Interacting or independent?

Systematic testing of drug combinations to identify synergistic and antagonistic drug interactions for melanoma

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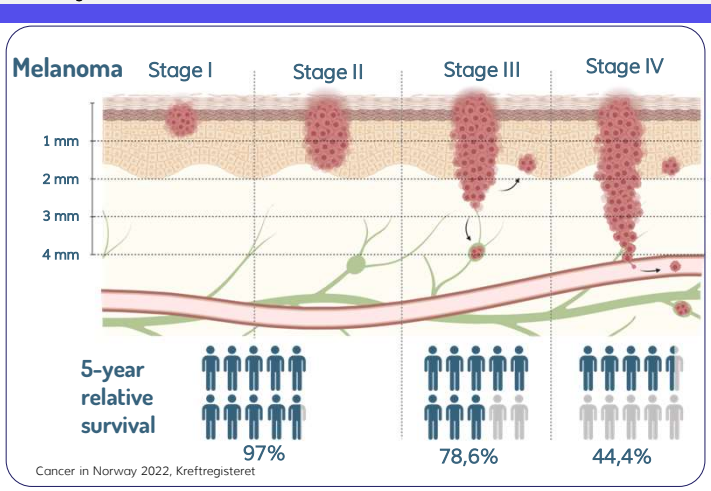


***Ex-vivo* drug sensitivity** and the use of **novel bioinformatics tools** can predict synergistic drug combinations and biomarkers associated with their efficacy in melanoma

BACKGROUND & AIM

Melanoma mortality is high for late-diagnosed tumors

Melanoma, an aggressive form of skin cancer, is a **malignant disease** that starts in melanocytes and it involves mutations in the components of the Ras-Raf-MEK-ERK pathway, cell cycle regulation and DNA damage repair.

Globally, the number of cases of melanoma is increasing, and **Norway has the second highest mortality rate in the World**, related to late diagnosis. There is **a need for new treatments** that can improve patient survival.

METHODS

We have combined 61 anticancer drugs two-by-two in full drug combination matrices and tested them against well-characterized melanoma cell lines (n=23) and immortalized melanocytes (n=2).

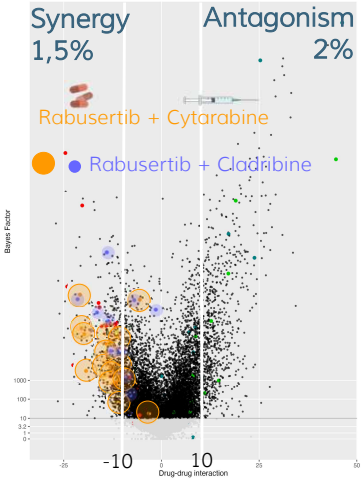
The drug effect was measured as **relative viability** after measuring ATP levels with CellTiter-Glo.

We also developed new bioinformatics tools for the design and analysis of drug combination screenings (**screenwerk**[1]) and for synergy assessment (**bayesynergy**[2]).

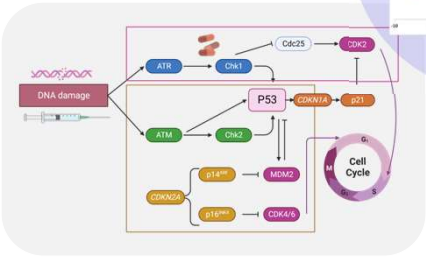
[1] screenwerk [2] bayesynergy

RESULTS

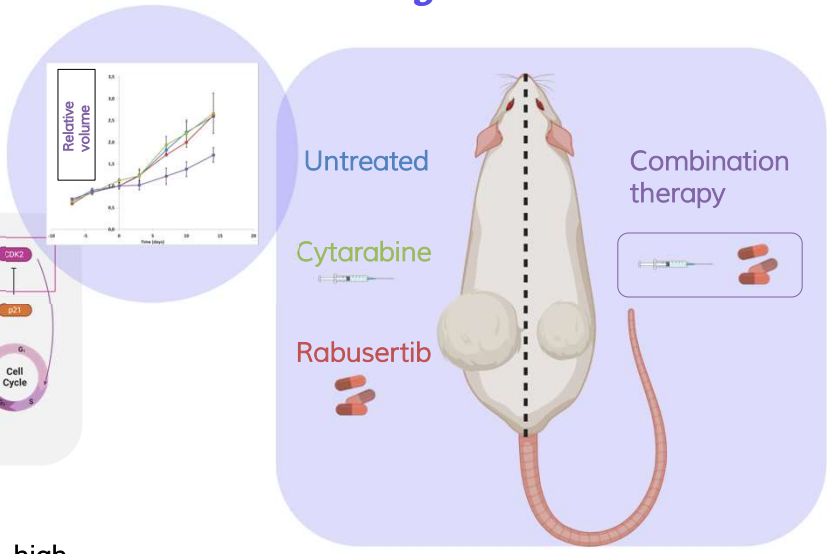
The combination of DNA-damaging agents and Chk1 inhibitors is synergistic in melanoma cell lines with mutations in either TP53 or CDKN2A.



The occurrence of **drug interaction** out of an additive effect is known to be **rare**, and we observe that in our results, but we still can identify interesting drug combinations for synergy and antagonism.



A synergistic drug combination identified in the screen blocks the growth of tumors in vivo



CONCLUSION

A synergistic drug combination identified in our high-throughput drug sensitivity screening works in an *in vivo* model and could be developed for a clinical setting.

FUTURE WORK

We will study other synergistic and antagonistic drug combinations identified in the screen. We will also use bioinformatic tools to assign biomarkers to the relevant combinations to contribute to patient stratification.

GET IN TOUCH!
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