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CD19-mediated DNA Damage Boost in Lymphoma Cells Treated with Loncastuximab Tesirine in Combination with PARP Inhibitors

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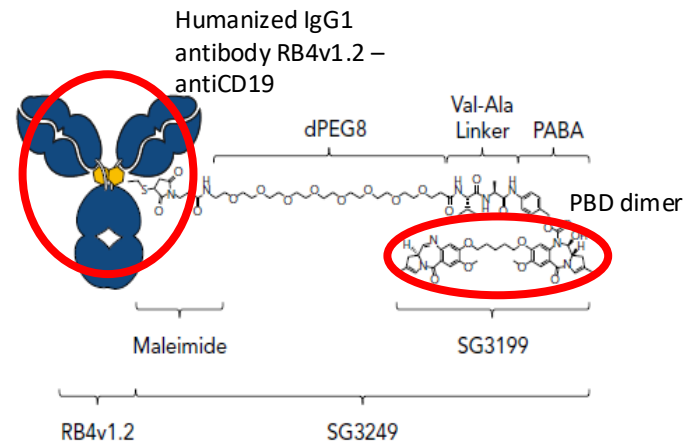
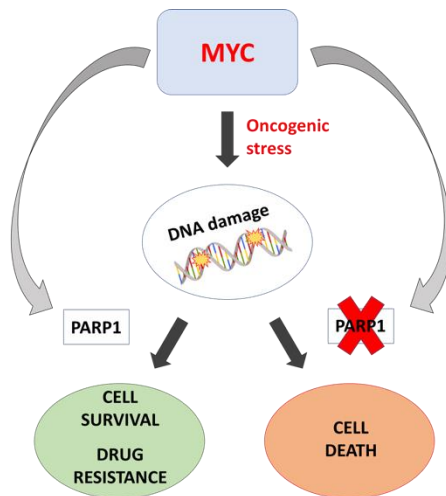
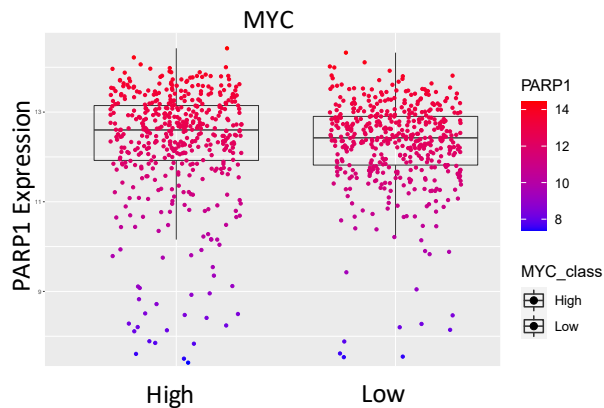


63RD ASH ANNUAL MEETING AND EXPOSITION – DECEMBER 11-14, 2021 – ATLANTA, GA



Targeting PARP in combination with CD19-selective delivery of DNA damage in DLBCL

Caracciolo D, *et al.* Exploiting MYC-induced PARPness to target genomic instability in multiple myeloma. *Haematologica*. 2021 Jan 1.

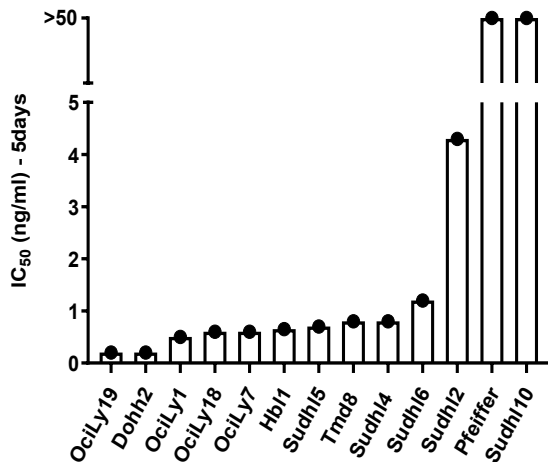


Zammarchi F, *et al.* *Blood*. 2018 Mar 8;131(10):1094-1105.

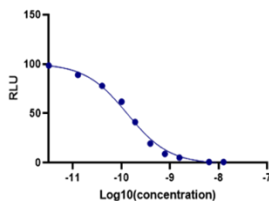


In vitro single agent activity of Loncastuximab tesirine and Talazoparib

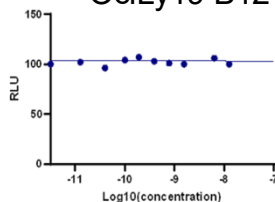
Lonca



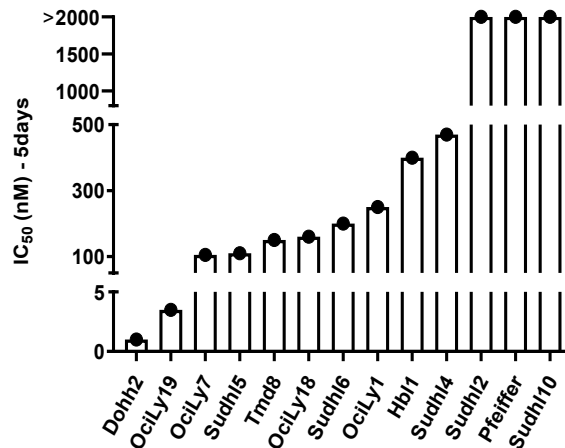
OciLy19 Lonca



OciLy19 B12



Talazoparib



Cell origin	OciLy19	Dohh2	OciLy1	OciLy18	OciLy7	Hbl1	Sudh15	Tmd8	Sudh14	Sudh16	Sudh12	Pfeiffer	Sudh10
MYC	Red	Green	Green	Green	Green	White	White	White	Green	Green	White	Green	Green
BCL-2	Green	Green	Green	Green	White	White	White	White	Green	Green	White	Green	Green
TP53	White	Orange	Orange	Orange	Orange	White	White	White	Orange	Orange	Orange	Orange	Orange
BRCA2	White	Orange	White	White	White	White	White	White	White	White	White	White	White
ATM	White	White	White	White	White	White	White	White	White	White	White	White	Orange

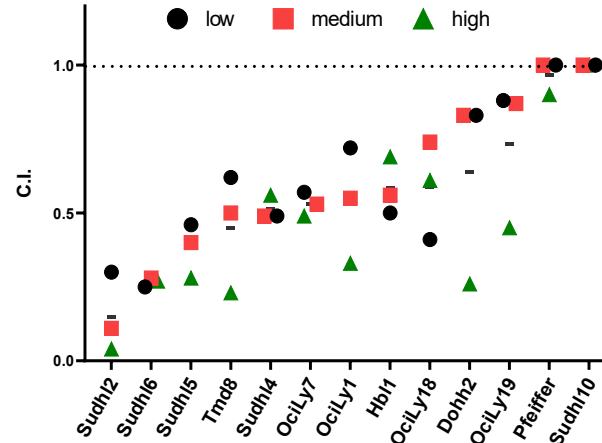
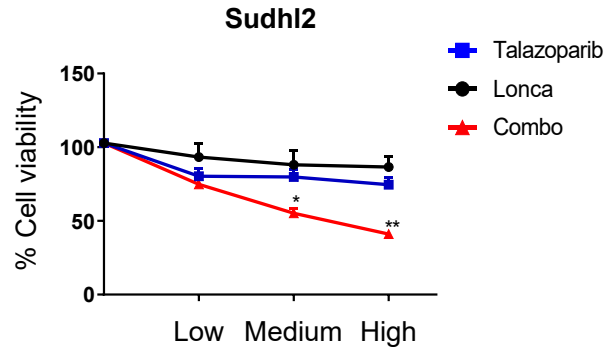
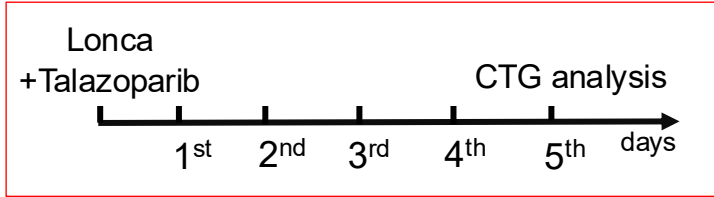
Cancer Cell Line Encyclopedia; canSAR BLACK; COSMIC-Catalogue of somatic mutations in cancer.

Cell origin	Dohh2	OciLy19	OciLy7	Sudh15	Tmd8	OciLy18	Sudh16	OciLy1	Hbl1	Sudh14	Sudh12	Pfeiffer	Sudh10
MYC	Green	Green	Green	White	White	Green	Green	White	White	Green	White	White	White
BCL-2	Green	Green	Green	White	White	Green	Green	White	White	Green	White	Green	Green
TP53	White	Orange	Orange	White	White	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange
BRCA2	Orange	White	White	White	White	White	White	White	White	White	White	White	White
ATM	White	White	White	White	White	White	White	White	White	White	White	White	Orange

■ GCB
■ ABC
■ Rearr.
■ Mut/del
■ Wt



DDR inhibition by Talazoparib enhances the cytotoxic effects of Loncastuximab tesirine in DLBCL cell lines



Combination index analysis:
 low dose:
 Lonca 0.25 ng/ml-Talazo 25nM
 med dose:
 Lonca 0.5 ng/ml-Talazo 50nM
 high dose:
 Lonca 1 ng/ml-Talazo 100nM

Cell origin	ABC		GCB		ABC		GCB		ABC		GCB	
MYC												
BCL-2												
TP53												
BRCA2												
ATM												
CD19 expr.	+	-	+	+	+	+	+	+	+	+	+	+

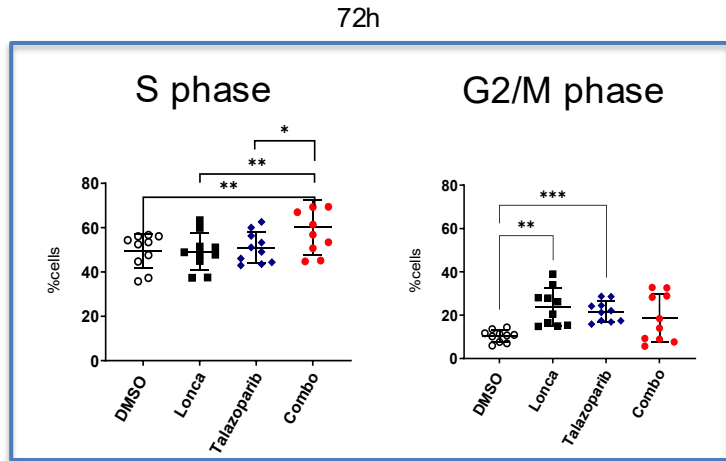
Legend: GCB (red), ABC (yellow), Rearr. (green), Mut/del (orange), Wt (white)

Cancer Cell Line Encyclopedia; canSAR BLACK; COSMIC-Catalogue of somatic mutations in cancer.



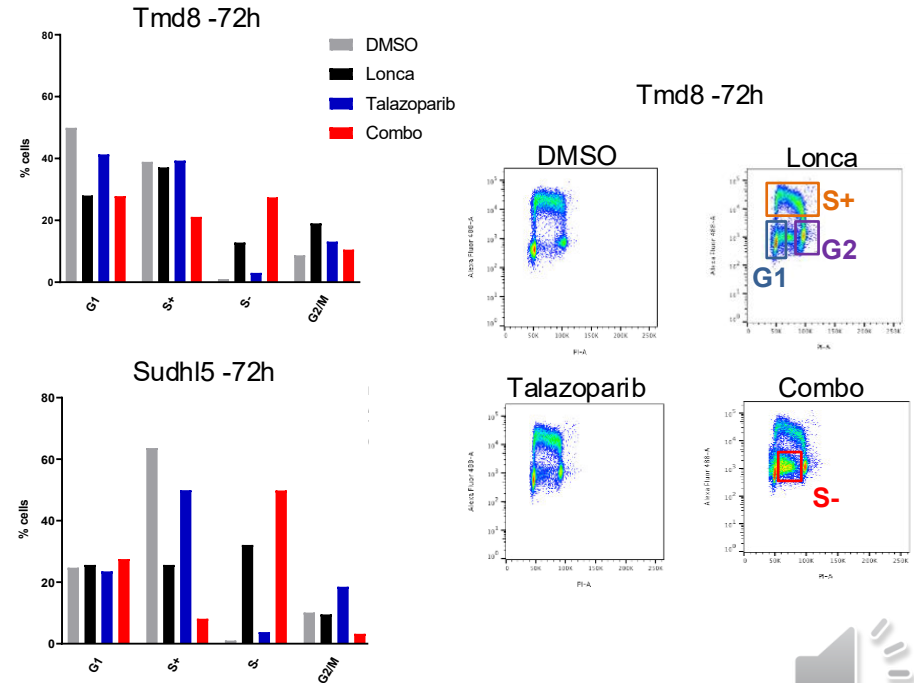
Talazoparib enhances Lonca-mediated S phase cell cycle arrest

1. Cell cycle analysis with Propidium Iodide



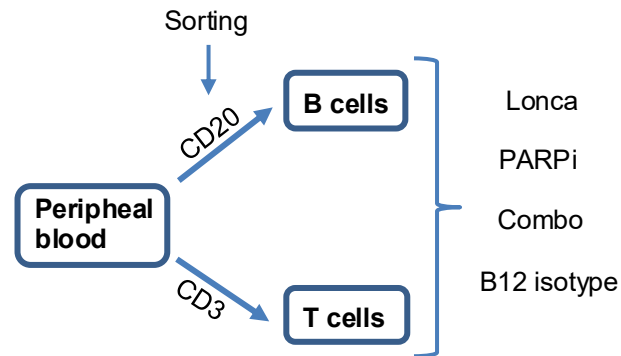
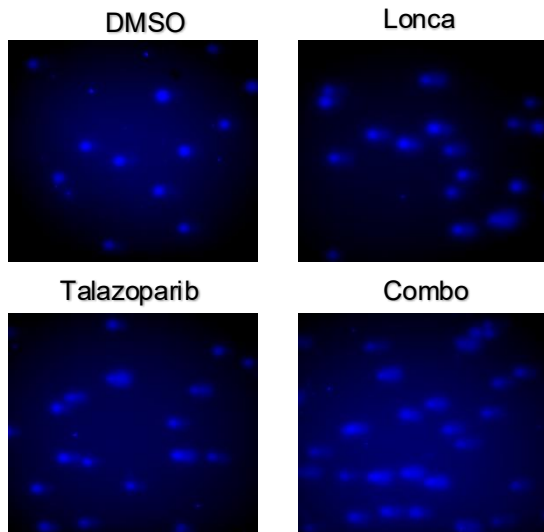
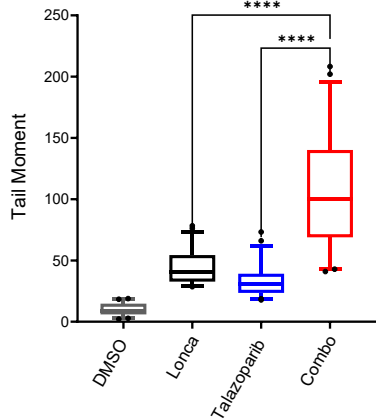
Aggregate data analysis of cell cycle variations after 72h of treatments in 10 representative DLBCL cell lines.

2. Cell cycle analysis with Propidium Iodide and Brdu

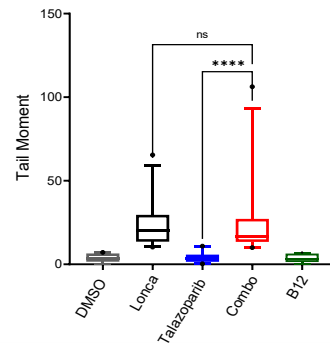


DNA damage detection in DLBCL cell lines and healthy donors-derived B and T cells

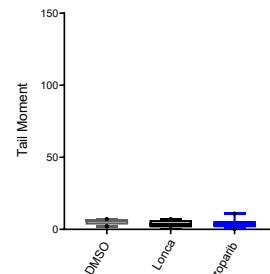
OciLy18 – 24h



B cells – 24h



T cells – 24h



Conclusions

1. Talazoparib significantly enhances Loncastuximab tesirine anti-proliferative effects in DLBCL cell lines.
2. Combinational treatment induces S-phase cell cycle arrest suggesting a mechanistic interaction between the two drugs
3. DDR inhibition by Talazoparib boosts Lonca-mediated DNA damage in neoplastic B cells.



Disclosures:

Zammarchi: *ADC Therapeutics:* Current Employment, Current equity holder in publicly-traded company, Patents & Royalties.

Van Berkel: *ADC Therapeutics:* Current Employment, Current equity holder in publicly-traded company, Patents & Royalties.

Pileri: *NANOSTRING:* Other: ADVISORY BOARD; *ROCHE:* Other: ADVISORY-BOARD; *CELGENE:* Other: ADVISORY BOARD.

Tarella: *ADC-THERAPEUTICS:* Other: ADVISORY BOARD; *Abbvie:* Other: ADVISORY BOARD.

Derenzini: *TG-THERAPEUTICS:* Research Funding; *ASTRA-ZENECA:* Consultancy, Other: ADVISORY-BOARD; *BEIGENE:* Other: ADVISORY BOARD; *TAKEDA:* Research Funding; *ADC-THERAPEUTICS:* Research Funding.

