

Addition of RP6530, a dual PI3K δ/γ inhibitor, accentuates Romidepsin activity in NHL cells in vitro



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Introduction

Relapsed or refractory Non-Hodgkin's Lymphoma (NHL) represents a significant unmet medical need. Novel treatment options currently being explored include Romidepsin, a histone deacetylase inhibitor, which has demonstrated significant preclinical and clinical activity¹. Because the PI3K pathway is often activated in NHL, combining Romidepsin with a PI3K δ/γ inhibitor may be a viable alternative to chemotherapy. RP6530 is a novel, potent, and selective PI3K δ/γ inhibitor that demonstrated high potency against PI3K δ (IC₅₀=25 nM) and γ (IC₅₀=33 nM) enzymes with selectivity over α (>300-fold) and β (>100-fold) isoforms². Dose-escalation and expansion trials to evaluate the safety and efficacy of RP6530 in patients with hematological malignancies are currently underway at several sites in US and Europe. The objective of this study was to evaluate the effect of a combination of Romidepsin and RP6530 in NHL cells.

RESULTS

Cell Line	Romidepsin (nM)	RP6530 (nM)	CI	Effect
JEKO-1	6	1000	0.68	Synergistic
SU-DHL-1	4	1000	0.86	Synergistic
OCI-LY-1	3	1000	0.31	Synergistic
OCI-LY-10	4	1000	0.43	Synergistic

Table 1. Cells were incubated with compounds for 72 h and growth was determined by an MTT assay. Combination Index (CI) was determined by the Chou & Talalay method using CompuSyn (representative concentrations provided in table).

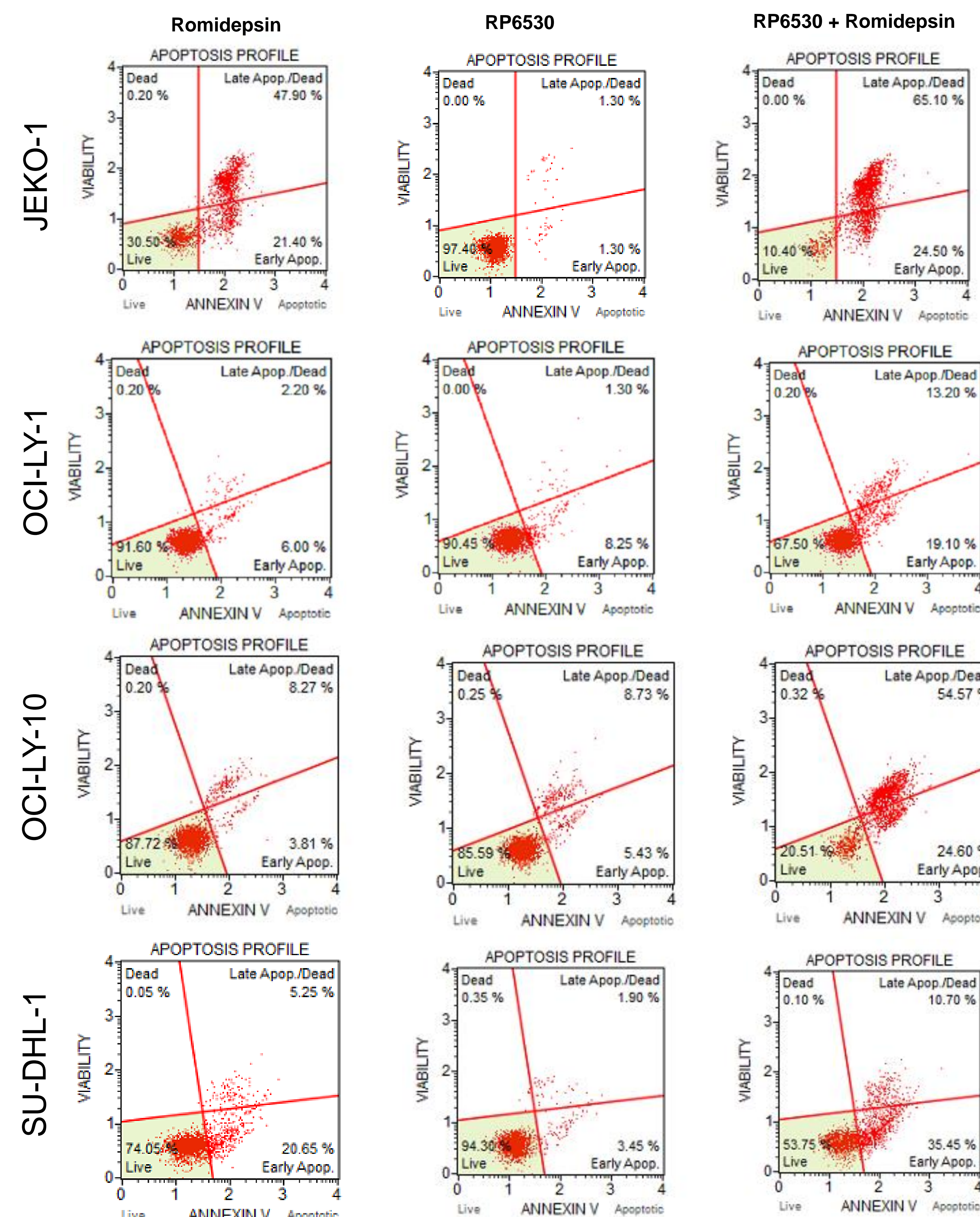


Fig. 1. Induction of apoptosis in NHL cell lines. Cells were incubated with compound for 72 h, pelleted, washed and stained with MUSE Annexin V and Dead Cell Assay Kit from Millipore. While Romidepsin was used at a concentration of 3 nM, concentrations of RP6530 were 1000, 3000, 3000, and 5000 nM for JEKO, OCI-LY-1, OCI-LY-10, and SU-DHL-1 cell lines, respectively.

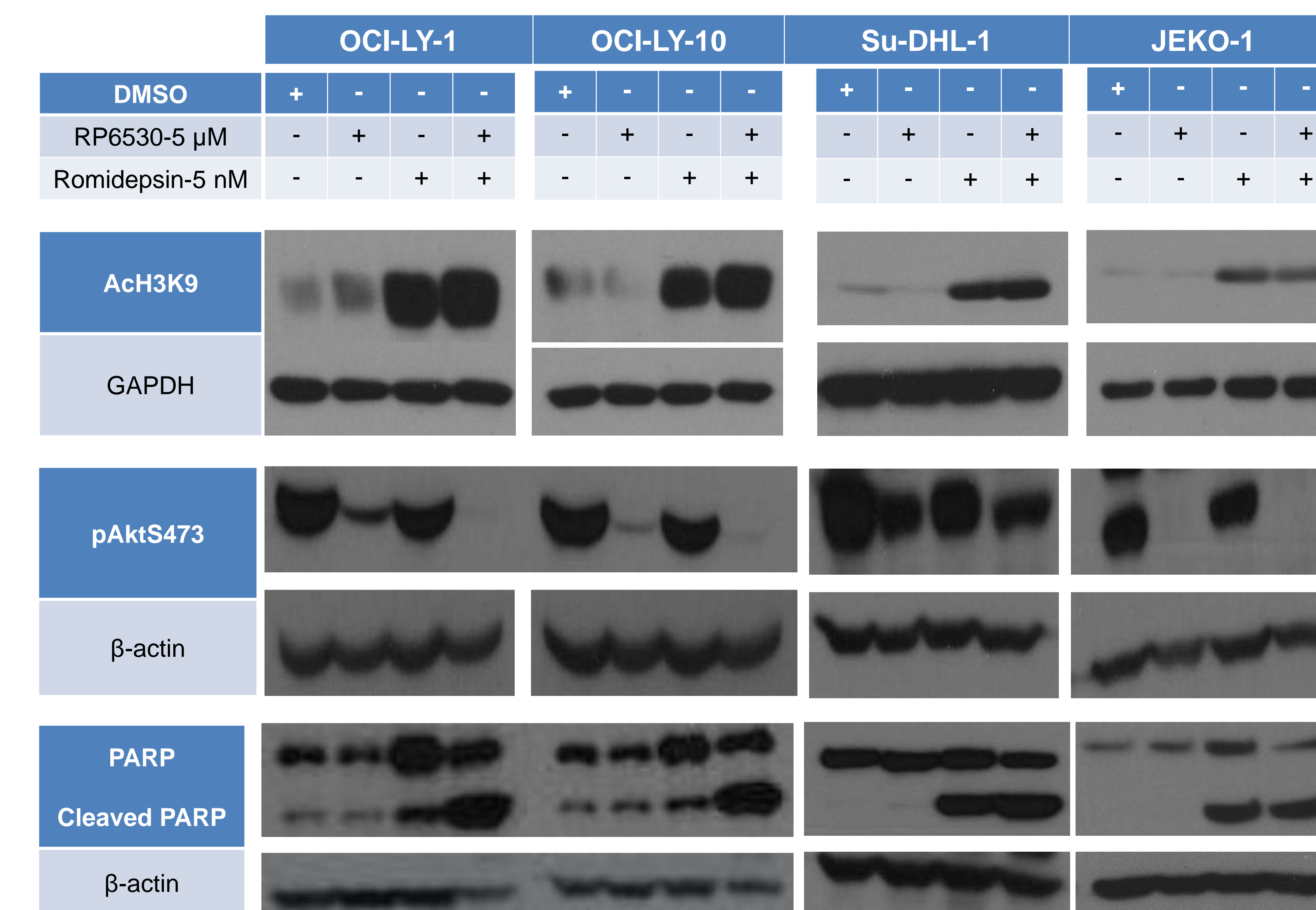


Fig. 2. Expression of ACh3K9, pAKT, and cleaved PARP in NHL cell lines. Synergistic effect for the combination of Romidepsin + RP6530 was noticed in the SU-DHL-1 cell line for ACh3K9, pAKT in OCI-LY-1, and cleaved PARP in OCI-LY-1, OCI-LY-10, and SU-DHL-1 cell lines

Summary & Conclusions

- Combining RP6530 with Romidepsin resulted in an increase in anti-proliferative effect in all the four NHL cell lines tested.
- Increase in the number of apoptotic cells was observed with the combination of RP6530 + Romidepsin with a maximum response seen in the ABC-DLBCL cell line, OCI-LY-10
- Combination of RP6530 + Romidepsin caused a reduction in the downstream oncogenic markers
- Findings provide a rationale for use of the combination in future clinical trials involving naïve or relapsed NHL patients thereby providing a safer alternative to currently available therapy

References:

1. **Yazbeck, V. Y., and Grant, S (2015).** Romidepsin for the treatment of Non-Hodgkin's lymphoma. *Expert Opin. Investig. Drugs*.24:965-79.
2. **Vakkalanka, S., Nyayapathy, S., and Viswanadha, S. (2015).** RP6530, a dual PI3K δ/γ inhibitor, potentiates ruxolitinib activity in the JAK2-V617F mutant erythroleukemia cell lines. *Proceedings: AACR 106th Annual Meeting 2015; April 18-22, 2015*