Farmacologicamente discutendo

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

REVOLUTIONARY ROAD IN CLL

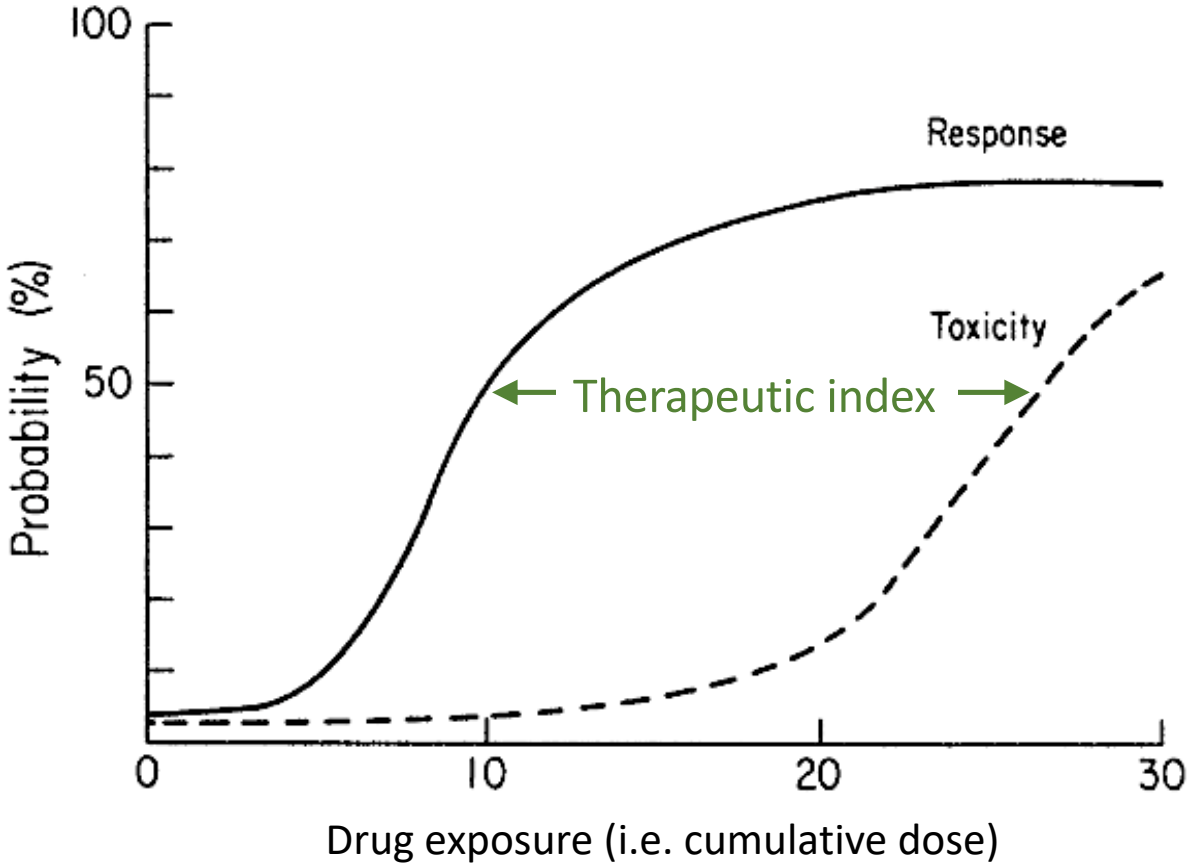
Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica

Bologna, 20 maggio 2024
Royal Hotel Carlton

Disclosures

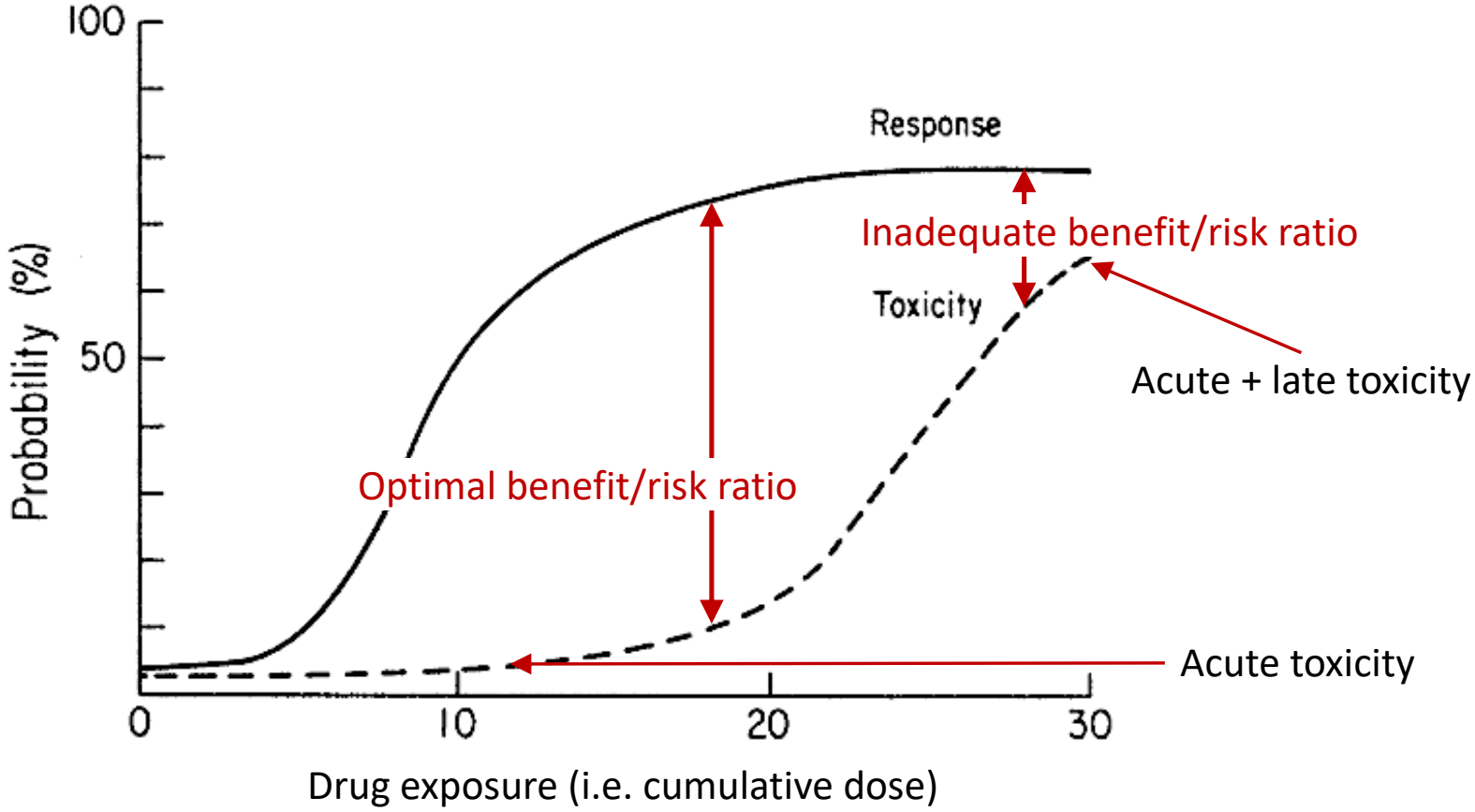
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
MSD			X		X		
Eisai			X		X	X	
AstraZeneca	X		X		X	X	
BeiGene					X		
Janssen	X		X		X		
Novartis			X		X		
Lilly			X		X		
Incyte			X		X		
AB Science			X				
Sanofi			X		X	X	
Abbvie			X		X		

Relationship between drug exposure and effects (therapeutic and adverse)



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

Relationship between drug exposure and effects (therapeutic and adverse)



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

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 (CD5hi CXCR4dim), mobilizes CLL cells from lymph nodes and lymphoid niches into the peripheral blood, and enhances their susceptibility to venetoclax-induced apoptosis.

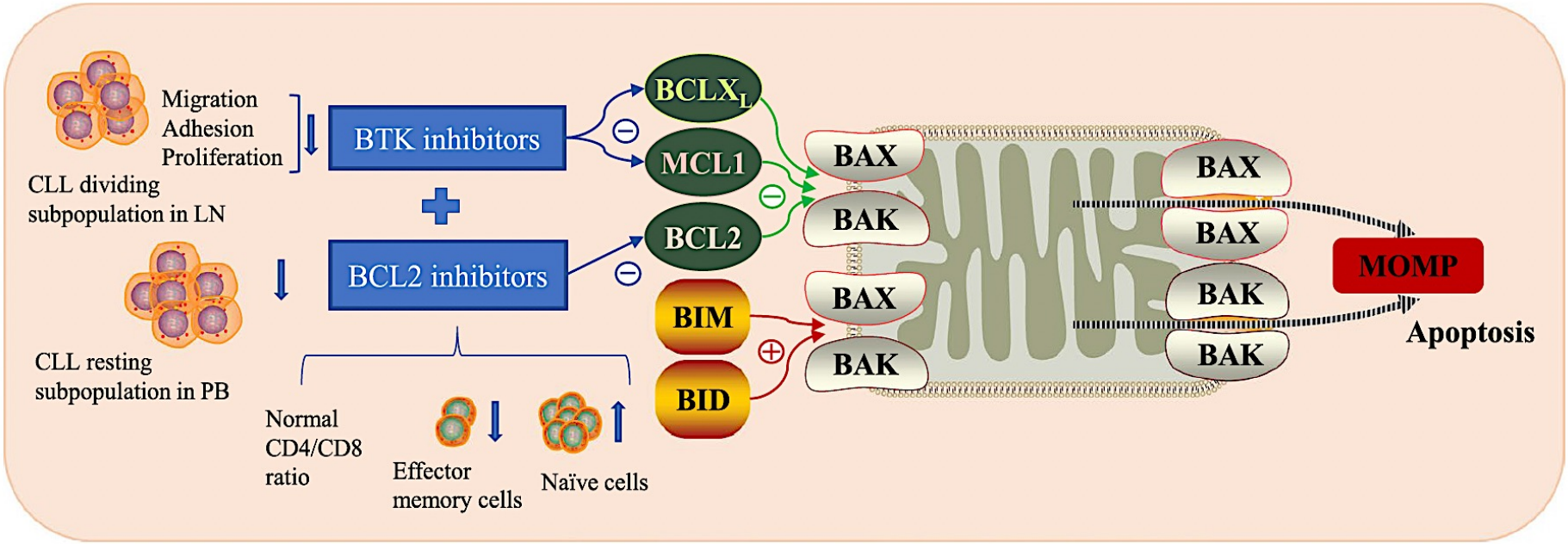
Moreno C et al. Blood Advances 2023; 7:5294-5303

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.

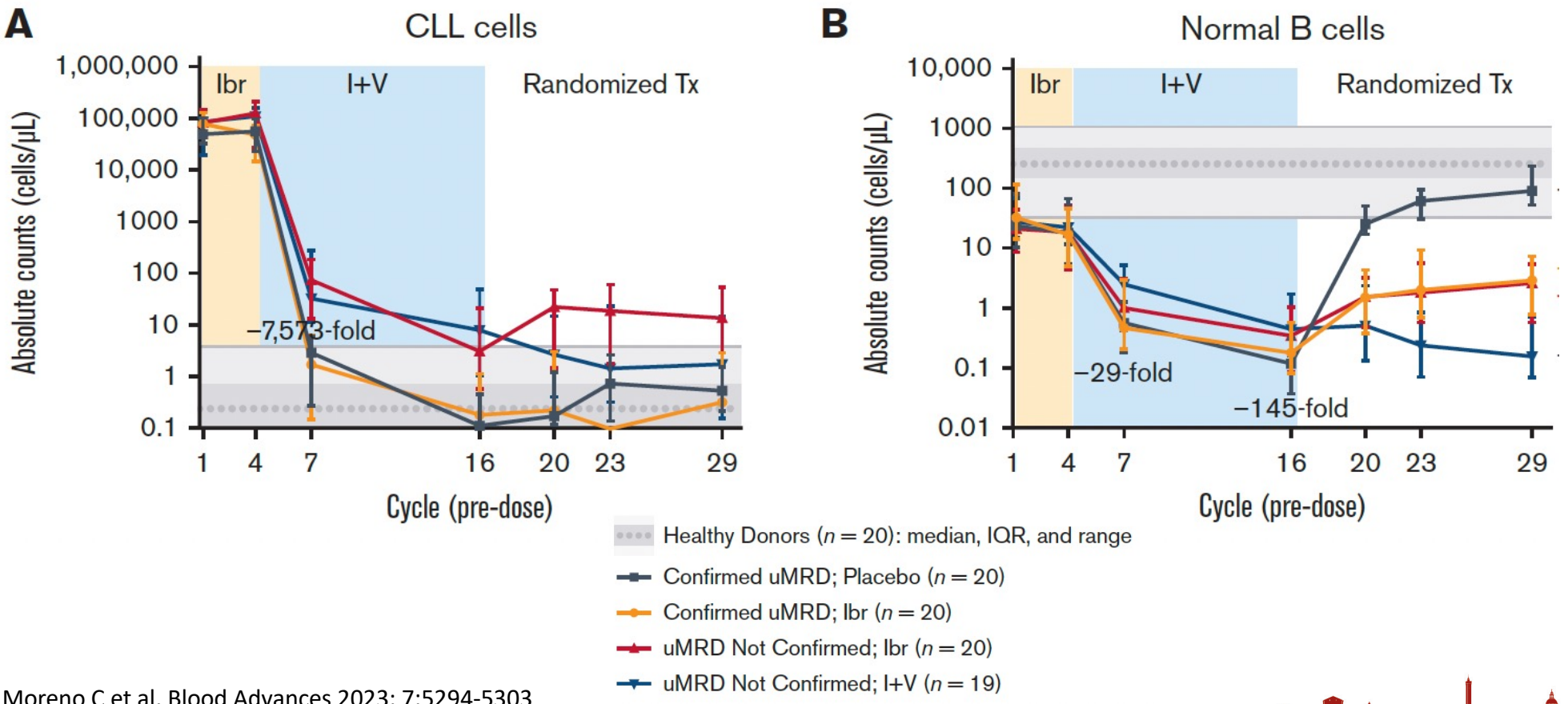
Tam CS et al. https://doi.org/10.1182/blood.2021014488

The distinct and complementary mechanisms of ibrutinib and venetoclax



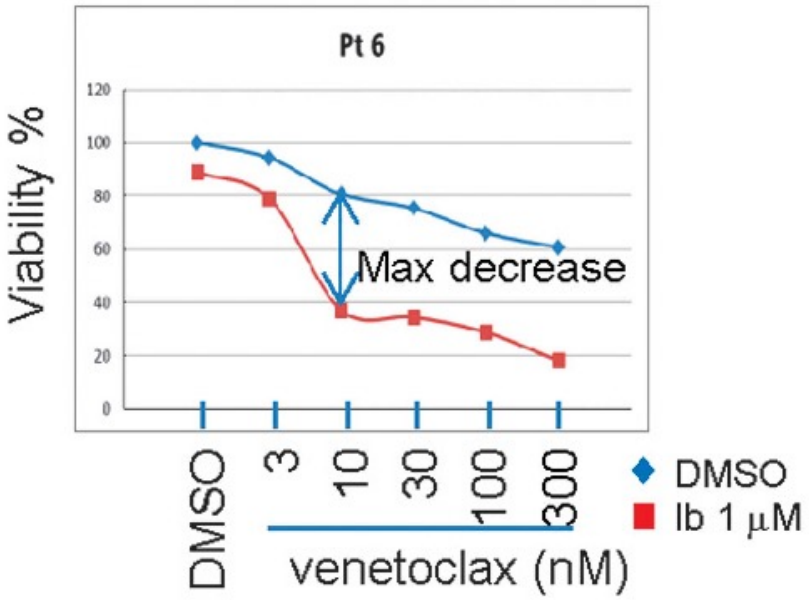
Zhang et al. Biomarker Research (2022) 10:17

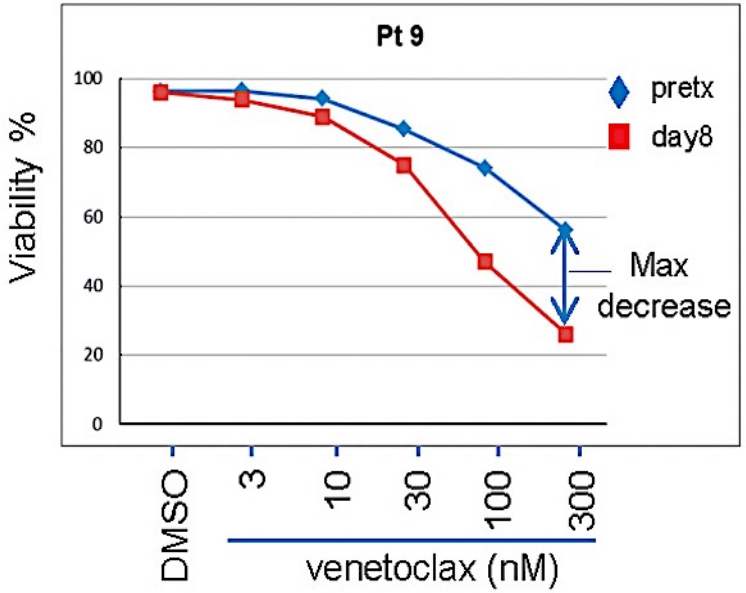
Ibrutinib plus venetoclax rapidly eradicates CLL cells (data from CAPTIVATE)



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

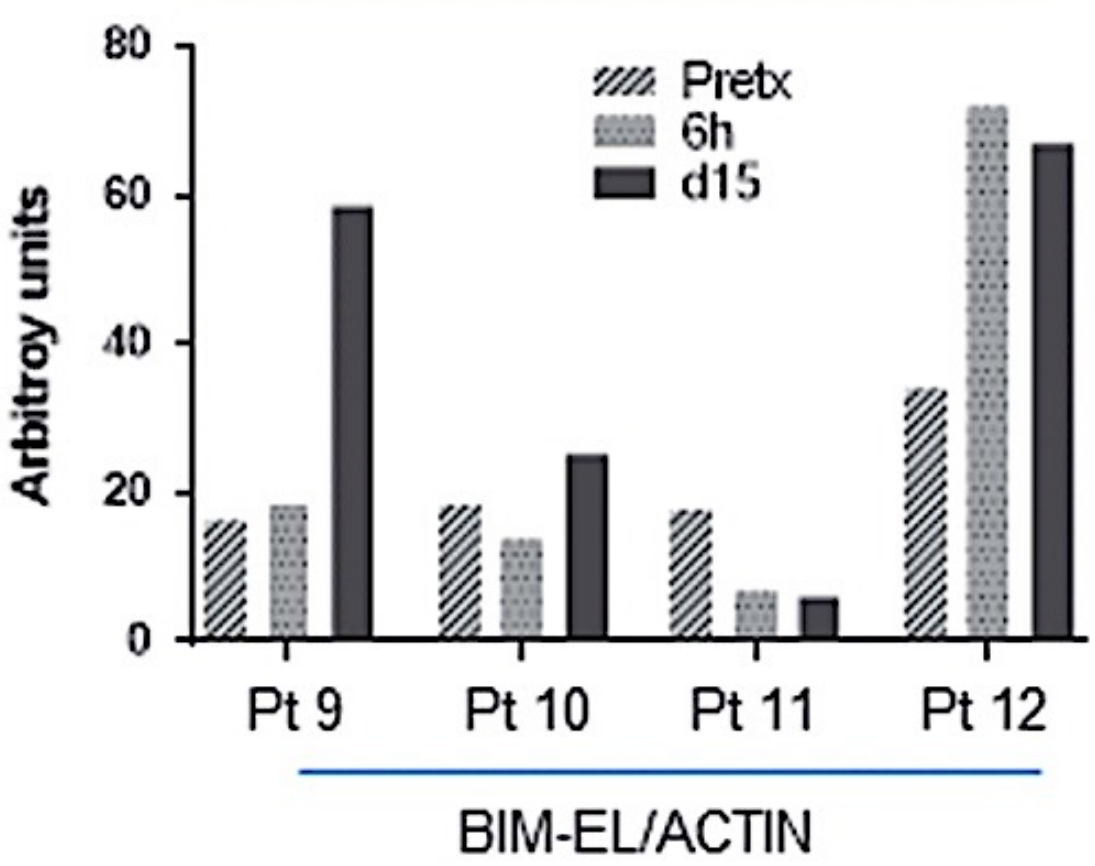
Pre-treatment with ibrutinib increases CLL cell sensitivity to venetoclax





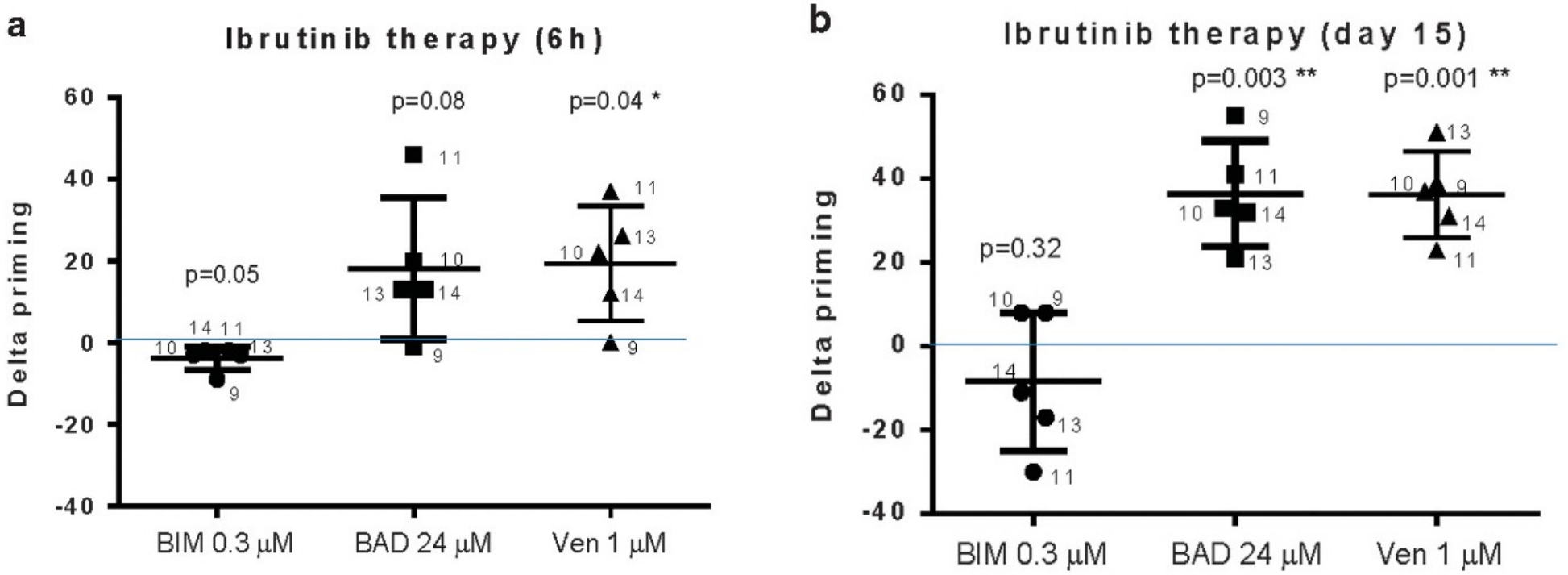
Deng J et al. Leukemia (2017) 31, 2075–2084

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



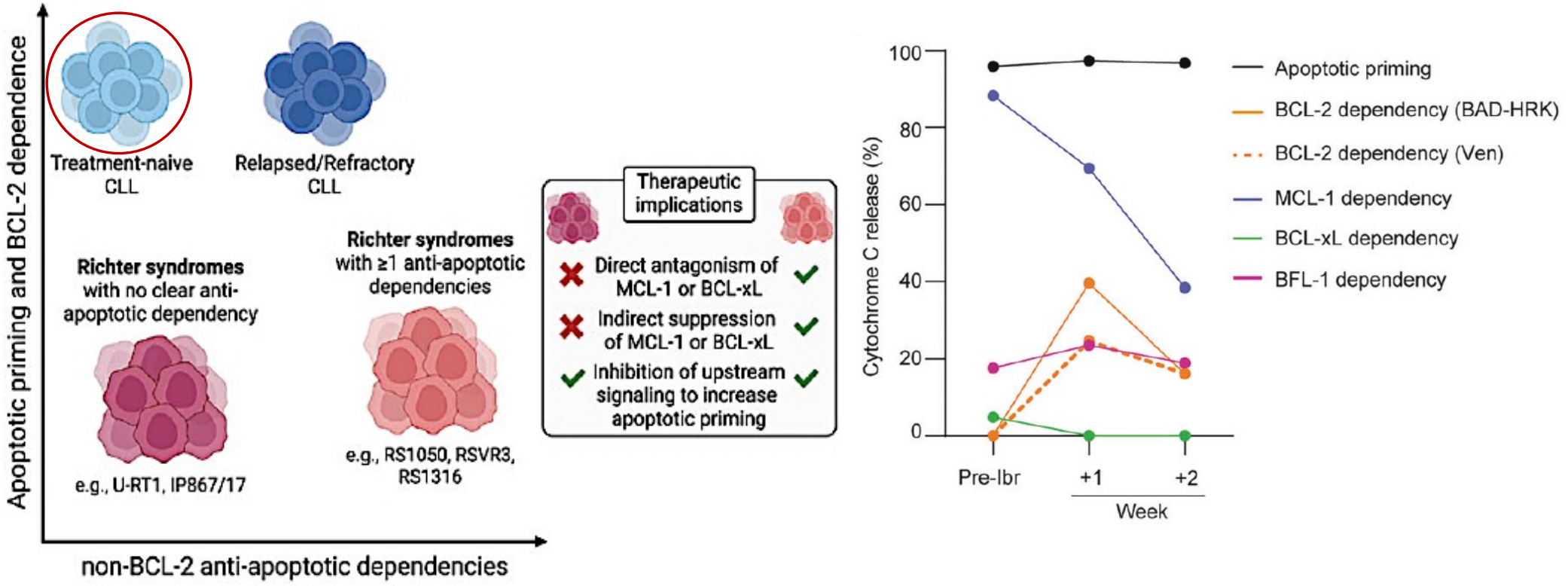
Deng J et al. Leukemia (2017) 31, 2075–2084

In vivo BTK inhibition increases BCL-2 dependence in cells from CLL patients



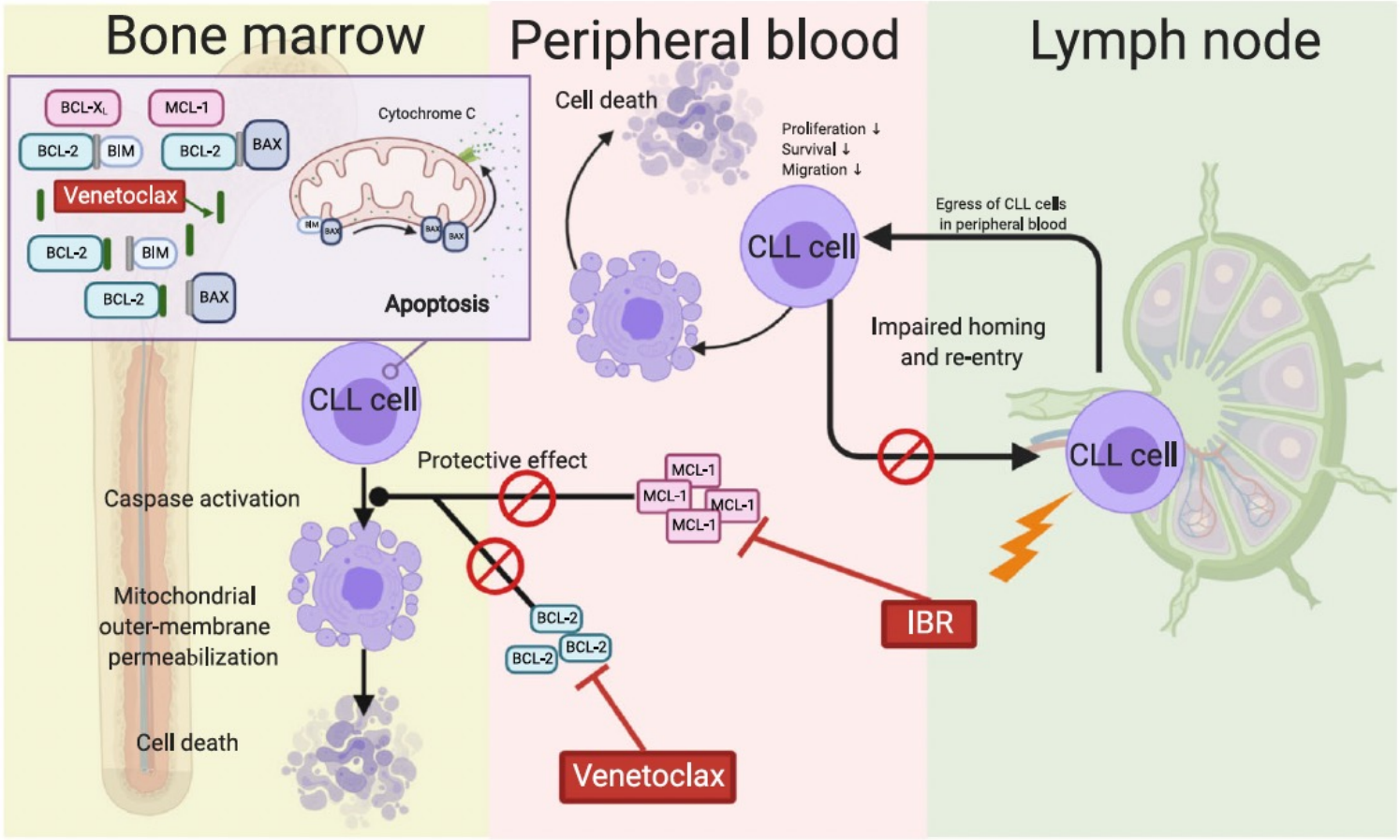
Deng J et al. Leukemia (2017) 31, 2075–2084

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

Conclusions

- The complementary effects of BTK inhibitors and venetoclax on CLL mitochondria strongly supports their exploration of these combinations in the clinic.
- The combinations of BTK inhibitors and venetoclax with or without anti-CD20 monoclonal antibodies are highly active and well-tolerated and provide fixed-duration options for patients with CLL and MCL.