B-Cell Lymphomas: Optimizing Treatment with Small Molecule Inhibitors

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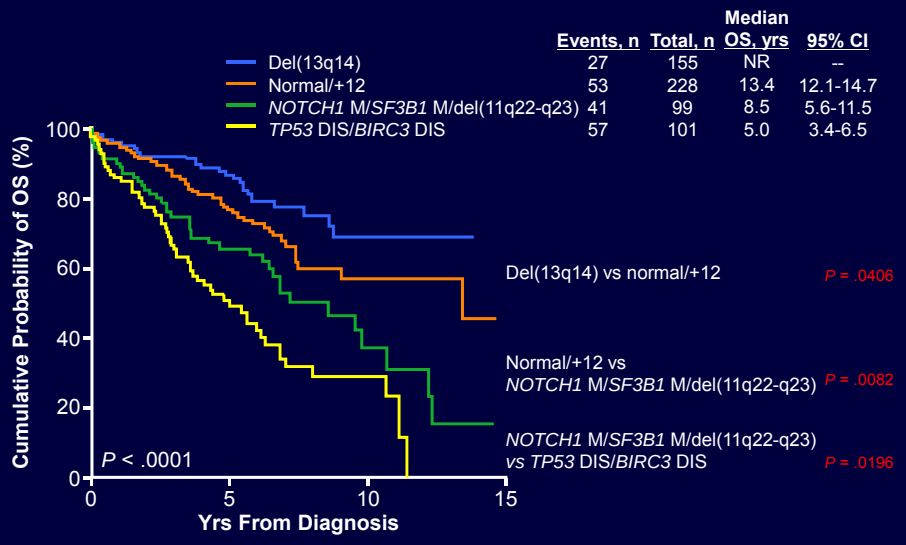
CLL is a Genetically Heterogeneous

Estimate of OS According to Cytogenetics



Rossi D, et al. Blood. 2013;121:1403-1412.

Clinical and Genetic Factors Influence Prognosis

CLL International Prognostic Index: CLL-IPI

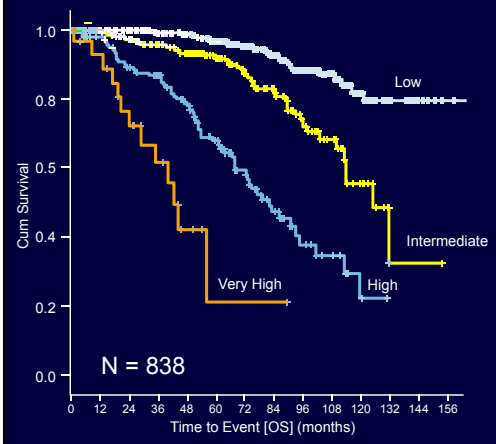
Variable	Adverse Factor	Grading
TP53/17p	Mutated/deleted	4
IGHV status	Unmutated	2
β2M	> 3.5 mg/L	2
Clinical stage	Binet B/C or Rai II-IV	2
Age	> 65 years	1
Prognostic score		0-10

Risk Group	Score
Low	0-1
Intermediate	2-3
High	4-6
Very High	7-10

Kutsch N, et al. ASCO *Annual Meeting Abstracts*. 2015. Abstract 7002.

CLL-IPI: Risk Groups and Outcomes

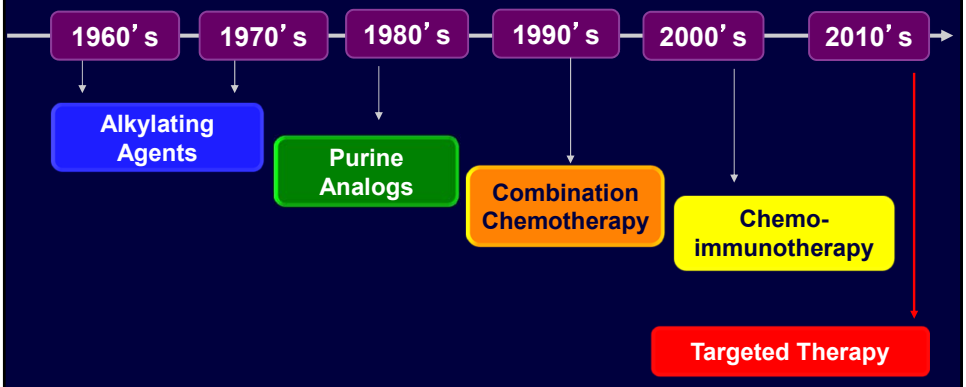
Mayo Clinic Validation Cohort



Risk Group	Patients	5-year OS
Low	47%	94%
Intermediate	33%	91%
High	18%	68%
Very High	73%	21%

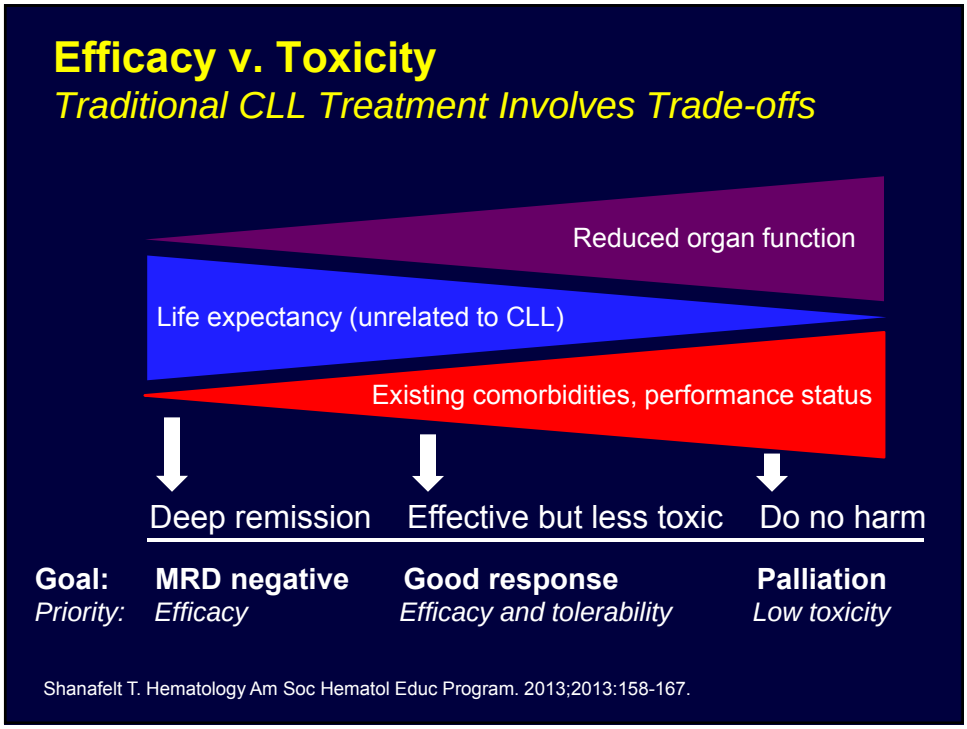
Kutsch N, et al. ASCO *Annual Meeting Abstracts*. 2015. Abstract 7002.

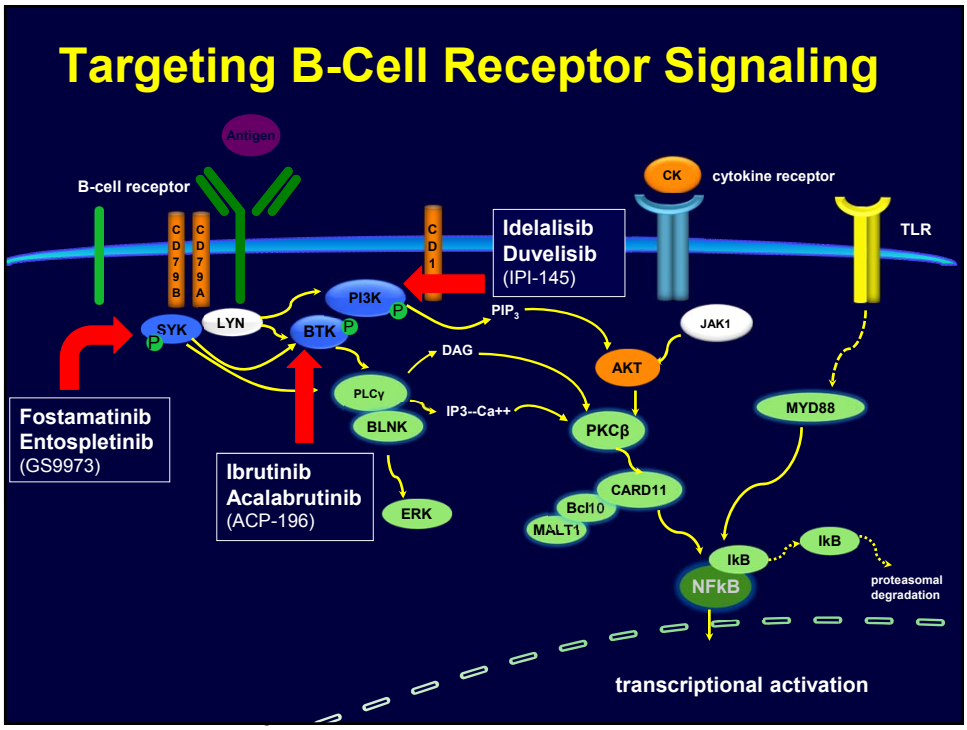
CLL: Evolving Treatment

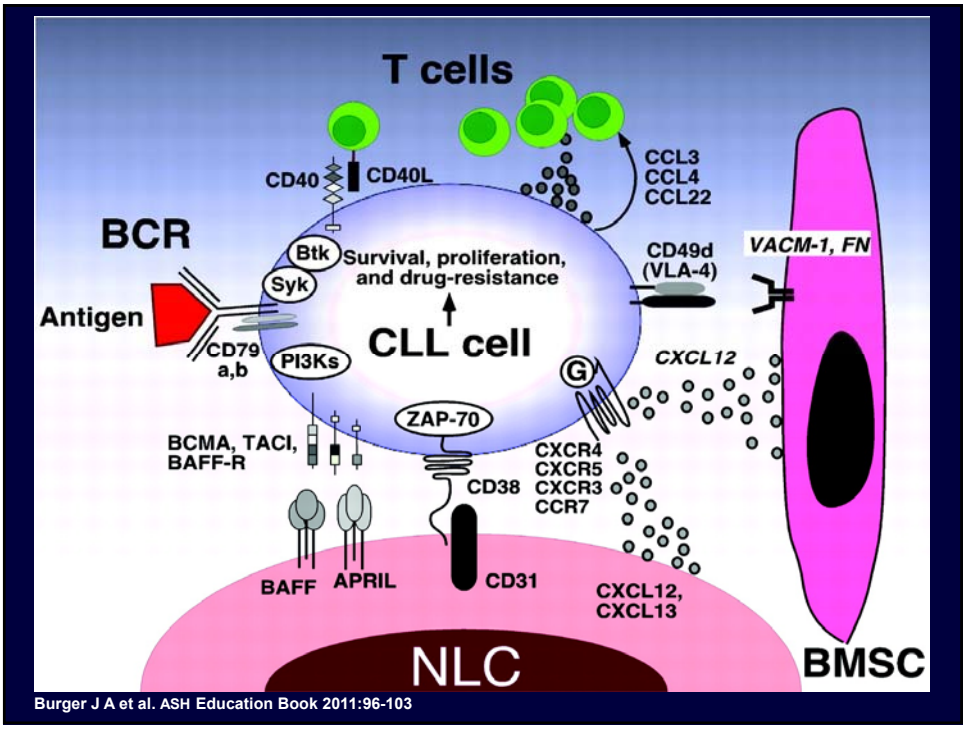


Overall Survival	1980-1984	2000-2004	*P*
5-Year	54.2%	60.2%	< 0.001
10-Year	27.8%	34.8%	< 0.001

Brenner H, et al. *Blood.* 2008;111(10):4916-1921.







Burger J A et al. ASH Education Book 2011:96-103

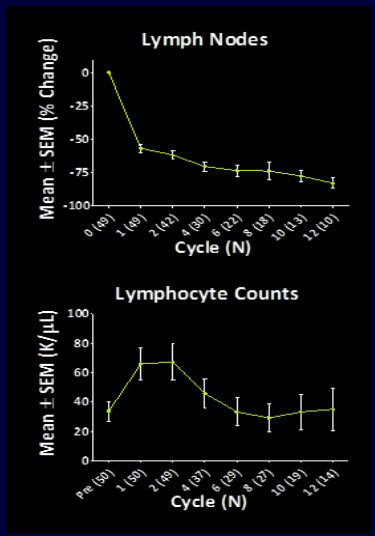
B-cell receptor (BCR) Pathway Inhibition in CLL:
Lymph node reduction with lymphocyte redistribution

- **Lymph node activity**:

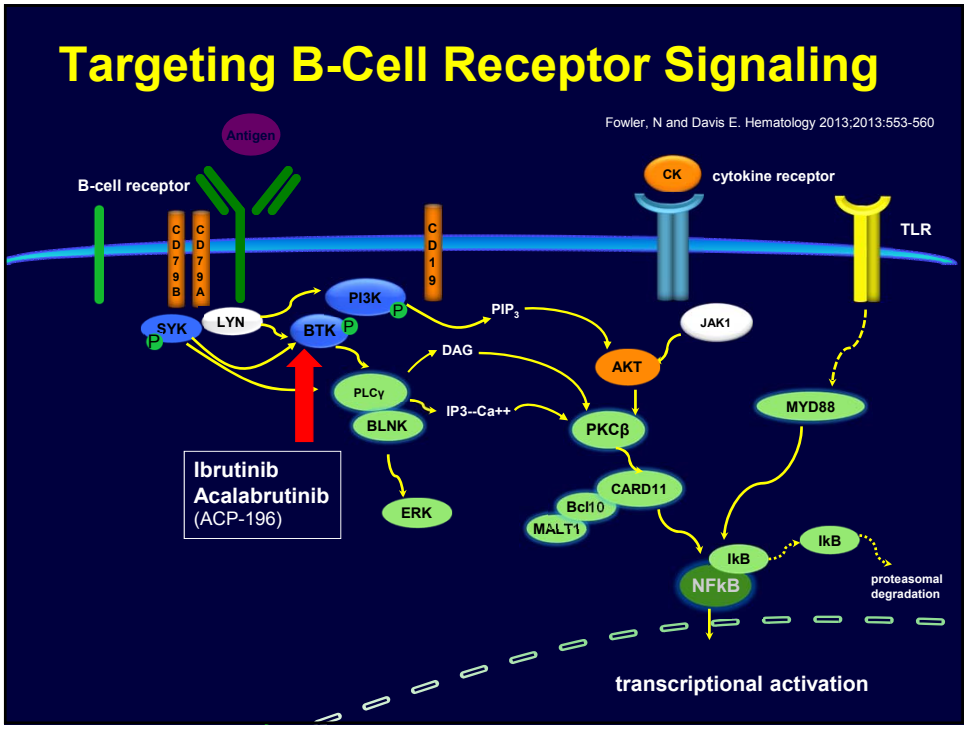
  Rapid, substantial, and sustained reduction in lymph node size

- **Lymphocyte redistribution**:

  A subset of patients have asymptomatic increases in circulating lymphocytes that is maximal during the first 2 cycles and usually decreased thereafter



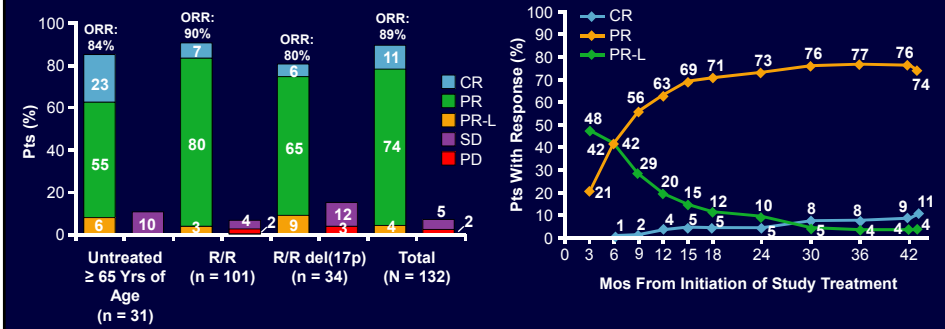
Targeting B-Cell Receptor Signaling



Phase II (PCYC-1102/PCYC-1103) Ibrutinib Monotherapy Trial in CLL/SLL

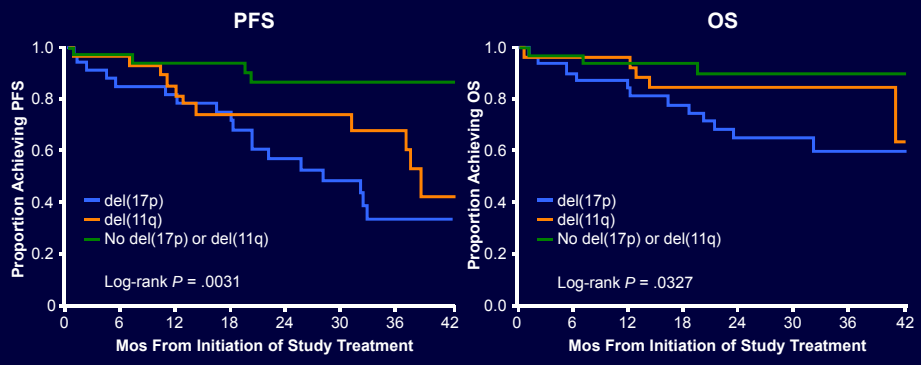
- Patients with CLL/SLL: tx naive (n = 31) and R/R with PD < 24 months after chemoimmunotherapy or failure to respond (n = 101)
  - Patients received ibrutinib 420 or 840 mg/day PO

Best response to ibrutinib improves over time



Byrd JC, et al. Blood. 2015;125:2497-2506.

Ibrutinib Monotherapy at 30 Months
PFS and OS by Cytogenetics

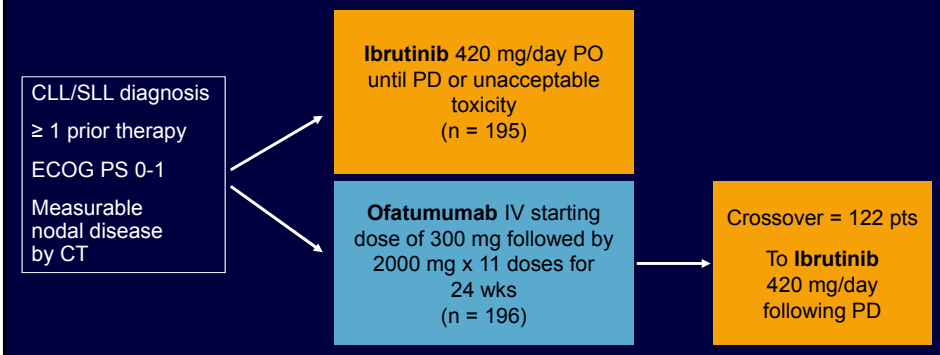


	del(17p) R/R (n = 34)	del(11p) R/R (n = 28)	No del(17p/11q) R/R (n = 34)
30-mo PFS, % (95% CI)	48 (29-65)	74 (53-87)	87 (68-95)
Median PFS, mos (95% CI)	28 (18.2-NE)	38.7 (31.2-NE)	NR (NE-NE)

	del(17p) R/R (n = 34)	del(11p) R/R (n = 28)	No del(17p/11q) R/R (n = 34)
30-mo OS, % (95% CI)	65 (46-79)	85 (65-94)	90 (73-97)
Median OS, mos (95% CI)	NR (21.5-NE)	NR (41.4-NE)	NR (NE-NE)

Byrd JC, et al. Blood. 2015;125:2497-2506.

Phase III RESONATE: Ibrutinib vs Ofatumumab in Previously Treated CLL/SLL

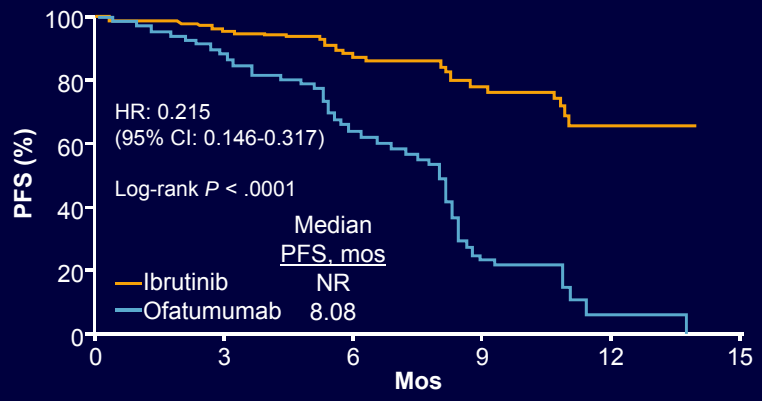


- Primary goal: updated efficacy results, with median treatment duration of 16 mos, relative to genetic features and prior treatment exposure, and updated AE data

Brown JR, et al. ASH 2014. Abstract 3331.
Byrd JC, et al. N Engl J Med. 2014;371:213-223.

Ibrutinib vs Ofatumumab in R/R CLL/SLL

RESONATE: Progression-Free Survival

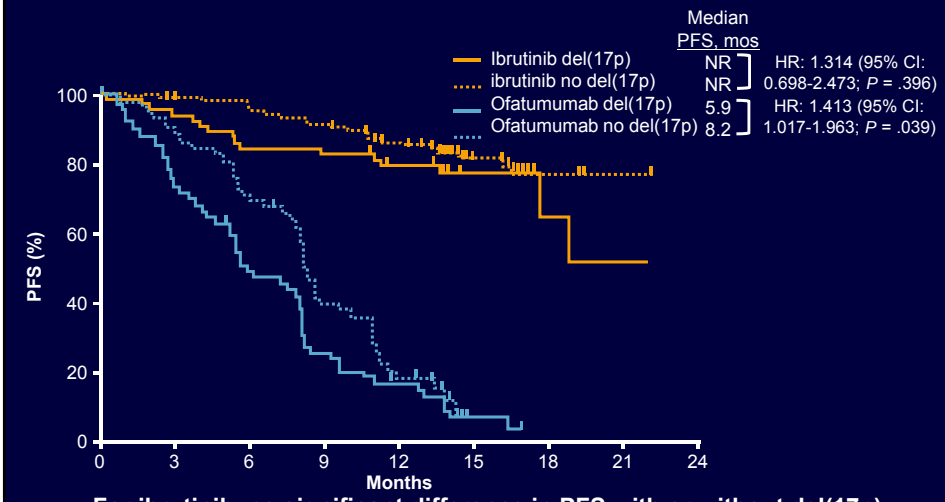


Richter's transformation confirmed in 2 patients on each arm

Byrd JC, et al. N Engl J Med. 2014;371:213-223.

Ibrutinib vs Ofatumumab in CLL/SLL

RESONATE: Progression Free Survival by del(17p)



For ibrutinib, no significant difference in PFS with or without del(17p)

Brown JR, et al. ASH 2014. Abstract 3331.

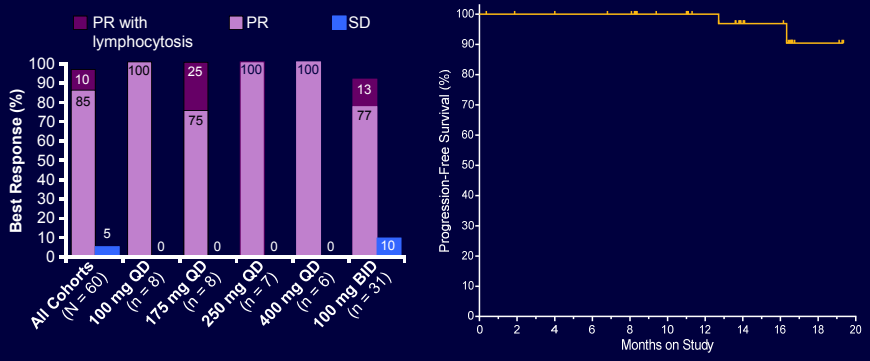
Ibrutinib
Important Toxicities

Diarrhea	Arthralgias	Atrial Fibrillation	Bleeding
▪ Usually occurs early in treatment ▪ Typically mild, self-limiting, and responsive to antidiarrheal agents ▪ RESONATE: Grade 1/2: 48%	▪ Usually mild ▪ RESONATE: Grade 1/2: 17%	▪ 6 to 9% of patients ▪ Increased risk in patients with cardiac risk factors, acute infection, or history of atrial fibrillation ▪ RESONATE: 10 cases (ibrutinib) v. 1 case (ofat)	▪ Fatal bleeding events have occurred ▪ Any grade, including bruising and petechiae: ~50% of patients ▪ Grade ≥3: 6% patients ▪ HOLD drug for 3-7 days pre-/post-surgery depending on bleeding risk of procedure ▪ CAUTION with concomitant anticoagulants

Ibrutinib [package insert] 2016; Byrd JC, et al. *N Engl J Med.* 2014;371(3):213-223.

Acalabrutinib Monotherapy for Relapsed CLL:
Phase I/II Trial in Relapsed CLL

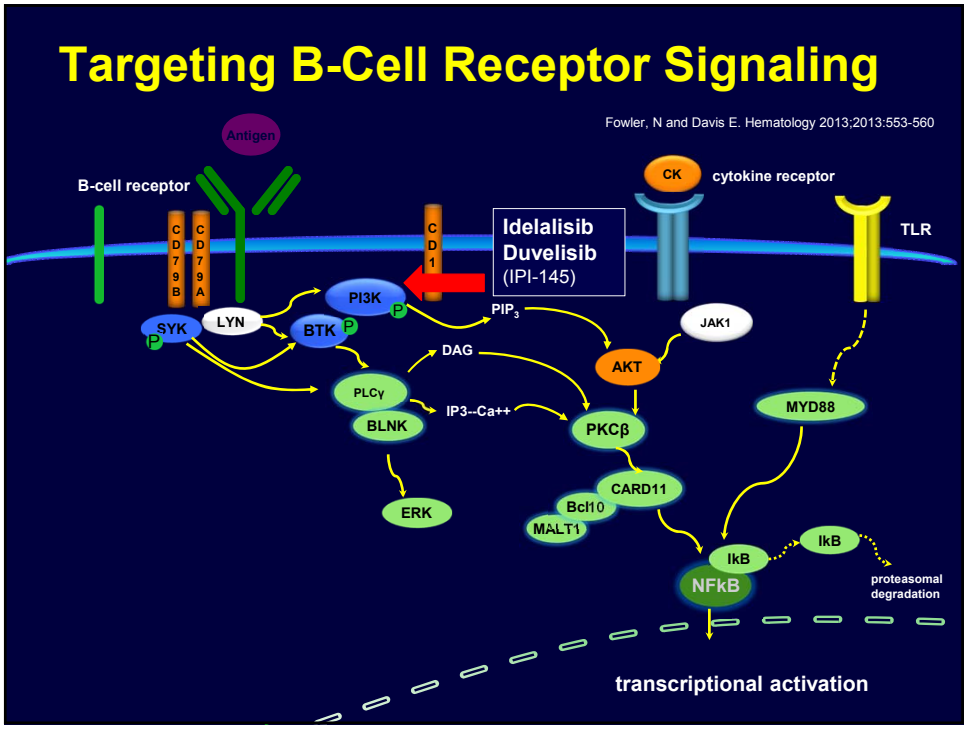
- Patients received oral acalabrutinib QD with dose-escalation (100-400 mg) for phase I cohort or 100 mg BID for phase II (N = 61)
  - Median number of prior therapies: 3 (range: 1-13)



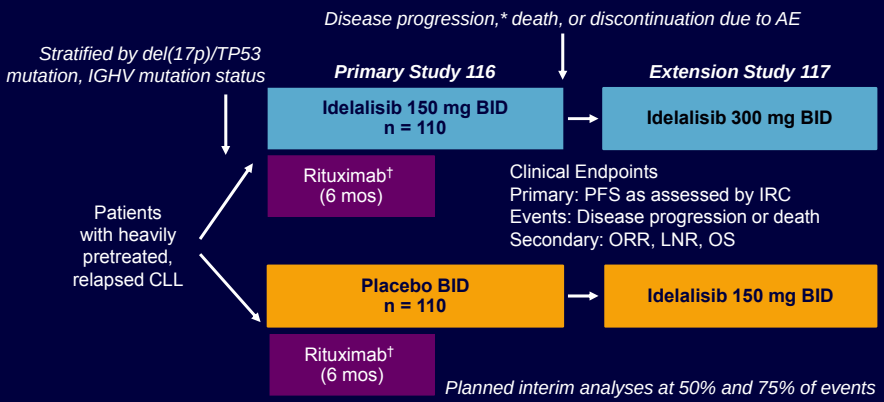
Most AEs observed were grade 1/2 and resolved over time

Byrd JC, et al. N Engl J Med 2016; 374:323-332.

Targeting B-Cell Receptor Signaling



Idelalisib and Rituximab for Relapsed CLL

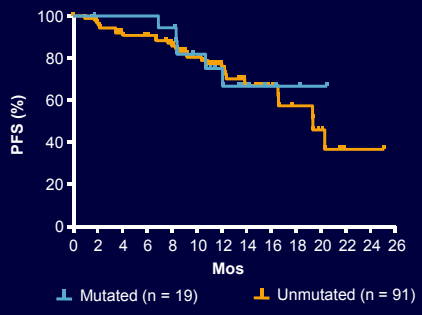


*Patients with disease progression continued on idelalisib Extension Study 117.
†Rituximab schedule: 375 mg/m^2, then 500 mg/m^2 every 2 wks x 4, then 500 mg/m^2 every 4 wks x 3.

Furman R, et al. ASH 2013. Abstract LBA-6; Furman R et al. *NEJM* 2014 [Epub ahead of print]

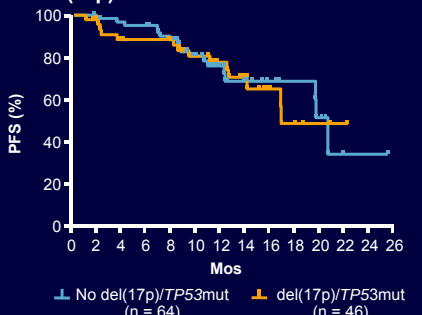
Idelalisib + Rituximab in Relapsed CLL:
Progression Free Survival by Subgroup

***IGHV*: Unmutated vs Mutated**



	Median PFS, Mos (95% CI)	*P* Value
Mut	NR (10.7-NR)	.75
Unmut	19.4 (16.6-NR)	

del(17p)/*TP53*mut: Present vs Not Present



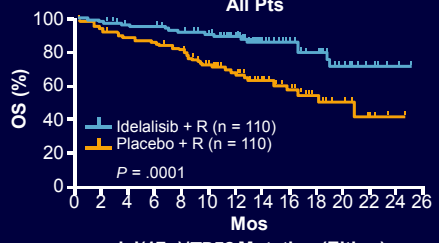
	Median PFS, Mos (95% CI)	*P* Value
No del	20.3 (19.4-NR)	.94
Del	16.6 (13.9-NR)	

*Including extension study.

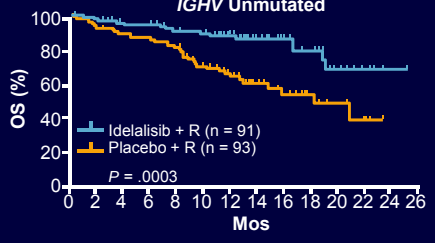
Sharman JP, et al. ASH 2014. Abstract 330.

Idelalisib + Rituximab in Relapsed CLL:
Overall Survival by Subgroup

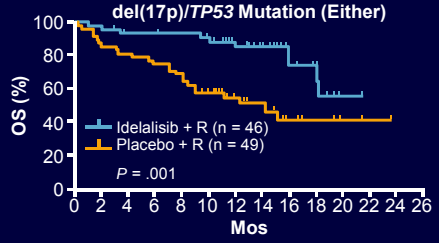
All Pts



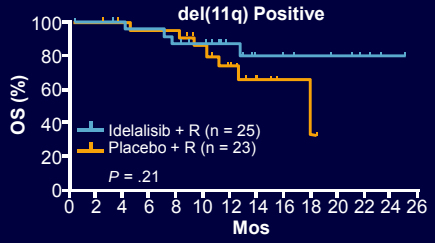
***IGHV* Unmutated**



del(17p)/*TP53* Mutation (Either)



del(11q) Positive



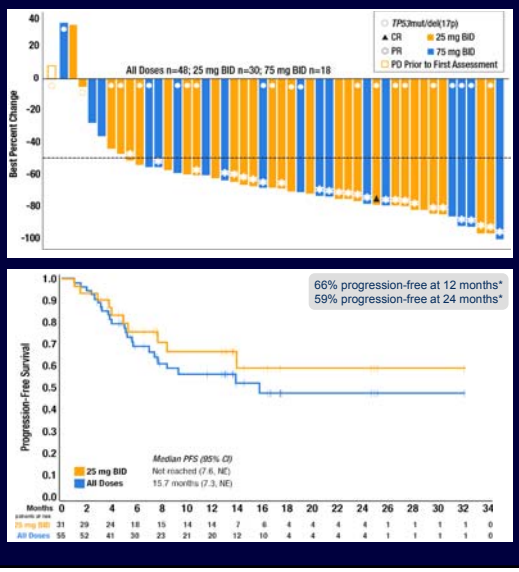
Sharman JP, et al. ASH 2014. Abstract 330.

Idelalisib
Important Toxicities

Diarrhea: occurs in 2 forms	**Transaminase elevations:** generally reversible	**Pneumonitis:** must be distinguished from pneumonia
▪ **Self-limiting:** usually mild; early onset (median 1.5 months); responds to common antidiarrheal agents ▪ **Severe diarrhea:** late onset (median 7 months) responds poorly to antimotility agents but appears to be responsive to budesonide and/or systemic corticosteroids	▪ Usually occurs within first 12 wks ▪ 74% of patients with treatment interruption able to resume idelalisib at a lower dose without recurrence ▪ Permanently discontinue idelalisib if ALT/AST > 20 x ULN	▪ Any patient who presents with pulmonary symptoms should be evaluated for pneumonitis ▪ Hold idelalisib with any symptomatic pneumonitis ▪ Often treated with corticosteroids in addition to continuing antibiotics and holding idelalisib if no improvement

Coutre SE, et al. Leuk Lymphoma. 2015;56:2779-2786.

Duvelisib Monotherapy for R/R CLL
Phase 1b Study Outcomes



- 57% ORR by IWCLL at 25 mg BID, including 1 CR
- 83% (25/30) nodal response rate (≥50% reduction in adenopathy)
- Adverse events were mostly Grade 1 or 2, reversible and clinically manageable

O'Brien et al., ASH 2014, Abstract #3334

NCCN Therapy Recommendations

Relapsed/Refractory Suggested Treatment Regimens†
(in order of preference)

No del(17p)

< 70 yrs without significant comorbidities

- **Ibrutinib***
- **Idelalisib ± rituximab***
- Chemoimmunotherapy
- Ofatumumab
- Obinutuzumab
- Lenalidomide ± rituximab
- Alemtuzumab ± rituximab
- HDMP ± rituximab

≥ 70 yrs and younger patients with comorbidities

- **Ibrutinib***
- **Idelalisib ± rituximab***
- Chemoimmunotherapy
- Ofatumumab
- Obinutuzumab
- Lenalidomide ± rituximab
- Alemtuzumab ± rituximab
- Dose-dense rituximab#

del(17p)/TP53 mutation

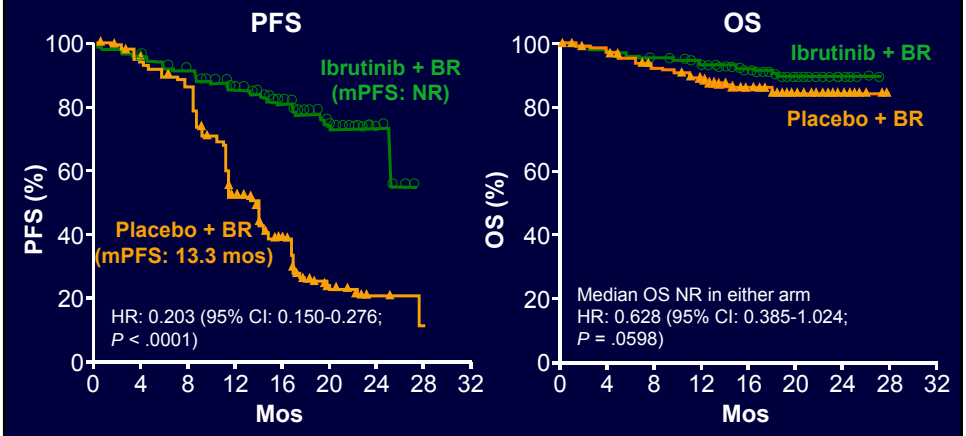
- **Ibrutinib**
- **Idelalisib ± rituximab**
- HDMP ± rituximab
- Lenalidomide ± rituximab
- Alemtuzumab ± rituximab
- Ofatumumab
- OFAR

†All recommendations category 2A unless otherwise stated; *Category 1; #Category 2B recommendation
HDMP = High-Dose Methylprednisolone; OFAR = oxaliplatin, fludarabine, cytarabine, rituximab

Adapted from National Comprehensive Cancer Network. Available at: www.nccn.org; Version 2.2016; Accessed 30 March 2016.

Kinase Inhibitors in Combination with CIT

HELIOS: Phase 3 bendamustine-rituximab +/- ibrutinib

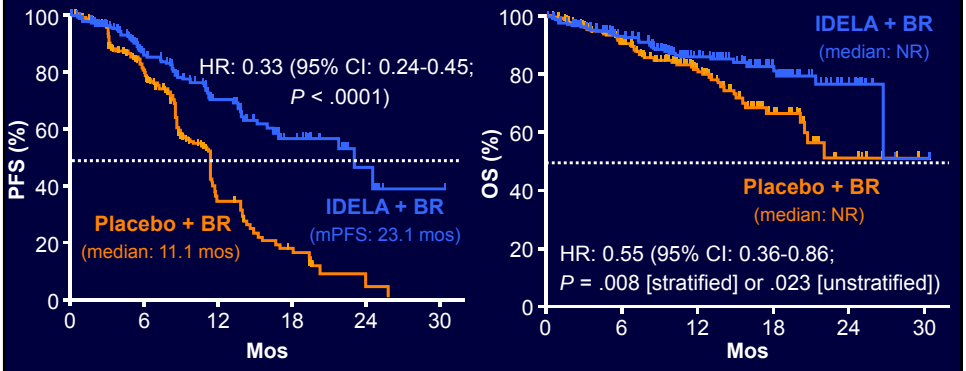


- ORR higher with ibrutinib + BR vs placebo + BR: 82.7% vs 67.8% ($P < .0001$)
- % MRD- higher with ibrutinib + BR vs placebo + BR: 12.8% vs 4.8% ($P = .001$)

Chanan-Khan AAA, et al. *Lancet Oncology* (2016) 17: 200–211.

Kinase Inhibitors in Combination with CIT

Study 115: Phase 3 bendamustine-rituximab +/- idelalisib



ORR higher with idelalisib + BR vs placebo + BR: 68% vs 45%

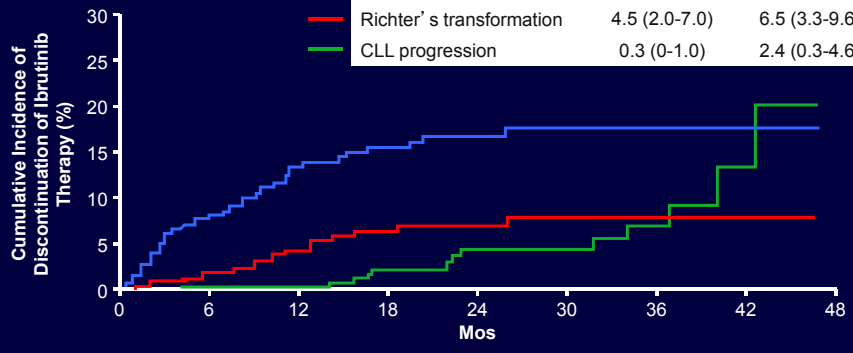
Zelenetz AD, et al. ASH 2015. Abstract LBA-5.

Time Course of Ibrutinib Discontinuation

OSU Cohort (N = 308)

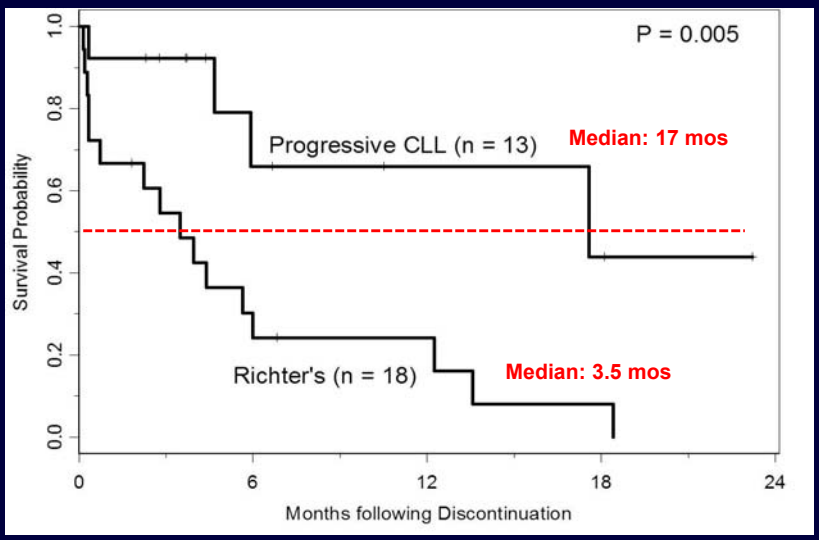
Retrospective analysis of 308 pts in 4 sequential trials

Cumulative Incidence, % (95% CI)	12 Mos	18 Mos
Other event	13.5 (9.5-17.6)	15.6 (11.1-20.0)
Richter's transformation	4.5 (2.0-7.0)	6.5 (3.3-9.6)
CLL progression	0.3 (0-1.0)	2.4 (0.3-4.6)



Maddocks KJ, et al. JAMA Oncol. 2015;1:80-87.

Survival after Ibrutinib Discontinuation:
Progressive CLL vs Richter's Transformation

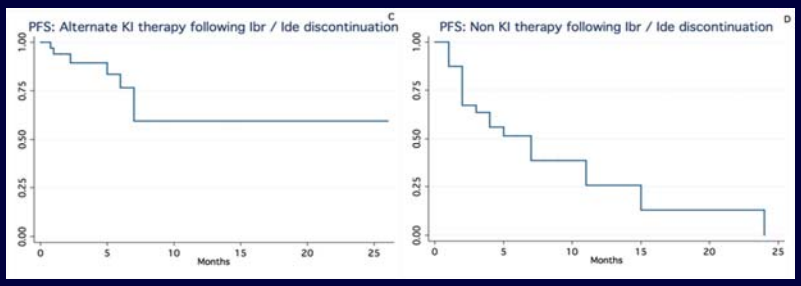


Maddocks KJ, et al. JAMA Oncol. 2015;1:80-87.

Outcomes Post KI Discontinuation in CLL
Response to subsequent therapy

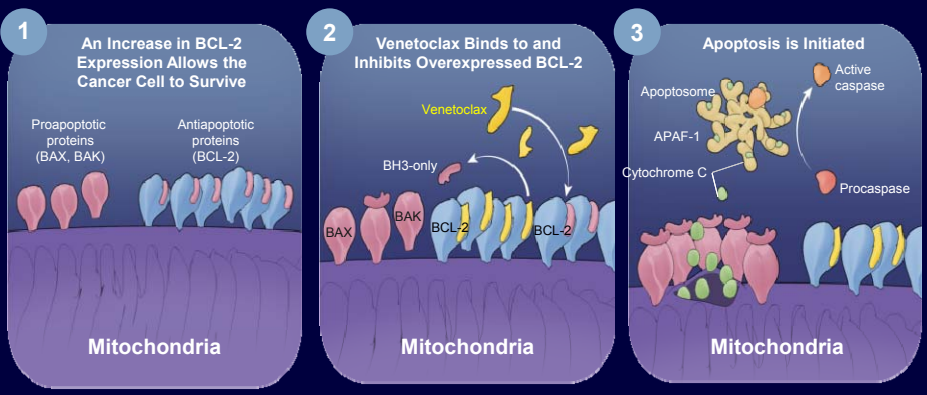
Response, %	Alternate KI (n = 38)	BCL2-i (CT) (n = 13)	CITs (n = 12)	CD20 Tx (n = 11)
ORR	50	76	25	36
CR	0	7	17	9
PR	50	69	8	27
SD	30	16	33	45
PD	20	8	42	19

No direct comparisons performed.



Mato A, et al. ASH 2015. Abstract 719.

Venetoclax: Mechanism of Action



Fowler, N and Davis E. Hematology 2013;2013:553-560

Venetoclax: Phase I Dose Finding Study

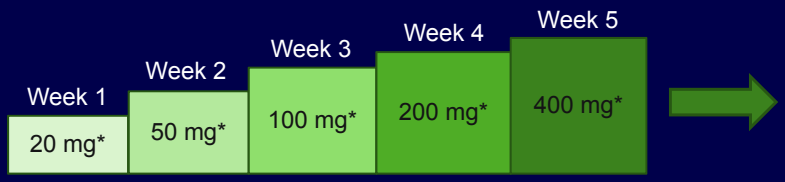
Dose ramp-up to reduce tumor lysis risk

Daily 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 20 mg as initial dose
†Step-up doses: 100-400 mg
‡DCD: 150-1200 mg

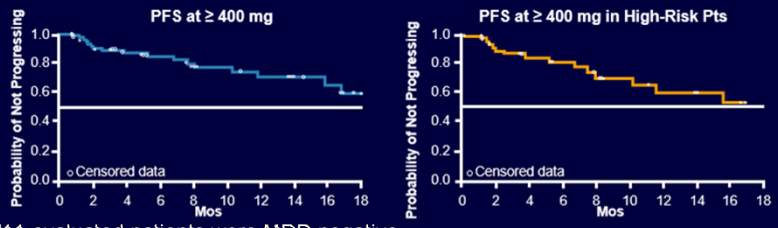
- Ramp-Up Schema: Expanded Safety Cohort



Seymour JF, et al. EHA 2014. Abstract S702.

Venetoclax (ABT-199) in R/R CLL/SLL

Response	All (n = 78)	del(17p) (n = 19)	F-Refractory (n = 41)	IGHV Unmutated (n = 24)
Overall response	77%	79%	76%	75
CR	23%	26%	22%	29
PR	54%	53%	54%	46



- 6/11 evaluated patients were MRD negative
- Most common AE: diarrhea, neutropenia, nausea, upper respiratory tract infection, fatigue, and cough
- Most common grade 3/4: neutropenia, anemia, febrile neutropenia, thrombocytopenia, hyperglycemia, tumor lysis syndrome, and hypokalemia

Seymour JF, et al. *ASCO Annual Meeting.* 2014. Abstract 7015.

Venetoclax Monotherapy:
Phase II trial in R/R CLL with del(17p)

- Patients received venetoclax monotherapy once daily with dose ramp-up (20-400 mg over 5 wks) with TLS prophylaxis (N = 107)

Outcome	Pts (N = 107)
Overall response, % ▪ CR or CRi ▪ nPR ▪ PR	79.4 7.5 2.8 69.2
Pts with MRD- test, %	40
Time to first response, mos (range)	0.8 (0.1-8.1)
Time to CR/CRi, mos (range)	8.2 (3.0-16.3)
1-yr PFS, % (95% CI)	72 (61.8-79.8)
1-yr OS, % (95% CI)	86.7 (78.6-91.9)

Tx-Emergent AE,* %	Any Grade	Grade 3/4
Any	96	76
Neutropenia	43	40
Diarrhea	29	0
Nausea	29	1
Anemia	27	18
Fatigue	22	0
Pyrexia	20	1
Thrombocytopenia	19	15
Hyperphosphatemia	16	1
Vomiting	15	1
Infection	72	20

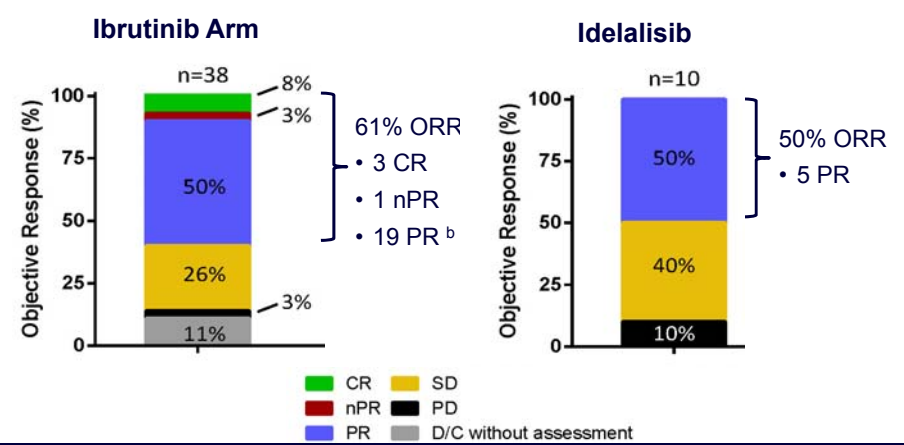
Stilgenbauer S, et al. ASH 2015. Abstract LBA-6.

Venetoclax Monotherapy

Phase II Trial in Patients R/R to Ibrutinib or Idelalisib

Venetoclax weekly ramp-up to a final dose of 400 mg

Wk 8 Response Assessment



Jones J, et al. ASH 2015. Abstract 715.

Venetoclax + Rituximab in R/R CLL:

Responses by Subgroup

Best Response, n (%)	All (N = 49)	del17p (n = 9)	Fludarabine-refractory (n = 9)	IGVH unmutated (n = 19)
Overall Response	41 (84)	7 (78)	5 (56)	16 (84)
CR/CRi	20 (41)	3 (33)	4 (44)	7 (37)
PR/nodular PR	21 (43)	4 (44)	1 (11)	9 (47)
SD	5 (10)	1 (11)	2 (22)	1 (5)
Disease progression	2 (4)	0	1 (11)	1 (5)
Death (TLS) [a]	1 (2)	1 (11)	1 (11)	1 (5)

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

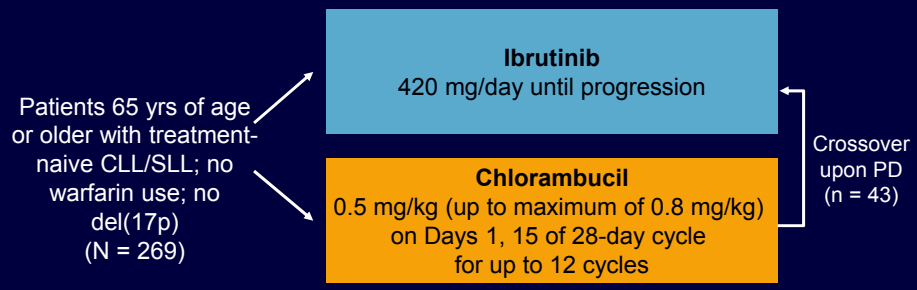
As of 2015-01-21, 38 patients remain on study
11 discontinued (6 due to PD; 3 withdrew consent; 2 due to AE)

Roberts AW, et al. EHA 2015. Abstract S431.

Ibrutinib vs Chlorambucil for CLL in Elderly

RESONATE-2: Study Design

- An international, randomized phase III trial

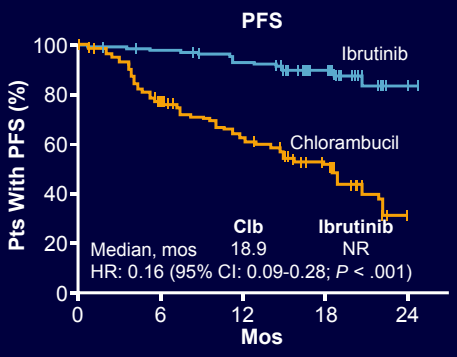


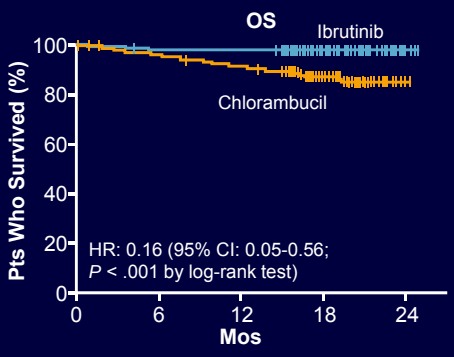
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, EFS, rate of hematologic improvement, and safety

Burger JA, et al. N Engl J Med. 2015; 373:2425-37.

Ibrutinib vs Chlorambucil for CLL in Elderly

RESONATE-2: Outcomes



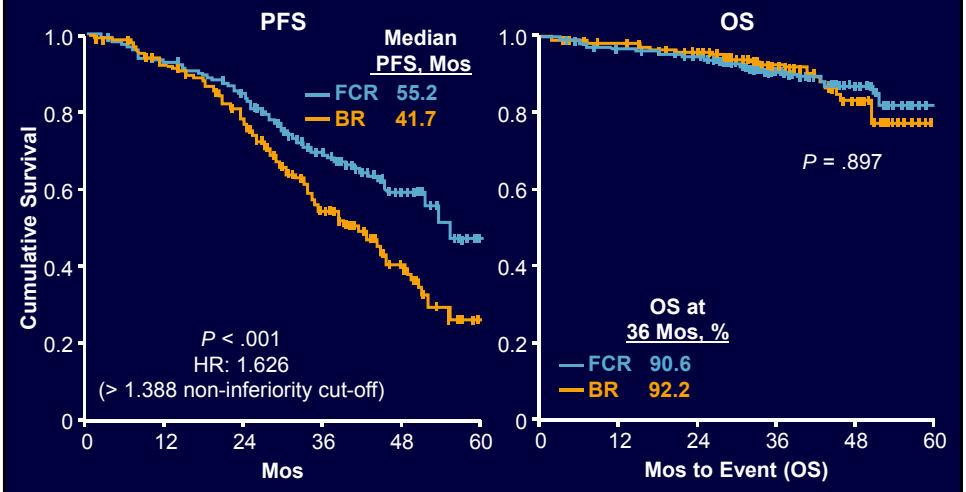


AEs Summary	Ibrutinib	Chlorambucil
Most frequent AEs	Diarrhea, fatigue, cough and nausea	Nausea, fatigue, neutropenia, anemia, and vomiting
AEs leading to discontinuation, %	9	23

Burger JA, et al. N Engl J Med. 2015; 373:2425-37.

CLL10: FCR vs BR for Frontline CLL

PFS (Primary Endpoint) and OS

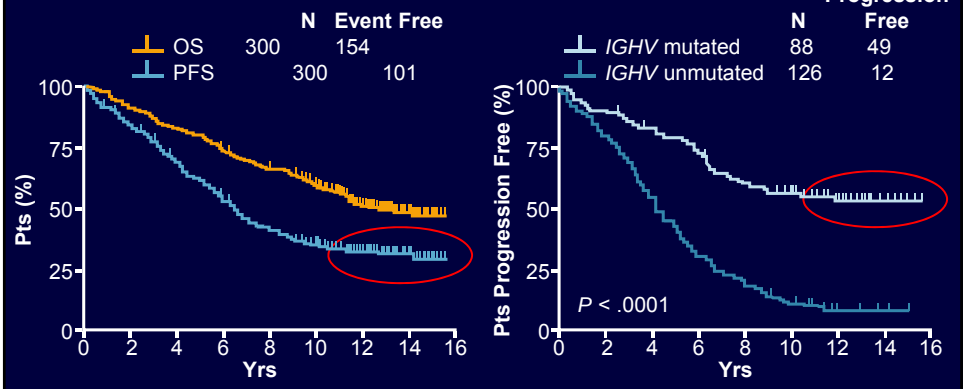


Eichhorst B, et al. ASH 2014. Abstract 19.

FCR300 Phase II Trial:

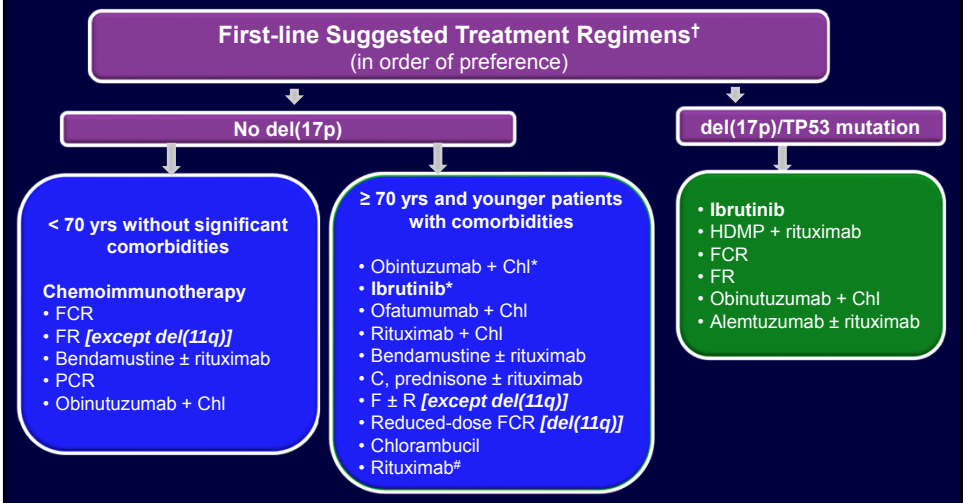
PFS plateaus with FCR as Initial Therapy

- With extended follow-up, PFS shows plateau at Yrs 10-11
- Last relapses occurred around Yr 10, with a plateau in PFS for *IGHV*-mutated pts



Thompson PA, et al. Blood. 2016;127(3):303-9

NCCN Therapy Recommendations

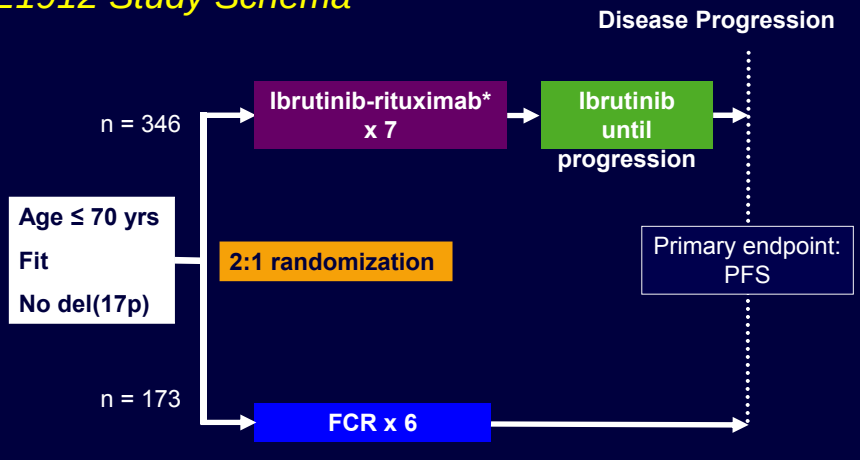


†All recommendations category 2A unless otherwise stated; *Category 1; #Category 3
F = fludarabine; C = cyclophosphamide; R = rituximab; P = pentostatin; Chl = chlorambucil; HDMP = high-dose methylprednisolone

Adapted from National Comprehensive Cancer Network. Available at: www.nccn.org; Version 2.2016; Accessed 30 March 2016.

Reconsidering the Role of Chemotherapy in Treatment-Naïve CLL

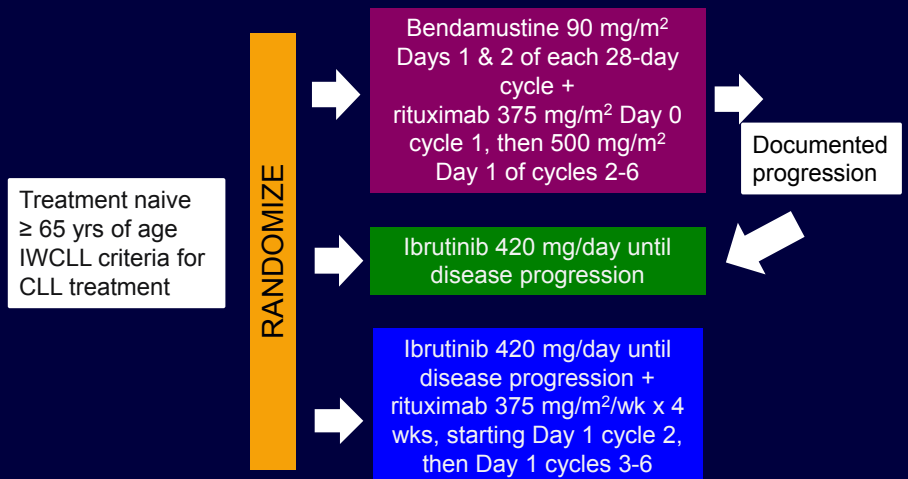
E1912 Study Schema



ClinicalTrials.gov. NCT02048813.

Reconsidering the Role of Chemotherapy in Treatment-Naïve CLL

A041202 Study Schema



ClinicalTrials.gov. NCT01886872.

Summary Points

- **Small molecule inhibitors of B-cell receptor signaling are highly effective for the treatment of relapsed CLL**
  - Category 1 evidence supports their first choice for all relapsed CLL
  - Advantages of combination therapy yet to be clearly characterized
  - Patients and treating physicians should be aware of unique response characteristics and toxicities before beginning therapy
- **Emerging evidence suggests alternate tyrosine kinase inhibitors can be effective after failure of first-choice**
  - Venetoclax (pending FDA approval) also active in this group
- **Ibrutinib now approved as first-line therapy for CLL**
  - First choice for patients with del(17p) or TP53 mutated CLL
  - Category 1 recommendation for frail patients, patients ≥70 years, and patients <70 years with significant comorbidities
  - Chemoimmunotherapy remains standard of care for fit patients <70 years
  - Ongoing trials will better clarify role v. cytotoxic chemotherapy

Optimizing Treatment with Small Molecule Inhibitors

Mantle Cell Lymphoma

Barbara Pro, MD
Robert H Lurie Cancer Center
Northwestern University

Disclosures:

The faculty listed below have the following relevant financial relationships to disclose:

Barbara Pro, MD
Celgene Corporation: Consulting Fees; Honoraria
Takeda: Honoraria

Mantle Cell Lymphoma

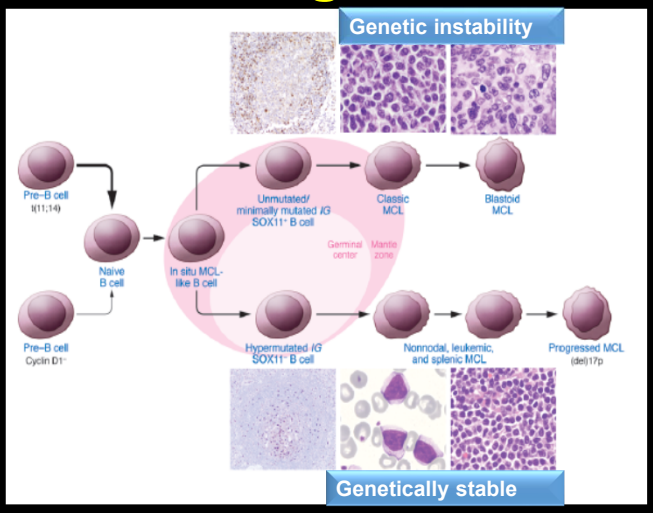
- A distinct and uncommon subtype of NHL
- t (11;14)(q13;q32) chromosomal translocation
  - Overexpression of cyclin D1
- MCL is derived from CD5-positive cells within the mantle zone
- Median age : 68
- High response rate to initial treatment but inevitable relapses
- Response to salvage treatments poor

Yatabe Y et al. Blood 2000;95:2253-2261;
Cheah CY et al J Clin Oncol. 2016 Apr 10;34(11):1256-69

Strategies in the Treatment of MCL

- When to treat
  - Stratify
  - " Indolent subtype"
  - Mantle Cell Lymphoma International Prognostic Index (MIPI)
- What to treat with

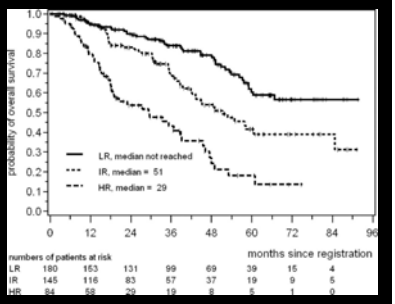
Molecular Pathogenesis and Progression



Jares P et al, J Clin Invest. 2012;122 (10): 3416-3423

Simplified MIPI

Points	Age, yrs	PS	LDH	WBC
0	<50	0-1	<0.67	<6.700
1	50-59	-	0.67-0.99	6.700-9.999
2	60-69	2-4	1.00-1.49	14.999
3	70	-	1.5	≥15.000

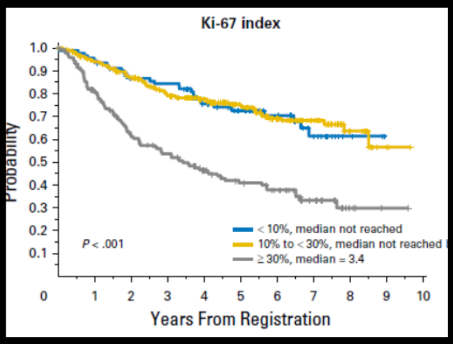


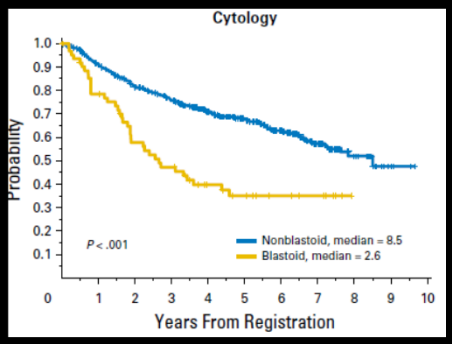
Hoster E. et al. Blood 2008;111:558-565

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

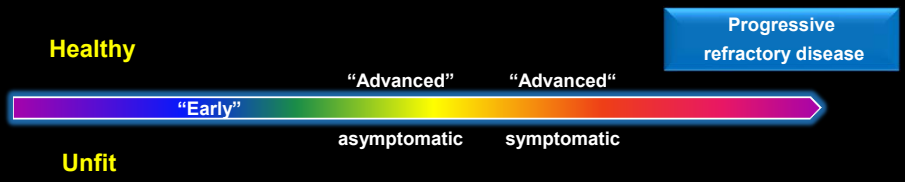
Prognostic Value of Ki-67 Index, Cytology, and Growth Pattern in Mantle-Cell Lymphoma: Results From Randomized Trials of the European Mantle Cell Lymphoma Network

Eva Hoster, Andreas Rosenwald, Françoise Berger, Heinz-Wolfram Bernd, Sylvia Hartmann, Christoph Loddenkemper, Thomas F.E. Barth, Nicole Brousse, Stefano Pileri, Grzegorz Rymkiewicz, Roman Kodet, Stephan Stilgenbauer, Roswitha Forstpointner, Catherine Thieblemont, Michael Hallek, Bertrand Coiffier, Ursula Vehling-Kaiser, Réda Bouabdallah, Lothar Kanz, Michael Pfreundschuh, Christian Schmidt, Vincent Ribrag, Wolfgang Hiddemann, Michael Unterhalt, Johanna C. Kluin-Nelemans, Olivier Hermine, Martin H. Dreyling, and Wolfram Klapper

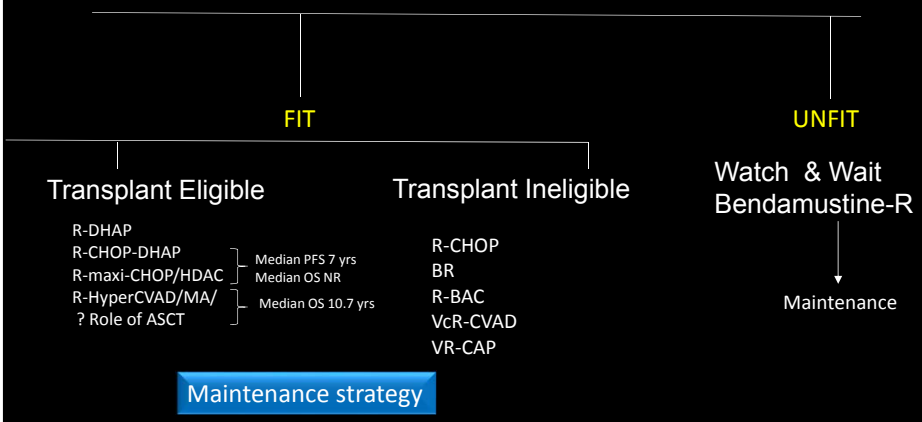




Treatment of MCL: The Ongoing Challenge



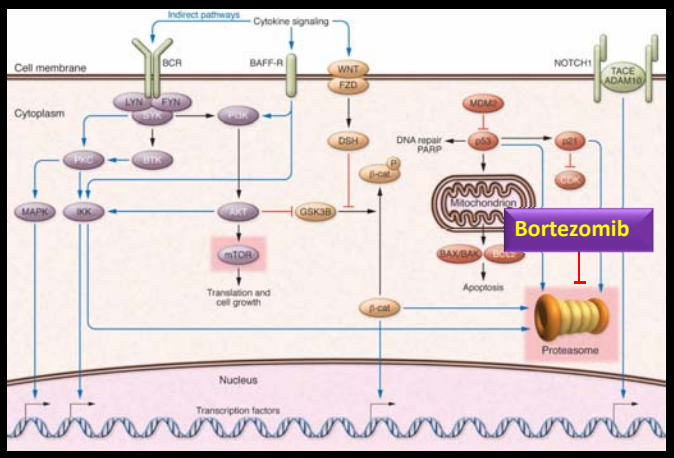
MCL: Frontline Treatment



Relapsed/Refractory Disease

- **Use of chemoimmunotherapy regimens produce ORR 58%-93%**
- **Median PFS < 2 years**
- **Consolidation with allogeneic stem cell transplant results in best outcome in transplant eligible patients**
- **Four agents have received regulatory approval:**
  - **Bortezomib**
  - **Lenalidomide**
  - **Temsirolimus**
  - **Ibrutinib**

Aberrant pathways in MCL susceptible to targeted therapies



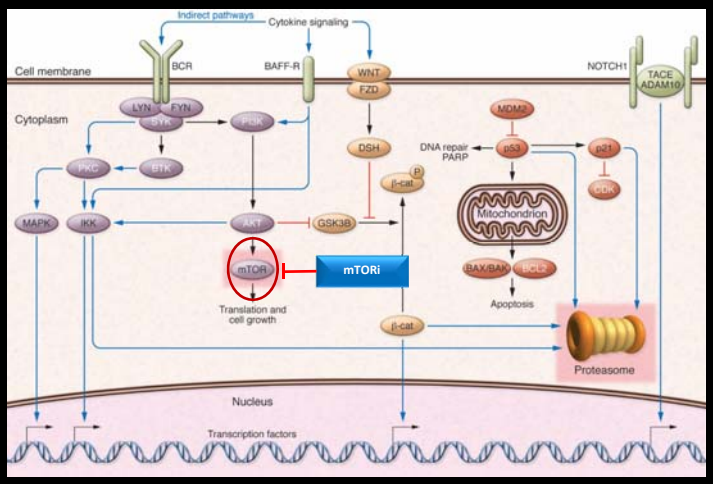
Jares P et al, J Clin Invest. 2012;122 (10): 3416-3423

Bortezomib: Summary of Efficacy in MCL

Study	N	CR	PR	ORR%
O'Connor	40	5 (13)	14 (35)	47
Goy	29	6 (20.5)	6 (20.5)	41
Strauss	24	1 (4)	6 (25)	29
Belch	13 untreated/ 15 relapsed	0 1	6 6	46 47
PINNACLE, n (%)	141	11 (8)	36 (26)	33

O'Connor OA, et al. Br J Haematol. 2009;34-39. Goy A et al. J Clin Oncol. 2005;23:667-675.
Strauss SJ, et al. J Clin Oncol. 2006;13:2105-2112. Belch et al. Ann Oncol. 2007;18:116-121
Fisher RI, et al. J Clin Oncol. 2006;24:4867-4874

Aberrant pathways in MCL susceptible to targeted therapies



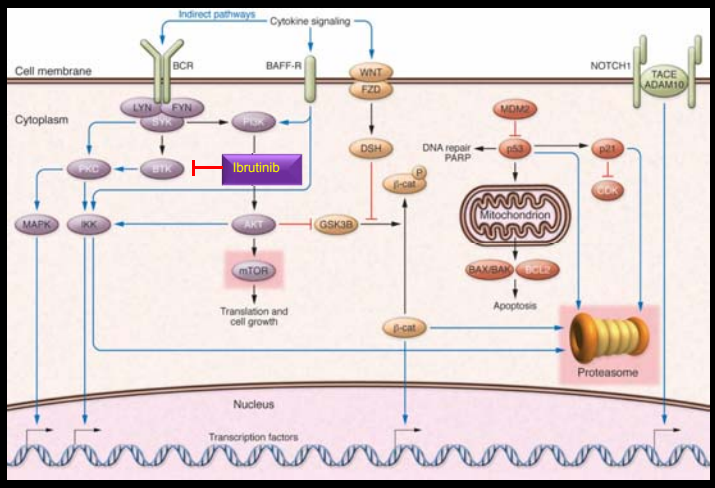
Jares P et al, J Clin Invest. 2012;122 (10): 3416-3423

mTOR inhibitors (mTORi) in Relapsed Mantle Cell Lymphoma

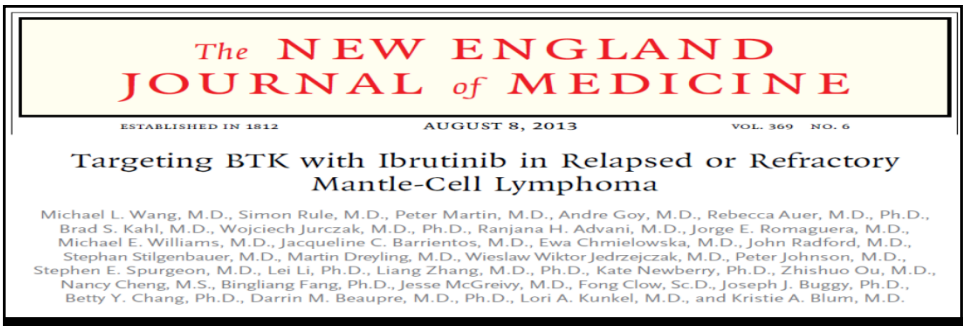
	n	ORR	CR	mDOR
Temsirolimus	54	22	5	7.1
Everolimus (Wang)	58	8.6	0	1.6-13.2
Everolimus (Renner)	35	20	6	5.5

Hess G et al. J Clin Oncol. 2009;27:3822-3829. Wang M Br J Haematol 2014;165:510-518.
Renner C et al. Haematologica 2012;97:1085-1091.

Aberrant pathways in MCL susceptible to targeted therapies



Jares P et al, J Clin Invest. 2012;122 (10): 3416-3423



- Phase II international study

Relapsed/refractory with at least 1 measurable lesion ≥ 2 cm PS ≤ 2 (N=111) → Ibrutinib 560 mg po QD → Continued until PD or toxicity

- Primary endpoint : ORR
- Secondary endpoints: DoR, PFS, OS, and safety

Patient Characteristics (n=111)

Characteristics		
Age, y	Median [range]	68 [40 – 84]
Gender, n (%)	Male	85 (77)
ECOG	0-1	99 (89)
Simplified MIPI, n (%)	Low-risk	15 (14)
	Intermediate risk	42 (38)
	High risk	54 (49)
Number of prior therapies	Median [range]	3 [1 - 5]
Refractory disease, n (%)		50 (45)
Advanced disease, n (%)		80 (72)
At least one node ≥ 5 cm		43 (39)

Wang ML et al. N Engl J Med 369:507-516, 2013

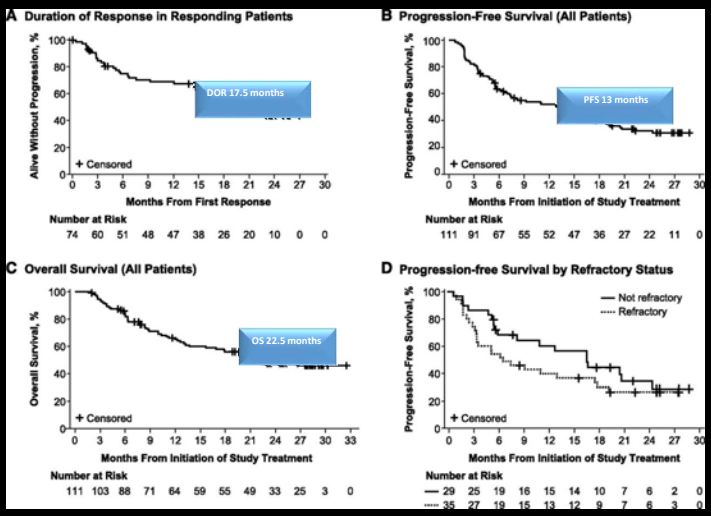
Objective Responses

Responses	All n (%), n = 111
Overall response	75 (68)
Complete response	23 (21)
Partial response	52 (47)
Stable disease/PD	35 (32)
Response duration-mo	13.9
Median	6 (8)

- Common adverse events: diarrhea, fatigue, and nausea
- Hematologic toxicity was uncommon

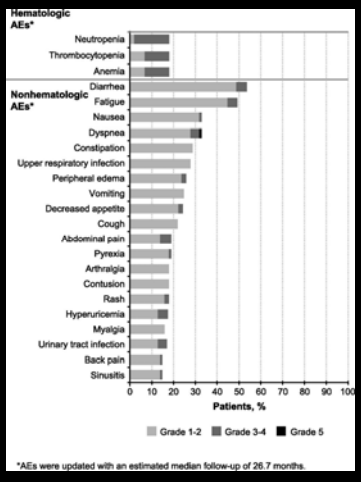
Wang ML et al. N Engl J Med 369:507-516, 2013

Long-term follow-up: updated safety and efficacy results



Wang M et al. Blood 2015;126:739-745

Treatment-emergent adverse events ≥ 15% of patients

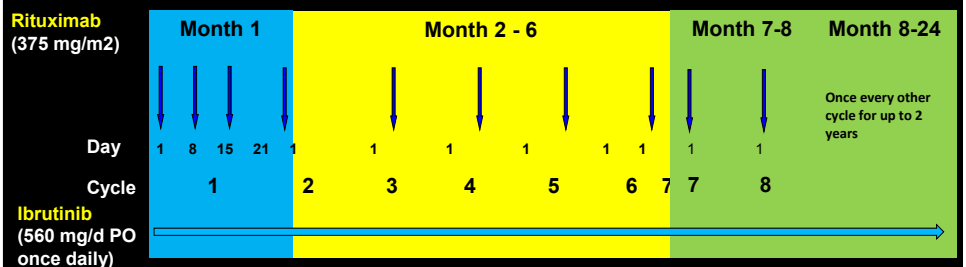


Prevalence of select AEs by 6-month intervals

Select AEs* n (%)	1-6 mo (n = 111)	7-12 mo (n = 72)	13-18 mo (n = 51)	19-24 mo (n = 41)	>24 mo (n = 22)
Any diarrhea	49 (44%)	21 (29%)	15 (29%)	8 (20%)	6 (27%)
Grade 3†	5 (5%)	0	0	1 (2%)	0
SAE	1 (1%)	0	0	0	0
Any infection	76 (69%)	43 (60%)	30 (59%)	22 (54%)	9 (41%)
Grade ≥3	20 (18%)	11 (15%)	6 (12%)	5 (12%)	1 (5%)
SAE	16 (14%)	9 (13%)	4 (8%)	5 (12%)	1 (5%)
Any bleeding	46 (41%)	17 (24%)	17 (33%)	14 (34%)	5 (23%)
Major bleeding	6 (5%)	1 (1%)	3 (6%)	2 (5%)	2 (9%)

Wang M et al. Blood 2015;126:739-745

Ibrutinib and Rituximab in Relapsed/Refractory MCL



Primary endpoints: ORR and safety
All patients had received previous rituximab-containing regimens
Median number of prior treatments: 3

Wang et al. Lancet Oncol 2016;17:48-56.

Ibrutinib and Rituximab in Relapsed/Refractory MCL

Response	All Patients (N = 50)	Patients with Ki-67 <50% (n = 37)
ORR	44 (88%)	37 (100%)
CR	22 (44%)	20 (54%)
PR	22 (44%)	17 (46%)
SD	3 (6%)	0
PD	3(6%)	0
Median PFS	NR	NR

Toxicity

- Grade 3 bleeding events: nose bleed in 2 patients (4%), nipple bleeding in 1 (2%)
- Grade 3 atrial fibrillation in 6 patients (12%)
- Grade 3 hematologic events
  - Leucocytosis 1 patient (2%)
  - Thrombocytopenia 2 patients (4%)
  - Neutropenia 1 patient (2%)

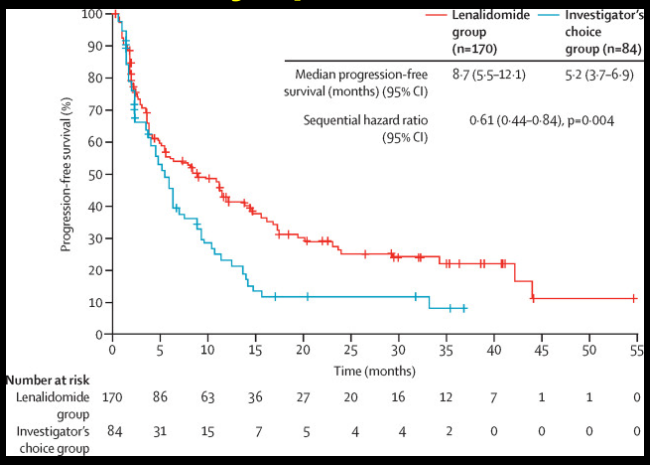
Wang et al. Lancet Oncol 2016;17:48-56.

Lenalidomide in Relapsed Mantle Cell Lymphoma

	n	ORR	CR	mDOR
Trneny	170	40	5	16.1
Zinzani	56	35	12	16.3
Goy	134	28	7.5	16.6

Trneny M . et al, ASH 2014 , Abstr # 626. Zinzani PL, et al. Ann Oncol 24: 2892-2897, 2013.
Goy A et al. J Clin Oncol 31:3688-3695

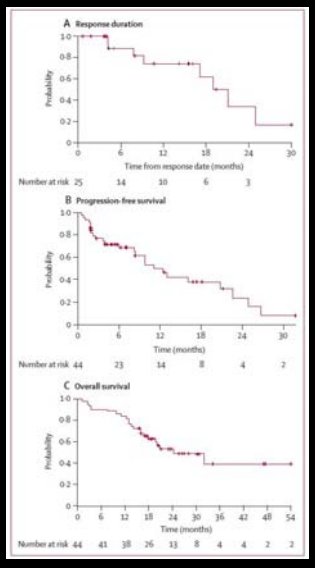
Progression-free survival with lenalidomide compared with investigator's choice in relapsed or refractory mantle cell lymphoma



Trněný M et al. Lancet Oncol 2016; 17:319-31

Lenalidomide and Rituximab in MCL

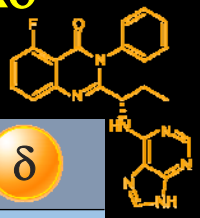
	Phase 2 (n=44)*
Complete response	16 (36%)
Partial response	9 (20%)
Overall response	25 (57%)
Stable disease	10 (23%)
Progressive disease	9 (20%)
Response duration (months)	18·9 (17·0–NR)
Progression-free survival (months)	11·1 (8·3–24·9)
Overall survival (months)	24·3 (19·8–NR)
Time to first response (months)	2 (2–8)
Time to best response (months)	2 (2–12)
Follow-up time (months)	23·1 (15·6–54·2)



Wang M et al. Lancet Oncol 13:716-723

Idelalisib: Potent and Selective Inhibitor of PI3Kδ

Idelalisib/ GS-1101



Class I PI3K Isoform	α	β	γ	δ
Cell Type	Mouse embryonic fibroblasts	Mouse embryonic fibroblasts	Human basophils	**Human basophils**
Cell-Based Activity	PDGF-induced pAKT	LPA-induced pAKT	fMLP-induced CD63+	**FceR1-induced CD63+**
EC_{50} (nM)	>20,000	1,900	3,000	**8**

- Selectivity relative to Class I PI3K isoforms involved in insulin signaling and other physiological functions
- No off-target activity against Class II or III PI3K, mTOR, or DNA-PK
- No off-target activity seen in screen of >350 protein kinases

Lannutti, BJ et al. Blood, 2011; 117(2):591-4

Idelalisib: Phase I Relapsed/Refractory MCL

50-350 mg/daily
Primary outcome: safety and DLT
Patients without DLT and progression after 48 weeks enrolled in the expansion cohort

Efficacy Outcome N=40	All patients	< 150 mg BID	> 150 mg BID
ORR	16 (40)	5(21)	11 (69)
CR	2 (5)	0	2 (12.5)
PR	14 (35)	5 (21)	9 (56.3)
SD	19 (47.5)	15 (62.5)	4 (25)
PD	4 (10)	4 (16.7)	0
Median PFS (all)	3.7		
Median DOR	2.7		

Kahl B et al , Blood 2014;123:3398-3405

Idelalisib: Phase I Relapsed/Refractory MCL

AEs >10%	All AEs	Grade ≥3 AEs
Diarrhea	16 (40)	7 (17.5)
Nausea	13 (32.5)	2 (5)
Pyrexia	11 (27.5)	0
Fatigue	10 (25)	1 (2.5)
Rash	9 (22.5)	1 (2.5)
Decreased appetite	8 (20)	6 (15)
Upper respiratory infection	8 (20)	0
Asthenia	7 (17.5)	0
Constipation	6 (15)	0
Headache	6 (15)	0
Cough	5 (12.5)	0
Pneumonia	5 (12.5)	4 (10)
Vomiting	5 (12.5)	0
Weight loss	5 (12.5)	0
Laboratory abnormality		
ALT/AST elevation*	24 (60)	8 (20)
Neutropenia	12 (30)	4 (10)
Anemia	9 (22.5)	1 (2.5)
Thrombocytopenia	8 (20)	2 (5)

Kahl B et al , Blood 2014;123:3398-3405.

Other Agents

CDK4/6 inhibitors

- **Palbociclib[1]**
- 17 patients
- ORR: 18 % (1CR, 2PR)
- Five patients with PFS > 1 year
- **Abemaciclib[2]**
- 22 patients ORR: 35% (5 PR)

BCL-2 inhibitors

- **Venetoclax[3]**
- 28 patients
- ORR: 75% (CR 21%, PR 54%)
- Median PFS: 14 months

1. Leonard JP et al. Blood. 2012 ;119:4597-6073;
2. Morschhauser F et al. ASH 2014; Abstrat 3067
3. Gerecitano JF et al. ASH 2015; Abstract 254.

Conclusions

- The heterogeneous biology and clinical course of MCLs represents a major challenge to define standard therapies
- The increasing understanding of the pathogenetic mechanisms is leading to a more precise diagnosis and the identification of attractive and promising targets
- The increasing numbers of effective agents in the relapse setting is likely to translate in more effective “targeted” frontline therapy