Memorial Sloan Kettering
Cancer Center

BCL-2 Inhibitors in Follicular Lymphoma

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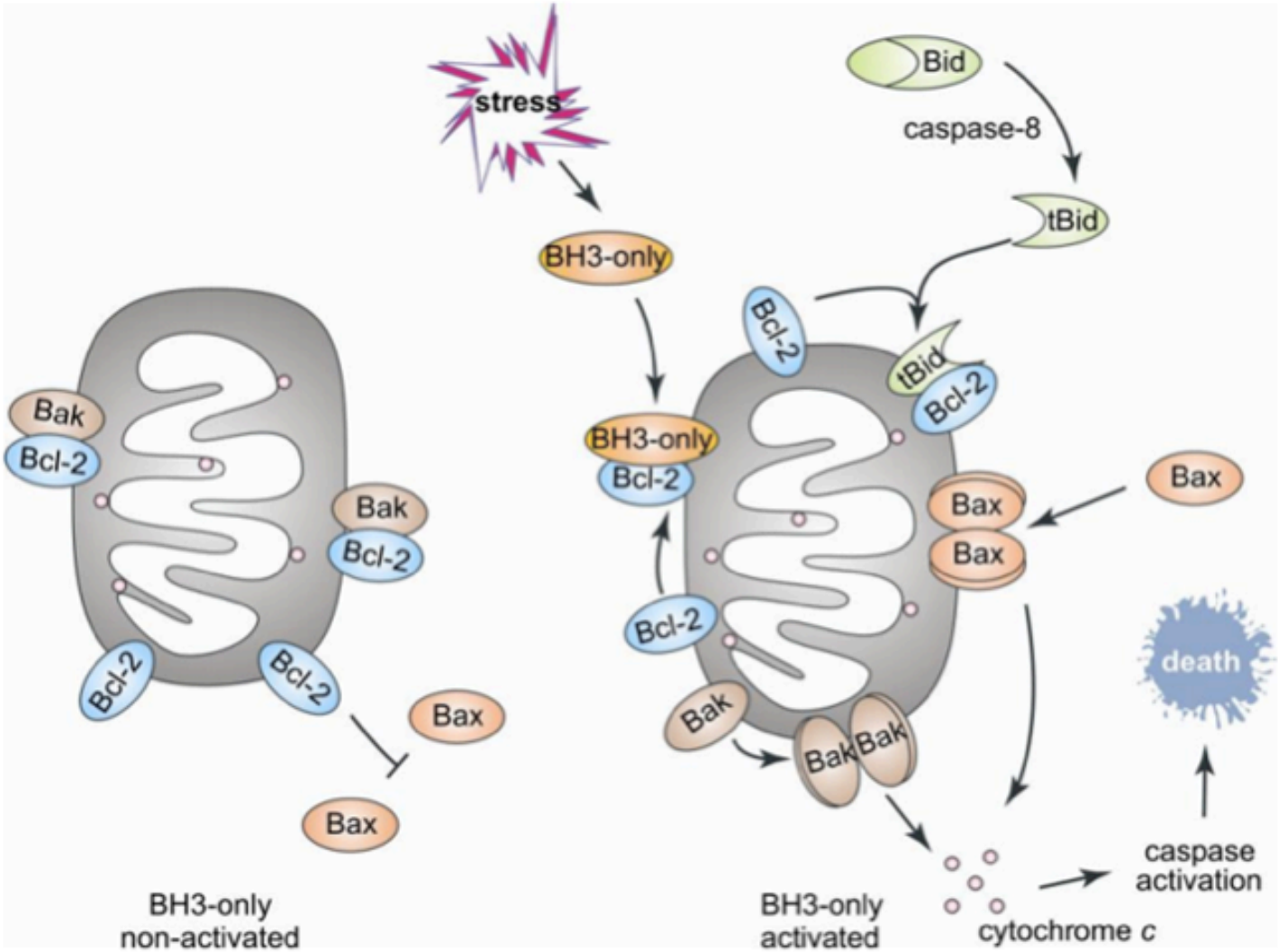
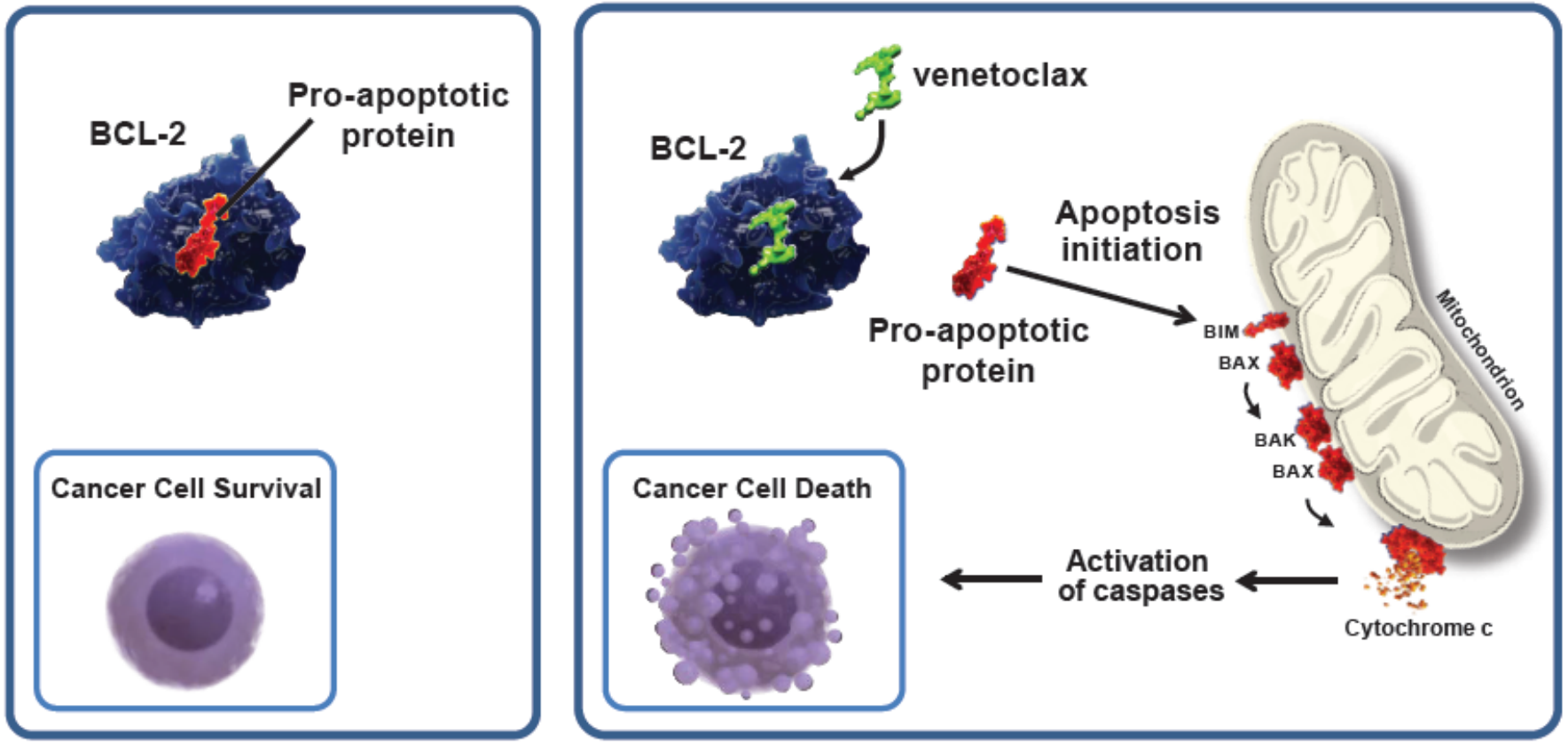
BCL-2 is an Important Inhibitor of Apoptosis in Many Types of NHL



BCL-2 Inhibitors in NHL/CLL



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]

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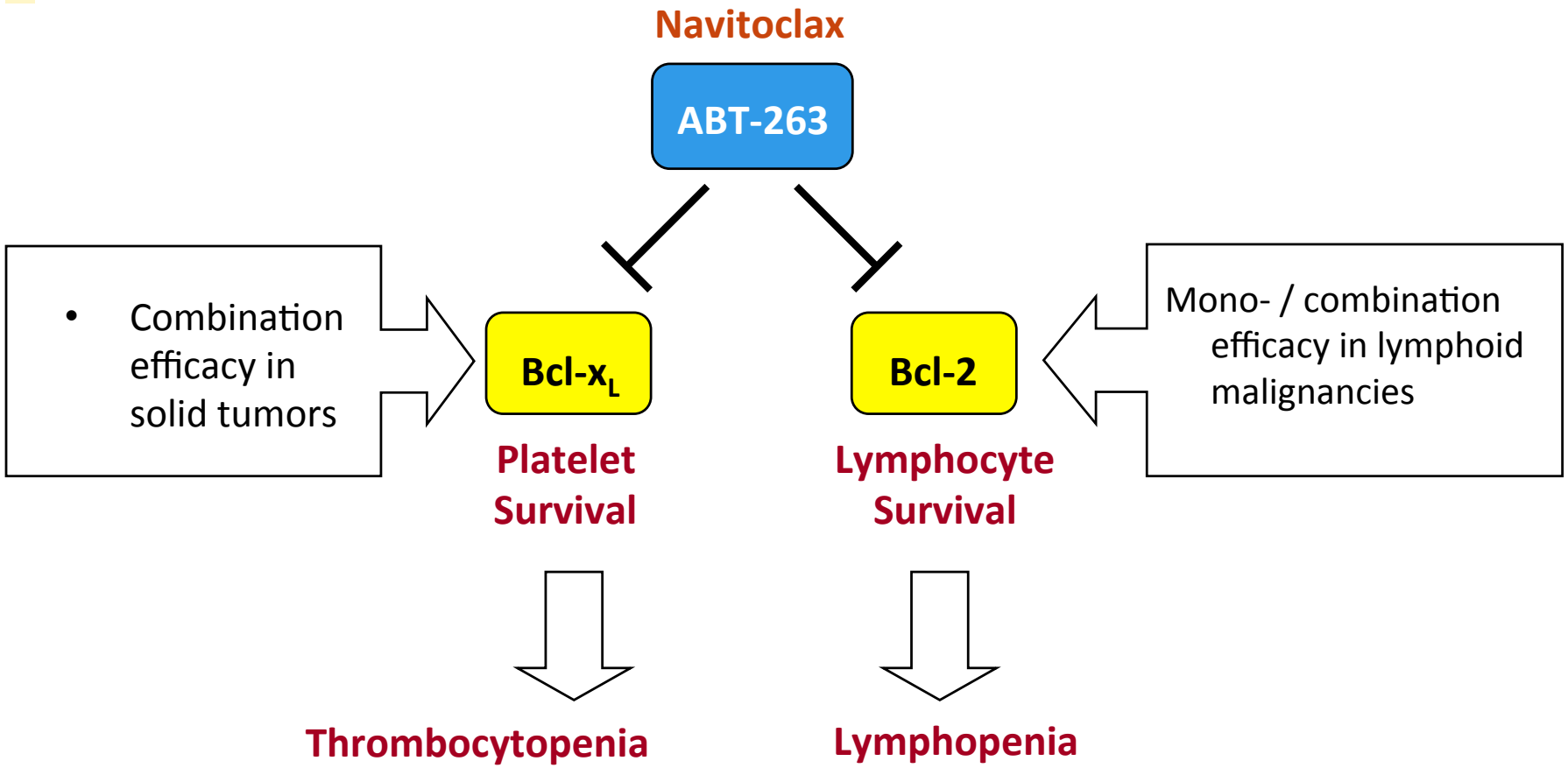
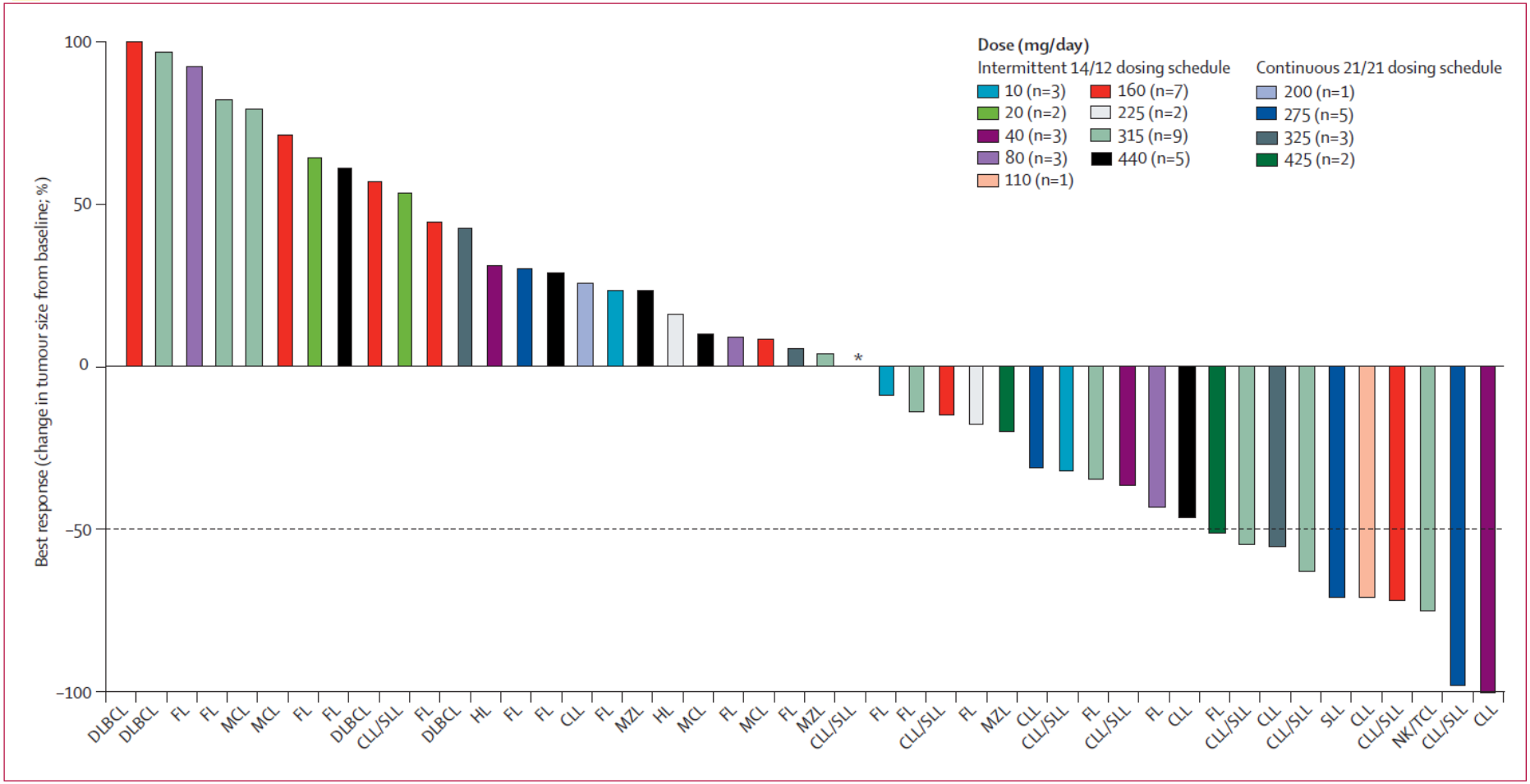
BCL-2 Inhibitors in NHL/CLL



Navitoclax Phase 1 Trial in NHL



Wilson *et al*, Lancet Onc 2010

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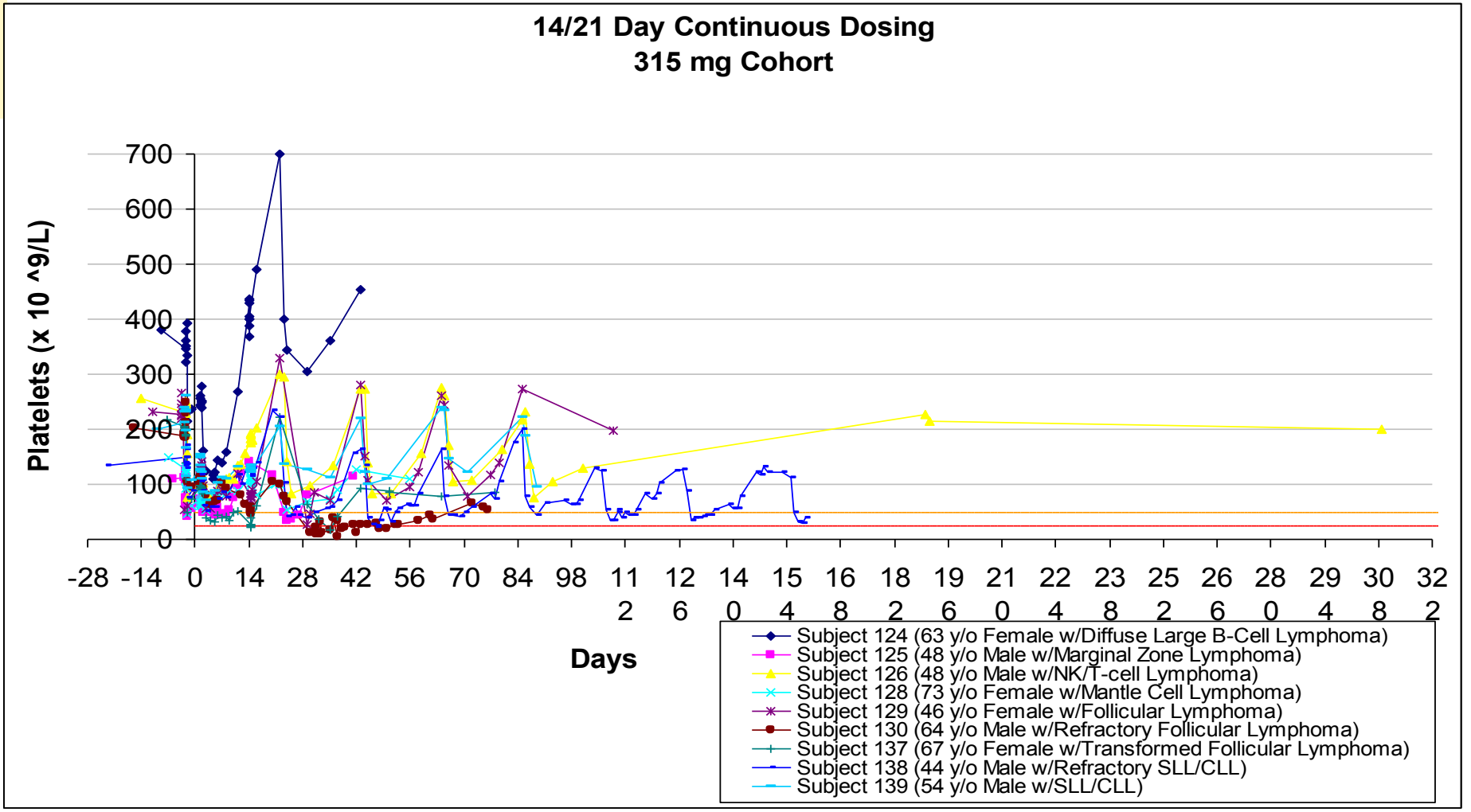
Navitoclax Phase 1 Trial in NHL



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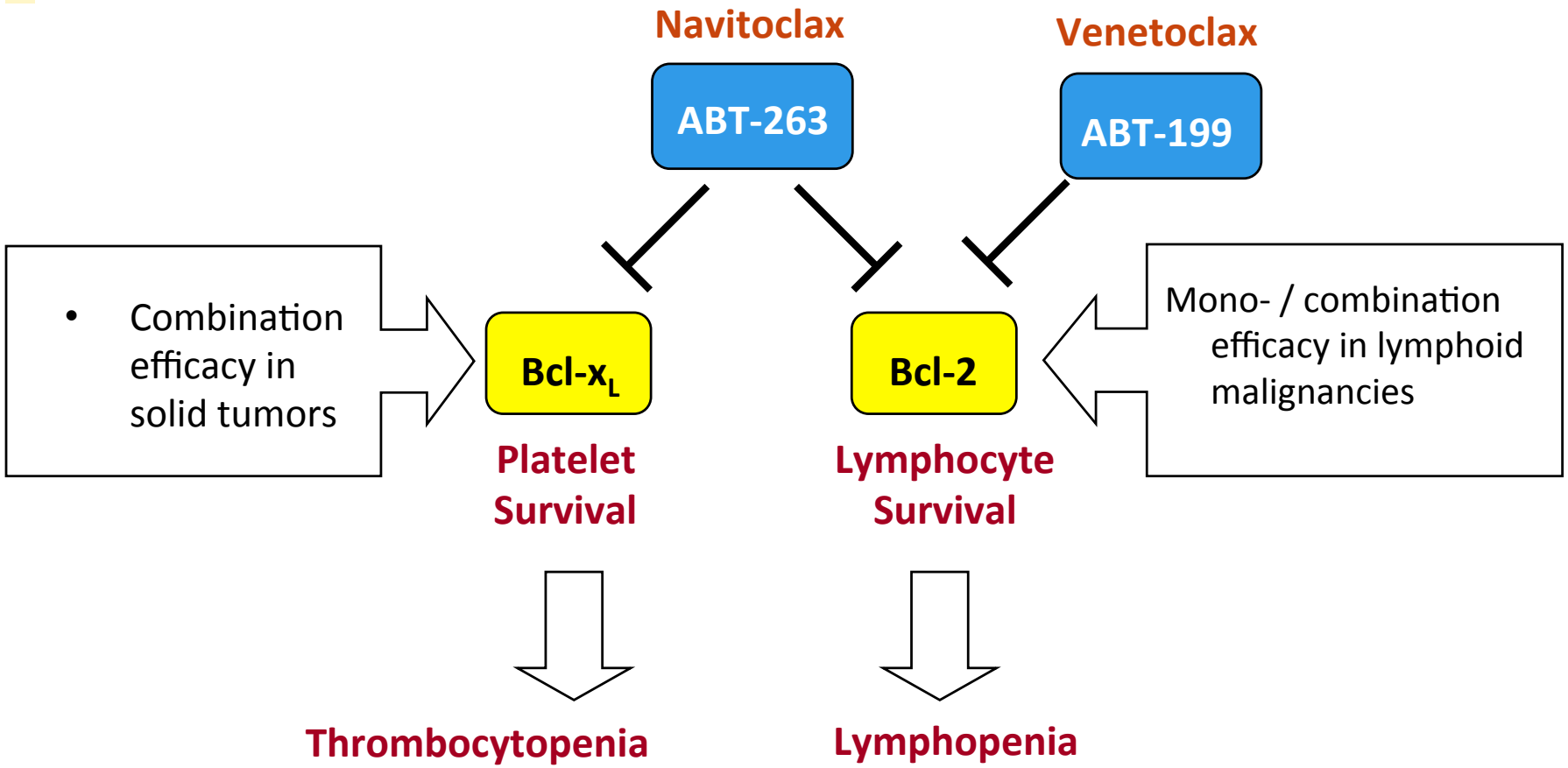
BCL-2 Inhibitors in NHL/CLL



Venetoclax Arm B (NHL) Treatment-Emergent Adverse Events (TEAEs)

All Grade AEs (in ≥ 15% patients), n (%)	N=106
Any AE	103 (97)
Nausea	51 (48)
Diarrhea	47 (44)
Fatigue	43 (41)
Decreased appetite	22 (21)
Vomiting	22 (21)
Anemia	19 (18)
Constipation	19 (18)
Headache	19 (18)
Neutropenia	19 (18)
Cough	18 (17)
Back pain	17 (16)
Upper respiratory tract infection	16 (15)

Grade 3/4 AEs (in ≥ 5% patients), n (%)	N=106
Any Grade 3/4 AE	57 (54)
Anemia	17 (16)
Neutropenia	13 (12)
Thrombocytopenia	10 (9)
Fatigue	6 (6)

Serious Adverse Events (in ≥2 patients), n (%)	N=106
Any SAE	35 (33)
Diarrhea	3 (3)
Hyponatremia	3 (3)
Influenza	3 (3)

Gerecitano *et al*, ASH 2015
Davids…Gerecitano JCO 2016

As of September 15, 2015

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Venetoclax Phase 1 NHL Responses by Histology – All Doses

Best Objective Response, n (%)	All N=106	MCL n=28	FL n=29	DLBCL n=34	DLBCL-RT n=7	WM n=4	MZL n=3
Overall Response	**47 (44)**	**21 (75)**	**11 (38)**	**6 (18)**	**3 (43)**	**4 (100)**	**2 (67)**
CR	14 (13)	6 (21)	4 (14)	4 (12)	0	0	0
PR	33 (31)	15 (54)	7 (24)	2 (6)	3 (43)	4 (100)	2 (67)
SD	32 (30)	5 (18)	17 (59)	8 (24)	2 (29)	0	0
PD	23 (22)	1 (4)	1 (4)	19 (56)	1 (14)	0	0

- 4 patients discontinued prior to assessment
- n=1 with MM had PD

Gerecitano *et al*, ASH 2015

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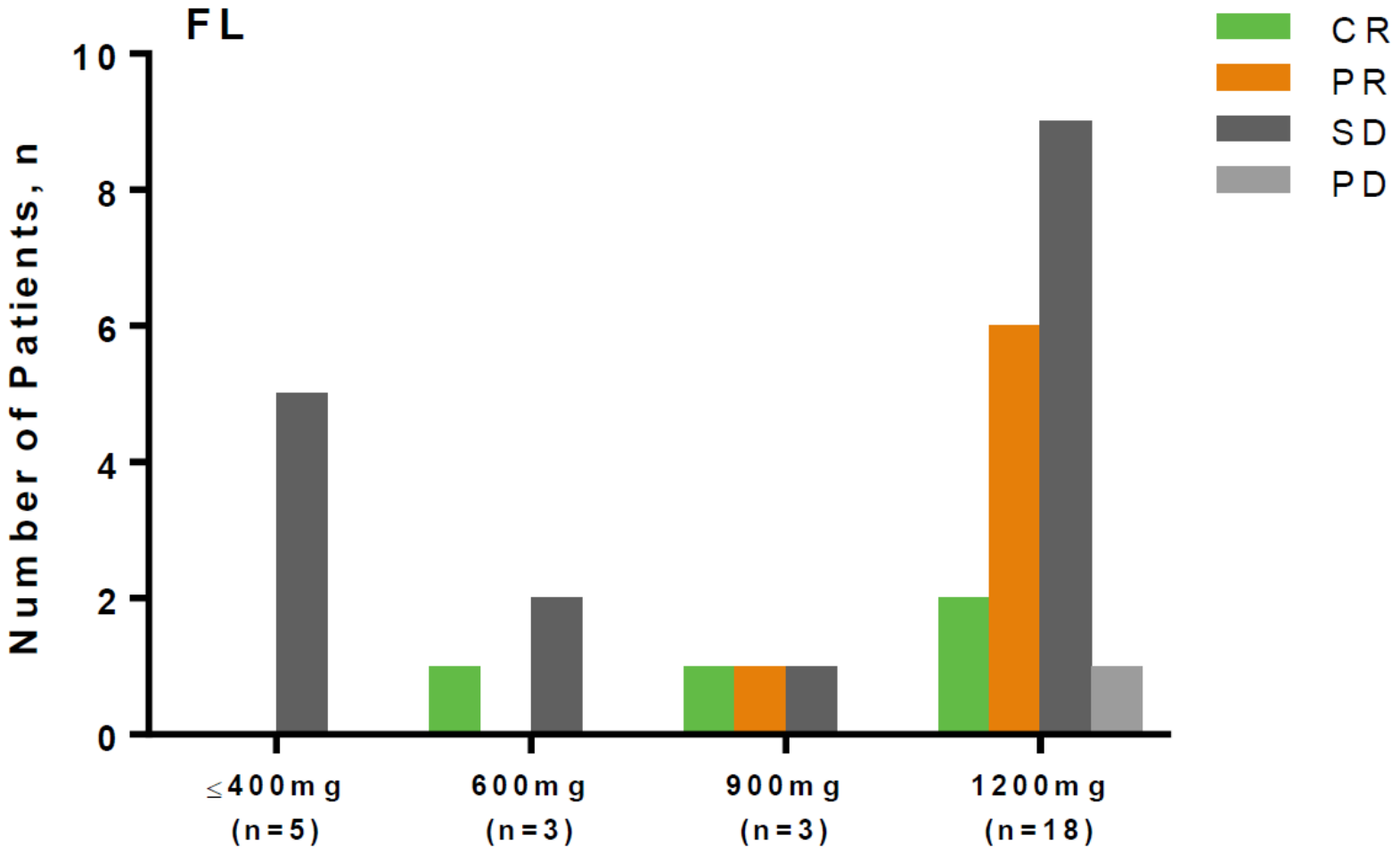
Venetoclax in FL: Responses May Be Dose-Related



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Gerecitano *et al*, ASH 2015

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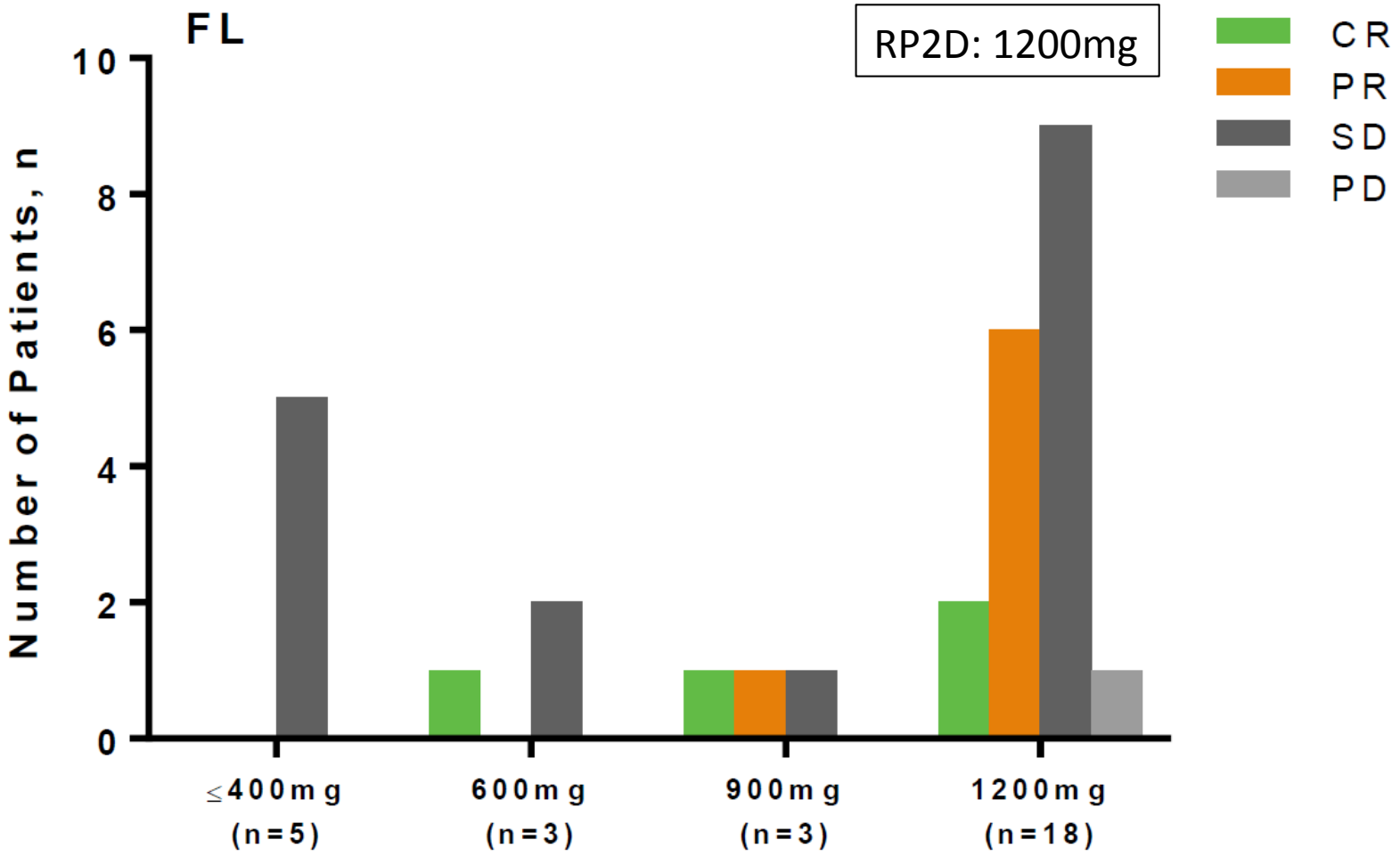
Venetoclax in FL: Responses May Be Dose-Related



Gerecitano *et al*, ASH 2015
Davids *et al*, JCO 2016

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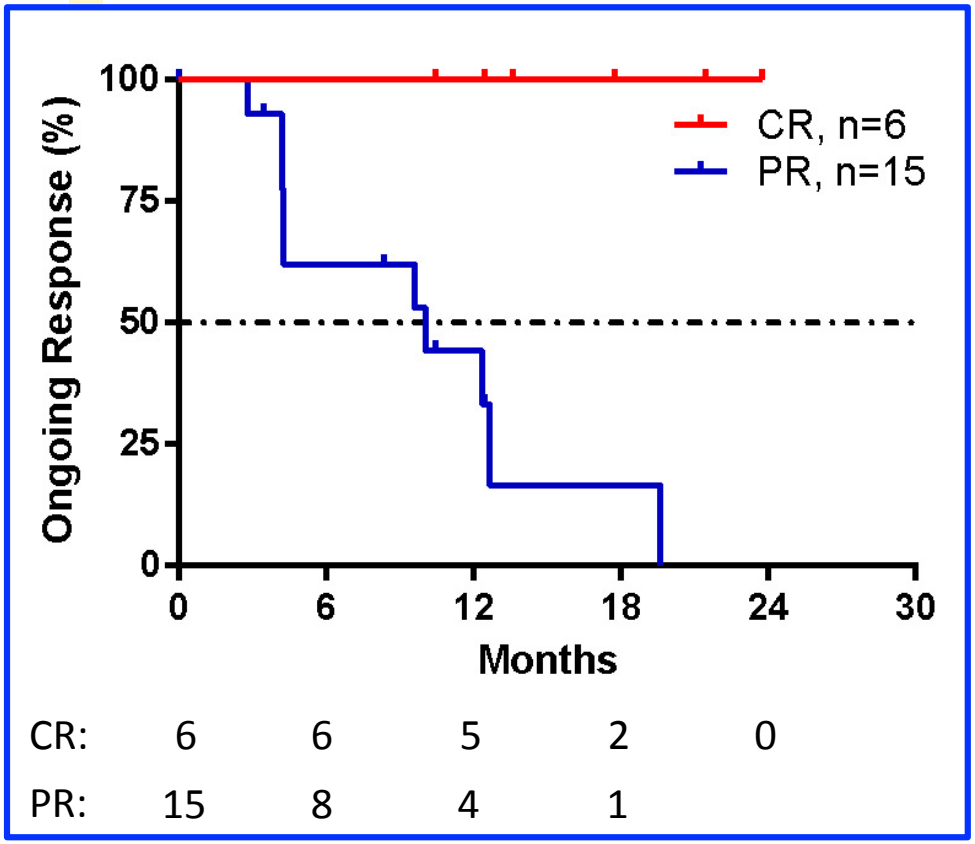
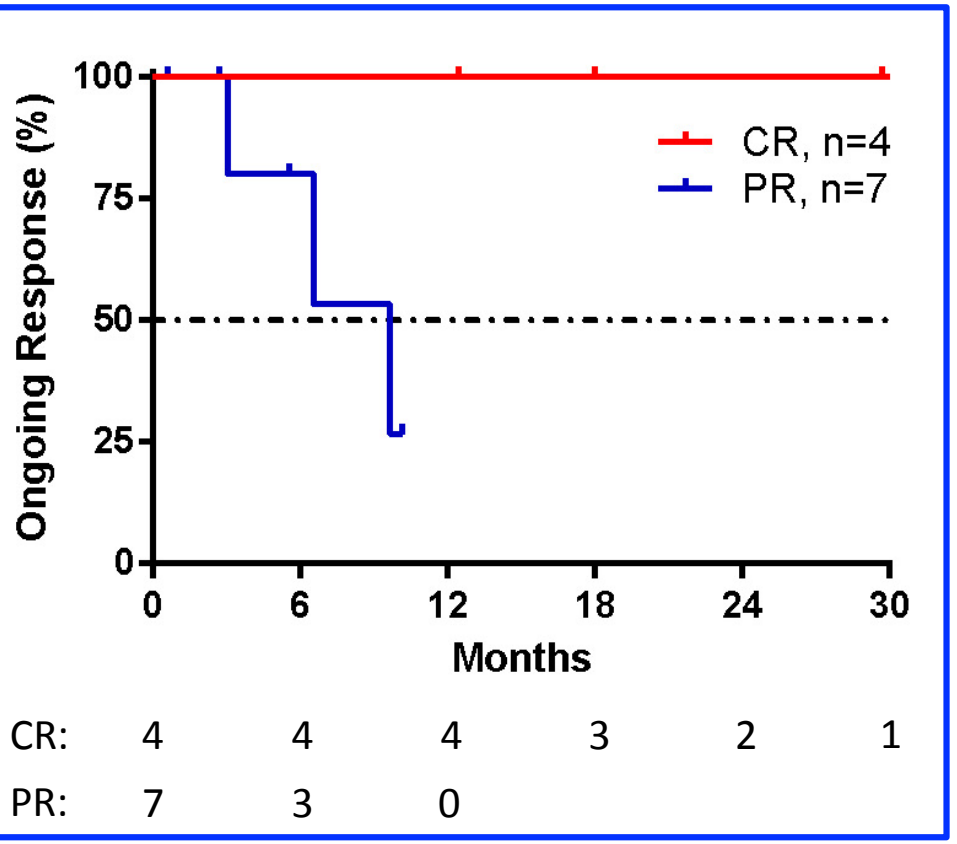
Venetoclax Phase 1 Duration of Response in MCL and FL

Mantle cell lymphoma



CR:	6	6	5	2	0
PR:	15	8	4	1	

Follicular lymphoma



CR:	4	4	4	3	2	1
PR:	7	3	0			

Gerecitano *et al*, ASH 2015

As of September 15, 2015

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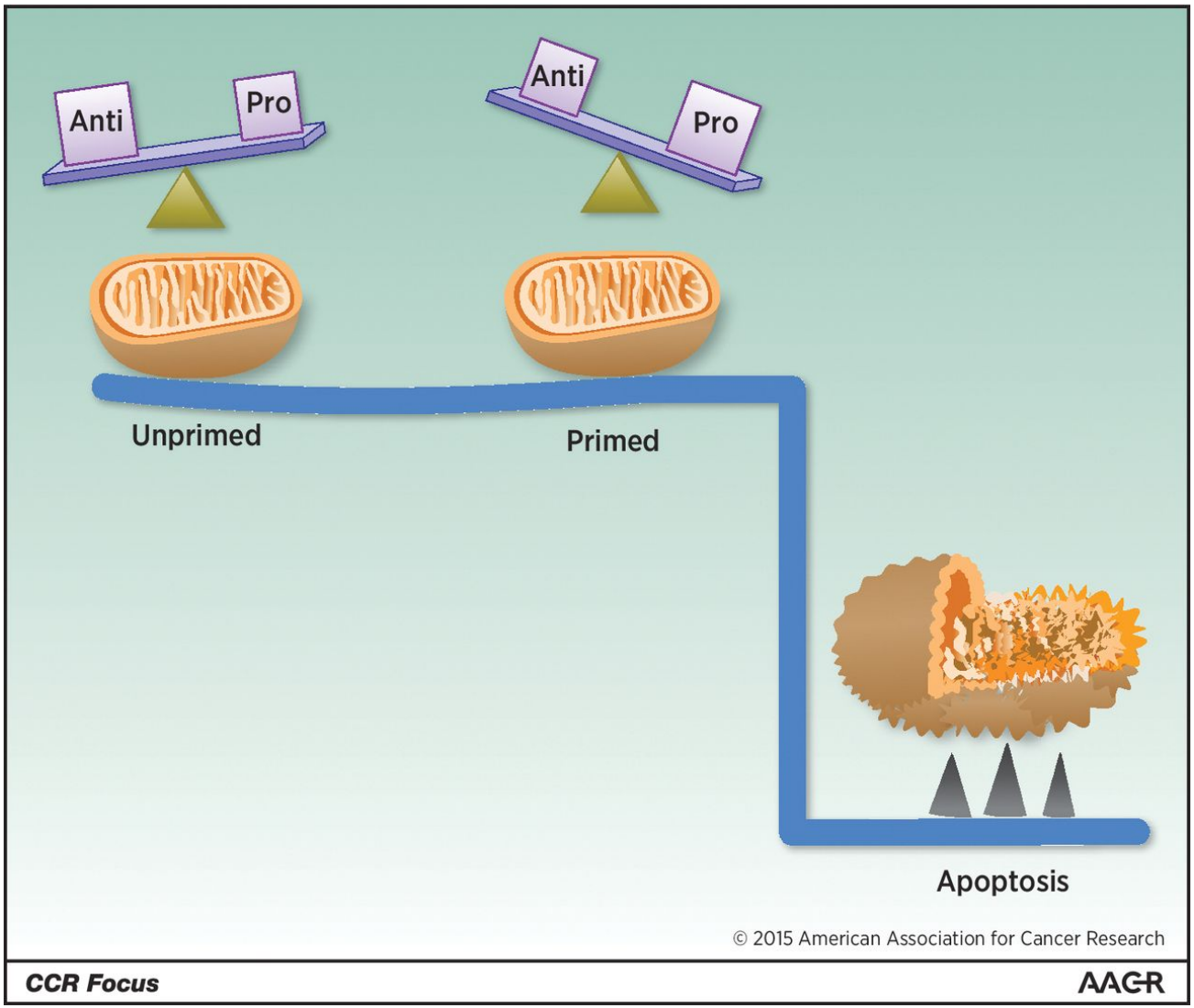
Is Priming a Determinant of Response?



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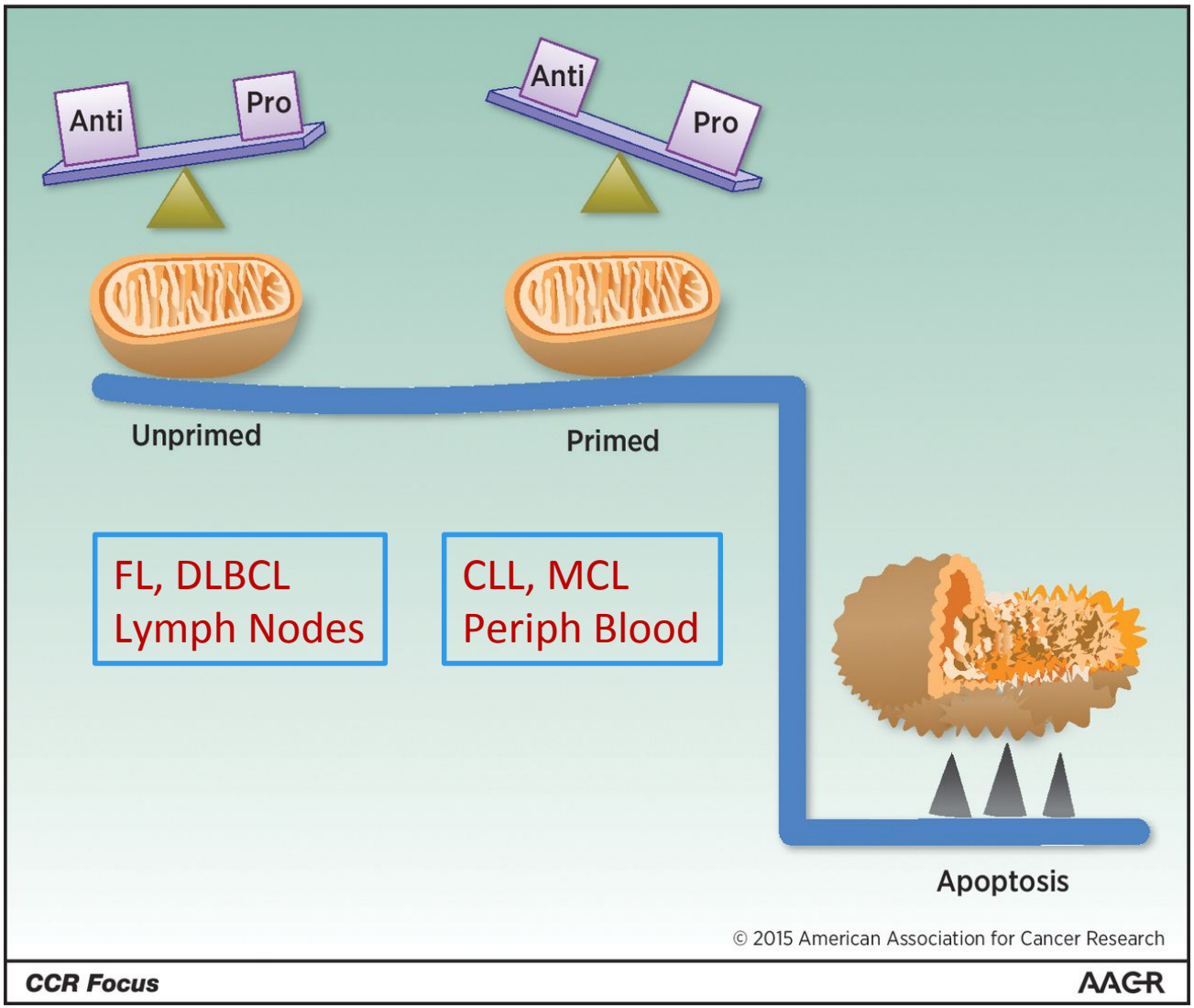
Letai CCR 2015

Does Priming Differ Between Histologies/Sites?



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Letai CCR 2015

Venetoclax in NHL Conclusions

- Venetoclax demonstrated an acceptable safety profile in patients with R/R NHL
  - The maximum tolerated dose was not reached with doses up to 1200 mg evaluated
  - Lab TLS was observed in 2 patients with high risk disease and was managed effectively
  - Limited cytopenias could be managed in most patients without treatment interruption
- The ORR was 75% in MCL, 38% in FL, and 18% in DLBCL
  - The majority of responses were seen at higher doses in FL and DLBCL, whereas responses were seen at all target dose levels in MCL
  - Complete responses in patients with FL and MCL were durable with sustained treatment
- Venetoclax is being evaluated with combination chemotherapy and targeted agents

BCL-2 Inhibitors in FL: Unanswered Questions

- What determines response
- Duration of treatment
- Combine vs. sequence
  - Will combination tx overcome lack of priming/ microenvironment?
  - Curative potential vs. treatment as chronic conditions
- Best combinations with traditional agents or other targeted therapies
- Combinations with immunotherapies

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    - Owen O'Connor
  - Venetoclax Investigators
    - Mathew Davids
    - Andrew Roberts
    - John Seymour
    - Sari Enschede
    - Su Young Kim
- Trial Participants and their Caregivers

Backup Slides

- APG-1252 Ascentage Pharma Group Inc.
- Oblimersen
- SPC2996, a LNA antisense molecule against Bcl-2 Santaris Pharma A/S
  - oligonucleotide comprising 16 monomeric units (16-mer), of which four DNA nucleotides are replaced with locked nucleic acid nucleotides.11 Although SPC2996 differs in only three nucleotides from the oblimersen sequence, the incorporation of novel locked nucleic acid into the molecule may offer several advantages over the traditional phosphorothioate oligonucleotides, including increased target