

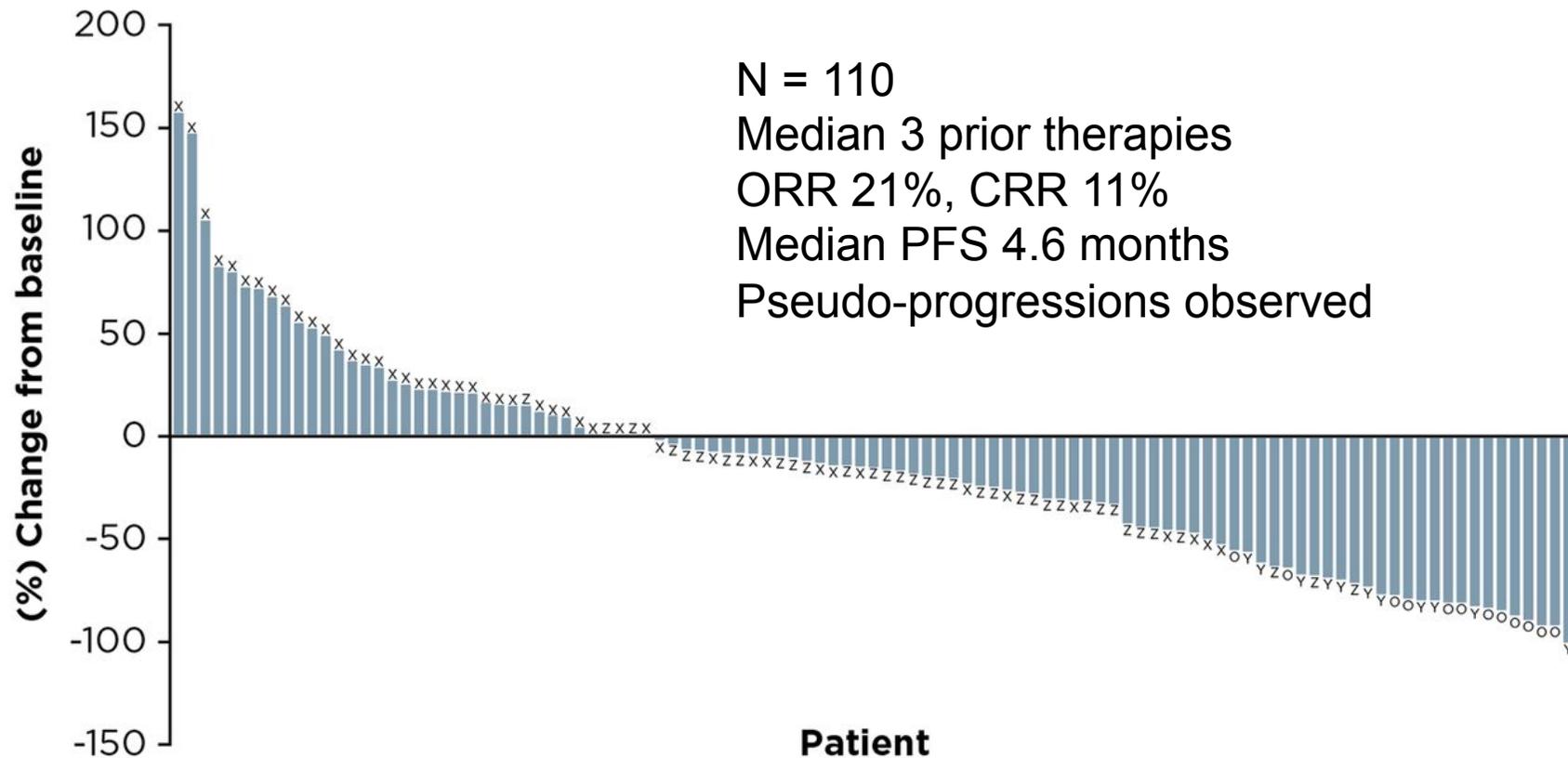
BTK Inhibitors and BCL2 Antagonists

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Ibrutinib Phase 2 in R/R Follicular Lymphoma (DAWN study, Gopal ASH 2016)

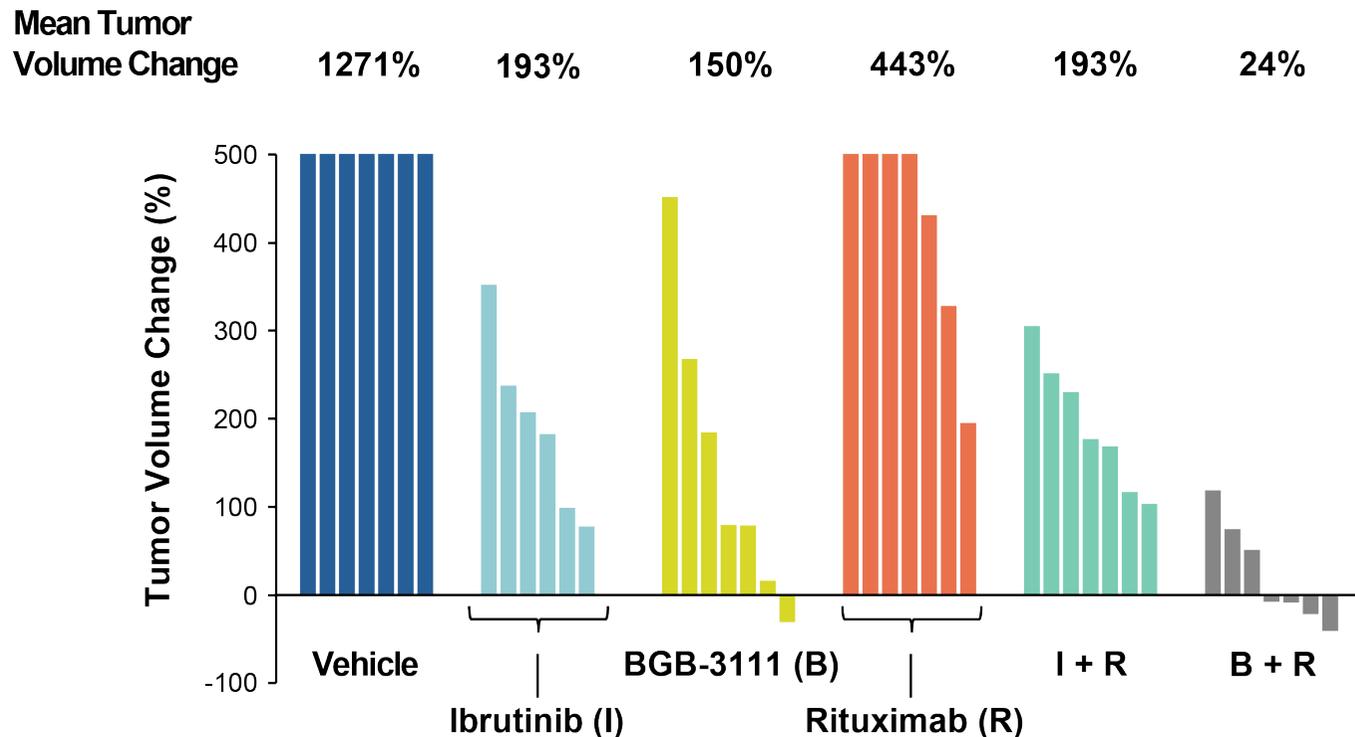
Percent change in tumor size (IRC-assessed, ITT population*)



O=CR, Y=PR, Z=SD and X=PD

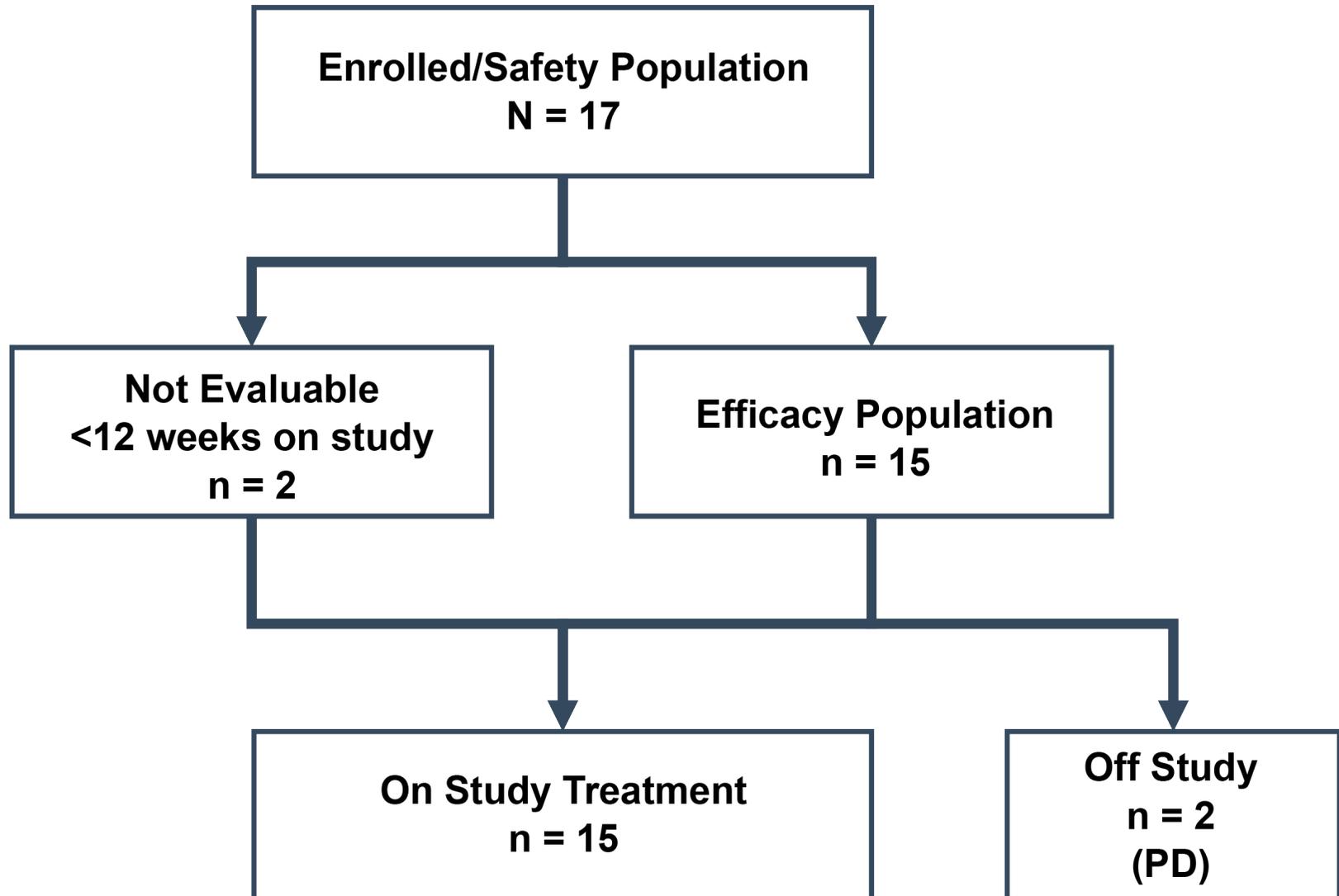
*Only pts with both baseline and at least 1 post-baseline tumor measurement (105 out of 110 pts) are included in the graph.

BGB-3111 Does Not Impair Rituximab-Induced ADCC



- Published preclinical data suggest that off-target effects of ibrutinib may be detrimental to CD20 mAb-induced ADCC and the activity of the combination
- In a human MCL xenograft model, the combination of BGB-3111 and CD20 antibody demonstrated improved anti-tumor activity as compared to monotherapies and combination of ibrutinib and CD20 antibody

Zanubrutinib + Obinutuzumab Phase I : Follicular Lymphoma Patients (as of 31 March 2017)



Patient and Disease Characteristics

Characteristic	CLL/SLL (n = 45)	FL (n = 17)
Age, years, median (range)	68 (38-82)	56 (41-86)
ECOG Performance Status, (%)		
0	19 (42.2)	14 (82.4)
1	25 (55.6)	2 (11.8)
2	1 (2.2)	1 (5.9)
Follow-up, months, median (range)	6.5 (0.5-14.0)	7.9 (0.1-14.2)
Prior Treatment Status		
Treatment-naïve, n (%)	20 (44.4)	0
Relapsed/refractory, n (%)	25 (55.6)	17 (100)
Number of prior therapies, median (range)	1 (1-4)	3 (1-7)
Bulky Disease*, n (%)	0	2 (11.8)
Molecular Risk Factors, n (%)		
del17p/p53mut (n = 37)	6 (16.2)	N/A
11q- (n = 37)	6 (16.2)	N/A
IGHV unmutated (n = 37)	19 (51.4)	N/A
Complex karyotype (n = 37)	7 (18.9)	N/A

* Any lymph node >10 cm in maximum diameter.

Selected Adverse Events

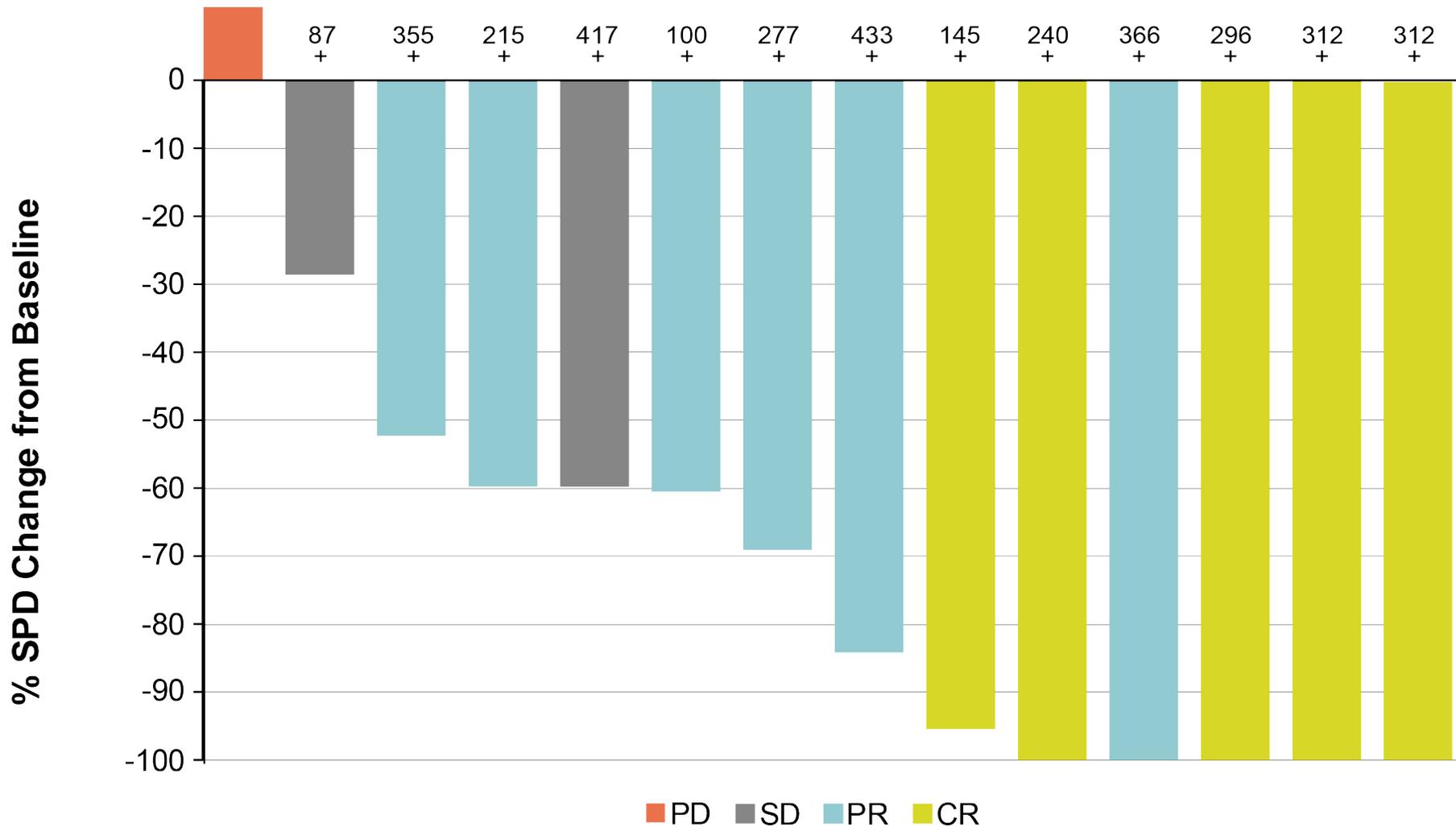
Event, n (%)	CLL/ SLL (n = 45)	FL (n = 17)
Patients with at least one AE Grade \geq 3	19 (42.2)	4 (23.5)
Patients with at least one SAE	11 (24.4)	4 (23.5)
Events leading to treatment discontinuation	1 (2.2)*	0

* Patient with a history of squamous cell carcinoma discontinued due to squamous cell carcinoma

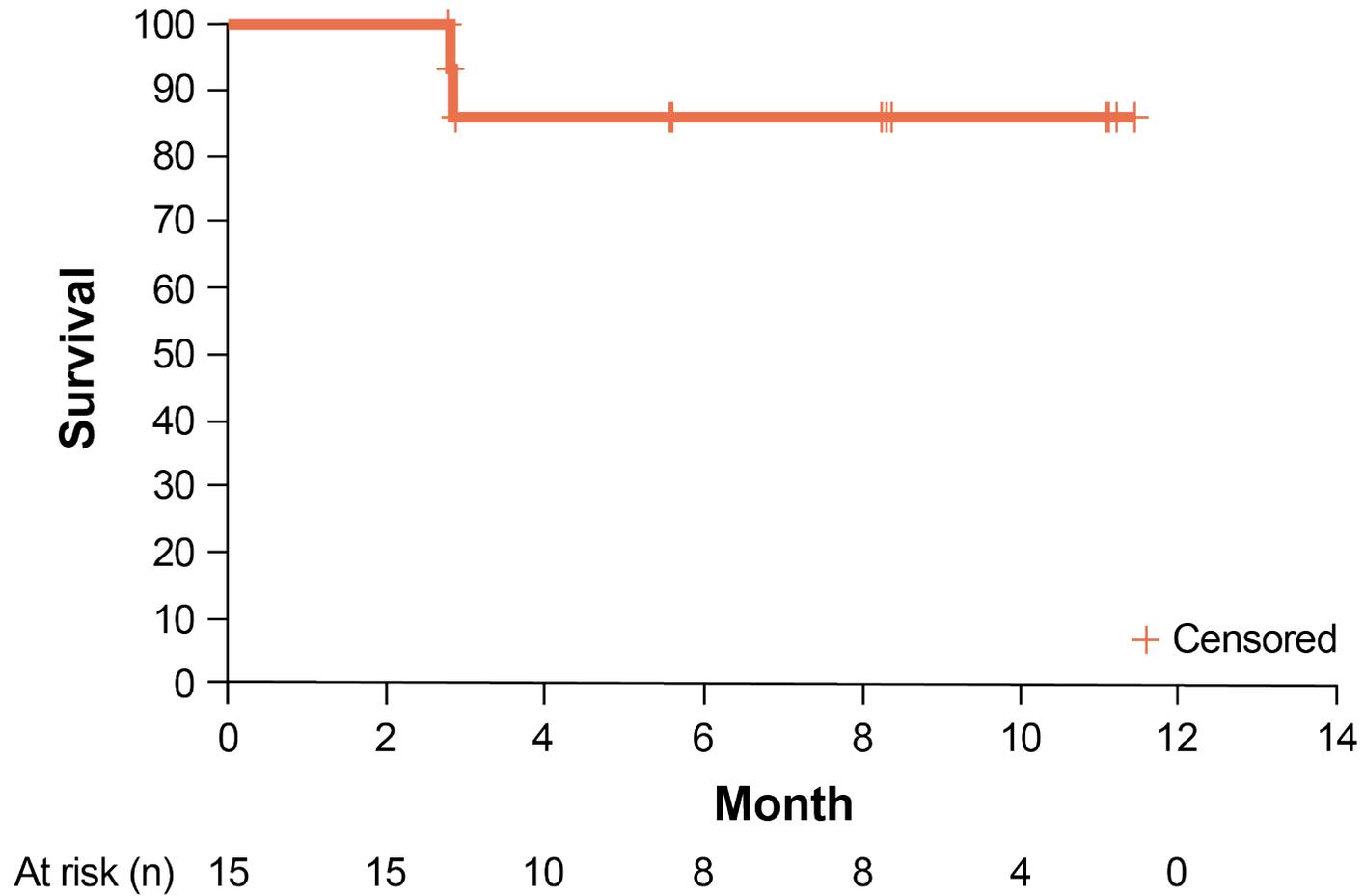
AE of Special Interest, n (%)	CLL/SLL (n = 45)		FL (n = 17)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Diarrhea	7 (15.6)	0	3 (17.6)	0
Serious hemorrhage*	0	0	0	0
Atrial fibrillation	0	0	0	0
Infusion-related reactions	11 (24.4)	1 (2.2)	1 (5.9)	0

* \geq Grade 3 hemorrhage, or central nervous system hemorrhage of any grade.

Zanubrutinib + Obinutuzumab in Follicular Lymphoma : ORR 73%, CRR 33%



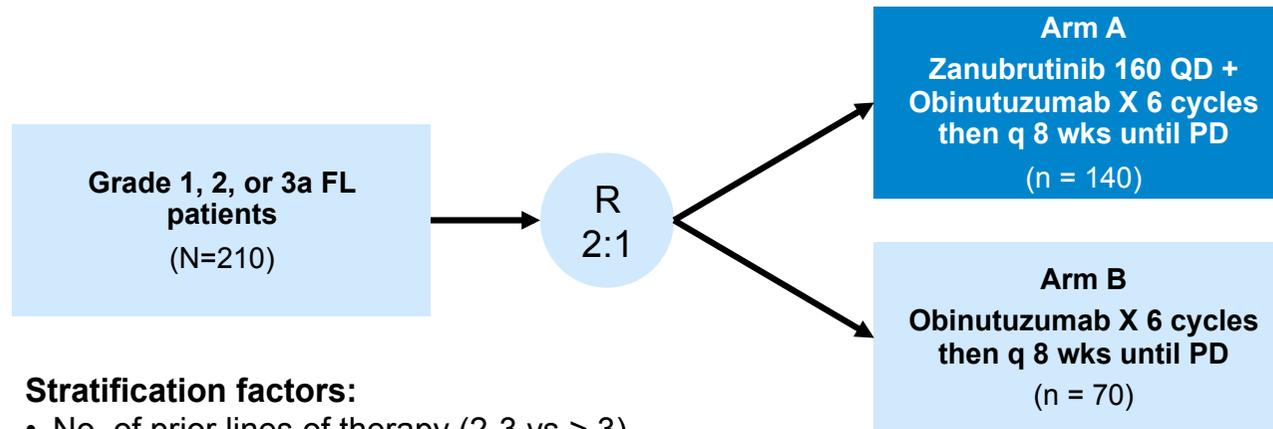
FL: Progression-Free Survival



BGB-3111-212: Relapsed FL Phase 2 Trial Design

Relapsed/Refractory FL (Received ≥ 2 prior treatments*)

*Must have received prior treatment with rituximab and an alkylator; relapsed <12 months from end of last treatment OR Refractory to last treatment (no CR, no PR)

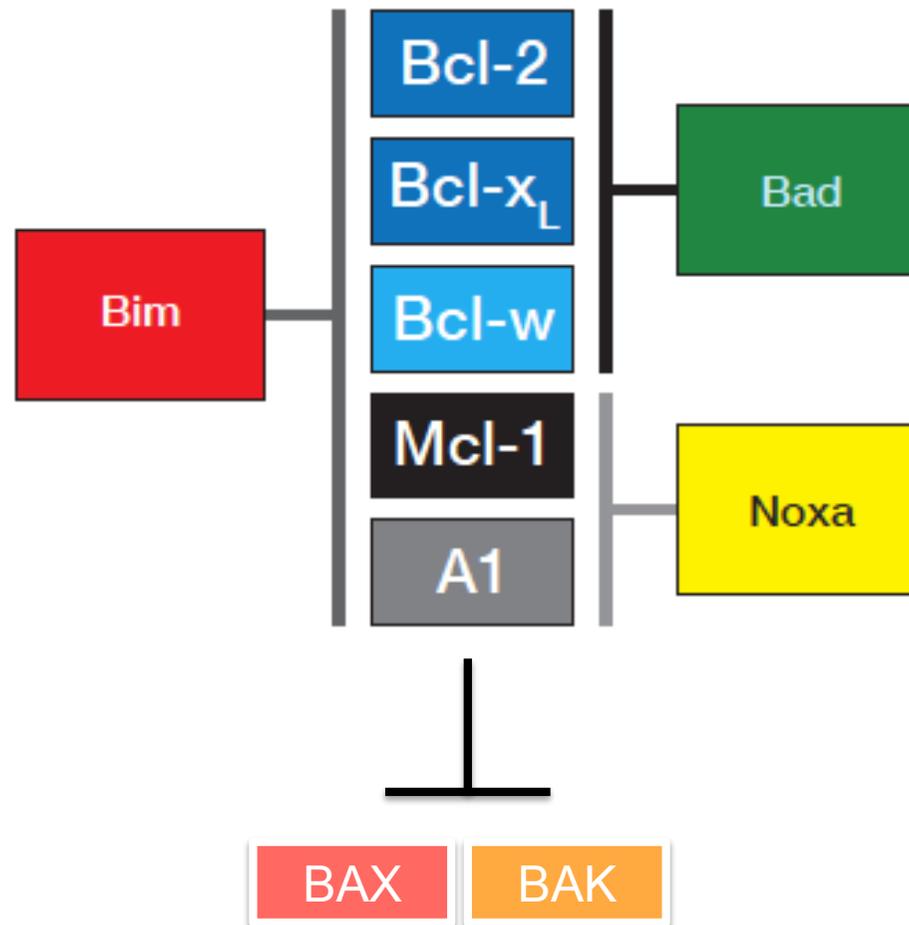


Stratification factors:

- No. of prior lines of therapy (2-3 vs > 3)
- Rituximab refractory status (yes/no)

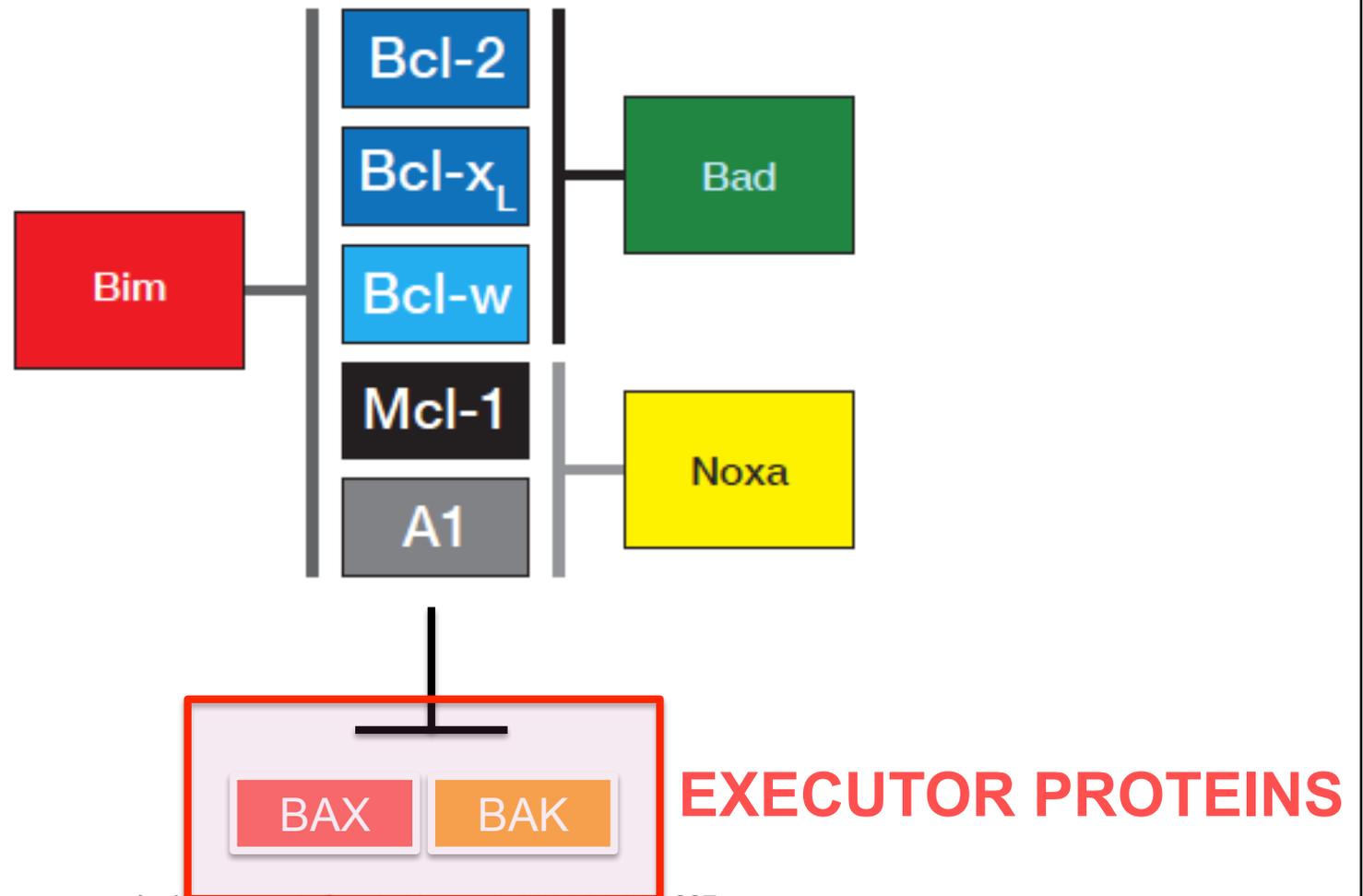
Option to add BGB-3111 after 12 months if no response OR at PD

Bcl-2 Family Proteins



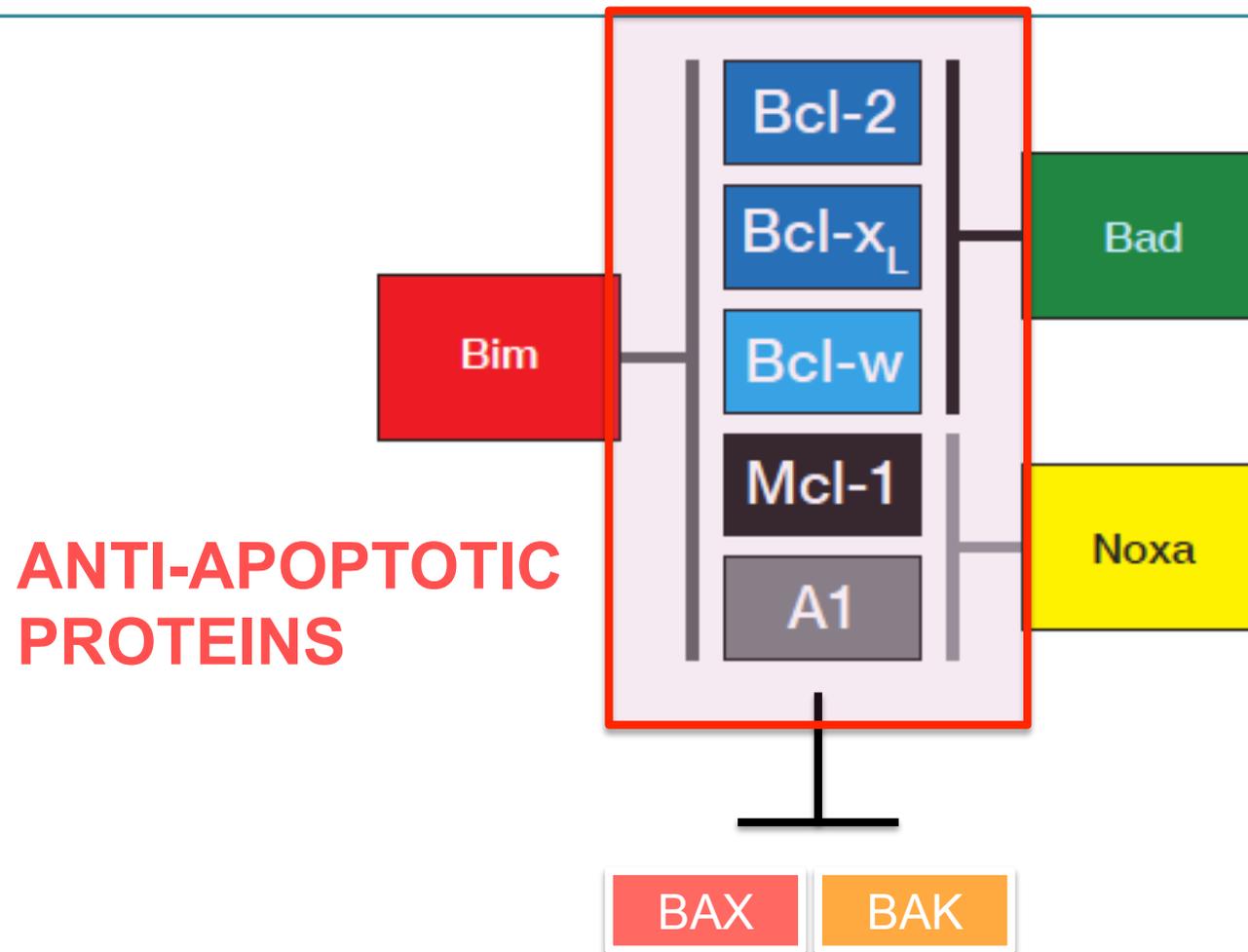
Anderson et al. *Semin Hematol.* 2014;51:219-227.

Bcl-2 Family Proteins



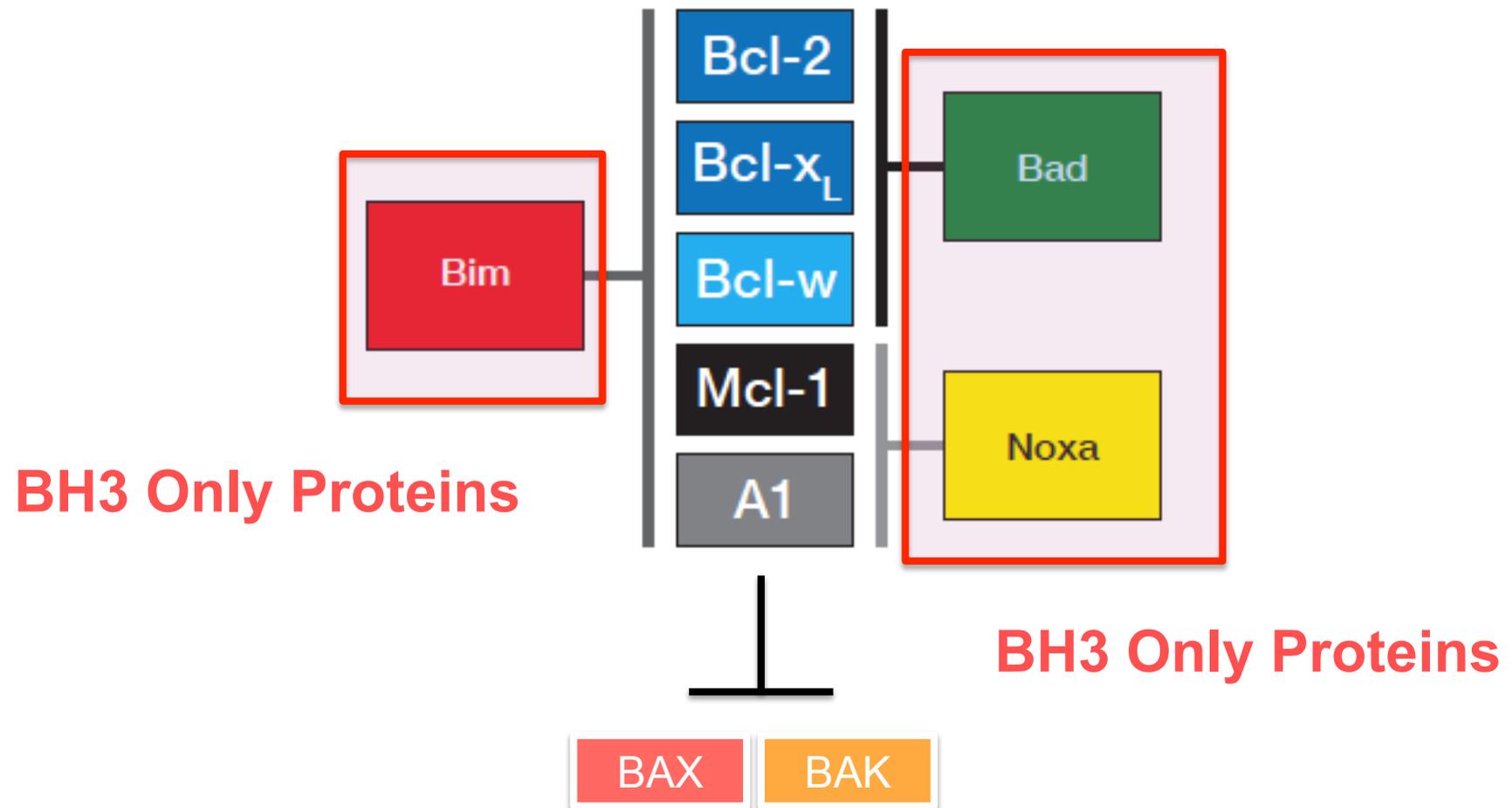
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Bcl-2 Family Proteins



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Bcl-2 Family Proteins

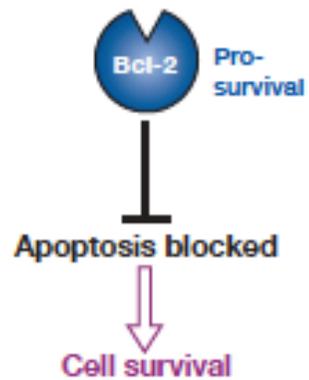


Anderson et al. *Semin Hematol.* 2014;51:219-227.

Nonmalignant B Cells

Normal Lymphoid Cell

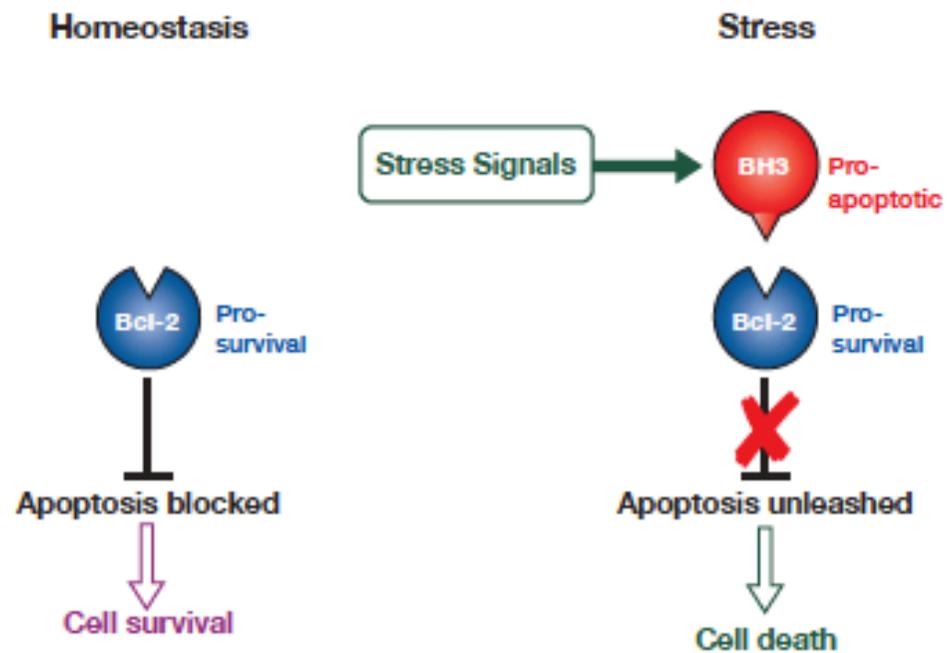
Homeostasis



Anderson et al. *Semin Hematol.* 2014;51:219-227.

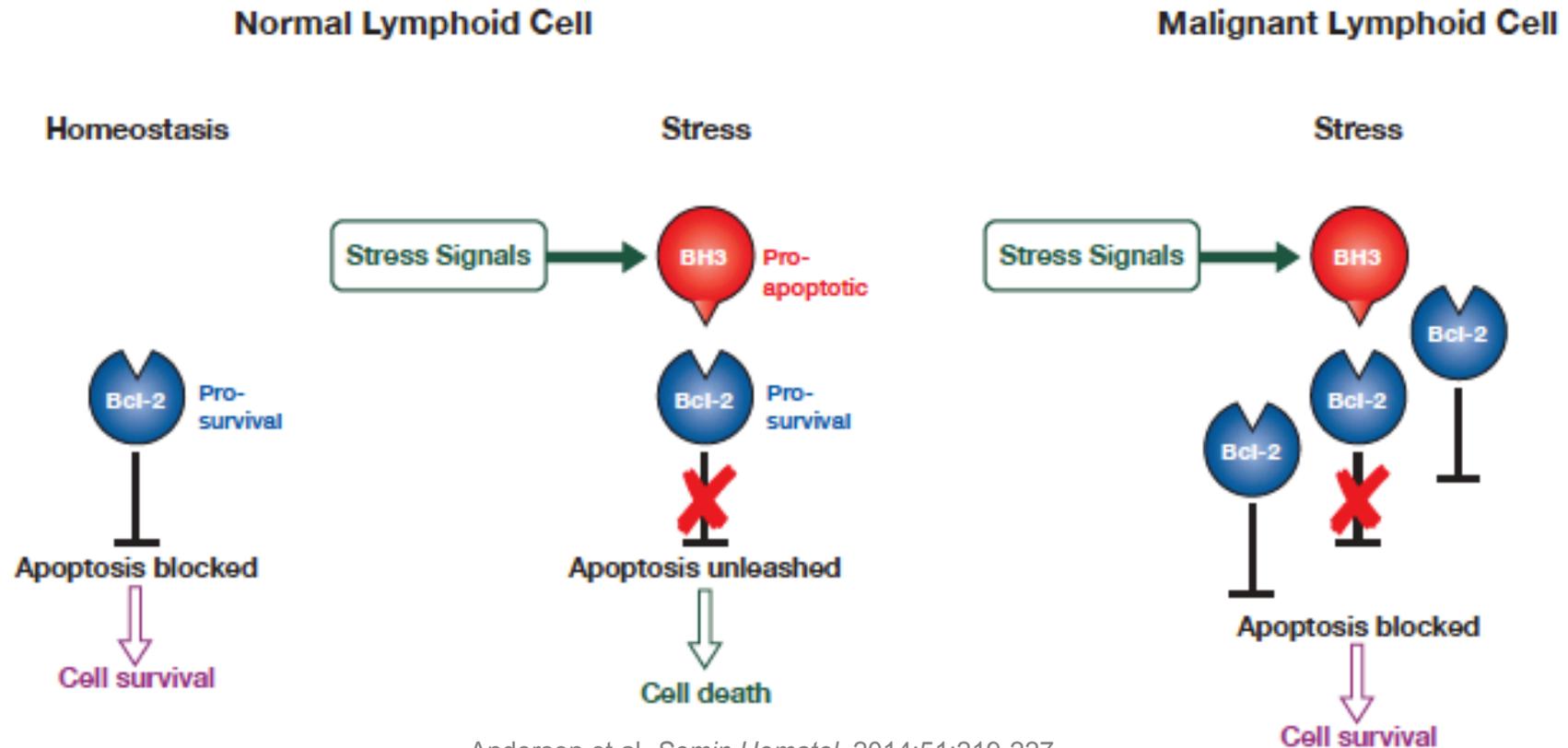
Nonmalignant B Cells

Normal Lymphoid Cell



Anderson et al. *Semin Hematol.* 2014;51:219-227.

Malignant B Cells



Anderson et al. *Semin Hematol.* 2014;51:219-227.

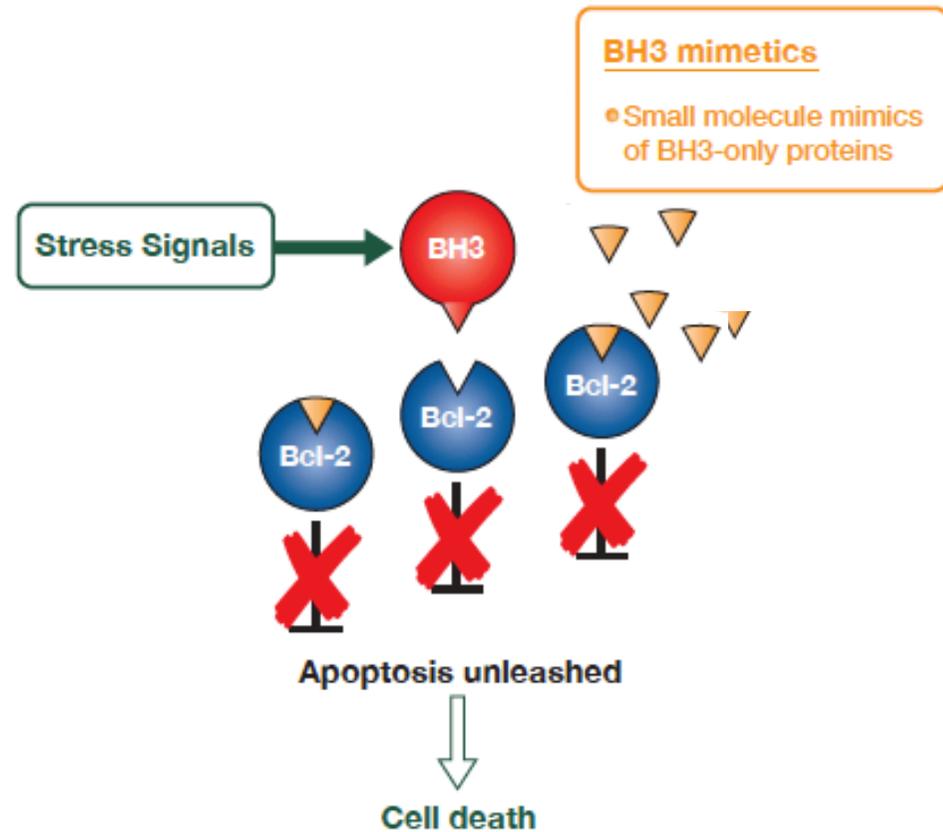
Overexpression of Bcl-2 → inappropriate survival of cells under stress

Mason et al. *Proc Natl Acad Sci U S A.* 2008;105:17961-17966.

BH3 Mimetics

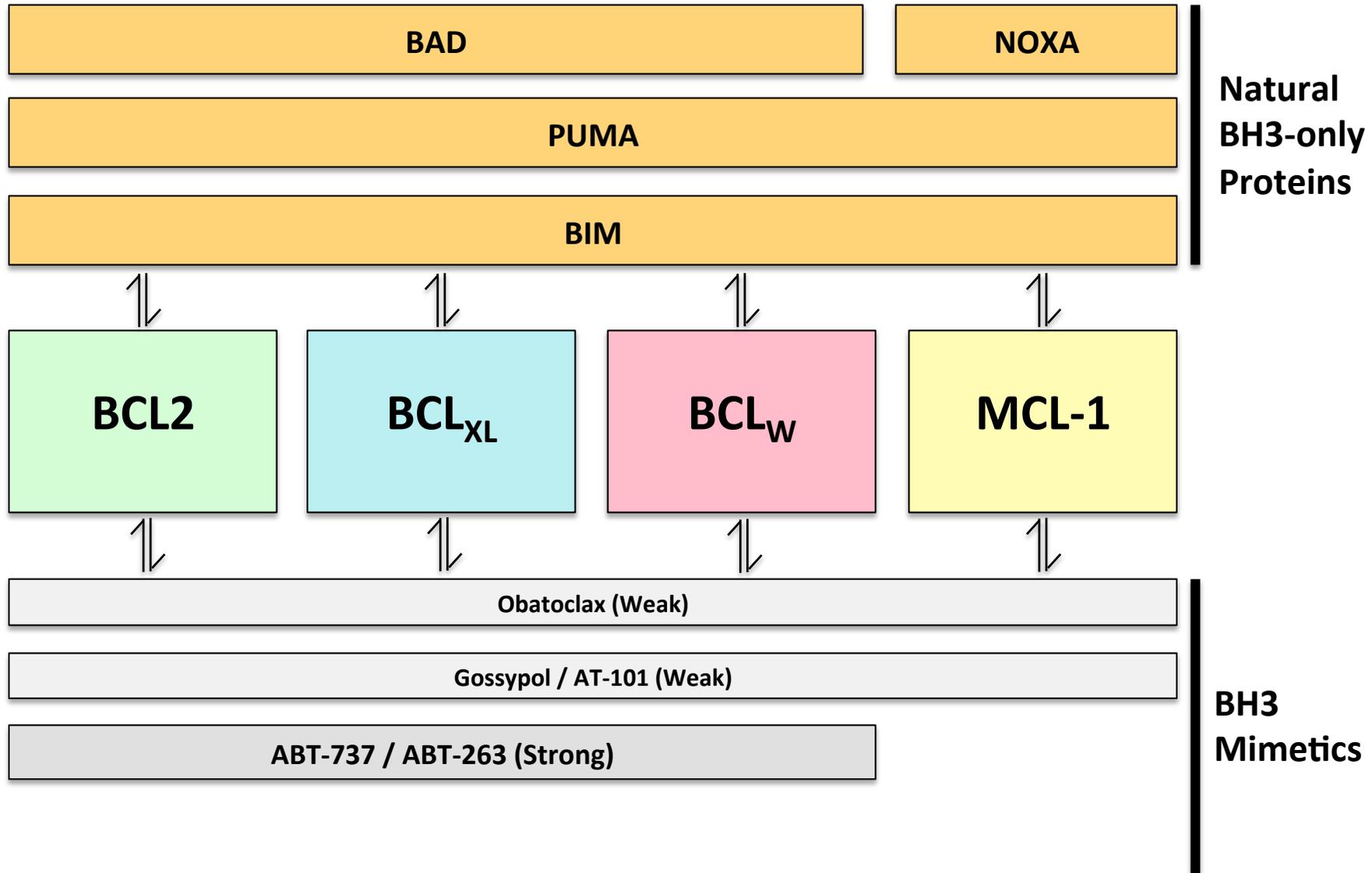
BH3 mimetics

- Mimics the action of the BH3-only proteins
- Restores the cell's ability to undergo apoptotic death



Anderson et al. *Semin Hematol.* 2014;51:219-227.

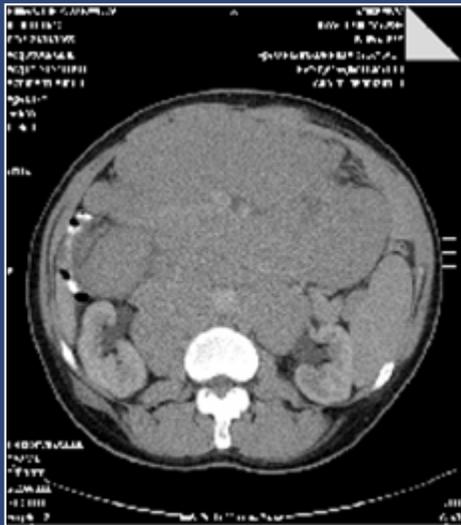
BH3-Mimetics in the Clinic



Navitoclax (ABT-263) Phase II study in CLL: Rapid cytoreduction in refractory CLL

- 44 year-old man, Rai stage 3, del(11q)
 - Prior treatments: R-FC x 6 (PR 15 months) then R-CHOP x 6 (PR 6 months)
 - Tumor lysis after first 100 mg dose

Baseline



Week 10



Baseline

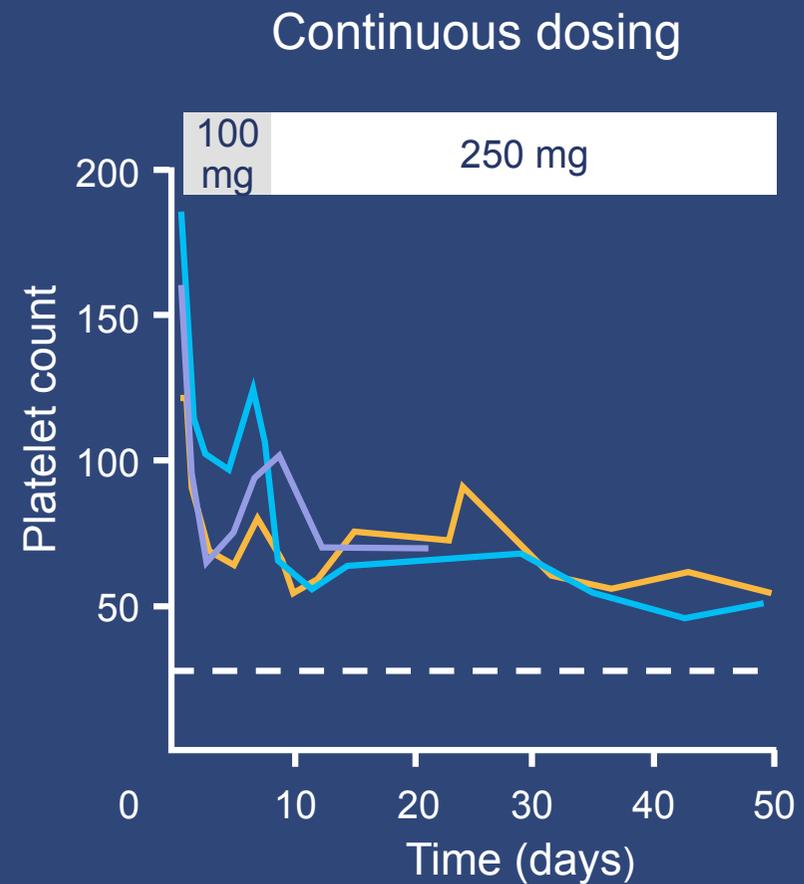
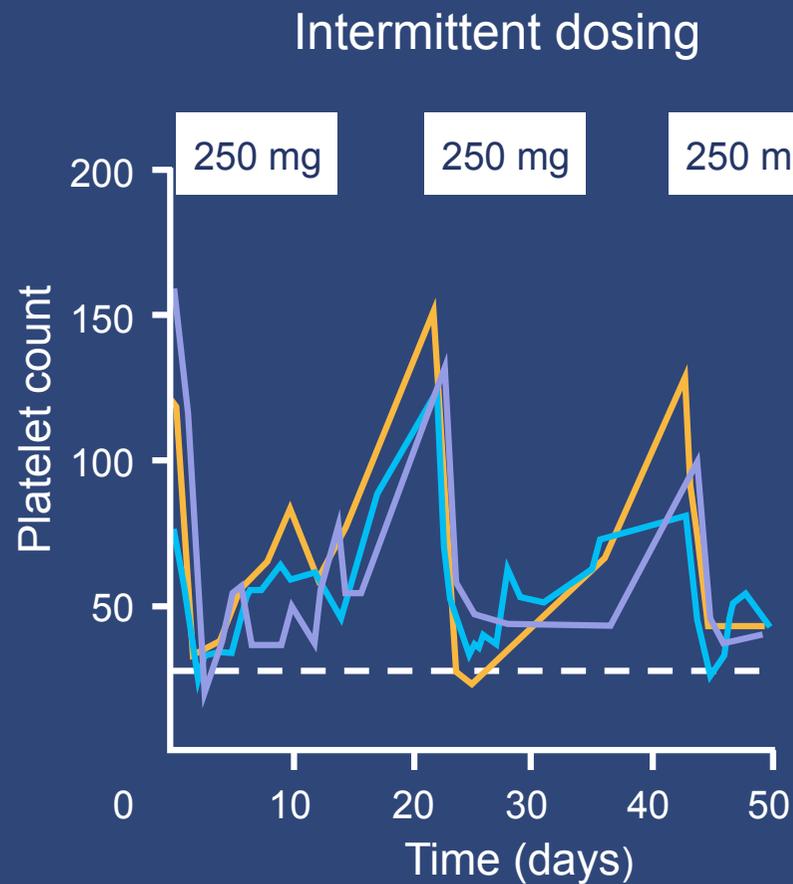


Week 10

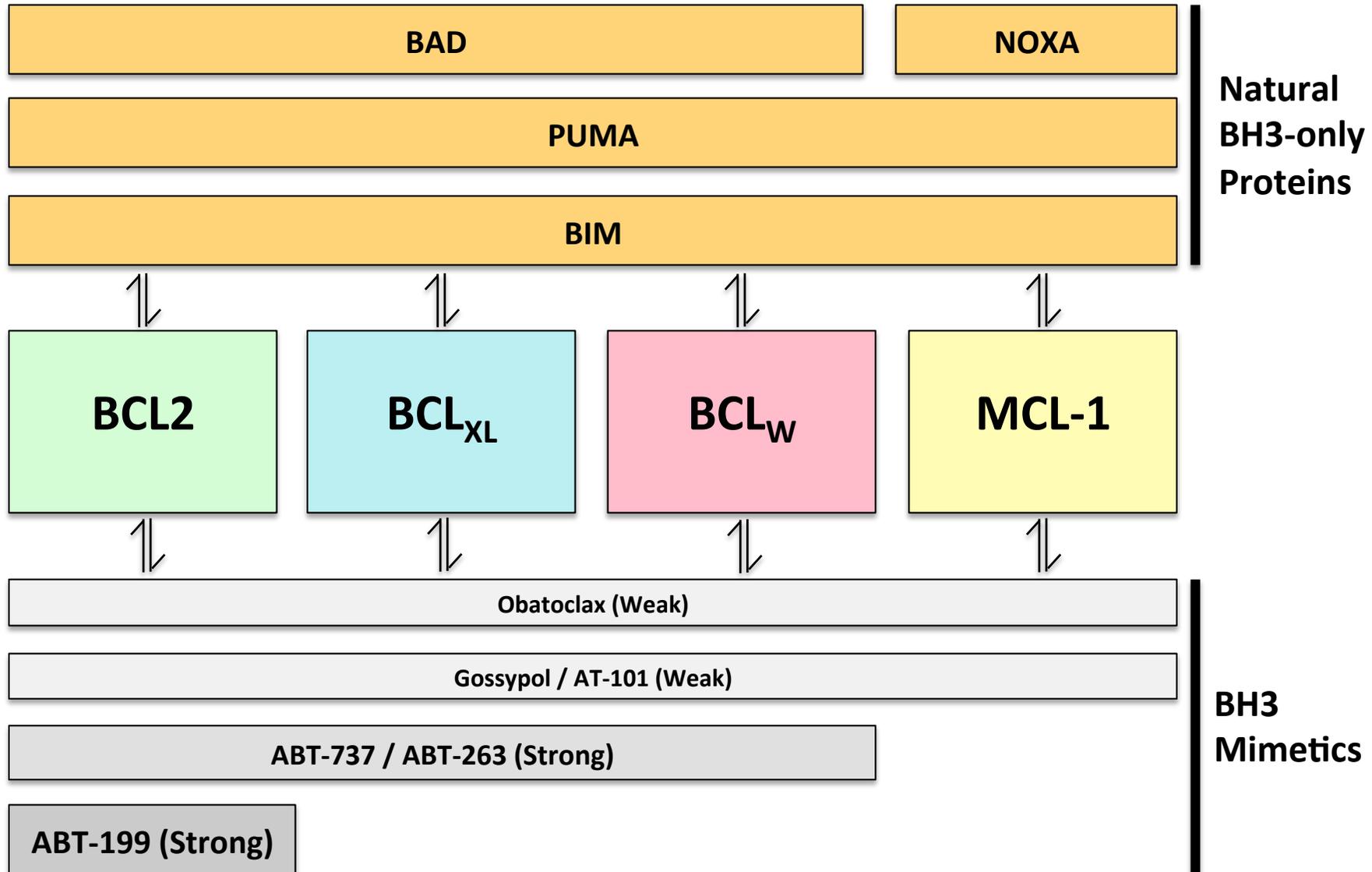


19 month PR on study

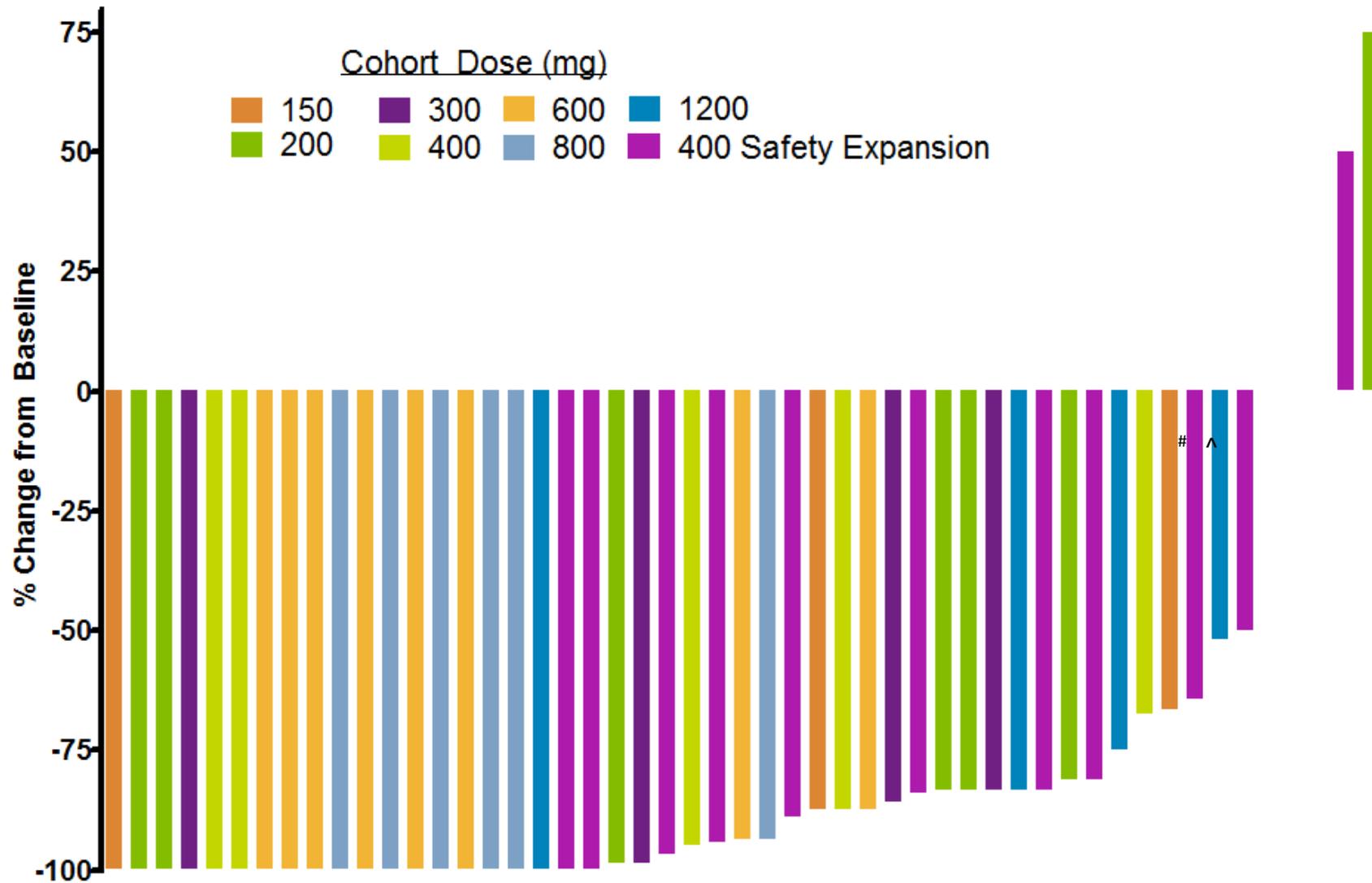
Navitoclax Phase I study in CLL: Thrombocytopenia



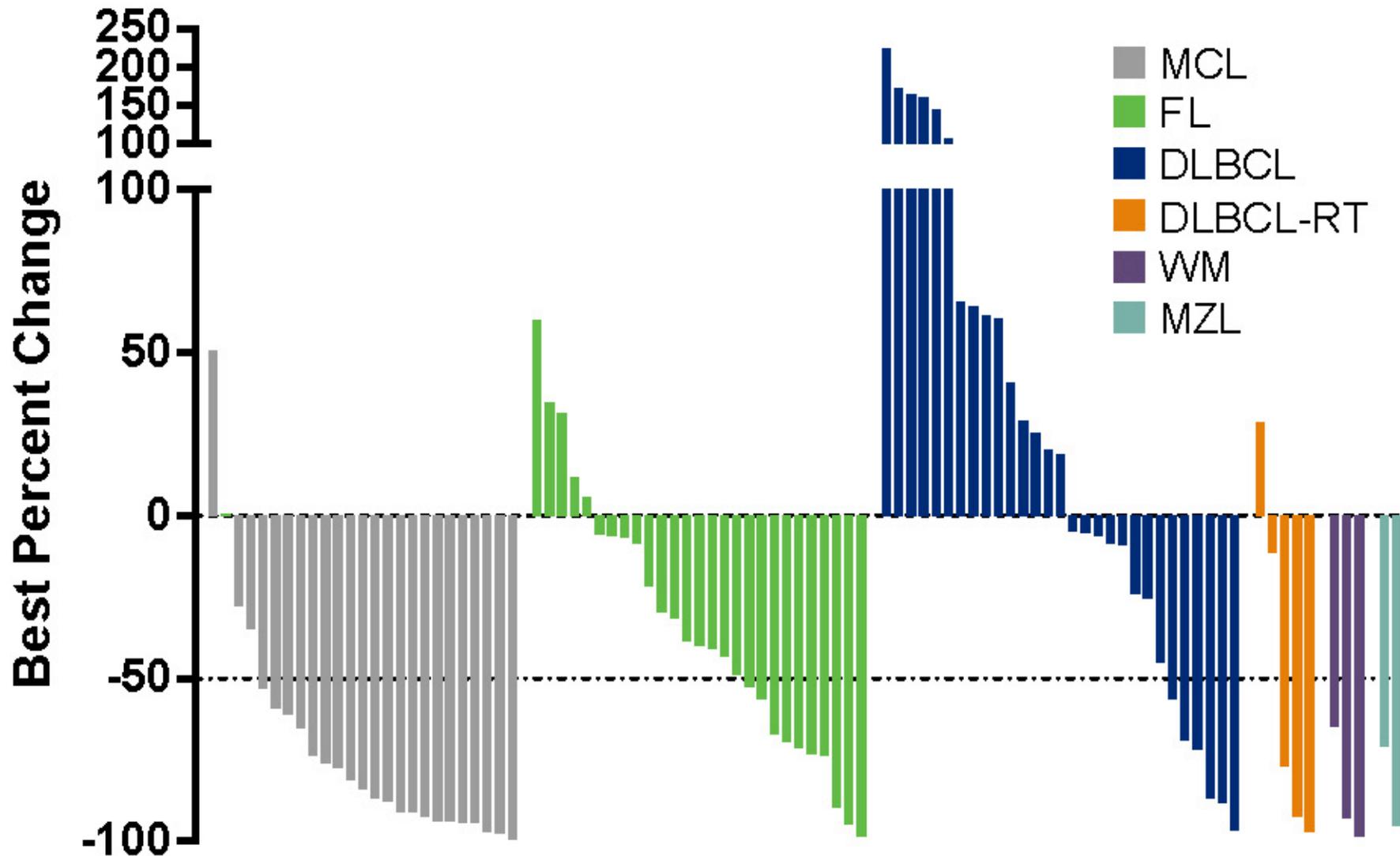
BH3-Mimetics in the Clinic



Venetoclax Single-Agent Activity in R/R CLL (Marrow)



Venetoclax Activity in Non-Hodgkin Lymphoma



Conclusions

- Ibrutinib has relatively low activity in FL
- Combinations of second generation BTKi and anti-CD20 may improve efficacy
 - Randomized zanubrutinib + obinutuzumab vs obinutuzumab underway
- BCL2 inhibitors are highly potent in CLL and MCL
 - Tumour lysis is an important risk in sensitive histologies
 - Surprisingly, despite the IgH-BCL2 translocation, follicular lymphoma is relatively resistant to venetoclax monotherapy