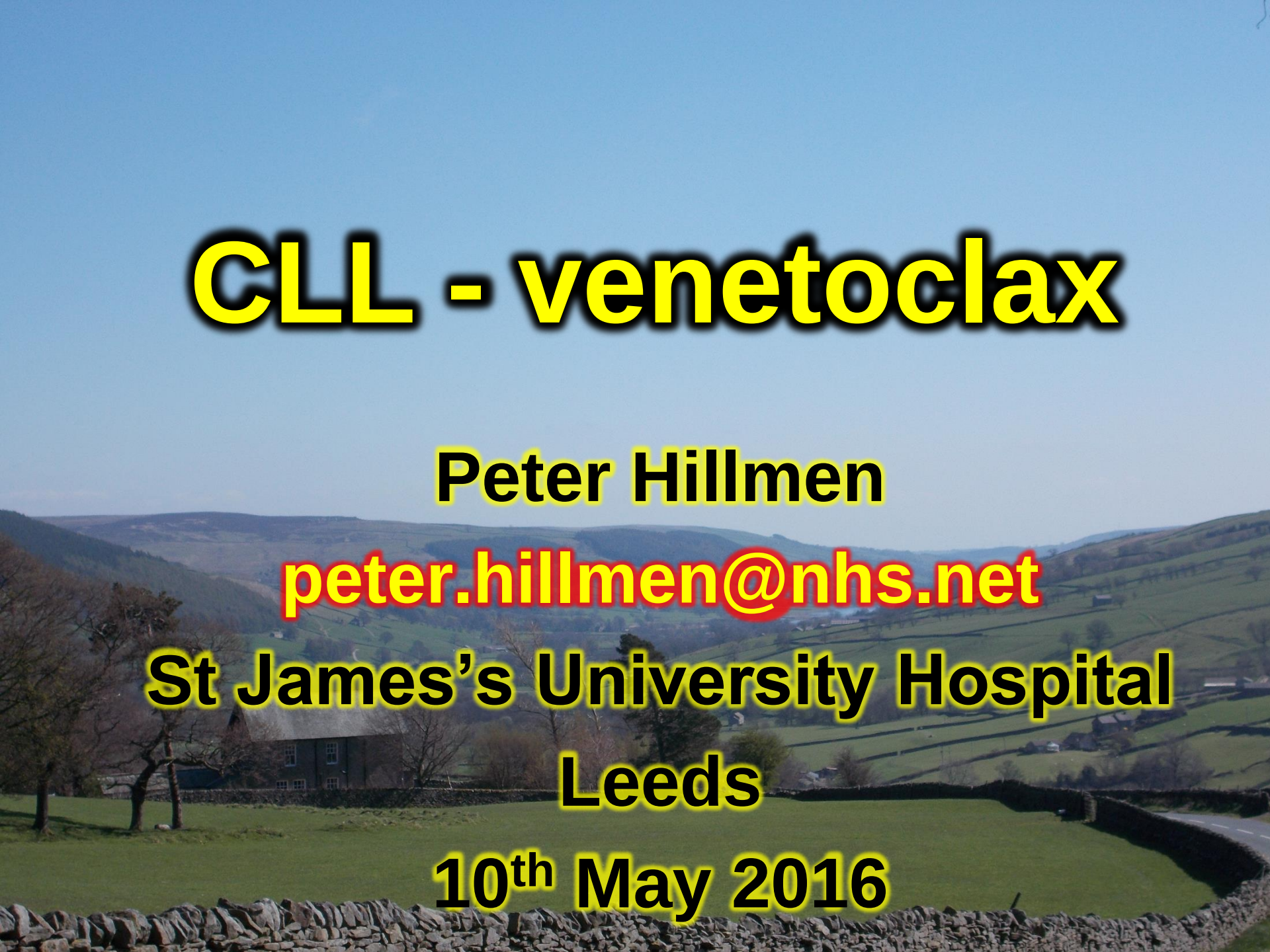

CLL - venetoclax

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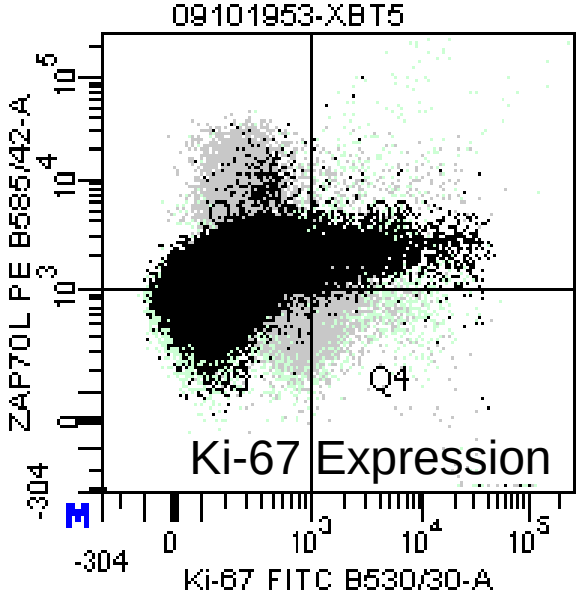
Leeds

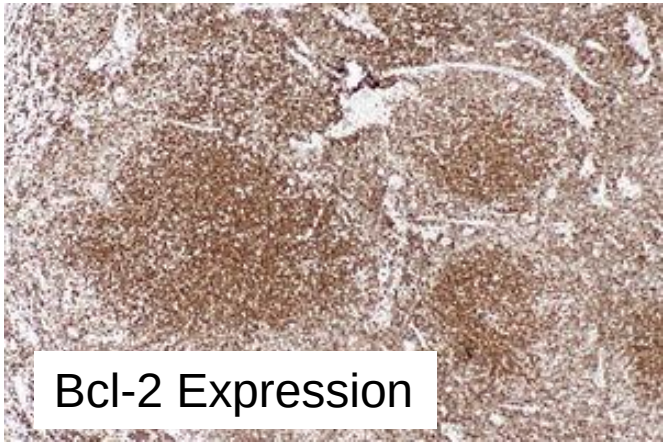
10th May 2016

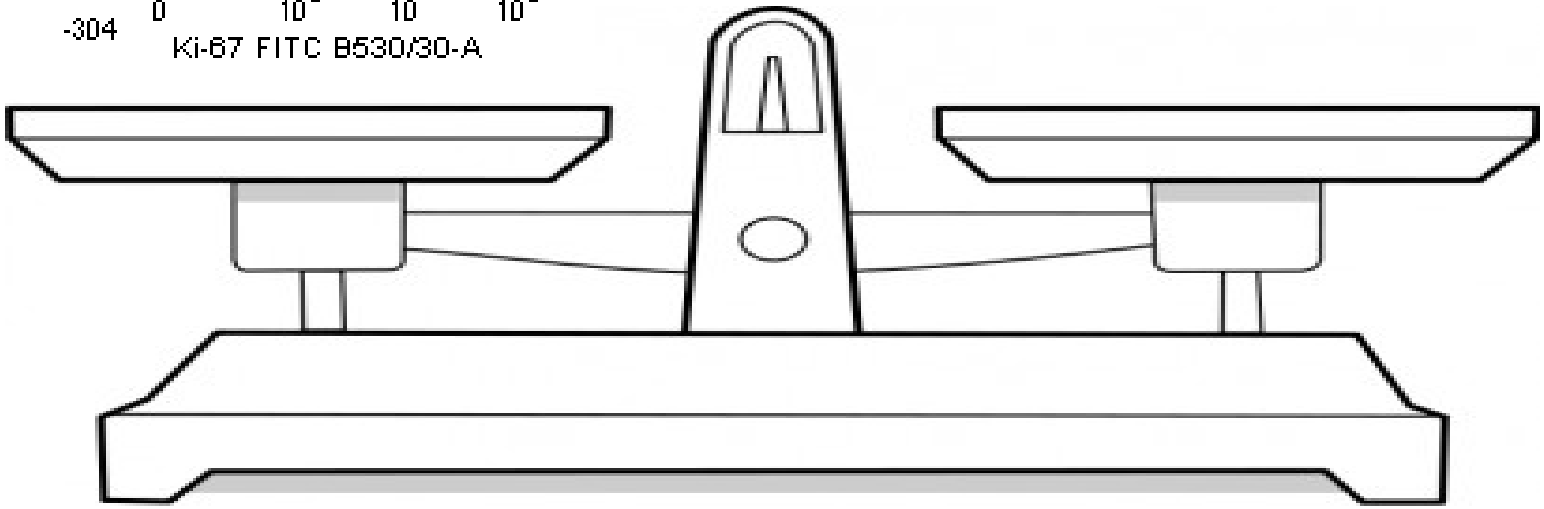
Pathophysiology of CLL: Proliferation vs Apoptosis

Proliferation

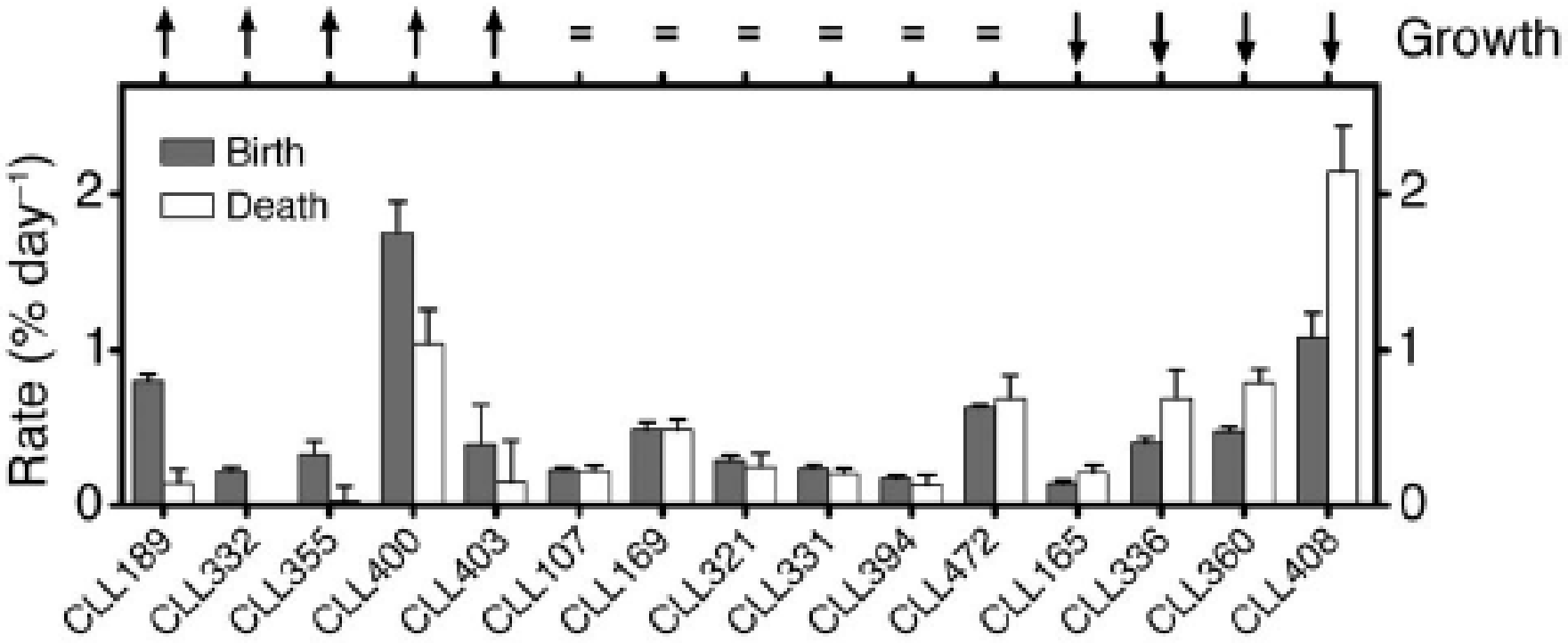


Apoptosis





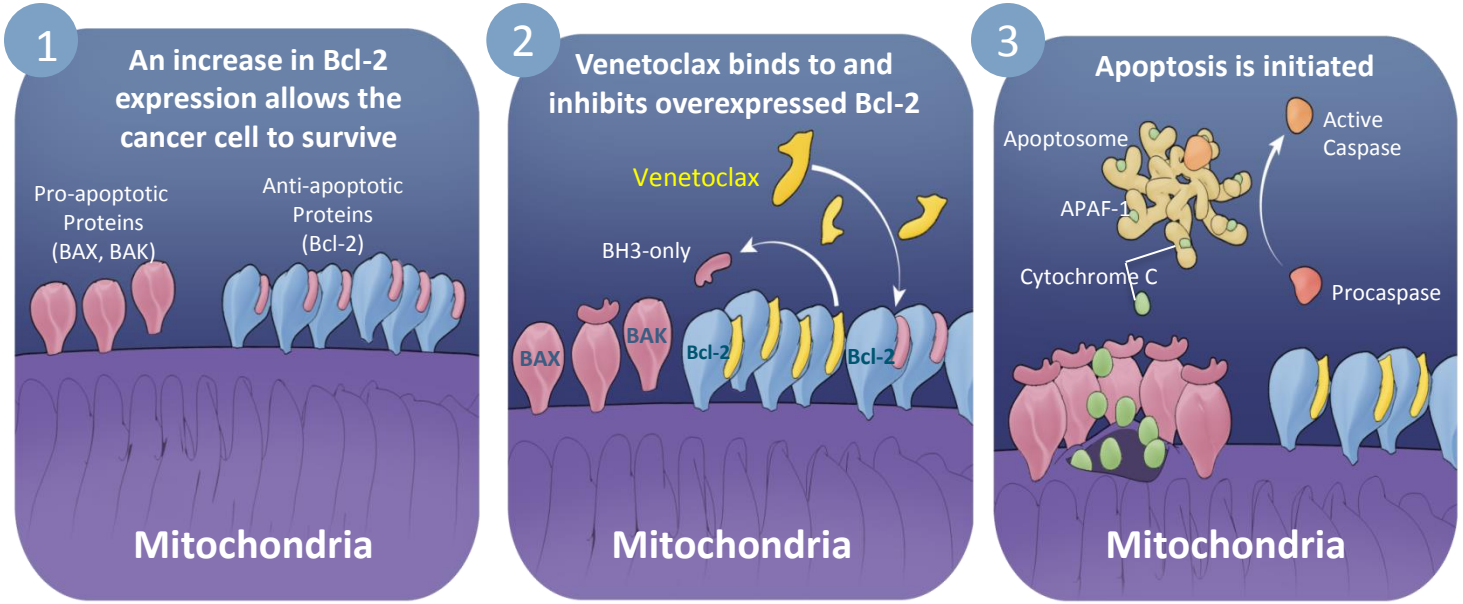
High birth and death rate of CLL cells *in vivo* ^2H_2O-labelling



Messmer *et al.*, J Clin Invest, 115:755-64 (2005)

Venetoclax (ABT-199 or GDC-199) in CLL

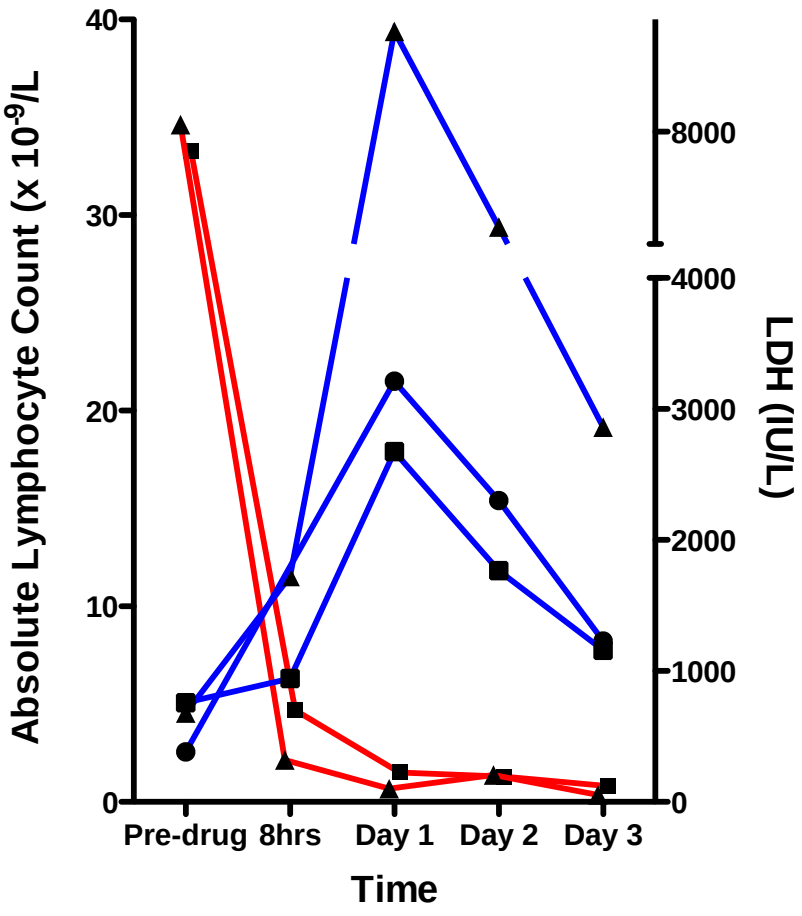
- Bcl-2 overexpression is observed in up to 95% of CLL cases[1–3]
- Venetoclax is a highly selective, orally bioavailable small-molecule Bcl-2 inhibitor which restores the ability of malignant cells to undergo apoptosis[4]
- Venetoclax is active against CLL irrespective of *TP53* functional status and is thought to achieve outcomes by acting downstream of *TP53*[5]



1. Del Gaizo Moore V, *et al. J Clin Invest* 2007; **117:**112–121.
2. Hanada M, *et al. Blood* 1993; **82:**1820–1828. 3. Marschitz I, *et al. Am J Clin Pathol* 2000; **113:**219–229.
4. Souers AJ, *et al. Nat Med* 2013; **19:**202–208. 5. Anderson MA, *et al. Blood* 2013;**122**(21)**:** Abstract 1304.

Early signs of activity with GDC-0199 (specific Bcl-2 inhibitor) in CLL in Phase I Study

- **ABT-199 200 mg, 200 mg, 100 mg given as single oral dose**
  - > 95% reduction in lymphocytosis within 24h in two patients with lymphocytosis
  - Rapid reduction in palpable lymphadenopathy
  - Dose-limiting laboratory tumor lysis syndrome (TLS), not clinical TLS/no organ dysfunction
    - Rises in LDH, phosphate
    - Rises in K^+ (max 5.9 mmol/L)
  - Daily dosing (50 – 100mg) commenced within 7 days



Lymphocyte Counts (Red; n = 2) and LDH (Blue; n = 3) post first dose

Roberts *et al.*, EHA 2012; Davids *et al.*, GCLLSG 2012

DF, Born 1948, Male, Farmer

Aug 2010: Diagnosed with CLL needing therapy

October 2010: Entered ADMIRE study

FCM-R x 6 → MRD positive nodular remission

November 2013: Relapsed with large abdominal nodes

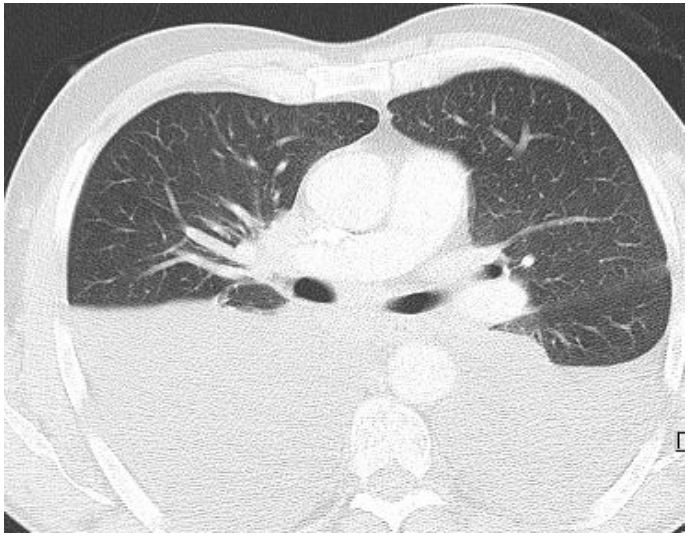
Feb 2014: Biopsy = CLL. 48% 17p deletion

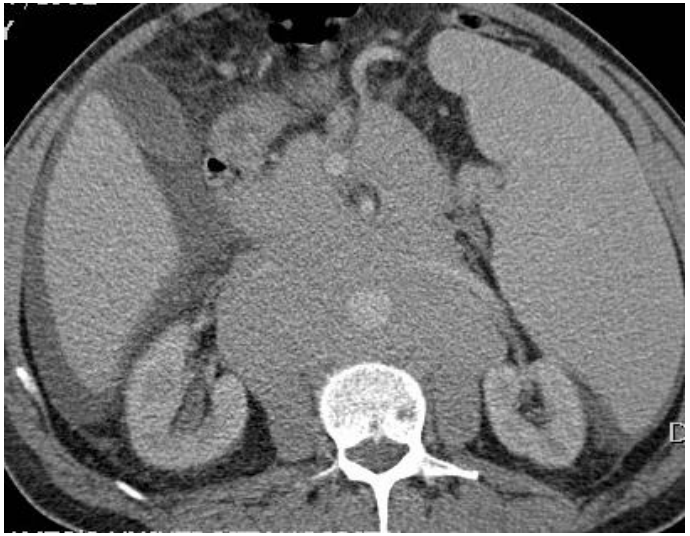
March 2014: Referred to Leeds for an opinion

Screened for Abbvie M13-982 trial of venatoclax (ABT-199) monotherapy for 17p deleted patients

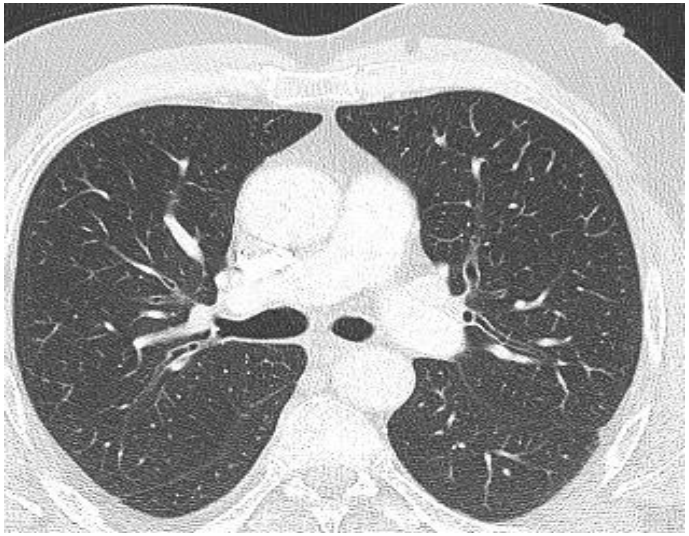
DF, Born 1948, Male, Farmer

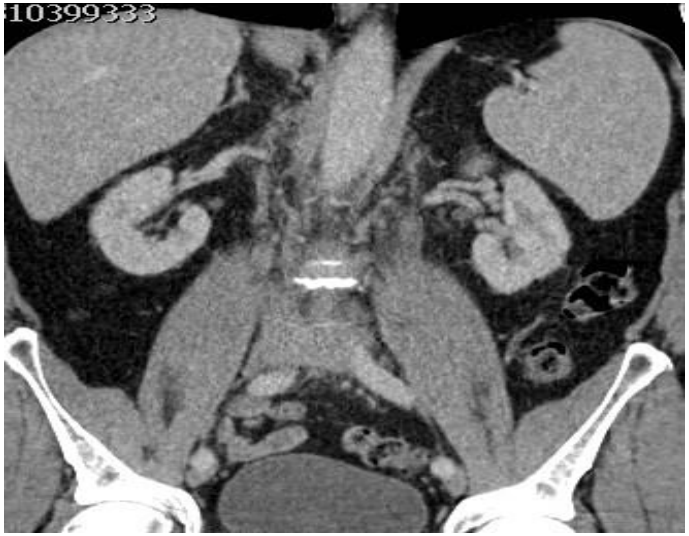
CT scan Pre-treatment





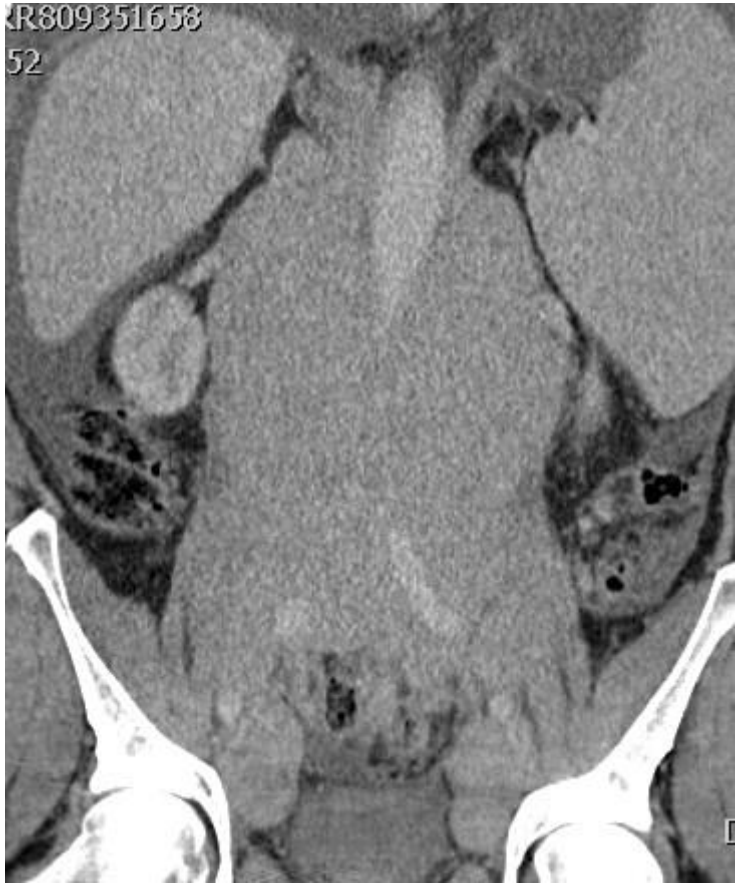
CT scan Week 24



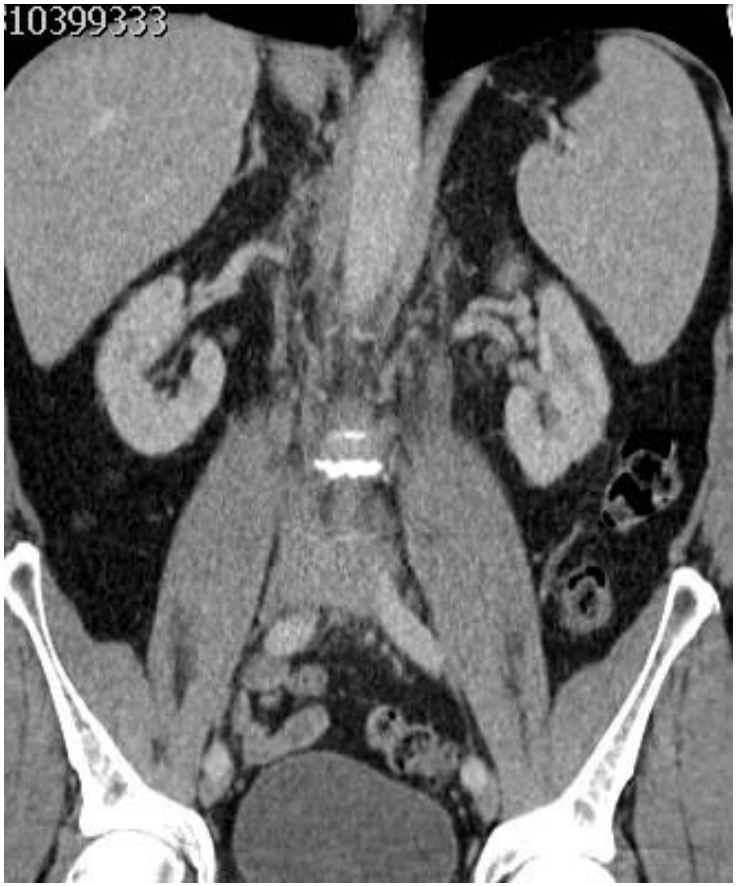


DF, Born 1948, Male, Farmer

CT scan
Pre- treatment



CT scan
Week 24

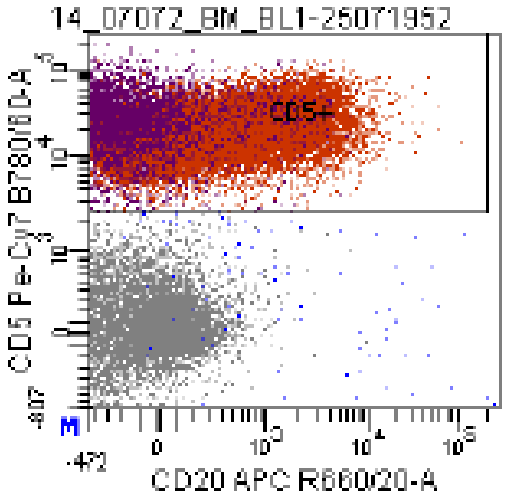


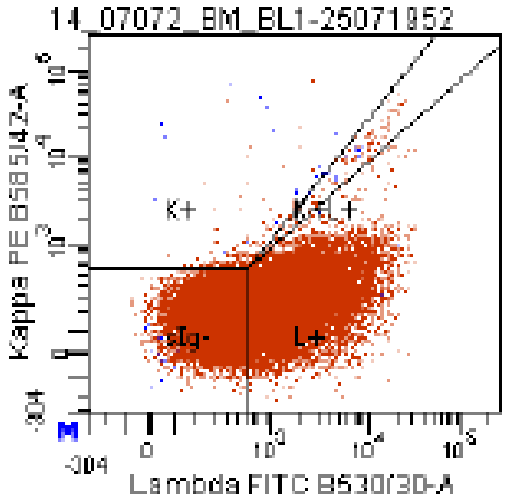
DF, Born 1948, Male, Farmer
Bone Marrow analysis

Orange events
= CLL cells

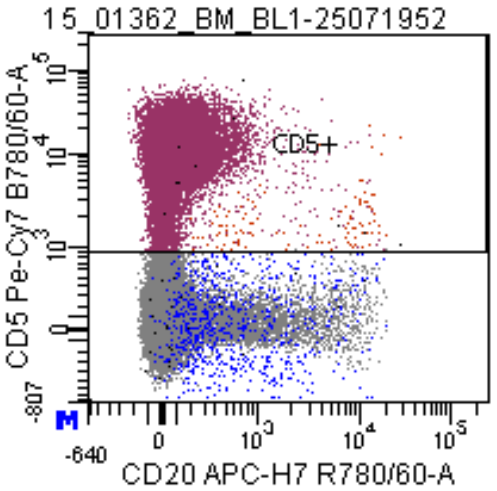
Purple events
= T-cells

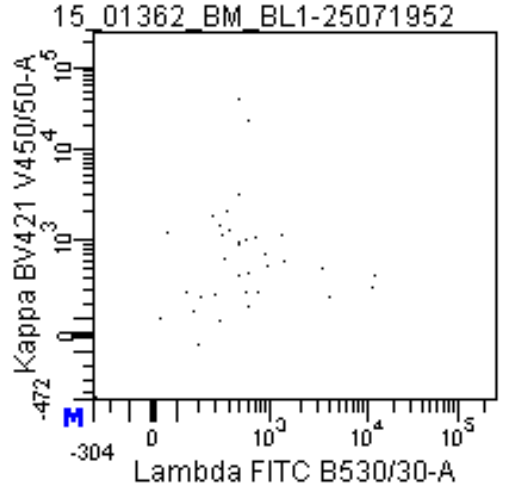
Pre-venetoclax





6 months of venetoclax





No detectable CLL <0.01%!!

DF, Born 1948, Male, Farmer

- Commenced venetoclax 25/4/14; reviewed 28/03/16 → remains well
- Early neutropenia: now off G-CSF
- 24 weeks CT scan: complete remission
- Normal blood counts
- Bone marrow: MRD-negative remission

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia

Andrew W. Roberts, M.B., B.S., Ph.D., Matthew S. Davids, M.D., John M. Pagel, M.D., Ph.D., Brad S. Kahl, M.D., Soham D. Puvvada, M.D., John F. Gerecitano, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Mary Ann Anderson, M.B., B.S., Jennifer R. Brown, M.D., Ph.D., Lori Gressick, B.S., Shekman Wong, Ph.D., Martin Dunbar, Dr.P.H., Ming Zhu, Ph.D., Monali B. Desai, M.D., M.P.H., Elisa Cerri, M.D., Sari Heitner Enschede, M.D., Rod A. Humerickhouse, M.D., Ph.D., William G. Wierda, M.D., Ph.D., and John F. Seymour, M.B., B.S., Ph.D.

Demographics in venetoclax Phase I trial

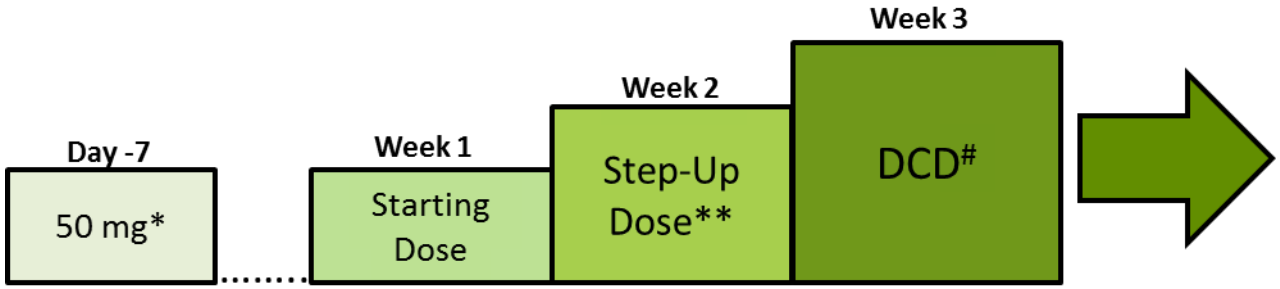
Characteristic	All patients (n=116)
Age (Median [range])	66 (36 – 86)
Gender (Male/Female)	77%/23%
Rai Stage III or IV	67 (58%)
Median no. prior therapies	3 (1-11)
Resistant to most recent therapy	45 (39%)
Previous fludarabine	100 (86%); 60% refractory
Bulky lymph nodes (>5cm)	67 (58%)
17p deleted	31/102 (30%)
11q deleted	8/102 (28%)
IgHV unmutated	46/63 (73%)

Roberts *et al.,* New Engl J Med, Dec 2015

Venetoclax (ABT-199) dosing schema

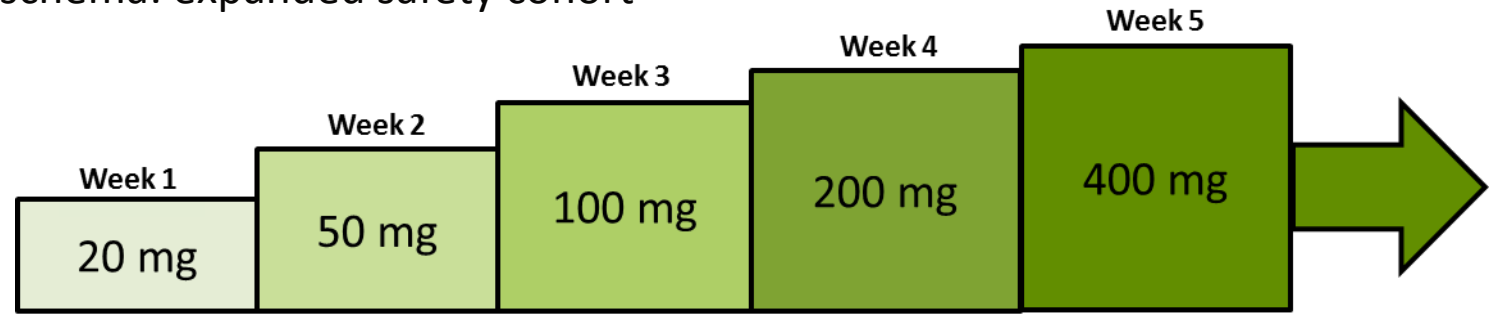
Daily ABT-199 doses increased weekly to the designated cohort dose (DCD)

Initial ramp-up schema: dose escalation

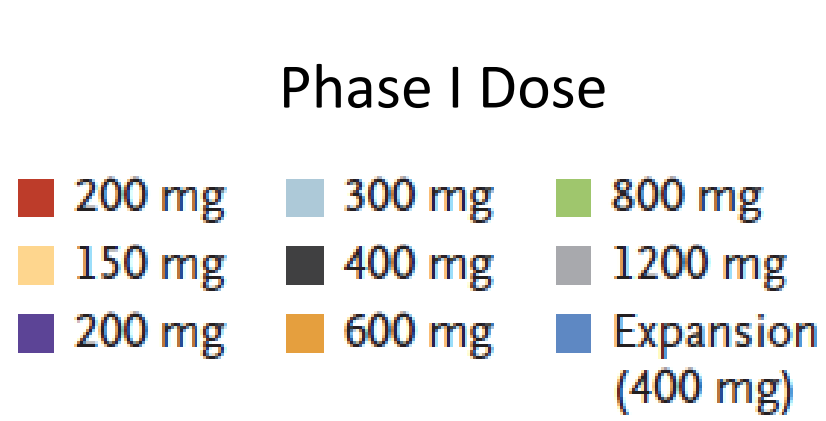


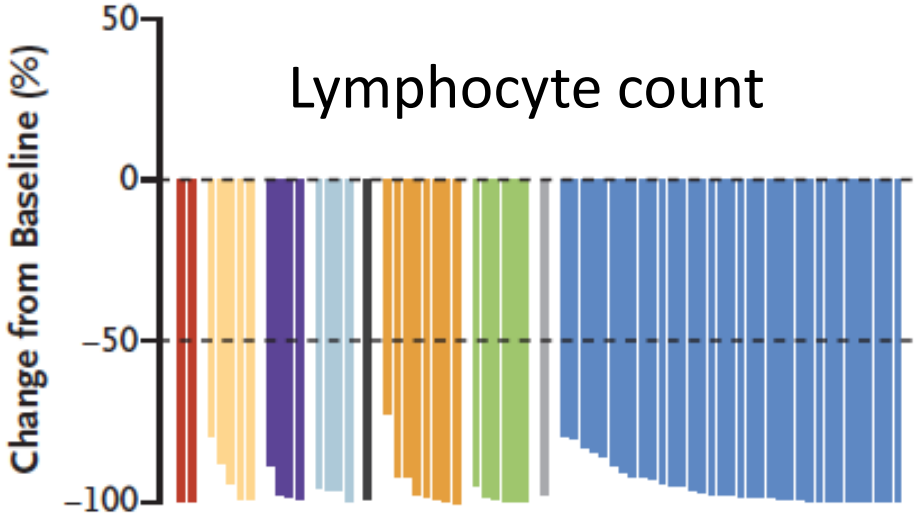
* 3 patients (1 each in cohorts 2, 3, & 5) received ABT-199 20 mg as initial dose
** Step-up doses range from 100 to 400 mg
# DCD ranges from 150 to 1200 mg

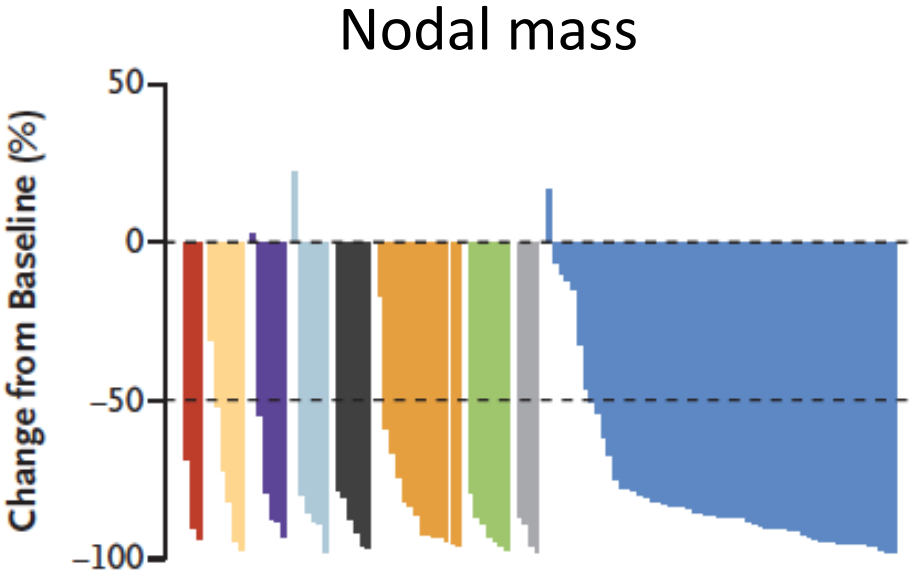
Ramp-up schema: expanded safety cohort

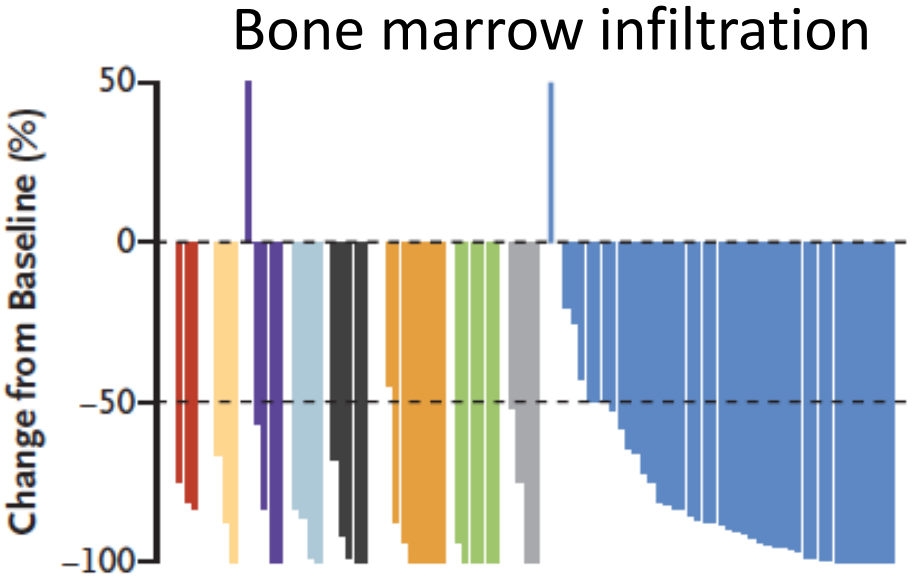


Responses by venetoclax dose



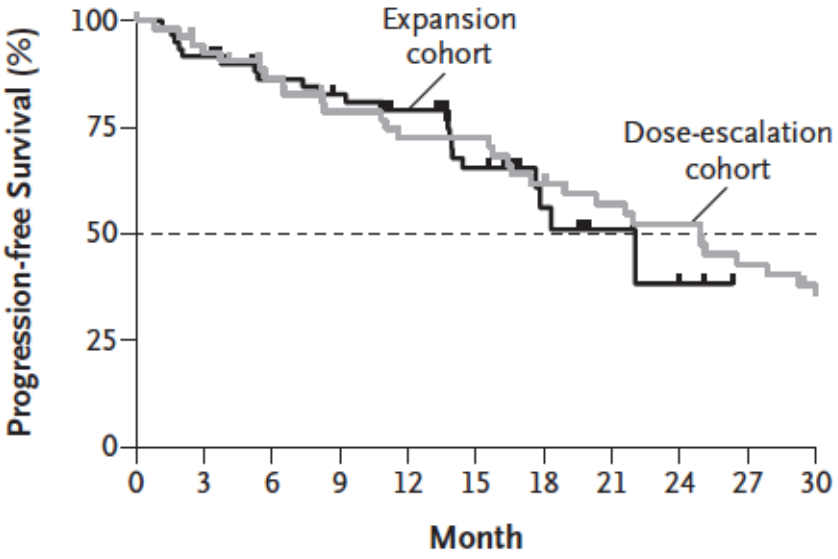


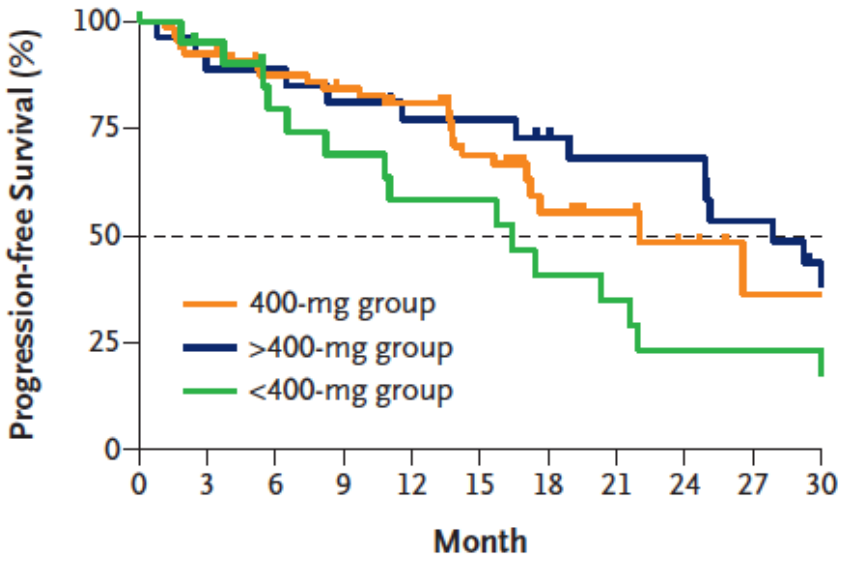


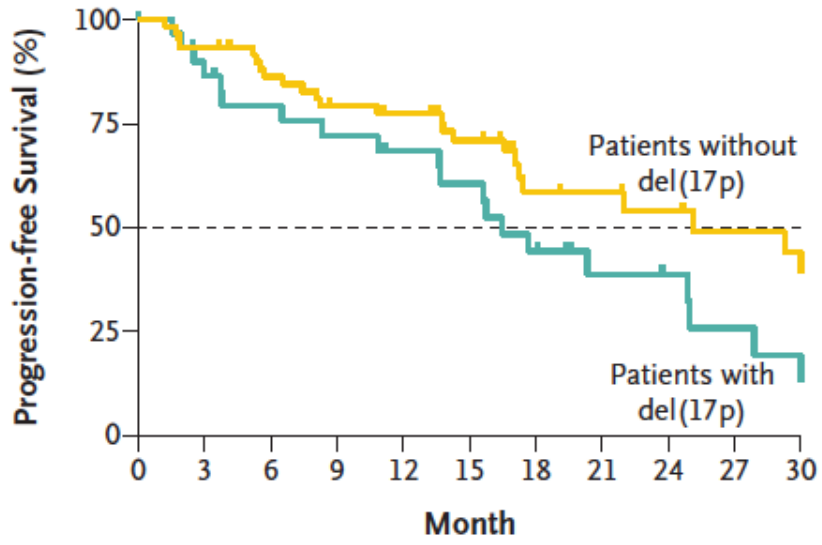


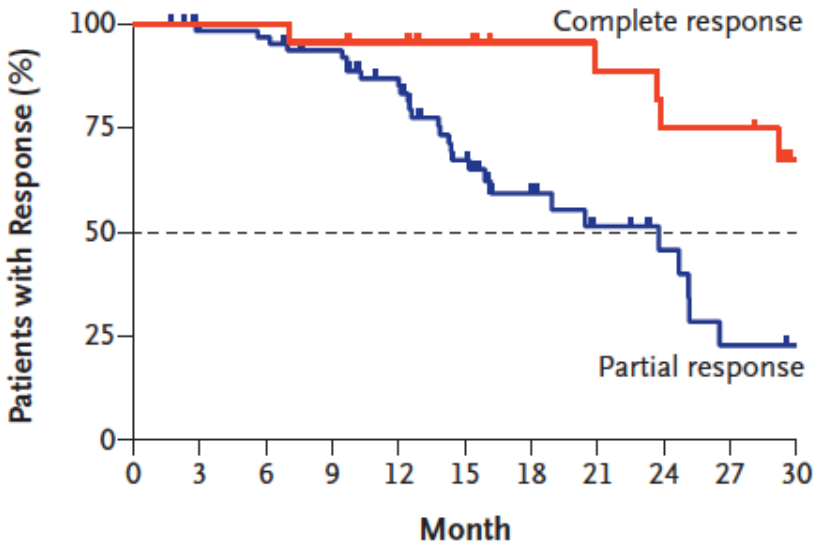
Roberts *et al.,* New Engl J Med, Dec 2015

Venetoclax monotherapy: PFS









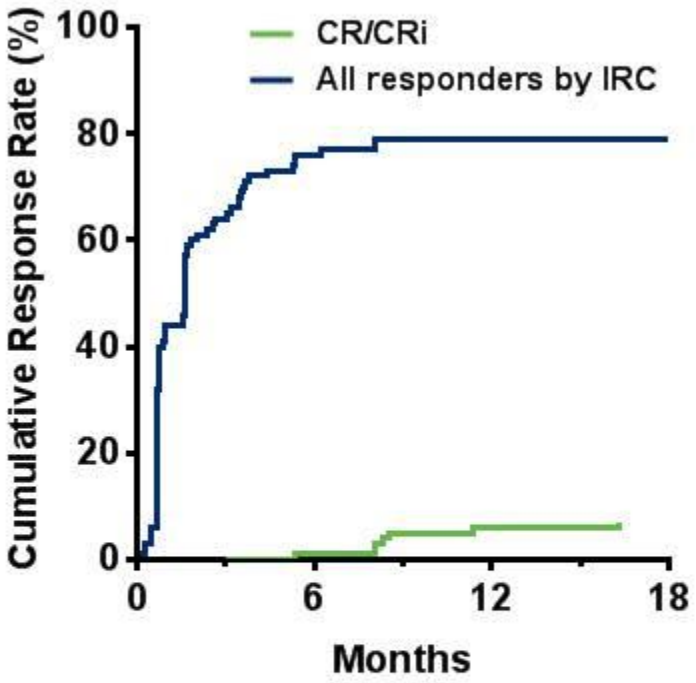
Roberts *et al.,* New Engl J Med, Dec 2015

M13-982 Trial: Venetoclax in 17p deleted CLL (Stilgenbauer *et al.*, ASH 2015)

N=107[a]	n (%)
Median age (years), range	67, 37–85
Male	70 (65)
Prior therapies: median, range	2, 1–10
Prior bendamustine / refractory	54 (50) / 38 (70)
Prior fludarabine / refractory	78 (73) / 34 (44)
Prior CD20 mAb	90 (84)
ECOG grade 1/2	56 (52) / 9 (8)
One or more nodes ≥ 5 cm	57 (53)
ALC ≥25 x 10^9/L	54 (51)
TLS risk category	
Low	19 (18)
Medium	43 (40)
High	45 (42)
Rai stage III or IV	51(48)
IGHV unmutated	30 (81)

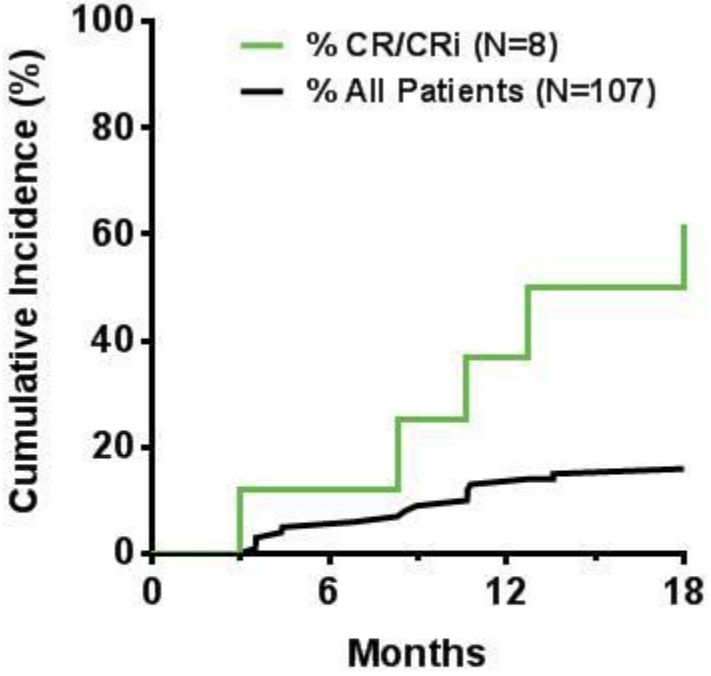
M13-982 Trial: Cumulative incidence of response (Stilgenbauer *et al.*, ASH 2015)

iwCLL Response



- Median time-to-first response: 0.8 months (0.1–8.1)
- Median time to CR/CRi: 8.2 months (3.0–16.3)

MRD-Negativity

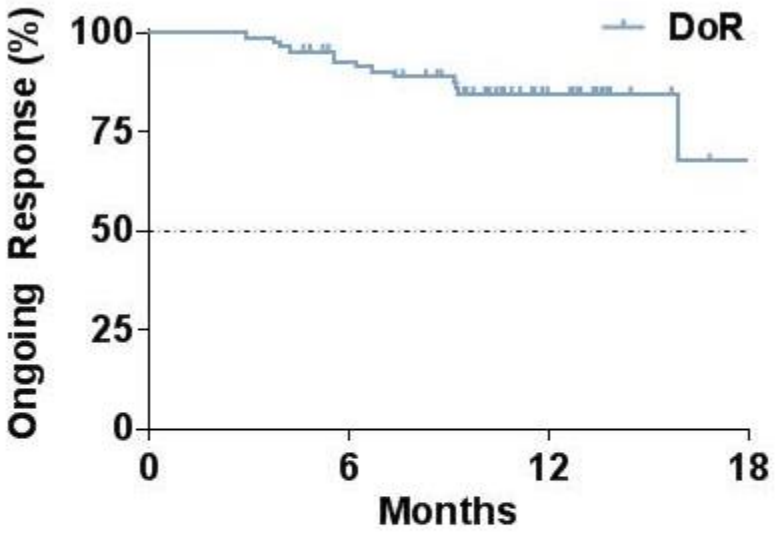


- Of 45 patients tested, 18 achieved MRD-negativity in peripheral blood

Adapted from Stilgenbauer et al. Oral Presentation at ASH 2015, Orlando, Florida.

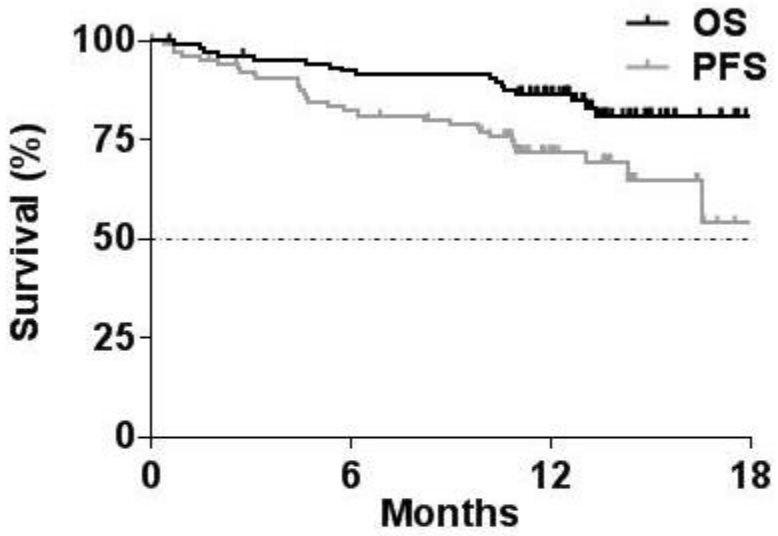
M13-982 Trial: Durability of response (Stilgenbauer *et al.*, ASH 2015)

Duration of Response (N=85)



- 12-month estimates:
  - All responders: 84.7%
  - CR/CRi/nPR: 100%
  - MRD-negative: 94.4%

PFS and OS (N=107)



- 12-month estimates (95% CI):
  - PFS: 72.0% (61.8, 79.8)
  - OS: 86.7% (78.6, 91.9)

Adapted from Stilgenbauer et al. Oral Presentation at ASH 2015, Orlando, Florida.

Deep and Durable Responses Following Venetoclax (ABT-199 / GDC-0199) Combined with Rituximab in Patients with Relapsed / Refractory Chronic Lymphocytic Leukemia: Results from a Phase 1b Study

Shuo Ma[1], Danielle Brander[2], John F. Seymour[3], Thomas J. Kipps[4], Jacqueline C. Barrientos[5], Matthew S. Davids[6], Mary Ann Anderson[7], Michael Choi[4], Constantine Tam[3], Tanita Mason-Bright[8], Betty Prine[8], Wijith Munasinghe[8], Ming Zhu[8], Su Young Kim[8], Rod A. Humerickhouse[8], Andrew W. Roberts[7]

[1]Northwestern University, USA; [2]Duke University Medical Center, USA; [3]Peter MacCallum Cancer Centre, Australia; [4]University of California San Diego, USA; [5]Hofstra North Shore-LIJ School of Medicine, USA; [6]Dana-Farber Cancer Institute, USA; [7]Royal Melbourne Hospital and Walter and Eliza Hall Institute of Medical Research, Australia; [8]AbbVie, USA

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

Patient Characteristics

Characteristics	N = 49
Median age, years [range]	68 [50–88]
Male sex, n (%)	30 (61)
Diagnosis CLL / SLL	48 / 1
Lymphocyte count (x 10^9/L), median [range] > 5 x 10^9/L, n (%)	18.6 [0.3–207.1] 32 (65)
Bulky nodes, n (%) > 5 cm	 22 (45)
Prior therapies – median [range] ≥ 3, n (%)	2 [1–5] 21 (43)
Rituximab-containing, n (%) - Rituximab Refractory [a]	45 (90) 14 (29)
Fludarabine-containing, n (%) - Fludarabine Refractory [a]	28 (57) 9 (18)
del17p and/or TP53 mutation, n/N (%)	15/45 (33)
Unmutated *IGVH*, n/N (%)	19/27 (70)

[a] Progressed on therapy or within 6 months of therapy

As of October 28, 2015

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

Objective Responses

Best Objective Response, n (%)	All Patients n=49
Overall Response	42 (86)
Complete response, CR (includes 7 CRi)	23 (47)
Partial response, PR (includes 1 nPR)	19 (39)
Stable disease	4 (8)
Disease progression	2 (4)
Death (TLS) [a]	1 (2)

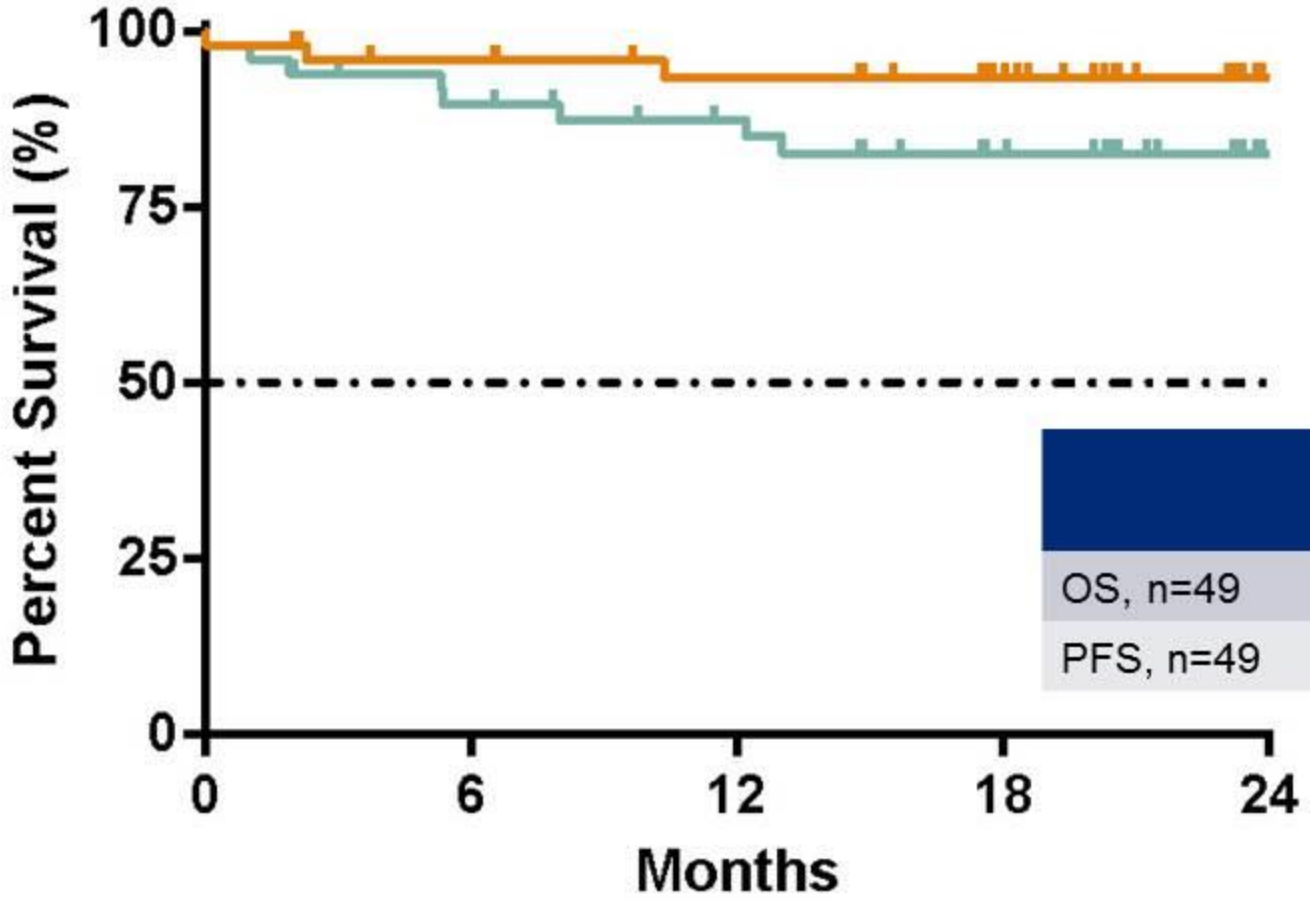
[a] Fatal TLS event previously reported; no other fatal TLS events occurred after May 2013 protocol amendment

- The median time on study is 21 months (<1 – 37) for all patients
  - 37 patients remain on study with a median time of 23 (15 – 37) months
  - 12 discontinued (6 due to PD including 5 Richter's; 3 due to AE; 3 withdrew consent)

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

As of October 28, 2015

Progression Free Survival and Overall Survival



	24-month estimate (95% CI)
OS, n=49	94% (81, 98)
PFS, n=49	83% (68, 90)

Patients at risk:	49	44	40	32	16
Patients at risk:	49	42	37	28	16

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

As of October 28, 2015

Bone Marrow Minimal Residual Disease (MRD)

MRD was assessed using local institutional methods and sensitivity $\leq 10^{-4}$

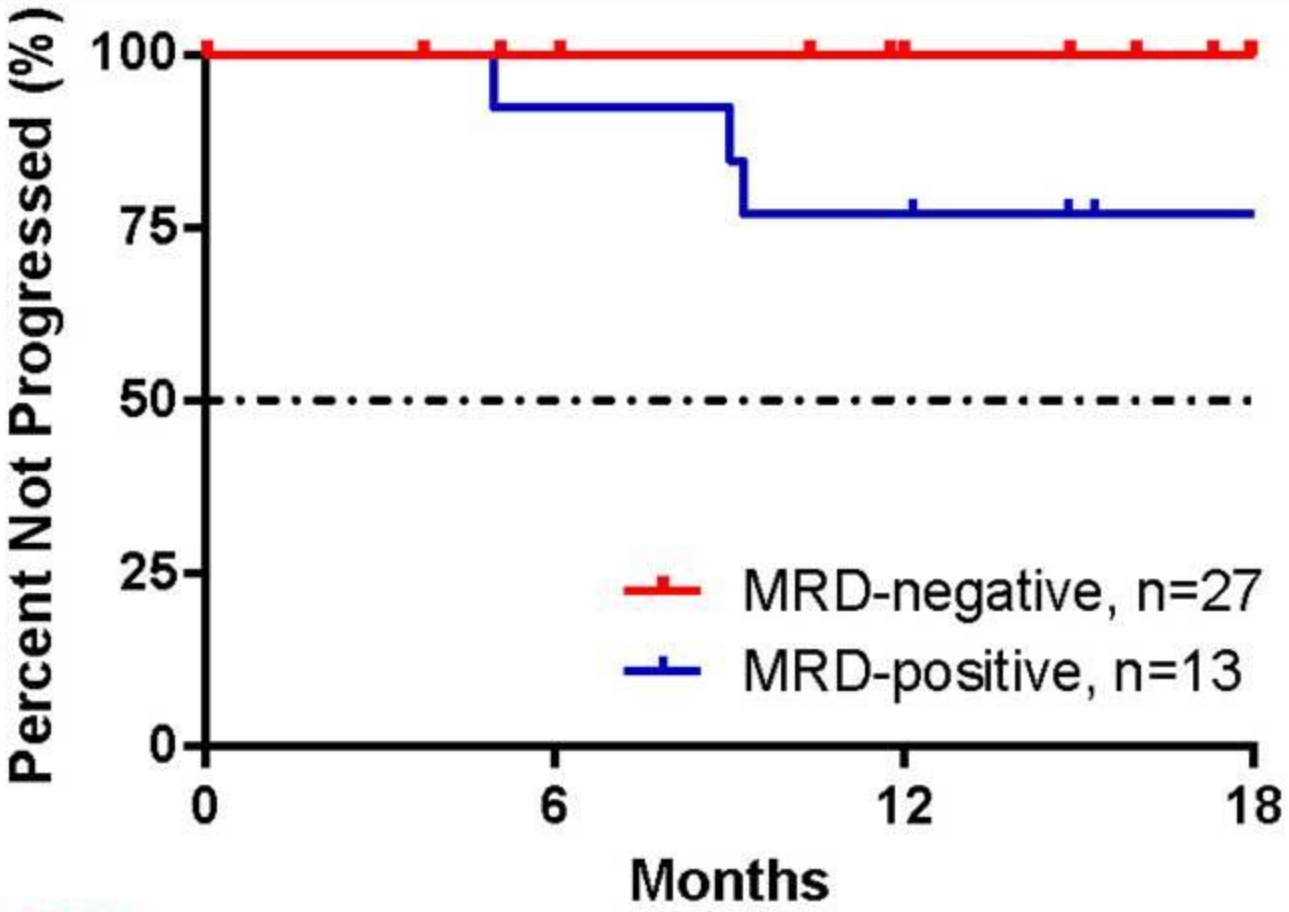
Response Classification	MRD-negative	MRD-positive	Not evaluable
CR (n=23)	17	5	1 [a]
PR (n=19)	10	8	1 [a]
Other (n=7)	0	1 [b]	6 [c]
Total, n/N (%)	27/49 (55)	14/49 (29)	8/49 (16)

[a] Samples inadequate for assessment
[b] SD
[c] no sample

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

As of October 28, 2015

Duration of Response Based on MRD Status



Patients at risk:	27	24	21	14
Patients at risk:	13	12	9	6

Duration of response is calculated from earliest response to last visit
MRD-negative includes 17 CR and 10 PR

Adapted from Ma et al. Oral Presentation at ASH 2015, Orlando, Florida.

As of October 28, 2015

Preliminary Results of a Phase Ib Study (GO28440) Combining Venetoclax (GDC-0199/ABT-199) With Bendamustine/Rituximab or Bendamustine/Obinutuzumab in Patients With Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia

Gilles Salles[1], Thomas Boyd[2], Franck Morschhauser[3], Clemens-Martin Wendtner[4], Michael Hallek[5], Barbara Eichhorst[5], Mark F. Kozloff[6], Guillaume Cartron[7], Yan Li[8], James Hilger[8], Mehrdad Mobasher[8], Stephan Stilgenbauer[9]

1. Hospices Civils de Lyon - Université de Lyon, Pierre-Bénite, France; 2. Yakima Valley Memorial Hospital, Yakima, WA, USA; 3. Hématologie, Centre Hospitalier Universitaire, Université de Lille 2, Lille, France; 4. Klinikum Schwabing, Academic Teaching Hospital of University of Munich, Munich, Germany; 5. Department I of Internal Medicine, Center of Integrated Oncology Cologne-Bonn, University Hospital Cologne, Cologne, Germany; 6. University of Chicago Medicine, Chicago, IL, USA; 7. Department of Clinical Hematology, University Hospital of Montpellier, Montpellier, France; 8. Genentech, Inc., South San Francisco, CA, USA; 9. Department of Internal Medicine III, Ulm University, Ulm, Germany

Adapted from Salles, et al Oral Presentation at ASH 2015, Orlando, FL

Preliminary Efficacy: Response and MRD Rates

Response rates with VEN + BR	R/R (n=25) n (%)	1L (n=13) n (%)	All (n=38) n (%)
Response evaluated	22 (88)	11 (85)	33 (87)
ORR	**22 (100)**	**11 (100)**	**33 (100)**
CR/CRi	4 (18)	3 (27)	7 (21)
nPR/PR	18 (82)	8 (73)	26 (79)
SD	0	0	0
MRD assessed[a]	21 (84)	9 (69)	30 (79)
MRD negative (peripheral blood)	**16 (76)[b]**	**5 (56)**	**21 (70)**
MRD positive	4 (19)	2 (22)	6 (20)
Undetermined[c]	1 (5)	2 (22)	3 (10)

[a] MRD negativity by flow at × 10^{-4}.
[b] Six of 11 (55%) assessed patients also negative in bone marrow.
[c] Patients have no detectable CLL, but sensitivity of their MRD test not 10^{-4} and thus considered undetermined instead of MRD negative.

- Responses and MRD evaluated at Cycle 4, after final BR cycle, at Month 9, and/or at time of suspected response

Safety Run-in for GCLLSG CLL14 Trial to Evaluate Tolerability of Obinutuzumab and Venetoclax

Fischer *et al.* ASH 2015. Abstract 496.

Key eligibility criteria

- Treatment-naïve
- Confirmed CLL
- Coexisting medical conditions assessed by CIRS total score >6 and/or estimated CrCl >70 mL/min

RUN IN →

6 cycles of obinutuzumab and venetoclax followed by 6 additional cycles of venetoclax
Obinutuzumab IV 100 mg on Day 1, 900 mg on Day 2, 1000 mg on Day 8 and Day 15 of cycle 1 and 1000 mg on day 1 for cycles 2-6
Weekly dose ramp-up of venetoclax with 20, 50, 100, 200, and up to 400 mg administered starting on Day 22 of cycle 1

- Safety run-in with 12 patients prior to initiation of randomized phase of CLL14 trial, successor trial to CLL11
- Risk assessment for TLS based on absolute lymphocyte count and largest diameter or measurable lymph nodes
- Study-defined stopping criteria for all patients was one treatment-related death or one grade 4 adverse event related to clinical tumor lysis syndrome despite prophylaxis

Safety Run-in for GCLLSG CLL14 Trial to Evaluate Tolerability of Obinutuzumab and Venetoclax: Efficacy

Fischer *et al.* ASH 2015. Abstract 496.

Efficacy Outcomes (N=12)	
After 3 cycles	
ORR	**92%**
CR	**92%**
PR	**8%**
After 6 cycles	
ORR	**100%**
PR	**100%**

Safety Run-in for GCLLSG CLL14 Trial to Evaluate Tolerability of Obinutuzumab and Venetoclax: Safety

Fischer *et al.* ASH 2015. Abstract 496.

Adverse Event, n (%)	N=13 Grade 1/2
Infusion-related reaction	61.5%
Infection	46.2%
Diarrhoea	38.5%
Hyperkalaemia	38.5%
Constipation	38.5%
Nausea	30.8%
Dizziness	30.8%
Cough	30.8%
Fatigue	23.1%
Headache	23.1%
Pruritus	23.1%

Adverse Event, n (%)	N=13 Grade 3/4
Neutropenia	38.5%
Infusion-related reaction	15.4%
Syncope	15.4%
Thrombocytopenia	15.4%
Tumour lysis syndrome*	15.4%
Febrile neutropenia	15.4%
Bradycardia	7.7%
Hyperglycaemia	7.7%
Influenza	7.7%
Leukopenia	7.7%
Pyrexia	7.7%
Respiratory tract infection	7.7%
Transaminase increased	7.7%

*Laboratory TLS

- Total number of adverse events: 134; patients with ≥1 adverse event: 13 (100%)
- Total number of grade 3 or 4 adverse events: 21; patients with ≥1 grade 3 or 4 adverse event : 9 (69.2%)
- Median time on treatment was 64.5 days (range, 34-155 days) at time of analysis for VEN

Safety Run-in for GCLLSG CLL14 Trial to Evaluate Tolerability of Obinutuzumab and Venetoclax: Summary

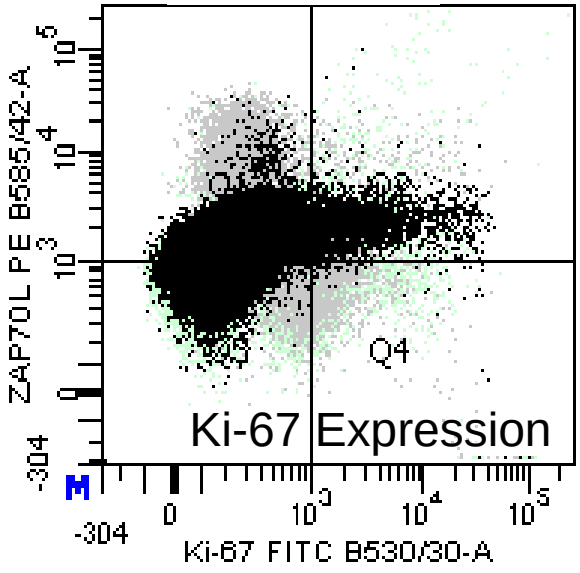
Fischer *et al.* ASH 2015. Abstract 496.

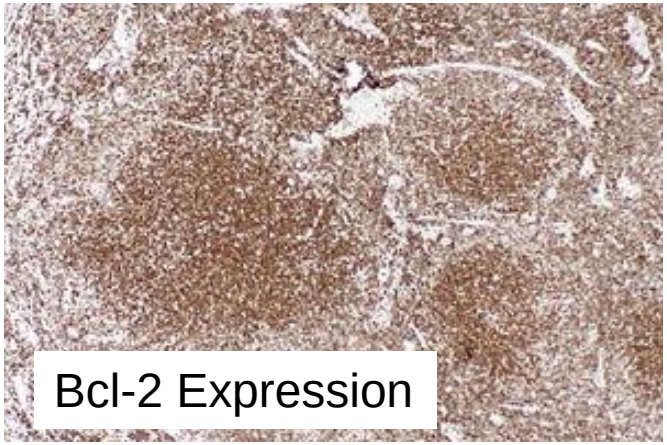
- None of the protocol-defined stopping criteria were met
- The events of laboratory TLS were transient and did not result in treatment delays
- Initiating treatment with obinutuzumab followed by venetoclax appeared tolerable in treatment-naïve, elderly patients with CLL and coexisting medical conditions
- Preliminary efficacy data appear promising; based on IDMC review of the safety data, a randomized trial has started enrolling

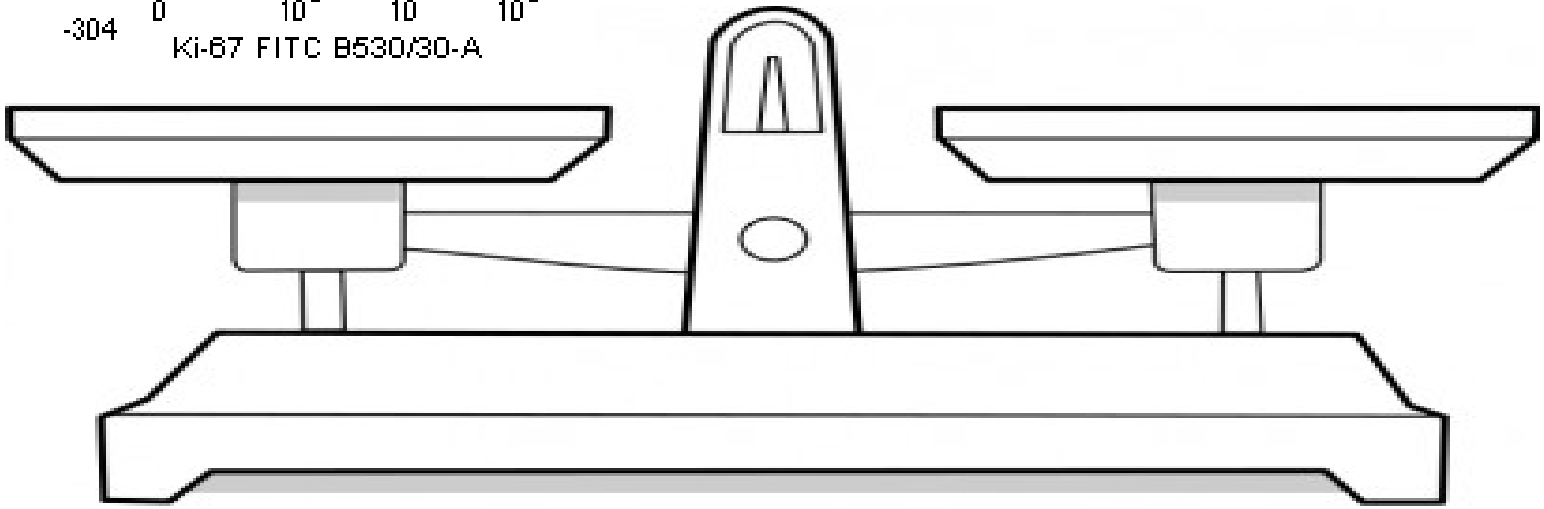
Pathophysiology of CLL: Proliferation vs Apoptosis

Proliferation

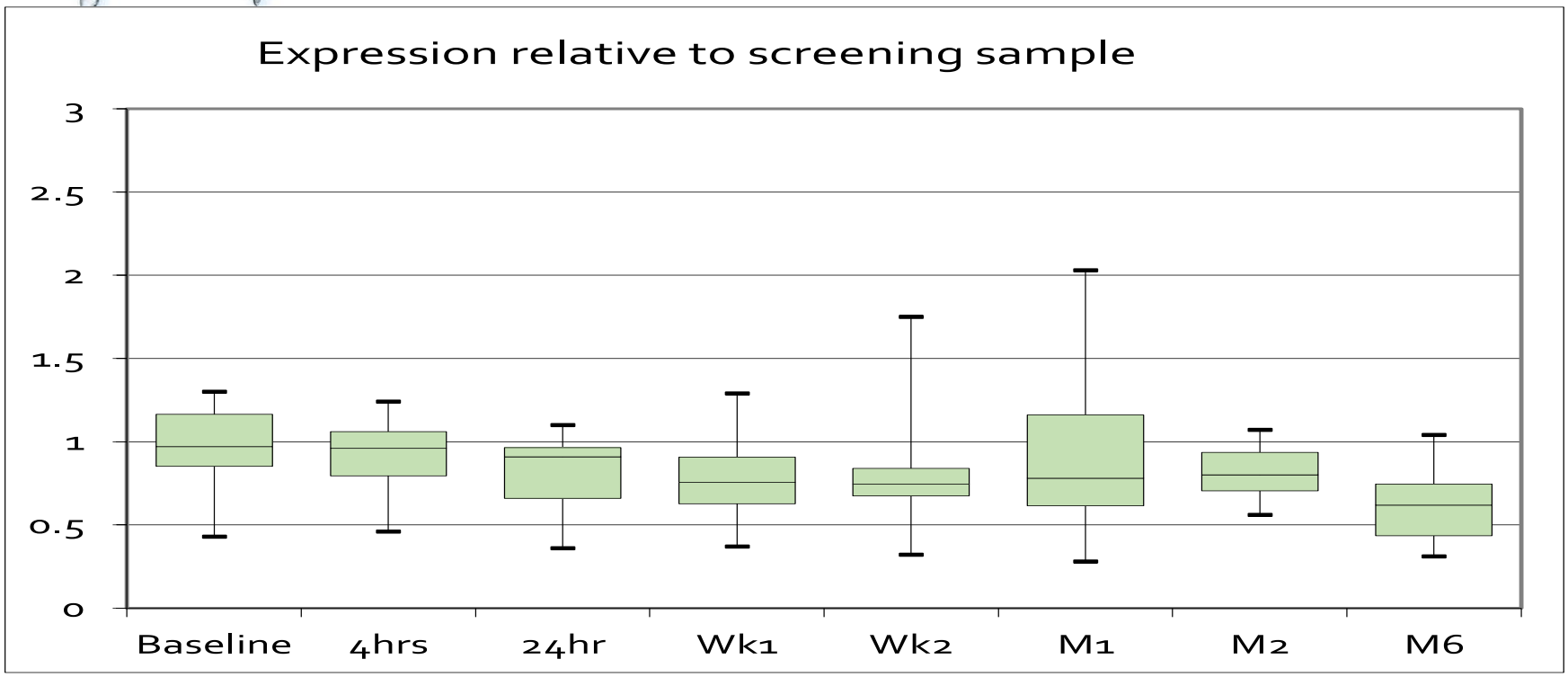
Apoptosis







Persistently strong BCL2 expression during ibrutinib treatment



Bloodwise
Beating blood cancer since 1960

TAP

Munir *et al.*, April 2016, BSH/ISH, Glasgow

CLARITY

Bloodwise TAP
Beating blood cancer since 1960

Assessment of venetoCLAx in combination with ibRutInib plus ABT-199 in relapsed/refracTory chronic lymphocYtic leukaemia

- Feasibility study to investigate the combination of ibrutinib and venetoclax (ABT-199) in relapsed refractory CLL.
- MRD response as the primary outcome measure to determine whether ibrutinib + venetoclax (ABT-199) shows sufficient evidence of activity and safety.
- Results from this trial will inform a potential modification of Flair

50 patients with relapsed/refractory CLL who are ibrutinib naïve

Conclusions: Venetoclax in CLL

Impressive single agent activity

- Minority of patients achieving MRD negative remissions
- Possibility of stopping therapy
- Well tolerated except for tumour lysis syndrome

Extremely promising activity in combination

- Apparent synergy with antibodies (rituximab and obinutuzumab) and chemoimmunotherapy (BR)
- Higher MRD eradication rates

Combinations with other targeted therapies, particularly ibrutinib, are attractive