

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

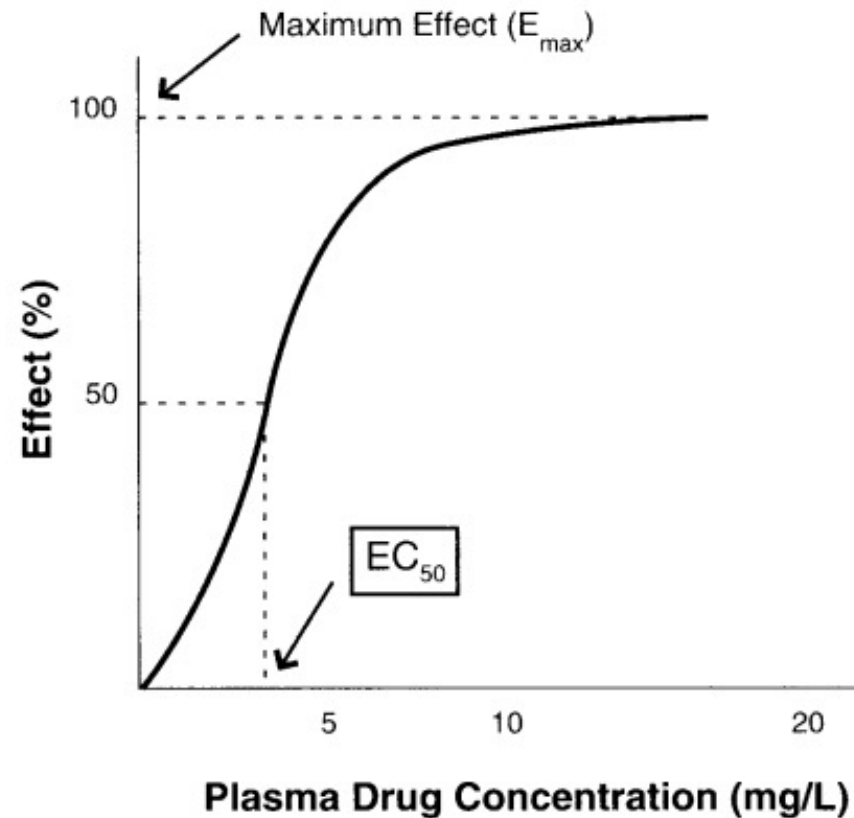
Roma, 11 aprile 2024
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Disclosures

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		



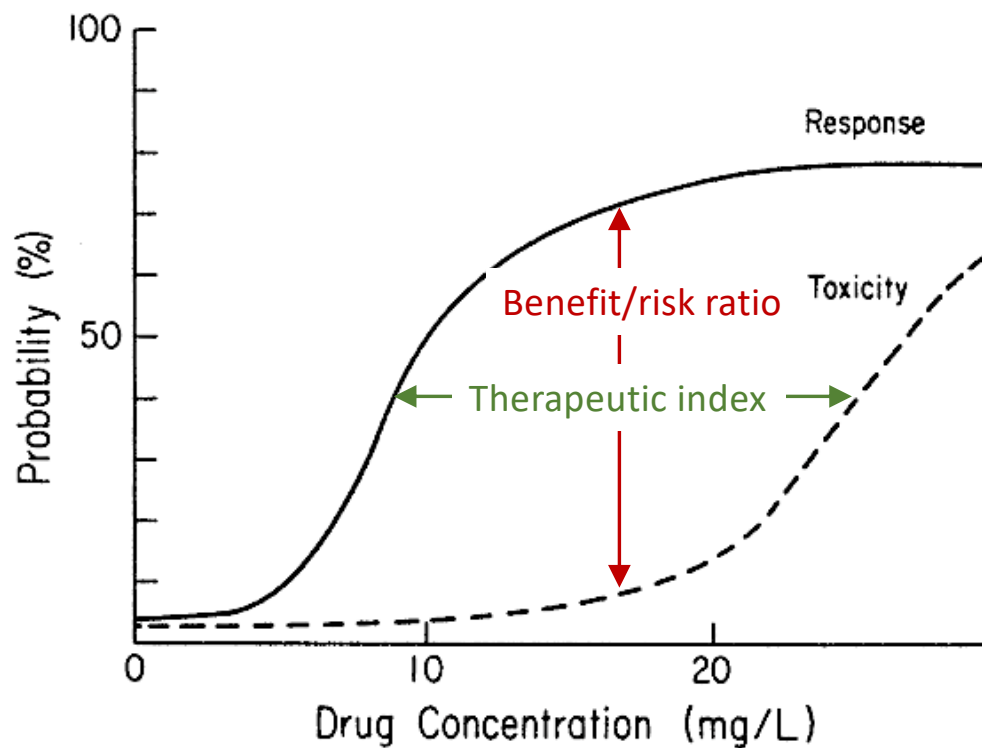
Relationship of drug concentration at the target to effect (as a percentage of maximal effect)



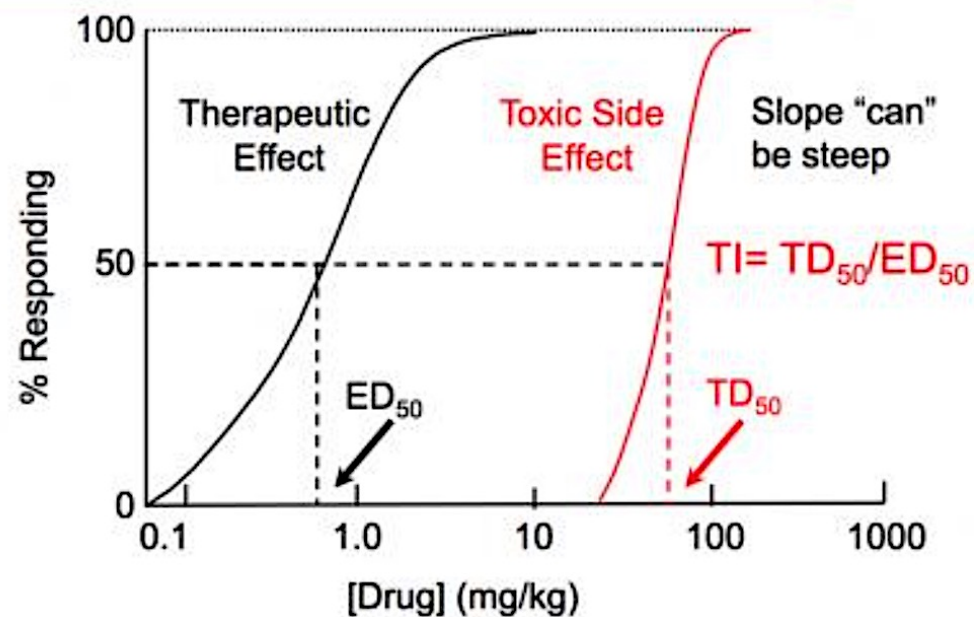
Applied Pharmacokinetics, 3rd ed. Vancouver, WA: Applied Therapeutics; 1992. pp.1-3



Relationship between drug concentration and drug effects for a hypothetical drug



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



<https://step1.medbullets.com/pharmacology/107009/therapeutic-index>



The concept of drug dose/duration response relationship

- Ibrutinib and venetoclax, through distinct and complementary modes of action, preferentially target distinct cell compartments and CLL subpopulations to eliminate both dividing and resting CLL cells.
- Ibrutinib mobilizes CLL cells out of lymph nodes and other lymphoid niches and into peripheral blood (PB), where they are more susceptible to venetoclax-induced apoptosis.

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

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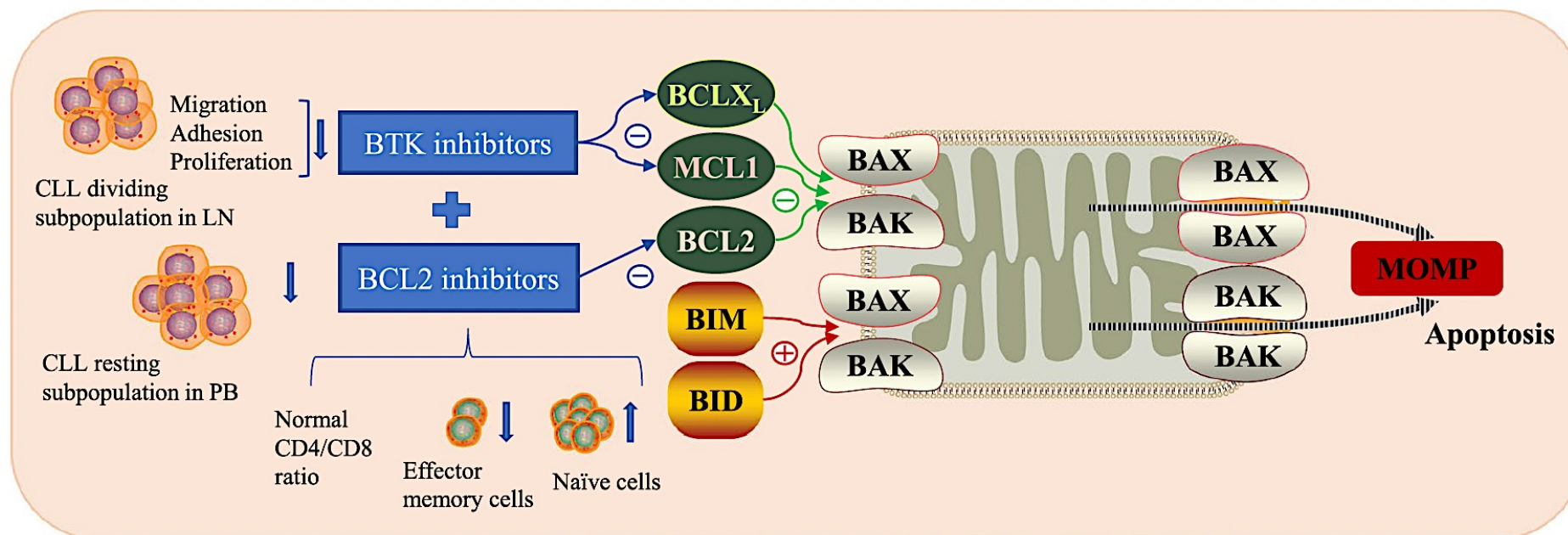
The concept of drug dose/duration response relationship

- Inhibition of BTK by ibrutinib also enhances the dependence of CLL cells on BCL-2, thereby increasing sensitivity to venetoclax and accelerating apoptosis.
- Combined ibrutinib plus venetoclax 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 ibrutinib plus venetoclax demonstrated high uMRD rates in both PB and BM in patients with CLL or SLL.

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

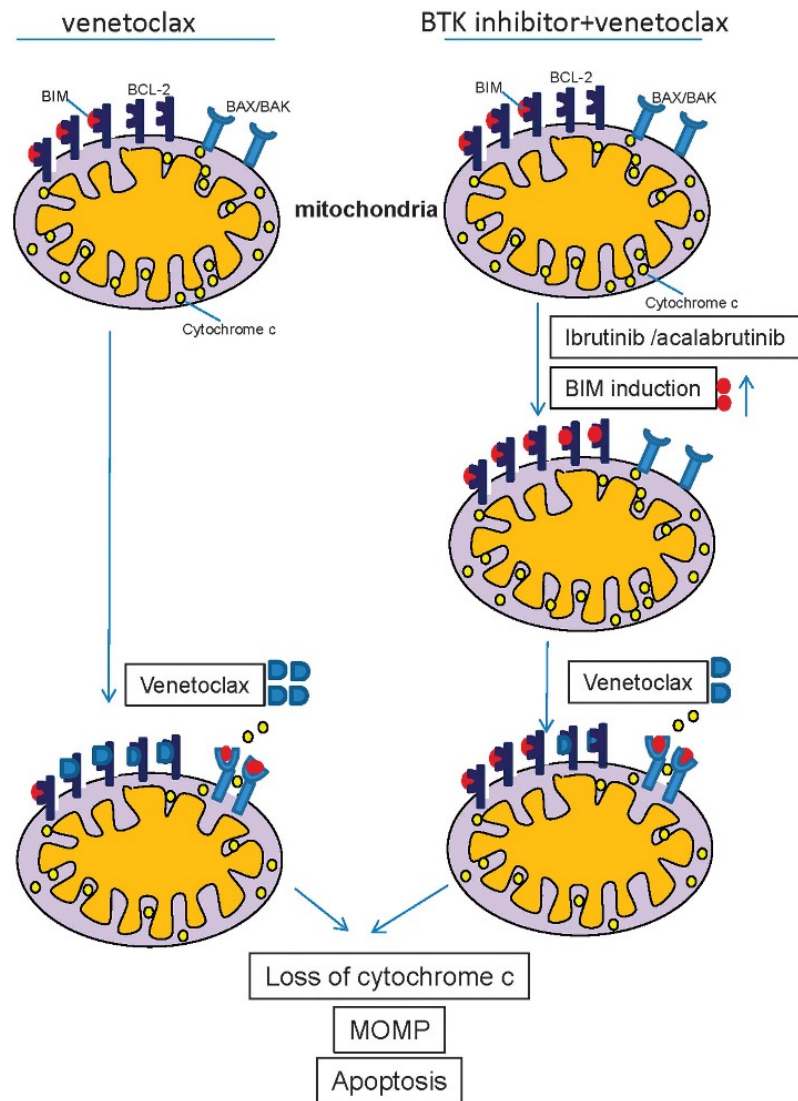
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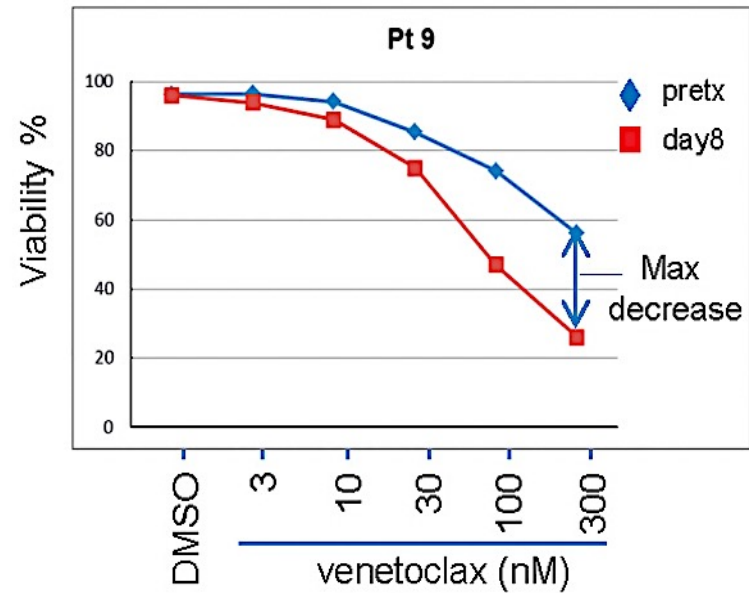
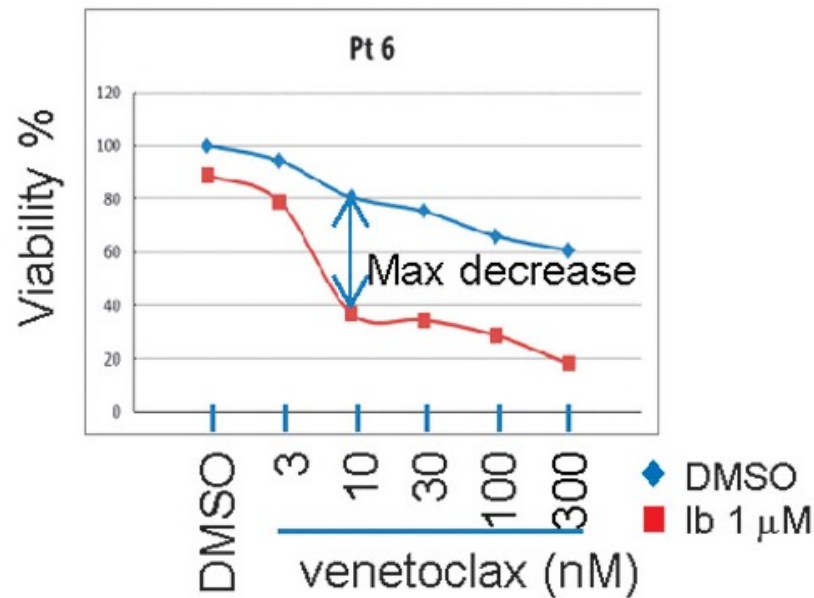
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Complementary effects of BTK and BCL-2 inhibition on CLL cell mitochondria



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

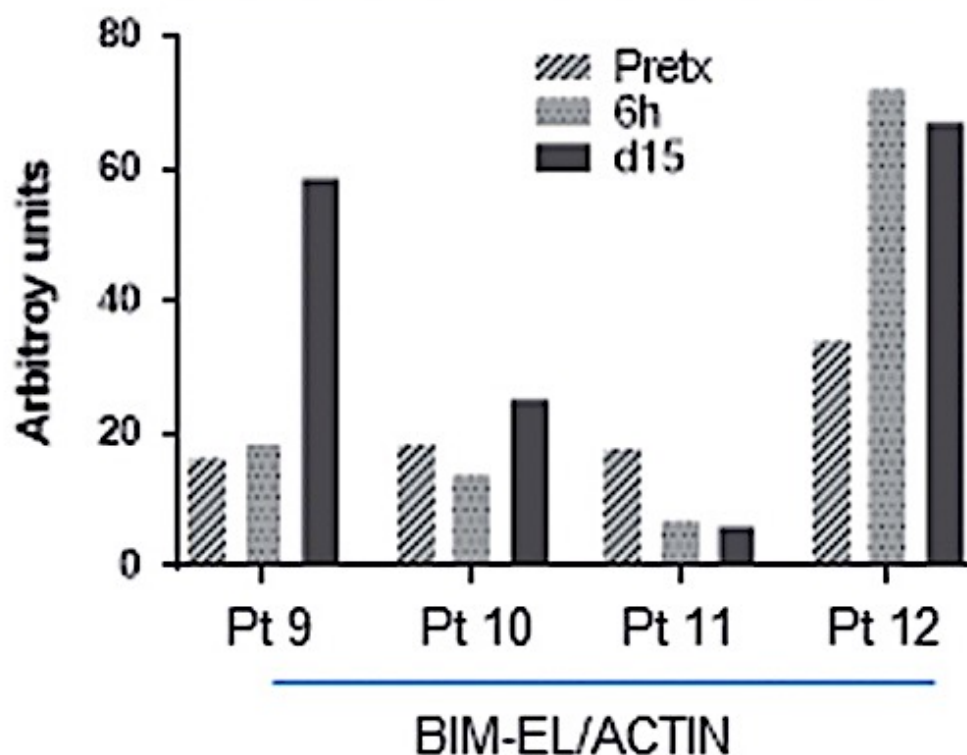
Pre-treatment with ibrutinib increases CLL cell sensitivity to venetoclax



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

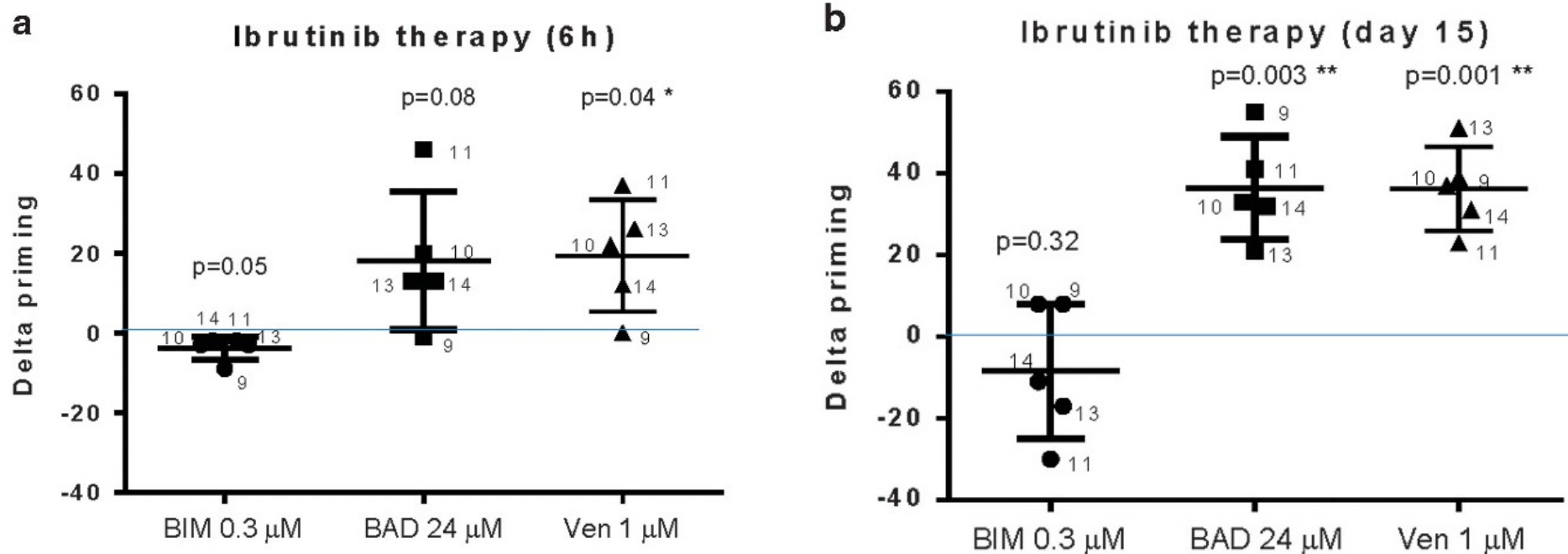
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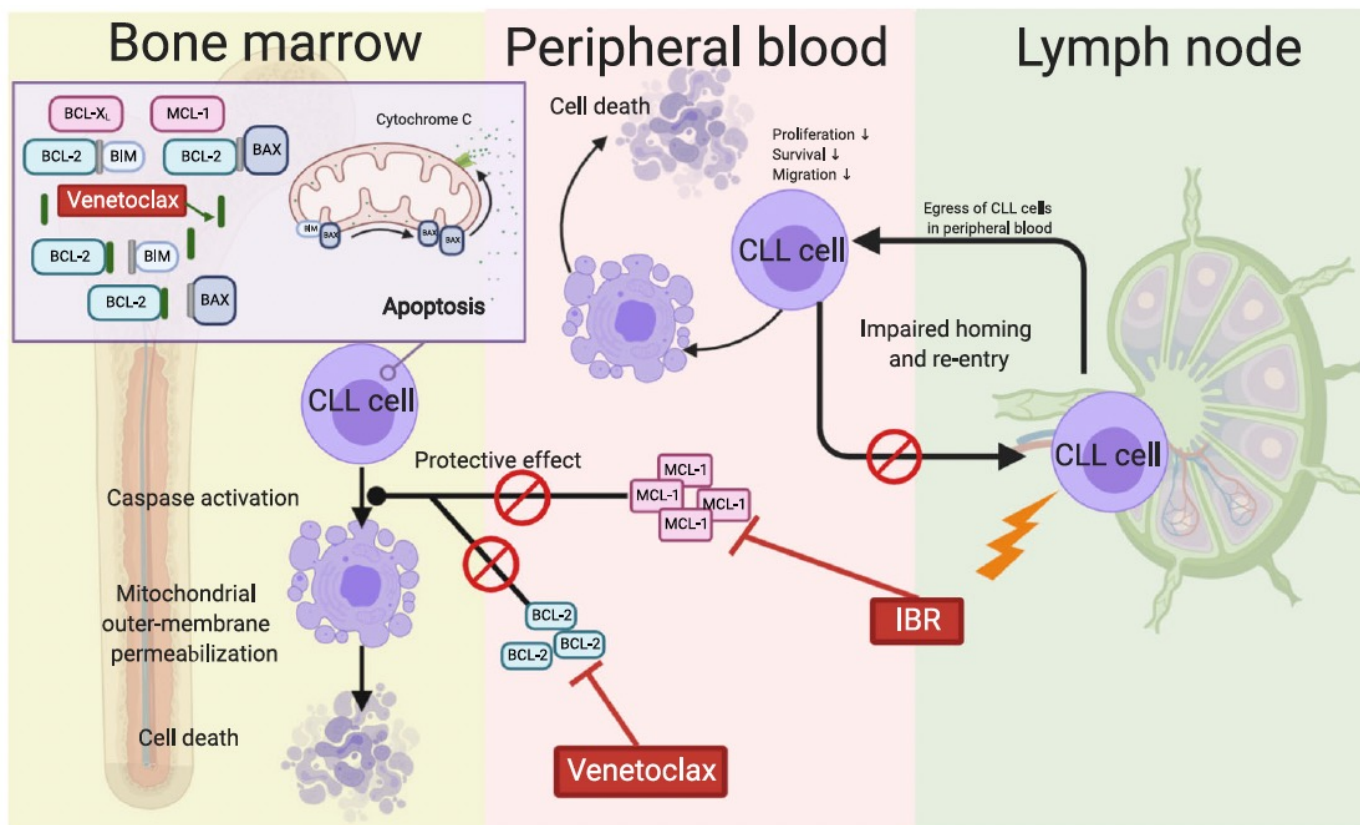
In vivo BTK inhibition increases BCL-2 dependence in cells from CLL patients



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



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.

