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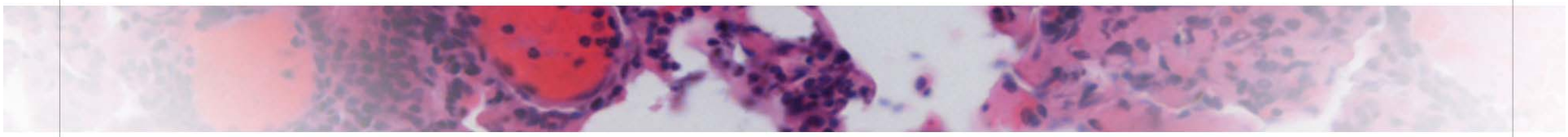

Combination of Loncastuximab Tesirine and Polatuzumab Vedotin Shows Increased Anti-Tumor Activity in Pre-Clinical Models of Non-Hodgkin Lymphoma

Nikoleta Sachini, Asma Jabeen, Patrick H. van Berkel, Francesca Zammarchi

ADC Therapeutics UK (Ltd), London, UK

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Conflict of Interest Disclosure

	Name of organization	Type of relationship
Nikoleta Sachini, PhD	ADC Therapeutics	Current Employment and Equity Ownership
Asma Jabeen, PhD	ADC Therapeutics	Current Employment and Equity Ownership
Patrick H. van Berkel, PhD	ADC Therapeutics	Current Employment, Equity Ownership and Patents & Royalties
Francesca Zammarchi, PhD	ADC Therapeutics	Current Employment, Equity Ownership and Patents & Royalties

Background & Aim of the Study

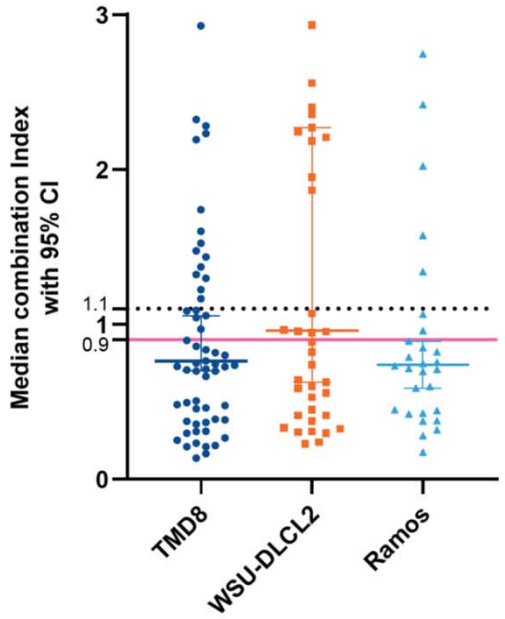
- Loncastuximab tesirine-lpyl (formerly ADCT-402) is a pyrrolobenzodiazepine (PBD) dimer-based antibody-drug conjugate (ADC) targeting human CD19. Loncastuximab tesirine has been recently approved by the United States Food and Drug Administration for the treatment of relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and it is currently being tested in multiple clinical trials, either as monotherapy or in combination with other anti-lymphoma drugs.

- Polatuzumab vedotin is an ADC composed of a humanized anti-CD79b monoclonal antibody conjugated to monomethyl auristatin E (vcMMAE) and it is approved for treatment of r/r DLBCL when used in combination with bendamustine and rituximab.

- The purpose of this study was to investigate the *in vitro* and *in vivo* anti-tumor activity of loncastuximab tesirine (lonca) combined with polatuzumab vedotin (pola) in pre-clinical models of non-Hodgkin lymphoma (NHL).

Combination of lonca with pola shows additive/synergistic effects in NHL-derived cell lines

A

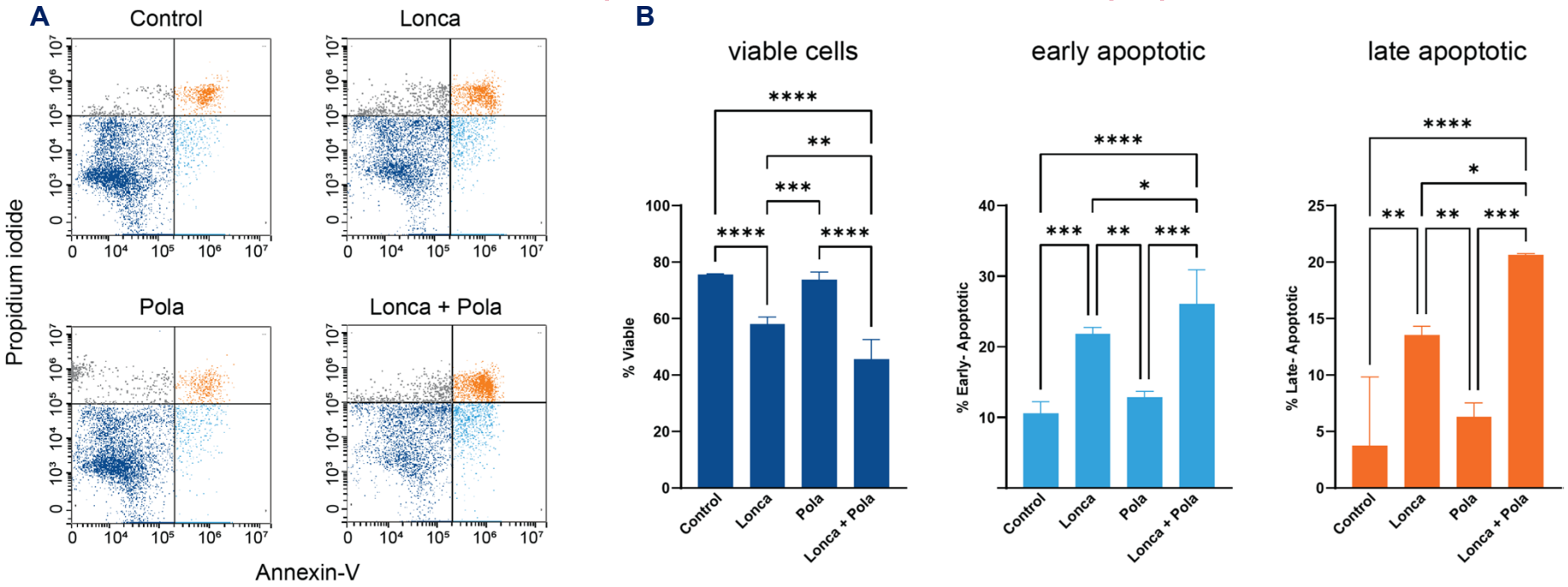


B

	Lonca +Pola	
	median combination index (CI)	95% confidence interval
TMD8	0.76	0.70-1.06
WSU-DLCL2	0.96	0.63-2.27
Ramos	0.74	0.59-0.89

A. Distribution of Chou-Talalay Combination Index (C.I.) values obtained combining lonca with pola in TMD8, WSU-DLCL2 and Ramos cell lines. In each plot, the horizontal line indicates median CI and the whiskers represent 95% confidence interval values. Pink horizontal line indicates threshold for synergy; dotted horizontal line indicates threshold for additivity. CI values > 3 have been omitted from the figure. **B**. Table summarizing median CI values with 95% confidence interval values (synergism CI<0.9, additive CI=0.9-1.1, antagonism/no benefit CI>1.1).

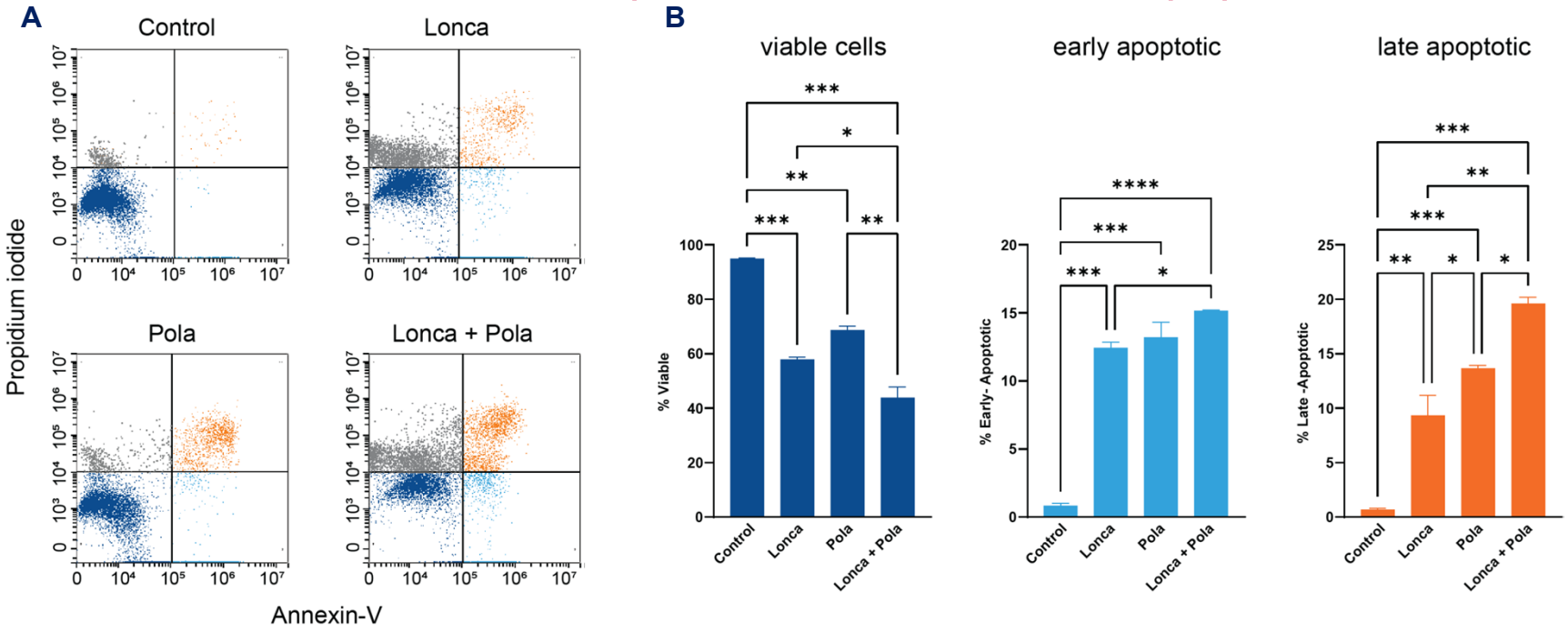
Combination of lonca with pola induces increased apoptosis



Annexin-V-FITC/PI flow cytometry analysis of **TMD8** cells treated with lonca, pola or combination of lonca with pola for 48 hours.

A. Representative flow cytometry plots showing viable (lower left quadrant), early apoptotic (lower right quadrant) and late-apoptotic (upper right quadrant) cells. **B.** Percentage of viable, early and late apoptotic cells. Data represent mean± S.E.M. of two independent experiments (*p ≤ 0.05, ****p ≤ 0.0001 calculated by ANOVA using the uncorrected Fisher's LSD multiple comparisons test with 95% confidence).

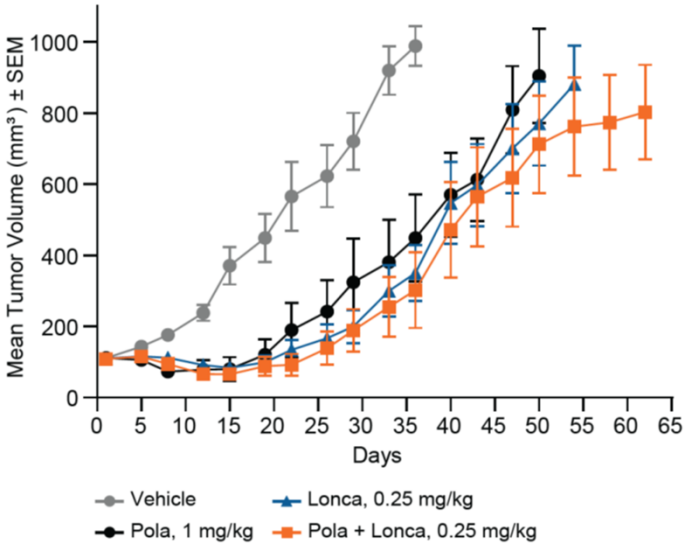
Combination of lonca with pola induces increased apoptosis

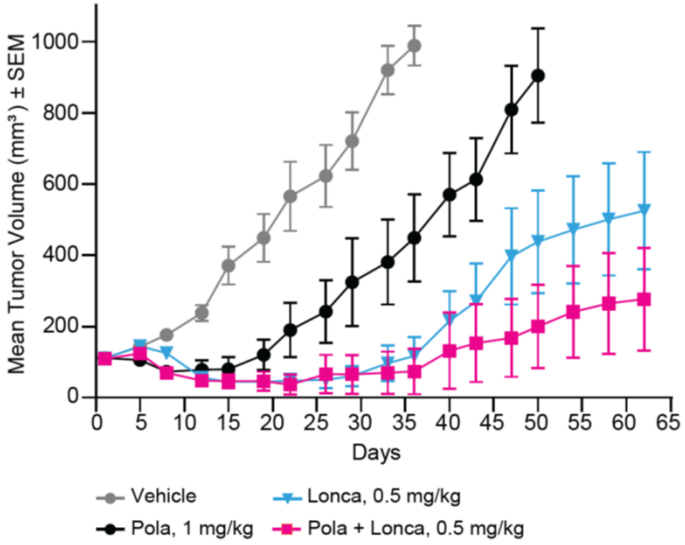


Annexin-V-FITC/PI flow cytometry analysis of **WSU-DLCL2** cells treated with lonca, pola or combination of lonca with pola for 72 hours.

A. Representative flow cytometry plots showing viable (lower left quadrant), early apoptotic (lower right quadrant) and late-apoptotic (upper right quadrant) cells. **B.** Percentage of viable, early and late apoptotic cells. Data represent mean± S.E.M. of two independent experiments (*p ≤ 0.05, ****p ≤ 0.0001 calculated by ANOVA using the uncorrected Fisher's LSD multiple comparisons test with 95% confidence).

Combination of lonca with pola shows improved anti-tumor activity in the WSU-DLCL2 xenograft model





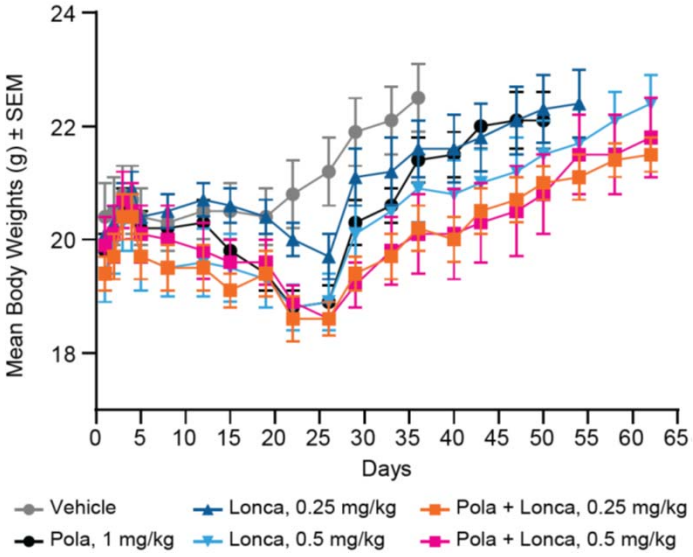
Lonca and pola were administered on day 1 once either alone or concomitantly (each group n=10 mice). A vehicle-treated group served as control.

Combination of lonca with pola shows improved anti-tumor activity in the WSU-DLCL2 xenograft model, cont.

B

response summary	PR	CR	TFS
vehicle	0	0	0
Pola, 1 mg/kg	3	3	1
Lonca, 0.25 mg/kg	3	0	0
Pola, 1 mg/kg + lonca, 0.25 mg/kg	2	3	1
Lonca, 0.5 mg/kg	2	5	3
Pola, 1 mg/kg + lonca, 0.5 mg/kg	1	8	6

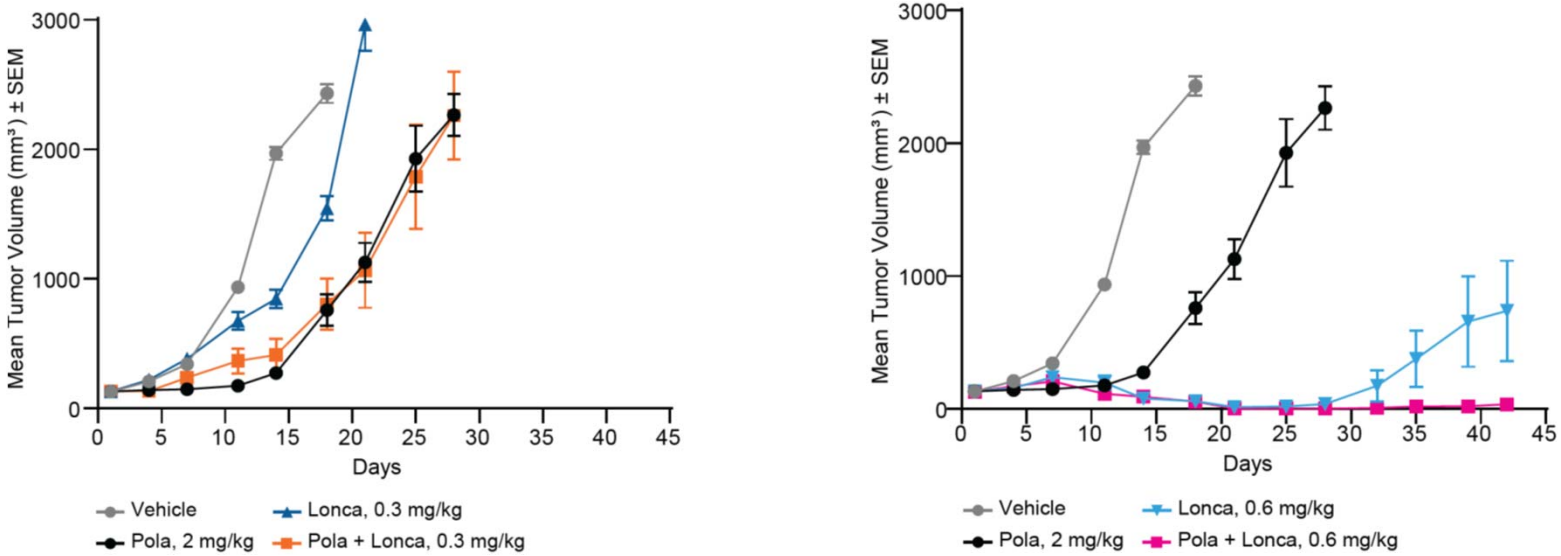
C



Lonca and pola were administered on day 1 once either alone or concomitantly (each group n=10 mice). A vehicle-treated group served as control.

B. Response summary. PR, partial response; CR, complete response; TFS, tumor-free survivors. **C**. Mean body weights ± standard error of the mean (SEM) for each treatment group.

Combination of lonca with pola shows improved anti-tumor activity in the Ramos xenograft model



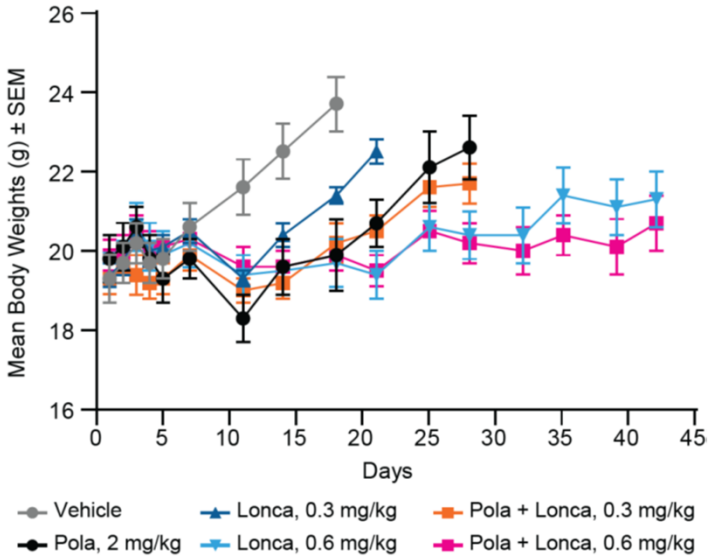
Lonca and pola were administered on day 1 once either alone or concomitantly (each group n=10 mice). A vehicle-treated group served as control.

Combination of lonca with pola shows improved anti-tumor activity in the Ramos xenograft model, cont.

B

response summary	PR	CR	TFS
vehicle	0	0	0
Pola, 2 mg/kg	0	0	0
Lonca, 0.3 mg/kg	0	0	0
Pola, 2 mg/kg + lonca, 0.3mg/kg	1	0	0
Lonca, 0.6 mg/kg	0	7	7
Pola, 2 mg/kg + lonca, 0.6 mg/kg	0	10	9

C



Lonca and pola were administered on day 1 once either alone or concomitantly (each group n=10 mice). A vehicle-treated group served as control.

B. Response summary. PR, partial response; CR, complete response; TFS, tumor-free survivors. **C**. Mean body weights ± standard error of the mean (SEM) for each treatment group.

Conclusions

- *In vitro*, combination of lonca with pola resulted in additive/synergistic effects in three NHL-derived cell lines and increased apoptosis (both early and late apoptosis) in TMD8 and Ramos cell lines.

- *In vivo*, combination of lonca with pola resulted in improved anti-tumor activity and better response rates in the WSU-DLCL2 and Ramos xenograft models . The combination was acceptably well tolerated in both models.

- In conclusion, these results suggest that combining lonca with pola is efficacious both *in vitro* as well as in *in vivo* in NHL preclinical models.

- Translation of these pre-clinical data in the clinic is currently being investigated in a phase I trial evaluating the safety and tolerability of loncastuximab tesirine in combination with polatuzumab vedotin in patients with r/r NHL (NCT04970901).