# Il concetto della "durata fissa" dal farmacologo all'ematologo

## Farmacologicamente discutendo

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REVOLUTIONARY ROAD IN CLL

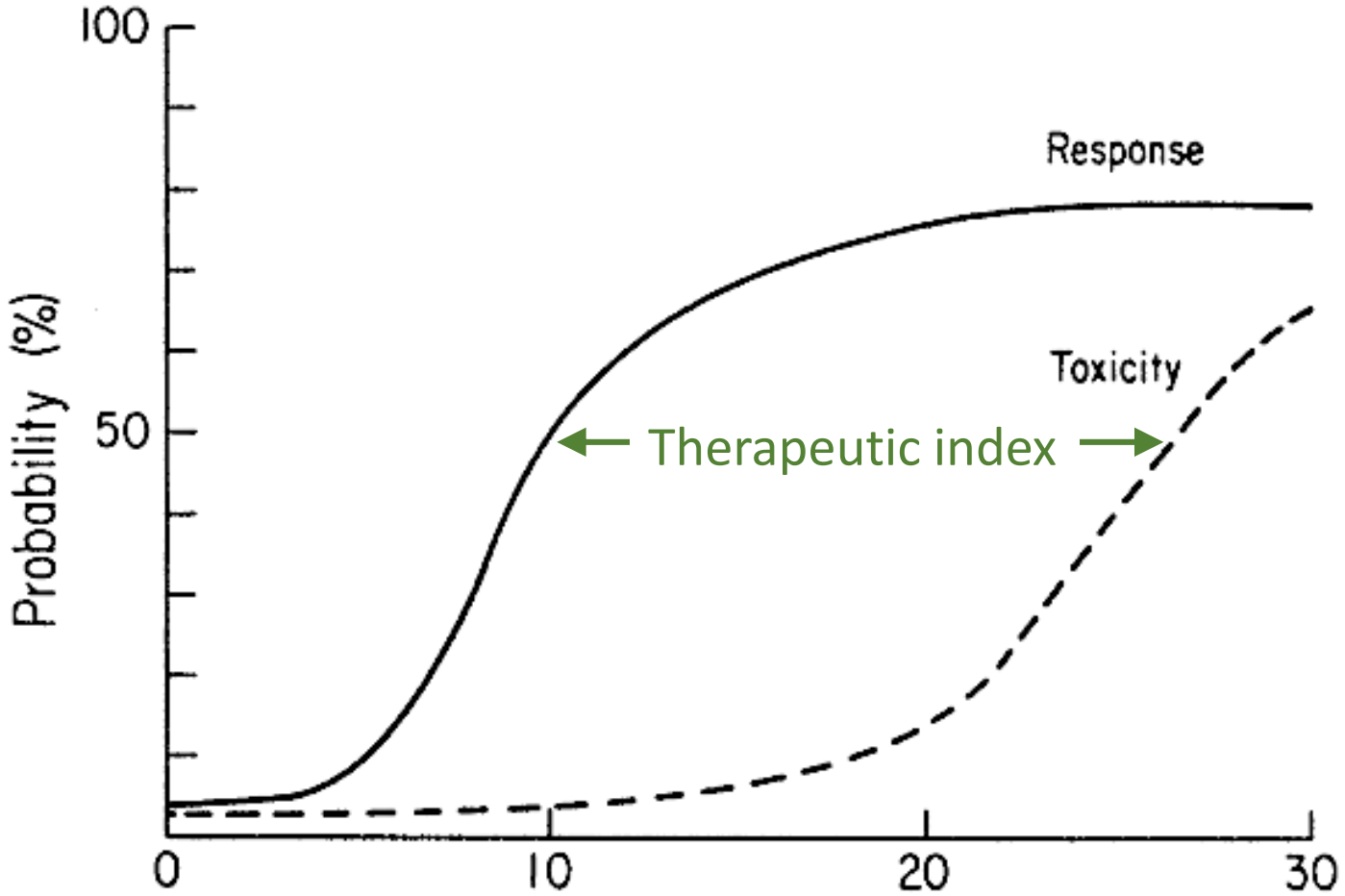
Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Milano, 10 luglio 2024
Starhotels E.c.ho.

# Disclosures

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| MSD | | | X | | X | | |
| Eisai | | | X | | X | X | |
| AstraZeneca | X | | X | | X | X | |
| BeiGene | | | | | X | | |
| Janssen | X | | X | | X | | |
| Novartis | | | X | | X | | |
| Lilly | | | X | | X | | |
| Incyte | | | X | | X | | |
| AB Science | | | X | | | | |
| Sanofi | | | X | | X | X | |
| Abbvie | | | X | | X | | |

# Relationship between drug exposure and effects (therapeutic and adverse)




Applied Pharmacokinetics, 3rd ed. Vancouver, WA: Applied Therapeutics; 1992. pp.1–3

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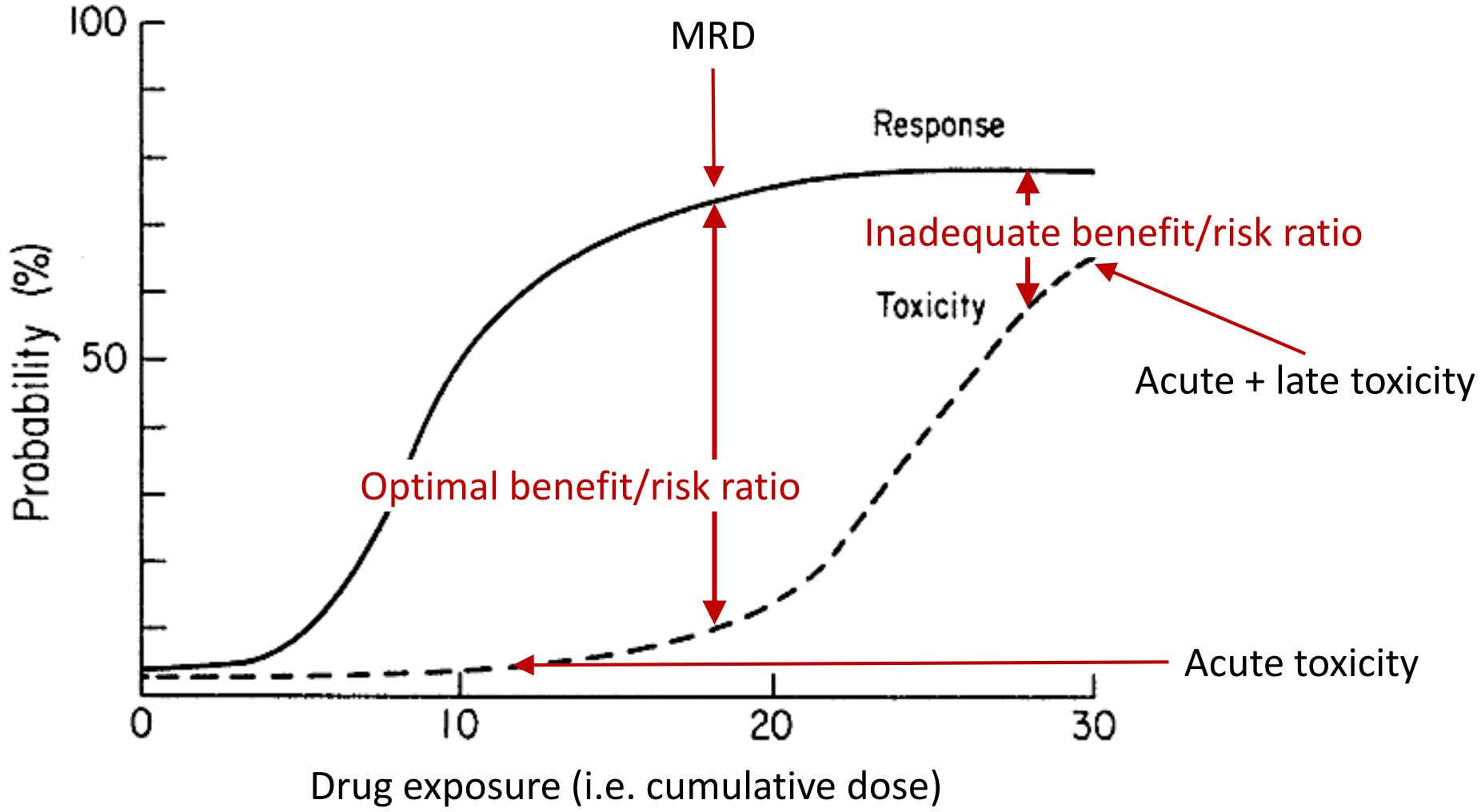
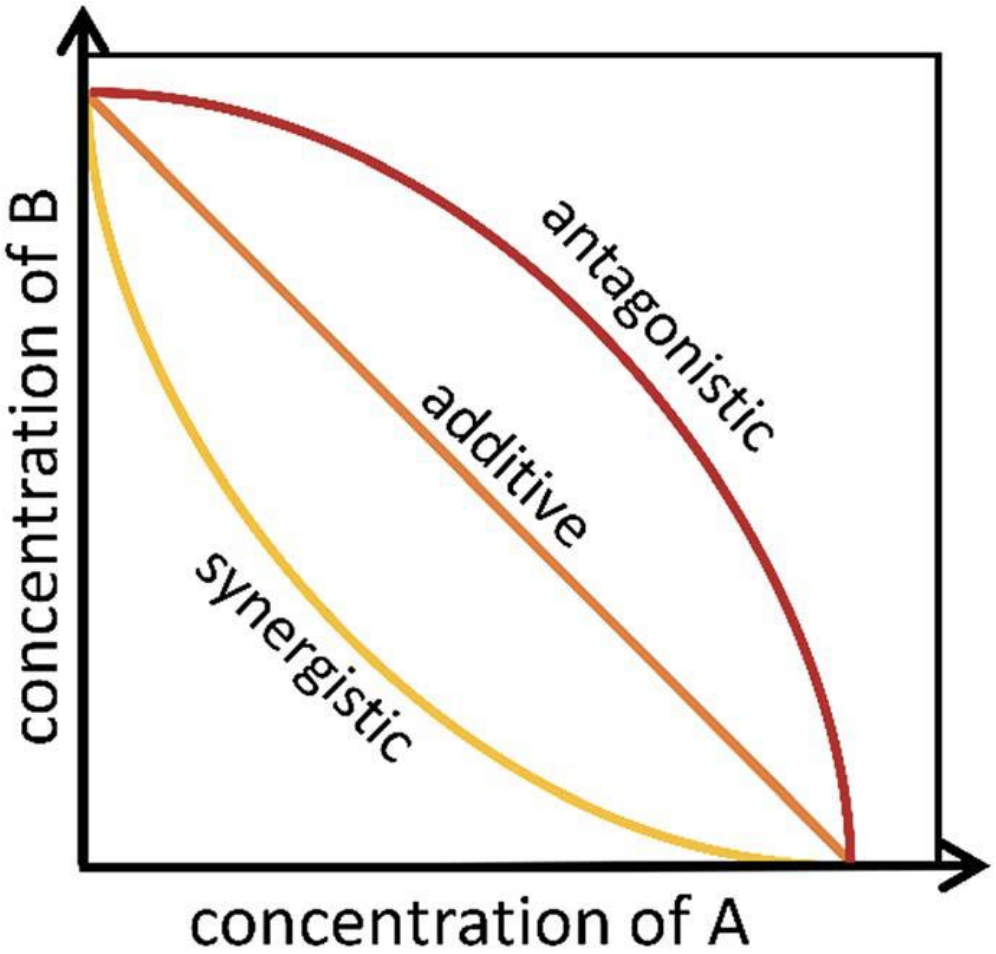


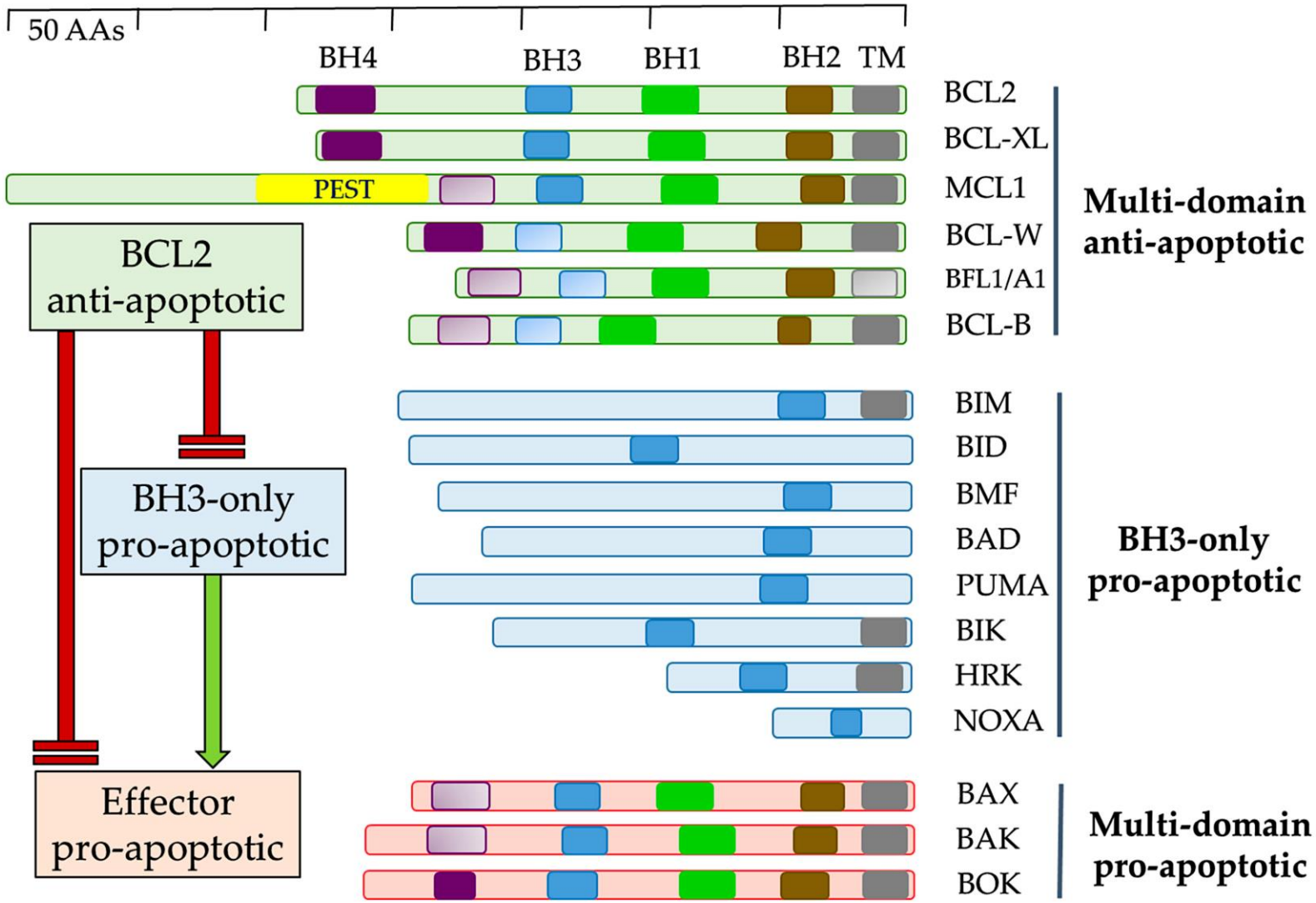

Applied Pharmacokinetics, 3rd ed. Vancouver, WA: Applied Therapeutics; 1992. pp.1–3

# Example of isobolograms for antagonistic, additive, and synergistic components



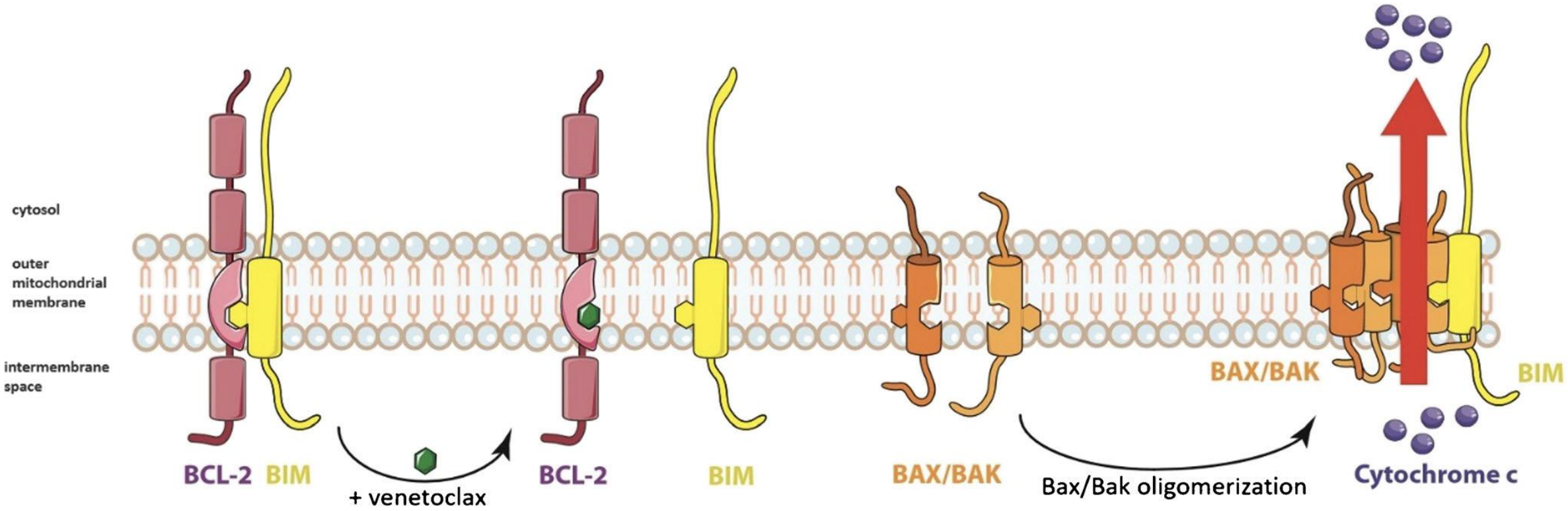

Lindsay K. Caesar et al. DOI: 10.1039/c9np00011a

# Overview of mammalian proteins of the BCL-2 family



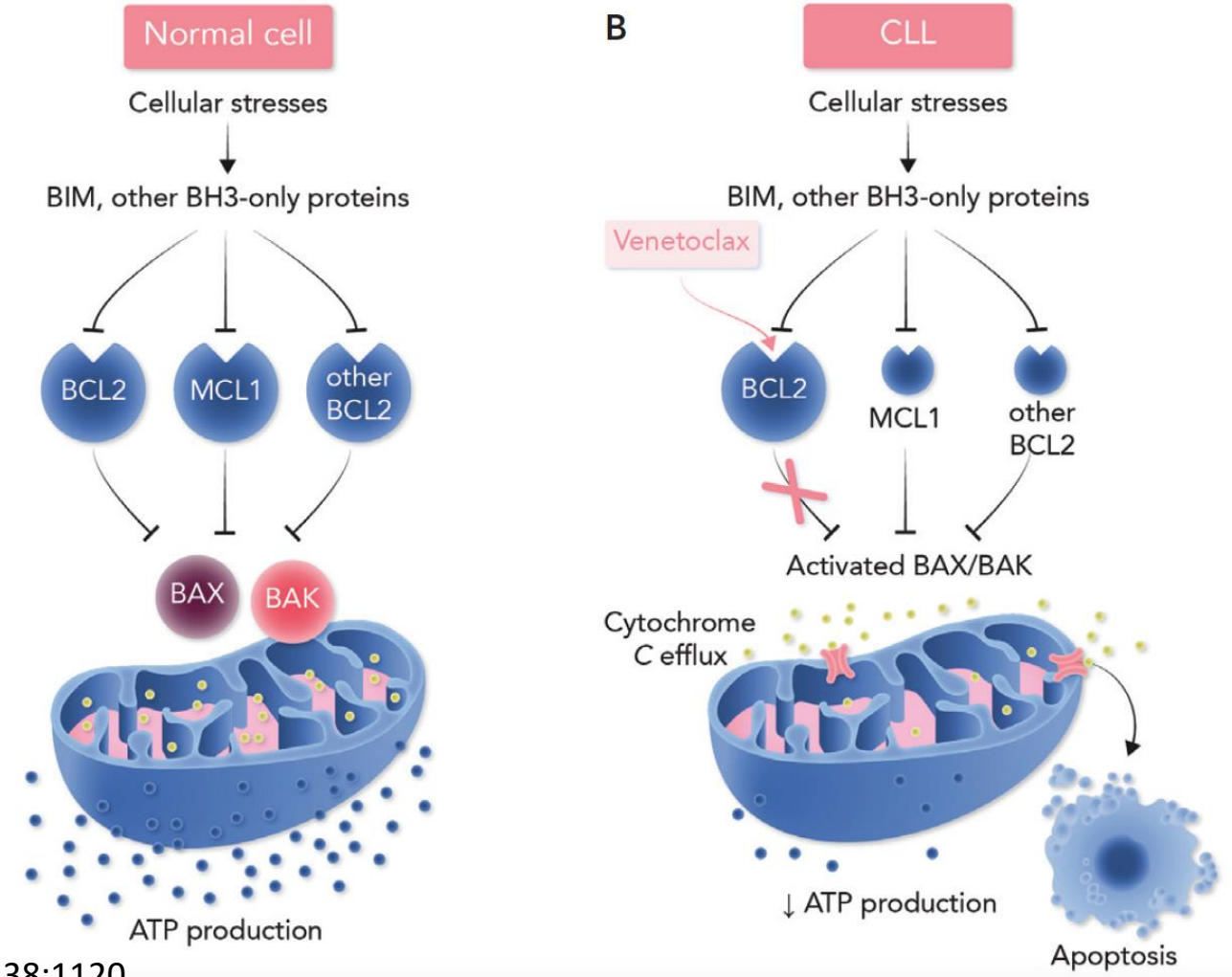

Klener P et al. Int J Mol Sci 2021, 22, 10157. https://doi.org/10.3390/ijms221810157

# Mechanism of action of venetoclax



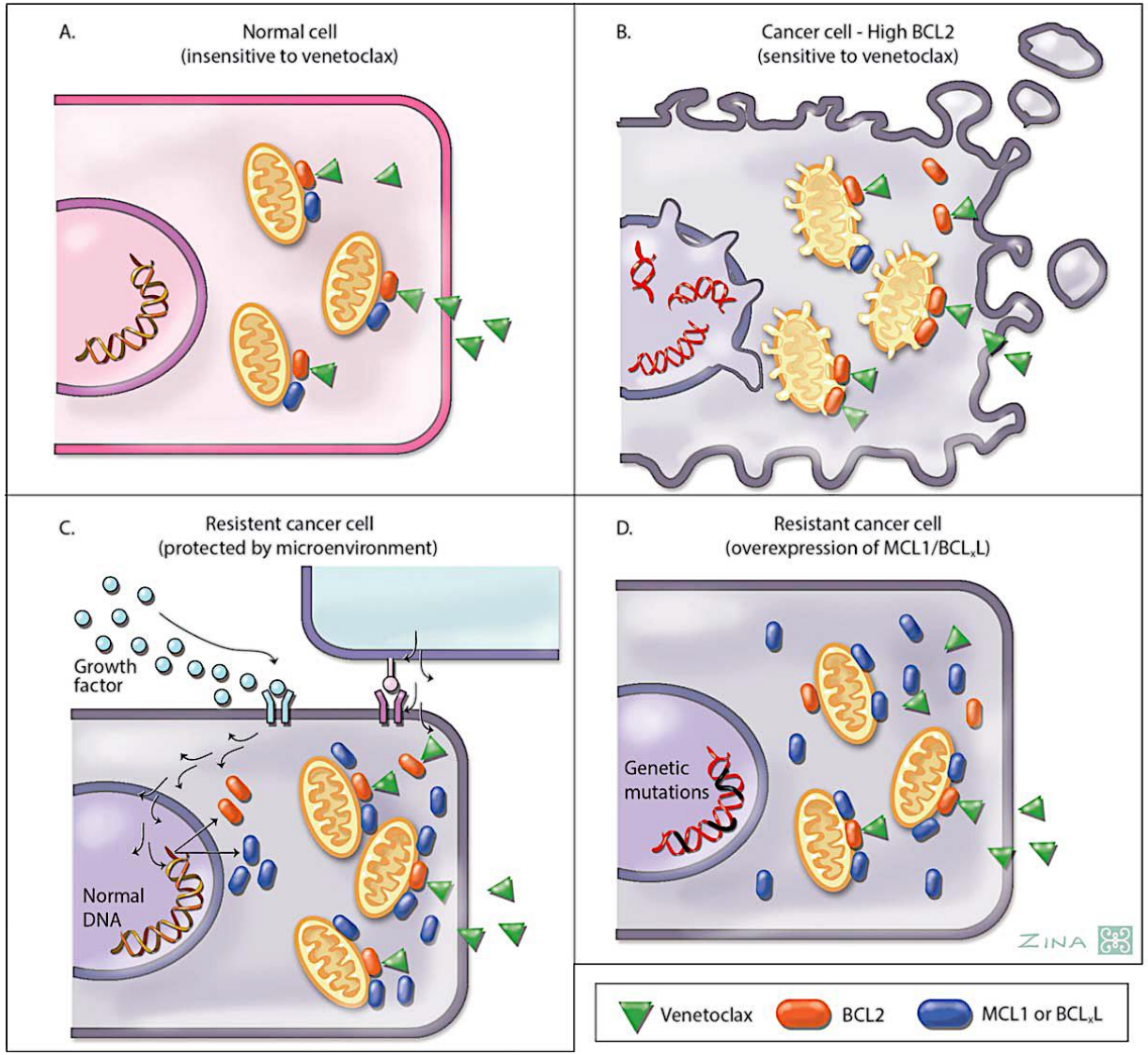

Lampson BL et al. Curr Hematol Malig Rep DOI 10.1007/s11899-017-0359-0

# Regulation of the intrinsic pathway to apoptosis by BCL2 family and mechanism of action of BH3 mimetics in normal and CLL cells




Andrew W. Roberts et al. Blood 2021;138:1120

# Cellular sensitivity or resistance to cytotoxicity induced by venetoclax




Illustrated by Zina Deretsky

Roberts AW et al. Clinical Pharmacology and Therapeutics doi:10.1002/cpt.553

# The rationale of venetoclax-ibrutinib combination

- Ibrutinib and venetoclax have distinct and complementary modes of action that work synergistically to eliminate distinct CLL cell populations.
- CLL cells rely on the overexpression of antiapoptotic proteins (BCL-2, BCL extralarge [XL], and myeloid cell leukemia-1 [MCL-1]) for survival.
- Ibrutinib decreases BCL-XL and MCL-1, but not BCL-2, in highly proliferative lymph node emigrant B cells, mobilizes CLL cells from lymph nodes and lymphoid niches into the peripheral blood, and enhances their susceptibility to venetoclax-induced apoptosis.

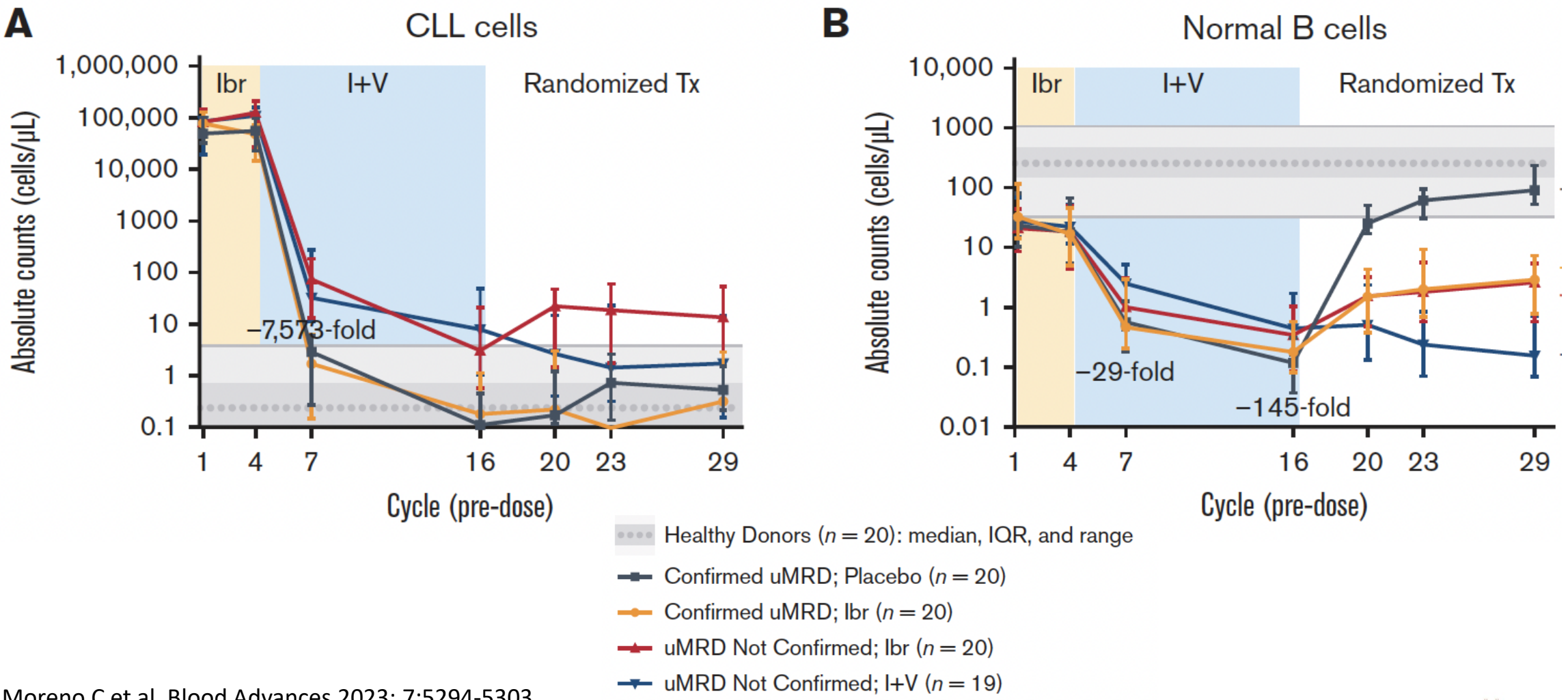
Moreno C et al. Blood Advances 2023; 7:5294-5303

# The rationale of venetoclax-ibrutinib combination

- Combined venetoclax plus ibrutinib demonstrated synergistic antitumor activity in preclinical CLL models, with greater cytotoxicity observed with the combination than with either agent alone.
- Additionally, recent clinical studies with venetoclax plus ibrutinib demonstrated high undetectable minimal residual disease rates in both peripheral blood and bone marrow in patients with CLL.

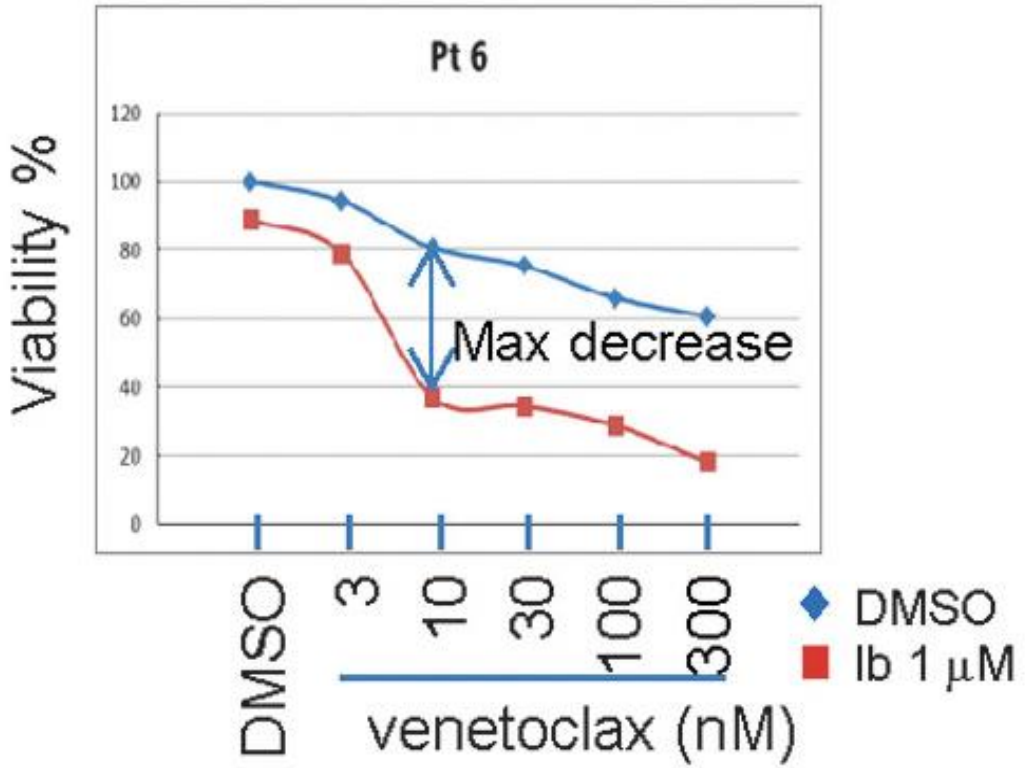
Tam CS et al. https://doi.org/10.1182/blood.2021014488

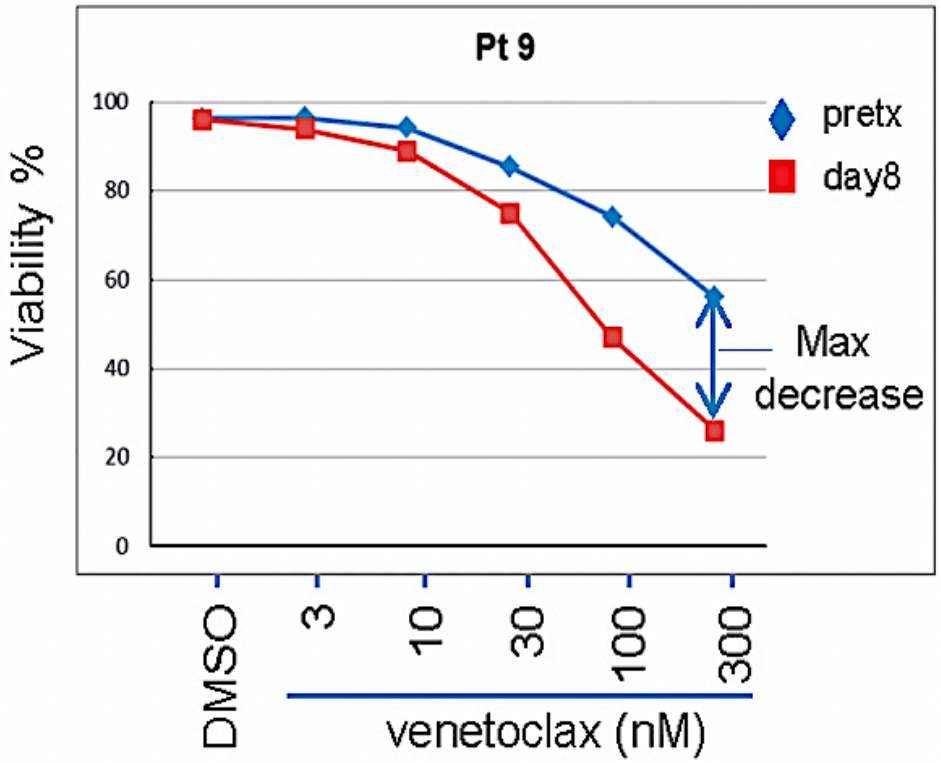
# Ibrutinib plus venetoclax rapidly eradicates CLL cells (data from CAPTIVATE)




Moreno C et al. Blood Advances 2023; 7:5294-5303

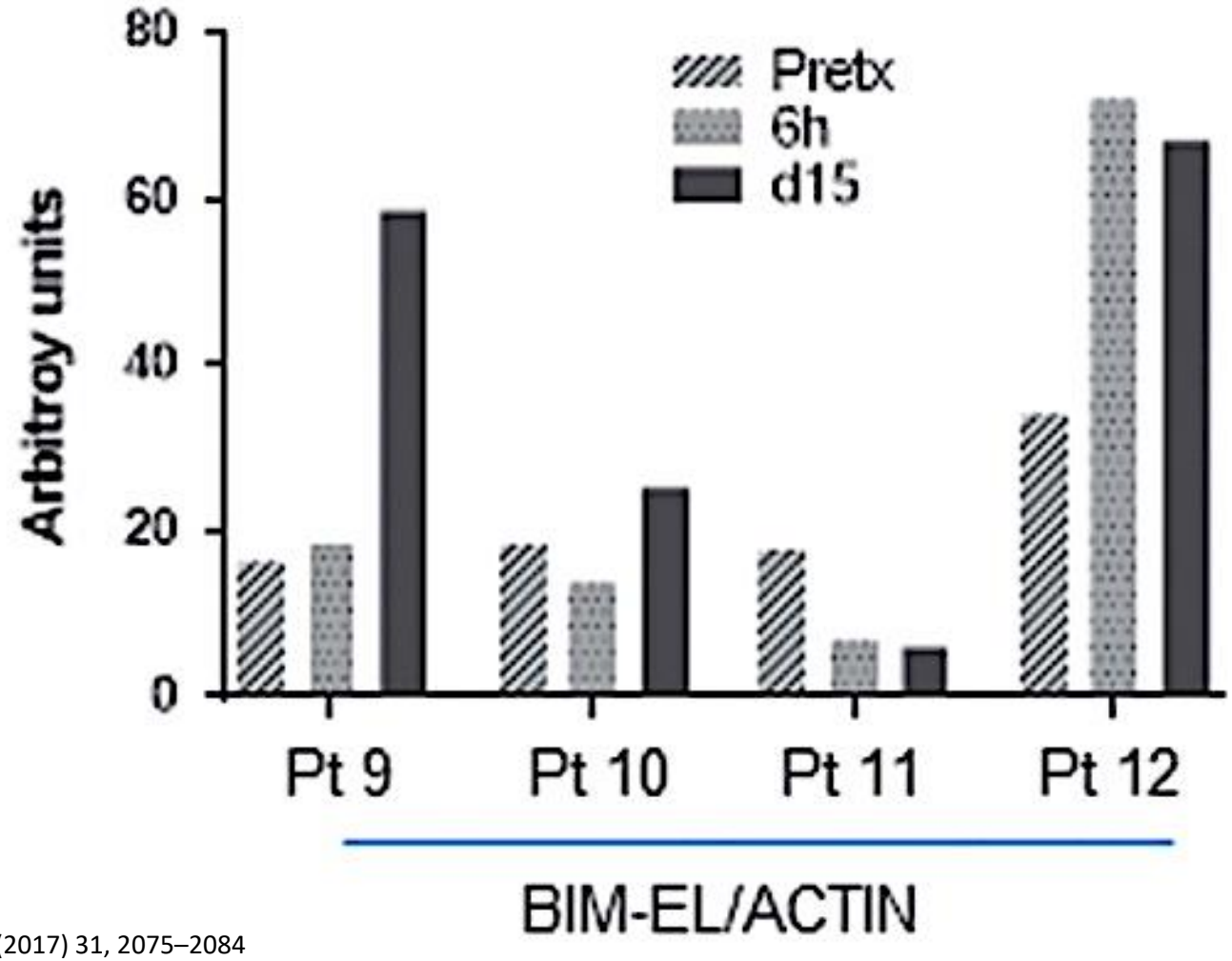
# Pre-treatment with ibrutinib increases CLL cell sensitivity to venetoclax



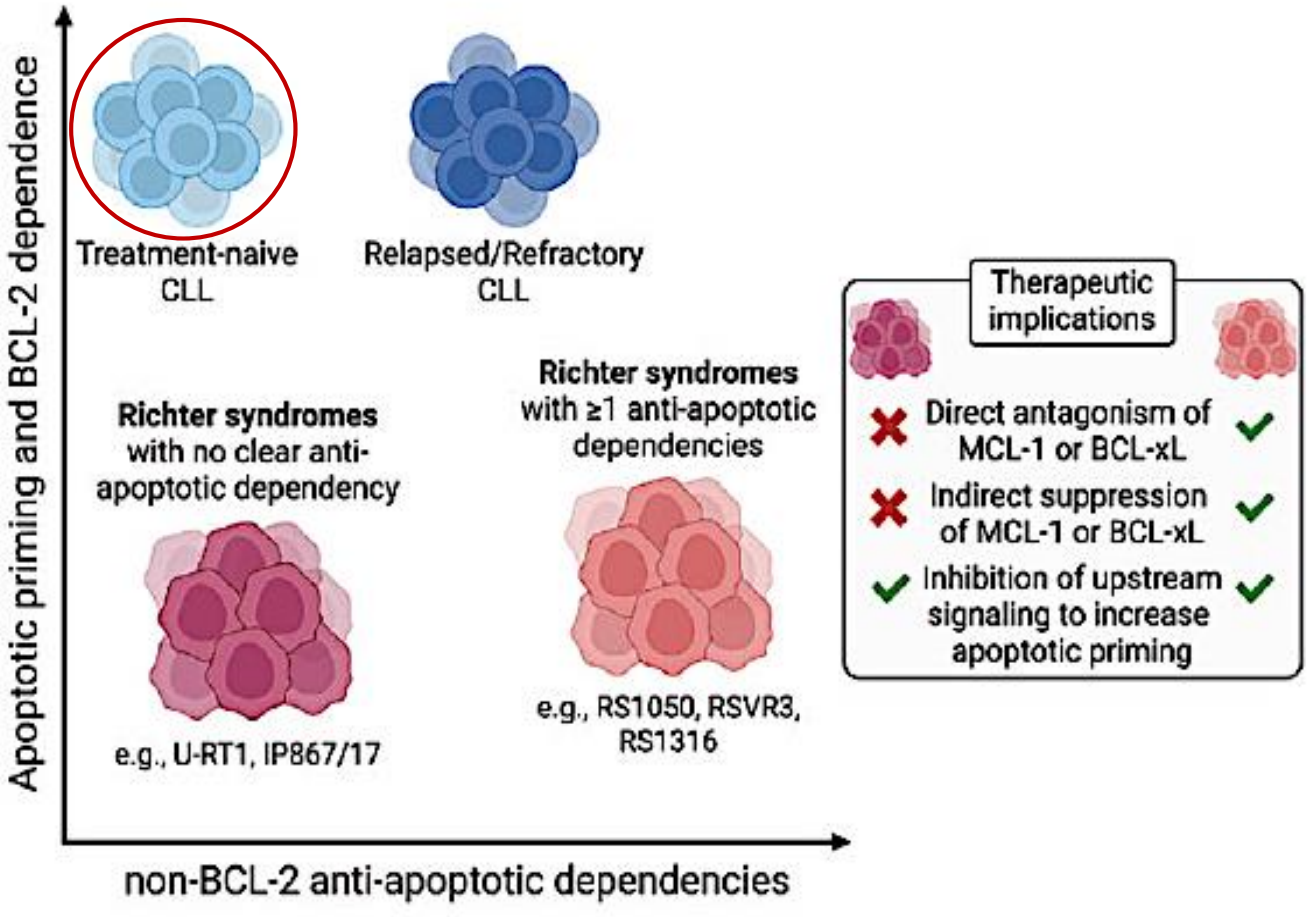

Deng J et al. Leukemia (2017) 31, 2075–2084

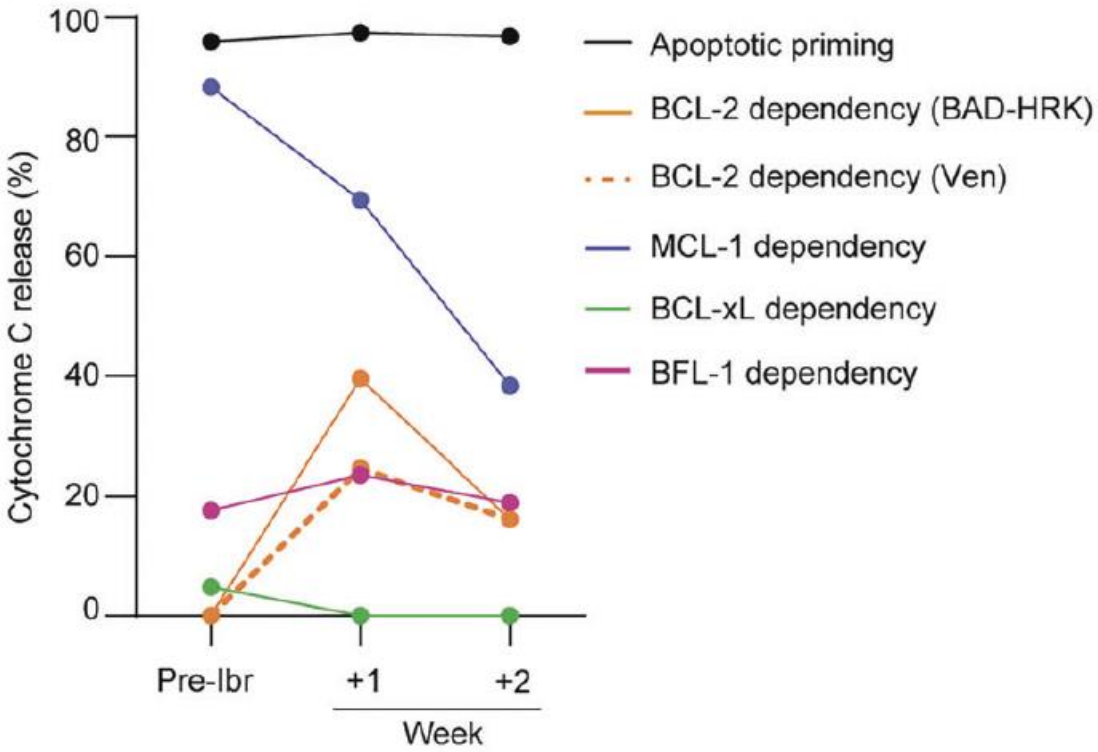
# BIM expression is increased in CLL cells treated in vivo with BTK inhibition




Deng J et al. Leukemia (2017) 31, 2075–2084

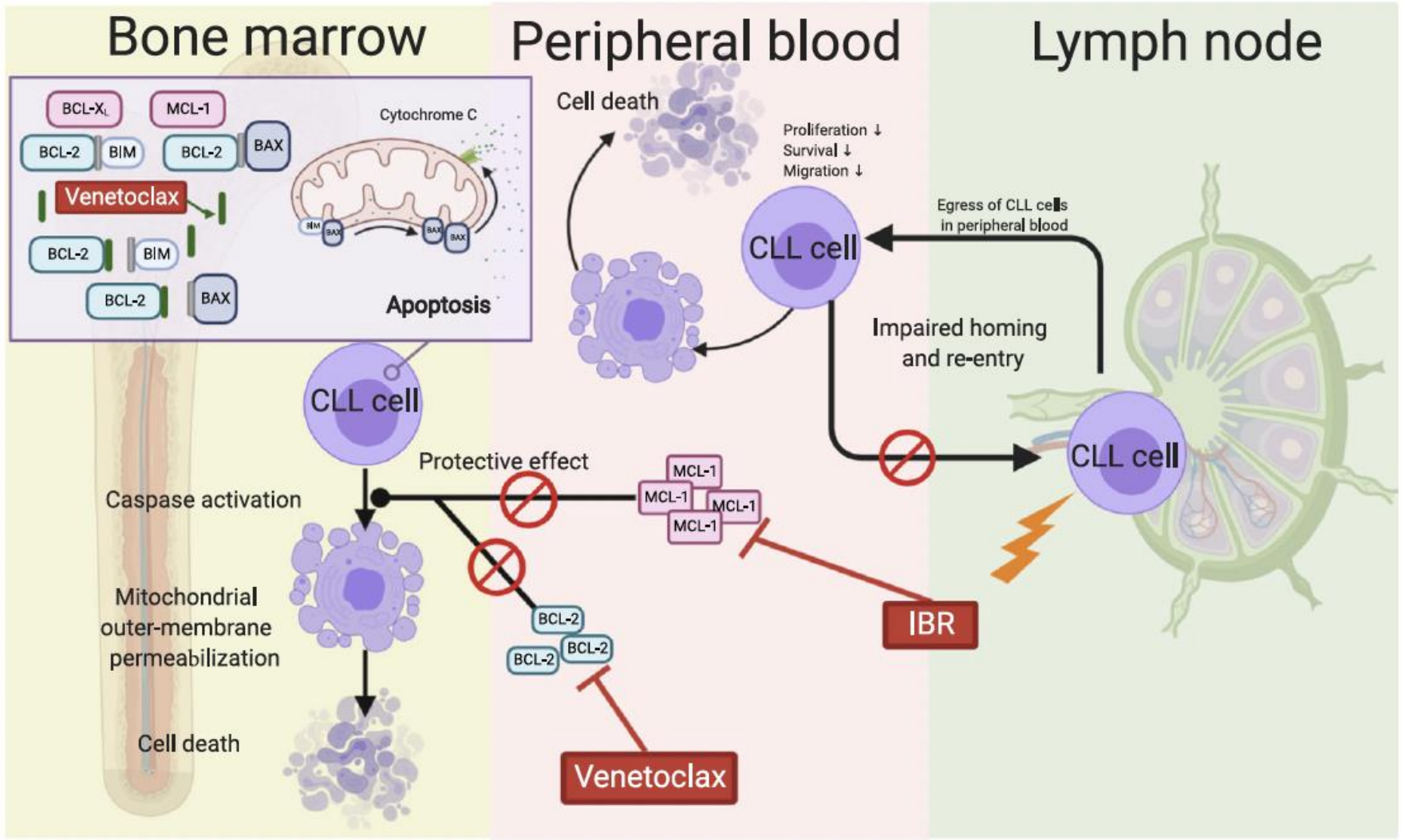
# Treatment-naive CLL cells are characterized by both high BCL-2 dependency and apoptotic priming




Rigo A et al. Cell Death and Disease (2024) 15:323

# Rationale for ibrutinib combination with targeted agent venetoclax




Timofeeva and Gandhi Blood Cancer Journal ( 2021) 11:79

# Therapy choice drivers in older patients with CLL

## Continuous therapy

***Ibrutinib / Acalabrutinib / Zanubrutinib***

- Logistically easy to administer
- Long follow-up support efficacy and tolerability (I)
- Preferred option in patients with high-risk disease (especially *TP53* aberrations)

## Fixed-duration therapy

***Venetoclax+Obi / Venetoclax+Ibrutinib***

- Undetectable MRD in up to ≈75% of cases
- Prolonged treatment-free interval
- Drug-related AE rare after end of treatment

***Ibrutinib / Acalabrutinib / Zanubrutinib***

- Afib/VA (< with A and Z)
- Hypertension (< with A)
- Hemorrhage (< with A)
- Anticoagulants
- Arthralgia (< with A and Z)
- Cumulative incidence of AE over time

***Venetoclax+Obi***

- Grade 3-4 infusion reactions
- Need monitoring TLS
- Neutropenia
- Shorter PFS in high-risk disease

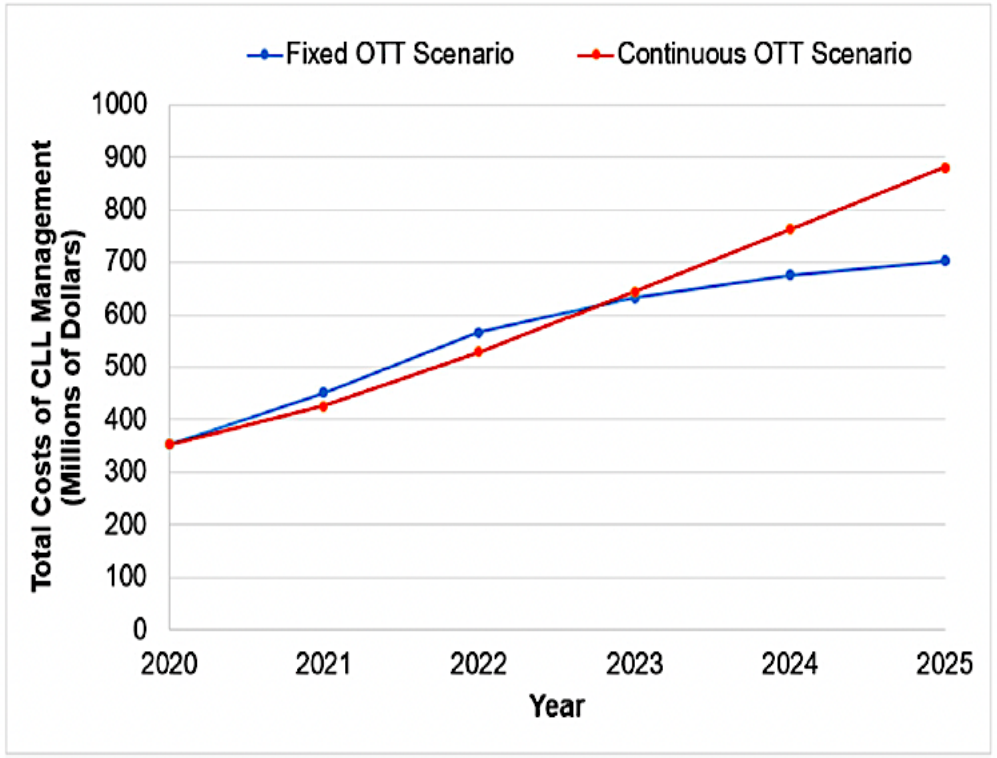
***Venetoclax+Ibrutinib***

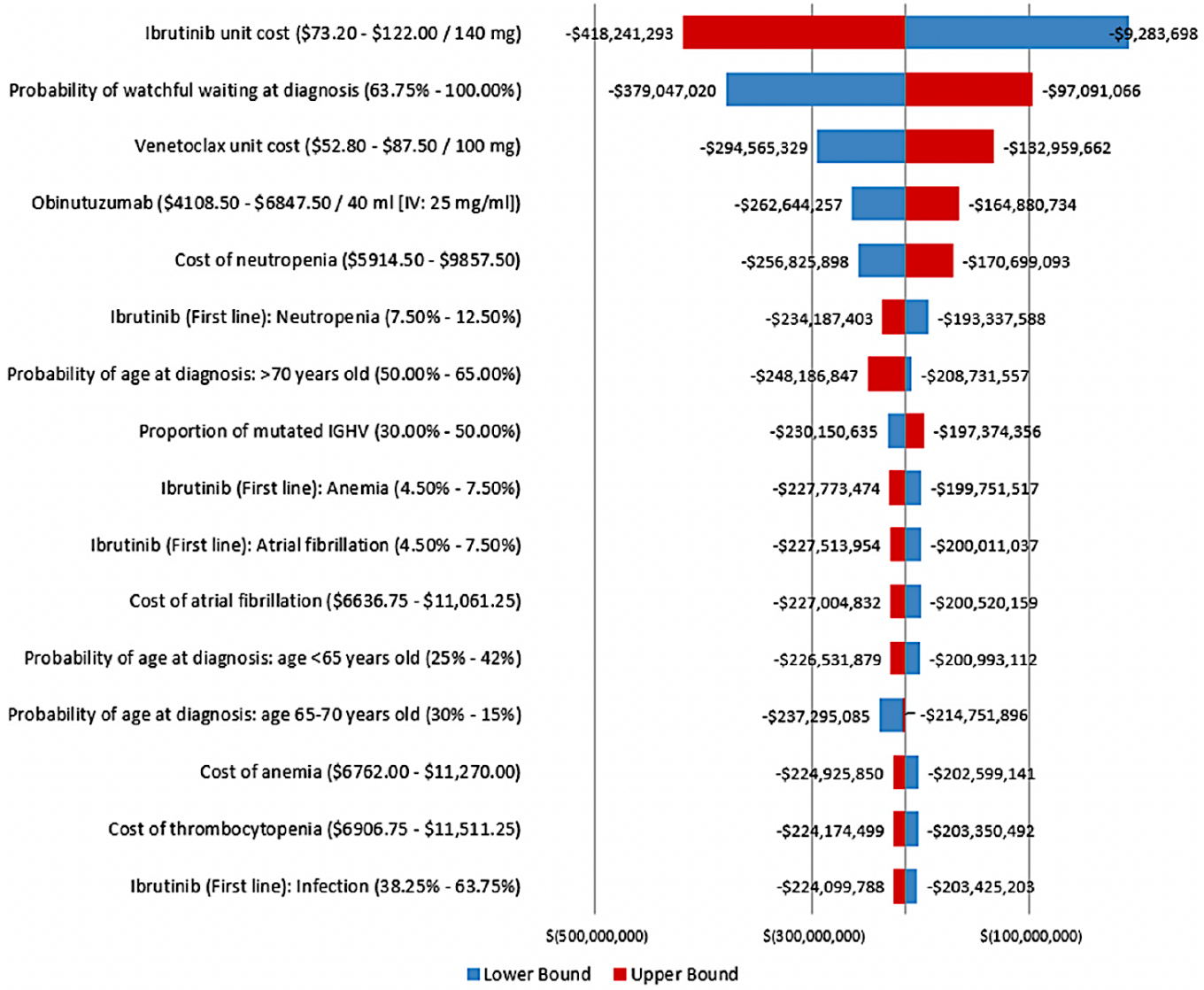
- Afib/VA
- Hypertension
- Neutropenia
- Short follow-up
- Subsequent treatment?

Urso A et al. Cancers 2023, 15, 3859

# Pharmacoeconomic considerations

Data from Canada




Jean Lachaine et al. Curr Oncol 2023, 30, 4483–4498

# Conclusions

- BCL2 and MCL1 are commonly expressed antiapoptotic proteins in hematologic cancers and play important roles in their biology either through dysregulation or by virtue of intrinsic importance to the cell-of-origin of the malignancy.
- Venetoclax is the only small molecule preventing a protein-protein interaction and a first-in-class orally bioavailable BCL-2–selective inhibitor that shows potent cell killing in vitro and antitumor efficacy in vivo.
- The lack of BCL-XL inhibition with venetoclax should allow for higher circulating concentrations of the drug to be achieved in patients with CLL without dose-limiting thrombocytopenia.

# Conclusions

- The complementary effects of venetoclax and ibrutinib on CLL mitochondria strongly supports their exploration of these combinations in the clinic.
- The combination of venetoclax and ibrutinib is highly active and well-tolerated and provide fixed-duration options for patients with CLL.