Mutations and Treatment Resistance: Finding Better Answers for CLL Patients

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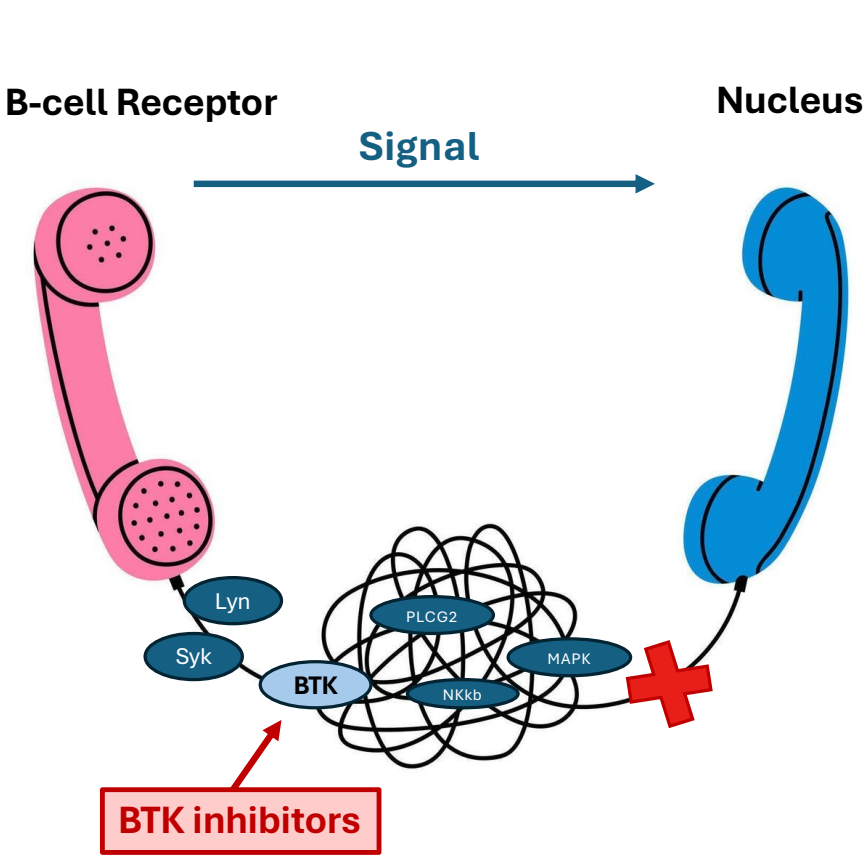
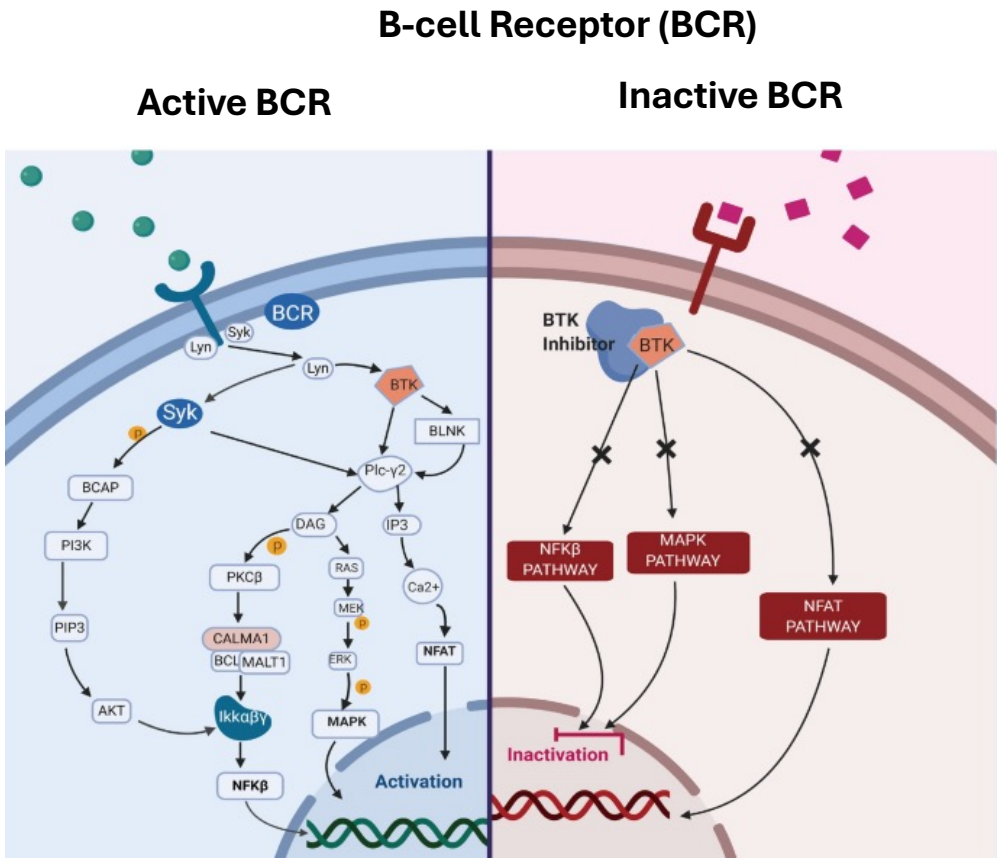
How Targeted Treatments Work?

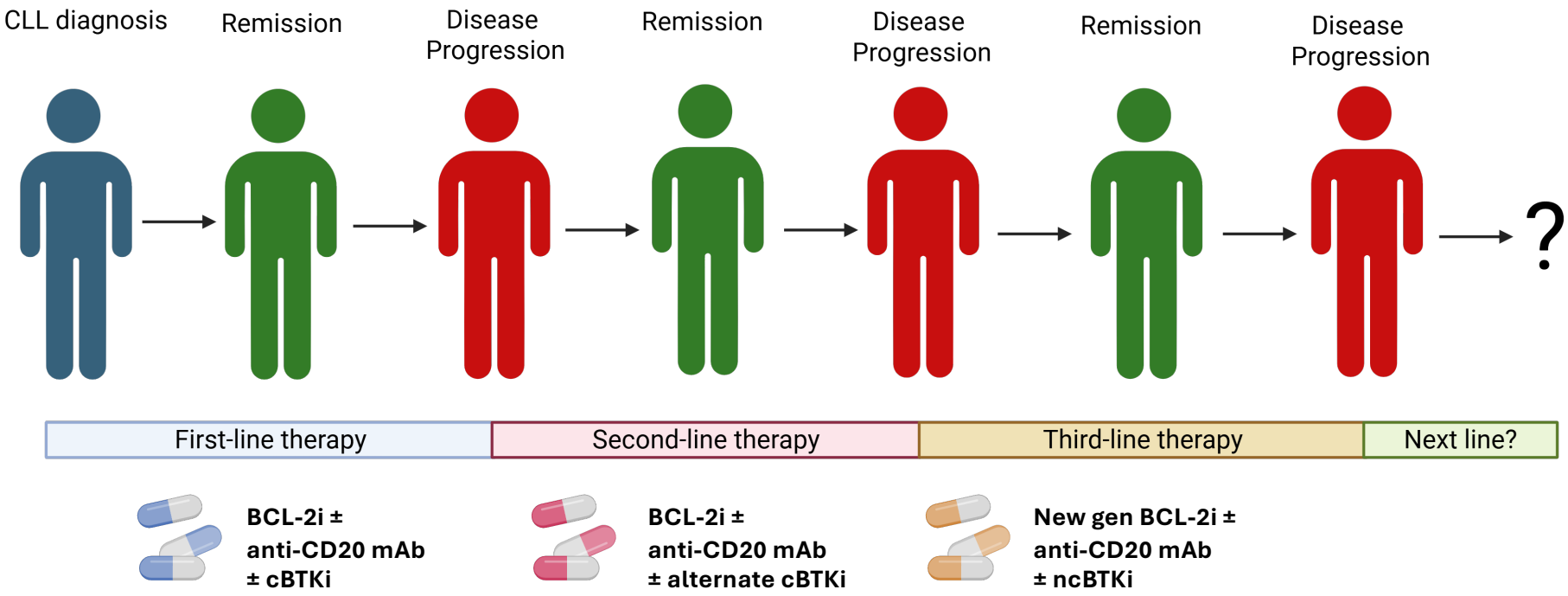




cBTKi/ncBTKi – covalent/non-covalent BTK inhibitors
BCL-2i – BCL-2 inhibitors
mAb – monoclonal antibodies

Chao Xue et al, Cancer Cell International, 2020

The CLL Therapy Journey: Remission and Relapse Cycle



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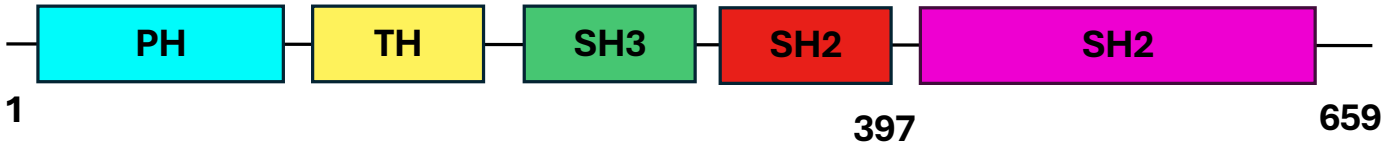
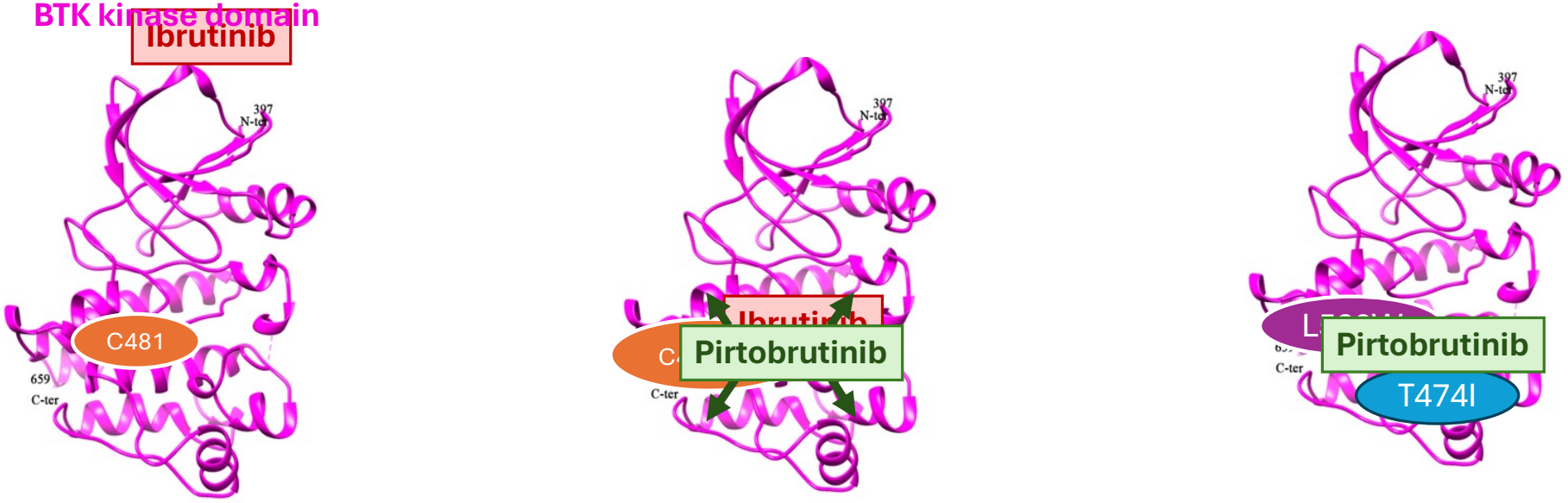
Why the Drugs Stop Working?

BTK structure

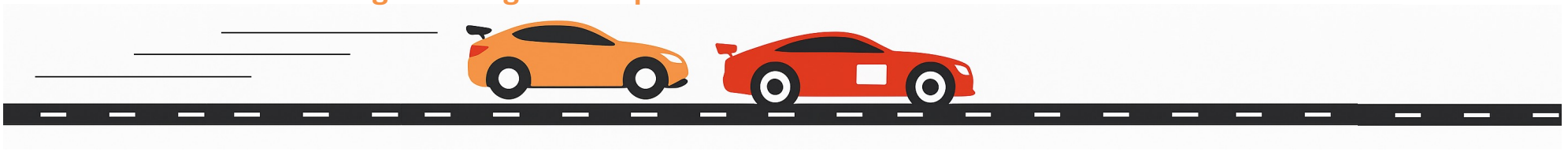


BTK kinase domain



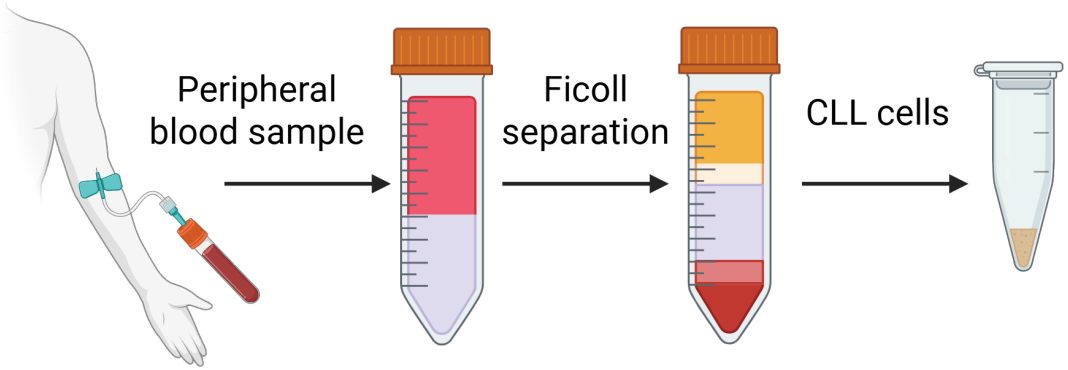
Targeted drugs development

Resistance mechanisms

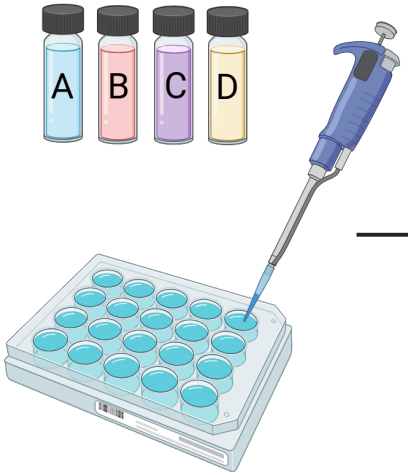


What is “Ex Vivo” drug profiling?

Ex vivo – “outside the living”

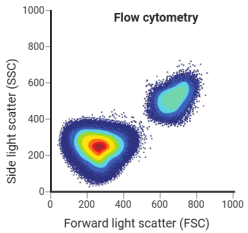


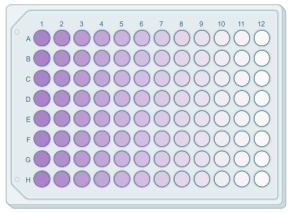
Compounds of interest



Specific Proteins

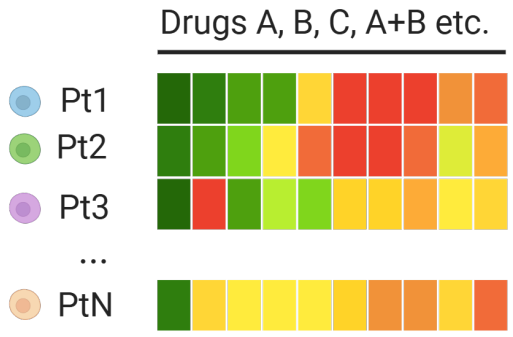
Apoptosis



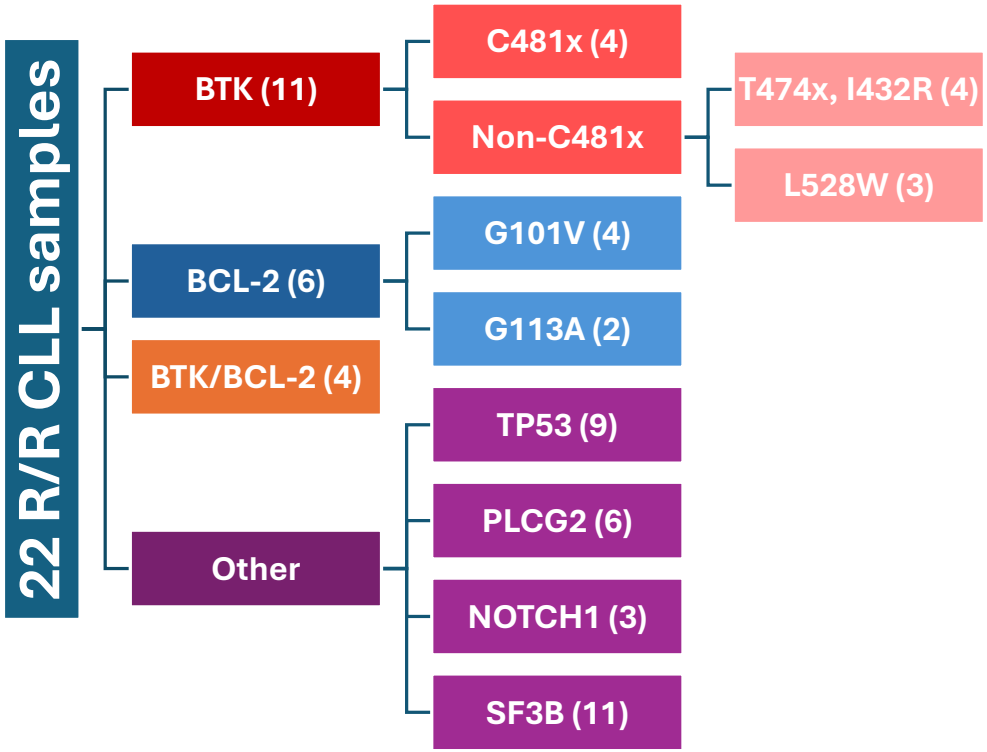


Cell viability

Drug Sensitivity Profile



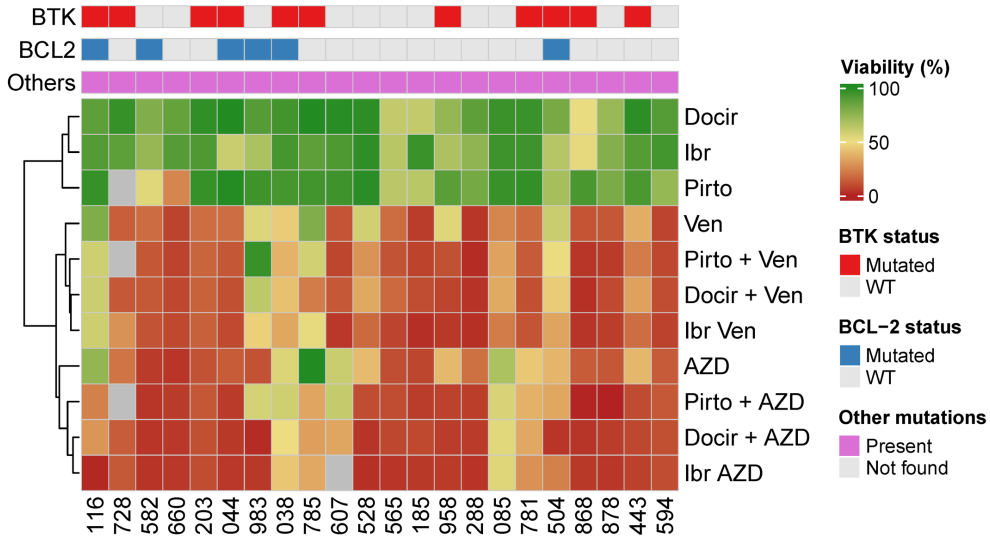
Ex vivo drug profiling of samples from relapsed CLL patients



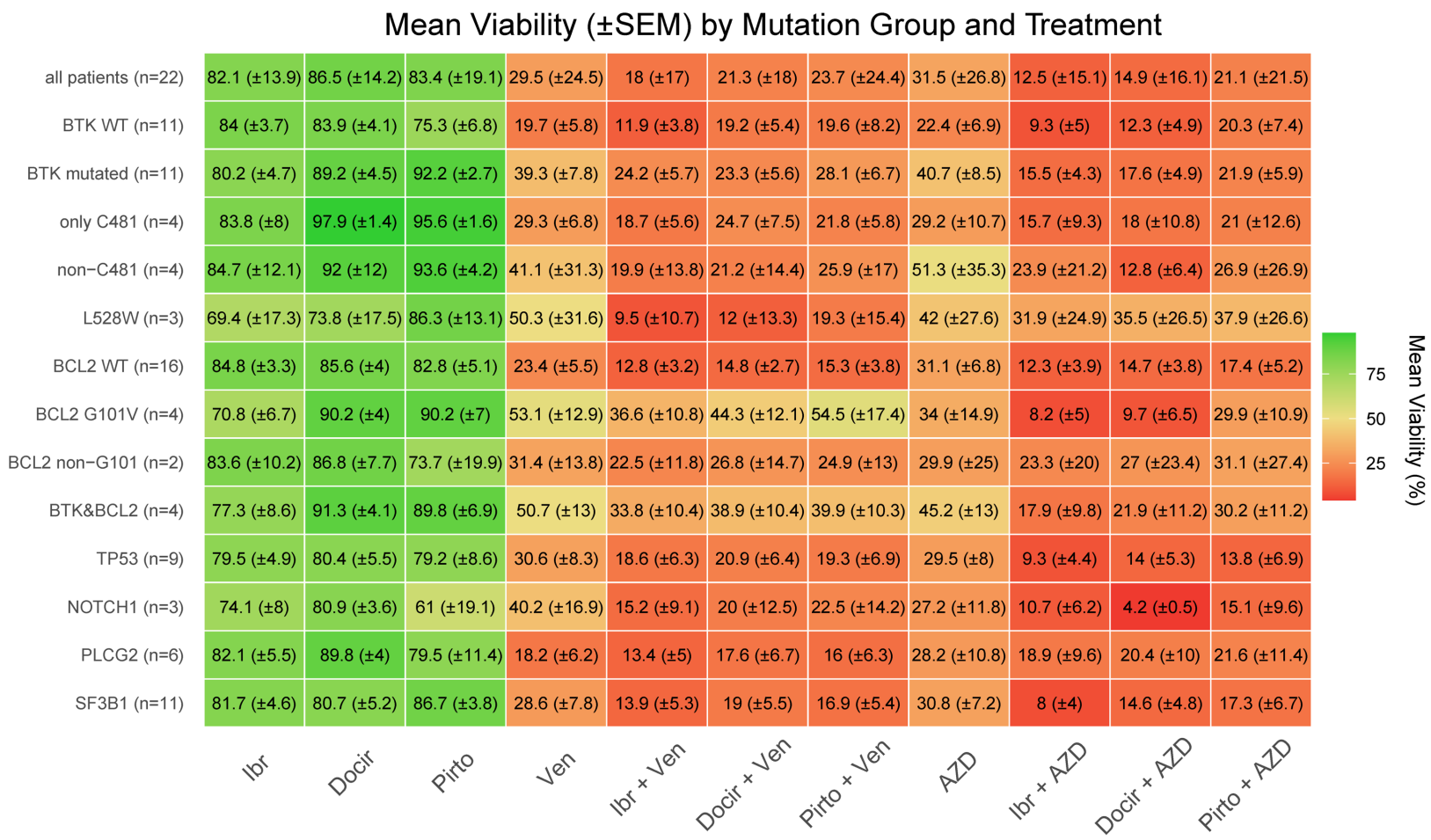
Drugs:

- BTKi (covalent: *ibrutinib*; non-covalent: *pirtobrutinib, docirbrutinib*)
- BCL-2 inhibitor (*venetoclax*)
- MCL-1 inhibitor (*AZD5991*)

Ex vivo treatment for 72 hrs → Cell death assessment

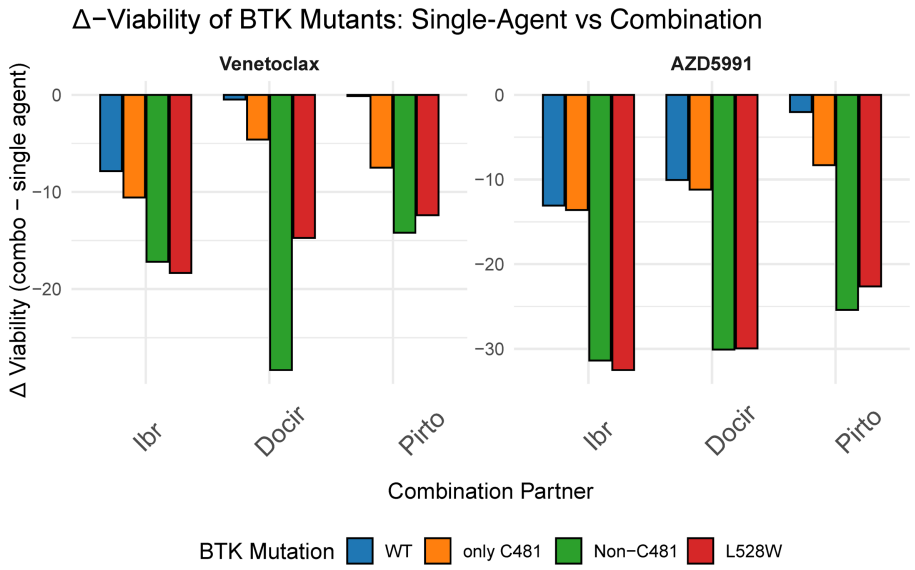


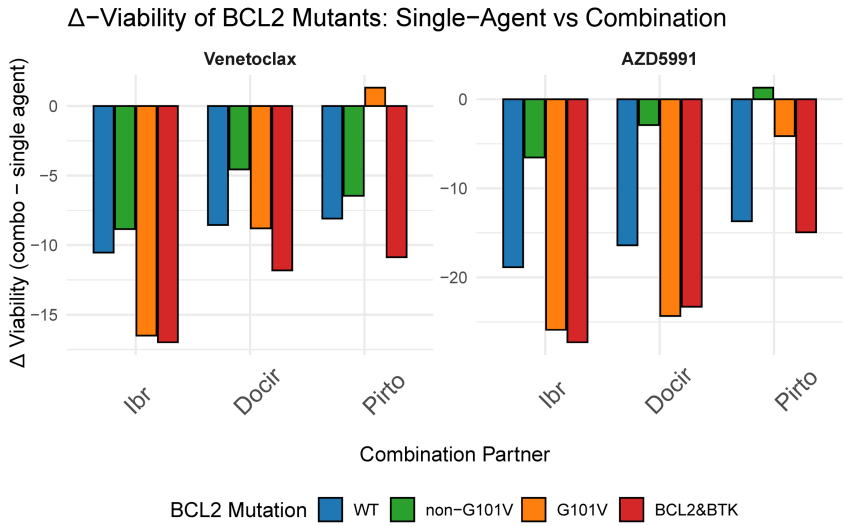
Why One Treatment Doesn’t Fit All



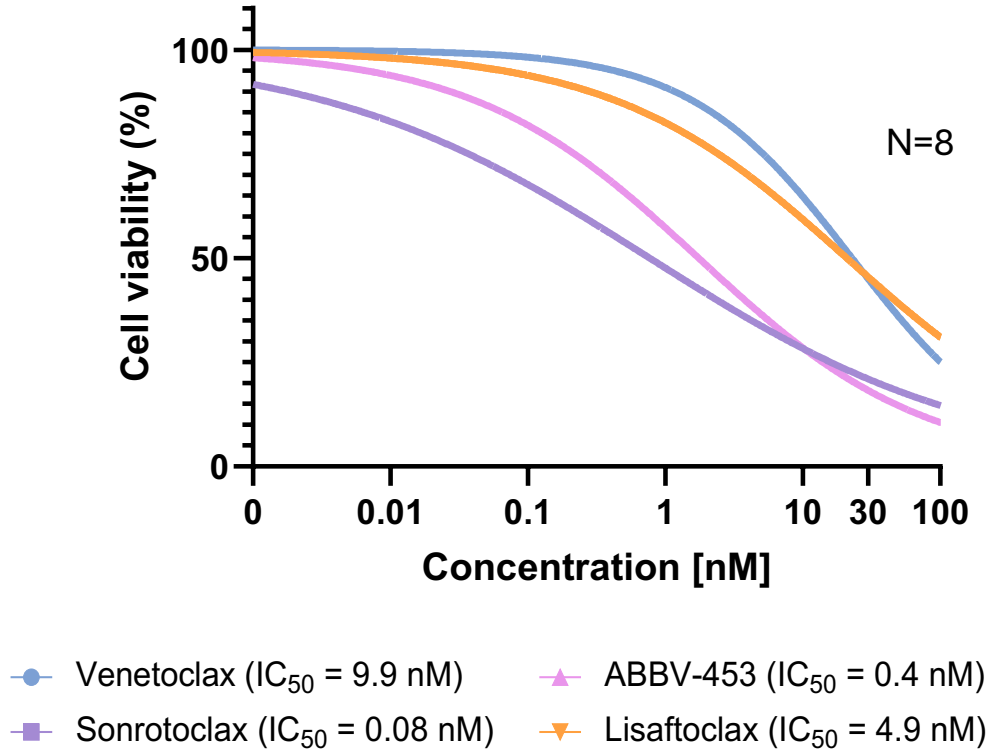
Combination Of Drugs With Different Mechanism Of Actions Helps To Increase Efficacy

Combining drugs can be powerful when chosen correctly

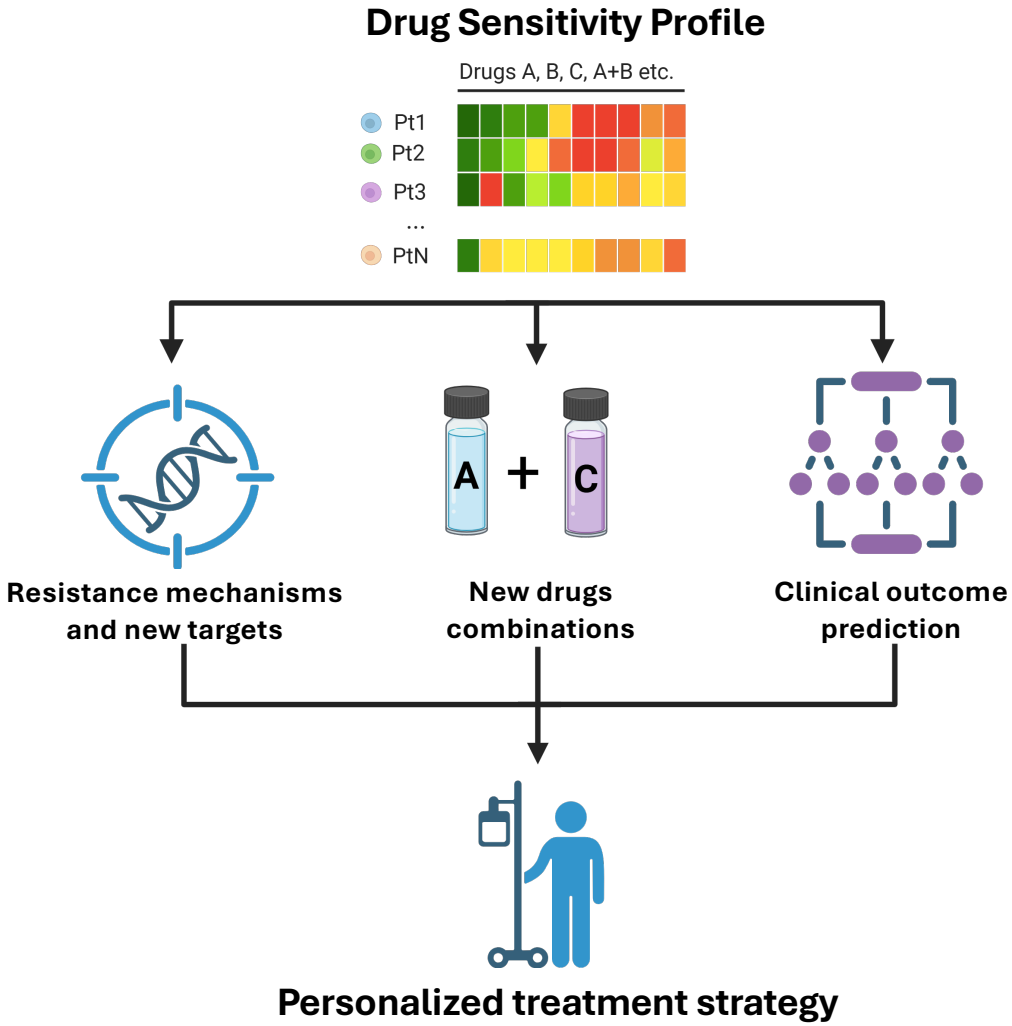




Newer BCL-2 inhibitors are more potent than first-generation venetoclax in relapsed CLL samples



How *ex vivo* drug profiling can help CLL patients?



Conclusions & Acknowledgements

•CLL cells from different patients show very different sensitivities to the same drugs.

•Genetic mutations (like those in **BTK** or **BCL-2**) influence how well treatments work.

•Some resistant samples still respond to new or combination therapies.

•Studying these differences *ex vivo* helps predict which treatments are most effective for each patient.

•Understanding resistance patterns guides the design of smarter, more durable therapies.

Translational Molecular Pathology Department

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