THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

Chronic Lymphocytic Leukemia

Relapsed CLL Treatment

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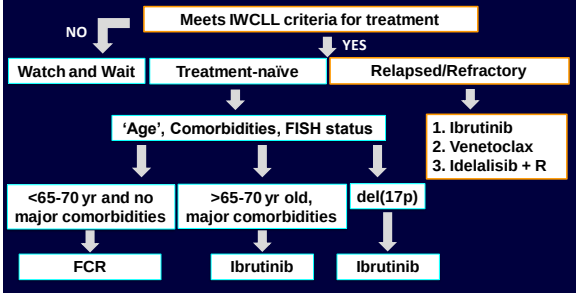
Financial Disclosures

Research Funding
Pharmacyclics, Abbvie, Genentech, Infinity, BMS, Pfizer, ADC Therapeutics, Seattle Genetics, Incyte, Celgene, AstraZeneca, Servier, Verastem, Cellectis, Adaptive Biotechnologies

Advisory Board
Pharmacyclics, Novartis, ADC Therapeutics, Pfizer, Servier, Novimmune, Abbvie, Verastem, Adaptive Biotechnologies, Janssen

Current Standard Rx of CLL

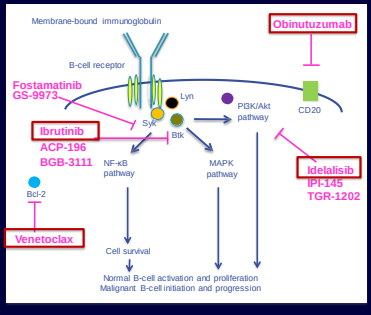


Jain N, O'Brien S. Blood Rev. 2016;233-44.

Presentation Outline

- Approved therapies in R/R CLL
  - BTK inhibitor Ibrutinib
  - PI3K inhibitor Idelalisib + Rituximab
  - BCL2 inhibitor Venetoclax
- Combination therapies in R/R CLL
- CART therapy in CLL

Targeting Key Signaling Pathways in CLL

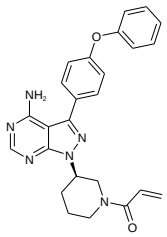


Friedman DR, Weinberg JB. The Hematologist. 2013.

IBRUTINIB

BTK Inhibitor

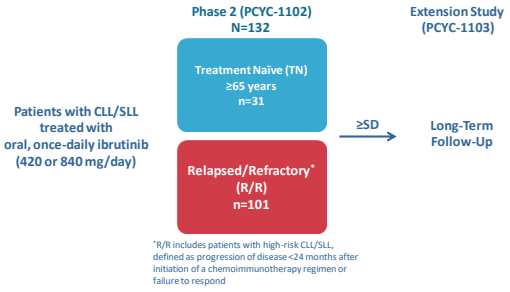
Ibrutinib (PCI-32765)
A Selective Inhibitor of BTK



- Forms a specific bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC_{50} = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- In chronic lymphocytic leukemia (CLL) cells promotes apoptosis and inhibits CLL cell migration and adhesion

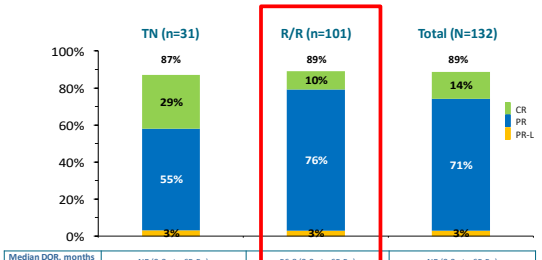
Advani, R. et al, *J Clin Oncol*. 2012;42:7906.
Honigberg LA. et al, *Proc Natl Acad Sci U S A*.2010;107:13075.
Herman SEM et al, *Blood*.2011;117: 6287-6296.
Ponader, et al, ASH Meeting Abstracts. 2010; 116:45.

5-Year Experience With Ibrutinib Monotherapy
PCYC-1102/1103 Phase 2 Study Design



O'Brien et al. ASH 2016, Abstract 233

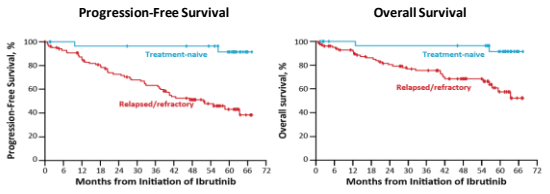
5-Year Experience With Ibrutinib Monotherapy
Best Response



Median DOR, months (range)	NR (0.0+ to 65.5+)	56.8 (0.0+ to 65.5+)	NR (0.0+ to 65.5+)
Median follow-up, months (range)	62 (1–67)	49 (1+–67)	56 (1+–67)

O'Brien et al. ASH 2016, Abstract 233

5-Year Experience With Ibrutinib Monotherapy Survival Outcomes: Overall Population

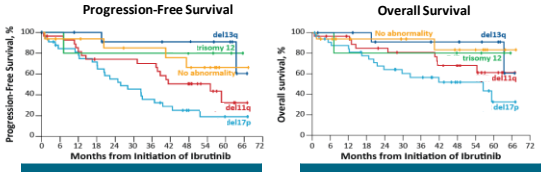


	Median PFS	5-year PFS
TN (n=31)	NR	92%
R/R (n=101)	52 mo	43%

	Median OS	5-year OS
TN (n=31)	NR	92%
R/R (n=101)	NR	57%

O'Brien et al. ASH 2016, Abstract 233

5-Year Experience With Ibrutinib Monotherapy Survival by FISH in R/R Patients*



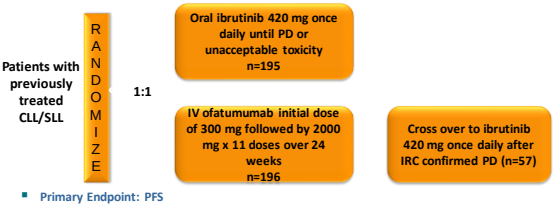
	Median PFS	5-year PFS
Del17p (n=34)	26 mo	19%
Del11q (n=28)	55 mo	33%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	66%

	Median OS	5-year OS
Del17p (n=34)	57 mo	32%
Del11q (n=28)	NR	61%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	83%

*Only 2 patients in the TN group showed PD or death. Subgroup analyses, therefore, focused on the R/R population.
**No del17p, del11q, del13q, or trisomy 12; in hierarchical order for del17p, and then del11q.

O'Brien et al. ASH 2016, Abstract 233

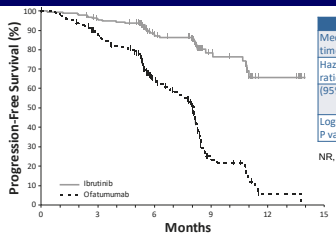
RESONATE™ Phase 3 Study Design



- Primary Endpoint: PFS
- Stratification according to:
  - Disease refractory to purine analog chemoimmunotherapy (no response or <12 months)
  - Presence or absence of 17p13.1 (17p del)
- At time of interim analysis, median time on study was 9.4 months

Byrd J et al. NEJM 2014

Progression-Free Survival

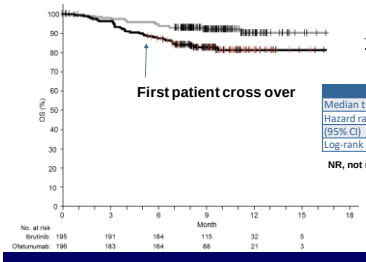


	Ofatumumab	Ibrutinib
Median time (mo)	8.08	NR
Hazard ratio	0.215	
(95% CI)	(0.146-0.317)	
Log-rank P value	< 0.0001	

NR, not reached

Byrd J et al. NEJM 2014

Overall Survival



Ibrutinib (n=195, 16 events)
Ofatumumab (n=196, 33 events

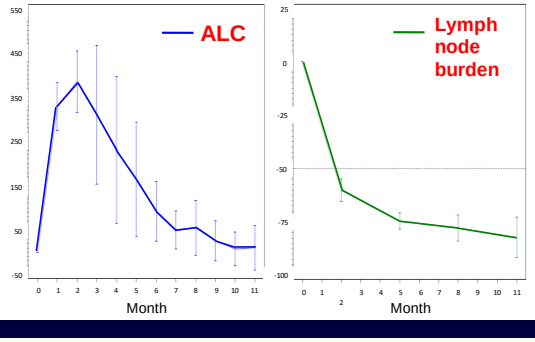
First patient cross over

	Ofatumumab	Ibrutinib
Median time (mo)	NR	NR
Hazard ratio	0.434	
(95% CI)	(0.238-0.789)	
Log-rank P value	< 0.0049	

NR, not reached

Byrd J et al. NEJM 2014

Pattern of Response: Blood Lymphocytes vs. Lymph Nodes



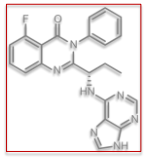
IDELALISIB

PI3K-δ Inhibitor

Idelalisib, A Novel Small Molecule Inhibitor

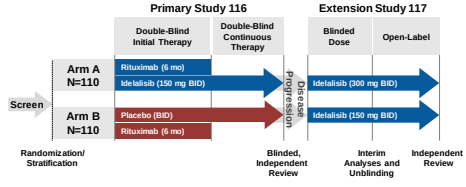
Class I PI3K Isoform	α	β	γ	δ
Expression	Ubiquitous	Ubiquitous	Leukocytes	Leukocytes
EC_{50} (nM)	>10,000	1,419	2,500	9

- Targeted, highly selective, oral inhibitor of PI3K-delta (δ)
- Inhibits proliferation and induces apoptosis in CLL cells
- Inhibits homing and retention of CLL cells in lymphoid tissues reducing cell survival



Coutre et al. EHA 2014:S704

Phase 3 Trial of Idelalisib + Rituximab in Relapsed CLL: Subgroup Analysis of High-Risk Groups

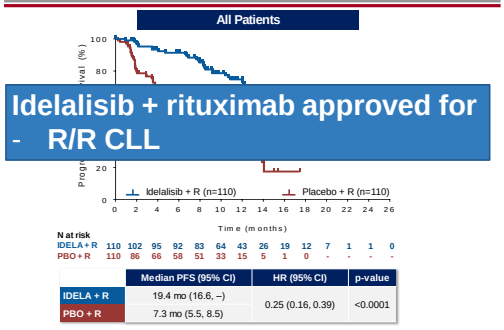


	Median Follow-up, months		
	IDELA + R	PBO + R	
1st Interim Analysis	4	4	DMC halted trial (Furman NEJM 2014)
2nd Interim Analysis	6	5	Blind ended (Coutre ASCO 2013) • Arm A continues • Arm B crosses over
Update	13	11	PFS, OS by subgroup analysis

Sharman et al., ASH 2014, Abstract 330

PFS, Including Extension Study*

Idelalisib + R vs Placebo + R



	Median PFS (95% CI)	HR (95% CI)	p-value
IDELA + R	19.4 mo (16.6, –)	0.25 (0.16, 0.39)	<0.0001
PBO + R	7.3 mo (5.5, 8.5)		

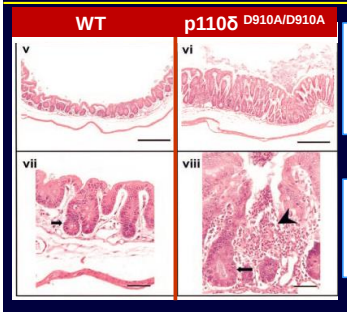
*Placebo + R includes those patients who received open-label idelalisib after unblinding without prior progression (n=42).

Sharman et al., ASH 2014, Abstract 330

Serious Adverse Events In ≥2 Patients On IDELA + R

SAE, n (%)	IDELA + R (N=110)	Placebo + R (N=108)
Patients with any SAE	54 (49)	41 (38)
Pneumonia	10 (9)	11 (10)
Pyrexia	10 (9)	3 (3)
Febrile neutropenia	5 (5)	5 (5)
Sepsis	5 (5)	3 (3)
Pneumonitis	4 (4)	1 (1)
Pneum. jirov. pneumonia	3 (3)	1 (1)
Diarrhea	3 (3)	0
Hypercalcemia	2 (2)	2 (2)
Abdominal pain	2 (2)	1 (1)
Hypoxia	2 (2)	1 (1)
Colitis	2 (2)	0
Deep vein thrombosis	2 (2)	0
Sepsis syndrome	2 (2)	0
Neutropenia	2 (2)	0
Neutropenic sepsis	2 (2)	0
Lung infection	2 (2)	0
Transient ischemic attack	2 (2)	0

Colitis with PI3K-δ Inhibition



p110δ D910A/D910A

- IBD like picture
- Mucosal hyperplasia
- Crypt abscess

Clinical Management

- Late event (>6mos)
- Drug hold
- Oral/IV steroids

Okkenhaug et al. Science 2002.

Idelalisib Summary

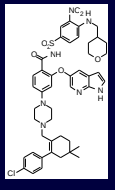
- Approved for patients with relapsed CLL in combination with rituximab
- Immune-mediated colitis, transaminitis, pneumonitis
- EMA/FDA Advisory (March 2016)
  - Increased deaths due to infections in Phase III trials of idelalisib vs. placebo
  - All patients PCP prophylaxis
  - CMV monitoring

VENETOCLAX (ABT-199)

Bcl-2 Inhibitor

Bcl-2 in CLL

- Bcl-2 expression is uniformly high in CLL
- ABT-199 is a selective, potent, orally bioavailable Bcl-2 inhibitor
- ABT-199 binds Bcl-2 with high affinity and with substantially lower affinity to Bcl-x_L, Bcl-w and MCL-1



ABT-199

Souers et al. Nature Med. 2013

Venetoclax CRR and ORR Rates by Subgroups

Variable	No.	ORR %	CR %
All patients	116	79	20
17p deletion	31	71	16
Unmutated IGHV	46	76	17
Flu - refractory	70	79	16
Prior Rx ≥ 4	56	73	16
Age ≥ 70	34	71	21
Nodes > 5 cm	67	78	8

Roberts et al N. Engl J Med 2016; 374; 311-22

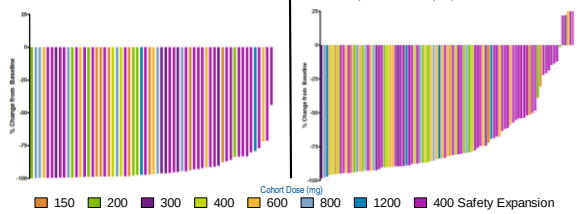
Best Percent Change from Baseline in Blood Lymphocyte Count and Nodal Mass by CT Scan

Blood Lymphocytes (n=60)

- Median Time to 50% reduction: 14 days, range [1 – 49]

Nodal Mass by CT Scan (n= 93)

- The median time to 50% reduction 1.4 months, range [0.65 – 13.7]*
- 78 (84%) evaluable patients had at least a 50% reduction in sum of the product of diameters (SPD) of nodal masses

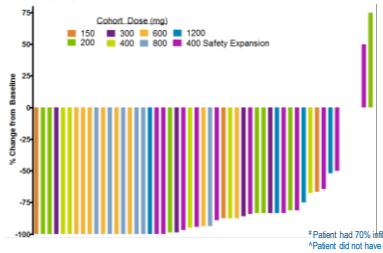


Data represents patients with lymphocyte count >5 x 10⁹/L at baseline

*coincides with first protocol specified CT scan at 6 weeks.

Best Percent Change from Baseline in Bone Marrow Infiltrate (n=51)

- Median time to 50% reduction: 5.5 months, range [1.9 – 17.4]*
- 46/51 (90%) evaluable patients have had at least a 50% reduction.



*Patient had 70% infiltrate at baseline and at Week 24
^Patient did not have CLL infiltrate at baseline.

Anti-tumor activity of ABT-199 was observed in all tumor compartments.

Relapsed CLL
Combination Therapy: Future?

BCRi

+/-

BCL2i

+/-

CD20 mAb

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Combined Venetoclax and Ibrutinib for Patients with Previously Untreated High-Risk CLL, and Relapsed/Refractory CLL A Phase II Trial

Nitin Jain, Philip Thompson, Alessandra Ferrajoli, Jan Burger, Gautam Borthakur, Koichi Takahashi, Prithviraj Bose, Zeev Estrov, Elias Jabbour, Marina Konopleva, Yesid Alvarado, Tapan Kadia, Musa Yilmaz, Courtney DiNardo, Maro Ohanian, Jorge Cortes, Rashmi Kanagal-Shamanna, Keyur Patel, Naveen Garg, Xuemei Wang, Nina Fru, Nichole Cruz, Varsha Gandhi, William Plunkett, Hagop Kantarjian, Michael Keating, William Wierda

Department of Leukemia, MDACC
ASH 2017, Abstract 429

VEN + IBR in CLL, ASH 2017

BCR vs. BCL2 Inhibitors

	BCR Inhibitor (Ibrutinib)	BCL2 Inhibitor (Venetoclax)
Response	Blood ++ LN +++ Marrow +	Blood +++ LN ++ Marrow +++
Lymphocytosis	+++	-
CR in R/R CLL	10%	20-25%
AE profile	Atrial fibrillation, neutropenia, bleeding	TLS, neutropenia

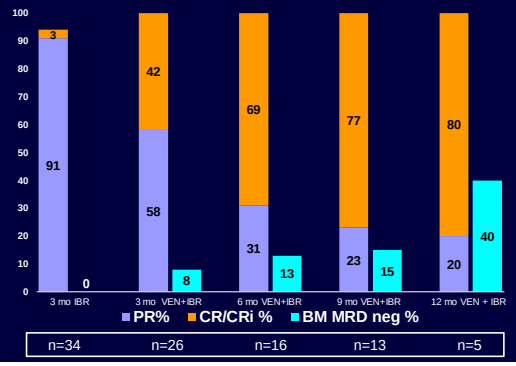
VEN + IBR in CLL, ASH 2017

Ibrutinib + Venetoclax Clinical Trial

- Investigator-initiated phase II trial
- Patients with a diagnosis of CLL/SLL
  - Cohort 1: relapsed/refractory CLL
  - Cohort 2: untreated with at least one high-risk feature
    - del(17p) or mutated *TP53*
    - del(11q)
    - unmutated *IGHV*
    - ≥65 yrs

VEN + IBR in CLL, ASH 2017

Response: R/R Cohort



Venetoclax Plus Rituximab is Superior to Bendamustine Plus Rituximab in Patients with Relapsed / Refractory Chronic Lymphocytic Leukemia – Results from Pre-Planned Interim Analysis of the Randomized Phase 3 MURANO Study

Adapted from the Seymour presentation at ASH on December 12, 2017

John F. Seymour[1], Thomas Kipps[2], Barbara Eichhorst[3], Peter Hillmen[4], James D'Rozario[5], Sarit Assouline[6], Carolyn Owen[7], John Gerecitano[8], Tadeusz Robak[9], Javier De la Serna[10], Ulrich Jaeger[11], Guillaume Cartron[12], Marco Montillo[13], Rod Humerickhouse[14], Elizabeth A. Punnoose[15], Yan Li[15], Michelle Boyer[16], Kathryn Humphrey[16], Mehrdad Mobasher[15], Arnon P. Kater[17]

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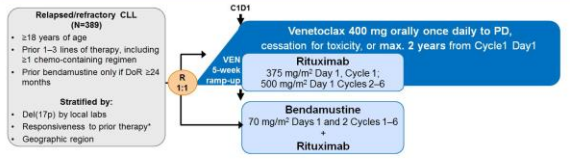
The American Society of Hematology – 59th Annual Meeting and Exposition
Atlanta, Georgia ● December 9–12, 2017

Seymour, JD et al. ASH 2017, Abstract LBA-2

MURANO Study Design



Adapted from the Seymour presentation at ASH on December 12, 2017

NCT02005471
*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≤24 months after chemoimmunotherapy.

4

Patient Demographics and Disease Characteristics Balanced Between Arms

Status	Venetoclax + Rituximab (N=194)	Bendamustine + Rituximab (N=195)
Age, median (range), years	64.5 (28–83)	66.0 (22–85)
Lymphocyte count (×10⁹/L), median (range)	43.1 (0.3–703)	54.7 (0.3–536)
Del(17p)*, n/N (%)	46/173 (27)	46/169 (27)
Unmutated IGHV*, n/N (%)	123/180 (68)	123/180 (68)
Mutated *TP53**, n/N (%)	48/192 (25)	51/184 (28)
Number of prior therapies, n (%)		
1	111 (57)	117 (60)
2	57 (29)	43 (22)
3	22 (11)	34 (17)
>3	4 (2)	1 (1)
Prior therapies, n (%)		
Alkylating agent	182 (93)	185 (95)
Purine analog	157 (81)	158 (81)
Anti-CD20 antibody	153 (78)	148 (76)
B-cell receptor pathway inhibitors	5 (3)	3 (2)

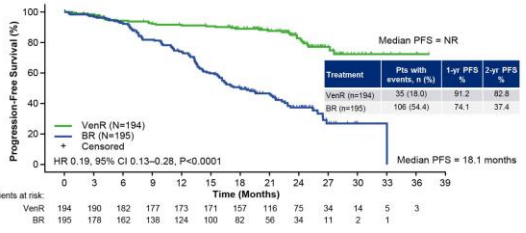
*Central lab

Adapted from the Seymour presentation at ASH on December 12, 2017

As of 8 May 2017

6

Superiority of VenR vs. BR Confirmed by Independent Review Committee-Assessed PFS



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As of 8 May 2017

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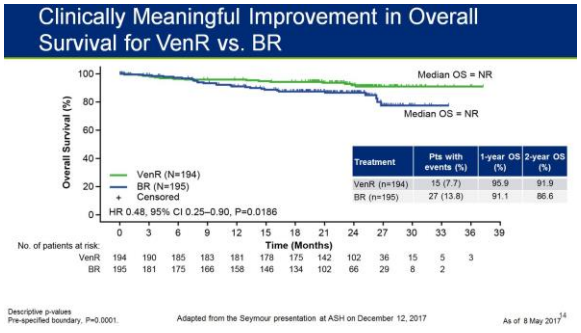

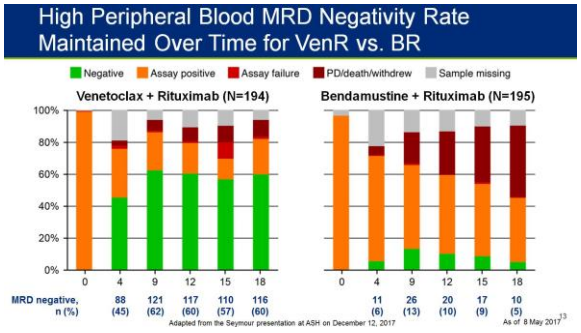

JCAR014 CART in High-risk R/R CLL

- 24 pts with R/R CLL
  - No of prior therapies 5
  - Ibrutinib refractory 79%
  - Venetoclax refractory 25%
  - FDG-avid PET 93%
  - Documented RT/PLL 33%
- Response at 4 weeks (JCAR014 + Cy/Flu)
  - ORR 74%, CR 21%
  - PET+ disease CR 64%
  - Bone marrow disease 88% MRD^{neg}

Turtle C et al. ASH 2016

Conclusions

- Targeted therapies – great future in CLL
  - Ibrutinib – Approved for CLL
  - Idelalisib – Approved for R/R CLL
  - Venetoclax – Approved for R/R del(17p) CLL
- Combination therapies are the future

Thank you!

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Ibrutinib intolerance and resistance in CLL

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KNIGHT CANCER INSTITUTE
Oregon Health & Science University

1

Disclosures for Danilov

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  - Leukemia & Lymphoma Society
  - Lymphoma Research Foundation
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  - Takeda Oncology
  - Gilead Sciences
  - Genentech
- **Consultancy/Honoraria**:
  - Genentech
  - Verastem
  - TG Therapeutics
  - Astra Zeneca
  - Juno Therapeutics
  - Gilead Sciences

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Post-ibrutinib world

- **Ibrutinib intolerance**
  - Role of other BTK inhibitors (acalabrutinib)
  - Alternative pathway medications
  - Factors predicting poor ibrutinib outcomes
- **Ibrutinib resistance**
  - Mechanisms (in CLL)
  - What to do?

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Ibrutinib clinical trials experience

Disposition	TN (n=31)	R/R (n=101)
Median time on study, months (range)	62 (1–67)	49 (1–67)
Patients remaining on ibrutinib therapy, n (%)	20 (65%)	30 (30%)
Primary reason for discontinuation, n (%)		
Progressive disease	1 (3%)	33 (33%)
Adverse event	6 (19%)	21 (21%)
Consent withdrawal	3 (10%)	5 (5%)
Investigator decision	0	11 (11%)
Lost to follow-up	1 (3%)	1 (1%)

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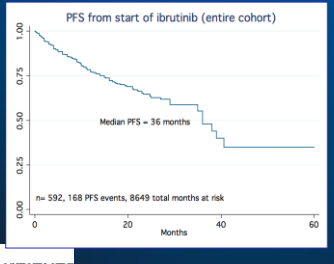
O'Brien, Furman et al, ASH 2016 4

Ibrutinib 'real world' experience

d/c rate = 42% after median f/u of 17 months

Toxicity: 50%

Disease progression: 10-20%



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Mato AR et al, ASH 2016 5

Reasons for Discontinuation

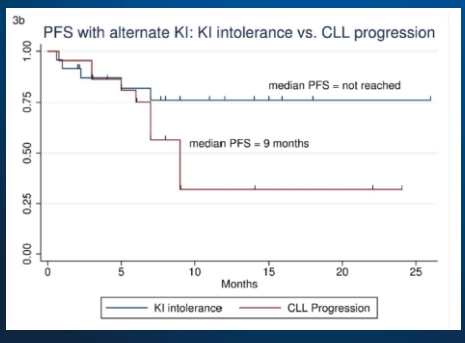
Front Line (%)	Relapsed (%)
arthralgias (42)	atrial fibrillation (12.3)
Afib (25)	Infection (11)
Rash (16)	Pneumonitis (10)
	Bleeding (9)
	Diarrhea (7)

Median Time to Discontinuation

Bleeding	8 months
Diarrhea	7.5 months
Atrial fibrillation	7 months
infection	6 months
arthralgia	5 months
pneumonitis	4.5 months
rash	3.5 months

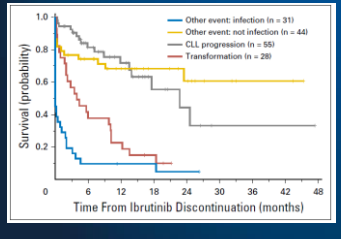
Mato AR et al, ASH 2016 6

Outcomes following ibrutinib failure



Mato et al, 2017

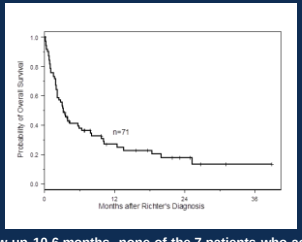
Outcomes following ibrutinib failures



OS 4 months (Richters)
OS 22 months (progression)

Woyach et al, 2017

Richters syndrome on novel agents: The median OS for the entire cohort was 3.3 months



With a median follow-up 10.6 months, none of the 7 patients who achieved CR had died

Presented by: Matthew S. Davids, MD, MMSc

ASCO ANNUAL MEETING '17 | #ASCO17

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

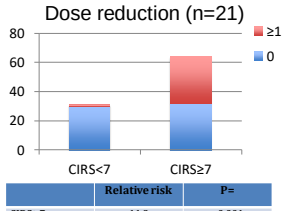
Medical comorbidities assessed by CIRS negatively impact survival in the era of targeted therapies in CLL: a multicenter retrospective analysis

Max J. Gordon MD[1], Stephen M. Amrock MD SM[1], Xavier Rivera[3], Spencer James MD MPH[2], Sudhir Manda MD FACP[2], Stephen E. Spurgeon MD[1], Daniel Persky [3], Alexey V. Danilov MD PhD[1]

[1]Oregon Health & Science University, Portland, OR [2]Geisel School of Medicine at Dartmouth, Hanover, NH [3]University of Arizona, Tucson, AZ

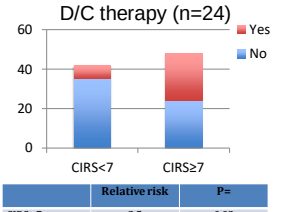
Tolerance of ibrutinib

Dose reduction (n=21)



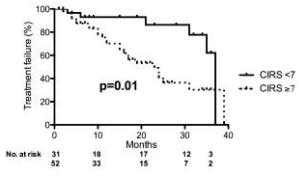
	Relative risk	P=
CIRS≥7	11.9	<0.001
CIRS3-4	4.6	0.01

D/C therapy (n=24)

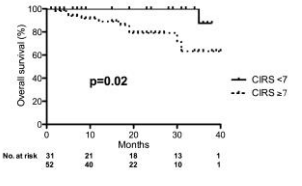


	Relative risk	P=
CIRS≥7	2.5	0.02
CIRS3-4	3.8	0.005

Outcomes with ibrutinib

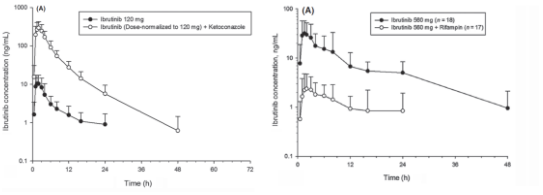


- Median 37 vs 23 months



- OS at 24 months 100 vs 79%

Ibrutinib is a CYP3A4 substrate



Black dots – ibrutinib alone
White dots – ibrutinib PLUS

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De Jong et al, 2015

Acalabrutinib Monotherapy in Patients With Ibrutinib Intolerance: Results From the Phase 1/2 ACE-CL-001 Clinical Study

Farrukh T. Awan,[1] Anna Schuh,[2] Jennifer R. Brown,[3] Richard R. Furman,[4] John M. Pagel,[5] Peter Hillmen,[6] Deborah M. Stephens,[7] Ahmed Hamdy,[8] Raquel Izumi,[8] Priti Patel,[8] Min Hui Wang,[9] John C. Byrd[1]

[1]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [2]University of Oxford, Oxford, UK; [3]Dana-Farber Cancer Institute, Boston, MA; [4]Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY; [5]Swedish Medical Center, Seattle, WA; [6]St. James's University Hospital, Leeds, UK; [7]University of Utah Huntsman Cancer Institute, Salt Lake City, UT; [8]Acerta Pharma, Redwood City, CA

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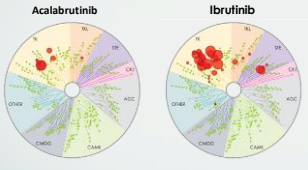
Awan F, et al. ASH 2016

Acalabrutinib (ACP-196)

- Acalabrutinib is a highly selective, potent BTK inhibitor
- Minimal off-target effects on TEC, EGFR, or ITK signaling in vitro

Kinase Selectivity Profiling at 1 µmol/L[1]



Larger red circles represent stronger inhibition

Kinase Inhibition IC_{50} (nmol/L)[1]

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	93	7.0
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

[1]Covey AACR 2015. Abstract 2596.

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Awan F, et al. ASH 2016

ACE-CL-001: Acalabrutinib Monotherapy in CLL

- ACE-CL-001 is an ongoing, multinational, phase 1/2 study designed to evaluate acalabrutinib monotherapy in patients with CLL/SLL.
- Previously reported ORR with acalabrutinib monotherapy:
  - Relapsed/refractory: 95% (85% PR, 10% PRL; n = 60).[1]
  - Treatment-naïve: 97% (87.5% PR; 10% PRL; n = 72).[2]
- Data are presented for 33 patients in the ibrutinib-intolerant cohort with data cut on 01 September 2016.

[1]Byrd JC, et al. *N Engl J Med*. 2016;374(4):323-332. [2]Byrd JC, et al. ASCO 2016 [poster presentation].

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Awan F, et al. ASH 2016

Patient Disposition

Disposition, n (%)	
Treated	33 (100)
Discontinued treatment	9 (27)
Progressive disease	3 (9)
Adverse event[a]	3 (9)
Physician decision[b]	1 (3)
Other[c]	2 (6)
On treatment	24 (73)

[a]Stroke (hemorrhagic) and fungal infection led to death (n = 1 patient each); metastatic endometrial cancer (n = 1).
[b]Concurrent hemophilia.
[c]Increase in BTK C481S mutation frequency in peripheral blood and central nervous system involvement (n = 1 patient each).

- Median time on treatment: 12.2 months (range, 0.2-23.6 months)

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Awan F, et al. ASH 2016

Recurrence of Prior Ibrutinib-Related AEs

	Grade Change in Severity on Acalabrutinib vs on Ibrutinib		
Adverse Event	**Increased**	**Decreased**	**Unchanged**
Arthralgia (n = 1)		2 → 1	
Atrial fibrillation (n = 1)			2 → 2
Contusion (n = 1)	1 → 2[a]		
Diarrhea (n = 2)		2 → 1 3 → 1	
Ecchymosis (n = 1)		2 → 1[a]	
Fatigue (n = 3)	1 → 2[a]	2 → 1	1 → 1
Muscle spasms (n = 1)			1 → 1
Myalgia (n = 1)			1 → 1
Peripheral edema (n = 1)			1 → 1
Panniculitis (n = 1)		3 → 2[a]	
Rash (n = 3)		3 → 1*	1 → 1 1 → 1[a]

Multiple occurrences of the same AE for a given patient were counted once for each Preferred Term.
*Determined by investigator as related to acalabrutinib.

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Awan P, et al. ASH 2016

Key Findings

- Acalabrutinib was well tolerated in ibrutinib-intolerant patients.
  - A total of 12 of 33 (36%) patients experienced AE recurrence, most of which were decreased or the same severity.
- No patients discontinued because of a recurrent AE.
- Acalabrutinib has promising activity in ibrutinib-intolerant patients.
  - ORR: 79%
  - 81% of responding patients have a duration of response (PRL or better) ≥12 months.
  - Median PFS has not been reached.
- Acalabrutinib efficacy in ibrutinib-intolerant patients is being evaluated in an ongoing phase 2 trial (NCT02717611).

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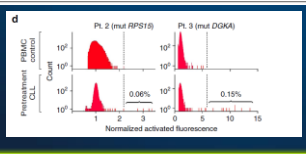
Ibrutinib RESISTANCE

Table 1. Characteristics of Six Patients with Resistance to Ibrutinib.

Patient No.	Age	Prior Therapies	Baseline Cytogenetic Features*	Study Treatment and Daily Dose†	Duration of Ibrutinib Treatment	Best Response	Time to First Response	Identified Mutations of Interest‡
	yr	mo.			days		days	
1	59	5	del(17p13.1), trisomy 12	Ibrutinib, 560 mg	621	Partial	70	C481S mutation in BTK
2	59	3	del(11q22.3)	Bendamustine–rituximab for 6 cycles; ibrutinib, 420 mg	388	Complete	70	C481S mutation in BTK
3	51	2	complex karyotype	Ofatumumab for 24 wk; ibrutinib, 420 mg	674	Complete	85	C481S mutation in BTK
4	69	9	del(17p13.1), complex karyotype	Ibrutinib, 840 mg	868	Partial	133	C481S mutation in BTK
5	61	4	del(17p13.1), complex karyotype	Ofatumumab for 24 wk; ibrutinib, 420 mg	505	Partial	85	L845F, R665W, and S707Y mutations in PLCγ2 and C481S mutation in BTK
6	75	2	del(17p13.1), complex karyotype	Ibrutinib, 420 mg	671	Partial	159	R665W mutation in PLCγ2



Woyach et al, 2014
Burger J et al, 2016

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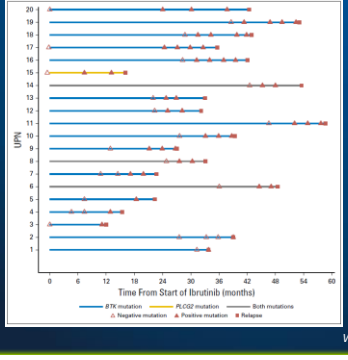
Mutations in BTK/PLCγ precede ibrutinib RESISTANCE



Woyach et al, 2017

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After ibrutinib – what's next?

- **Acalabrutinib (ibrutinib-intolerant only)**
- **Alternative BTK inhibitors which do not bind C481S:**
  - GDC-0853
  - SNS-062
  - ARQ-531
- **Venetoclax**
- **Idelalisib (Duvelisib, Umbralisib)**
- **Other: PD-1; CART; CDK inhibitors (dinaciclib, voruciclib)**

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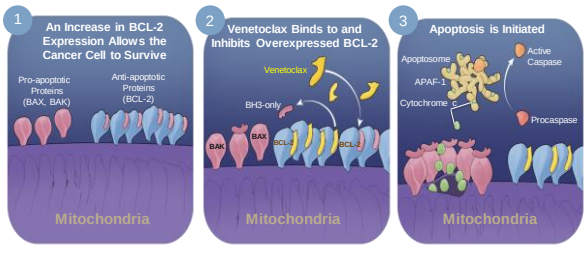
Venetoclax: Selective BCL-2 Inhibitor



- Venetoclax is a potent, orally bioavailable agent with a BCR-independent mechanism of action and substantial activity in heavily pre-treated CLL (Roberts AW et al, *NEJM* 2015)

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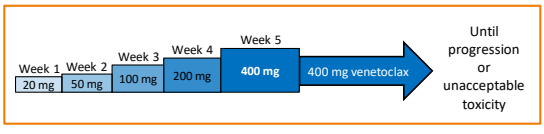
Venetoclax Dosing Schedule



- All patients
  - had tumor burden assessment by imaging for nodal size and absolute lymphocyte count at enrollment
  - received prophylaxis for tumor lysis syndrome (TLS) with uric acid reducers and hydration
- Patients with high tumor burden were hospitalized prior to dosing to facilitate TLS prophylaxis
- Laboratory values were monitored for evidence of tumor lysis for at least 24 hours after the first dose at each dose level

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Venetoclax in IBRUTINIB resistance

	Main cohort (n=43)	Expansion cohort (n=48)	All patients (n=91)
Prognostic factors based on site-reported data‡			
Non-mutated *IGHV*	25/29 (86%)	25/38 (66%)	50/67 (75%)
del(17)(p13.1)	21/43 (49%)	21/47 (40%)	42/90 (47%)
del(11)(q22.3)	13/43 (30%)	17/48 (33%)	30/91 (33%)
TP53 mutation	15/41 (37%)	14/46 (30%)	29/87 (33%)
CD38 positive	21/42 (50%)	16/44 (36%)	37/86 (43%)
ZAP-70 positive	12/24 (50%)	17/40 (43%)	29/64 (45%)
Treatment history			
Number of previous therapies	5 (1–12)	4 (1–15)	4 (1–15)
Previous ibrutinib use	43 (100%)	48 (100%)	91 (100%)
Time on ibrutinib (months)	18 (1–56)	21 (1–61)	20 (1–61)
Relapsed during or after ibrutinib	11 (26%)	17 (35%)	28 (31%)
Refractory to ibrutinib	32 (74%)	30 (63%)	62 (68%)
Previous idelalisib use§	4 (9%)	7 (15%)	11 (12%)
Time on idelalisib (months)	16 (2–31)	9 (2–33)	9 (2–33)

Jones J et al, 2018 25

Venetoclax after ibrutinib therapy

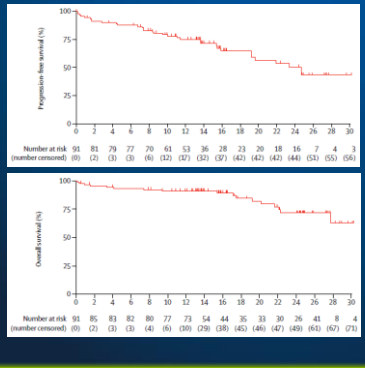
	Main cohort (n=43)	Expansion cohort (n=48)	All patients (n=91)
Overall response	30 (70%, 54-83)	29 (60%, 43-72)	59 (65%, 53-74)
Complete response or complete response with incomplete bone marrow recovery	4 (9%)	4 (8%)	8 (9%)
Nodular partial response	2 (5%)	1 (2%)	3 (3%)
Partial response	24 (56%)	24 (48%)	48 (52%)
Stable disease	8 (19%)	14 (29%)	22 (24%)
Disease progression	1* (2%)	4* (8%)	5 (5%)
Discontinued before response assessment	4 (9%)	2 (4%)	6 (7%)

Data are n (%) or n (%, 95% CI). *Patients who discontinued because of progression.

Table 2: **Response with venetoclax monotherapy as assessed by the investigator**

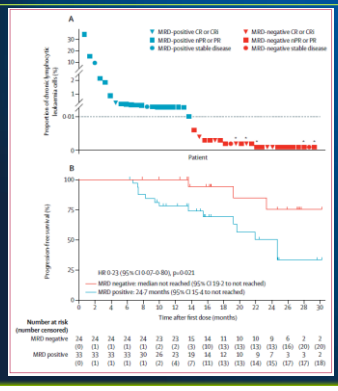
Jones J et al, 2018 26

Venetoclax after ibrutinib therapy



Jones J et al, 2018 27

Venetoclax after ibrutinib therapy



42% blood MRD-negative;
5/13 bone marrow MRD-negative

Jones J et al, 2018

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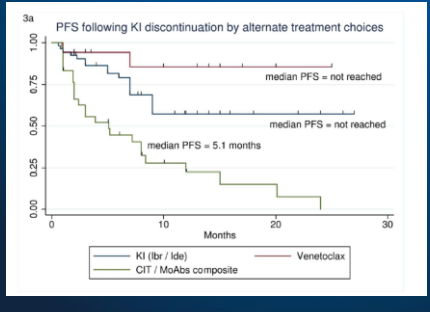
Failed ibrutinib – what to do?



Mato et al, 2017

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Summary

- Ibrutinib intolerance and resistance is becoming a common problem
- Ibrutinib does not 'protect' from Richter's transformation
- Second-generation BTK inhibitors may be a good option for patients intolerant of ibrutinib
- Venetoclax > PI3K in patients resistant to ibrutinib

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An update on Richter Transformation

Dr. Philip Thompson

The University of Texas M.D. Anderson Cancer Center, Department of Leukemia

Disclosures

- Pharmacyclics: Research support, Consultancy
- AbbVie: Research support, Consultancy
- Genentech: Consultancy
- Amgen: Research support, Consultancy

Background

- Richter Transformation (RT) is a transformation of CLL to an aggressive lymphoma, most commonly DLBCL and less commonly classical Hodgkin Lymphoma.[1]
- Rare cases of transformation to plasmablastic lymphoma, histiocytic sarcoma and other uncommon lymphomas[2]
- Occurs in 2-10% of patients with CLL (0.5-1% per year).

[1]Rossi, *Blood* 2011 [2]Jain, P, *Oncology* 2012.

Risk factors for transformation

- Tends to be associated with high-risk CLL biology:

1. Unmutated *IGHV*[1]
2. Del(17p), del(11q), trisomy 12[2]
3. Mutations in *NOTCH1,* which disrupt the PEST domain[3]

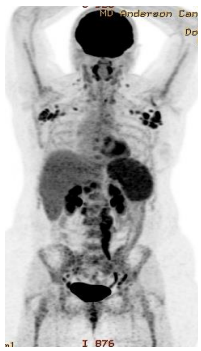
- Possible association with fludarabine-based chemotherapy.

[1]Rossi *Blood* 2011 [2]Strati *CLML* 2015 [3]Rossi Blood 2012.

Clinical features of transformation

- Non-specific.
- Fevers, drenching night sweats, weight loss.
- Rapidly enlarging lymph nodes.
- Elevated LDH. Sometimes hypercalcemia.

PET/CT as a screening tool



PET/CT as a screening/prognostic tool

- 332 MDA patients had PET/CT and subsequent biopsy. Biopsy results classified as RT, histologically-aggressive CLL (HAC) and histologically-indolent CLL (HIC).[1]
- SUV_{max} strongly correlated with histology: median 17.6 vs 6.8 vs 3.7 in RT vs HAC vs HIC, respectively.
- SUV_{max} ≥5 had NPV of 92% but only 38% PPV for RT. PPV improved by cut-off of ≥10 SUV_{max} ≥10 had the optimal discriminatory power for survival by ROC analysis. Median OS was 56.7mo if SUV_{max} <10 and 6.9mo if ≥10.
- Interestingly, the negative prognostic impact of SUV_{max} ≥10 was identical, regardless of the histology.
- PET/CT also very useful in identifying optimal biopsy site

[1]Falchi, *Blood* 2014

Why biopsy?

- Not all that is hot on PET/CT is RT.
- Multiple other entities may mimic RT:

i) "Accelerated CLL" Important to distinguish as treatment is different[1]

ii) EBV-driven lymphomas (eg. after treatment of CLL with alemtuzumab, post-alloSCT. In contrast, RT is usually EBV negative.[2]

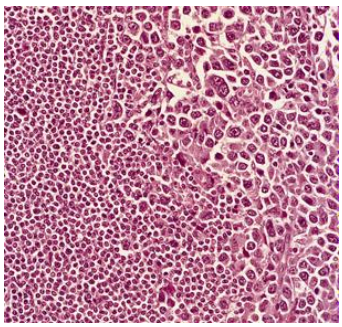
iii) Herpetic lymphadenitits[3], CMV, EBV.

iv) Nocardiosis, fungal infection (esp. histoplasmosis).

v) Granulomatous diseases (eg. TB).

[1]Gine *Haematologica* 2010 [2]Asano *Blood* 2009 [3]Joseph *AJH* 2001

RT DLBCL Histology



From: Warnke RA, Weiss LM, Chan JK, et al. Tumors of the lymph nodes and spleen. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 14, 1995, Washington, DC. Armed Forces Institute of Pathology.

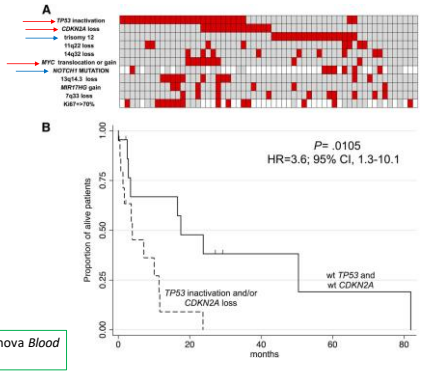
Genomic features of RT

- Clonal relationship to underlying CLL: 80% of DLBCL-RT arise from underlying CLL clone[1,2] through acquisition of additional mutations.
- Genomically less complex than *de novo* DLBCL and molecularly distinct:

1. RT frequently associated with *TP53* mutations, inactivating mutations in *CDKN2A/B*, MYC overexpression, mutations in the PEST domain of *NOTCH1*, stereotyped B-cell receptor.
2. *De novo* DLBCL frequently associated with BCL2 and BCL6 translocations (not seen in RT).

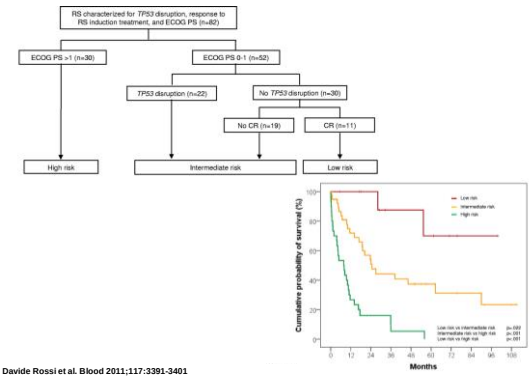
[1.] Rossi, *Blood* 2011. [2.] Chigrinova, *Blood* 2013

Major genomic aberrations in RT



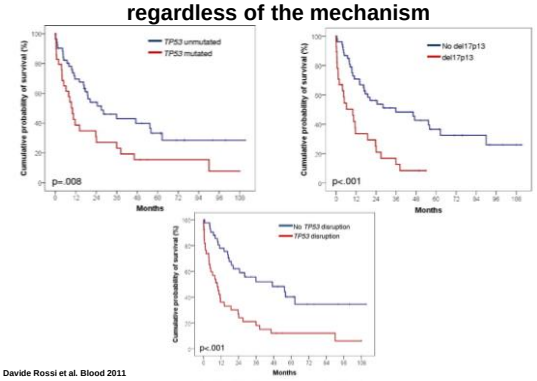
Chigrinova *Blood* 2013

Patients with ECOG >1 and *TP53* disruption have poor outcomes.



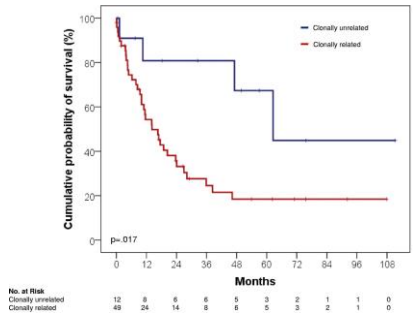
Davide Rossi et al. Blood 2011;117:3391-3401

Loss of functional p53 is a key prognostic marker, regardless of the mechanism



Davide Rossi et al. Blood 2011

Clonally-unrelated "RT" should be thought of as a different disease



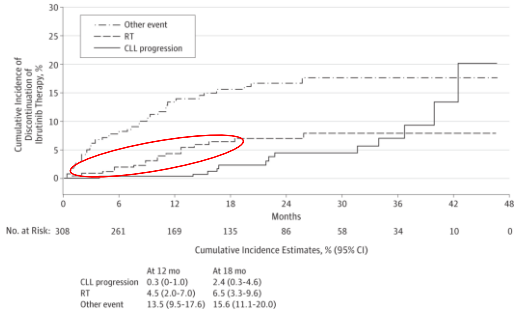
Davide Rossi et al. Blood 2011;117:3391-3401

RT is still a frequent event during targeted therapies for R/R CLL

- Ibrutinib ~5%.[1,2]
- Venetoclax up to 16%.[3]
- Transformation in these studies was an early event.
- Likely driven by disease biology rather than treatment *per se*. These early phase studies were enriched for patients with biologically high-risk disease.

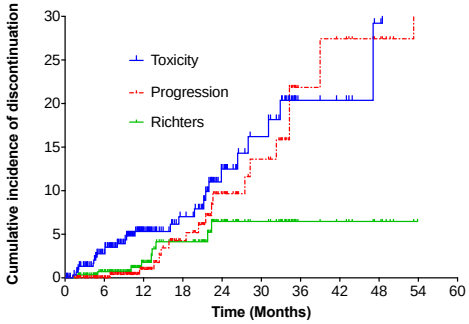
[1]Maddocks, *JAMA Oncol* 2015; [2]Jain, *Blood* 2015; [3]Roberts *NEJM* 2016

Ibrutinib discontinuations over time



Maddocks, K et al. *JAMA Oncology*. 2015;1:80

MDA Data on ibrutinib discontinuation



Jain, P *Cancer* 2017

Prognosis of RT with chemoimmunotherapy

Study	Regimen	n	Median age (years)	Results		
				ORR	CRR	Median OS
Anthracycline-containing Regimens						
Jenke et al, 2011	R-CHOP	15	69 (N/A)	67%	7%	27 months
Dabaja et al, 2001	HyperCVAD	29	61 (36-75)	41%	38%	10 months
Tsimberidou et al, 2003	Rituximab and GM-CSF with alternating hyperCVAD & MTX/cytarabine	30	59 (27-79)	43%	18%	8.5 months
Platinum-containing Regimens						
Tsimberidou et al, 2008	OFAR1	20	59 (34-77)	50%	20%	8 months
Tsimberidou et al, 2013	OFAR2	35	63 (40-81)	43%	8.6%	6.6 months
Fludarabine-containing Regimens						
Giles et al, 1996	PFA or CFA	12	59 (49-74)	45%	N/A	17 months
Tsimberidou et al, 2002	FACPGM	15	62 (42-74)	5%	5%	2.2 months
Radio-Immunotherapy						
Tsimberidou et al, 2004	^{90}Y-ibritumomab	7	56 (44-70)	0%	0%	N/A

Hematopoetic stem cell transplantation

- Durable responses achieved in patients who have achieved an objective response after chemoimmunotherapy (CIT).
- 3y OS 75% compared to 27% without transplant.[1]
- Prolonged survival also achieved after autoSCT.[2]
- Consolidative transplant should be offered to patients who respond to CIT, with the exception of patients who haven't received treatment for CLL and achieve CR with CIT.

[1]Tsimberidou, JCO 2006 [2]Cwynarski JCO 2012.

Treatment of Hodgkin variant

- Generally treated similarly to *de novo* HL (eg. ABVD or BEACOPP).
- Outcome better than for DLBCL-RT, but worse than for *de novo* HL.[1,2]

[1]Tsimberidou, *Cancer* 2006 [2]Brecher *Am J Clin Pathol* 1990

Novel therapeutic strategies for RT

Acalabrutinib

- 2nd generation BTK inhibitor.
- 29 patients with RT.
- Median 4 prior therapies.
- 21% del(17p).
- ORR 38% (14% CR). Median duration of response 5.7mo.
- Median PFS of 3mo.

Hillmen, P. ASH 2016.

Pembrolizumab

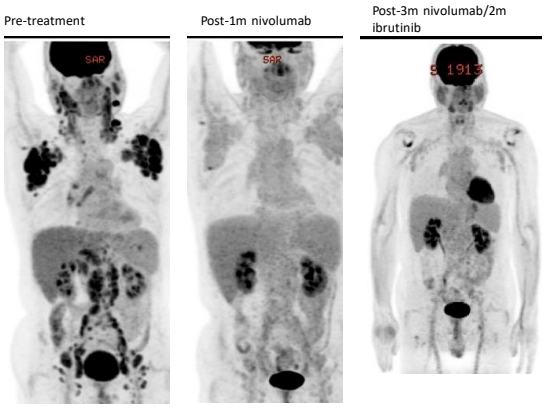
- A phase II trial of pembrolizumab in relapsed and transformed CLL included 9 patients with RT; ORR in these patients was 44% (CR 11%, PR 33%).[1]
- For RT patients, the median progression-free and overall survival was 5.4 months and 10.7 months respectively.
- 0/16 patients with CLL responded.
- PD-L1 expression on RT cells: potentially useful biomarker for response.

[1]Ding *Blood* 2017

Novel therapeutics – ibrutinib + nivolumab

- Encouraging activity.
- Approximately 40% response rate in the first 15 patients[1]
- Rapid responses in RT.

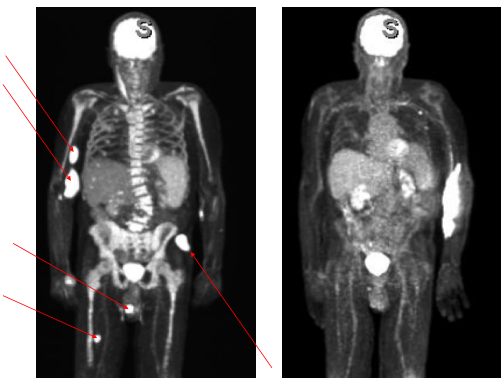
[1]Jain, N. ASH 2017.



Blinatumomab

- CD3x19 bispecific antibody, approved in ALL.
- In R/R DLBCL, overall response rate of 43% (CRR 19%), using high-dose therapy (max 112mcg/d).
- 1 of first 3 patients achieved CR.

75M, developed RT on ibrutinib. Failed CIT, obinutuzumab and ibrutinib + nivolumab

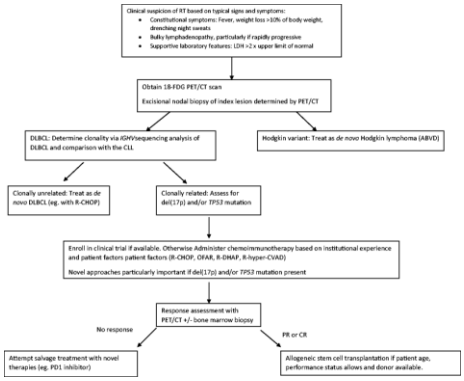


EPOCH-R + venetoclax.

- Multi-center study (DFCI, OSU, UCSD, us) of 20 patients.
- Addition of venetoclax to R-EPOCH.
- Some single-agent activity with venetoclax, but of limited duration. Combination of bcl-2 inhibitor with chemoimmunotherapy may prevent BCL2-mediated resistance to chemotherapy-induced apoptosis.

CAR T-cells

- KiTE CD19 CAR-T highly active in DLBCL. With in the group of DLBCL patients in ZUMA-1 study, ORR was 79% and CRR 52%. 3 patients had therapy-related death.
- Major toxicity. Grade 3 CRS in 13 cases. 28% neurotoxicity (all reversible). 3 treatment-related deaths.
- Despite the toxicity, this represents a major advance.
- Potential to be tested in RT.
- Turtle et al. reported 24 patients with CLL treated in Seattle. Mostly ibrutinib-refractory. Many also venetoclax refractory. ORR 74% (21% CR).
- Possibility to combine with checkpoint inhibition.



Khan and Thompson, Annals of Oncology 2017