Bcl-2 inhibition in NHL

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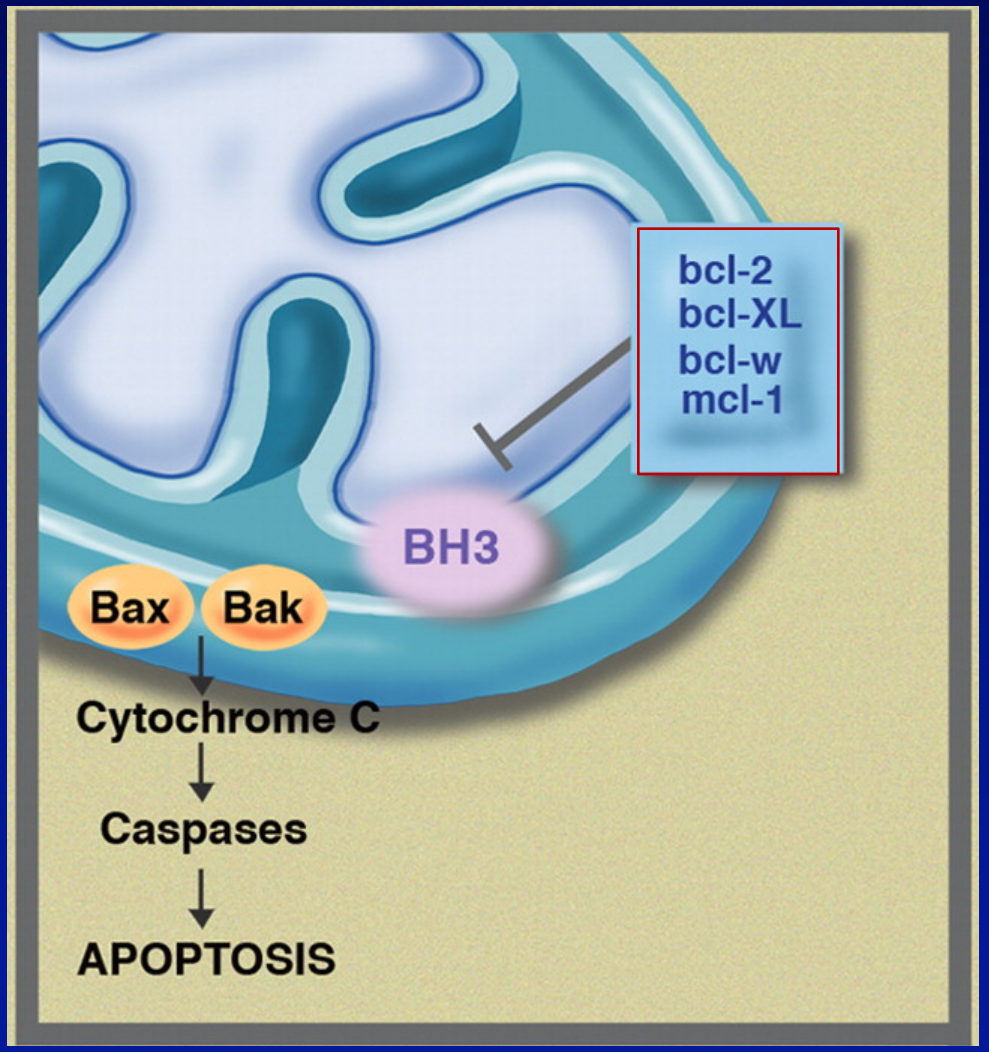
BCL-2, BH3 and apoptosis: Rational therapeutic targets in NHL

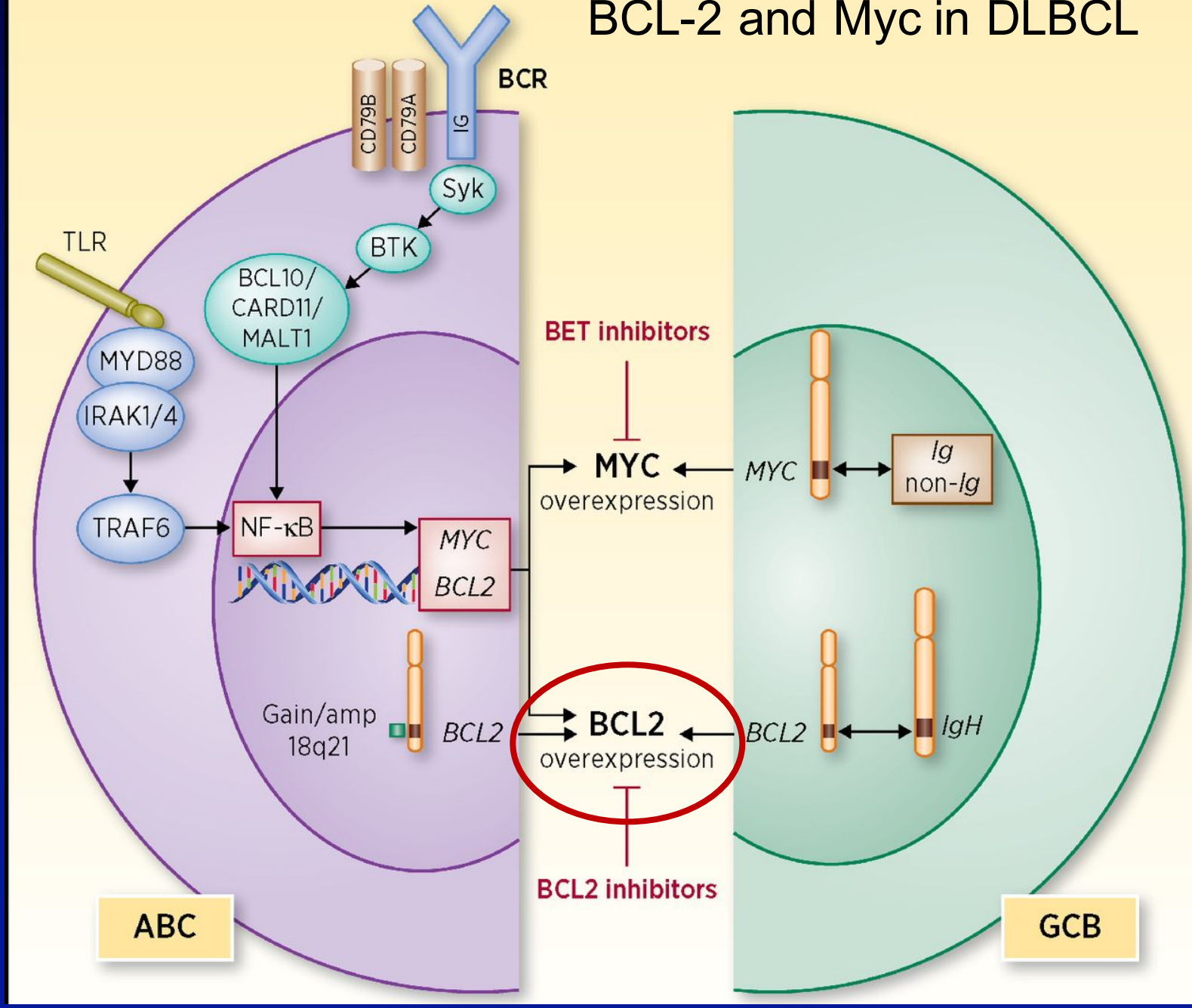
Antiapoptotic proteins, prevent activation of Bax and Bak, thus inhibiting apoptosis.

Pure BH3 mimetics, such as AT-101, allow activation of Bax and Bak, enhancing apoptosis.



Friedberg *Blood* 111:5263 2008

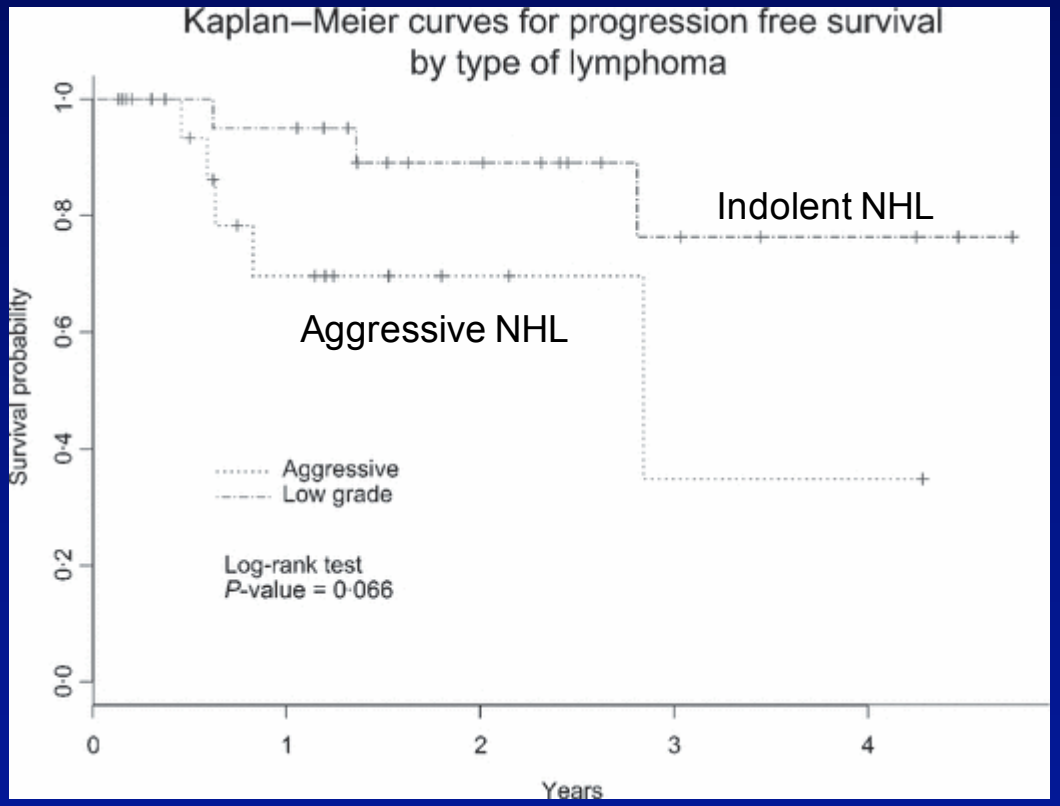
BCL-2 and Myc in DLBCL



Mottok A , and Gascoyne R *Clin Cancer Res* 2015;21:4-6

Oblimersen Sodium (bcl-2 antisense) and Rituximab for NHL

- Single arm nonrandomized trial.
- 70% prior rituximab
- 42 evaluable pts:
  - FL ORR 60%; 8CR
  - MCL ORR 20%
  - DLBCL ORR 28%
- Myelosuppression main toxicity
- Drug developed in melanoma and CLL; not approved.



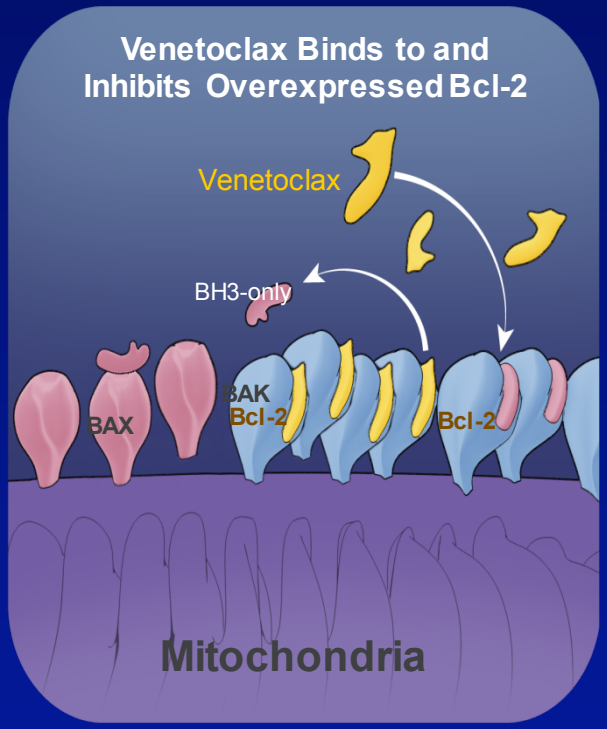
Pro et al, *British Journal Haematology* 143:355 2008

Venetoclax, a small molecule Bcl-2 inhibitor, tips balance toward apoptosis

High affinity for Bcl-2

Low affinity for Bcl-XL, MCL-1, Bcl-W

Activates apoptosis by disrupting Bcl-2 and BH3 interactions, leading to BH3 death signals in cell.

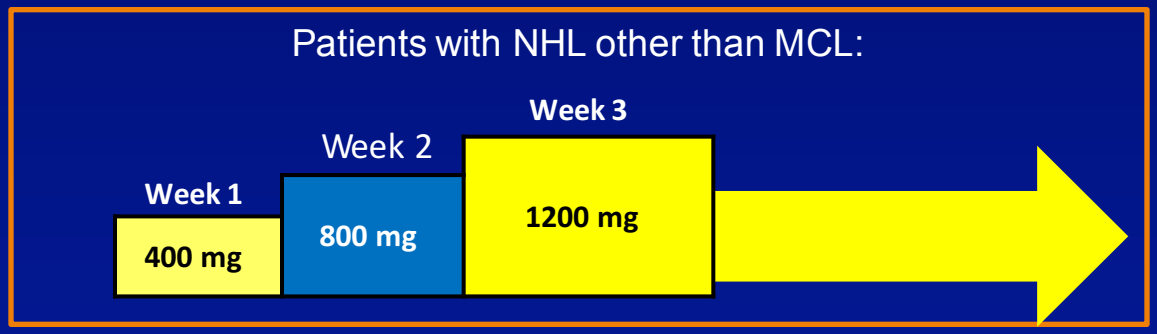


A Phase 1 Study of Venetoclax (ABT-199 / GDC-0199) Monotherapy in Patients with Relapsed/Refractory Non-Hodgkin Lymphoma

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]

Venetoclax Phase 1 Strategy

- 70 patients with R/R NHL 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)



Step-up dosing used to avoid tumor lysis; more prolonged step-up for MCL

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

Phase 1 venetoclax in NHL: Adverse Events

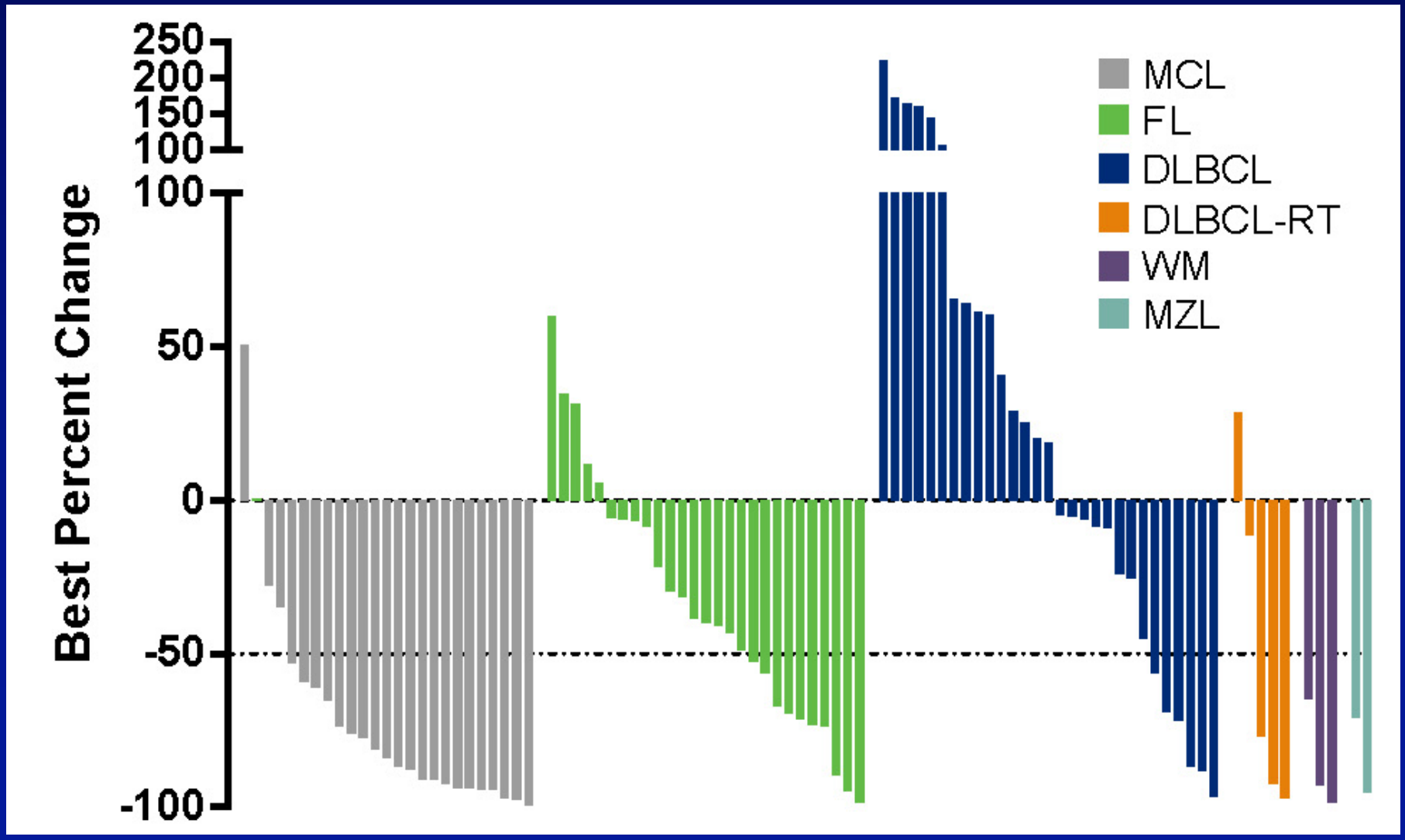
All Grade AEs (in ≥ 15% patients), n (%)	N=106
Any AE	103 (97)
Nausea	51 (48)
Diarrhea	47 (44)
Fatigue	43 (41)
Decreased appetite	22 (21)
Vomiting	22 (21)
Anemia	19 (18)
Constipation	19 (18)
Headache	19 (18)
Neutropenia	19 (18)
Cough	18 (17)
Back pain	17 (16)
Upper respiratory tract infection	16 (15)

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)

Two SAEs (600mg): both febrile neutropenia.

Two laboratory tumor lysis syndrome, both in patients with high tumor-burden disease; no clinical sequelae.

Phase 1 venetoclax: Waterfall plot by histology



Outcomes: Phase 1 venetoclax study

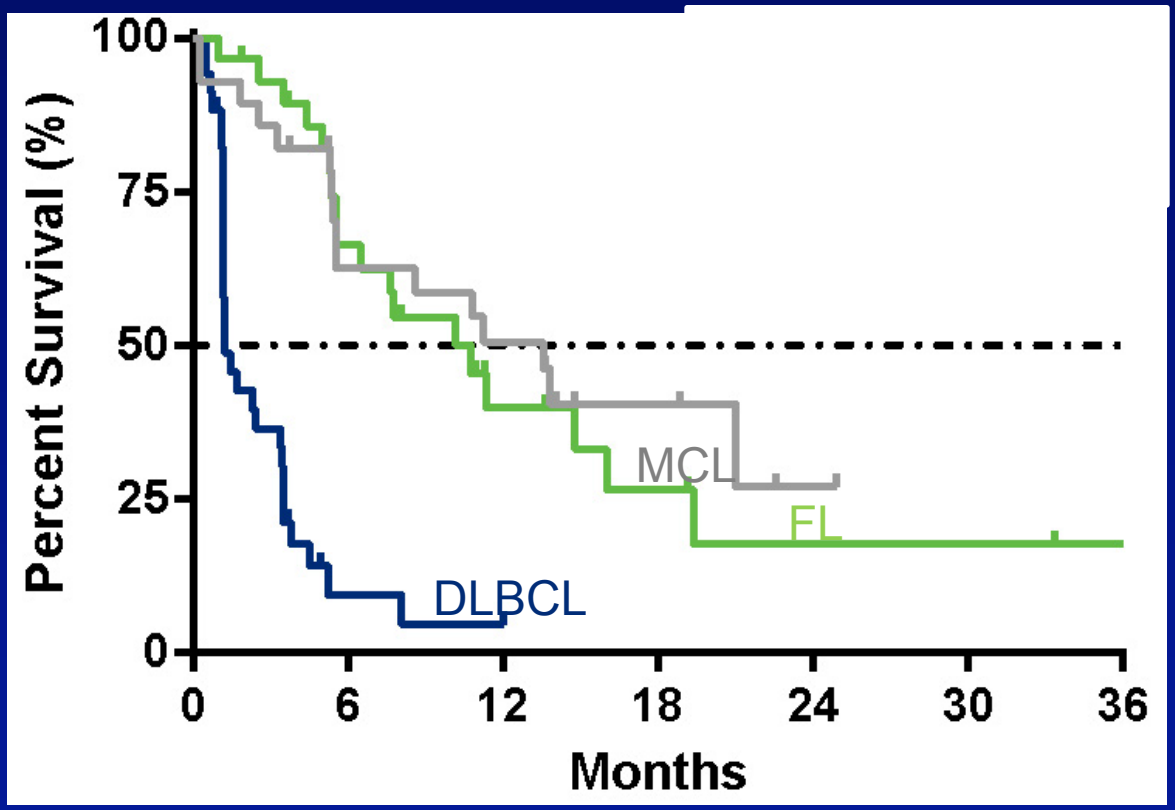
MCL: Objective responses observed across all dose cohorts.

FL: Objective responses more common at higher doses, including the 1200 mg expansion cohort.

82/106 (77%) patients have discontinued

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

Progression-Free Survival by Histology Subtype



	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)

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

Conclusions: Phase 1 venetoclax

- Venetoclax given in step up approach is safe in R/R NHL
  - MTD not reached with doses up to 1200 mg evaluated
  - Lab TLS was observed in 2 pts; no clinical sequelae
- The ORR was 75% in MCL, 38% in FL, and 18% in DLBCL
  - Complete responses in patients with FL and MCL had durability
  - Next steps: chemotherapy combinations.

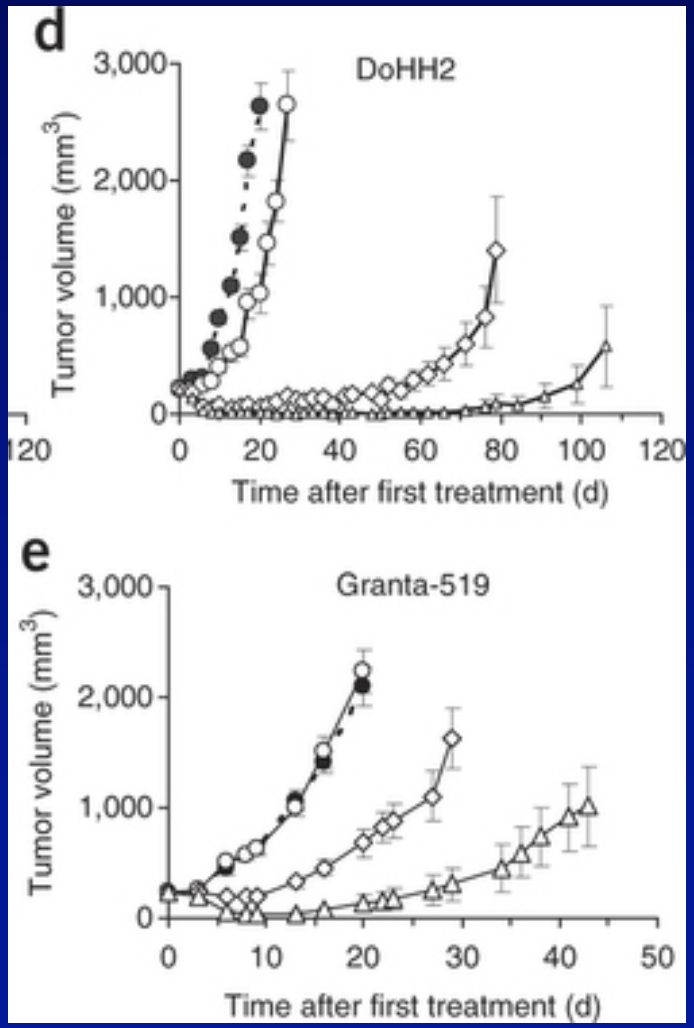
A Dose-Escalation Study of Venetoclax (ABT-199/GDC-0199) in Combination with Bendamustine and Rituximab in Patients with Relapsed or Refractory Non-Hodgkin's Lymphoma

Sven de Vos[1], Lode Swinnen[2], Mark Kozloff[3], Ding Wang[4], Erin Reid[5], Loretta Nastoupil[6], Nathan Fowler[6], Jaclyn Cordero[7], Diane D'Amico[7], Susan Diehl[7], Martin Dunbar[7], Ming Zhu[7], Shekman Wong[7], Sari Heitner Enschede[7], David Chien[7], Rod Humerickhouse[7], Christopher R. Flowers[9]

Synergy of venetoclax with bendamustine and rituximab

Xenograft experiments:

- Vehicle control
- Venetoclax
- Bendamustine/rituximab
- Benda/rituximab + venetoclax



Souers et al, *Nat Med* 19:202 2013

Dosing Schedule: BR + Venetoclax

- Dose-escalation portion
  - Patients were treated on a 28-day cycle with daily VEN on 3 dosing schedules (3-, 7-, and 28-day).
  - BR regimen was 6 Cycles: B (90 mg/m^2 x 2) and R (375 mg/m^2)

Patient Characteristics: BR + venetoclax

- 48 patients were enrolled in 10 dose escalation cohorts
  - Median age was 62.5 years (range: 29–90 years)
    - 31 (65%) patients were male

Cohort	
	Total N=48
Histology, n (%) FL **DLBCL MZL**	27 (56) 16 (33) 5 (10)
Prior therapy **R or R-based chemo, n (%) B or BR, n (%)** **Median (range)**	48 (100) 11 (23) 3 (1-8)

Dose-Limiting Toxicities: BR + Venetoclax

Cohort	1	2	3	4	5	6	7	8	9	10	
Dose-Limiting Toxicities during cycle 1, n (%)	50 mg 3/28d n=4	100 mg 3/28d n=4	100 mg 7/28d n=4	100 mg 28/28d n=3	200 mg 28/28d n=3	200 mg 7/28d n=4	400 mg 7/28d n=5	400 mg 28/28d n=8	600 mg 28/28d n=8	800 mg 28/28d n=5	Total N=48
Thrombocytopenia[a]					1				1		2 (4)
Febrile neutropenia					1						1 (2)
Stevens-Johnson Syndrome[b]								1			1 (2)

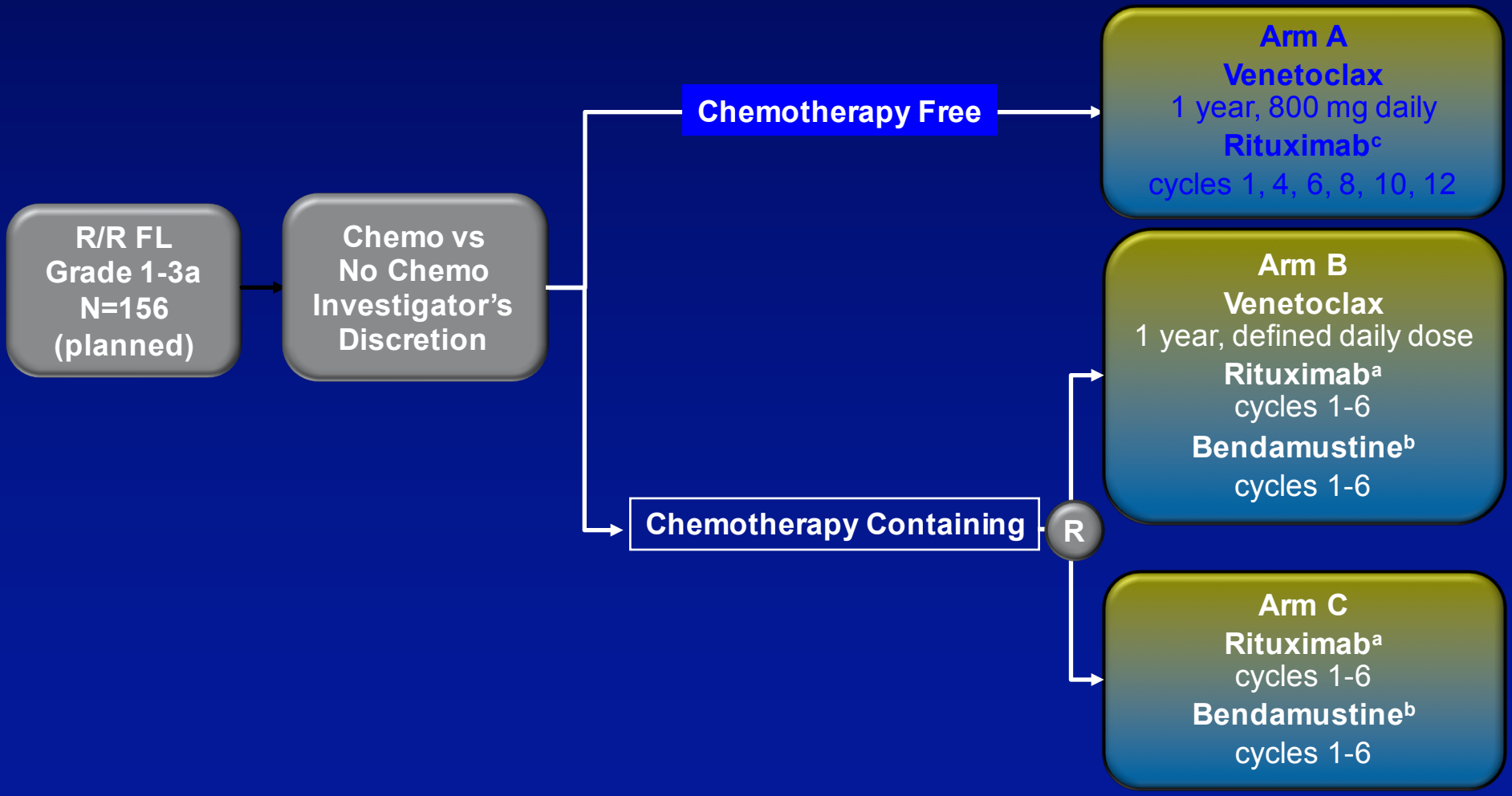
- Following cohort 5 (200 mg; 28/28d), a protocol amendment was filed in order to:
  - strongly encourage G-CSF prophylaxis during venetoclax administration, particularly in heavily pretreated patients
  - refine the DLT definition in the context of known BR toxicities[c]

Preliminary Efficacy: BR + Venetoclax

Response, n (%)	DLBCL n=16	Follicular Lymphoma n=27	Marginal Zone B-Cell Lymphoma n=5
Objective response	**6 (38)**	**21 (78)**	**4 (80)**
Complete response, CR	4 (25)	8 (30)	1 (20)
Partial response, PR	2 (13)	13 (48)	3 (60)
Stable disease, SD	**2 (13)**	**1 (4)**	**0 (0)**
Progressive disease, PD	**6 (38)**	**2 (7)**	**0 (0)**
Discontinued without assessment	**1 (6)**	**3 (11)**	**0 (0)**
Active (awaiting first assessment)	**1 (6)**	**0 (0)**	**1 (20)**

partial response; SD, stable disease.

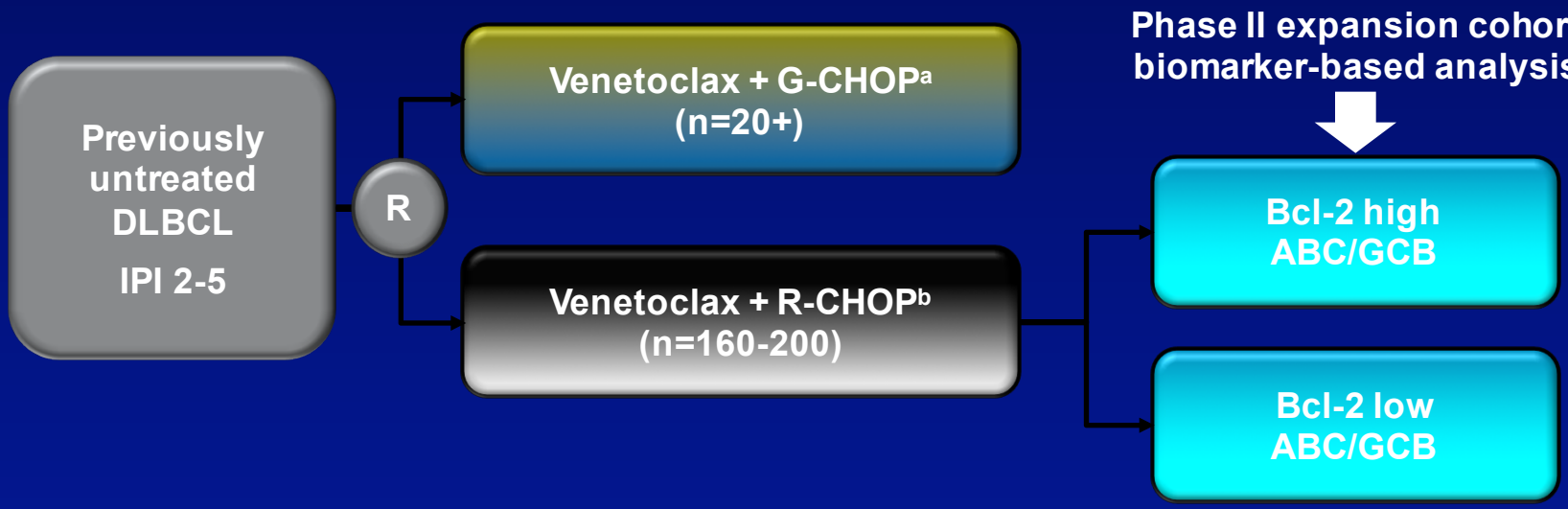
Ongoing enrollment: Phase 2 trial



Hiddeman W, et al. Presented at: ICML. 2015 (abstr OT04).
https://clinicaltrials.gov/ct2/show/study/NCT02187861. Accessed 7/29/15.

*Roche **Sponsored** Study

Ongoing enrollment: Venetoclax + R-CHOP or G-CHOP in Previously Untreated DLBCL:

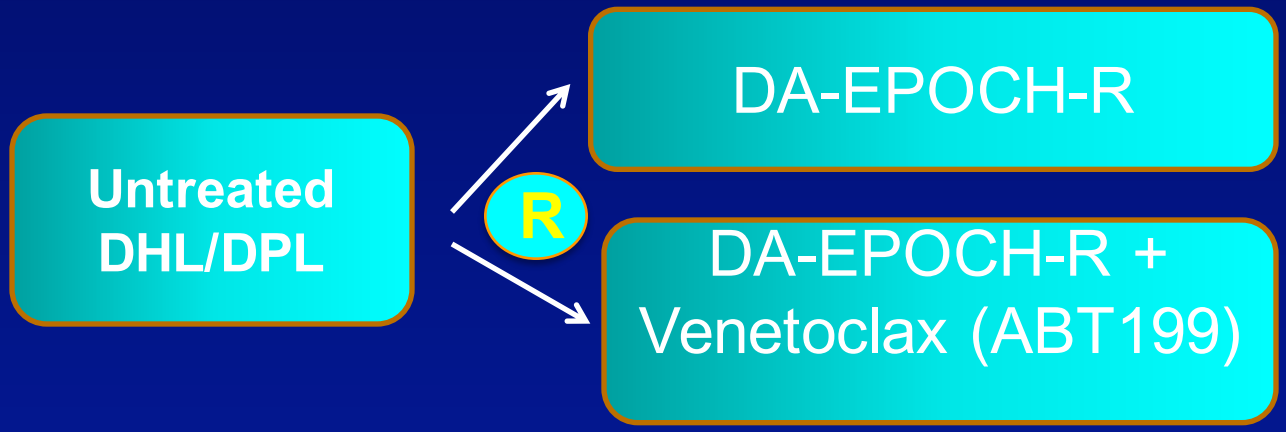


Phase Ib/II in 1L DLBCL evaluating the safety of venetoclax + R-CHOP or G-CHOP; expansion cohort evaluating the efficacy of venetoclax + R-CHOP in Bcl-2 high/low, cell of origin (ABC/GCB), and double-hit (Bcl-2/Myc)

GO27878 Protocol. Version 3. May 2014.

*Roche **Sponsored** Study

Intergroup Trial in Development: Phase II-III



DA-EPOCH-R +/- Venetoclax in DHL/DPL

- Primary Objective
  - Determine efficacy of venetoclax plus DA-EPOCH-R in MYC/BCL2 double-hit and double protein expressing lymphomas.
- Secondary Objectives
  - Evaluate safety of the combination of ventoclax with DA-EPOCH-R
  - Correlate outcome with MYC and BCL2 translocation status, cell of origin, and intensity of MYC and BCL2 protein expression

Endpoints

- Primary
  - Phase 2: Event-free survival at 12 months (EFS12)
  - Phase 3: Event-free survival at 24 months (EFS24)
- Secondary
  - Phase 2: Response rate (CR and PR), EFS24, progression-free survival, overall survival, incidence of adverse events and treatment discontinuation
  - Phase 3: Response rate, progression-free survival, overall survival , incidence of adverse events and treatment discontinuation
- Correlative
  - Correlate outcome with MYC and BCL2 translocation status, cell of origin, and intensity of MYC and BCL2 protein expression

Eligibility

- Age ≥ 18 years
- No prior systemic therapy
- Histologic diagnosis of DLBCL or BCLu
- Double hit lymphoma defined as dual translocations of MYC and BCL2, OR, Double protein expressing lymphoma defined as MYC IHC expression ≥ 40% and BCL2 ≥ 70%.*
- Ann Arbor stage II-IV
- Adequate organ and marrow function

* Registration will be based on local interpretation but all pathology will be centrally reviewed

Study Treatment

- Venetoclax at chosen dose on days 1-10 of each 21 day cycle
- DA-EPOCH R to be administered per routine on days 1-5 of a 21 day cycle for up to 6 total cycles
- Routine GCSF and prophylactic antibiotic support
- Restaging PETCT following cycle 2 and at end of treatment

Statistics

- Phase 2
  - 67 subjects will be required per arm to show an EFS12 of 75% compared to 60% with an alpha error 0.2 and 80% power
  - If this pre-specified endpoint is met, the study will convert to phase 3
  - Total accrual goal of 140 includes an additional 5% for dropouts and ineligible subjects
- Phase 3
  - 100 total subjects will be required per arm to show EFS24 of 60% compared to 40% using EFS24 with an alpha error of 0.05 and 82% power
  - Total accrual goal for phase 3: n= 210 (includes additional 5%). This is inclusive of patients enrolled on phase 2.
- Stratify on IPI score

Correlative studies

- Correlation of outcome with MYC and BCL2 translocation status
- Correlation of outcome based on COO using IHC and Nanostring
- Correlation of outcome based on DLBCL vs. BCLu histology
- Correlation with intensity of MYC and BCL2 expression

Phase I protocol in development

Venetoclax plus DA-EPOCH-R in aggressive B-cell lymphoma

- Phase I study at 4-5 sites
- Primary objective: Determine MTS/RP2D of venetoclax with DA-EPOCH-R
- Secondary objectives:
  - Evaluate toxicity of the combination
  - Preliminary estimation of efficacy based on response rate and EFS12

Eligibility

- Histologically confirmed chemo-naïve DLBCL or BCLu
- Transformed iNHL eligible if no prior anthracycline
- Age ≥ 18 years
- ECOG PS 0-2
- Adequate marrow and organ function
- No known CNS involvement, active uncontrolled infection, other active malignancies

Design

Phase 3+3 design (Bayesian designs also under review)

Dose Level	**Venetoclax** (mg po daily)	**Days**
-1	400	1-5
0 (starting level)	400	1-10
1	600	1-10
2	800	1-10

MTD/RP2D is highest dose level at which fever than 2/6

subjects experience DLT

Dose-limiting toxicity

- Grade 4 neutropenia or thrombocytopenia lasting >7 days and/or fails to resolve to grade 1 by cycle 2
- Grade 3 thrombocytopenia with bleeding
- Grade 4 neutropenic fever
- Grade 3 or greater non-hematologic toxicity related to study treatment, except alopecia, reversible grade 3 infusion reactions, nausea/vomiting lasting <7 days
- Any grade 5 toxicity

Thank you!
Discussion