same combination in primary CLL patient samples. To this end, we initially tested the tumor intrinsic activity of roginolisib by checking the effect on BCR downstream kinases such as AKT, ERK, FOXO1, and GSK3α/β in PBMCs isolated from CLL patients. Cells were treated with increasing concentrations of roginolisib from 0.625 μM to 5 μM in the presence of anti-IgM. The PI3K inhibitors idelalisib, duvelisib, and the BTK inhibitor acalabrutinib were used (5 μM) as positive controls. The expression of phospho-AKT, phospho-ERK, phospho-FOXO1, and phospho-GSK3α/β were measured by immunoblot assay and compared to cells treated with DMSO + anti-IgM. Roginolisib showed a dose-dependent suppression of BCR downstream kinases such as AKT and ERK. Roginolisib also showed a dose-dependent suppression of BCR-induced phosphorylation and inactivation of FOXO1 and GSK3α/β. The suppression of phosphorylation of AKT, ERK, FOXO1 and GSK3α/β was comparable to that seen with idelalisib or duvelisib, but the BTKi acalabrutinib showed modest inhibition of phosphorylation of ERK, FOXO1 and GSK3α/β (Figure 5A-E). Additionally, when apoptosis was evaluated by annexin/7AAD, roginolisib showed modest activity as a single agent which was comparable to the activity of idelalisib, duvelisib, or acalabrutinib at 5 μM concentration (*Online Supplementary Figure S7*). Induction of apoptosis by BCR pathway inhibitors in CLL cells is well known to be modest *in vitro*, consistent with our results.[31-33]

Roginolisib synergizes with venetoclax in chronic lymphocytic leukemia by modulating the apoptotic proteins MCL1 and BIM

Next, to investigate the possible synergy of roginolisib with venetoclax in CLL patient samples who are responders (N=6) or progressors (N=8) under BTK inhibitors, apoptosis analysis was carried out in patient peripheral blood mononuclear cells (PBMC). The viability of CLL cells following 48 hours of *ex vivo* treatment with increasing concentrations of roginolisib (0.625 to 5 μM) and venetoclax (1 to 8 nM) alone or in combination was evaluated. The CLL cells

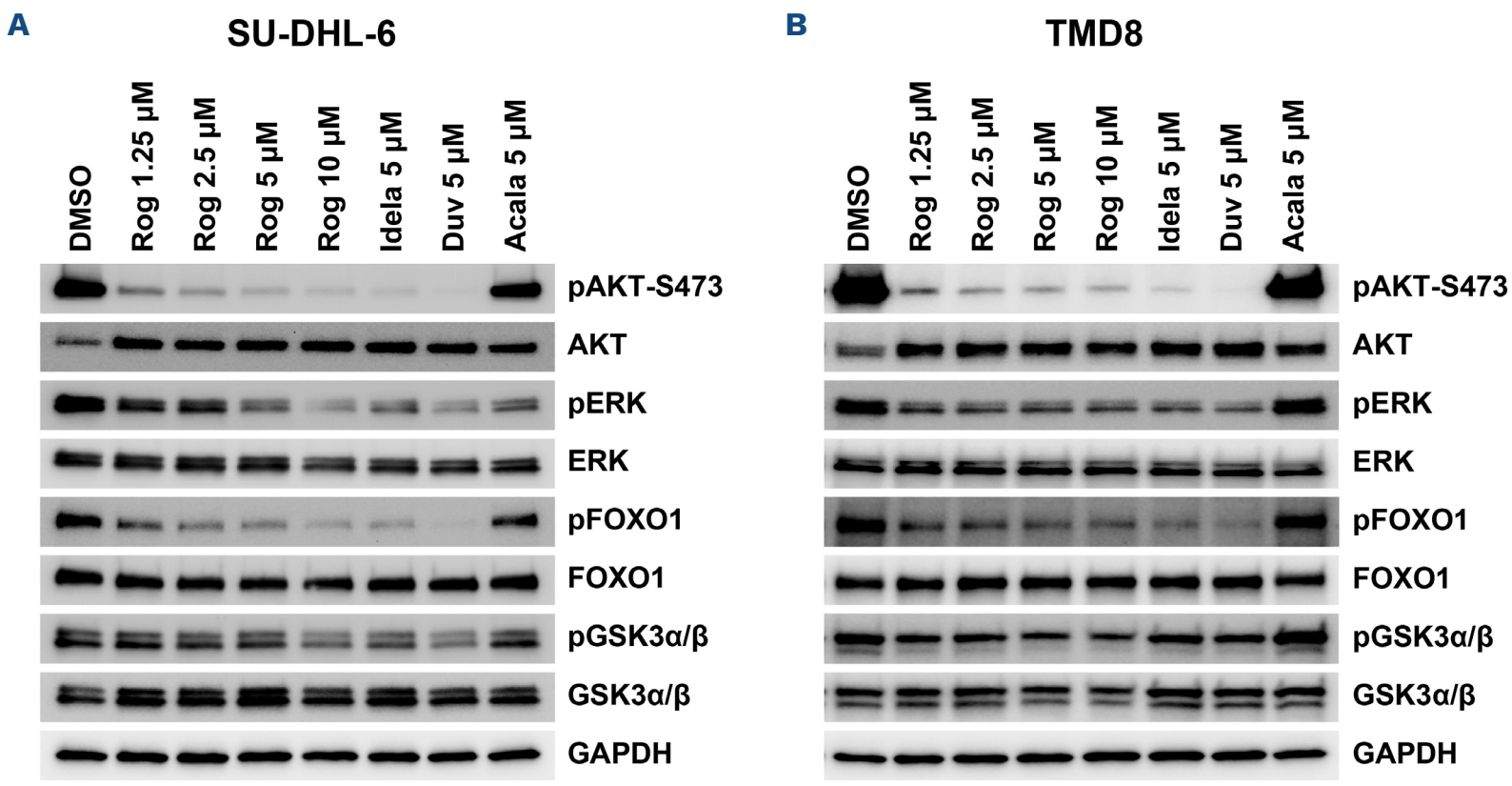

Figure 4. Effect of roginolisib on B-cell receptor downstream kinases in diffuse large B-cell lymphoma cell lines SU-DHL-6 and TMD8. (A, B) A representative western blot analysis of phosphorylated AKT, ERK, FOXO1 and GSK3α/β in SU-DHL-6 and TMD8 following 1-hour (h) treatment with increasing concentrations of roginolisib (Rog) (as indicated in the figure), or 5 μM of idelalisib (Idela), duvelisib (Duv) or acalabrutinib (Acala) followed by 30-minute stimulation with αIgM (10 μg/mL) and compared against cells treated with dimethyl sulfoxide (DMSO) + αIgM control. Phosphorylation was normalized to total AKT, ERK, FOXO1 and GSK3α/β levels.

from both the responders and progressors under BTK inhibitors showed strong synergy with the combination (responders have a median CI of 0.6 and a median HSA score of 16.0; progressors have a median CI of 0.26 and a median HSA score of 18.2), with slightly better cell killing activity in the progressors (P=0.0045) than the responders (P=0.0166) (Figure 6A). The synergy observed with the roginolisib/venetoclax combination was comparable to the synergy observed with idelalisib/venetoclax or duvelisib/venetoclax (*Online Supplementary Figure S8*). To address whether roginolisib + venetoclax-induced cell death occurs through the activation of the intrinsic apoptotic pathway, we included the pan caspase inhibitor ZVAD in our apoptosis experiments in the CLL patient samples. Both in the single and combination treatment with roginolisib or venetoclax, the addition of ZVAD significantly reduced the cell death in CLL. In addition, ZVAD reduced the cleavage of PARP and caspase 7 induced by either drug in CLL patient samples (*Online Supplementary Figure S9*).

To understand whether the mechanism by which roginolisib increases the sensitivity of CLL cells to venetoclax is like what we observed in cell lines, changes in the expression of BCL-2 family members such as BCL2, BCL_{XL}, MCL1, BIM, PUMA and A1 were measured by immunoblotting. Changes in expression were evaluated in patient PBMC after 24 hours treatment with 0.625 and 5 μM concentrations of roginolisib. A significant dose-dependent downregulation of MCL1 was observed at both the 0.625 μM (P=0.0004) and 5 μM (P<0.0001) concentrations compared to DMSO. In addition, a significant increase in proapoptotic BIM_{EL}

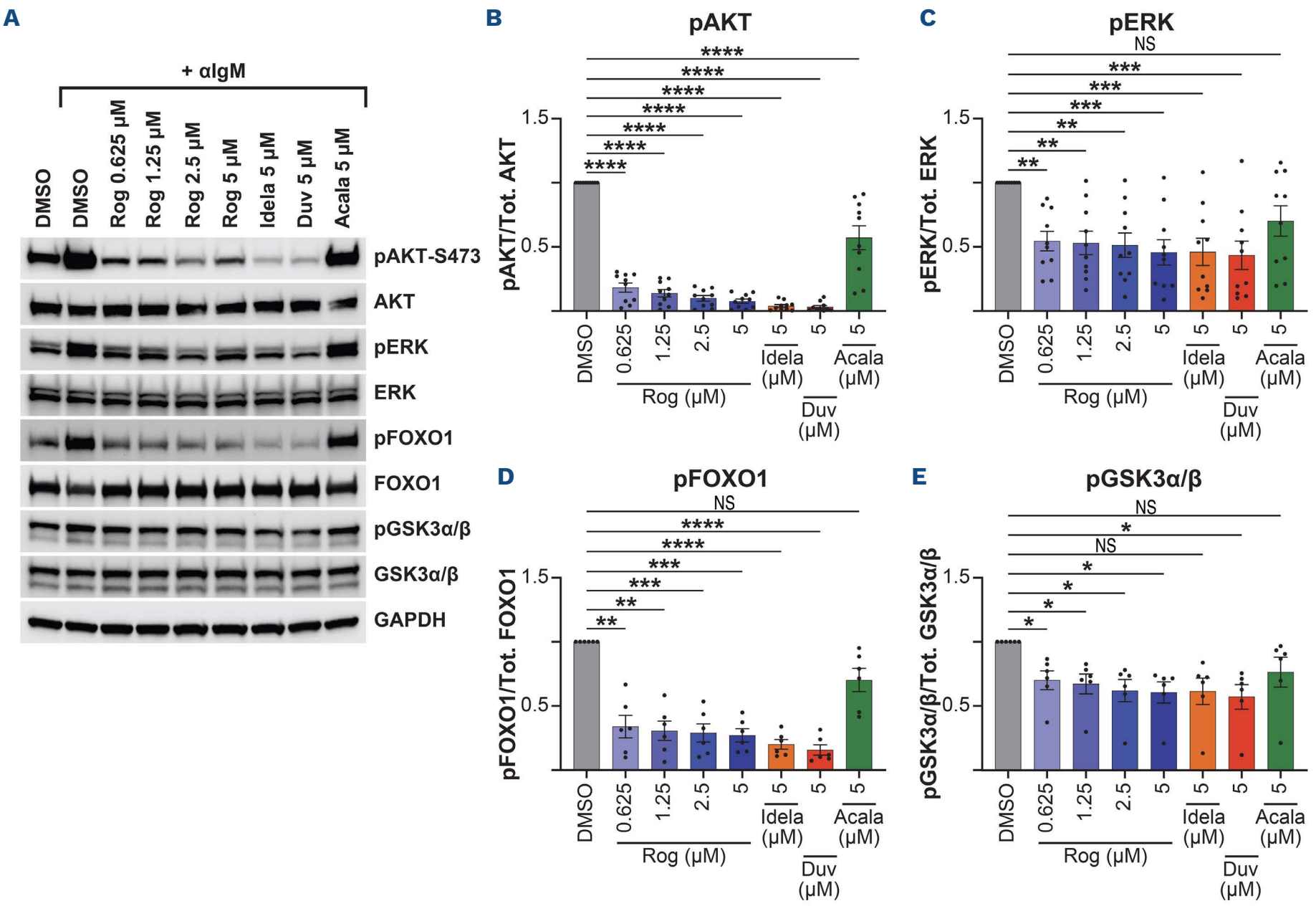

Figure 5. Effect of roginolisib on B-cell receptor downstream kinases in chronic lymphocytic leukemia patient samples. (A) A representative western blot analysis of phosphorylated AKT, ERK, FOXO1 and GSK3α/β in CLL peripheral blood mononuclear cells (PBMC) following 1-hour (h) treatment with increasing concentrations of roginolisib (Rog) (as indicated in the figure), or 5 μM of idelalisib (Idela), duvelisib (Duv) or acalabrutinib (Acala) followed by 30-minute stimulation with αIgM (10 μg/mL) and compared against cells treated with dimethyl sulfoxide (DMSO) + αIgM control. Total AKT, ERK, FOXO1 and GSK3α/β and GAPDH levels were used as controls. (B-E) Densitometry plots for phospho-AKT (S473) normalized to total AKT, phospho-ERK normalized to total ERK, phospho-FOXO1 normalized to total FOXO1 and phospho- GSK3α/β normalized to total GSK3α/β from biological replicates all in the presence of αIgM. Each dot represents a different patient sample. Data shown are ± standard error of the mean from biological replicates. Statistical analysis was done using one-way ANOVA and Dunnett's multiple-comparison *post hoc* test. Graphs were generated using GraphPad Prism 10.0 software. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001; NS: non-significant.

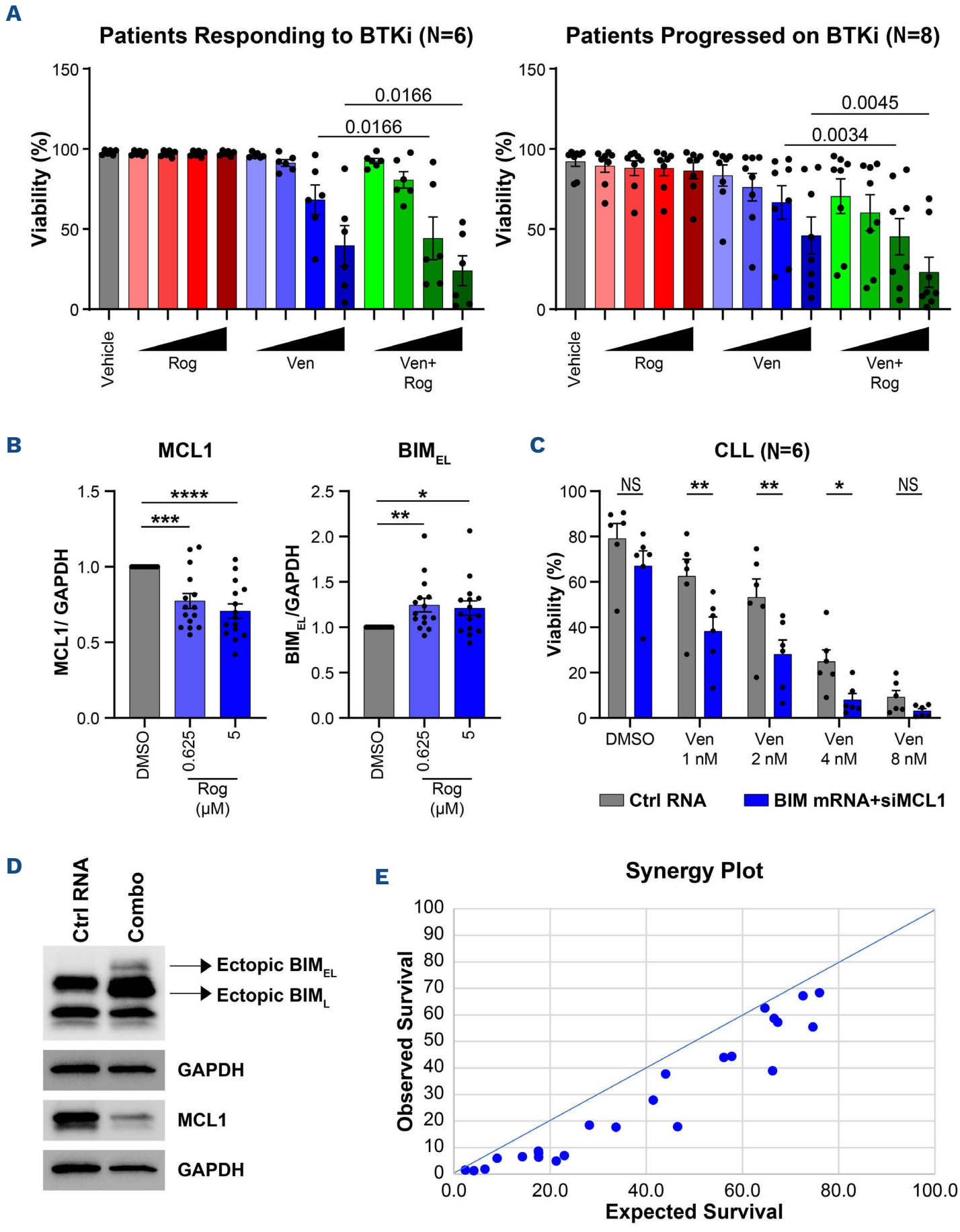

Figure 6. Roginolisib shows synergy with venetoclax in chronic lymphocytic leukemia patient samples. (A) Viability by Annexin V-APC/7AAD of chronic lymphocytic leukemia (CLL) patient peripheral blood mononuclear cells (PBMC) from patients responding to BTK inhibitor (BTKi) (N=6) or patients with prior progression on BTKi (N=8), following 48 hours (h) *in vitro* treatment with increasing concentrations of roginolisib (Rog) (0.625 μM, 1.25 μM, 2.55 μM or 5 μM) or venetoclax (Ven) (1 nM, 2 nM, 4 nM or 8 nM) alone or in combination (Ven+Rog), in the presence of HS5 stromal cell co-culture and compared with cells treated with dimethyl sulfoxide (DMSO). Data represent ± standard error of the mean (SEM) from biological replicates. Statistical analysis was done using paired *t* tests. (B) Densitometric quantification and fold changes of MCL1 and BIM$_{EL}$ protein following normalization with GAPDH are shown (N=15). The levels of proteins were measured following 24-h treatment with 0.625 μM or 5 μM of roginolisib stimulated with αIgM and compared with cells treated with DMSO stimulated with αIgM. Data shown are ± SEM from biological replicates. Statistical analysis was done using paired *t* test. Graphs were generated using GraphPad Prism 10.0 software. **P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001. NS: not significant. (C) Effect of MCL1 downregulation and BIM overexpression on sensitivi-

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ty of CLL cells to Ven. Viability of CLL cells was measured by Annexin V-APC/7AAD following 24 h of nucleofection with small interfering (si)*MCL1* + *BIM* mRNA (BIM_{EL} + BIM_L) or control (Ctrl) RNA in cells treated with increasing concentrations of Ven as indicated in the figure (1-8 nM) in the presence of HS5 stromal cell co-culture and compared with cells treated with DMSO. Each dot represents a biological replicate (N=6). (D) Western blot of ectopically expressed BIM_{EL} and BIM_L and the suppression of MCL1 following nucleofection with combo RNA (siMCL1 + BIM_{EL} + BIM_L) or control RNA from a representative experiment. (E) Analysis of synergistic or additive effects on the viability of primary CLL cells treated with varying concentrations of Ven following downregulation of MCL1 plus overexpression of BIM. Each dot represents 4 different concentrations of Ven from 6 replicates. The diagonal XY line represents the situation in which observed survival equals predicted survival. Dots beneath this line indicate synergistic interactions, whereas dots on the XY line represent additive interactions.

was also observed at both the 0.625 μM (P=0.0054) and 5 μM (P=0.0194) concentrations compared to DMSO (Figure 6B; *Online Supplementary Figure S10*). No significant changes were observed in BIML, BCL2, BCL_{XL}, PUMA and A1 (*Online Supplementary Figure S10*).

To further demonstrate the effect of downregulation of MCL1 and overexpression of BIM in sensitizing CLL cells to venetoclax, we transfected CLL patient PBMC with *siMCL1* + *BIM* (BIM_{EL}+ BIM_L) mRNA combination or control RNA and evaluated cell viability in the presence or absence of increasing concentrations of venetoclax (1-8 nM). Downregulation of MCL1 and overexpression of BIM modestly reduced the viability of the CLL cells; however, co-treatment with venetoclax significantly increased apoptosis in cells transfected with *siMCL1* + *BIM* mRNA as compared to cells transfected with control RNA (Figure 6C, D). Comparison of observed *versus* expected tumor cell survival showed a strong synergistic sensitizing effect in cells with reduced MCL1 and increased BIM levels (Figure 6E). Altogether, these data suggest that roginolisib synergizes with venetoclax in primary CLL cells by modulating the levels of the BCL-2 family proteins MCL1 and BIM.

Discussion

Here, we demonstrate for the first time the tumor intrinsic activity of a novel PI3Kδ inhibitor roginolisib and its synergistic activity with the BCL2 inhibitor venetoclax in hematological malignancies including DLBCL, MCL and CLL. Given its semi allosteric non-ATP dependent inhibition of PI3Kδ, and the careful dose selection in phase I, tolerability has been improved in clinical studies in solid tumors and follicular lymphoma (FL) compared to first-generation PI3k inhibitors whose use was limited by their toxicity profile. First generation PI3K inhibitors are well known to modulate the tumor immune microenvironment due to PI3Kδ on target as well as off-target effects on other isoforms such as PI3Kγ, all of which effects are implicated in an antitumoral immune response as well as immune-mediated AE.[7,20,34] We hypothesized that the clinical activity of roginolisib observed in solid tumors and in FL could be extended to more hematological malignancies, due to its PI3Kδ specificity which may also limit off-target immune activation and AE. In addition, the autoimmune toxicity of older inhibitors is less common in older heavily pretreated patients, in whom PI3K inhibitors could confer substantial benefit with minimal toxicity. In the current era, patients who develop disease progression after BTK inhibitors continue to have reduced benefit from subsequent therapies, including non-covalent BTK inhibitors[35] and single-agent venetoclax.[36] Thus, strategies to enhance the durable benefit of these therapies are desperately needed. Both preclinical work and two clinical trials in CLL, including one from our institution, have demonstrated substantial increases in undetectable minimal residual disease and progression-free survival compared to historical controls, with the combination of a PI3K inhibitor and venetoclax.[37,38] In both trials, some PI3Ki toxicity was observed. Thus, identifying novel combination strategies and dosing regimens with roginolisib is worthwhile to enhance clinical activity.

Our pharmacological screen identified BCL2 inhibitors, MCL1 inhibitors, and HDAC inhibitors as potentially active combination partners for roginolisib. As PI3Kδ inhibition has been shown to reshape the lymphoma-immune microenvironment and enhance sensitivity to the BCL2 inhibitor venetoclax in other models and in the clinic,[39,40] we then focused on the combination of roginolisib with BCL2 inhibitors. The strong benefit of combining the non-ATP-competitive selective PI3Kδ inhibitor with these agents was extended to a series of leukemia and lymphoma cell line models in combination with venetoclax or the novel BCL2 inhibitor S55746, already tested in a phase I trial,[41] as well as in CLL patient PBMC with venetoclax. Our data support the earlier preclinical and clinical findings that BCR inhibitors can be used in combination with a BCL2 inhibitor to improve outcome effectively in CLL, lymphomas and acute myeloid leukemia.[40,42-47]

The ability of roginolisib to sensitize tumor cells to venetoclax can be attributed to dynamic changes in the apoptotic pathway. Prior work has shown that, in both leukemia and lymphoma, inhibition of BCR kinases can alter the mitochondrial apoptotic pathway by altering the expression of MCL1, BIM, BCL_{XL} and PUMA.[40,47,48] PI3Kδ inhibition by roginolisib shifts the balance of the intrinsic apoptotic pathway by modulating anti-apoptotic MCL1 and inducing the expression of pro-apoptotic BIM in both the sensitive DLBCL cell lines and primary CLL cells by invoking the AKT/ GSK3α/β, ERK axis and the AKT/ FOXO1 axis, which has been previously recognized and is in line with the known modulation of apoptotic proteins in a BCR-dependent manner.[25,26] We observed a dose-dependent activity of roginolisib suggest-

ing the specificity of this drug for the downstream kinases. Moreover, our experiments suggest that clinical activity might be achieved at a tolerable low dosage. In addition, in the lymphoma model where we did not see synergy, only modest suppression of the BCR downstream kinases was observed and was not associated with significant changes in MCL1 and BIM. Although we observe synergy in most of the MCL cell lines tested, involvement of BCL-2 family proteins was limited, suggesting additional pathways may be involved in sensitizing roginolisib to venetoclax in these models. Detailed profiling is essential to identify these additional players to advance this combination to clinical practice in these lymphomas.

Consistent with other PI3Ki such as idelalisib or duvelisib and with BTK inhibitors, and as observed in various lymphoma cell lines,[15] the *ex vivo* cell killing efficacy of roginolisib was modest as a single agent in CLL patient samples, suggesting that a combination strategy targeting alternate survival pathways might be beneficial. The synergistic activity of roginolisib with venetoclax was comparable to that observed with idelalisib/venetoclax or duvelisib/venetoclax in primary CLL samples. This observation supports the clinical relevance of the roginolisib venetoclax combination, particularly as we have previously studied duvelisib venetoclax in relapsed CLL patients and shown this regimen to be highly effective.[38,40,42,43]

In summary, we demonstrate that roginolisib synergizes with venetoclax in lymphoma cell lines and CLL primary cells, through downmodulation of MCL1 and an increase in BIM as downstream effectors of BCR inhibition (Figure 7). Based on these results we are initiating a phase I-II clinical trial of roginolisib in combination with venetoclax and rituximab in relapsed CLL patients with progression after BTK inhibitors.

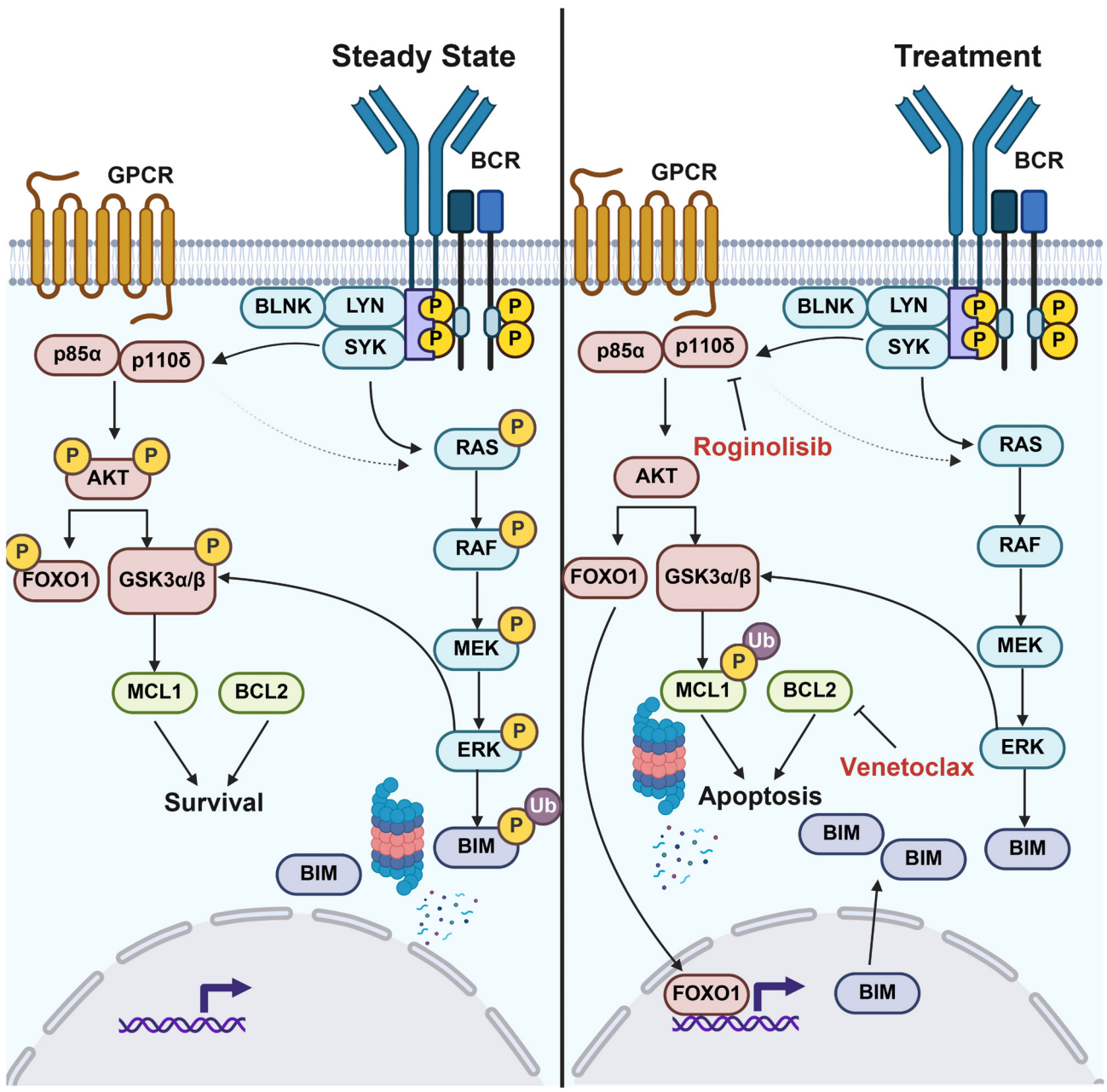

Figure 7. Sketch representing the molecular mechanism of synergy between roginolisib and venetoclax. Molecular pathways downstream of PI3Kδ signaling (AKT, ERK, FOXO1 and GSK3α/β phosphorylation). The signaling through B-cell receptor (BCR) and GPCR activates kinases such as AKT and ERK, whereas phosphorylation inactivates FOXO1 and GSK3α/β. Phosphorylated MCL1 and BIM undergo ubiquitination and proteasomal degradation. Non-phosphorylated and active FOXO1 gets transported to the nucleus and transactivates BIM expression. Following roginolisib treatment, PI3K signaling is inhibited resulting in GSK3α/β activation, subsequent MCL1 ubiquitination and degradation, and BIM transactivation by activated FOXO1. The simultaneous inhibition of BCL2 with venetoclax further enhances leukemia/lymphoma cell apoptosis. This sketch was created using BioRender software.

Disclosures

CT received a travel grant from iOnctura. AJA received a travel grant from Astra Zeneca; and consultants for PentixaPharm. ML, LV and GDC disclose employment at iOnctura and stock in iOnctura. FB has served as a consultant for BIMINI Biotech, Helsinn, Menarini; received institutional research funds from ADC Therapeutics, Bayer AG, BeiGene, Floratek Pharma, Helsinn, HTG Molecular Diagnostics, Ideogen AG, Idorsia Pharmaceuticals Ltd., Immagene, ImmunoGen, Menarini Ricerche, Nordic Nanovector ASA, Oncternal Therapeutics and Spexis AG; served on an advisory board for Novartis; and received travel grants from Amgen, Astra Zeneca, Beigene, Innocare and iOnctura. JRB has served as a consultant for Abbvie, Acerta/Astra-Zeneca, Alloplex Biotherapeutics, BeiGene, Bristol-Myers Squibb, EcoR1, Galapagos NV, Genentech/Roche, Grifols Worldwide Operations, InnoCare Pharma Inc, iOnctura, Kite Pharma, Loxo/Lilly, Magnet Biomedicine, Merck, Numab Therapeutics, Pfizer and Pharmacyclics; received research funding from BeiGene, Gilead, iOnctura, Loxo/Lilly, MEI Pharma, SecuraBio, and TG Therapeutics; serves on the data safety monitoring board for Grifols Therapeutics; and receives royalties from UpToDate. All other authors have no conflicts of interest to disclose.

Contributions

BKS, CT, GDC, FB and JRB designed the research. BKS, CT, SM, EC, EC, GS, AJ A, GDC, ML, and LvdV performed the research, collected and analyzed data. Statistical analysis was performed by ST and YR. Administrative support (i.e., bio-banking, managing and organizing patient samples) was provided by SMF, SJS and JM. BKS, CT, GDC, FB and JRB wrote the manuscript. JRB supervised the study.

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Data-sharing statement

All the data associated with this study are present in the manuscript or the Online Supplementary Appendix. For original data, please contact the corresponding author JRB.

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