

# Farmacologicamente discutendo

Romano Danesi  
Dipartimento di Oncologia ed Emato-Oncologia  
Università degli Studi di Milano



## REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia  
della leucemia linfatica cronica

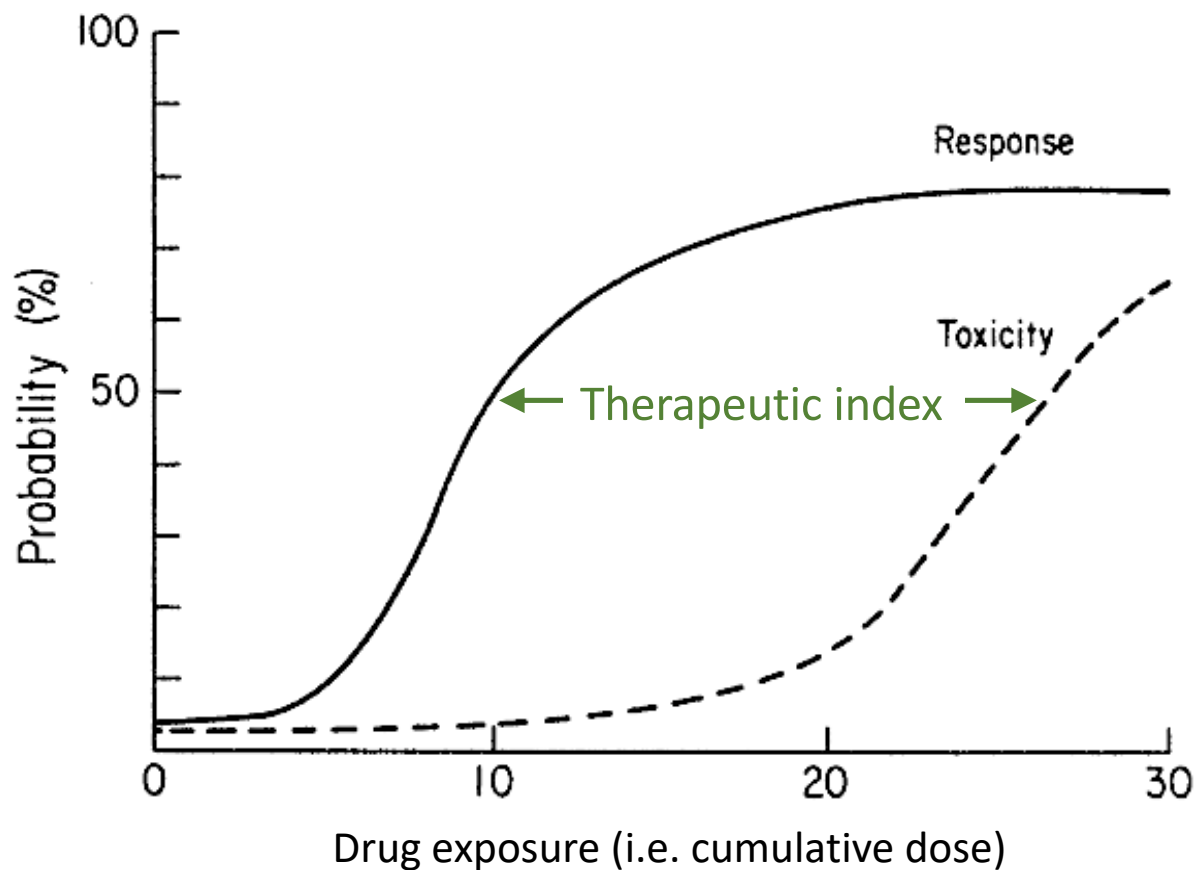
**Bari, 29 maggio 2024**  
Mercure Villa Romanazzi Carducci

# 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

**REVOLUTIONARY ROAD IN CLL**

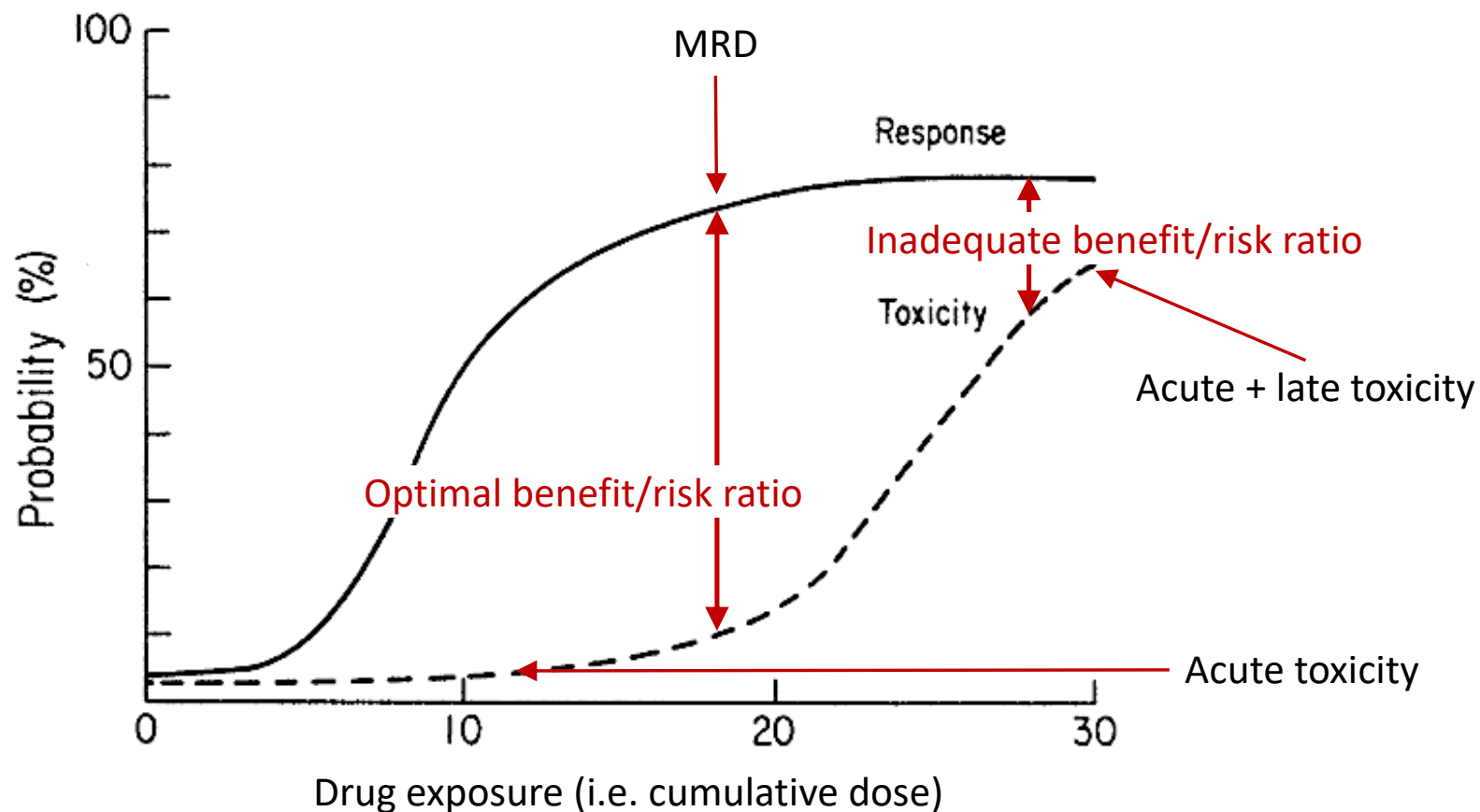
Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica



Bari, 29 maggio 2024

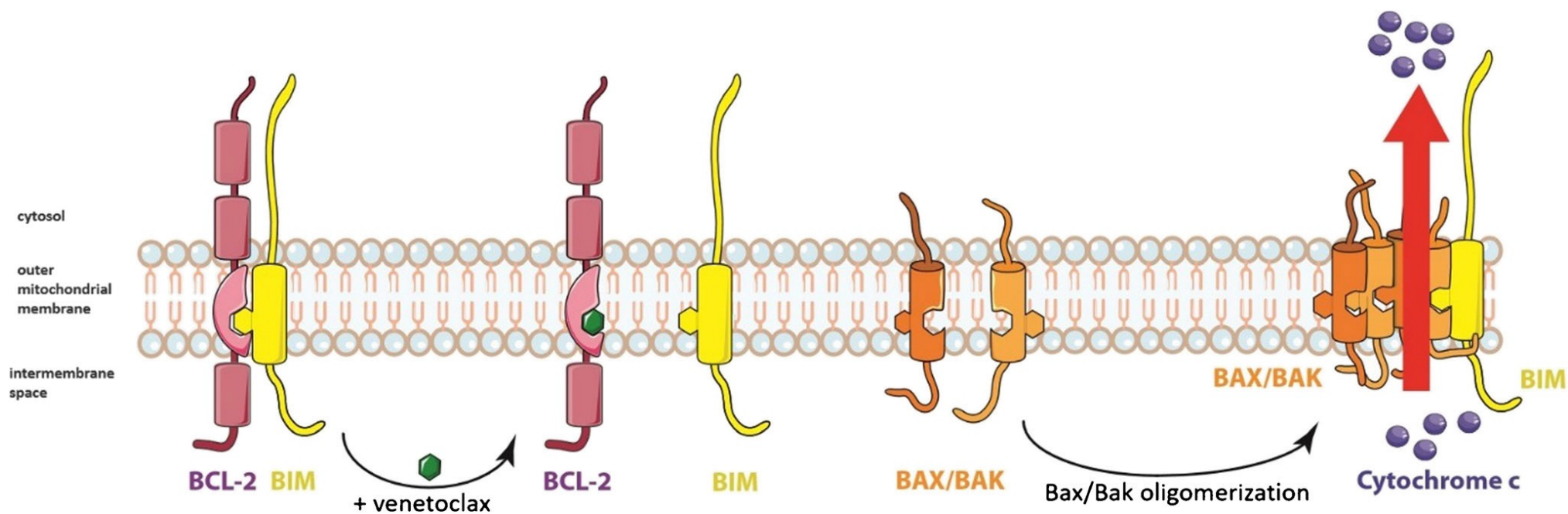
Mercure Villa Romanazzi Carducci

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



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

# Mechanism of action of venetoclax

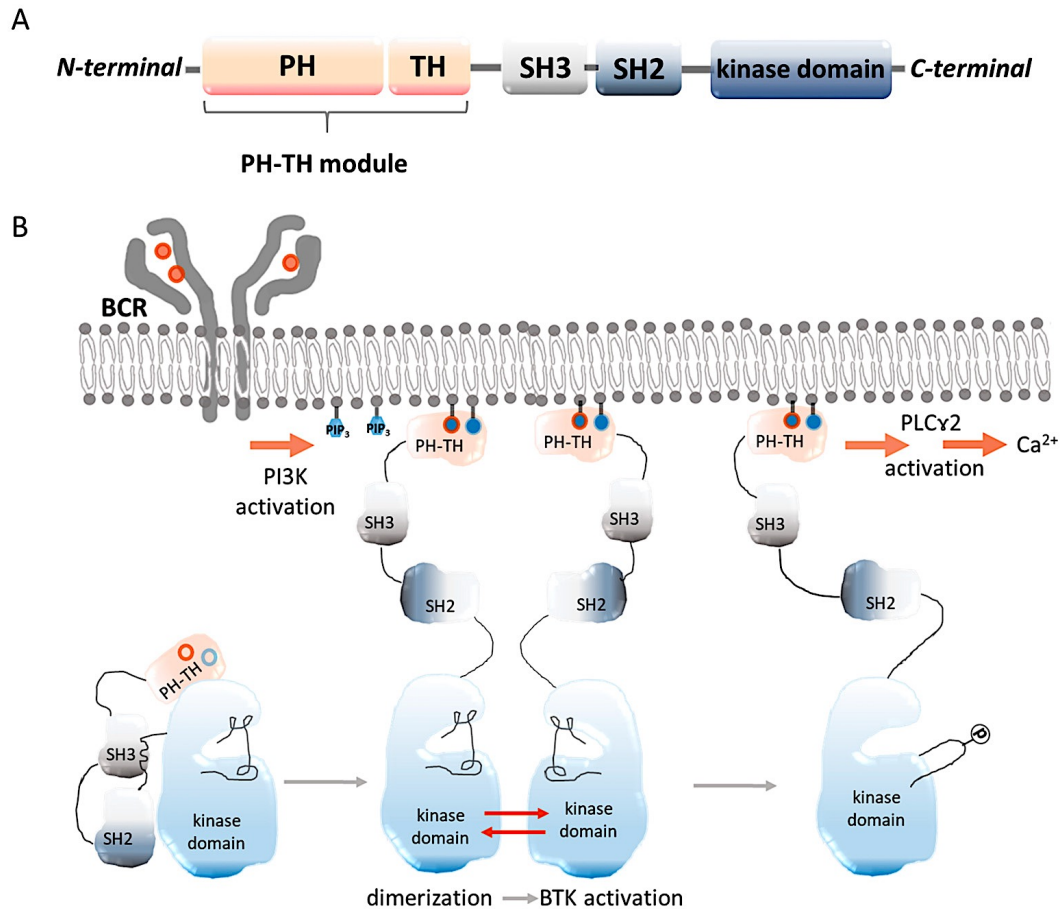


Lampson BL et al. Curr Hematol Malig Rep DOI 10.1007/s11899-017-0359-0

**REVOLUTIONARY ROAD IN CLL**  
Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

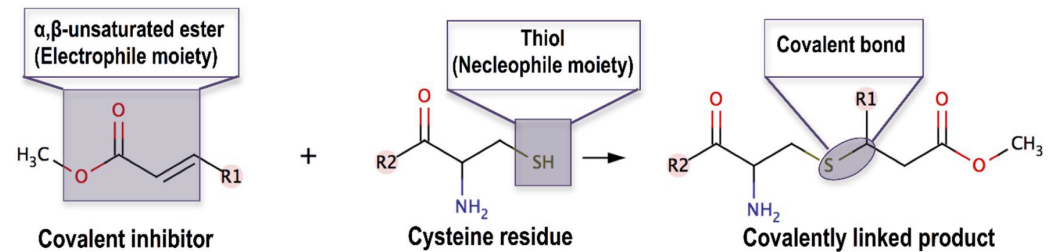
  
**Bari, 29 maggio 2024**  
Mercure Villa Romanazzi Carducci

# Activity of BTK and its inhibition by covalent binding



**PH:** the pleckstrin homology domain has the capacity to bind phospholipids, allowing BTK to be recruited from the cytosol to the plasma membrane.

**TH:** the Tec homology domain is required for the stability of BTK.



R1 = The non-covalent part of the inhibitor

R2 = Protein residues

# 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 (CD5<sup>hi</sup> CXCR4<sup>dim</sup>), 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

**REVOLUTIONARY ROAD IN CLL**

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica



Bari, 29 maggio 2024

Mercure Villa Romanazzi Carducci

# 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>

**REVOLUTIONARY ROAD IN CLL**

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

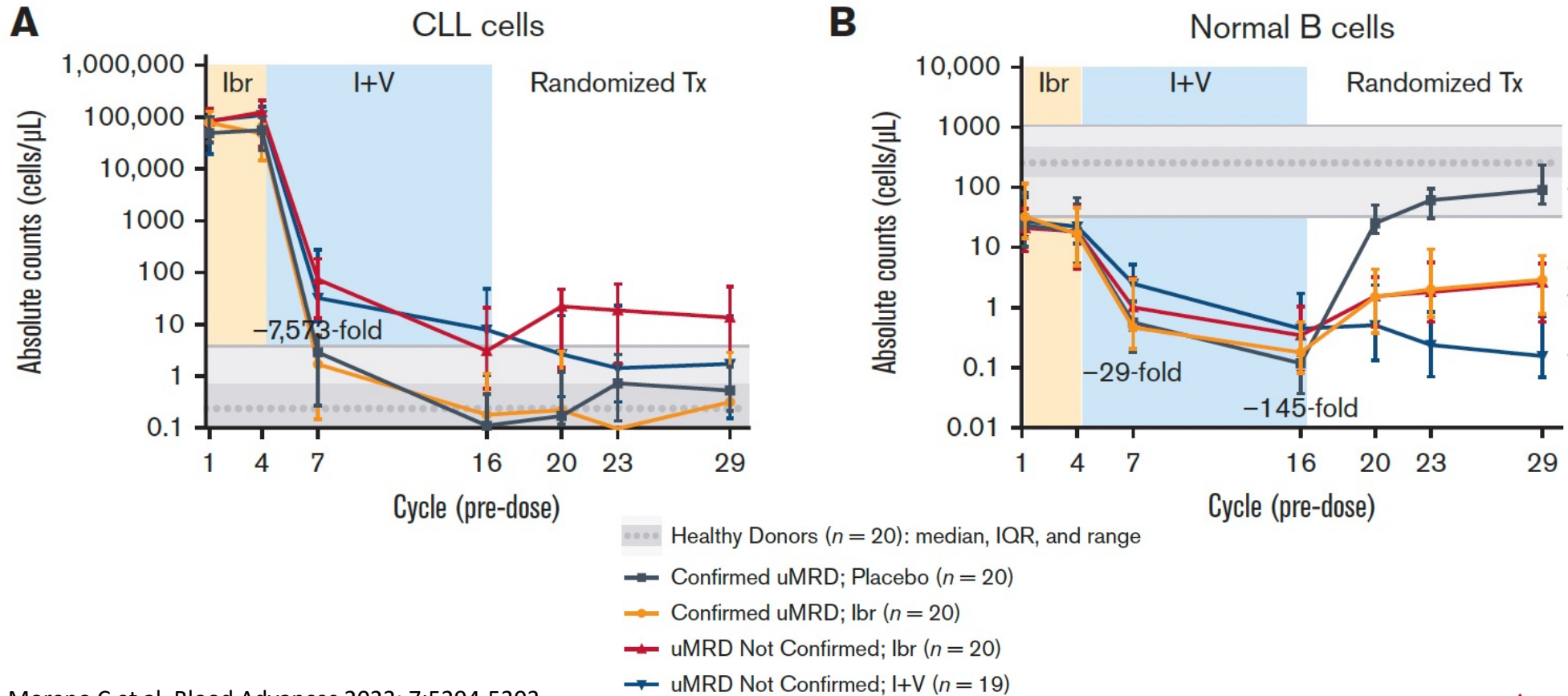


**Bari, 29 maggio 2024**

Mercure Villa Romanazzi Carducci

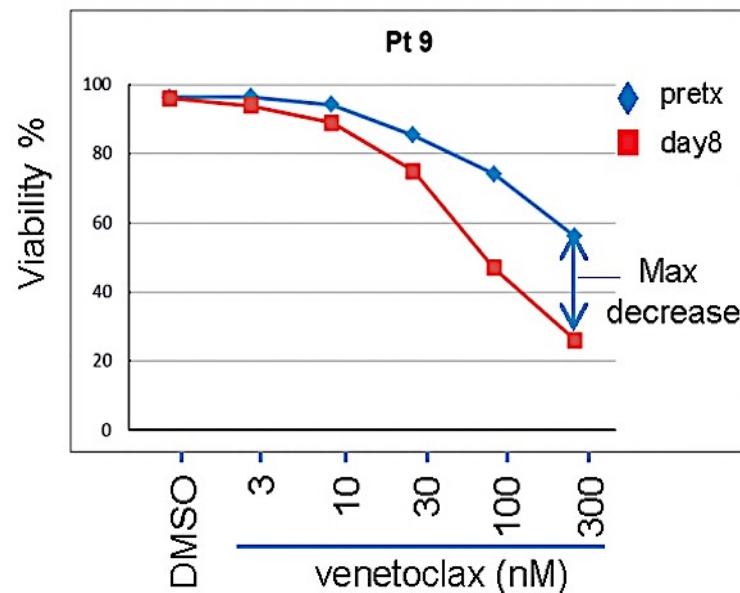
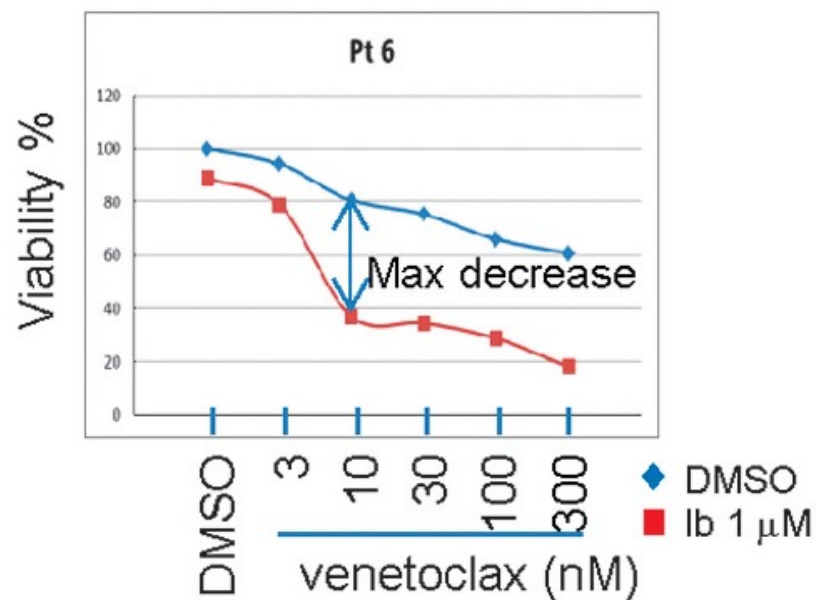


# Ibrutinib plus venetoclax rapidly eradicates CLL cells (data from CAPTIVATE)



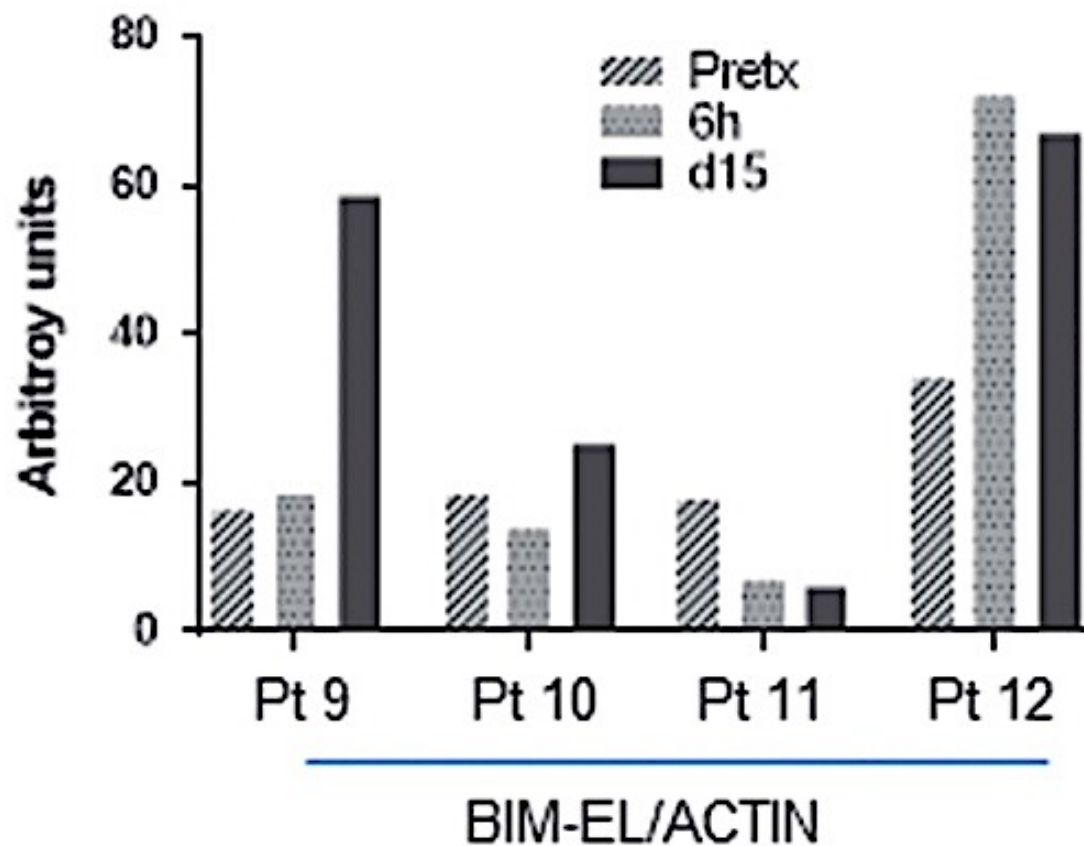
Moreno C et al. Blood Advances 2023; 7:5294-5303

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



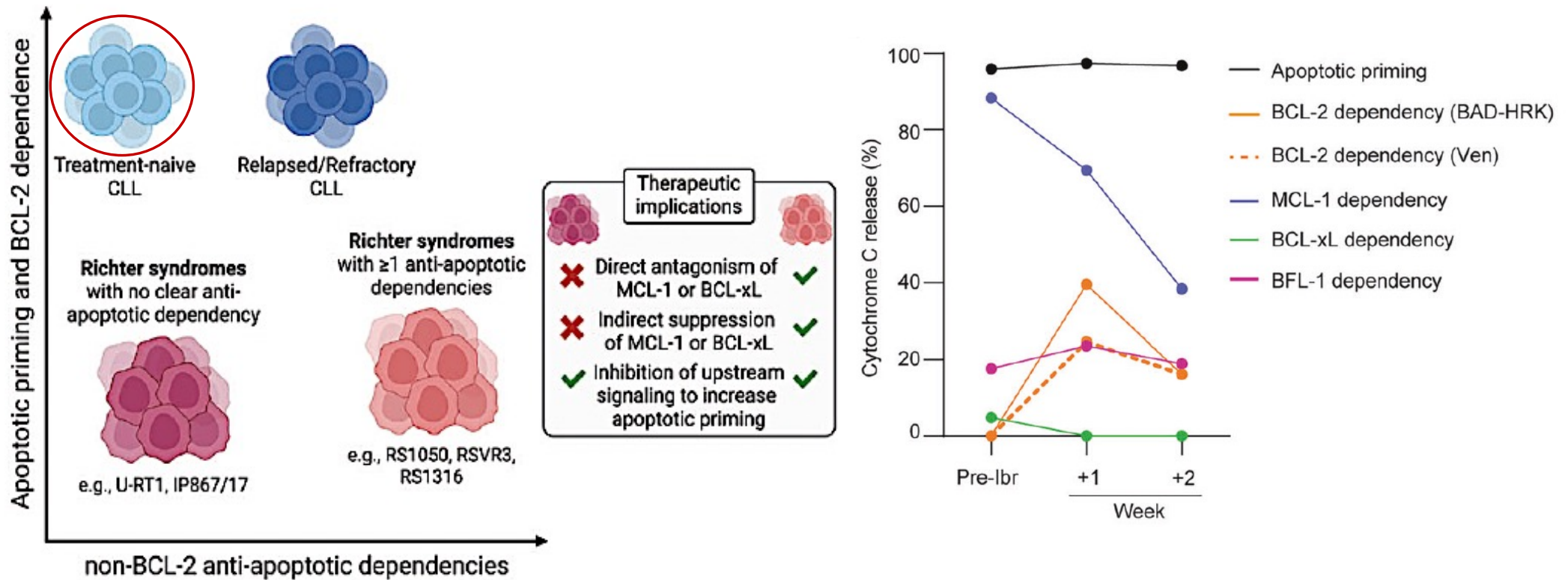
Deng J et al. Leukemia (2017) 31, 2075–2084

## 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

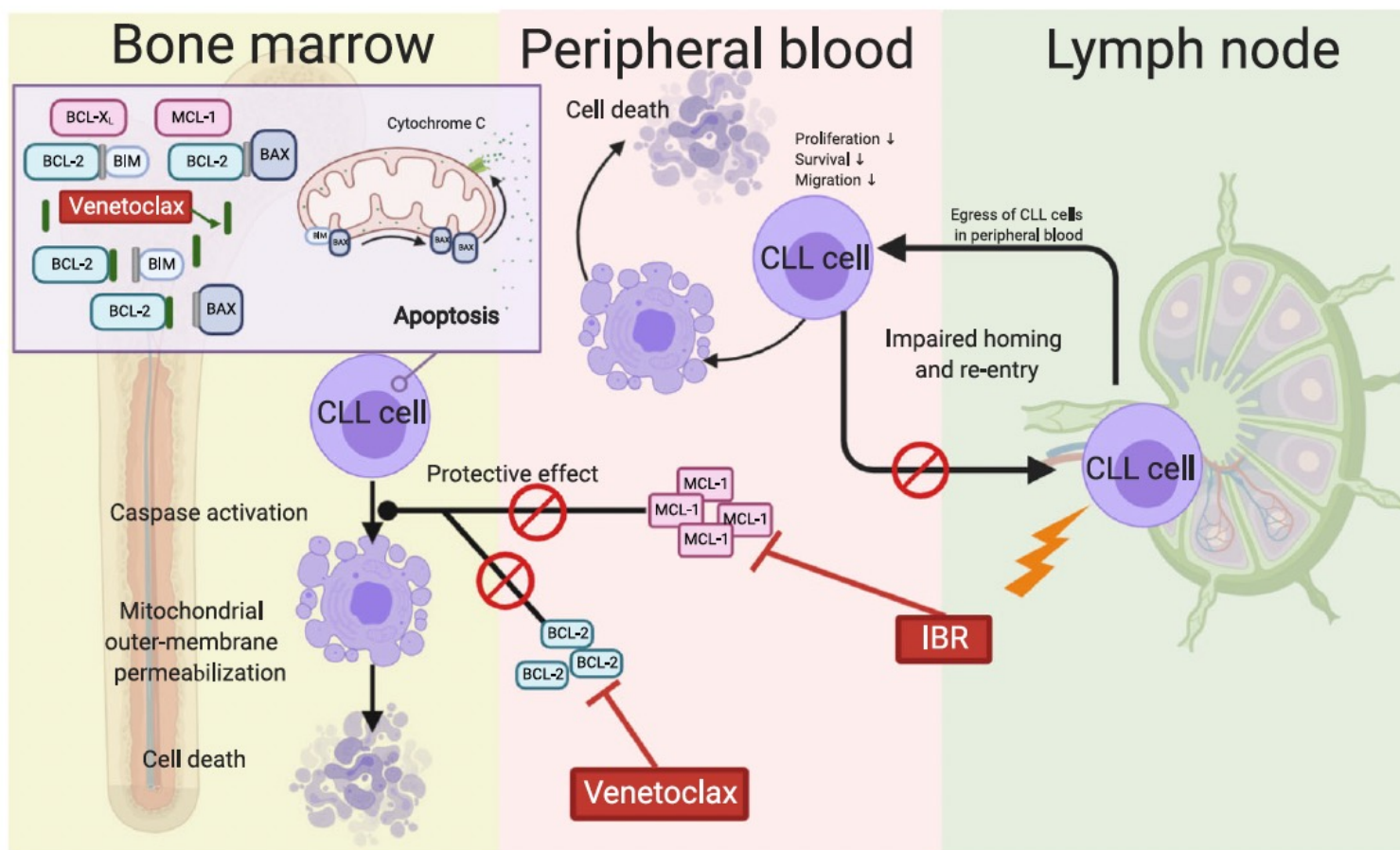


## REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Bari, 29 maggio 2024  
 Mercure Villa Romanazzi Carducci <sup>12</sup>

# Rationale for ibrutinib combination with targeted agent venetoclax





## 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.

