

**The PARP inhibitor olaparib induces
significant killing of
ATM deficient lymphoid tumour cells *in vitro* and *in vivo***

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Ataxia Telangiectasia Mutated (ATM)

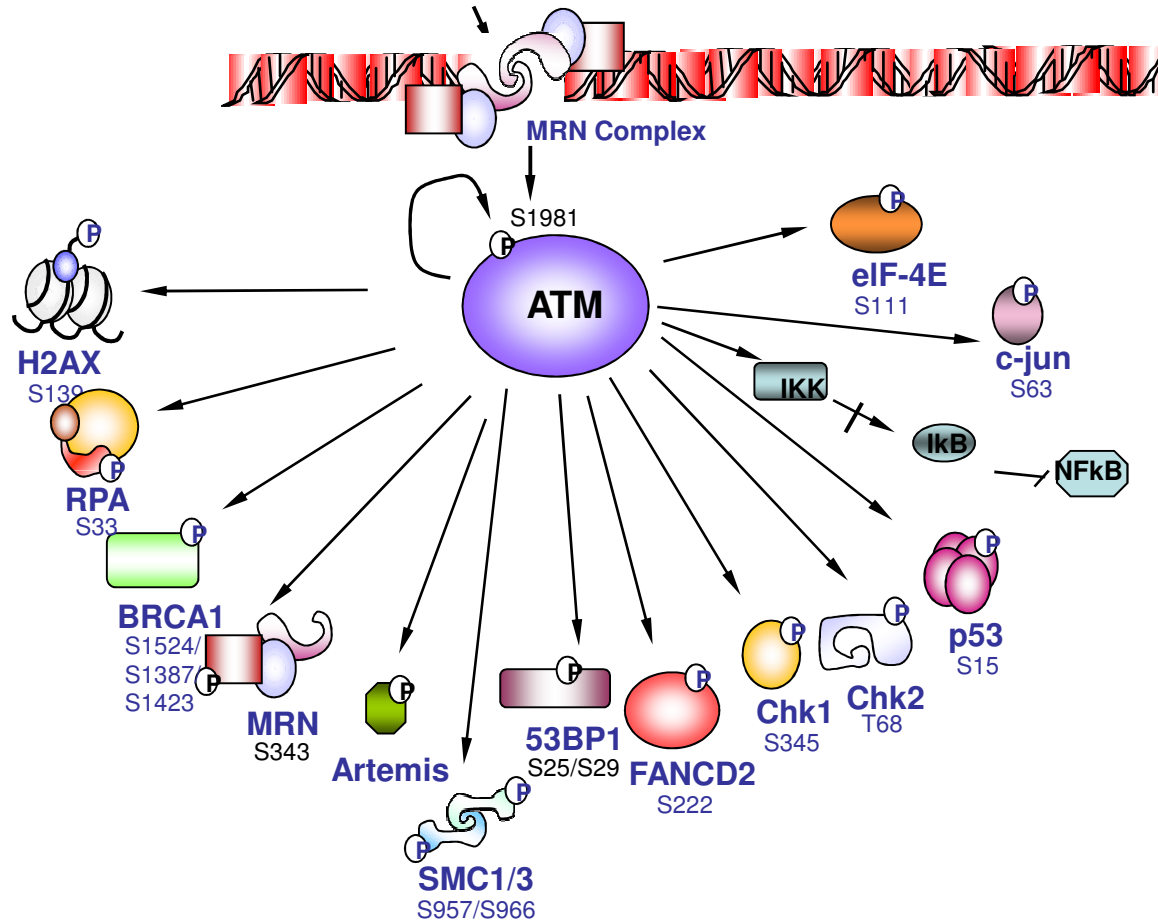
ATM mutations

- Present in up to one third of CLL
- Enriched in 11q deleted progressive CLL subsets
- Frequent in rarer T-PLL and MCL

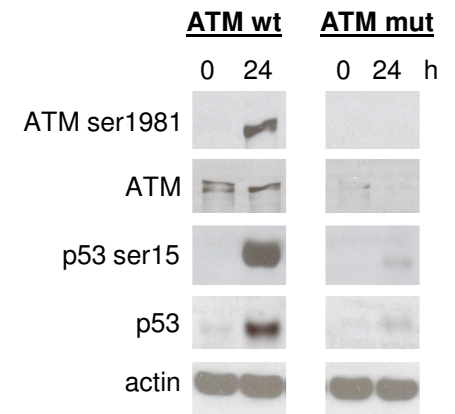
ATM is a key DNA damage response protein kinase

DNA DSB

(IR, chemotherapy, programmed immune system gene rearrangements...)



15μM fludarabine



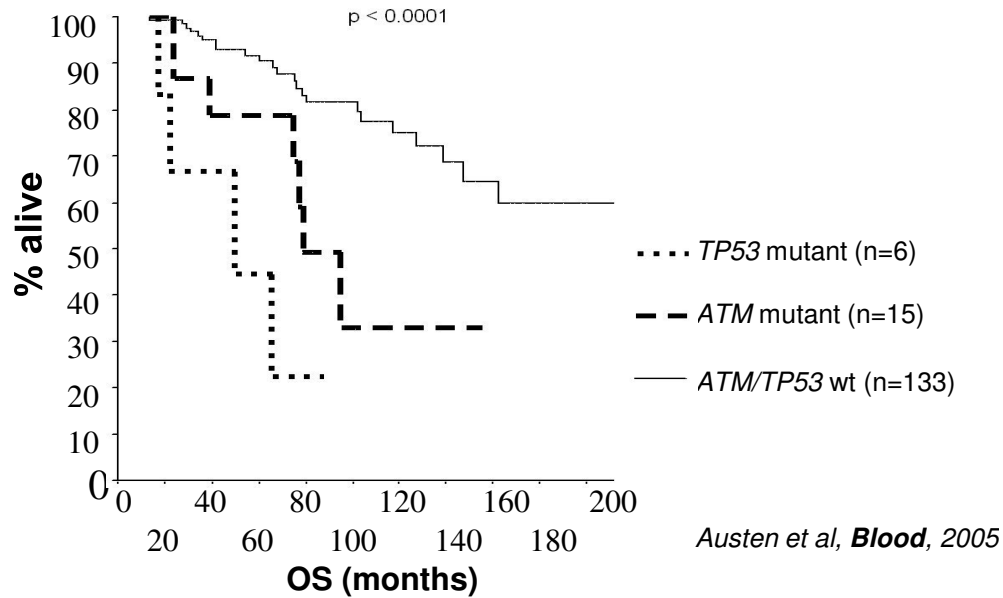
DNA repair

S-phase Checkpoint

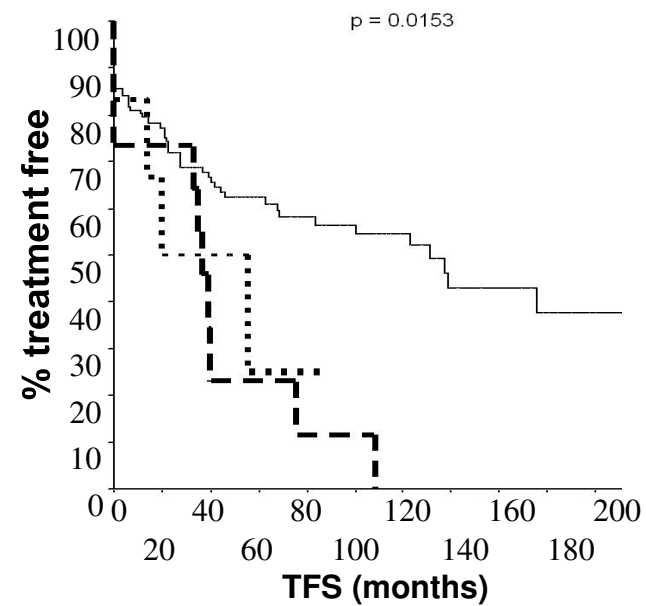
Cell cycle arrest/Apoptosis

Loss of ATM function significantly affects clinical outcome

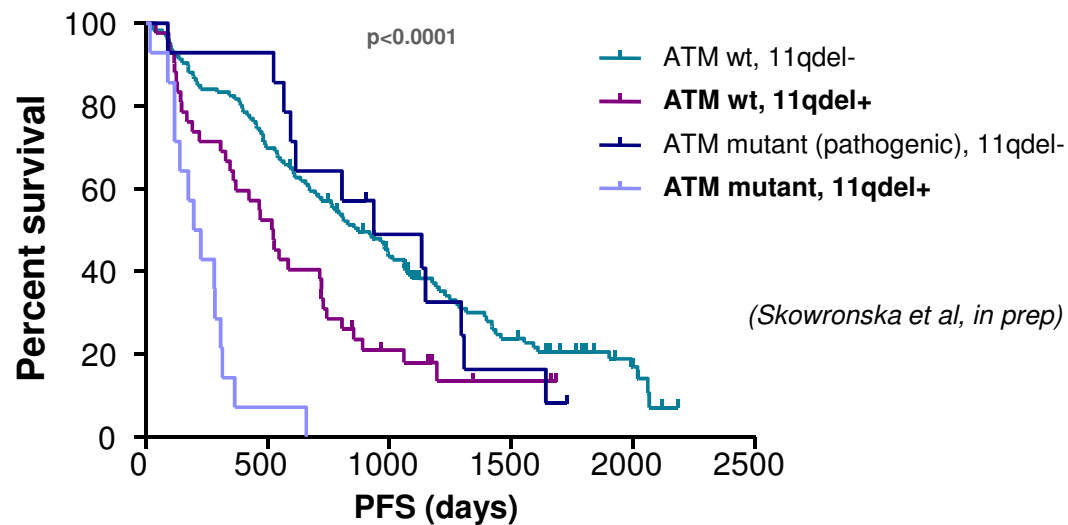
Overall survival (unselected cohort):



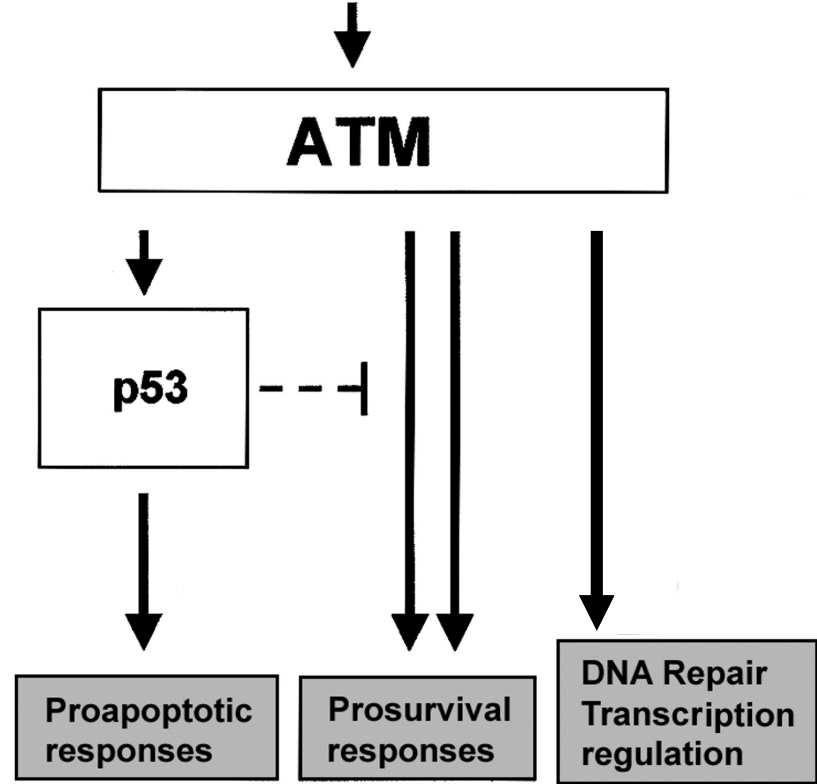
Treatment free survival (unselected cohort):



Progression free survival (CLL4 cohort):



DNA Double Strand Breaks

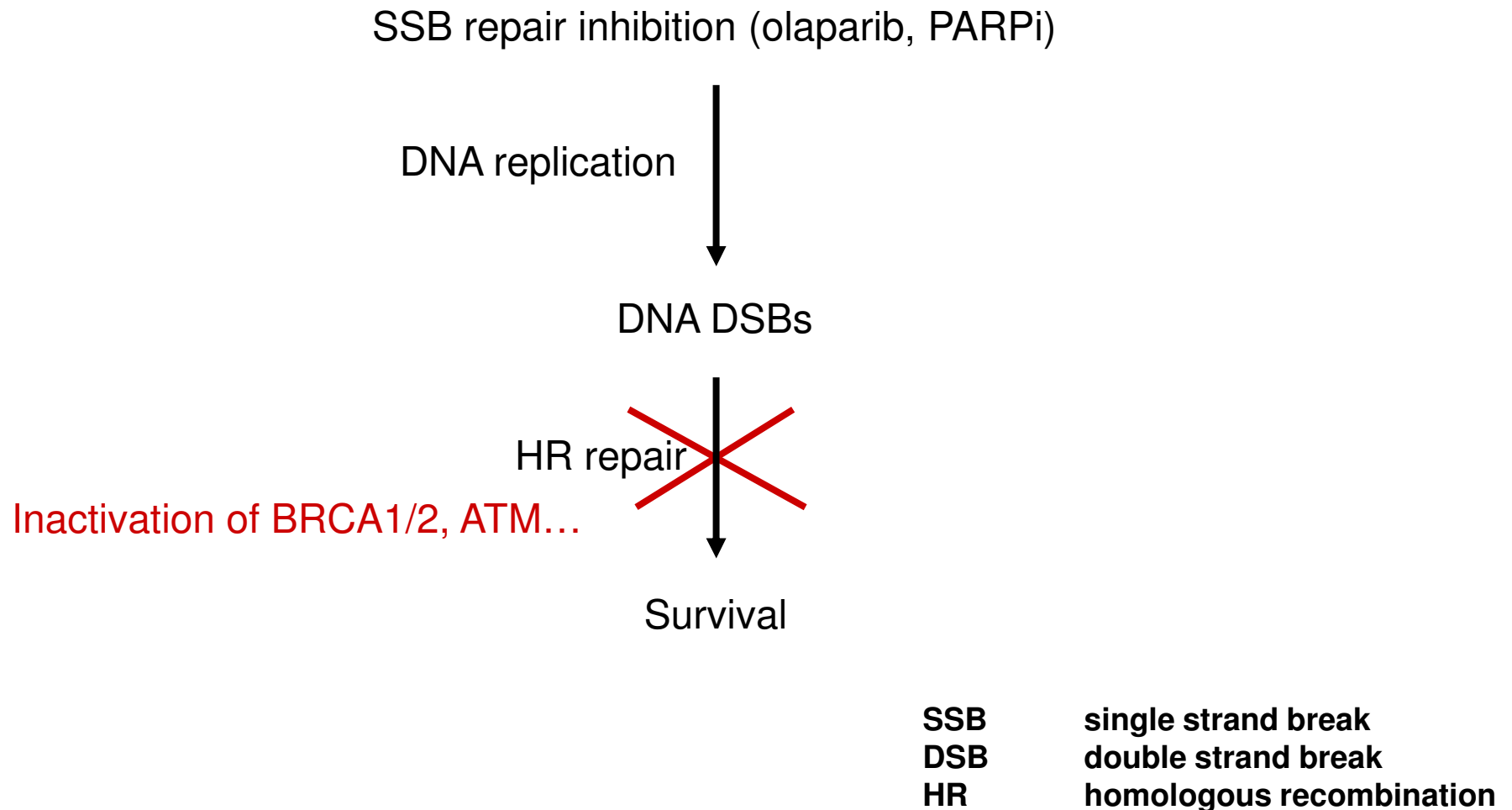


CLL 3 h after IR with 5Gy IR

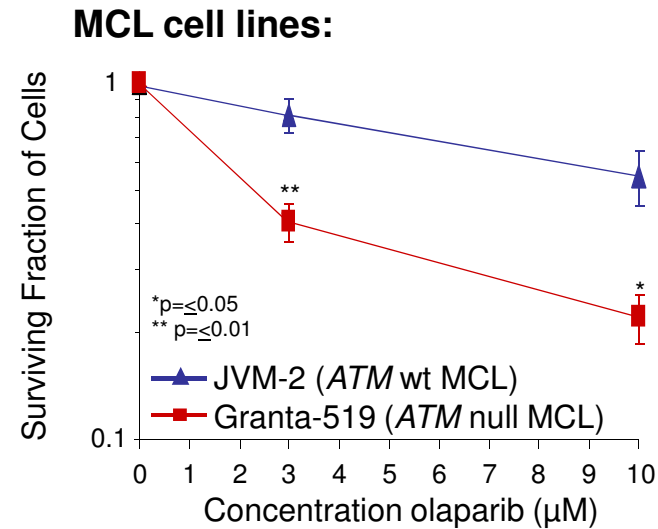
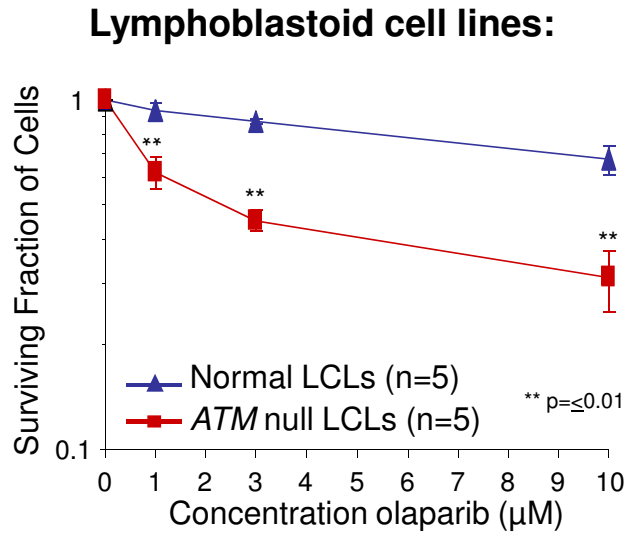
Targeting defective repair in *ATM* mutant CLL: PARP inhibition (PARPi)

Synthetic Lethality

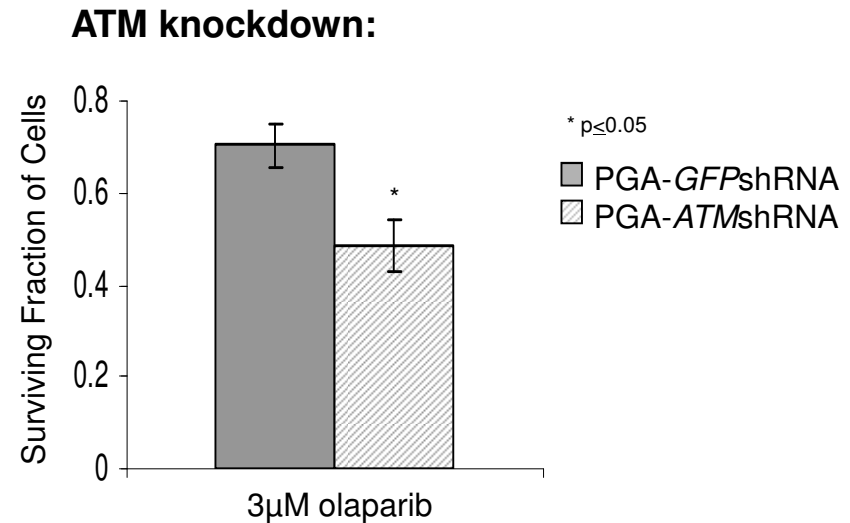
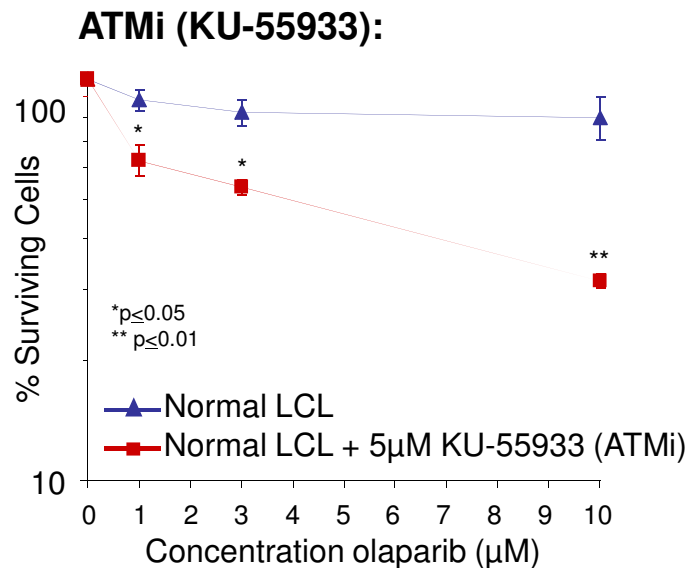
Two mutations which can exist individually in a cell but together cause loss of viability



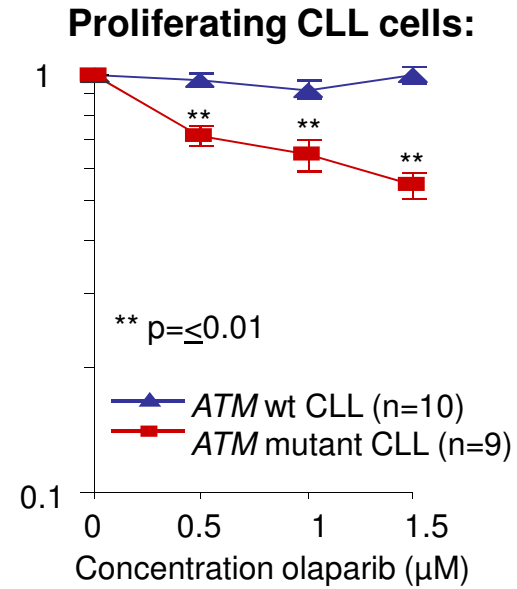
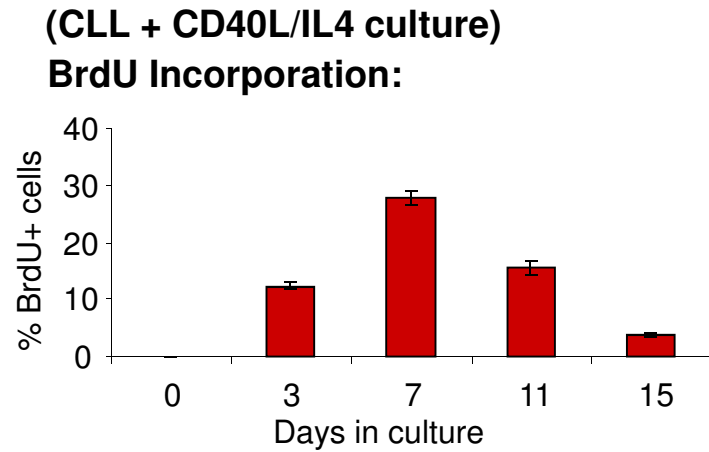
ATM mutant lymphoid cell lines are differentially sensitive to Olaparib



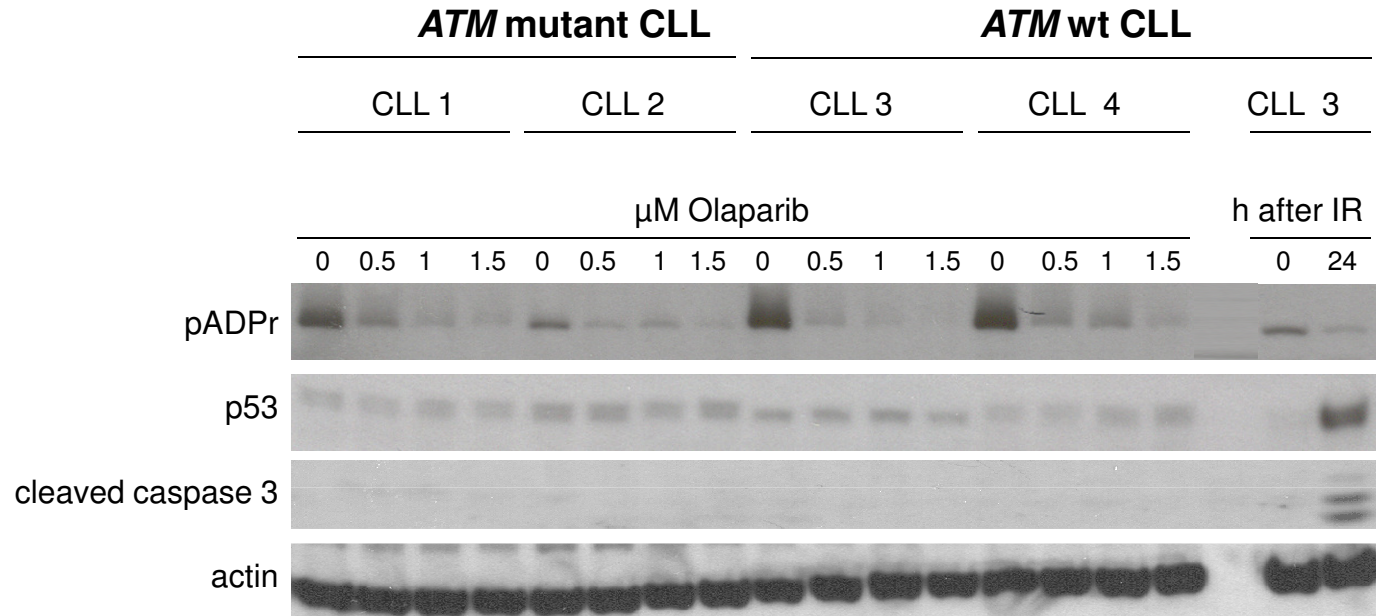
Sensitivity to Olaparib is mediated by ATM loss



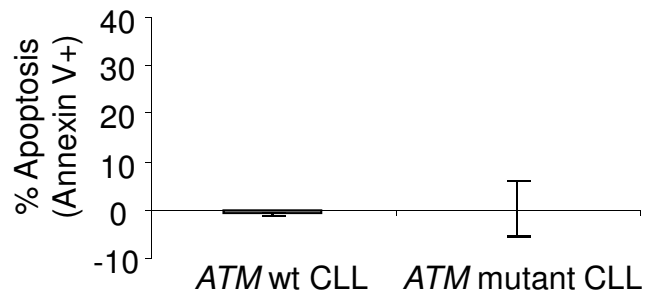
Proliferating *ATM* mutant CLL are sensitive to Olaparib *in vitro*



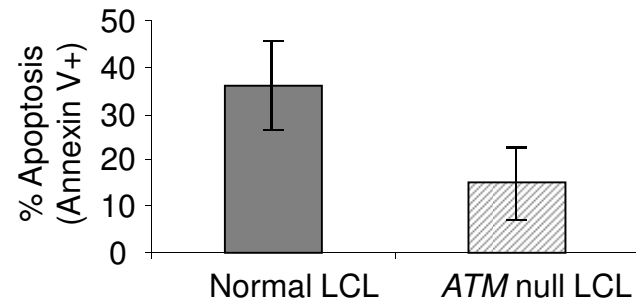
Olaparib does not induce p53-dependent apoptosis in *ATM* mutant CLL cells



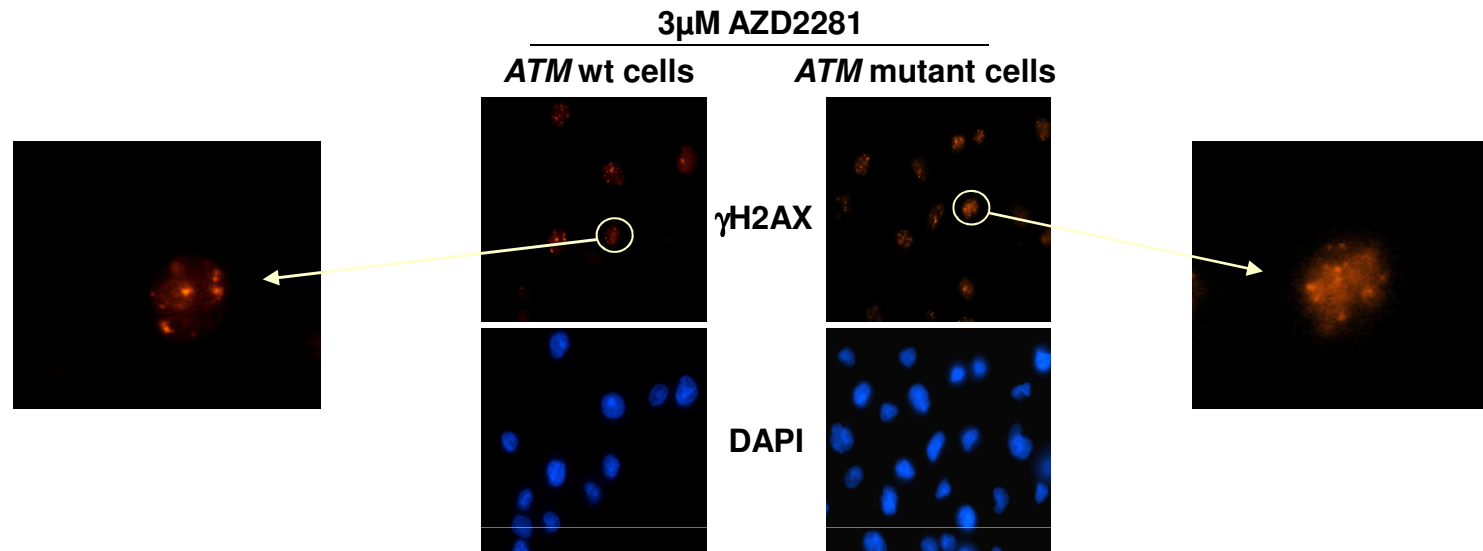
3 μM Olaparib:



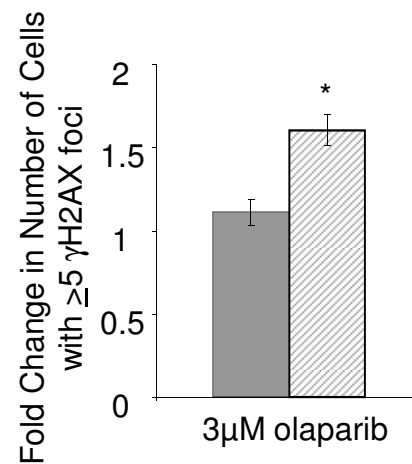
5Gy IR (Positive control):



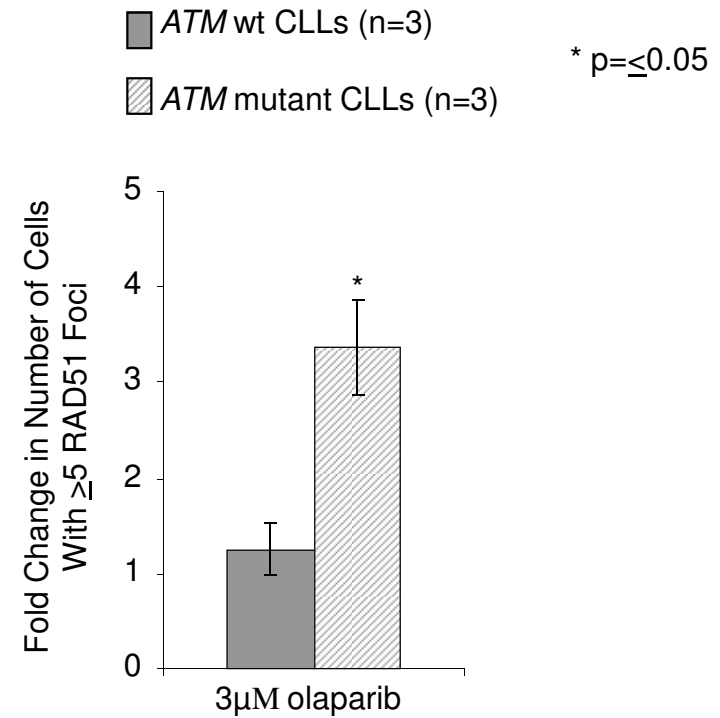
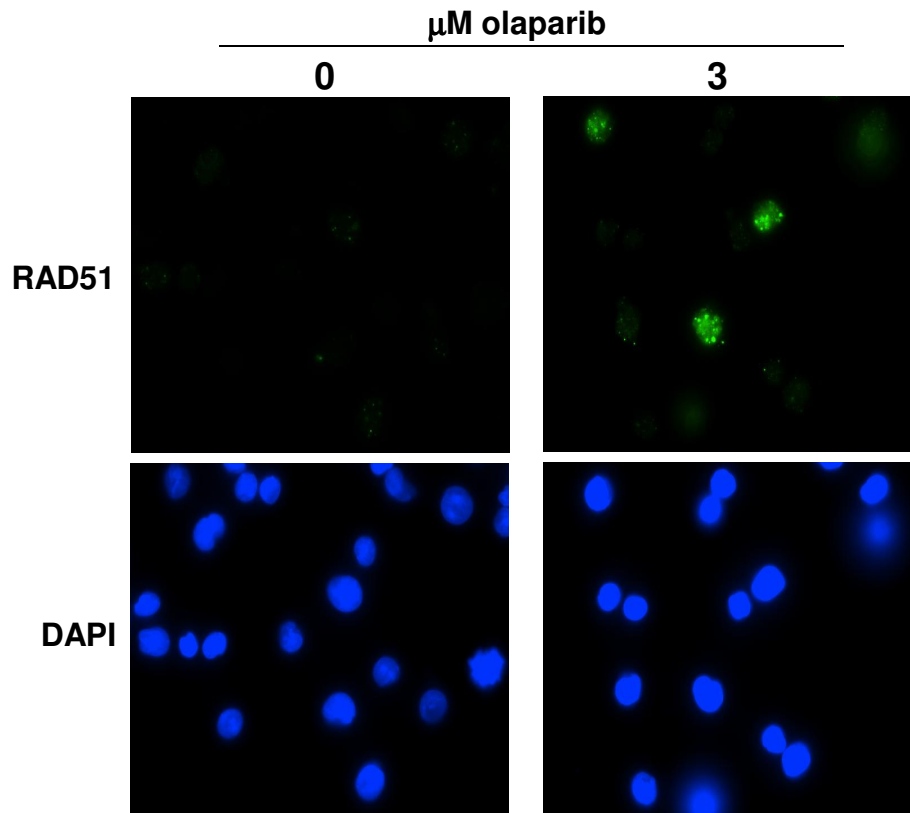
Accumulation of unrepaired DNA damage (γ H2AX) in *ATM* mutant CLL cells following olaparib treatment



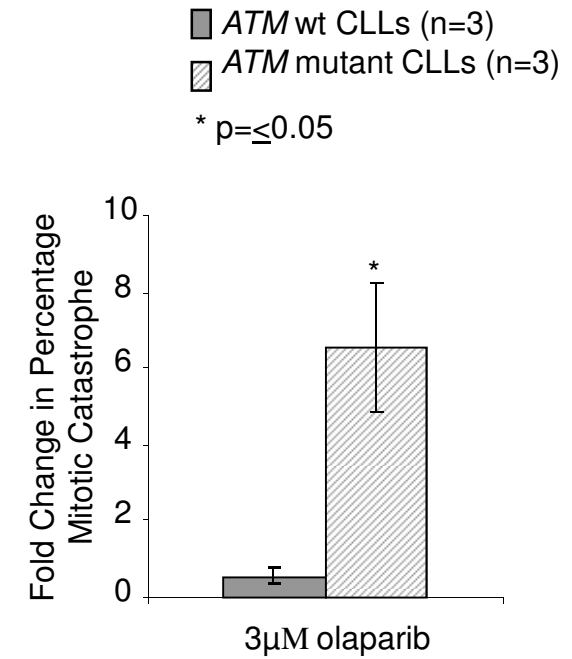
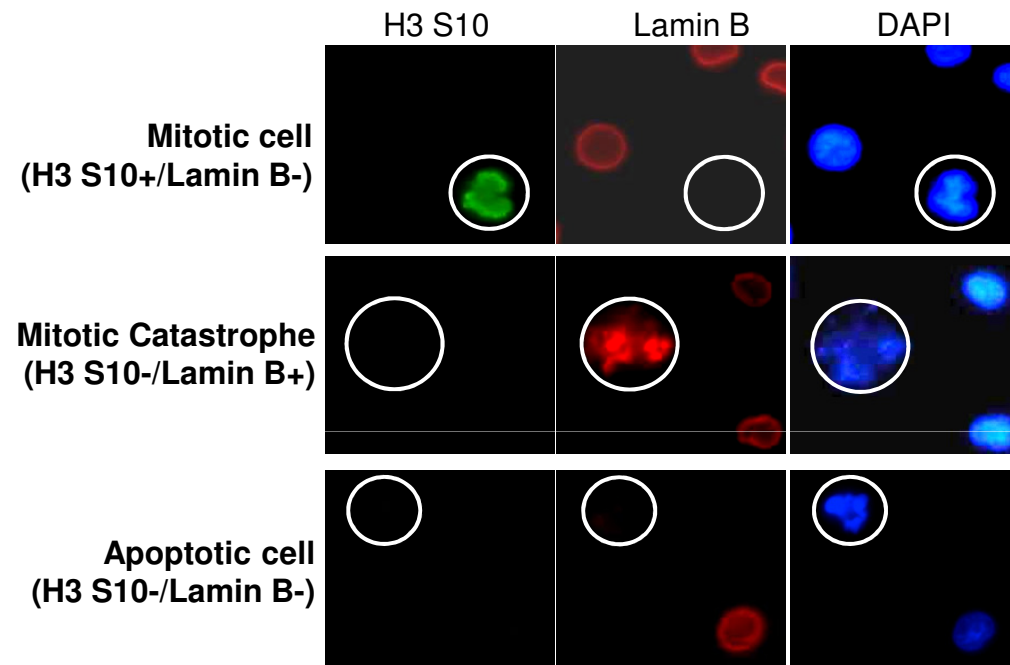
■ *ATM* wt CLLs (n=3) * $p \leq 0.05$
▨ *ATM* mutant CLLs (n=3)



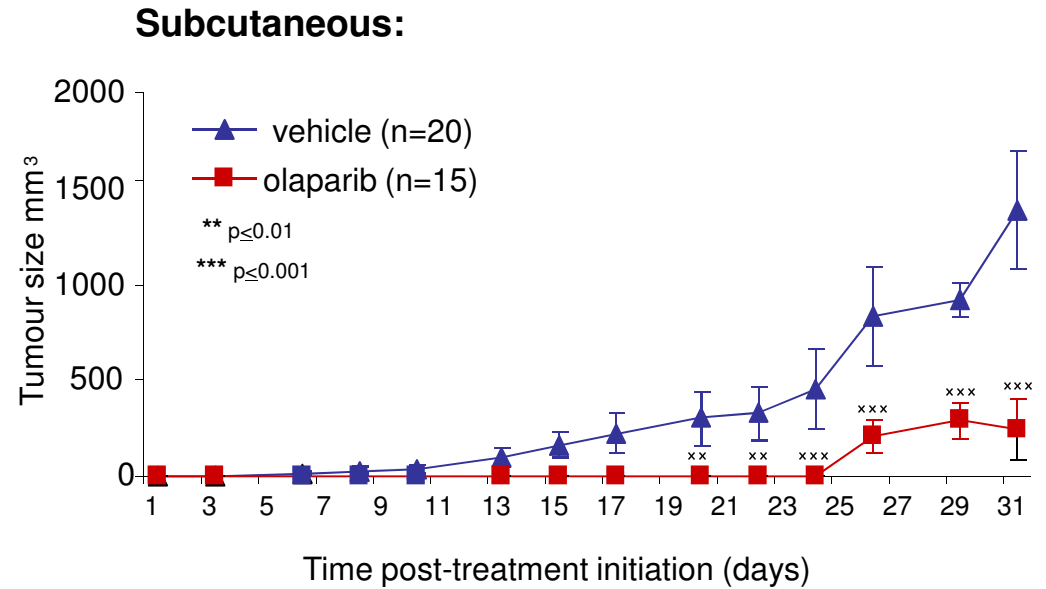
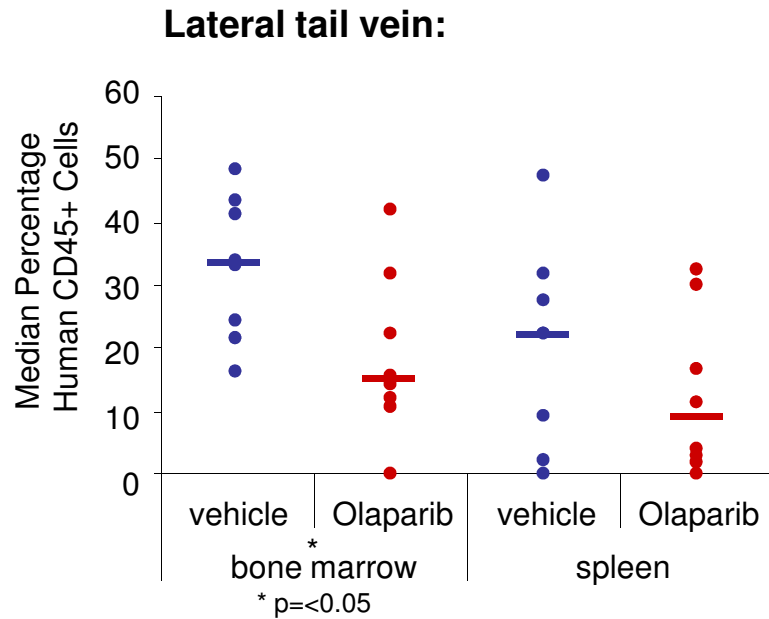
Persistent repair proteins (RAD51) at the sites of unrepaired DNA DSBs in *ATM* mutant CLL cells following PARPi



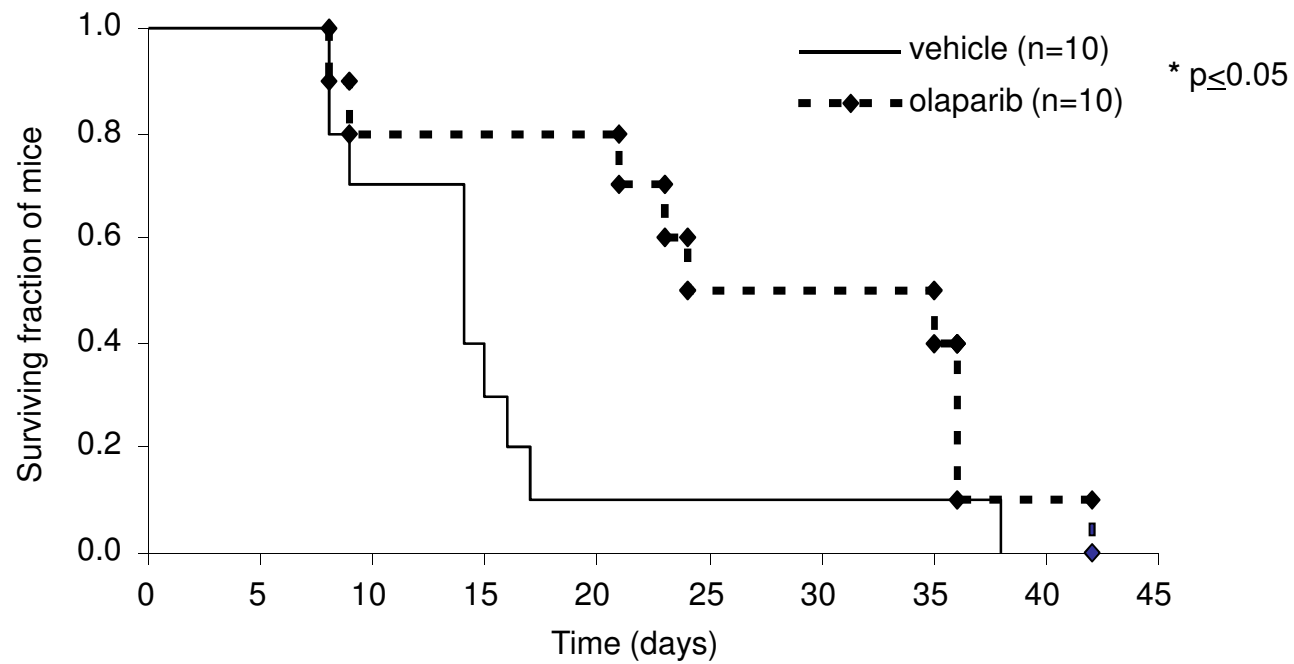
Olaparib induces mitotic catastrophe in *ATM* mutant CLL cells



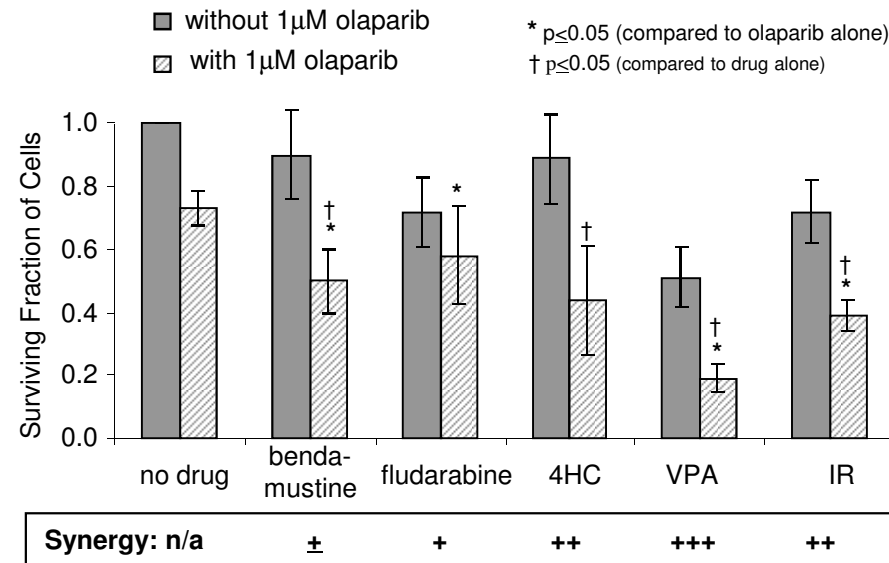
Olaparib reduces tumour load and size of *ATM* null tumour cells in NOD/SCID xenograft model



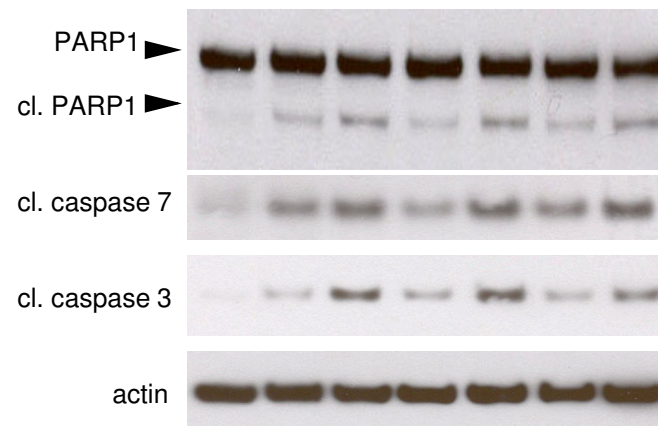
Olaparib increases survival of NOD/SCID mice engrafted with *ATM* null lymphoid tumour cells



Olaparib synergises with cytotoxic agents



1µM olaparib:	-	-	+	-	+	-	+
50nM 4HC:	-	+	+	-	-	-	-
2.5mM VPA:	-	-	-	+	+	-	-
1Gy IR:	-	-	-	-	-	+	+



Summary

- Olaparib targets cycling, *ATM* mutant CLL and MCL cells
- Most applicable to highly proliferating, aggressive tumour cells
- Non cycling and normal cells (including B and T cells) are not sensitive
- Viable therapeutic option for fragile patients (where fludarabine-based approaches are not an option)
- Prophylactic application

Phase I/II clinical trial for olaparib in refractory CLL

- All refractory CLL, MCL and T-PLL (irrespective of *ATM* status)
- Escalating olaparib doses (daily, oral)
- Identification of further Olaparib-sensitive subsets

Acknowledgements

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