VENETOCLAX (ABT 199)

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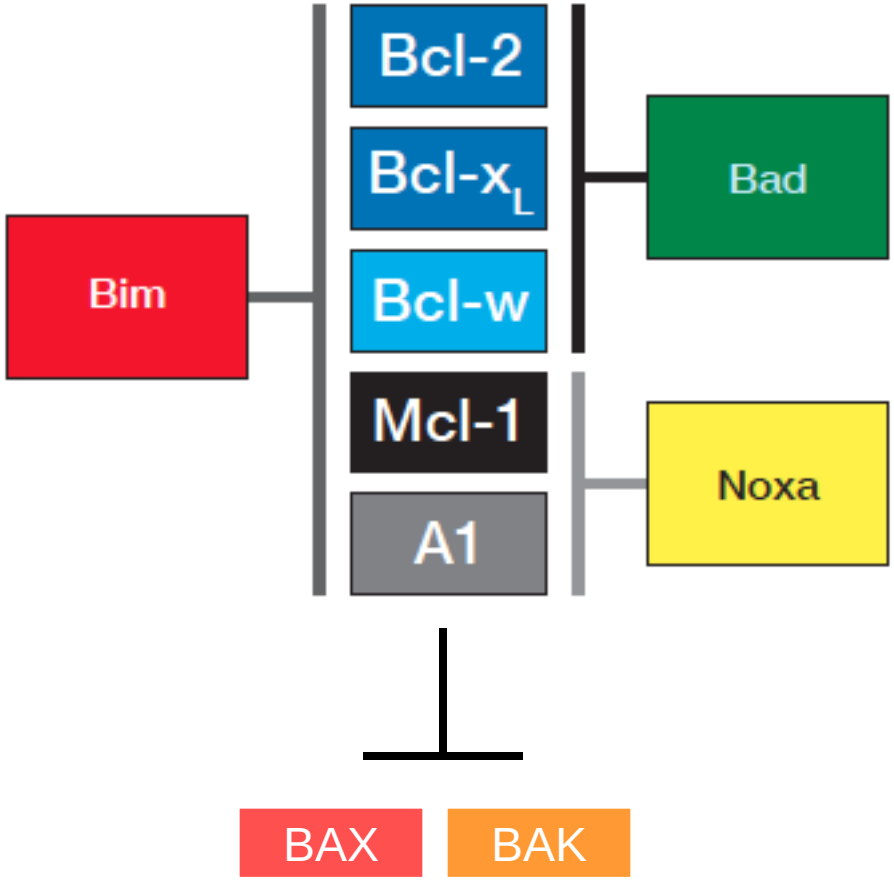
Introduction

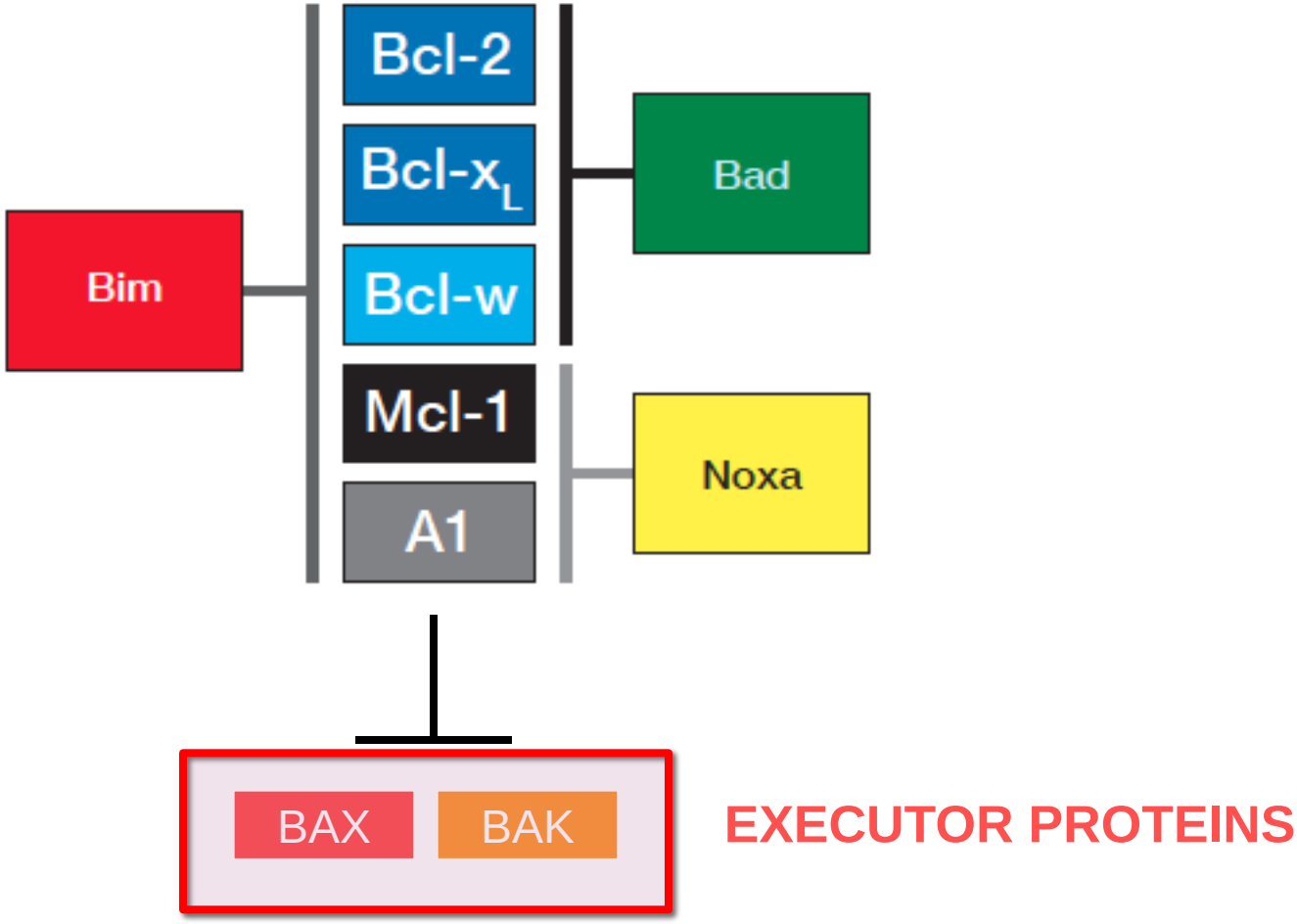
- The BCL-2 gene identified by cloning breakpoint of t(14;18) translocation (1984)
- First identified major apoptotic regulator
  - Regulate mitochondrial outer membrane permeability
- Multiple proteins in BCL-2 family
- Essentially Pro-death + pro-survival
- 3 subsets according to BCL-2 homology domains

Bcl-2 Family Proteins



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

Bcl-2 Family Proteins



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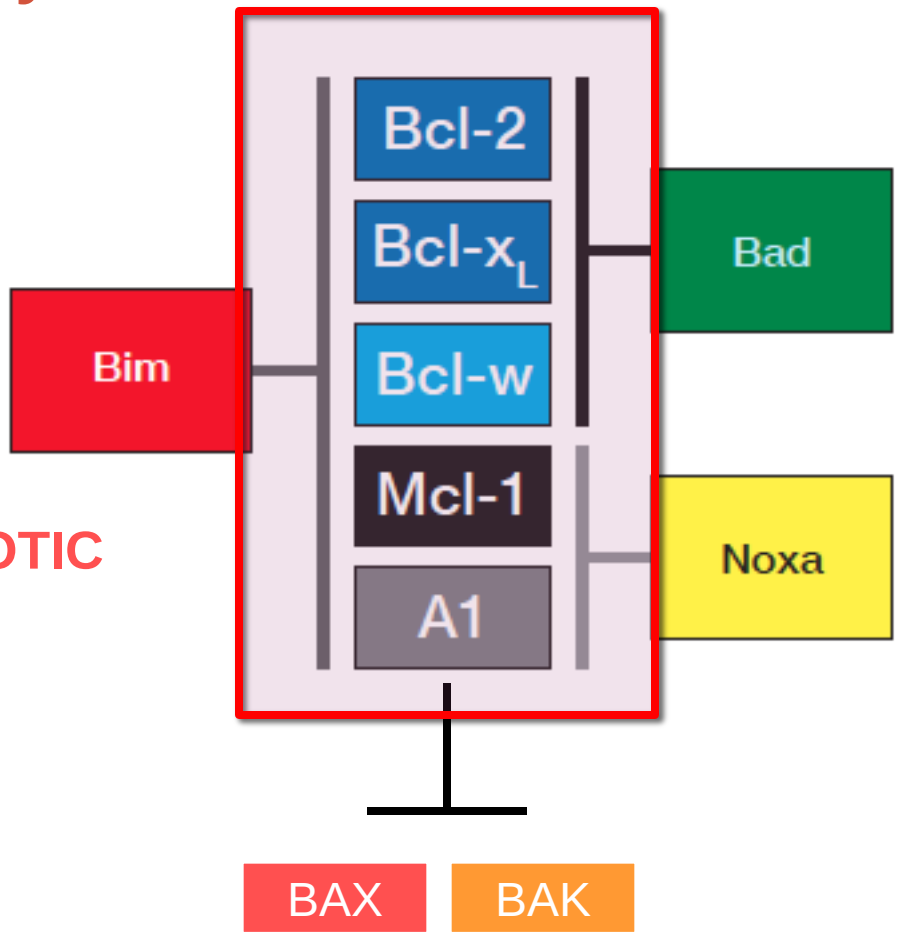
Bcl-2 Family Proteins

ANTI-APOPTOTIC PROTEINS



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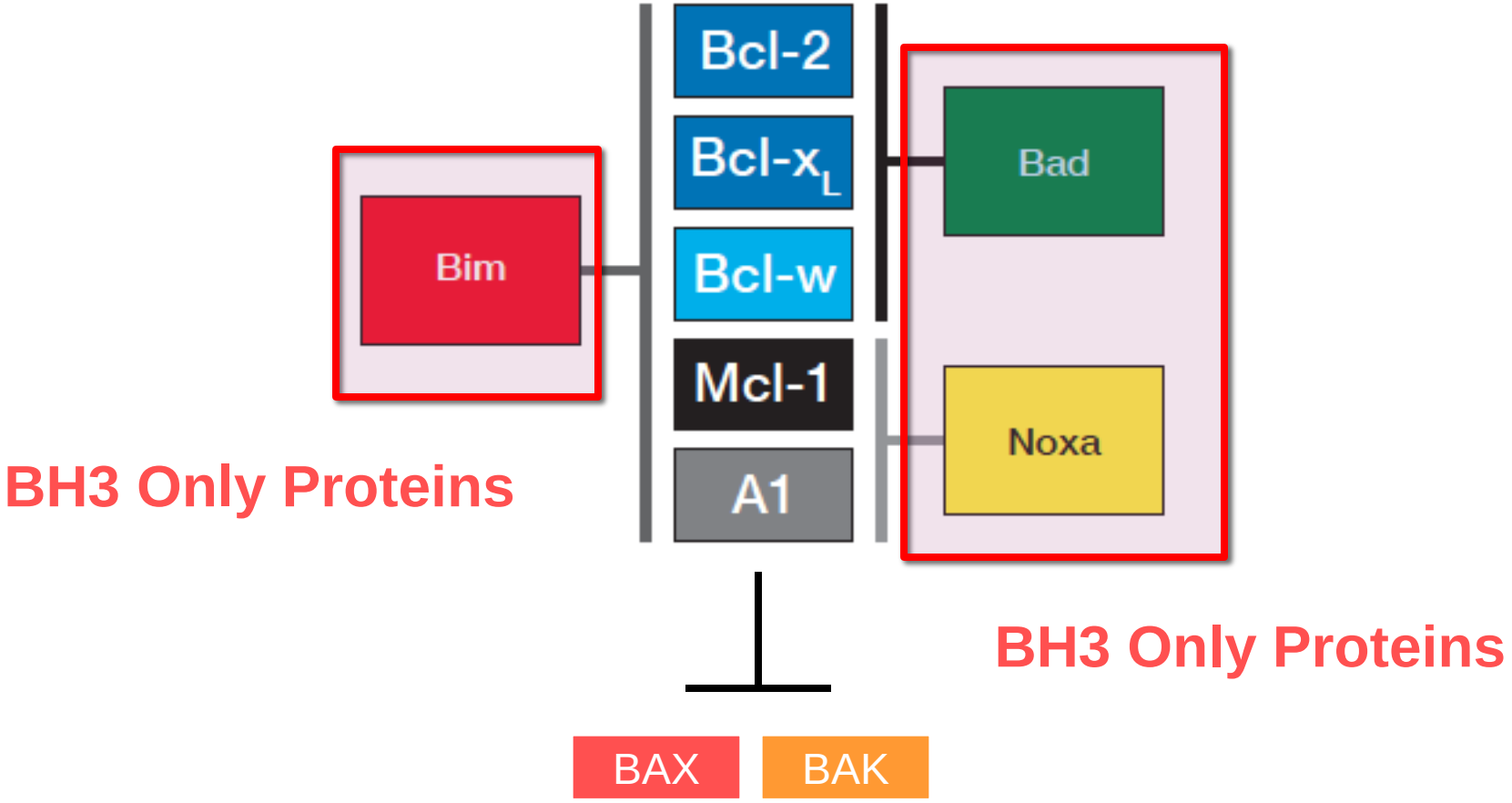
Bcl-2 Family Proteins



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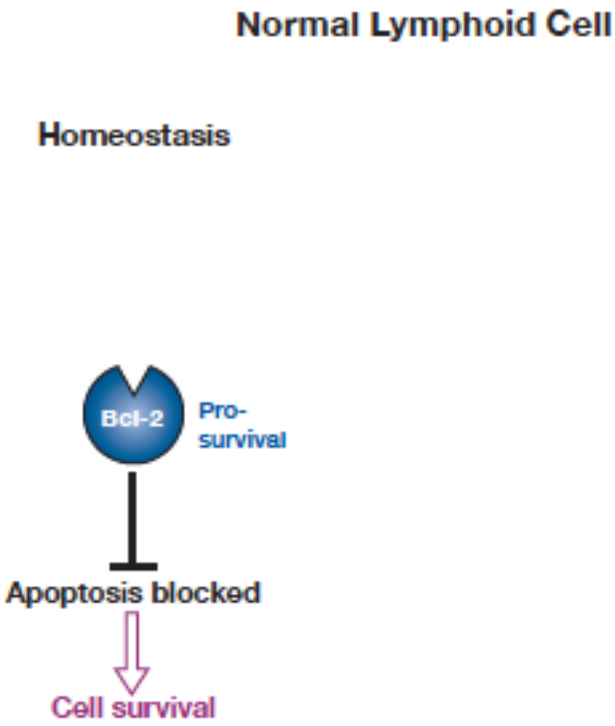
Non malignant B Cells



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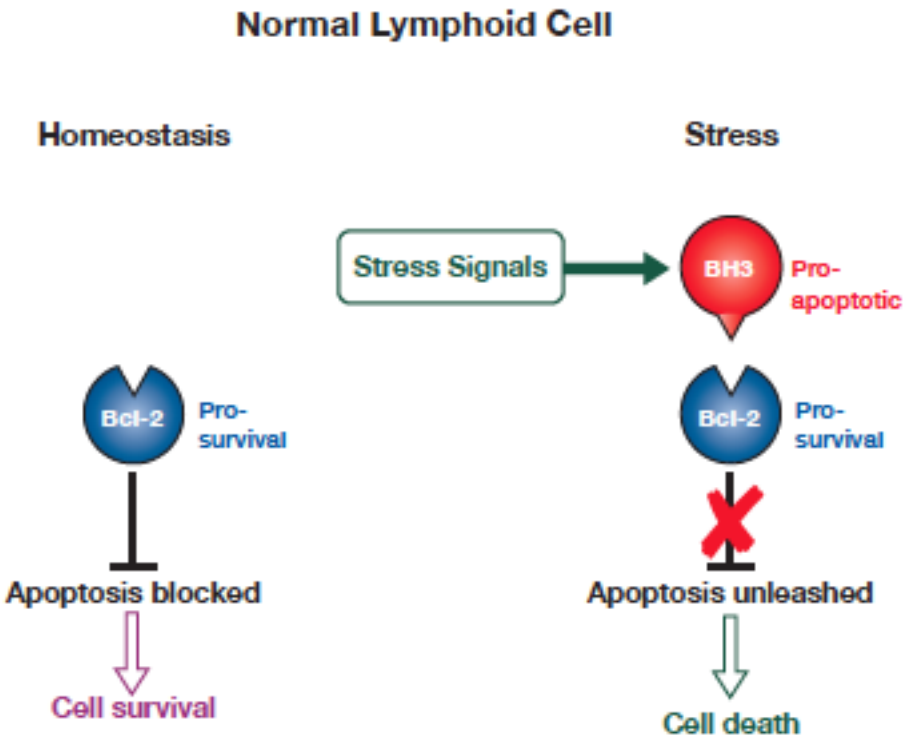
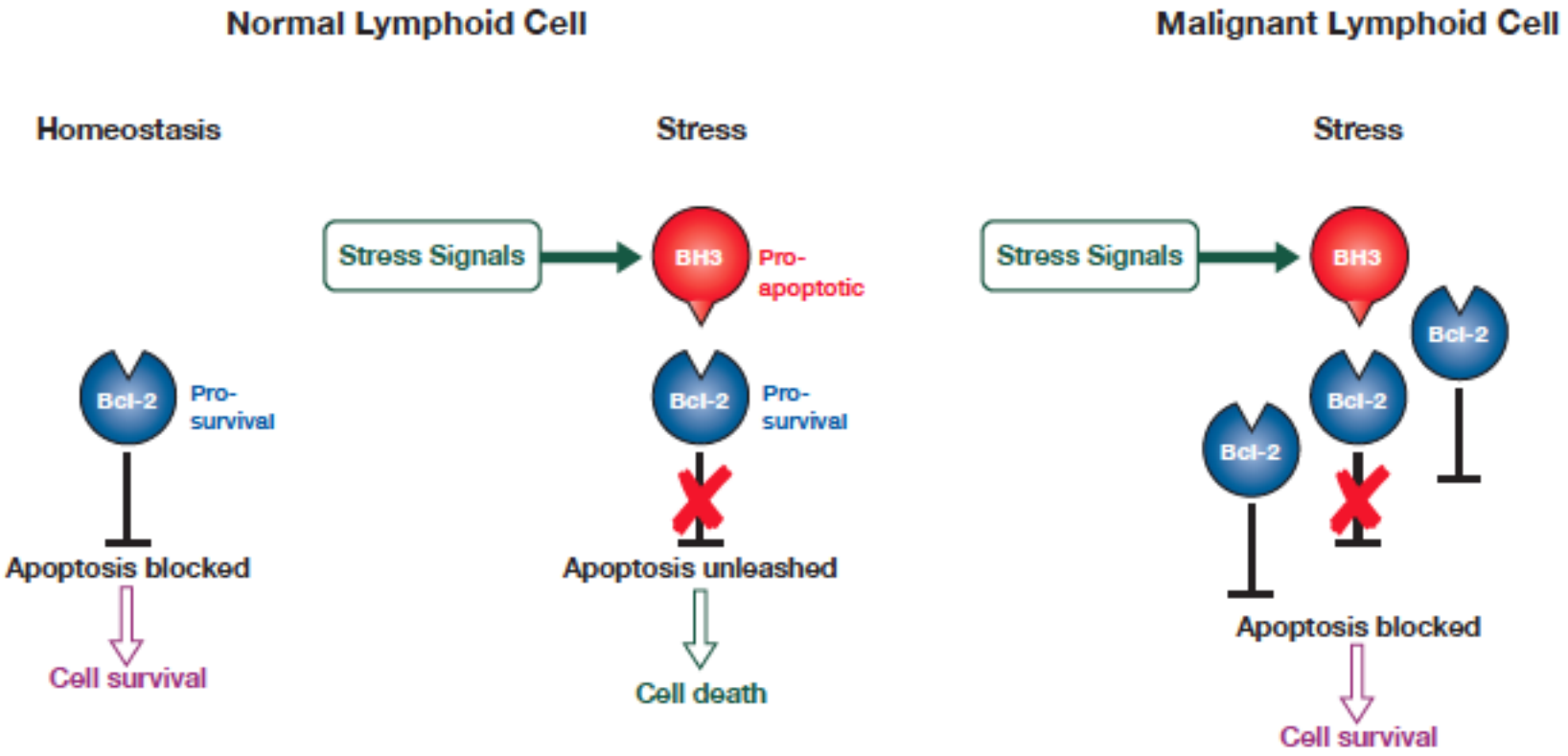
Non malignant B Cells



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

Malignant B Cells



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

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

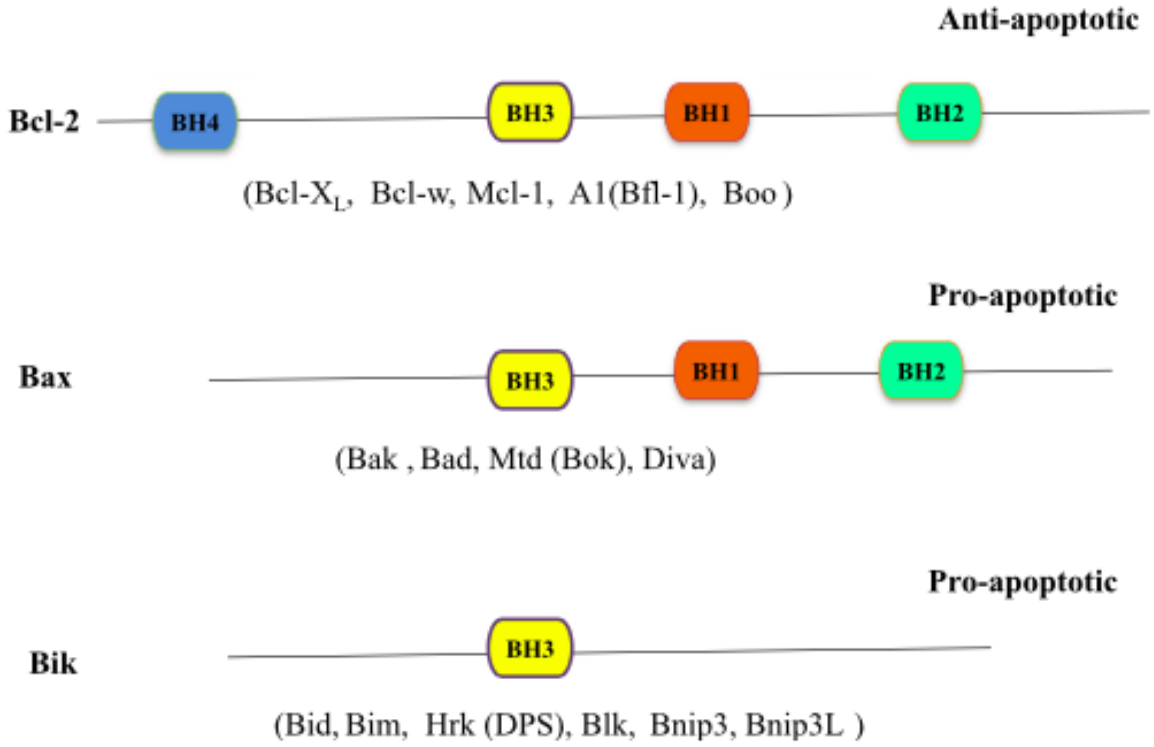
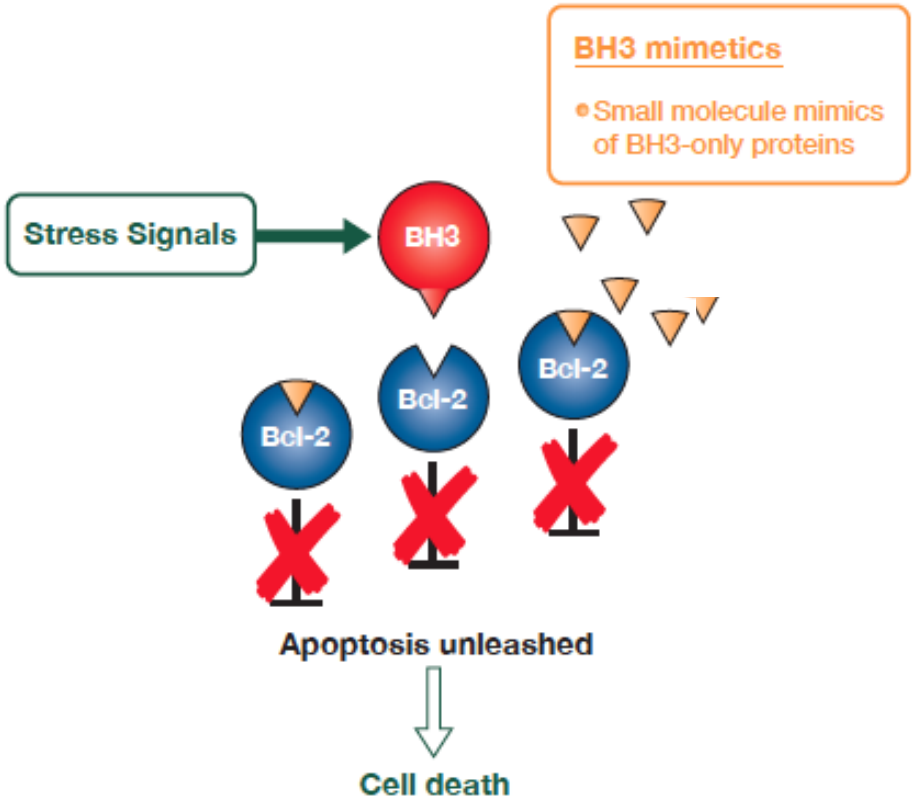


Fig. 1 Structures of BCL-2 family proteins. According to the BH domains, the BCL-2 family proteins can be categorized into three subsets. BH4-containing BCL-2 and related BCL-X_L, BCL-w, MCL-1, A1(BFL-1), and Boo are anti-apoptotic proteins. The remaining two subsets (BAX and Bik subgroups) do not have a BH4 domain and are pro-apoptotic proteins

BH3 Mimetics

BH3 mimetics

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



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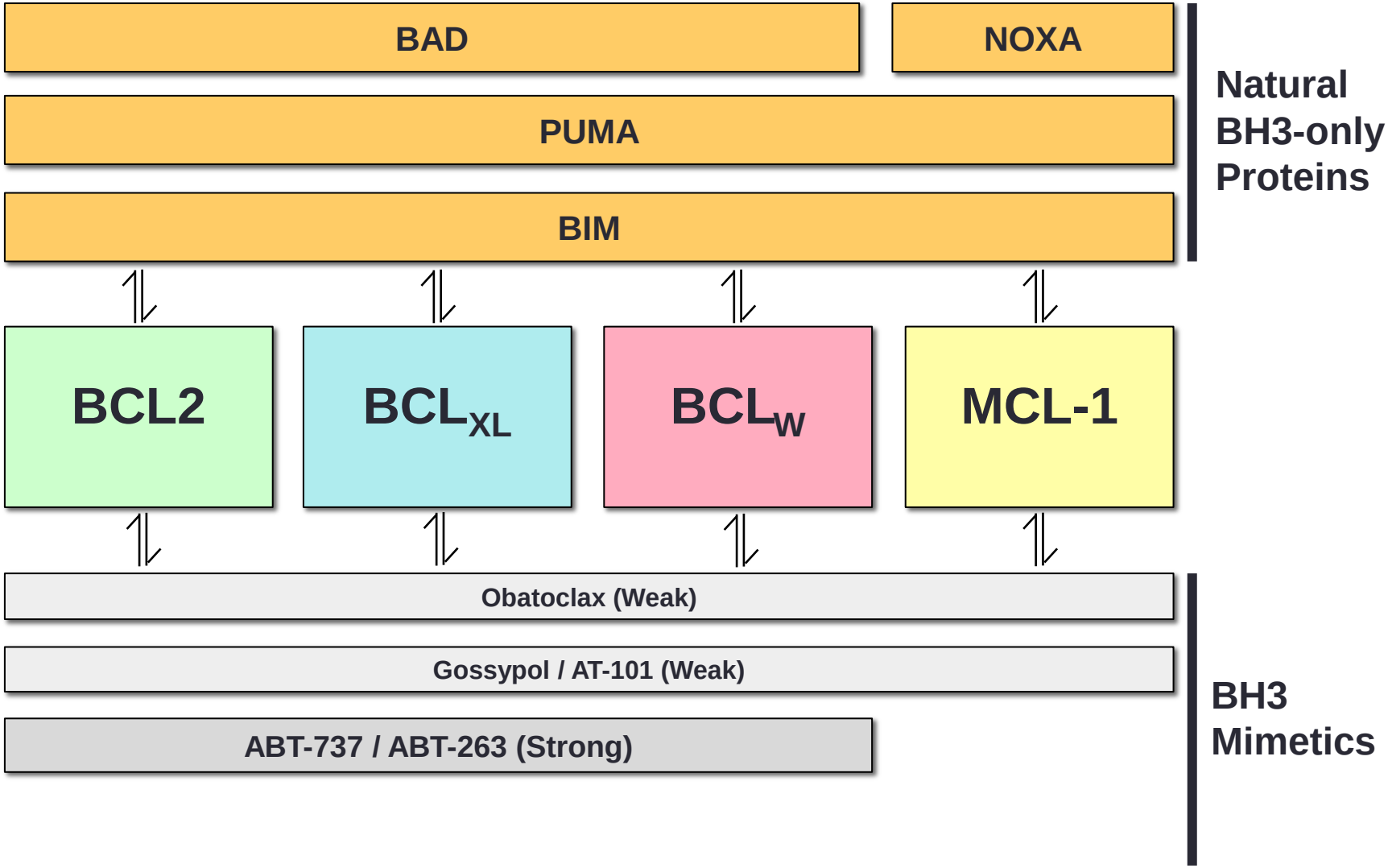
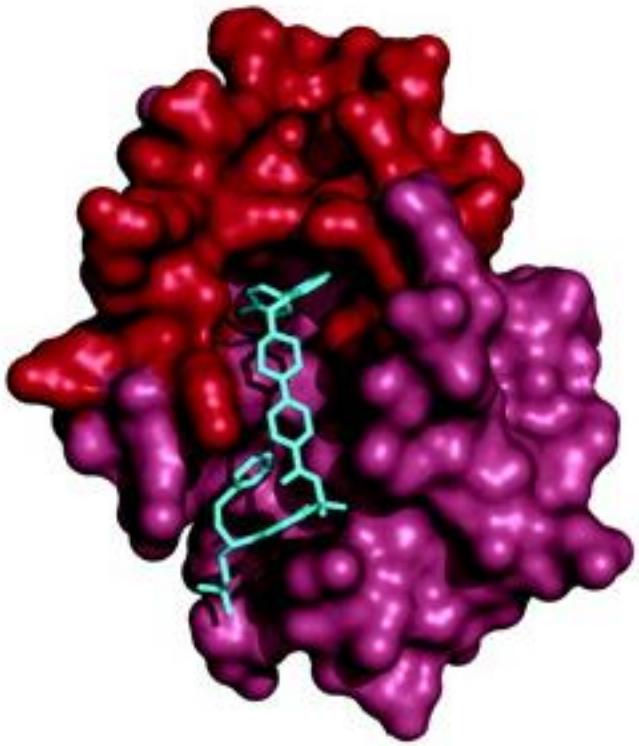
BH3-Mimetics in the Clinic



Tam Semin Oncol 2015

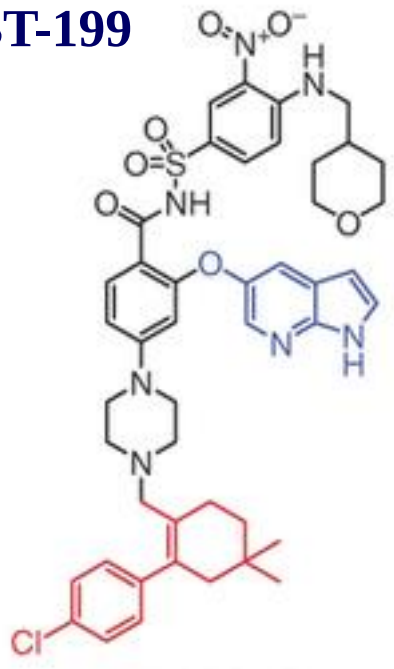
ABT-199

ABT-199 (GDC-199) Venetoclax



ABT-199 / Venetoclax : a potent and selective Bcl-2 inhibitor

ABT-199



ABT-199 Affinity

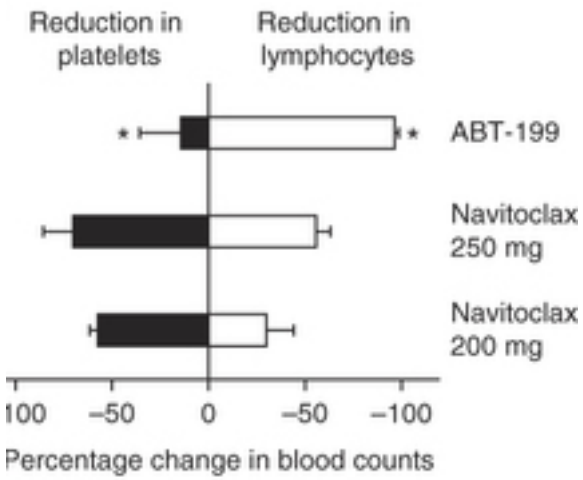
Bcl-2 < 0.01 nM

Bcl-x_L = 48nM

Bcl-w = 245nM

Mcl-1 >444nM

LLC patients



Souers et al Nature Medecine 2013

ABT-199 Venetoclax

- ABT-199 is a selective, potent, orally bioavailable, small molecule Bcl-2 inhibitor
- ABT-199 binds with high affinity to Bcl-2 and with substantially lower affinity to other Bcl-2 proteins (Bcl- x_L, Bcl-w and MCL-1)
- ABT-199 has shown preclinical activity in a wide range of hematologic malignancies as a single agent

UPDATED RESULTS OF A PHASE I FIRST-IN-HUMAN STUDY OF THE BCL-2 INHIBITOR ABT-199 (GDC-0199) IN PATIENTS WITH RELAPSED/REFRACTORY NON-HODGKIN LYMPHOMA

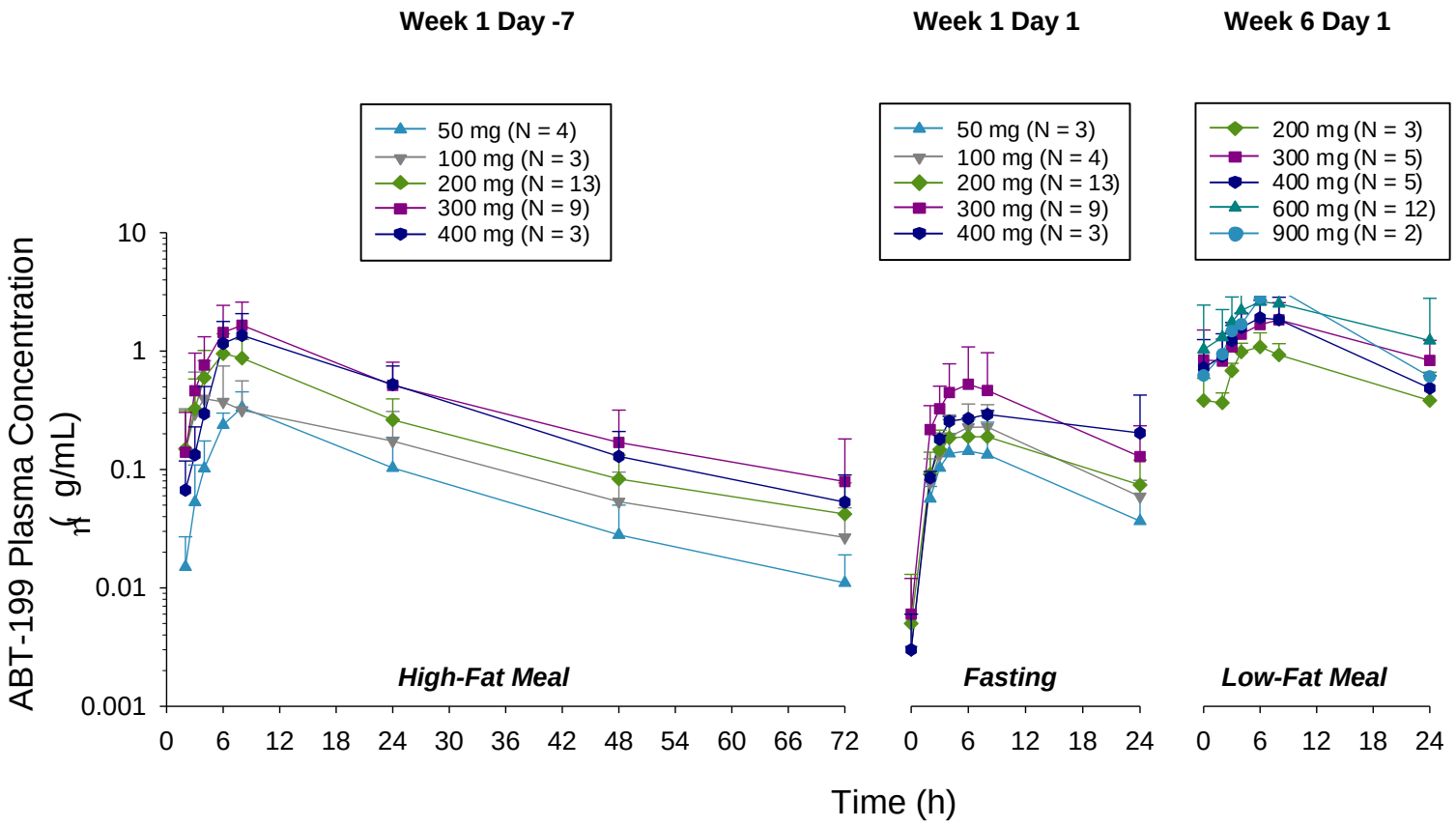
- Matthew S. Davids[1], John F. Seymour[2], John F. Gerecitano[3], Brad S. Kahl[4], John M. Pagel[5], William G. Wierda[6], Mary Ann Anderson[7,8], David E. Darden[9], Cathy E. Nolan[9], Lori A. Gressick[9], Jianning Yang[9], Todd A. Busman[9], Alison M. Graham[9], Elisa Cerri[9], Sari H. Enschede[9], Rod A. Humerickhouse[9], Andrew W. Roberts[7,8]
- [1]Dana-Farber Cancer Institute, USA; [2]Peter MacCallum Cancer Centre, Australia; [3]Memorial Sloan-Kettering Cancer Center, USA; [4]University of Wisconsin, USA; [5]University of Washington, USA; [6]University of Texas, USA; [7]Royal Melbourne Hospital, Australia; [8]Walter and Eliza Hall Institute of Medical Research, Australia, [9]AbbVie Inc., USA

Patient Dose Escalation Cohorts

	Patients Enrolled	ABT-199 Doses (mg) Weekly Escalations			
Cohort 1	3	50	100	150	<u>200</u>
Cohort 2	3	100	200	<u>300</u>	
Cohort 3	4	200	300	<u>400</u>	
Cohort 4	8	200	400	<u>600</u>	
Cohort 5[a]	10	300	<u>600</u>		
Cohort 6[b]	4	400	<u>900</u>		
TOTAL	**32**				

Designated Cohort Doses are <u>underlined.</u>
[a]Cohort 5 includes one MM patient started at 50 mg.
[b]Cohort 6 includes one MCL patient started at 200 mg.

Preliminary Pharmacokinetics of ABT-199



- After a single dose with high-fat meal: T_{max} ~ 8 hrs; $t_{1/2}$ ~ 15 hrs
- Food increased ABT-199 AUC by 3-4 fold
- Approximately dose proportional between 200 mg and 900 mg dose levels at steady state

Adverse Events in ABT-199 Treated NHL Patients

	All Grades >10% of Patients n (%)	Grades 3/4 n (%)
Nausea	13 (41)	-
Diarrhea	9 (28)	1 (3)
Pyrexia	6 (19)	1 (3)
Upper respiratory tract infection	6 (19)	1 (3)
Vomiting	6 (19)	-
Fatigue	6 (19)	-
Cough	6 (19)	-
Neutropenia	5 (16)	4 (13)
Thrombocytopenia	5 (16)	4 (13)
Constipation	5 (16)	1 (3)
Back pain	5 (16)	1 (3)
Dyspepsia	5 (16)	-
Pain in extremity	5 (16)	-
Anemia	4 (13)	4 (13)
Headache	4 (13)	-

One patient with MCL (initial dose 200 mg) experienced an AE of laboratory TLS

A PHASE 1 STUDY OF VENETOCLAX (ABT-199 / GDC-0199) MONOTHERAPY IN PATIENTS WITH RELAPSED/REFRACTORY NON-HODGKIN LYMPHOMA

John F. Gerecitano[1], Andrew W. Roberts[2,3], John F. Seymour[4], William G. Wierda[5], Brad S. Kahl[6], John M. Pagel[7], Soham Puvvada[8], Thomas J. Kipps[9], Mary Ann Anderson[2,3], Martin Dunbar[10], Ming Zhu[10], Lori Gressick[10], Lindsay Wagner[10], Su Young Kim[10], Sari Heitner Enschede[10], Rod Humerickhouse[10], Matthew S. Davids[11]

[1]Memorial Sloan-Kettering Cancer Center, USA; [2]Royal Melbourne Hospital, Australia; [3]Walter and Eliza Hall Institute of Medical Research, Australia; [4]Peter MacCallum Cancer Centre, Australia; [5]University of Texas MD Anderson Cancer Center, Houston, TX; [6]Washington University, USA; [7]Swedish Medical Center, USA; [8]University of Arizona, USA; [9]University of California San Diego, USA; [9]University of Texas, USA; [10]AbbVie, USA; [11]Dana-Farber Cancer Institute, USA

Study Overview

- This was a phase 1, open-label, multicenter study of venetoclax monotherapy in patients with:
  - Relapsed/refractory chronic lymphocytic leukemia, CLL (Arm A)
  - Relapsed/refractory NHL (Arm B)

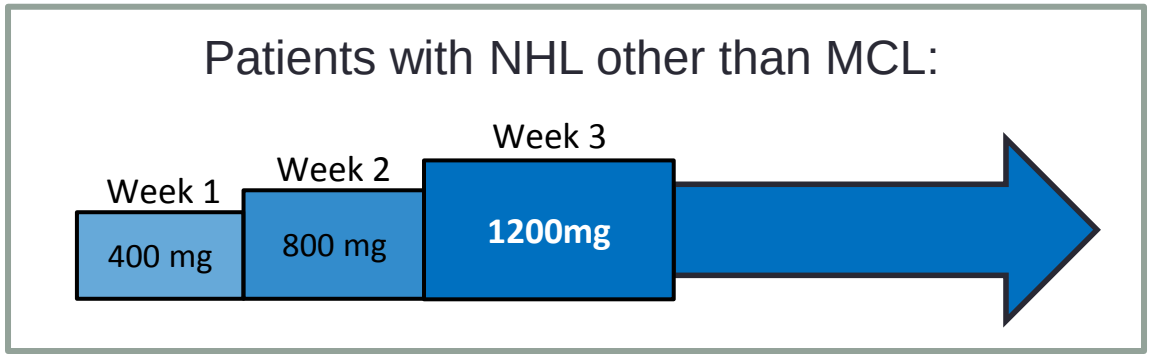
- Objectives:
  - Determine safety, maximum tolerated dose and recommended phase 2 dose and evaluate pharmacokinetics
  - Assess preliminary efficacy (ORR, PFS, OS, DoR)
  - Evaluate biomarkers and pharmacogenetics

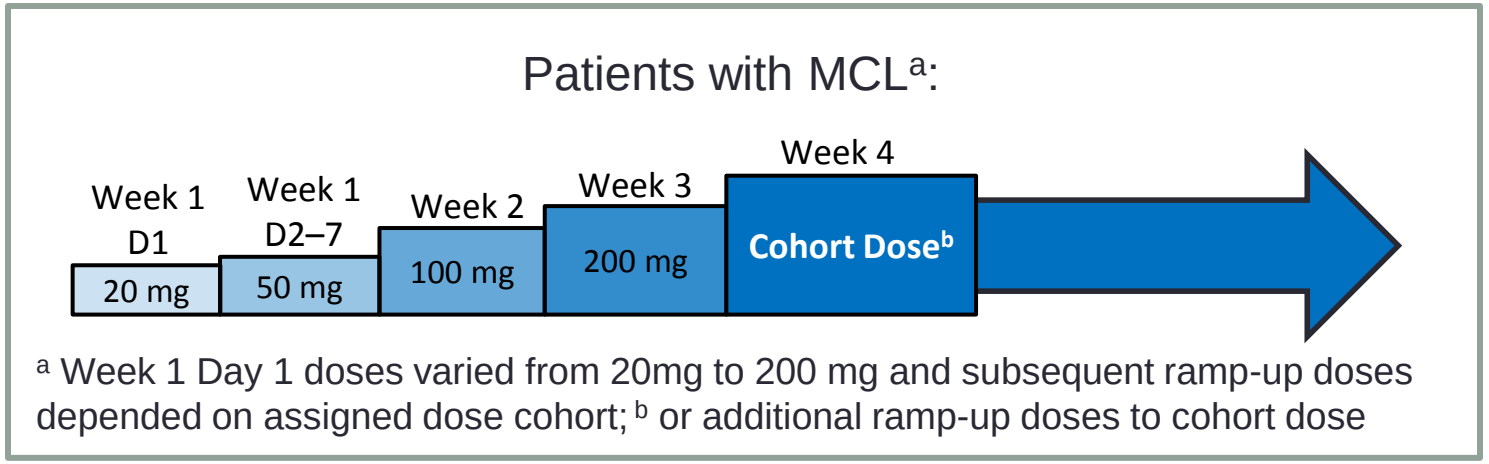
Arm B NHL Overview

- Inclusion criteria:
  - Relapsed or refractory NHL
  - ECOG Score ≤1
  - Adequate bone marrow function independent of growth factor support
- Exclusion criteria:
  - Prior allogeneic stem cell transplant
  - ≤6 months post-autologous transplant
  - Post-Transplant Lymphoproliferative Disease, Burkitt or Burkitt-like lymphoma, lymphoblastic lymphoma/leukemia
- Assessments:
  - Adverse events (AEs) were graded according to NCI-CTCAE version 4.0
  - Responses were assessed using 2007 IWG response criteria including CT scans beginning at week 6 and the 4th iwWM criteria

Venetoclax Escalation Strategy

- 70 patients with R/R NHL (multiple histology subtypes) were enrolled in dose-escalation cohorts (target daily dose: 200 – 1200mg)
- 15 patients with FL and 21 with DLBCL were enrolled in a safety expansion cohort (target daily dose: 1200 mg)





Patient Characteristics

Characteristic, n (%)		All N=106	MCL n=28	FL n=29	DLBCL n=41 [a]	Other [b] n=8
Age, years	Median (range)	66 (25–86)	72 (35–85)	64 (46–75)	67 (25–86)	63 (56–73)
Prior therapies	Median (range)	3 (1–10)	3 (1–7)	3 (1–10)	3 (1–8)	4 (2–6)
	Rituximab-refractory	33 (31)	8 (29)	8 (28)	16 (39)	1 (33)
Bulky nodes	>5 cm	49 (48)	16 (59)	8 (29)	22 (54)	3 (38)
	>10 cm	14 (14)	3 (11)	2 (7)	8 (20)	1 (13)
LDH	> Upper Limit of Normal	45 (44)	7 (27)	10 (35)	27 (68)	1 (13)

[a] Includes 7 patients DLBCL-Richter's transformation
[b] Includes n=4 WM, n=3 MZL, n=1 MM

As of September 15, 2015

Treatment-Emergent Adverse Events

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)

As of September 15, 2015

Treatment-Emergent Adverse Events

- There were two dose-limiting toxicities, both in the 600mg cohort:
  - Grade 3 febrile neutropenia (DLBCL) that resolved after a 2 day study drug interruption
  - Grade 4 neutropenia (DLBCL-RT) that resolved after pegfilgrastim and a 9 day study drug interruption

- There were two events of laboratory tumor lysis syndrome without clinical sequelae in patients with high-risk disease (maximum tumor burden >10 cm)
  - 1 (MCL) after 200mg (Day 1); resumed at same dose (Day 8)
    - Elevated phosphate (1.82 mmol/L; >1.45 mmol/L) and potassium (5.4 mmol/L; >25% increase from baseline of 4.2 mmol/L)
  - 1 (DLBCL-RT) after 300mg (Day 1); resumed at same dose (Day 8)
    - Elevated phosphate (1.49 mmol/L; >1.45 mmol/L) and uric acid (309 µmol/L; >25% increase from baseline of 220 µmol/L)

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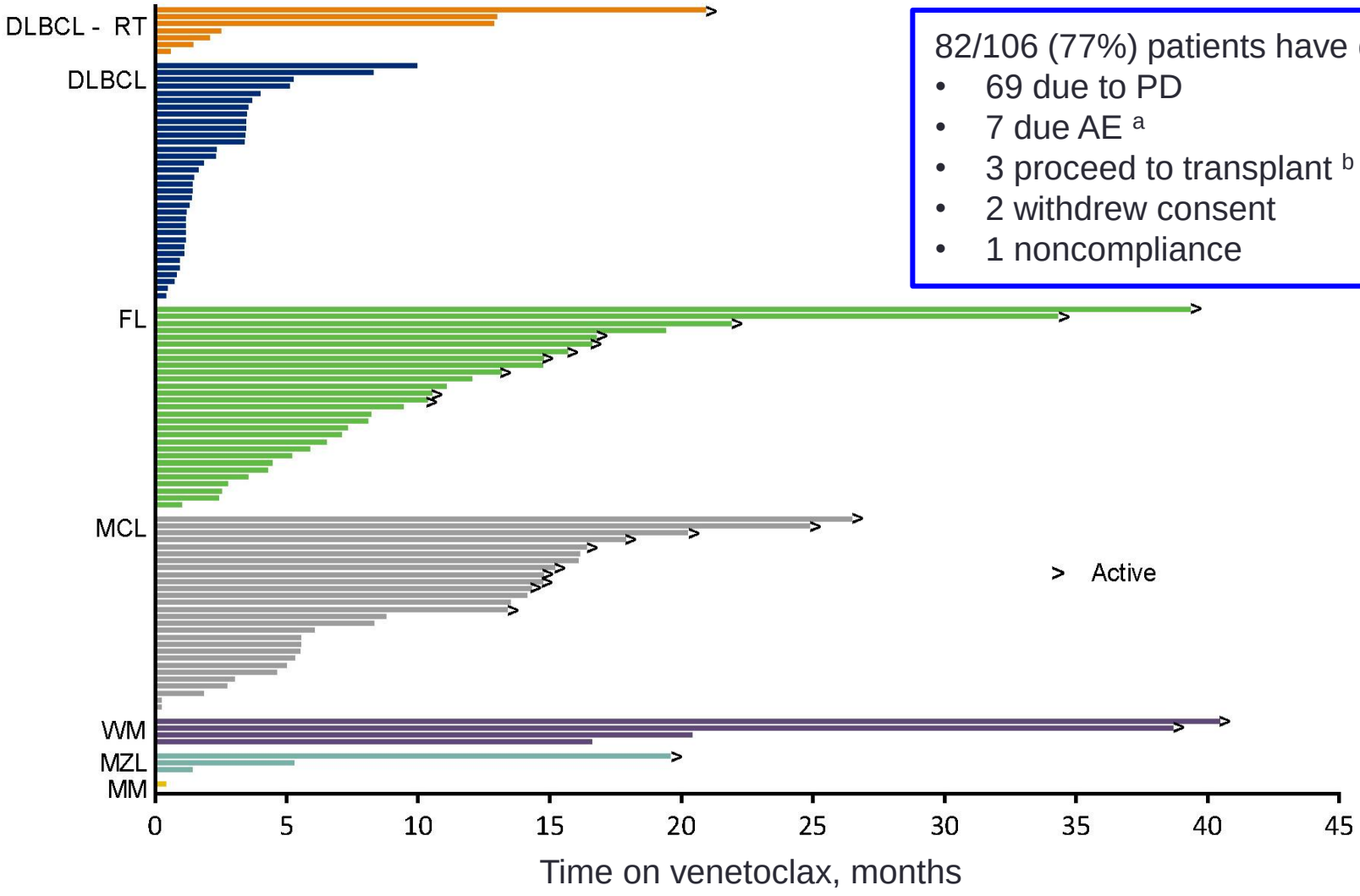
Current Status



82/106 (77%) patients have discontinued

- 69 due to PD
- 7 due 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

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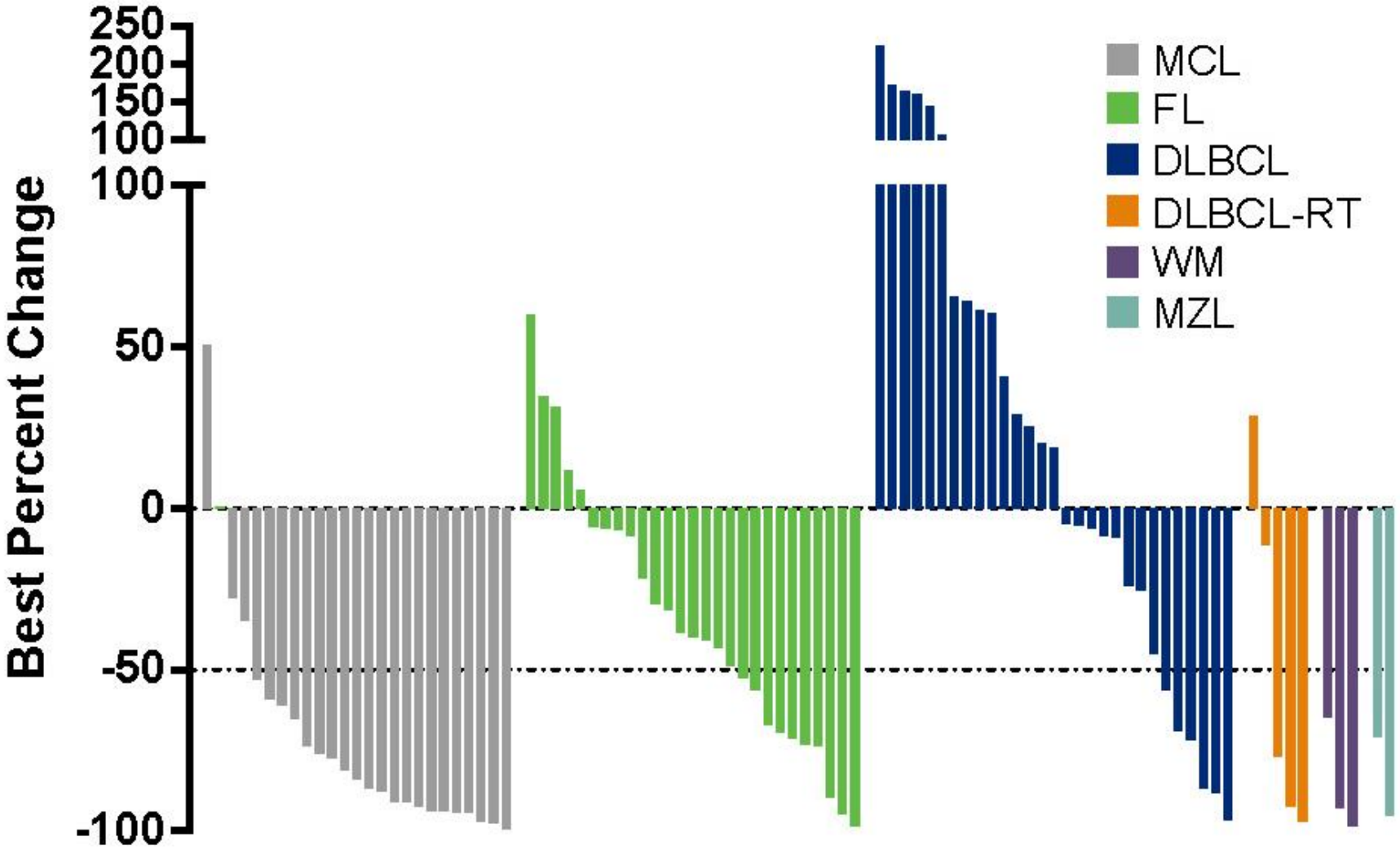
Best Percent Change From Baseline in Nodal Mass by CT Scan



As of September 15, 2015

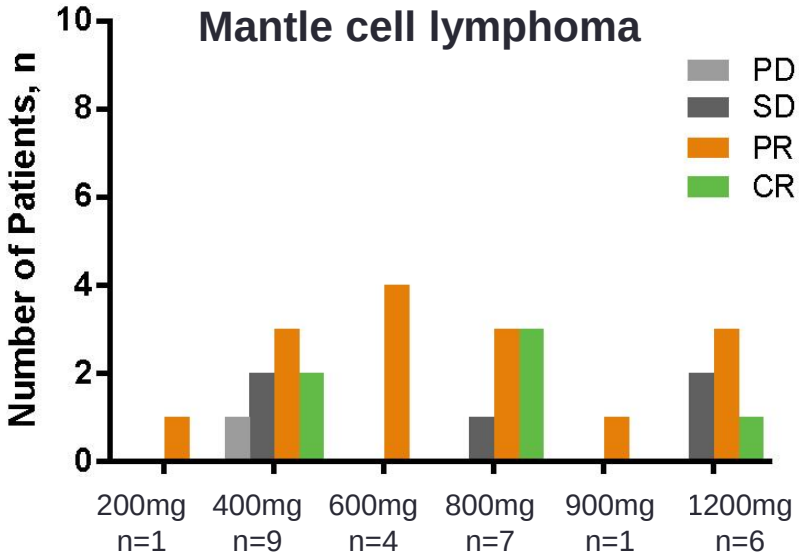
Objective Responses by Histology – All Doses

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

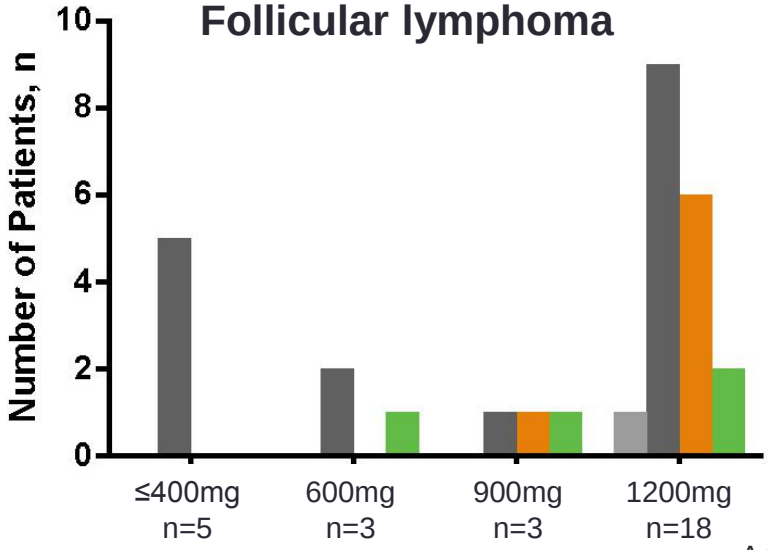
- 4 patients discontinued prior to assessment
- n=1 with MM had PD

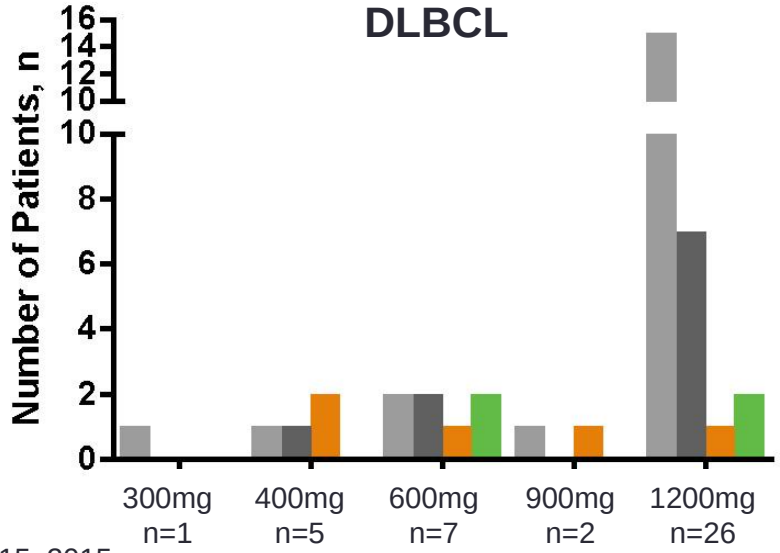
As of September 15, 2015

Objective Responses by Dose Cohorts



- MCL: Objective responses were observed across dose cohorts
- FL : Objective responses were more common at higher doses, including the 1200 mg dose evaluated in the safety expansion cohort

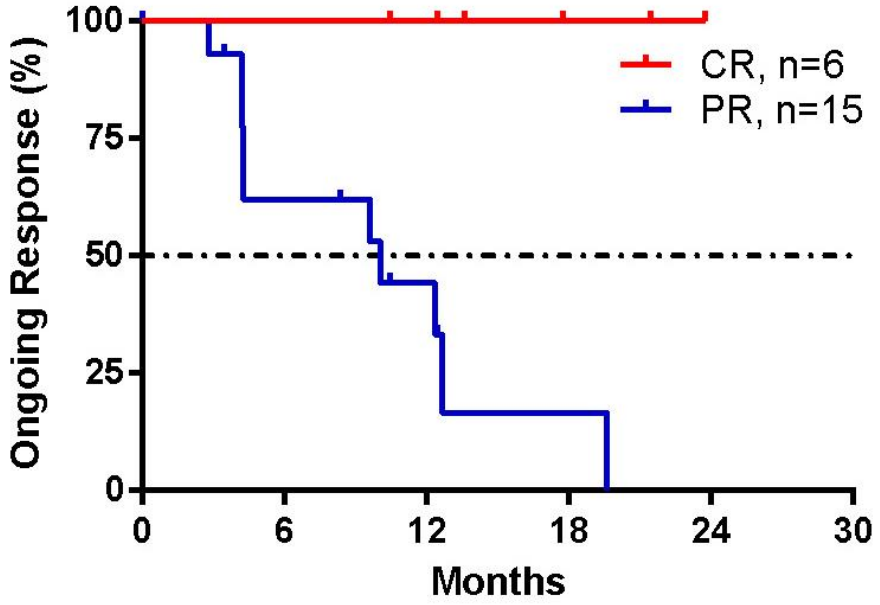




As of September 15, 2015

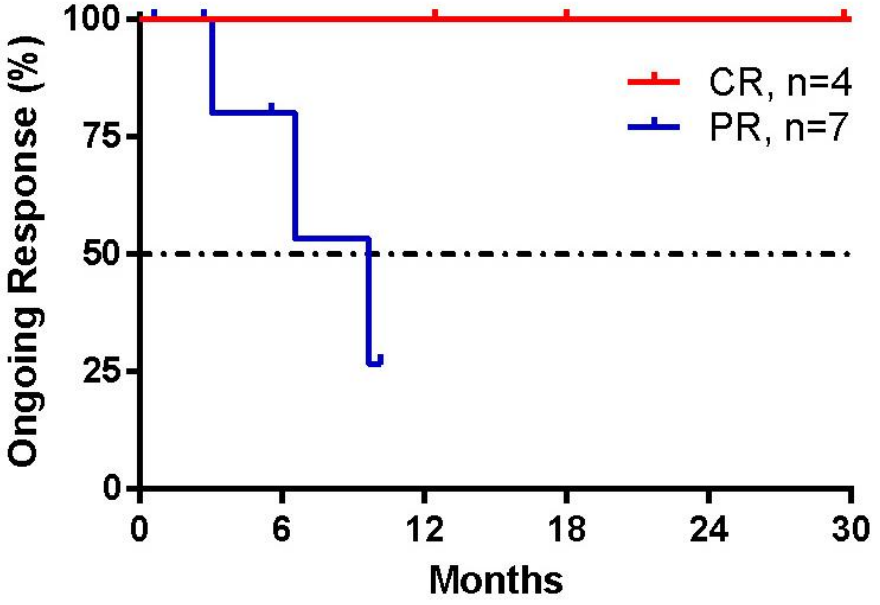
Duration of Response in MCL and FL

Mantle cell lymphoma



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

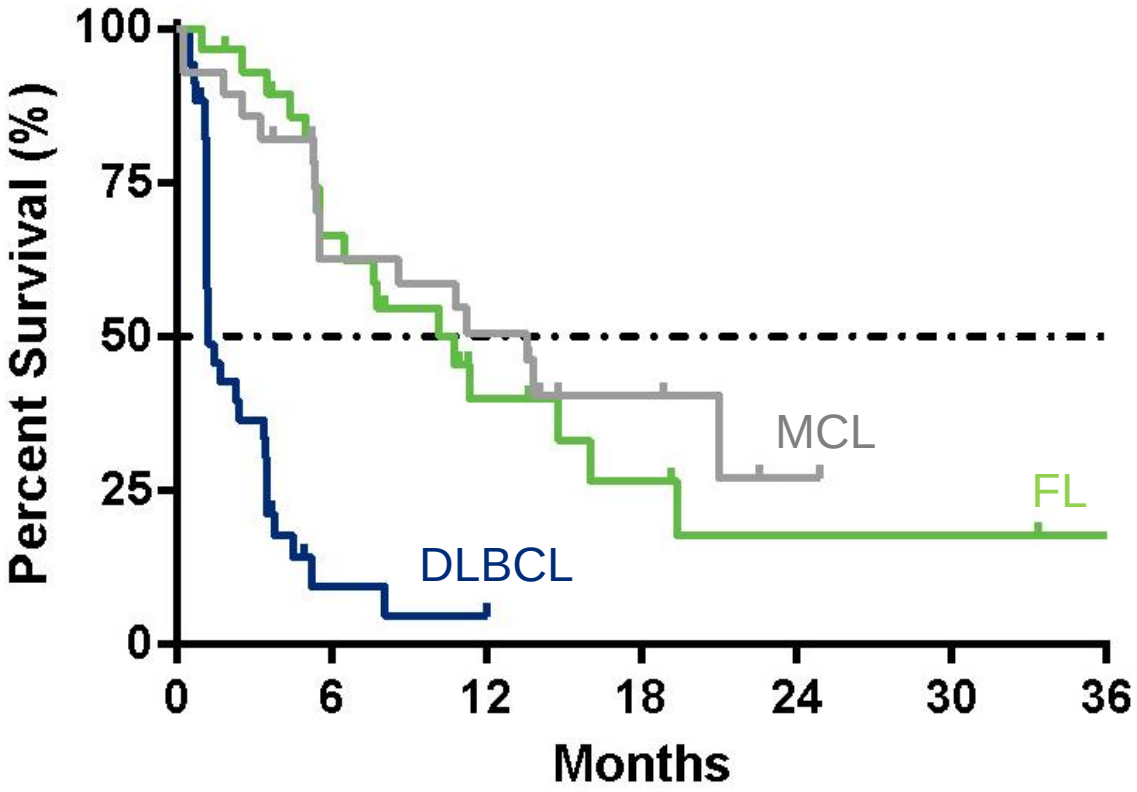
Follicular lymphoma



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

As of September 15, 2015

Progression-Free Survival by Histology Subtype

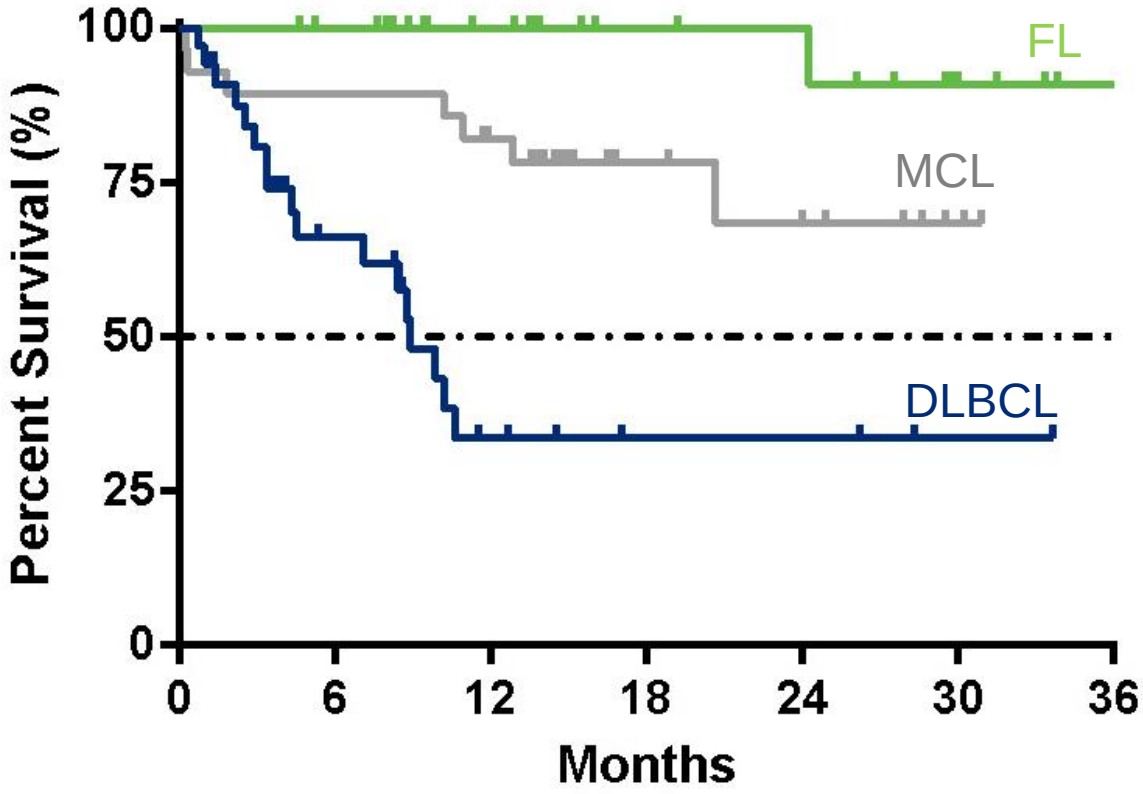


MCL:	28	16	12	4	1		
FL:	29	17	7	4	2	1	1
DLBCL:	34	2					

	Median PFS, Months (95% CI)
All, n=106	17 (14, 22)
MCL, n=28	14 (ND)
FL, n=29	11 (6, 19)
DLBCL, n=34	1 (1, 3)

As of September 15, 2015

Overall Survival by Histology Subtype



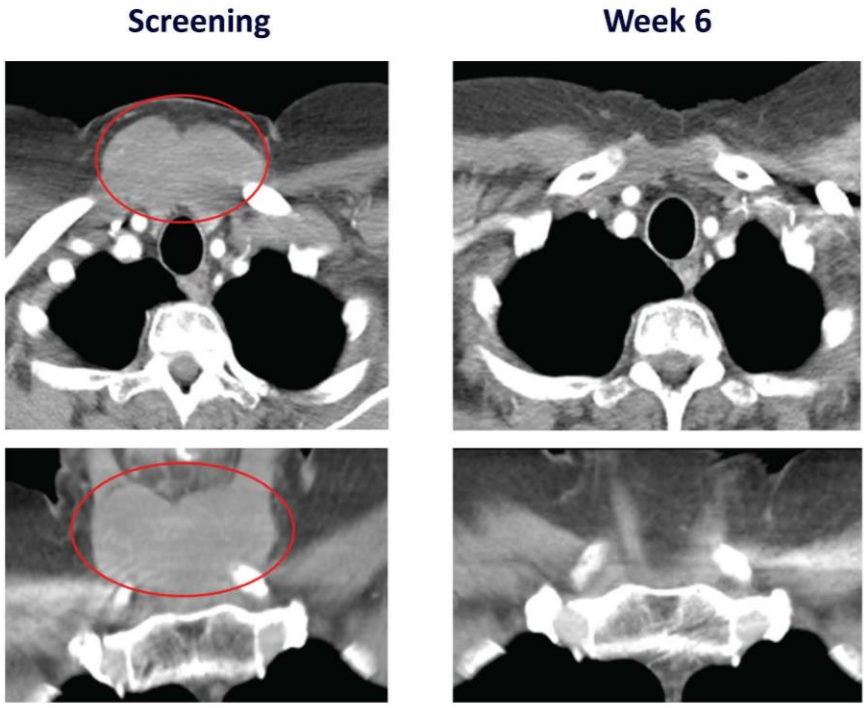
FL:	29	27	19	12	11	5	2
MCL:	28	25	21	9	7	2	
DLBCL:	34	16	6	3	3	1	

	12-month OS estimate
All, n=106	72%
FL, n=29	100%
MCL, n=28	82%
DLBCL, n=34	34%

As of September 15, 2015

ABT-199 Anti-tumor Activity in MCL Patient

- 66 year old female, diagnosed with Stage II MCL in May 2007
- Prior therapy (and best response):
  - 2007: 6 cycles R-CHOP, IFRT of residual mass (PR)
  - 2010: 2 cycles R-ICE (PR) then BEAM autograft with IFRT of residual mass 2011 (PR)
  - 2012: IFRT (PD)
- 2013: Referred for treatment of supramediastinal mass 7.6 x 3.6 cm with ABT-199
- Complete clinical resolution of node after 6 weeks of study drug and remains in CR for > 8 months



ABT Slide courtesy of John Seymour

Table 2 Clinical trials of venetoclax/ABT-199 in combination regimens

Clinical trials	Regimens	Diseases	Responses	References
Phase Ib	V + R	R/R CLL	ORR—88 % CR/CRi—32 % PR—56 %	86, 87
Phase I	V + BR	R/R NHL	ORR—61.5 %	89
Phase Ib	V + BR	R/R CLL Untreated CLL	Not reported	90
Phase Ib	V + O	R/R CLL Untreated CLL	Not reported	91

R/R relapsed/refractory, *ORR* overall response rate, *CLL* chronic lymphoid leukemia, *NHL* non-Hodgkin's lymphoma, *AML* acute myeloid leukemia. For regimens: *V* venetoclax, *R* rituximab, *B* bendamustine, *O* obinutuzumab

ABT + BR (de Vos ASH 2015)

- Standard dose BR with ABT + 2 yr ABT
- Cycle length ABT (3d,7d,28d)
- 47 patients (FL, DLBCL, MZ)
- On- going DLT not reached

Toxicity

- Nausea (51%), Diarrhoea (30%), Fatigue (30%)
- Haematological (III/IV)
  - 32% neutropenia
  - 21% Thrombocytopenia / Anaemia
  - Anaemia 15%
  - Febrile neutropenia (SAE) 9%

ABT 199 plus BR

Table 1: Responses in evaluable patients per NHL histology subgroups

Response, n (%)	FL	DLBCL	MZL	Total
Evaluable patients	23	13	4	40
Objective response (CR + PR) *(Dose range)*	20 (87) *(50 mg–600 mg)*	6 (46) *(100 mg–600 mg)*	3 (75) *(50 mg–400 mg)*	29 (73)
Complete response *(Dose range)*	7 (30) *(50 mg–600 mg)*	2 (15) *(400 mg–600 mg)*	1 (25) *(400 mg)*	10 (25)
Partial response *(Dose range)*	13 (57) *(50 mg–600 mg)*	4 (31) *(100 mg–400 mg)*	2 (50) *(50 mg–100 mg)*	19 (48)
Stable disease *(Dose range)*	1 (4) *(50 mg)*	2 (15) *(100 mg)*	1 (25) *(600 mg)*	4 (10)
Progressive disease *(Dose range)*	2 (9) *(200 mg)*	5 (38) *(100 mg–400 mg)*	0	7 (18)
Incomplete data	4	2	1	7

CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin's lymphoma; PR, partial response.

Sven de Vos et al. Blood 2015;126:255

Combination Trials (Clinical trials.gov)

- Duvelisib + Venetoclax (NHL + CLL)
- GA101 + Polatuzumab Vedotin + Venetoclax (FL/DLBCL)
- Ibrutinib + Venetoclax (MCL)

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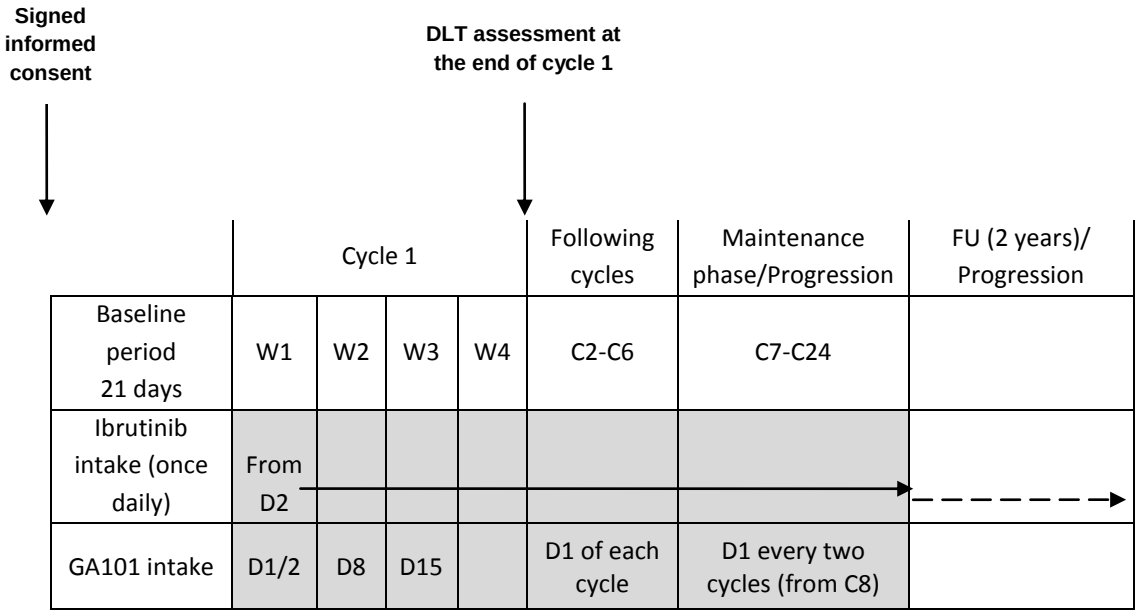
STUDY DESIGN: step A (n=9)

Cycle 1	Cycle 2-6	From Cycle 7 – maintenance phase
Ibrutinib 560mg day 2 – 28 GA101 1000mg day 1/2,8,15	Ibrutinib 560mg day 1-28 GA101 1000mg day 1	**Ibrutinib** 560mg day 1-28 for 18 months and until progression at investigator discretion **GA101** 1000mg day 1 every 2 cycles for 18 months (from C8)



STUDY DESIGN: STEP B (n=24)

Cycle 1	Cycle 2-6	From Cycle 7 – maintenance phase
Ibrutinib 560mg day 2 – 28 GA101 1000mg day 1/2,8,15	Ibrutinib 560mg day 1-28 GA101 1000mg day 1 **GDC-0199** : 100mg/d at W1, 200mg/d at W2, 400, mg/d at W3 and 400, 600, 800 or 1000 mg/d at W4 followed by 400, 600, 800 or 1000 mg/d from C3 to C6	**Ibrutinib** 560mg day 1-28 for 18 months and until progression at investigator discretion **GA101** 1000mg day 1 every 2 cycles for 18 months (from C8) **GDC-0199** : 400, 600, 800 or 1000 mg day 1-28 for 18 months

Signed informed consent ↓ **Administration of GDC-0199** ↓ **DLT assessment at the end of cycle 2** ↓

	Cycle 1				Cycle 2				Following cycles	Maintenance phase/Progression	FU (2 years)/ Progression
Baseline period 21 days	W1	W2	W3	W4	W1	W2	W3	W4	C3-C6	C7-C24	
Ibrutinib intake (once daily)	From D2 →									→	- - - - - →
GA101 intake	D1/2	D8	D15		D1				D1 at each cycle	D1 every two cycles (from C8)	
GDC-0199 intake (once daily)					→					→	