Disclosures of XXXXX

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			X			X	
Genentech			X			X	
Gilead						X	
Bayer			X			X	
Incyte						X	
Samus Therapeutics			X				

Memorial Sloan Kettering Cancer Center

BCL-2 Inhibitors in Follicular Lymphoma

John Gerecitano, MD, PhD

Clinical Director, Lymphoma Outpatient Services
Lymphoma Service/Developmental Therapeutics Clinic

Department of Medicine
Memorial Sloan-Kettering Cancer Center

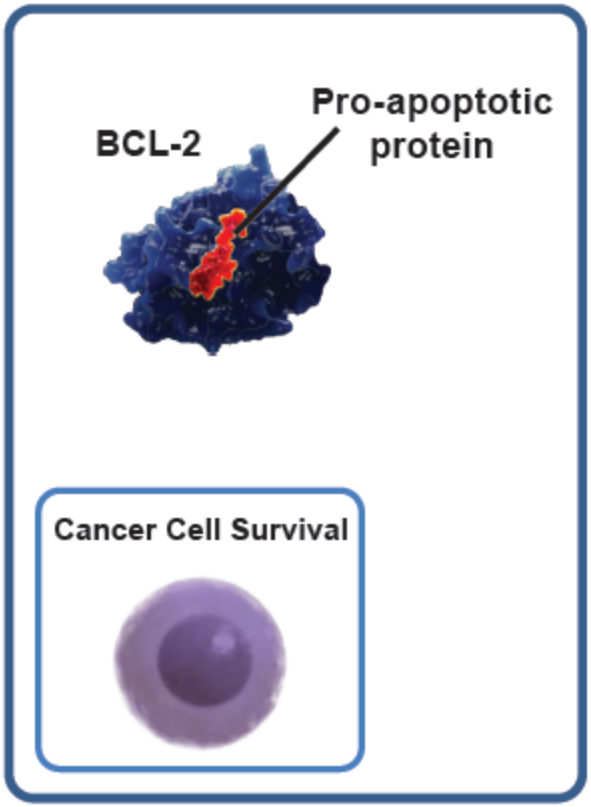
Memorial Sloan Kettering Cancer Center

Follicular NHL

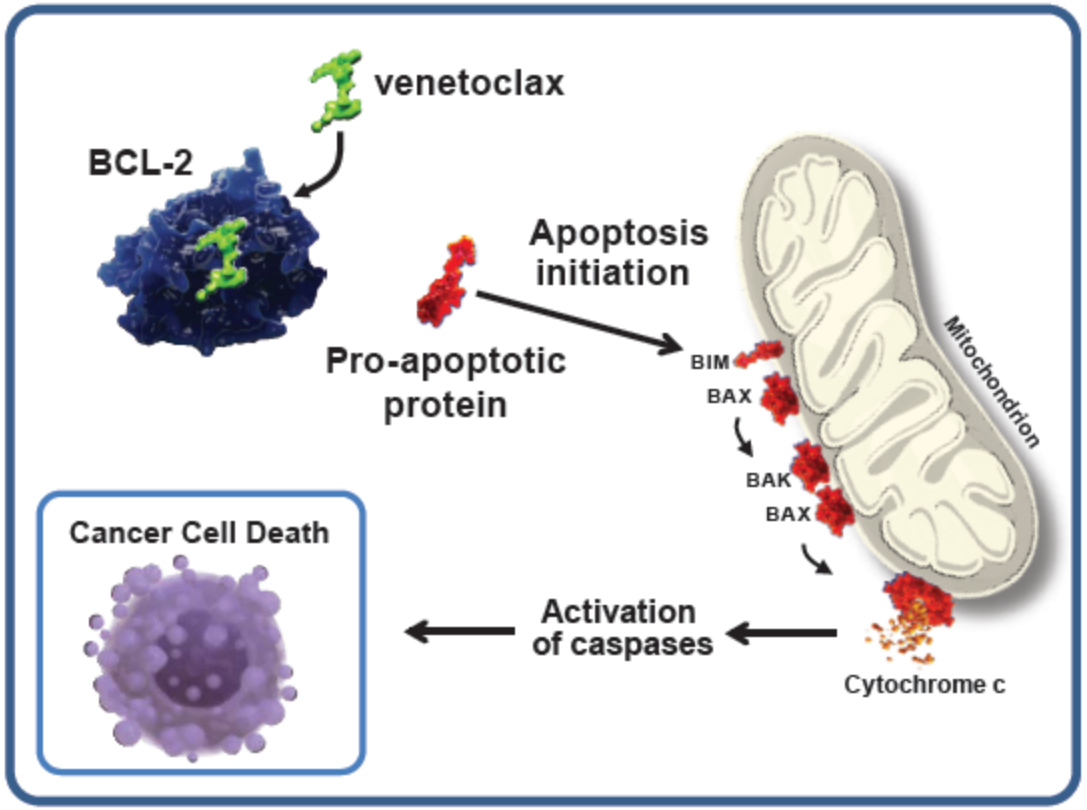
- **Characteristics**
  - 80% to 90% disseminated at diagnosis (lymph nodes, spleen, bone marrow, peripheral blood)
  - t(14:18) causes **BCL-2 overexpression in 90%** of cases
  - Relatively long median survival
  - Sensitive to chemotherapy and RT
  - Incurable with conventional therapies
    - possible cures with allo SCT
- **Histologic transformation**
  - Occurs in 30% to 40% of patients

Targeting BCL-2

BCL-2 Inhibitor Mechanism of Action

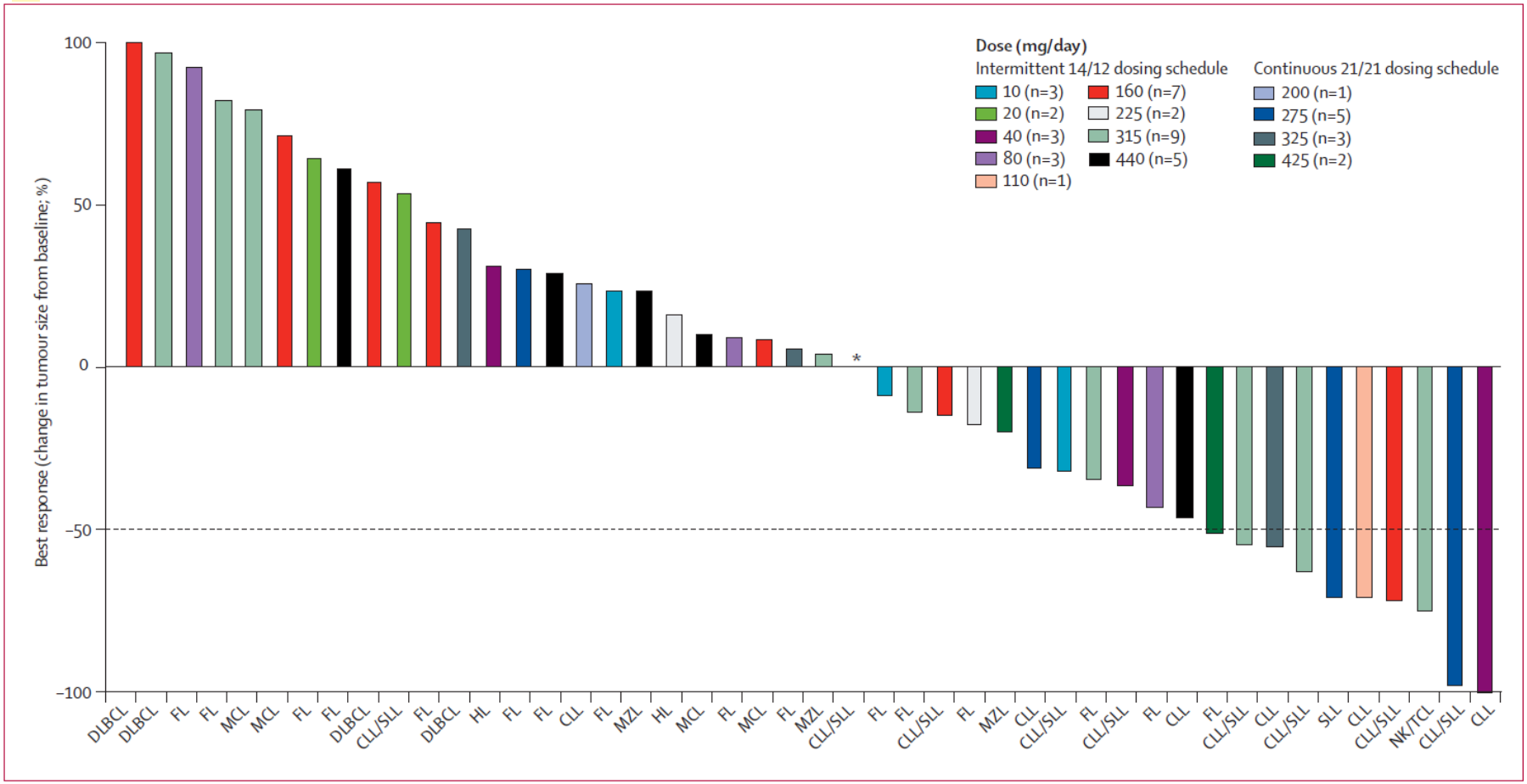


BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]



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

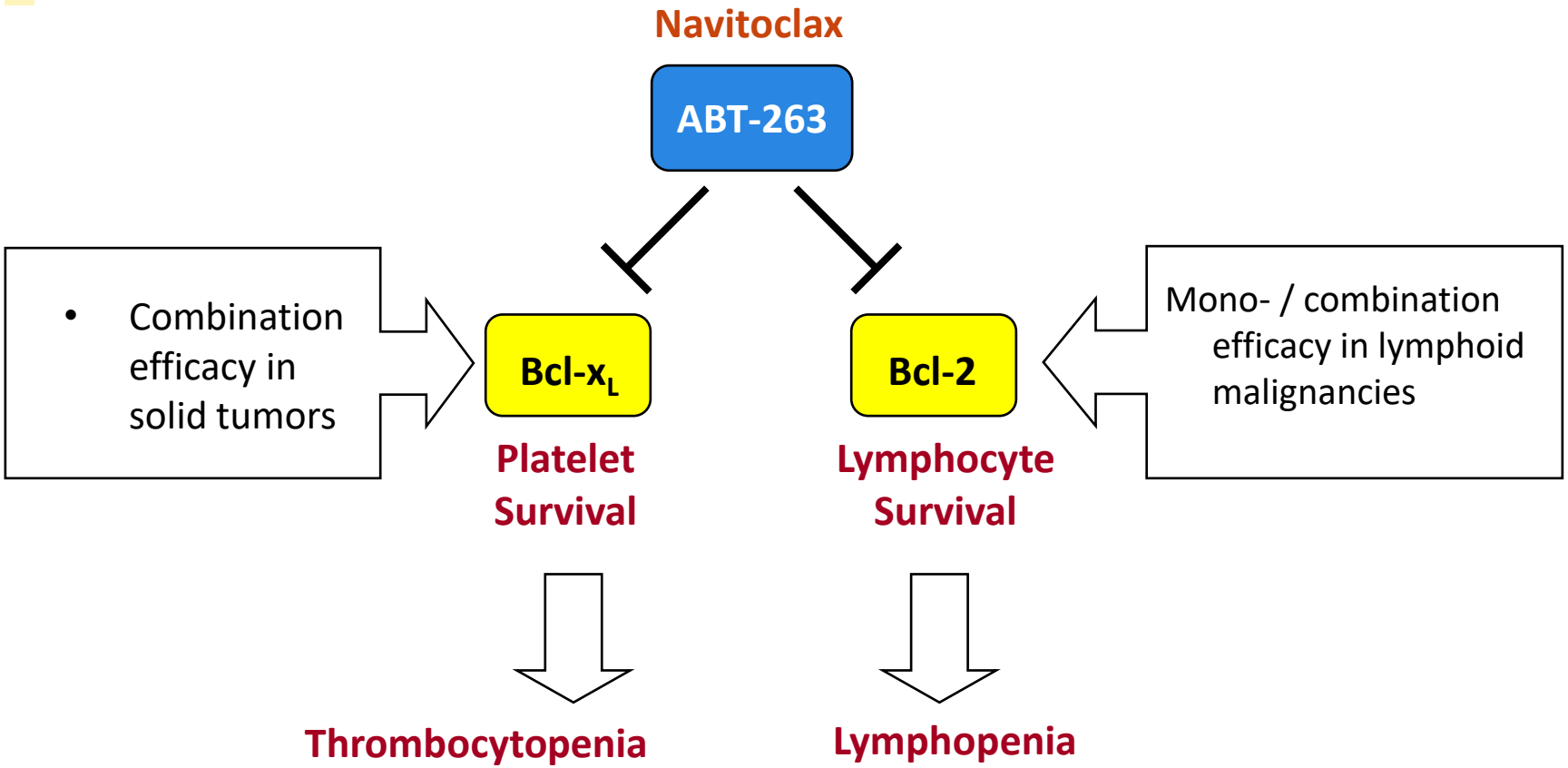
Navitoclax Phase 1 Trial in NHL



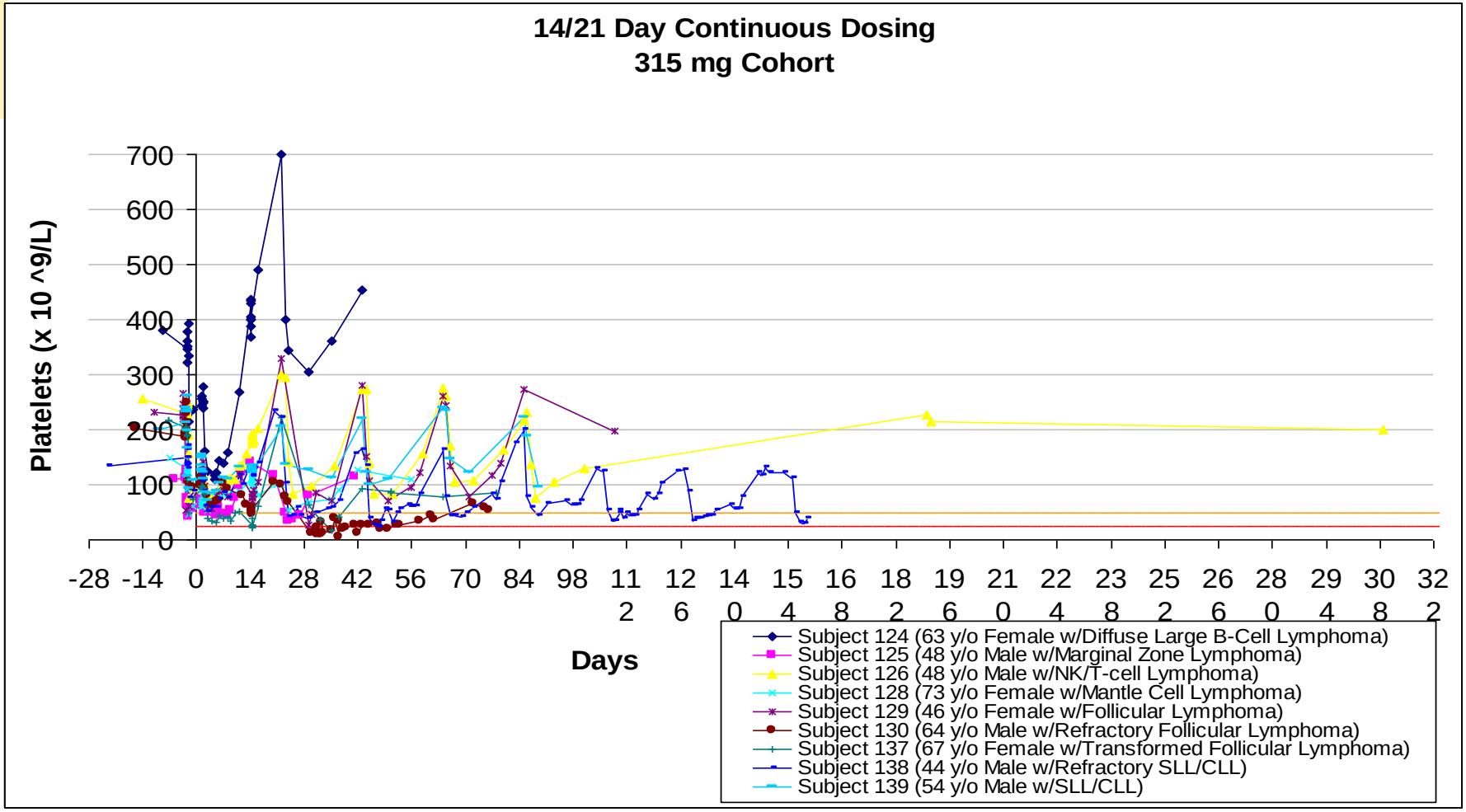
Wilson *et al*, Lancet Onc 2010

Memorial Sloan Kettering Cancer Center

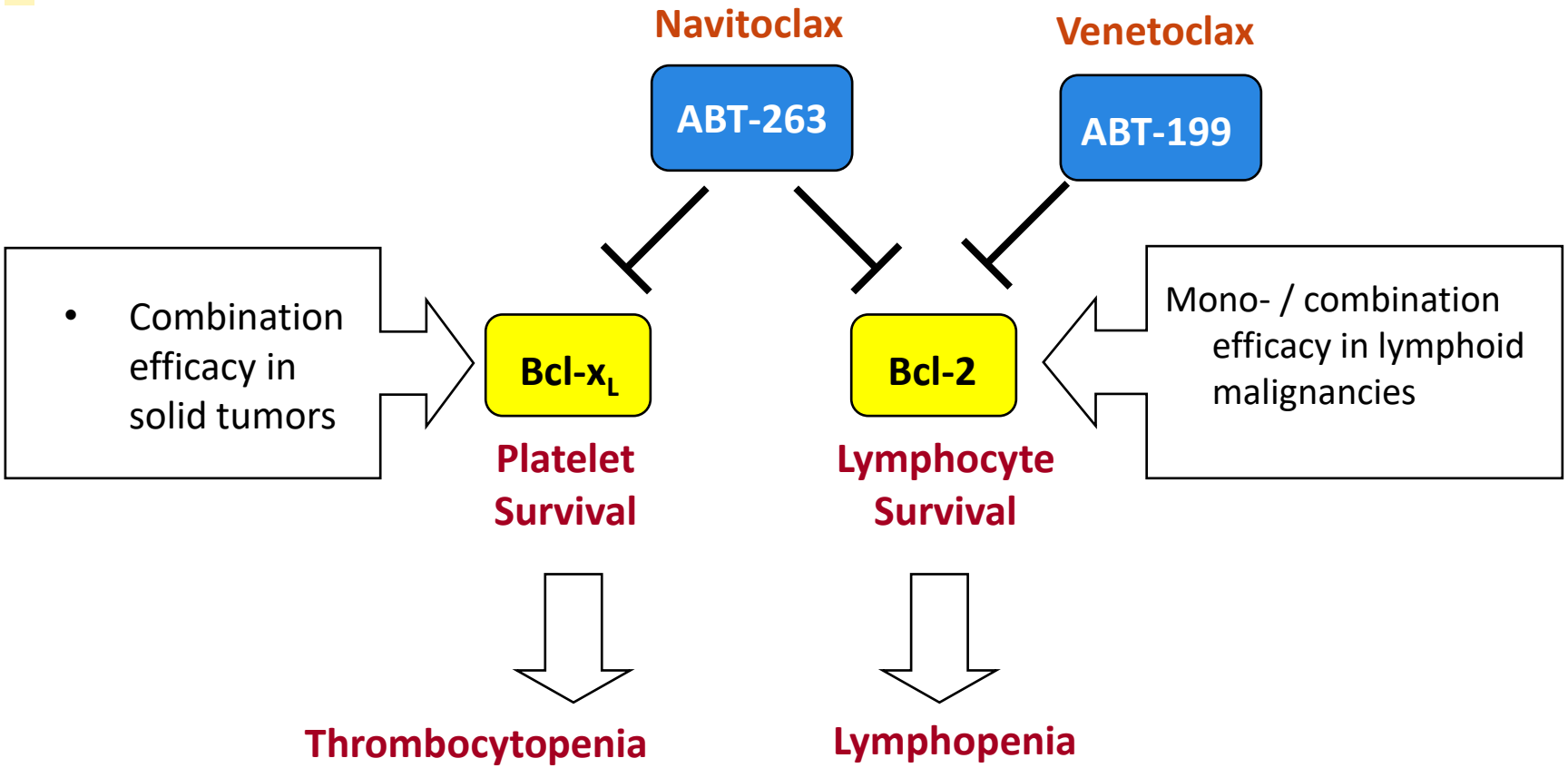
BCL-2 Inhibitors in NHL/CLL



Navitoclax Phase 1 Trial in NHL



BCL-2 Inhibitors in NHL/CLL



Treatment-Emergent Adverse Events (AEs)

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

Memorial Sloan Kettering Cancer Center

Objective Responses by Histology – All Doses

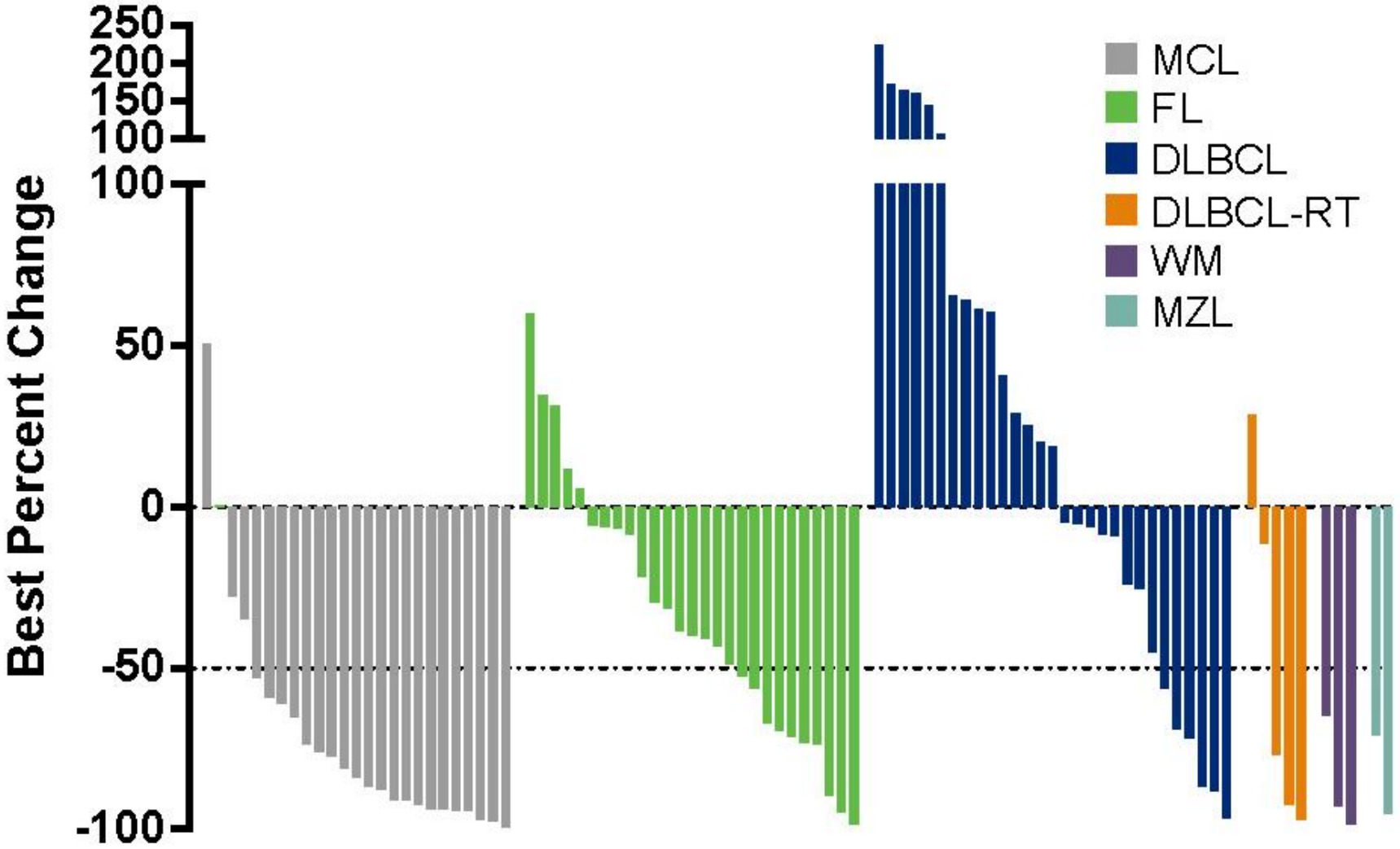
Best Objective Response, n (%)	All N=106	MCL n=28	FL n=29	DLBCL n=34	DLBCL-RT n=7	WM n=4	MZL n=3
Overall Response	**47 (44)**	**21 (75)**	**11 (38)**	**6 (18)**	**3 (43)**	**4 (100)**	**2 (67)**
CR	14 (13)	6 (21)	4 (14)	4 (12)	0	0	0
PR	33 (31)	15 (54)	7 (24)	2 (6)	3 (43)	4 (100)	2 (67)
SD	32 (30)	5 (18)	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
Davids…Gerecitano JCO 2016

Memorial Sloan Kettering Cancer Center

Best Percent Change From Baseline in Nodal Mass by CT Scan

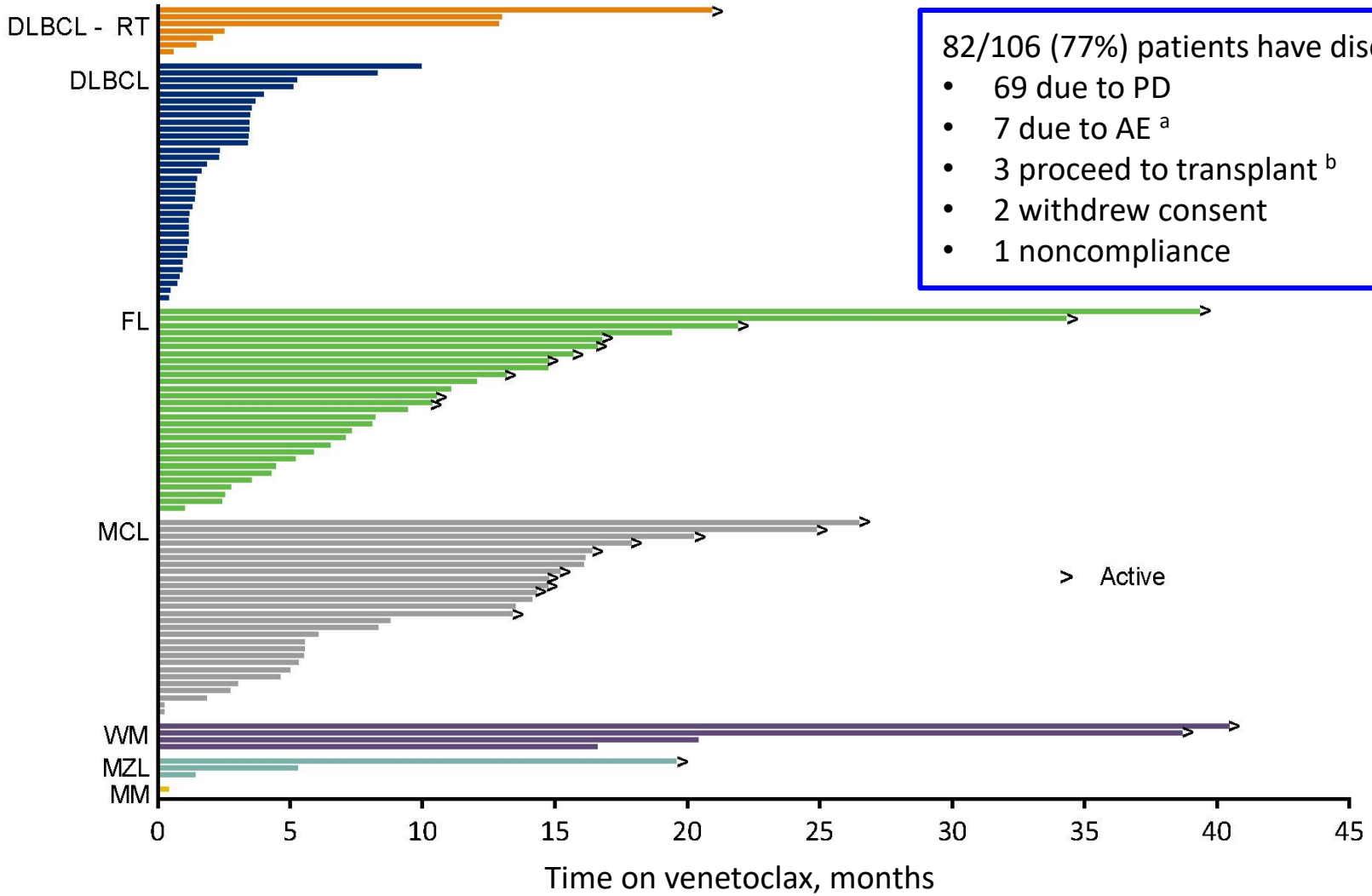


Gerecitano *et al*, ASH 2015
Davids…Gerecitano JCO 2016

As of September 15, 2015

Memorial Sloan Kettering Cancer Center

Current Status



82/106 (77%) patients have discontinued

- 69 due to PD
- 7 due to AE [a]
- 3 proceed to transplant [b]
- 2 withdrew consent
- 1 noncompliance

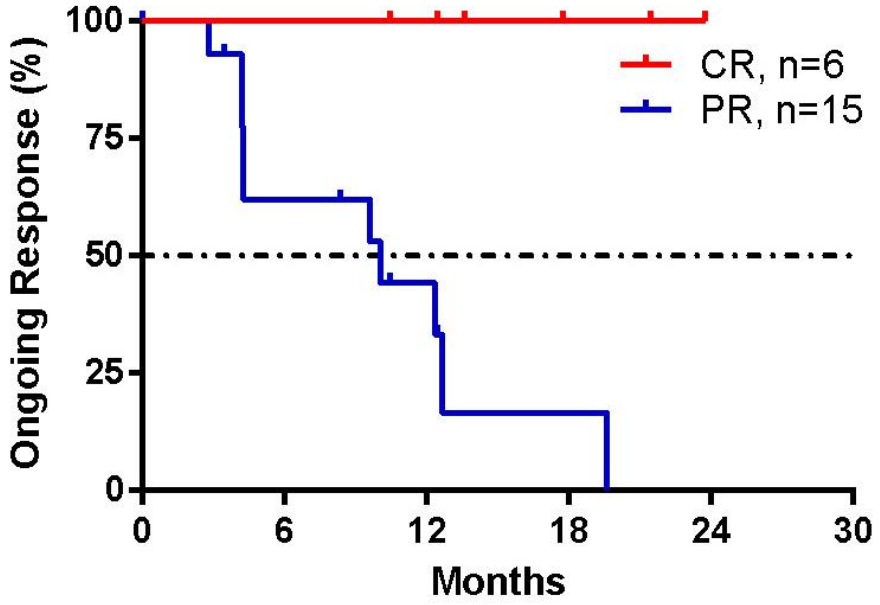
[a] 1 each sepsis, anemia, rheumatoid arthritis, type 2 respiratory failure, thrombocytopenia, toxic myopathy, diarrhea/nausea

[b] Two after achieving PR and one after achieving CR

As of September 15, 2015

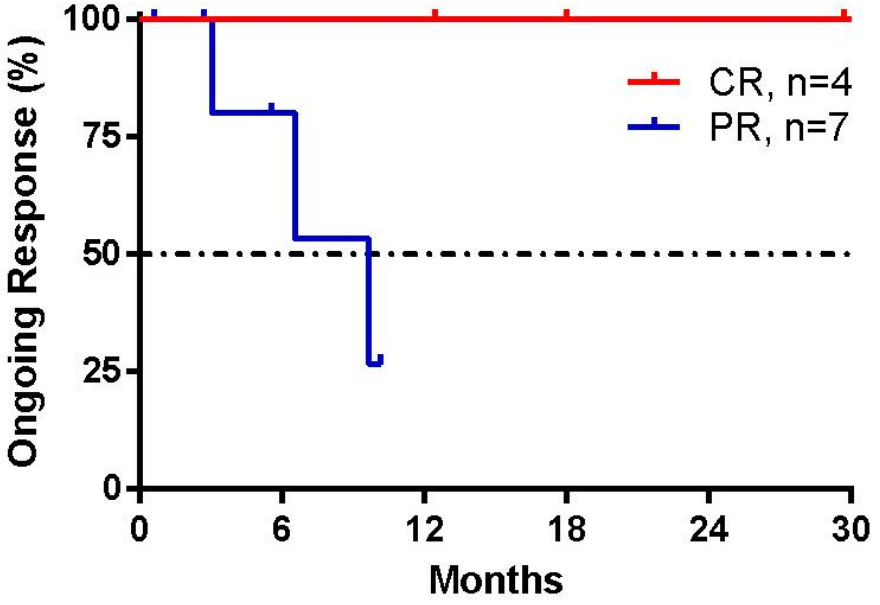
Duration of Response in MCL and FL

Mantle cell lymphoma



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

Follicular lymphoma



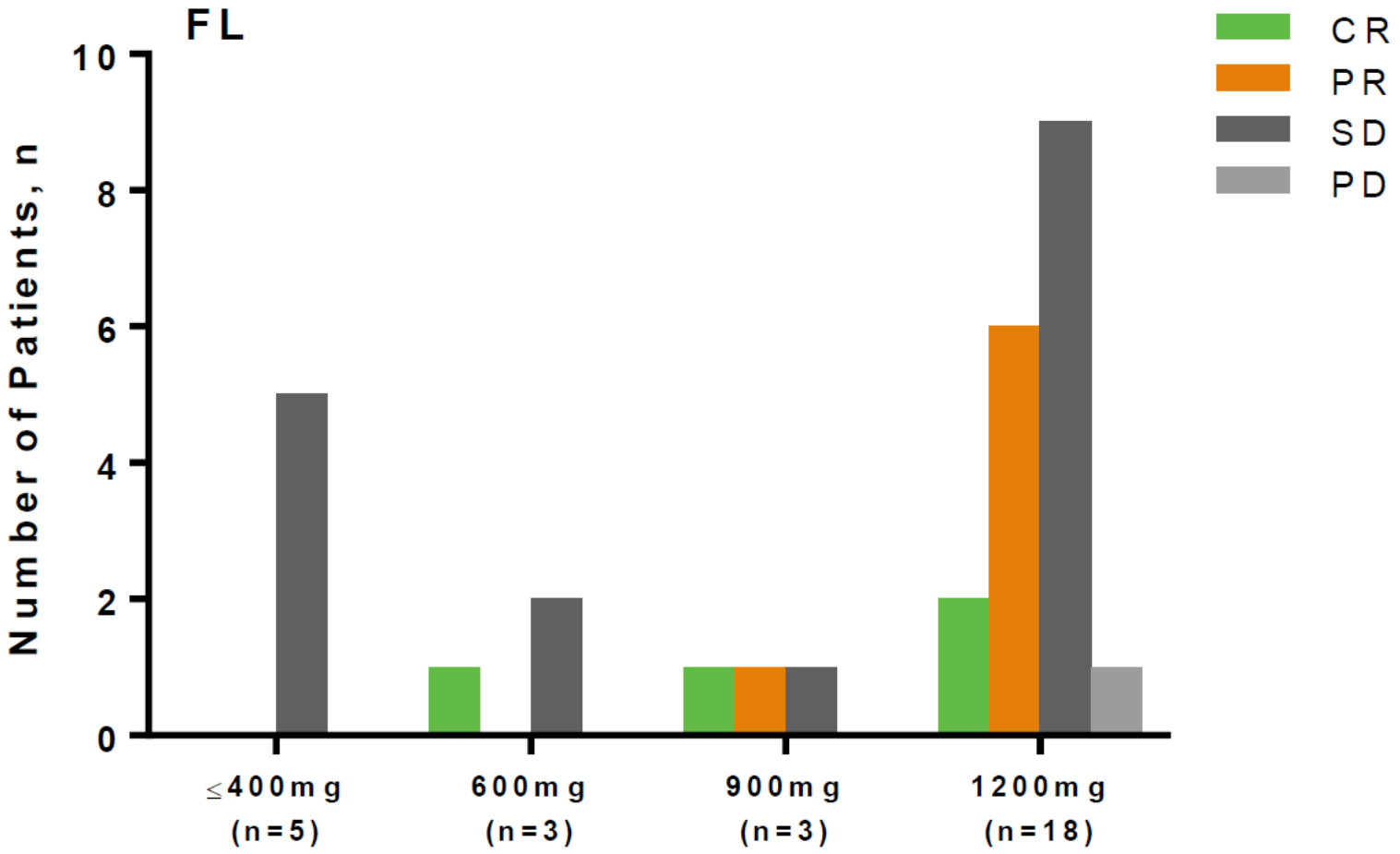
CR:	4	4	4	3	2	1
PR:	7	3	0			

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

As of September 15, 2015

Memorial Sloan Kettering Cancer Center

Best Percent Change From Baseline in Nodal Mass by CT Scan

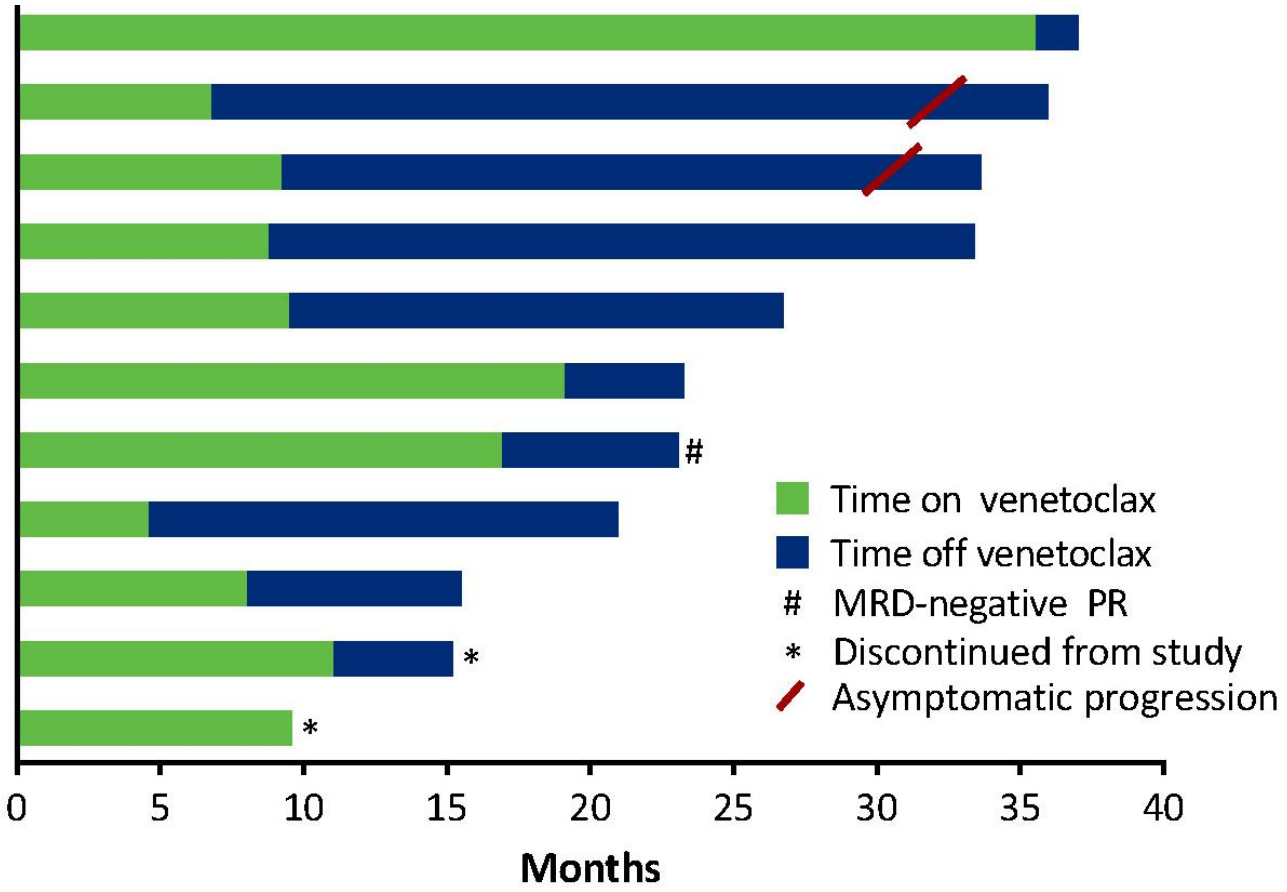


Gerecitano *et al*, ASH 2015

As of September 15, 2015

Memorial Sloan Kettering Cancer Center

Durability of Responses: Patients Who Stopped Venetoclax



- 11 patients stopped venetoclax after achieving objective response (9 MRD-negative)
  - 9 remain in follow-up with a median time off venetoclax of 16 (2 – 29) months
  - 2 patients with MRD-positive CR/CRi had asymptomatic progression

Ma et al, ASH 2015

As of October 28, 2015

Memorial Sloan Kettering Cancer Center

Conclusions

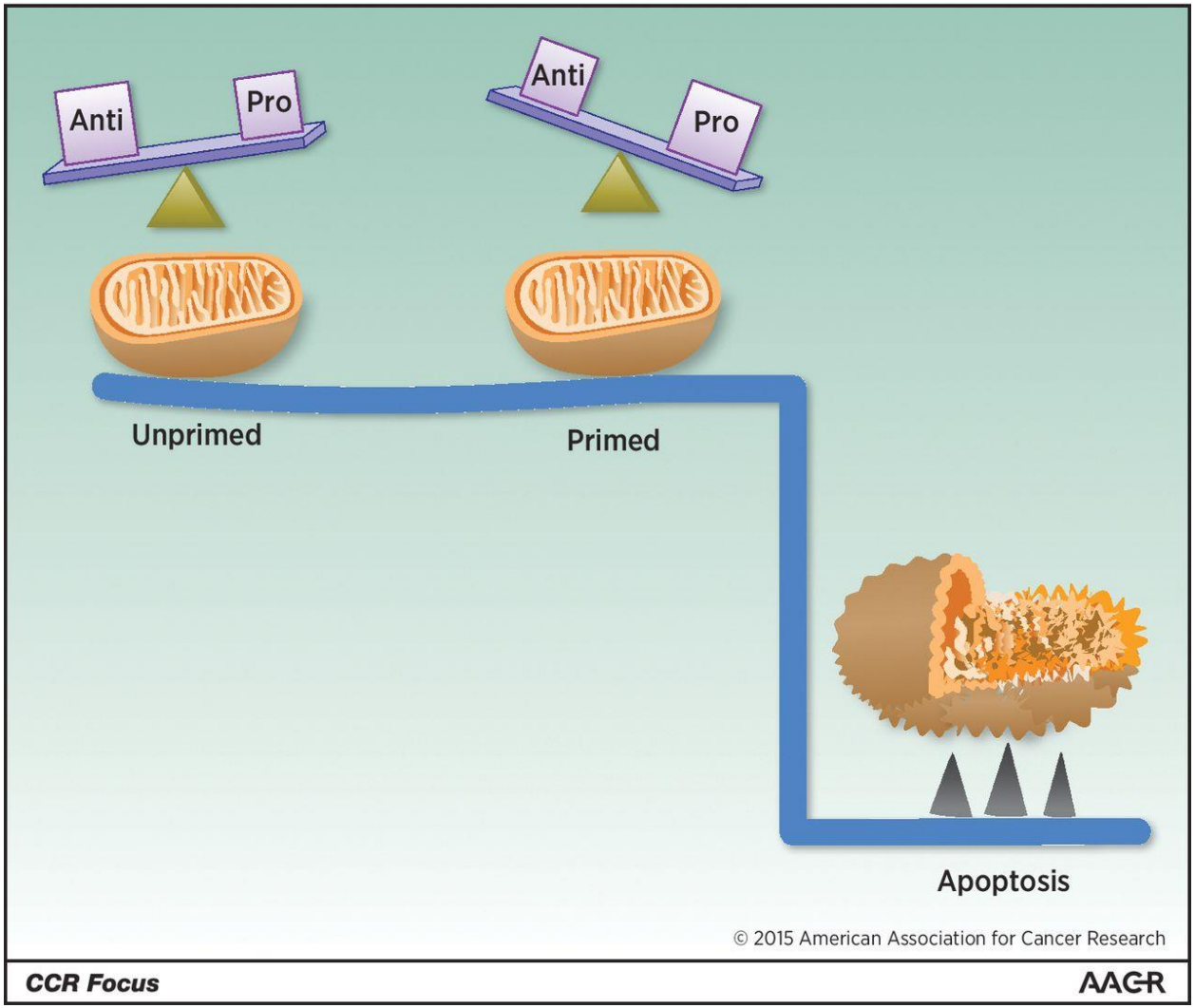
- Venetoclax demonstrated an acceptable safety profile in patients with R/R NHL
  - The maximum tolerated dose was not reached with doses up to 1200 mg evaluated
  - No laboratory or clinical TLS was seen in patients with FL
- The ORR was 75% in MCL, 38% in FL, and 18% in DLBCL
  - The majority of responses were seen at higher doses in FL and DLBCL,
  - Complete responses in patients with FL and MCL were durable
- Venetoclax is being evaluated with combination chemotherapy and targeted agents

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

Why Is Response In FL Inferior To Responses In MCL, CLL?

- Some possibilities:
  - Insufficient target
    - If t(14;18) isn't sufficient to cause cancer, perhaps targeting it is not sufficient for response
  - Insufficient dose
    - Dose-response relationship in FL and DLBCL stronger than that in MCL, CLL
  - Escape pathways
    - Increased expression on BH3 proteins like MCL-1

Is Priming a Determinant of Response?



BCL-2 Inhibitors in FL: Unanswered Questions

- What determines response
- Duration of treatment
- Best combinations with traditional agents or other targeted therapies
- Combinations with immunotherapies

Acknowledgements

- MSKCC Lymphoma Service
  - Anas Younes
  - Andrew Zelenetz
  - Paul Hamlin
  - Steven Horwitz
  - Anita Kumar
  - Matthew Matasar
  - Alison Moskowitz
  - Craig Moskowitz
  - Ariela Noy
  - Lia Palomba
  - Carol Portlock
  - David Straus
  - Jurgen Rademaker
  - Ahmet Dogan
  - Susan Dosil
  - Diane Llerandi
  - Donna Miale
- Collaborators
  - Venetoclax Investigators
    - Mathew Davids
    - Andrew Roberts
    - John Seymour
    - Sari Enschede
    - Su Young Kim
    - Windham Wilson
- Trial Participants and their Caregivers

Backup Slides

Combination Trials

- Combo trials of venetoclax/ibrutinib
  - MCL: Tam et al., ESH 2016; UVa
  - CLL: MDACC, Ulm
    - Up front: PCY, Ohio State
  - FL: Georgetown

- **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 sequence affinity, specificity, higher biostability and reduced immunostimulatory side effects**
- **Drug: PNT2258 Other Name: DNAi, BCL2 targeted therapy Sierra Oncology, Inc**
- **Obatoclax**