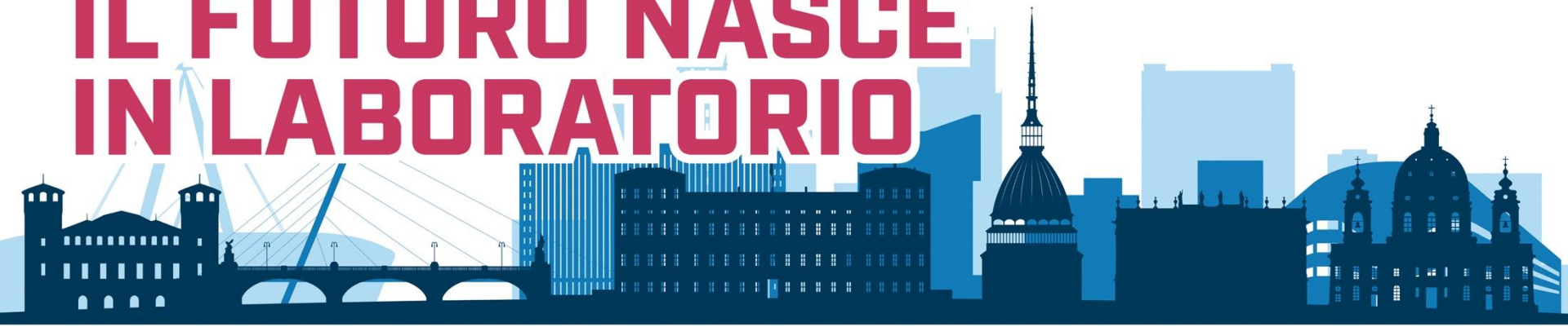
YOUNG SCIENCE FORUM: IL FUTURO NASCE IN LABORATORIO



L'oncosoppressore p53 nella Leucemia Linfatica Cronica: nuovi approcci per riattivare le proteine p53 mutate

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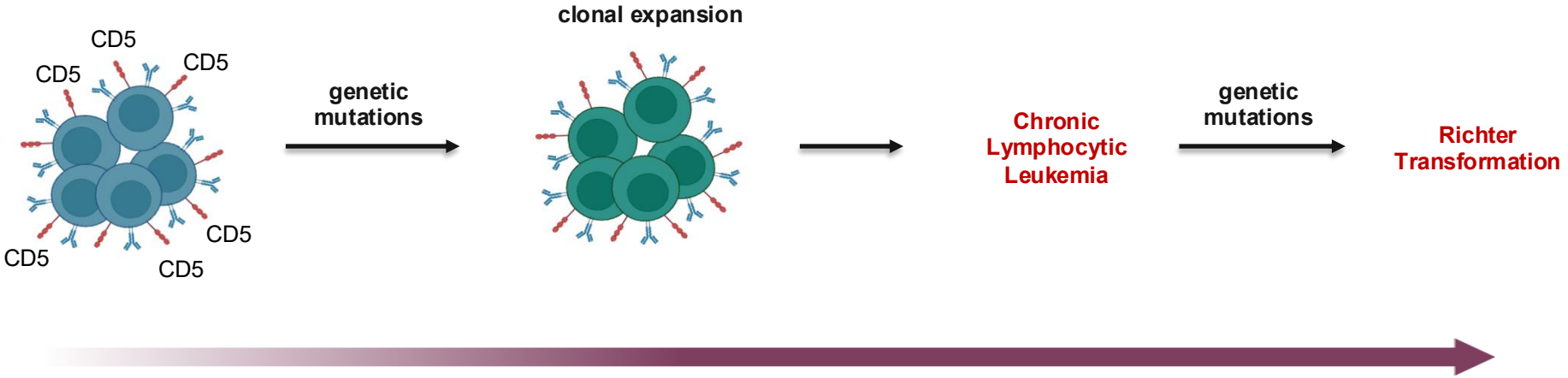
IRCCS AOM – Ospedale San Martino

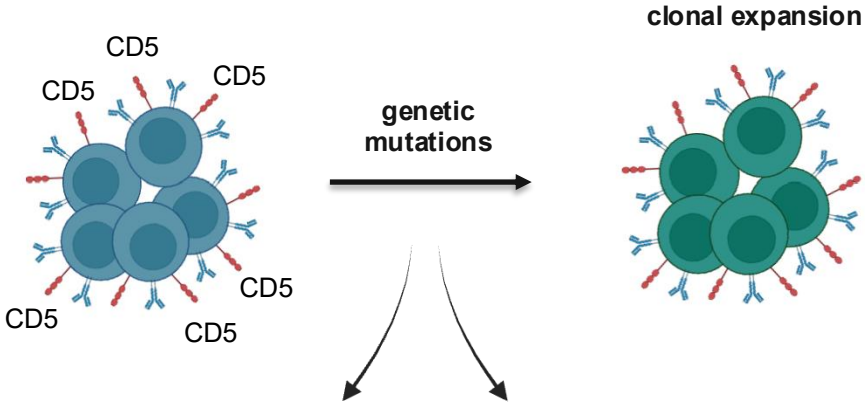
No disclosures to declare

Chronic Lymphocytic Leukemia

Monoclonal, slow-growing cancer characterized by the accumulation of mature, **CD5+ B lymphocytes** in the blood, bone marrow, and lymphoid tissues



Chronic Lymphocytic Leukemia



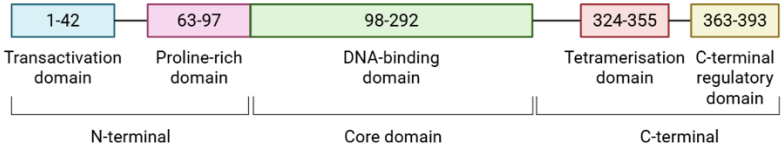
KARYOTYPE ABERRATIONS

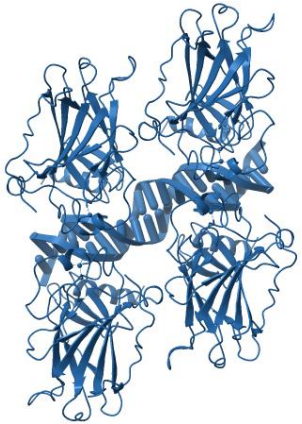
- Del 13q
- Del 11q
- **Del 17p**
- Trisomy 12

GENE MUTATIONS

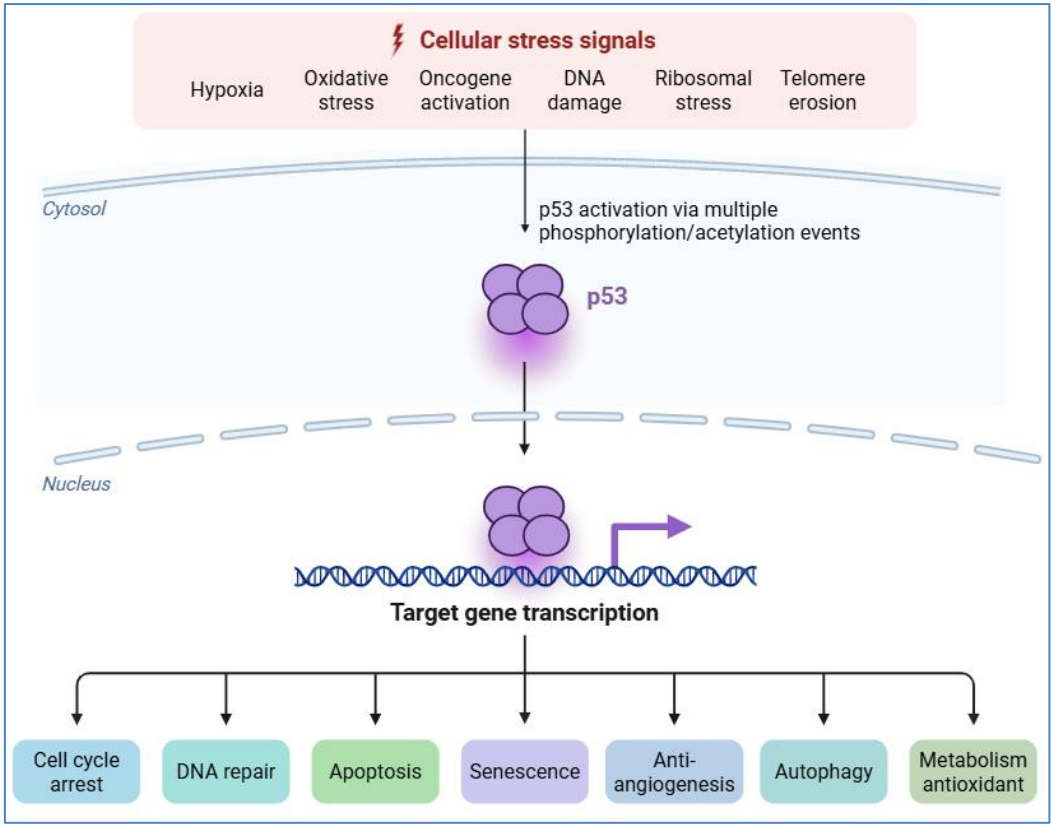
- ***TP53***
- *ATM*
- *NOTCH*
- *BIRC3*

The p53 protein



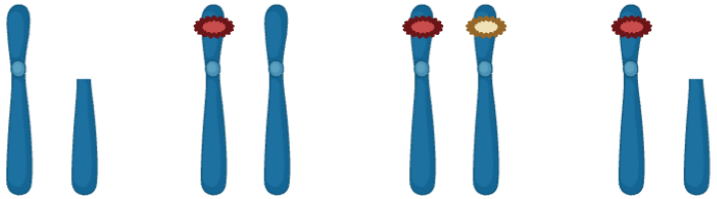


Crystal structure of the p53 core domain bound to a full consensus site as a self-assembled tetramer NIH 3D. https://doi.org/10.60705/3DPX/9324.2



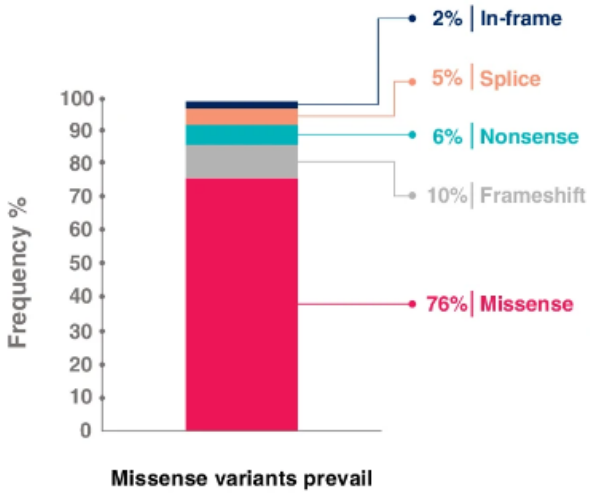
Adapted from Tanaka et al, *Oncotarget*, 2018 and Chéne, *Nature Rev Can*, 2003

TP53 mutations in CLL



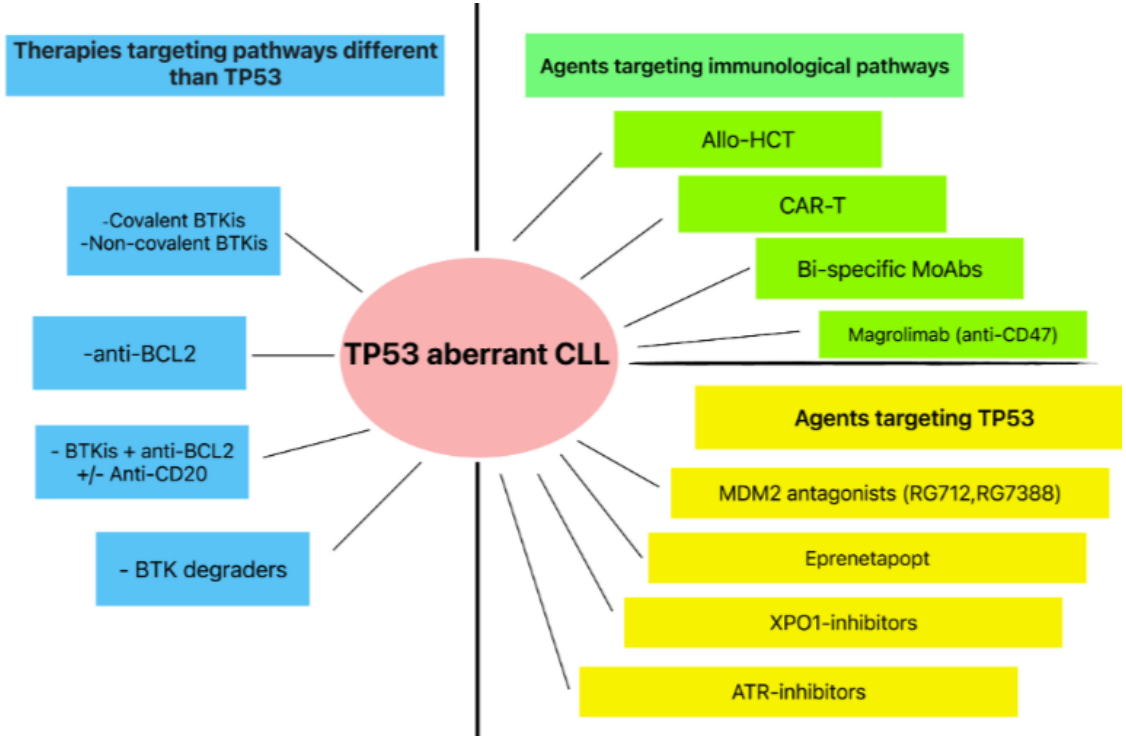
TP53 status	wt del (17p)	mut wt	mut mut	mut del (17p)
Proportions of *TP53* aberrations	~10%	~30%		~60%

Adapted from Campo et al, *Haematologica*, 2018



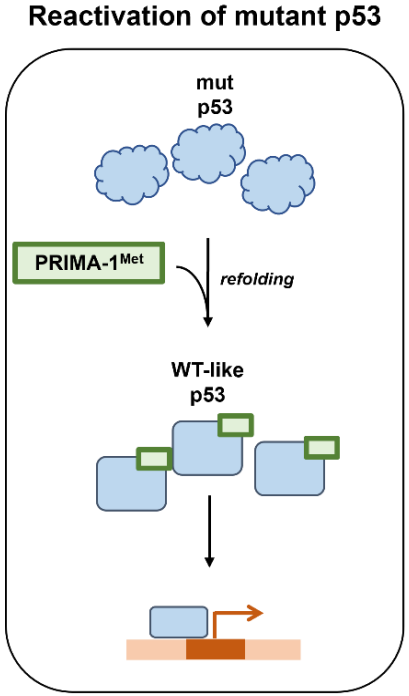
ERIC recommendations for *TP53* mutation analysis in CLL-2024 update. *Leukemia*, 2024

Current strategies for targeting *TP53* disruption in CLL

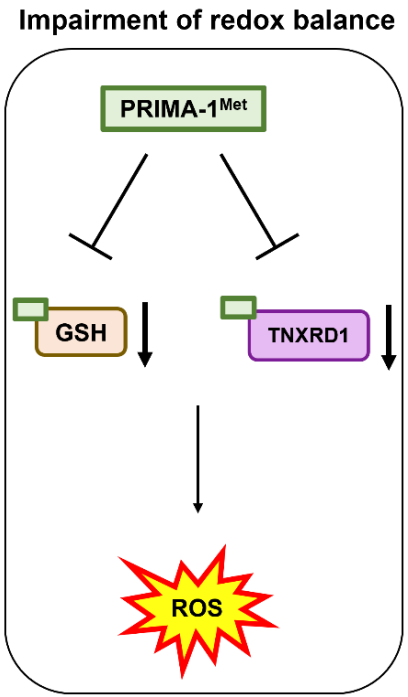


Molica et al, *Hematological Oncology*, 2024

The antitumor activity of PRIMA-1^{Met}



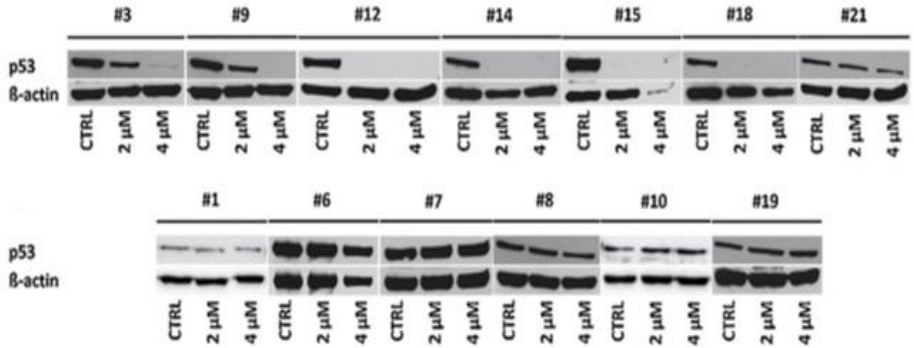
Target gene transcription
Pro-apoptotic activity

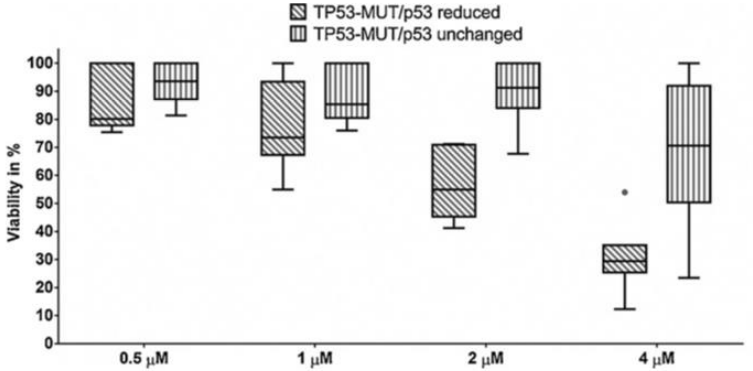


ROS accumulation

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

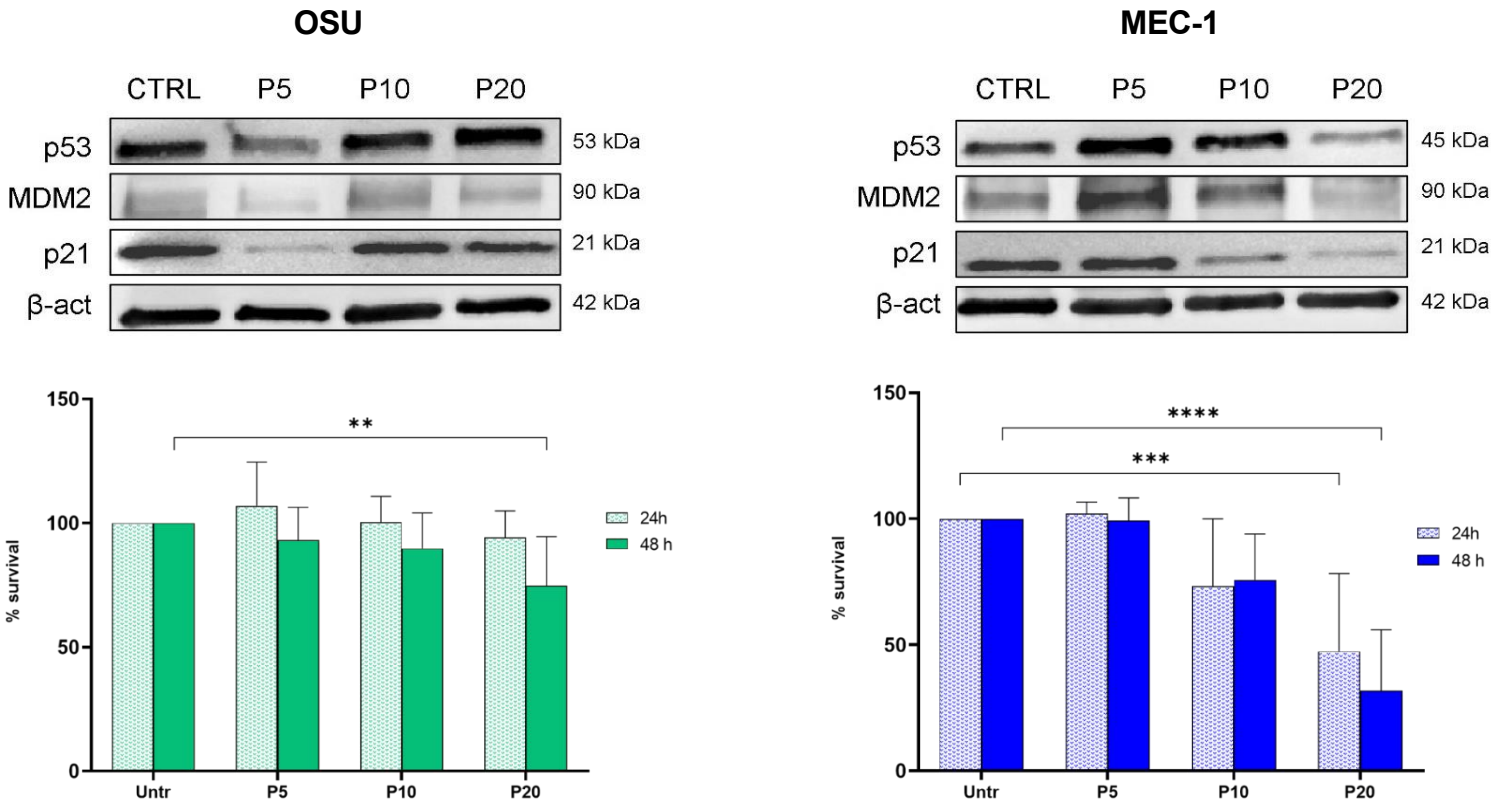
PRIMA-1^{Met} cytotoxic effect is similar in *TP53*-mutated and wild-type subsets





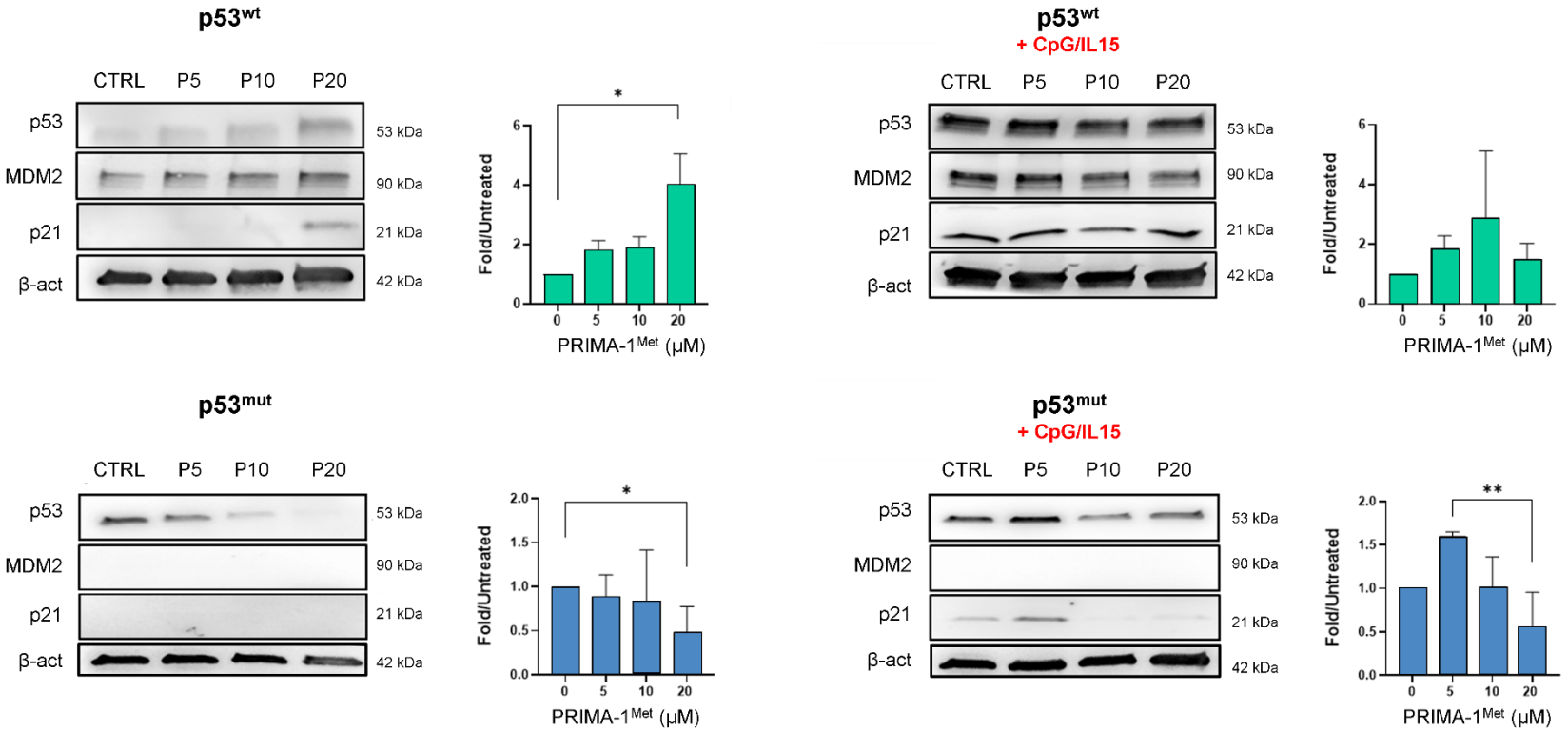
Jaskova et al, *Leukemia Research*, 2020

PRIMA-1^{Met} is unable to rescue mutant p53 transcriptional function in CLL cell models



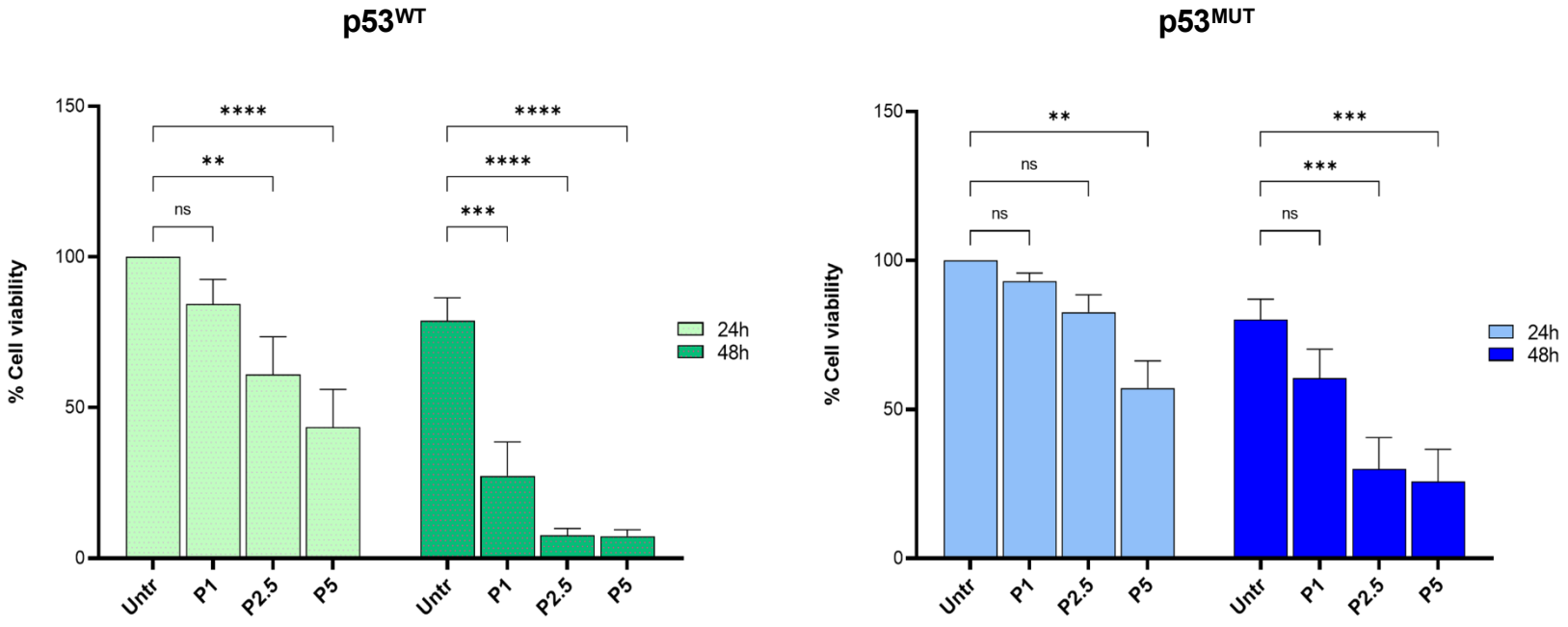
Pasino et al, *Int J Mol Sci*, 2025

PRIMA-1^{Met} is unable to rescue mutant p53 transcriptional function in primary CLL cells



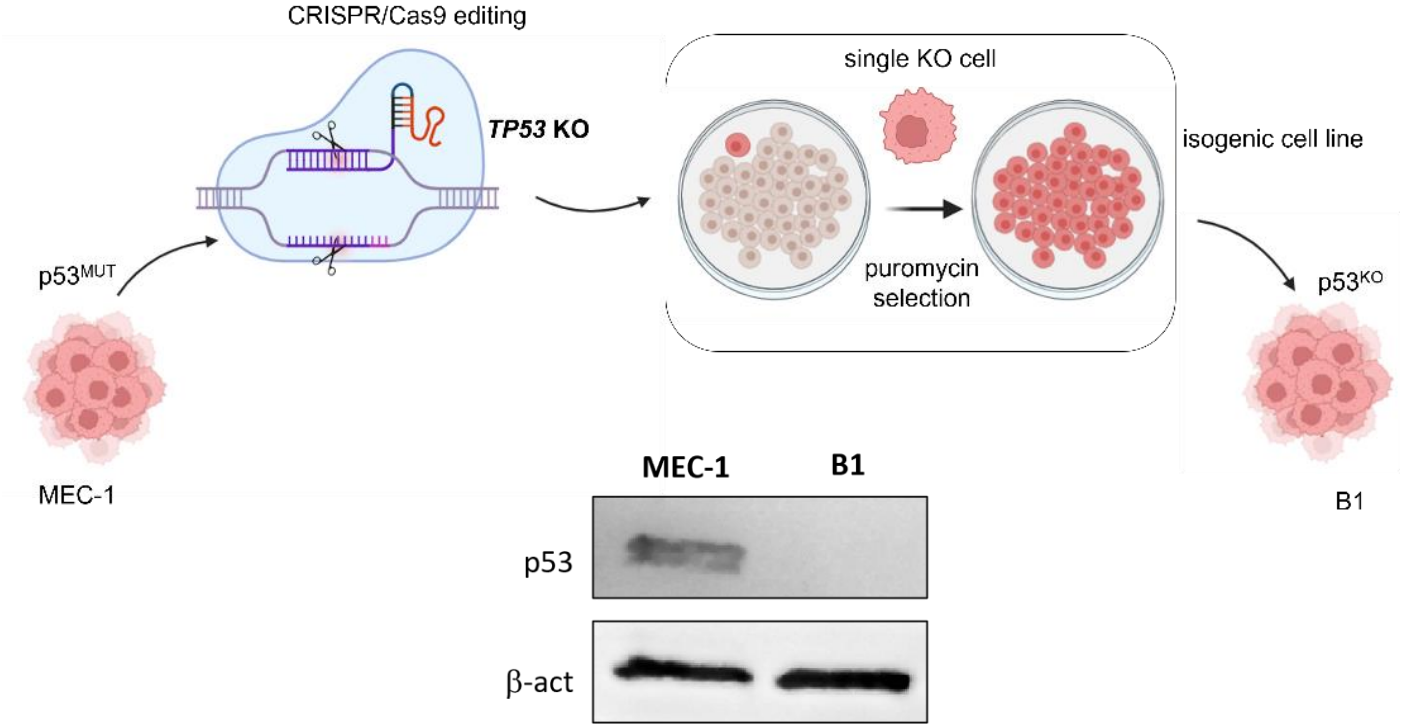
Pasino et al, *Int J Mol Sci*, 2025

PRIMA-1^{Met} reduces viability of both p53-wild-type and mutated primary CLL cells

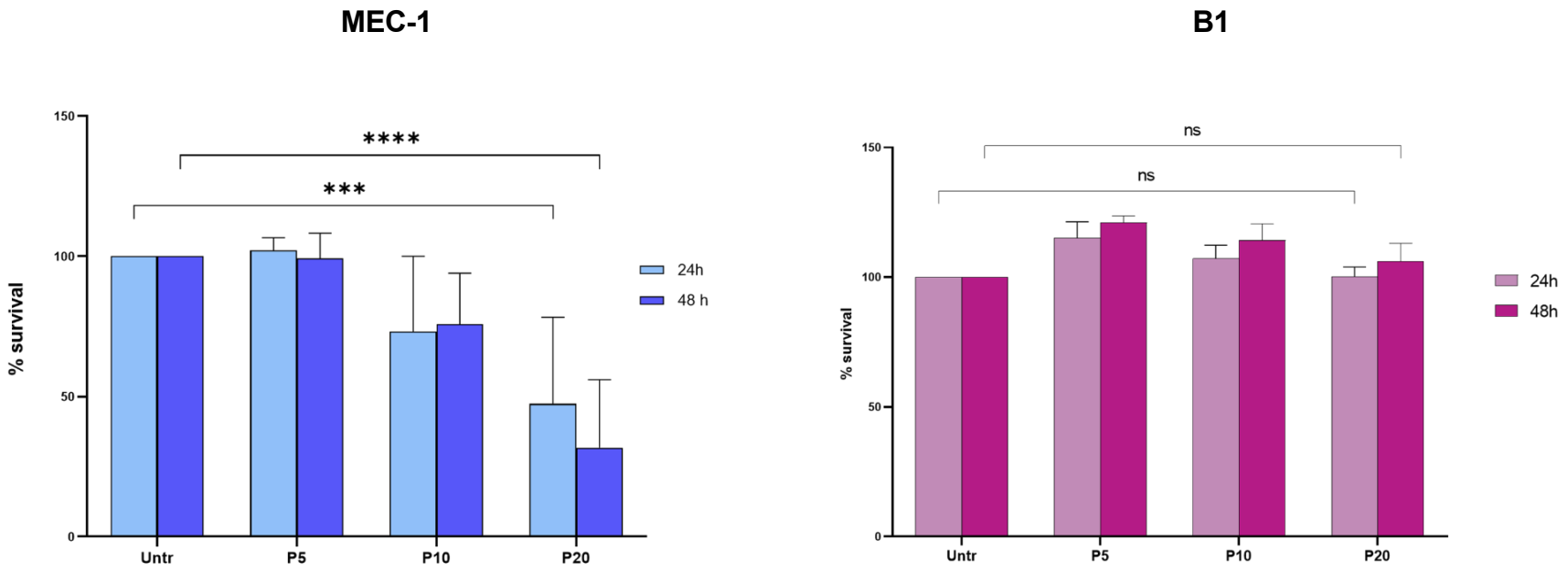


Pasino et al, *Int J Mol Sci*, 2025

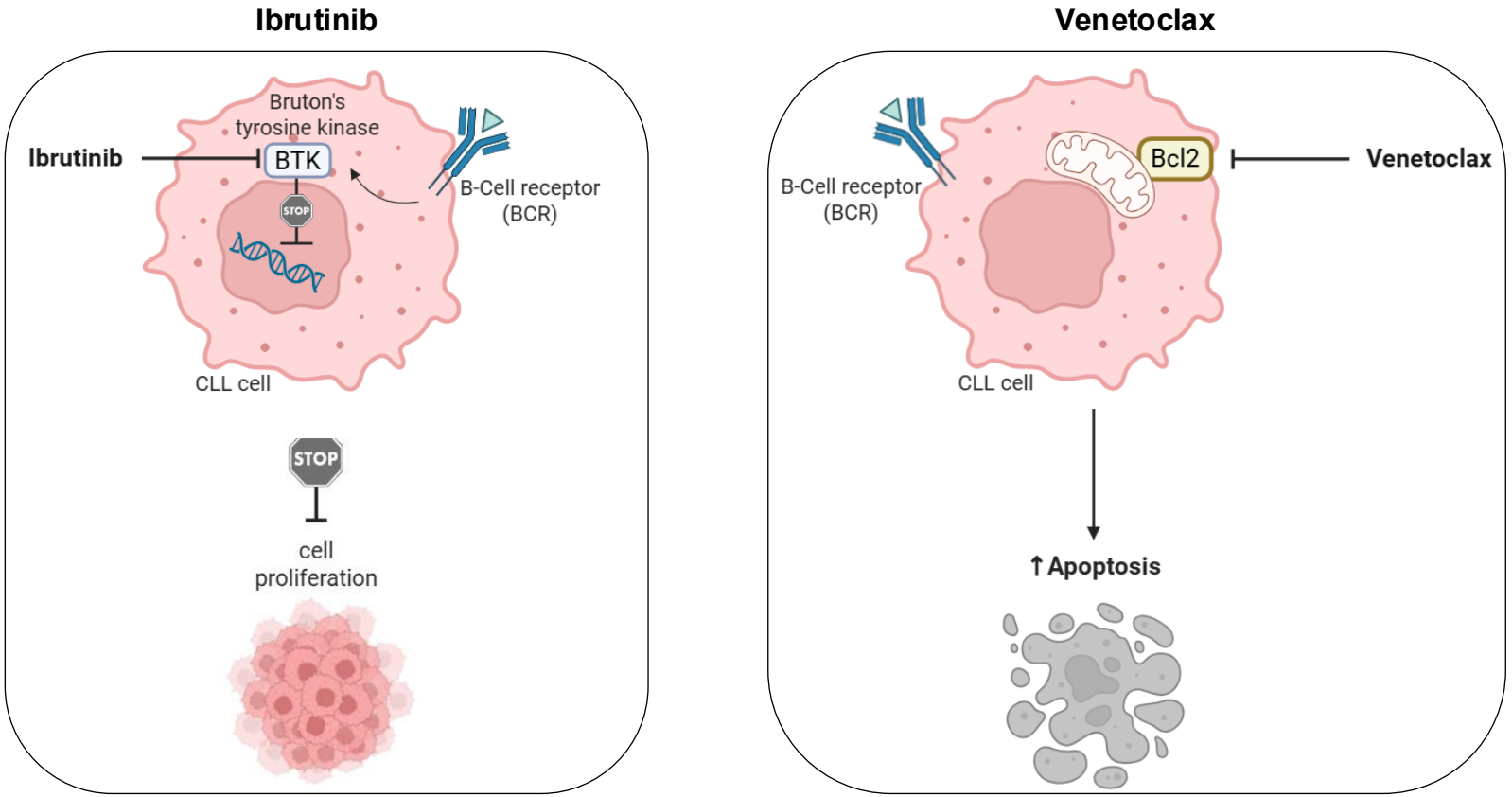
Generating an isogenic *TP53* knock-out model through CRISPR/Cas9 editing



Loss of p53 increases resistance to PRIMA-1^{Met}

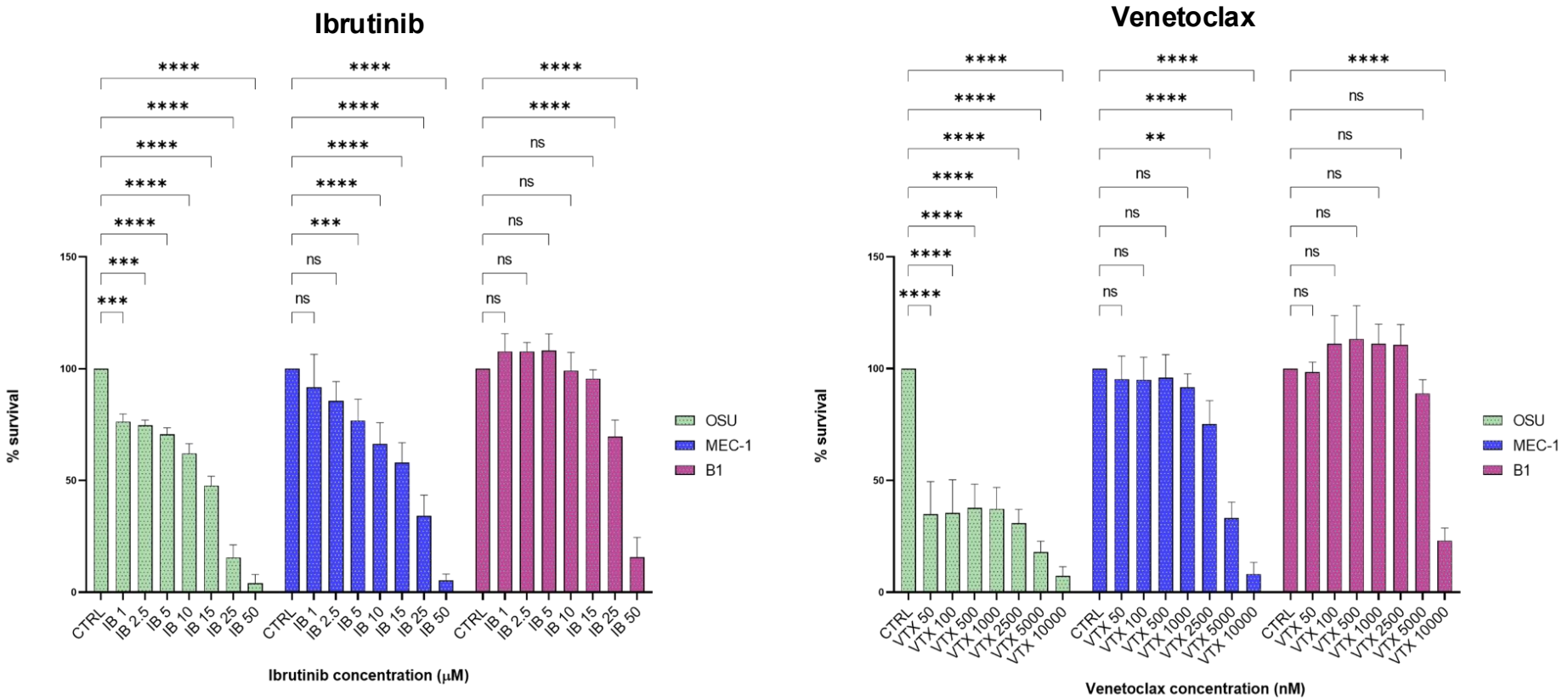


Targeted therapies in CLL: BTK and BCL2 inhibition



Adapted from Mhibik et al., *Blood Adv.*, 2023

TP53 loss confers increased resistance to targeted agents



Heterogeneity of *TP53* mutations

ACTIVITY	MUTATIONS
Loss of function 	e.g.: R175H, G245S, R248Q, R248W, S241F, R249S, R273C, R273H, C275Y, R280K
Partial function and/or Temperature sensitive 	e.g.: A161T, R181L, R202S, Y220H, S215C, D228V, V272L, R282W
Wild type-like or Super-transactivating 	e.g.: T123A, G199H, S240N, S288K, R337H, G360V
Altered specificity 	e.g.: K120R, S121F, V122A, T125R, G279E
Dominant 	e.g.: R175H, G245S, R248Q, R248W, S241F, R249S, R273C, R273H, C275Y, R280K
Gain of function 	e.g.: R175H, G245S, R248Q, R248W, S241F, R249S, R273C, R273H, C275Y, R280K, D281G, R282W

Monti et al, *Frontiers in Oncology*, 2020

Take home messages

- *TP53* alterations remain key determinants of CLL biology and therapeutic response
- PRIMA-1^{Met} does not induce canonical p53 reactivation in our CLL models
- Alternative mechanisms may contribute to PRIMA-1^{Met} cytotoxic effects in CLL
- *TP53* mutational status and complete *TP53* loss may have distinct biological and therapeutic consequences
- Functional heterogeneity of *TP53* alterations may influence therapeutic response

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