


YOUNG SCIENCE FORUM: IL FUTURO NASCE IN LABORATORIO



**L'asse p53/xCT/GSH come potenziale target
terapeutico nella Leucemia Linfatica Cronica**

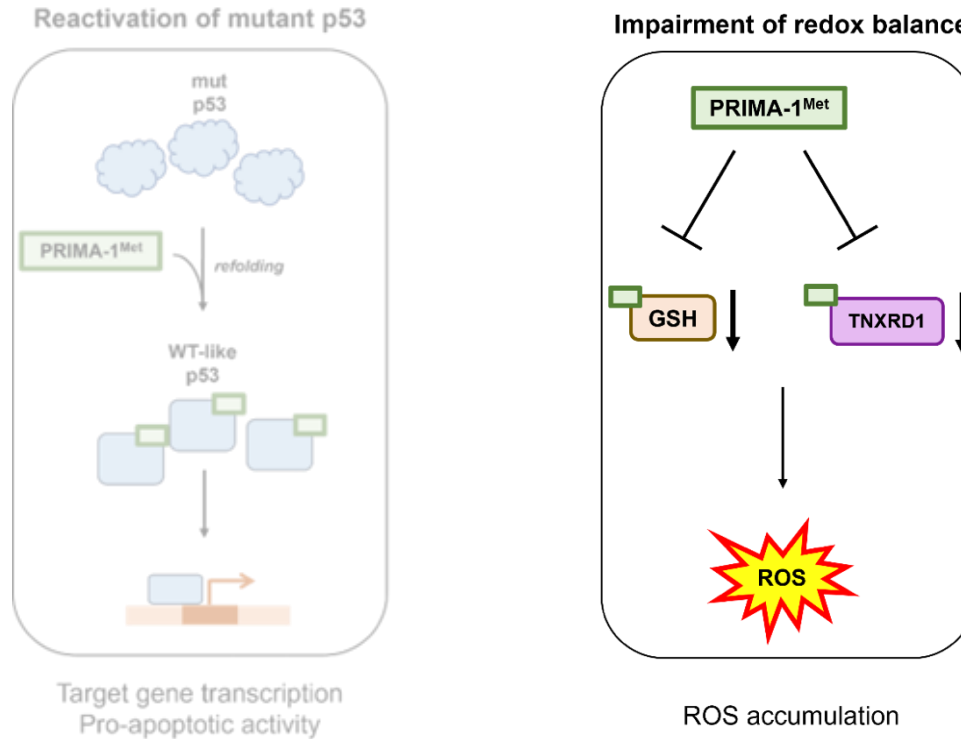
Martina Pasino

IRCCS AOM - Ospedale San Martino

TORINO, ACCADEMIA DI MEDICINA | 4-5 GIUGNO 2026

I have no disclosures to declare

The antitumor activity of PRIMA-1^{Met}



Adapted from Menichini et al, *Cells*, 2021 and Liu et al., *Nature Com*, 2017

PRIMA-1^{Met} and Sulfasalazine: rationale

ARTICLE

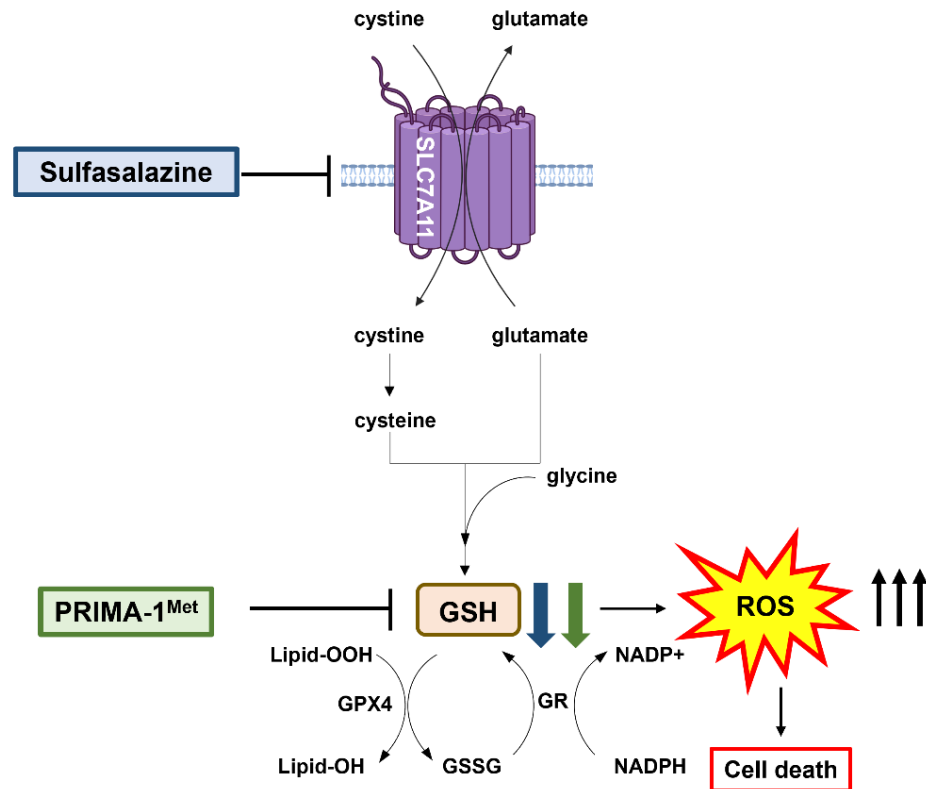
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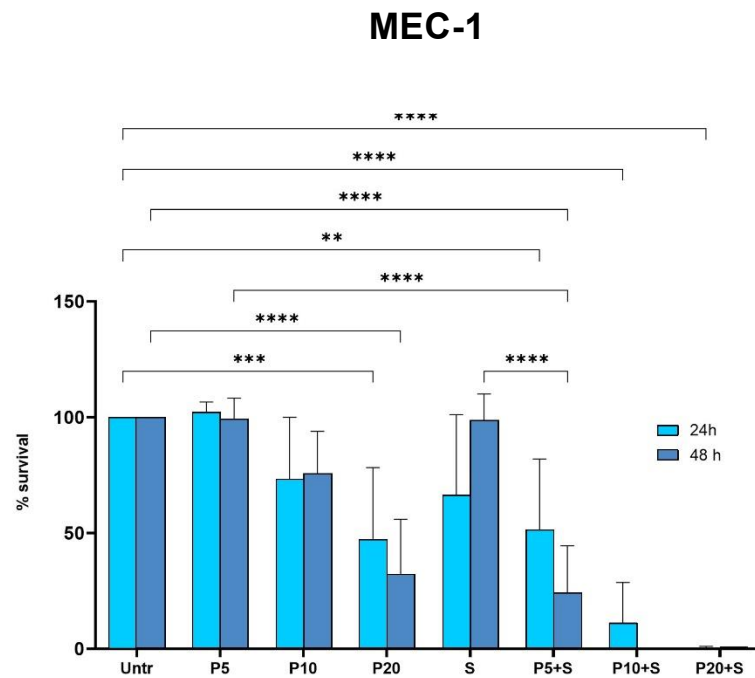
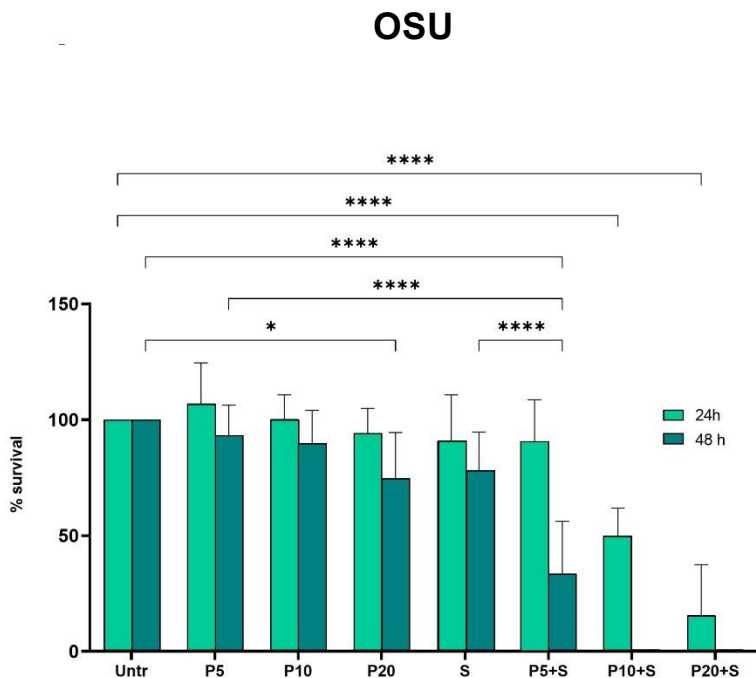
OPEN

Inhibiting the system x_C^- /glutathione axis selectively targets cancers with mutant-p53 accumulation

David S. Liu^{1,2,3}, Cuong P. Duong², Sue Haupt¹, Karen G. Montgomery¹, Colin M. House¹, Walid J. Azar¹, Helen B. Pearson^{1,3,†}, Oliver M. Fisher⁴, Matthew Read^{1,2,3}, Glen R. Guerra^{1,2,3}, Ygal Haupt^{1,3}, Carleen Cullinane^{1,3}, Klas G. Wiman⁵, Lars Abrahmsen⁶, Wayne A. Phillips^{1,2,3,7,*} & Nicholas J. Clemons^{1,3,*}



1. The combined treatment PRIMA-1^{Met} + SAS induces cell death in CLL cell lines



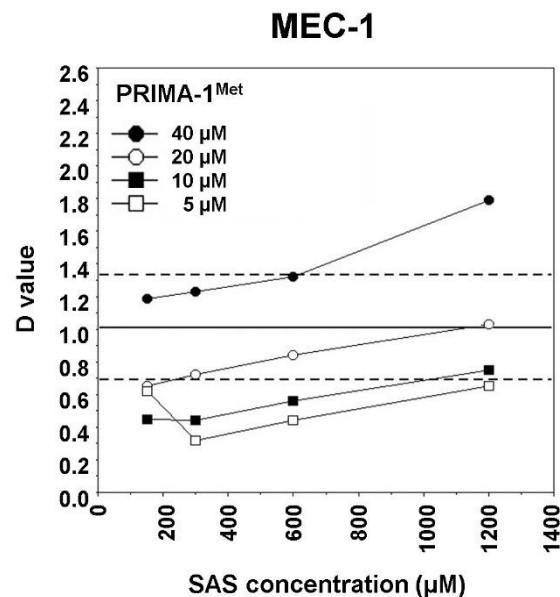
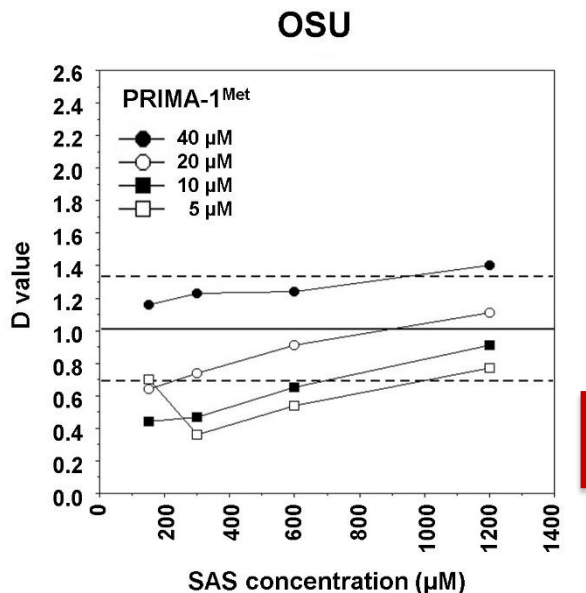
2. PRIMA-1^{Met} + SAS synergistically decrease CLL cells survival

$$D = \frac{Sc}{Se} + \frac{Pc}{Pe}$$

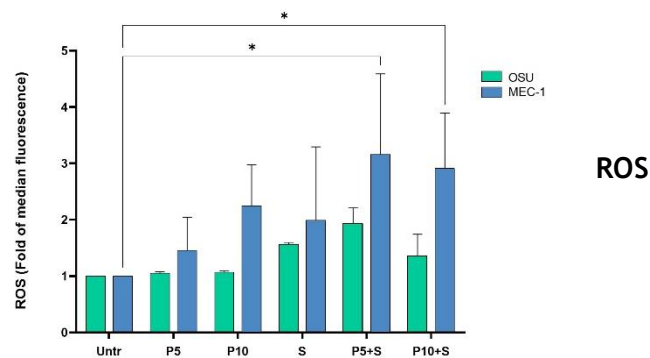
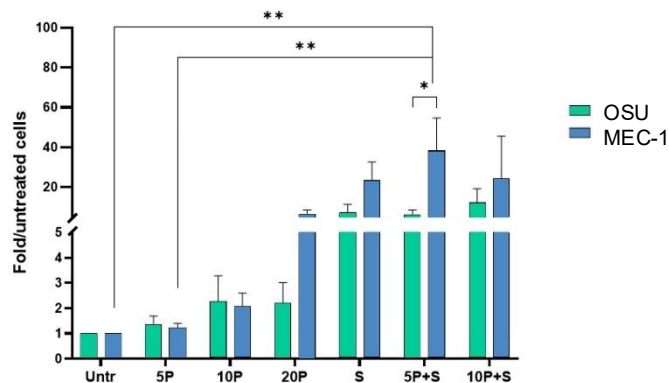
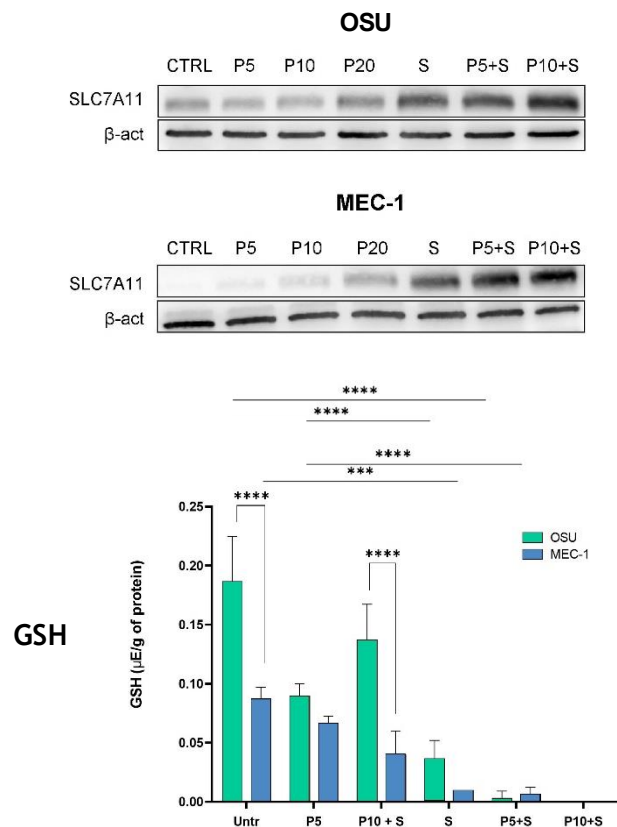
D > 1 antagonism

D = 1 additivity

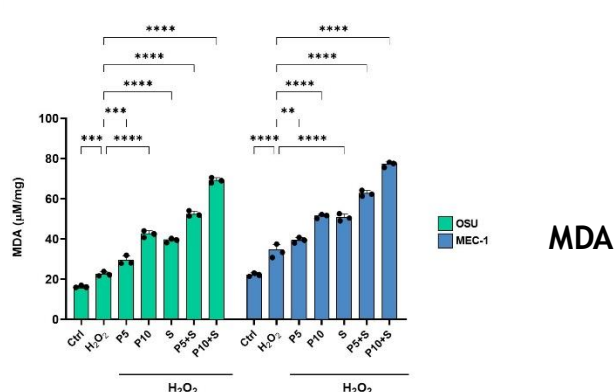
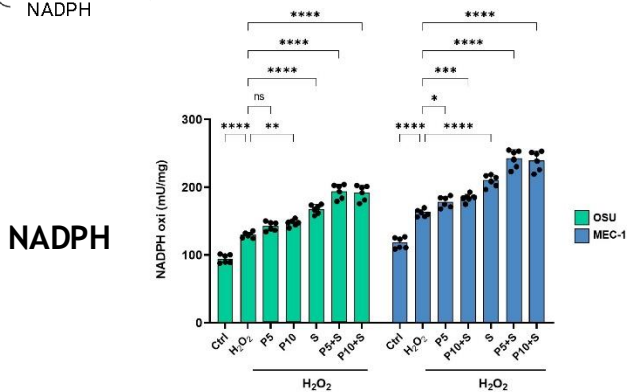
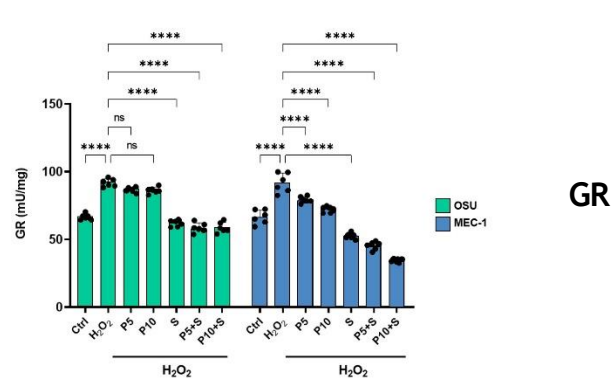
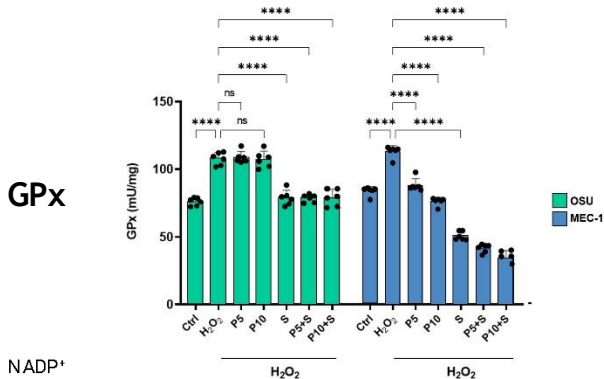
D < 1 synergism



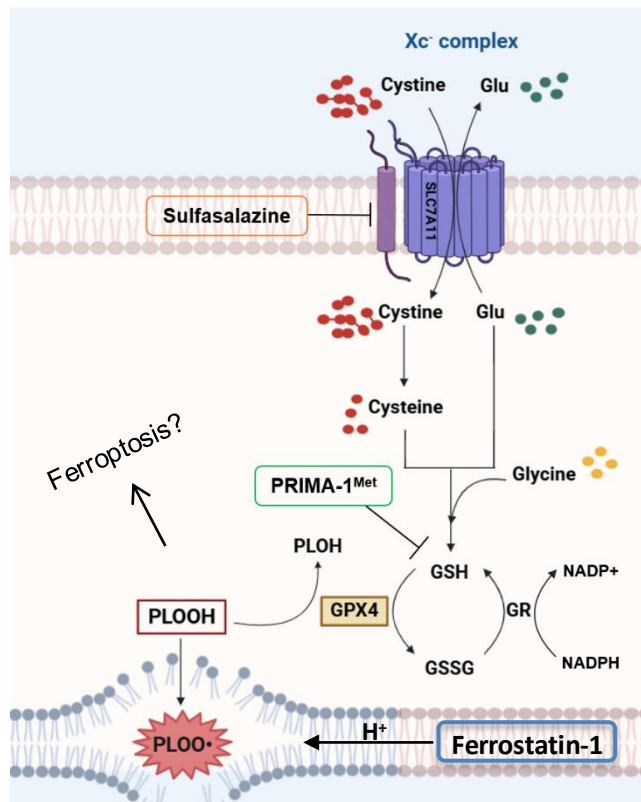
3. PRIMA-1^{Met} + SAS treatment depletes intracellular GSH and enhances ROS levels



4. PRIMA-1^{Met} + SAS treatment alters the redox balance in OSU and MEC-1 cells

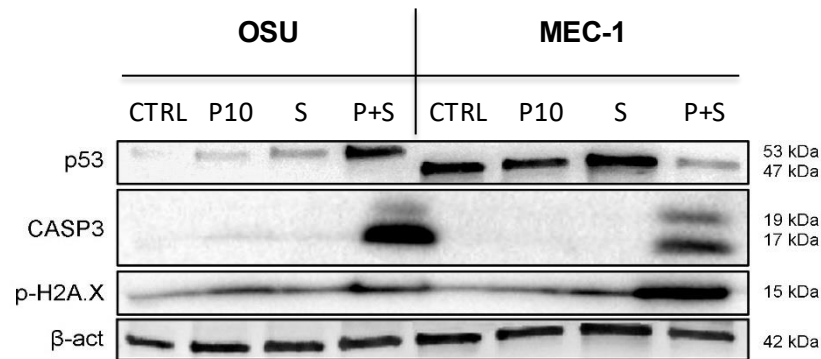
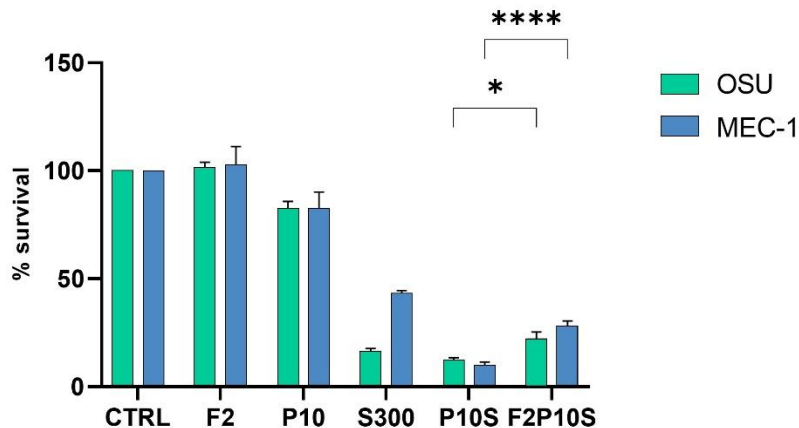


Can PRIMA-1^{Met} + SAS induce ferroptosis?

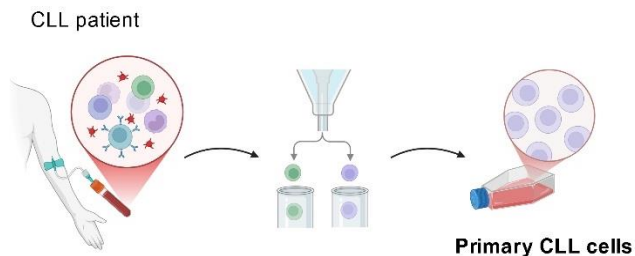


Adapted from Velkova et al., *J. Pers. Med.*, 2023

5. PRIMA-1^{Met} + SAS treatment induces ferroptosis as well as apoptosis in CLL cell lines



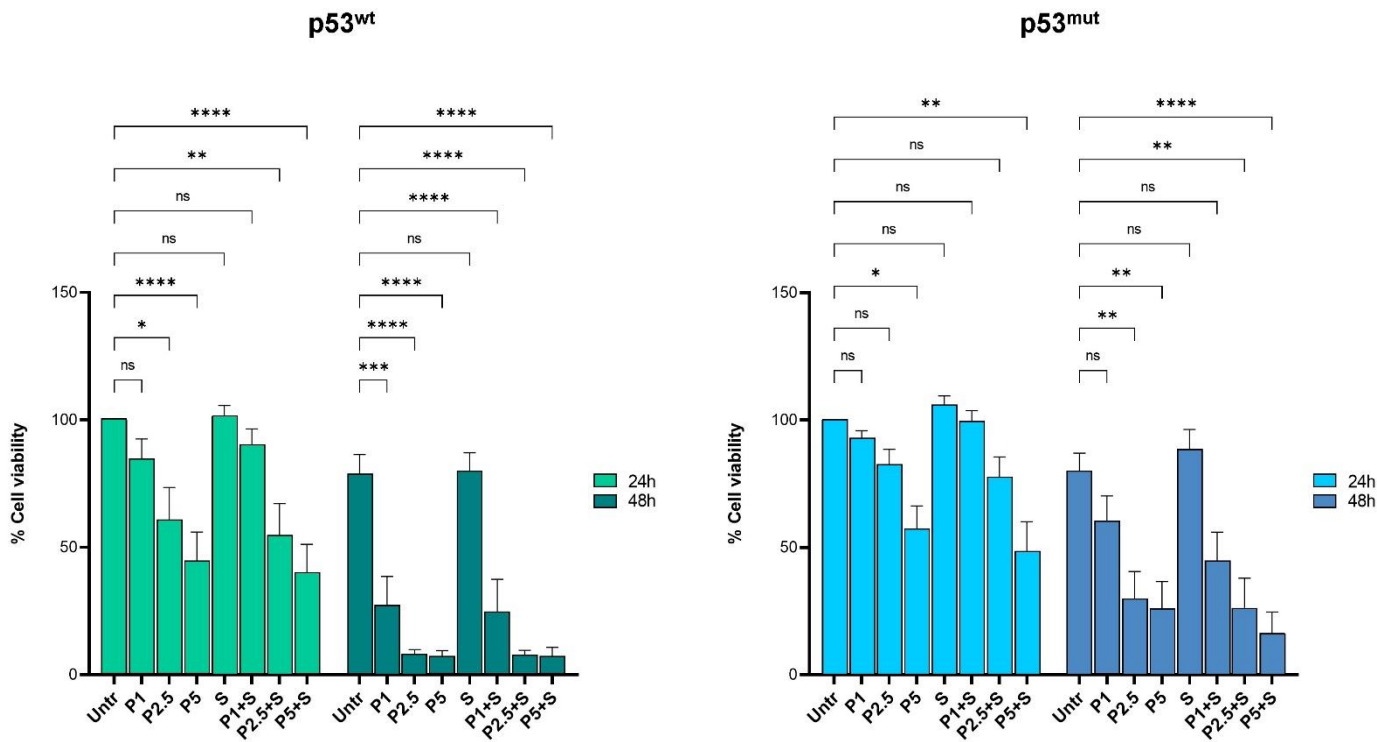
Primary CLL cells as *ex vivo* model of CLL



Biological and molecular features of CLL patient's samples

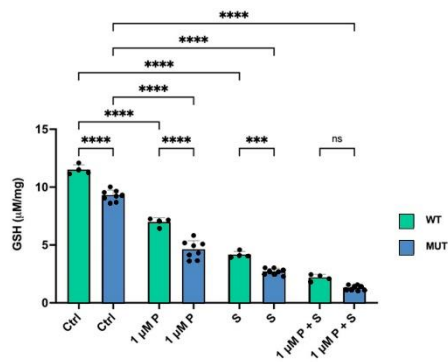
Patient ID	TP53 status	TP53 mutation	TP53 mutation (%)	Variant effect	FISH				IgHV status
					17p-	11q-	12	13q-	
#1	MUT	p.G245S	84	missense	yes (86%)	no	no	no	mut
		p.R213L	1.7	missense					
		p.R248W	1.5	missense					
		p.V197E	8.7	missense					
		p.143E	93.2	missense					
#2	MUT	p.I195T	43.87	missense	yes (64%)	no	no	yes (86%)	unmut
#3	MUT	p.I195T	100	missense	no	no	yes (12%?)	yes (93%)	mut
#4	MUT	p.I195T	100	missense	yes (80%)	no	no	no	unmut
#5	MUT	p.P89fs	78	frame shift deletion	yes (73%)	no	no	yes (89%)	mut
		p.T211I	4	missense					
		p.K164E	6	missense					
		p.S215G	7.5	missense					
		p.F134V	Sanger	missense					
#7	MUT	p.V272M	100	missense	yes (98%)	no	no	no	mut
#8	MUT	p.Y234C	Sanger	missense	yes (60%)	yes (62%)	no	yes (50%)	mut
#9	MUT	p.I195T		missense	yes (25%)	no	no	no	unmut
#10	WT				no	no	no	yes (92%)	unmut
#11	WT				no	no	no	yes (71%)	mut
#12	WT				no	no	no	yes (90%)	mut
#13	WT				no	no	no	yes (22%)	unmut
#14	WT				no	no	yes (68%)	no	unmut
#15	WT				no	yes (57%)	no	no	unmut
#16	WT				no	no	yes (72%)	no	mut
#17	WT				no	no	no	no	mut

6. Primary CLL cell survival is affected by PRIMA-1^{Met} + SAS treatment regardless of the p53 status

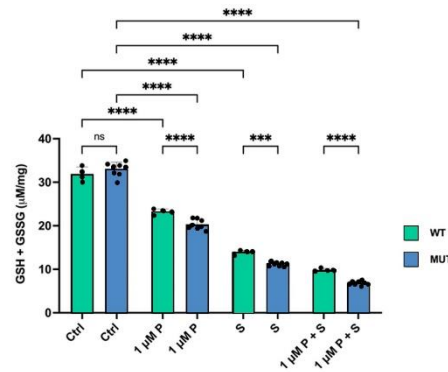


7. PRIMA-1^{Met} + SAS treatment modulates the redox status also in CLL primary cells

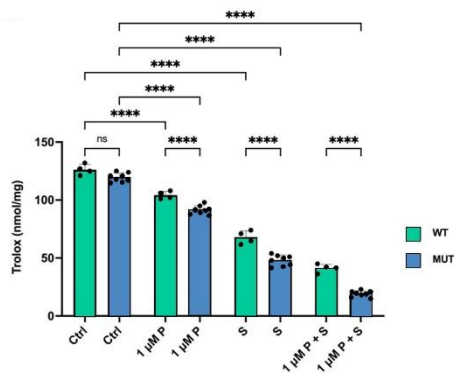
GSH



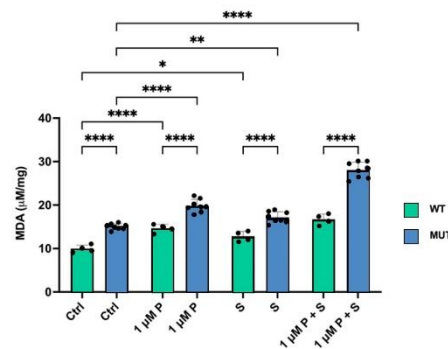
GSH + GSSG



Trolox



MDA



Conclusions

- ❑ The combination of PRIMA-1^{Met} and SAS synergistically causes a redox imbalance and increases oxidative stress in CLL cells.
- ❑ Mutant p53 CLL cells are more severely compromised in their ability to handle oxidative stress.
- ❑ The PRIMA-1^{Met} and SAS combined strategy seems to be a promising alternative for the treatment of CLL patients resistant to common therapies.



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5x mille



ALLEANZA
CONTRO
IL CANCRO



MARIE CURIE ACTIONS



European
Commission

Horizon 2020
European Union funding
for Research & Innovation



Fondazione
VERONESI



Ministero della Salute