Sequencing of Treatment in Indolent Lymphomas (CLL and FL)

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Learning Objectives

1. Implement a plan for monitoring patients with CLL for 17p deletion at diagnosis and throughout the course of the disease
2. Interpret emerging data supporting combination therapies in CLL
3. Evaluate clinical trial data for novel targeted therapies in the management of newly diagnosed and relapsed/refractory follicular lymphoma

Disclosures

- **Dr. Thompson**
  - Research funding: AbbVie, Pharmacyclics, Amgen, Adaptive Biotechnologies
  - Advisory board/honoraria: AbbVie, Pharmacyclics, Amgen, Genentech, Gilead
- **Ms. Nodzon**
  - Consulting fees from and served on speakers bureaus: AbbVie, Genentech, Gilead

Part I: Treatment of CLL

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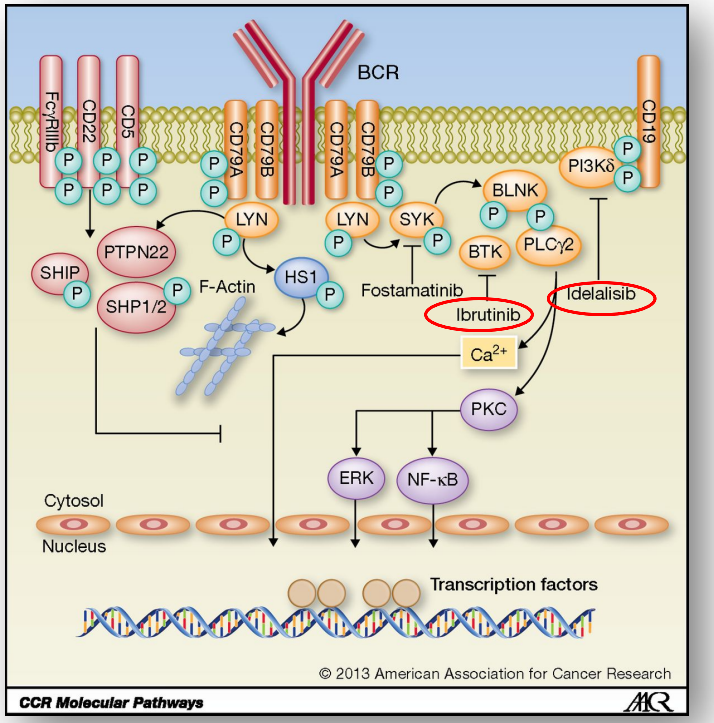
Novel Targets in CLL: Approved Therapies

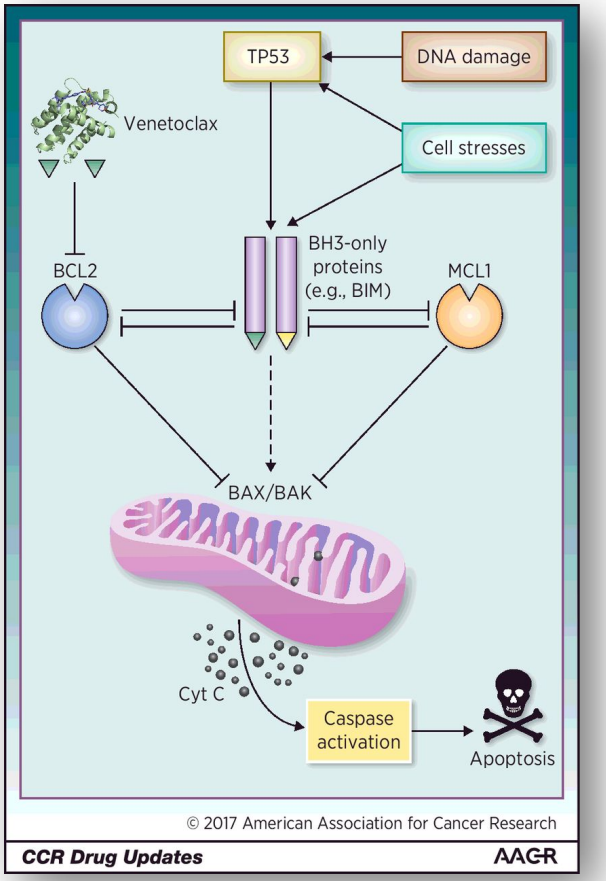
- Second generation CD20 monoclonal antibodies (mAb)
  - Ofatumumab
  - Obinutuzumab
- Bruton's tyrosine kinase (BTK) inhibitor
  - Ibrutinib
- Phosphoinositide 3-delta kinase (PI3K) inhibitor
  - Idelalisib
  - Duvelisib
- B-cell lymphoma 2 (BCL2) inhibitor
  - Venetoclax

Targeting B-Cell Receptor Signaling in CLL



ten Hacken E et al. Clin Cancer Res 2014;20:548-556.

Targeting BCL2 in CLL



Roberts AW, et al. Clin Cancer Res 2017;23:4527-4533.

Current First-Line Treatment of CLL

- Chemoimmunotherapy: FCR, BR, chlorambucil + obinutuzumab or chlorambucil + ofatumumab
- Ibrutinib monotherapy

What Do We Want From an Ideal First-Line CLL Treatment?

Attribute	CIT	Ibrutinib monotherapy
High rate of complete remission, ideally with undetectable MRD	Subgroups, esp. with FCR	No
Limited duration, leading to durable remissions (and potentially “cure”)	Yes	No
Tolerable and effective in all patients, including: 1. Older patients and those with comorbidities 2. Those with unfavorable genomic characteristics	No	Yes

Assessment of Fitness Critical in Treatment Choice

- CIRS score most frequently used; more important than chronologic age
- Patients with score <6 and adequate renal function (eGFR 70 or higher) generally considered “fit” for intensive regimens (e.g., FCR)

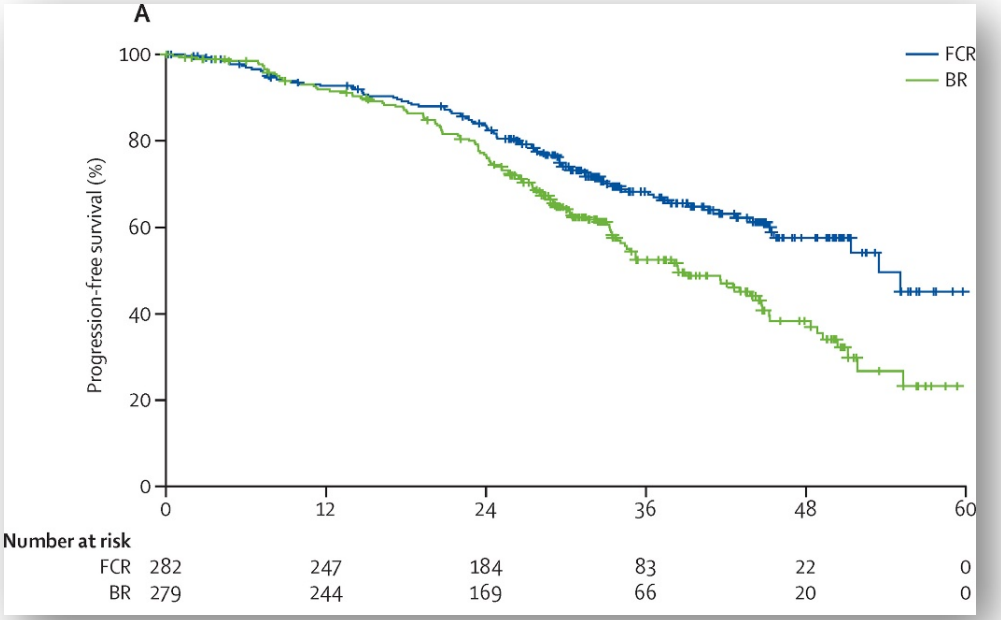
Chemoimmunotherapy Regimens in First-Line CLL

- FCR: Potent, high rates of CR and U-MRD[1]; first regimen to demonstrate improved overall survival[2]
- Bendamustine and rituximab (BR): Similar PFS with less toxicity in the subgroup of fit patients aged >65[3]; however, inferior PFS for BR compared to FCR in patients ≤65 and no evidence of plateau on PFS curve
- Chlorambucil + obinutuzumab showed improved PFS and OS compared to chlorambucil alone; PFS approx. 2.5 years[4,5]
- Chlorambucil + ofatumumab also improved PFS compared to chlorambucil alone; PFS approx. 22 months[6]

[1]Keating. J Clin Oncol 2005; [2]Hallek. Lancet 2010; [3]Eichhorst. Lancet Oncol 2016; [4]Goede N Engl J Med 2014; [5]Goede EHA 2018. [6]Hillmen. Lancet 2015.

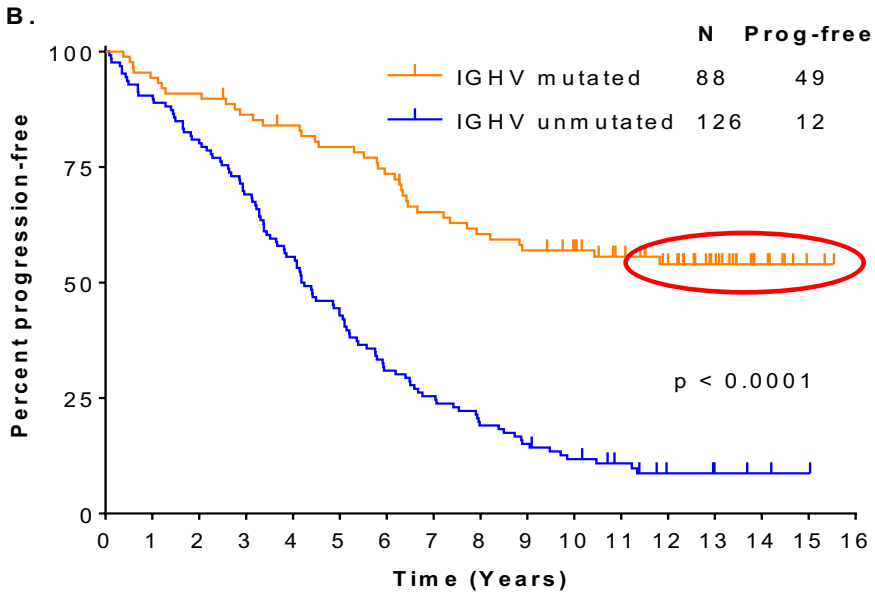
CLL10: FCR Achieves Superior PFS But BR Is Better Tolerated

- No PFS advantage (yet) for FCR vs. BR in patients >65



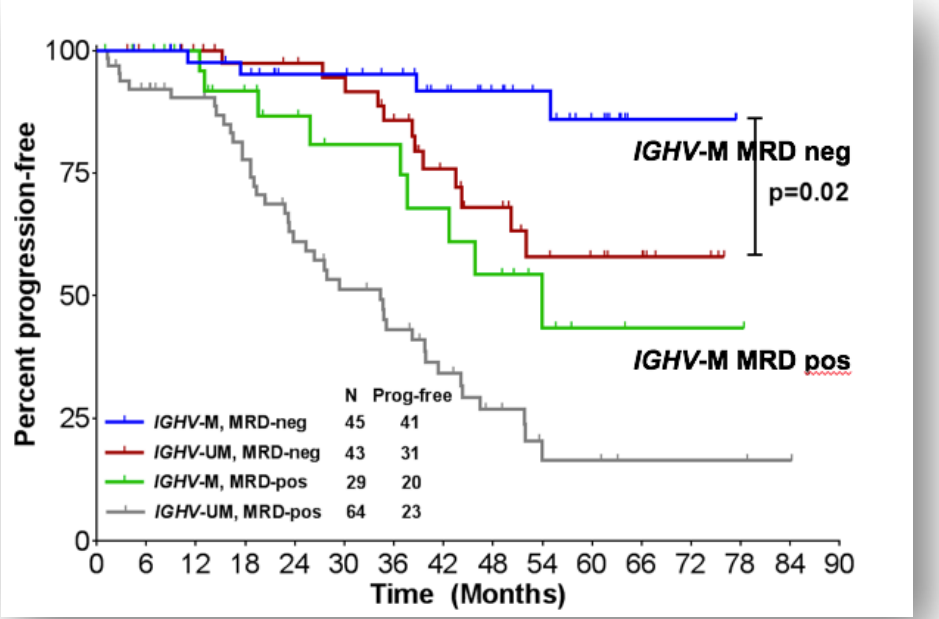
Eichhorst. Lancet Oncol 2016

IGHV-Mutated Patients Have Prolonged PFS After First-Line FCR



Thompson et al. Blood 2016.

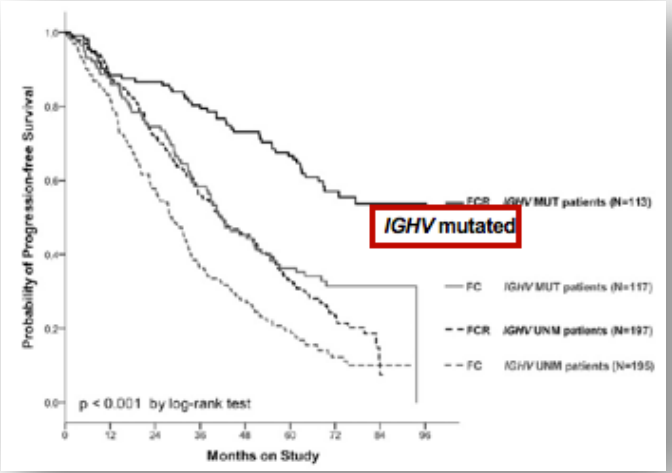
Patients With M-CLL and U-MRD Post-FCR Have Favorable PFS

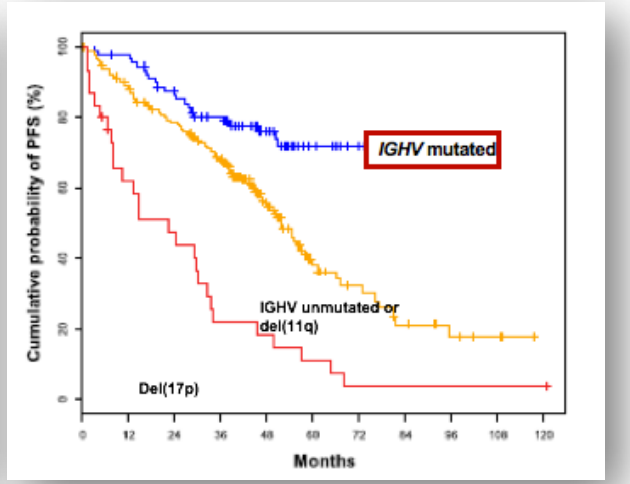


Thompson et al, Leukemia 2018.

Subset With Highly Favorable Outcomes After FCR Is Relatively Small

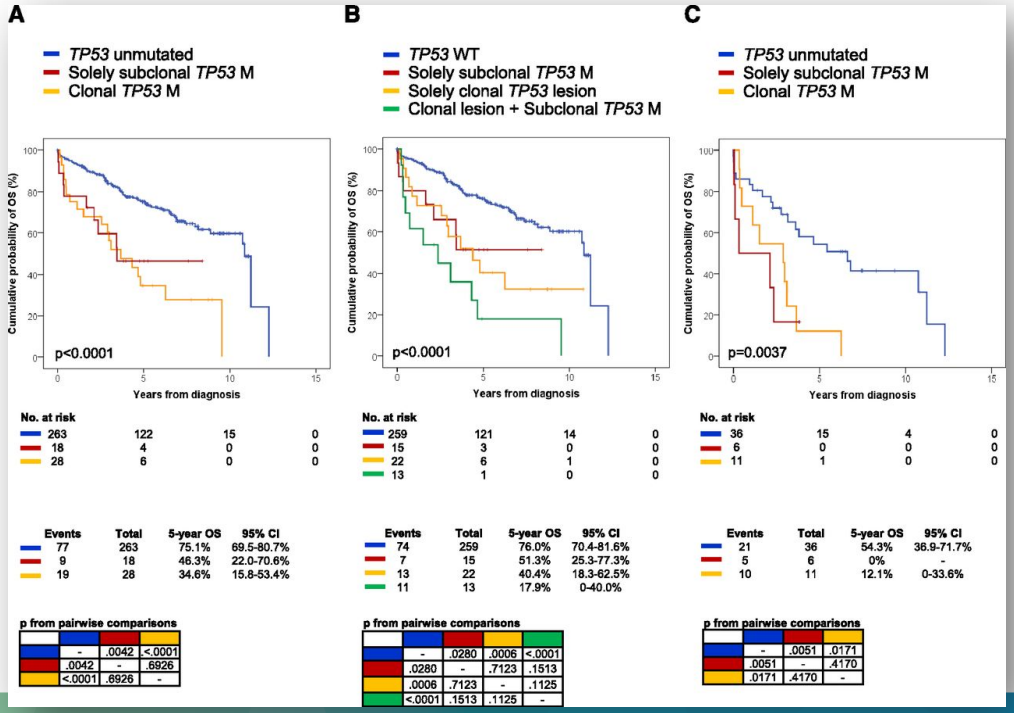
- Note: Patients were only eligible for CLL8 if they had eGFR >70 and limited comorbidities (CIRS score of ≤6)
- Note median PFS for patients with UM-CLL receiving FCR have median survival of 3.5-4.5 years
- Del(17p) associated with median PFS ~1 year





Fischer et al, Blood 2016. GCLLSG CLL8 study; Rossi, et al. Blood 2015.

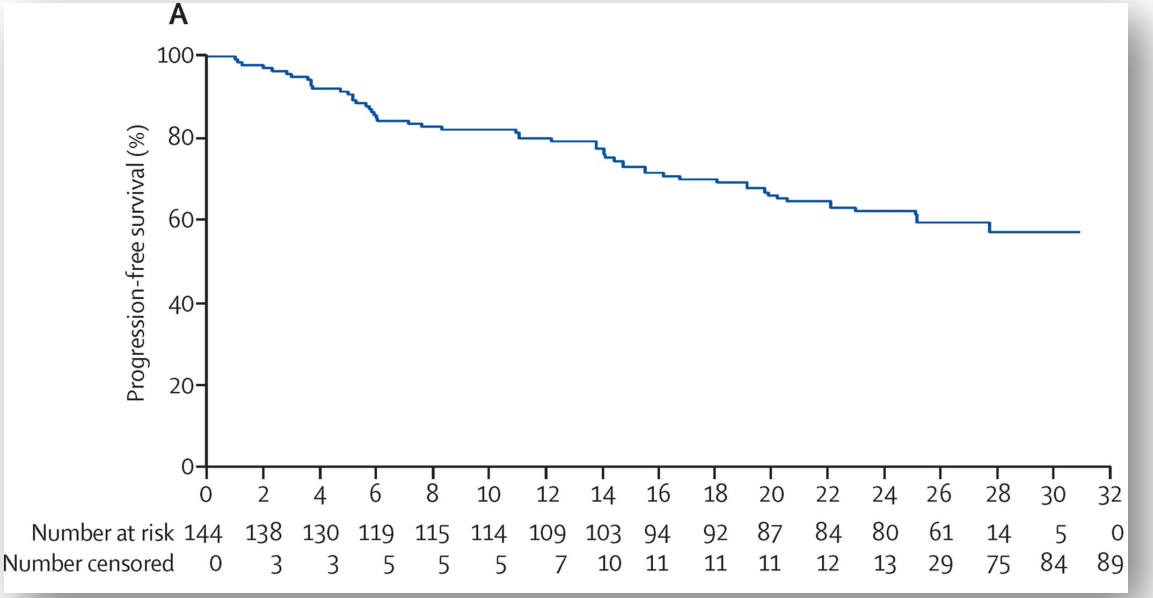
TP53 Mutation Negatively Impacts Survival After FCR, Even If Sub-Clonal



Rossi et al. Blood 2014;123:2139-2147.

Ibrutinib: Favorable PFS in R/R CLL With del(17p)

- Median PFS not reached at 2.5 years
- Compare this to ~1 year PFS seen in first-line patients with del(17p) or *TP53* mutation treated with FCR
- Standard-of-care for del(17p) or *TP53*-mutated patients first line

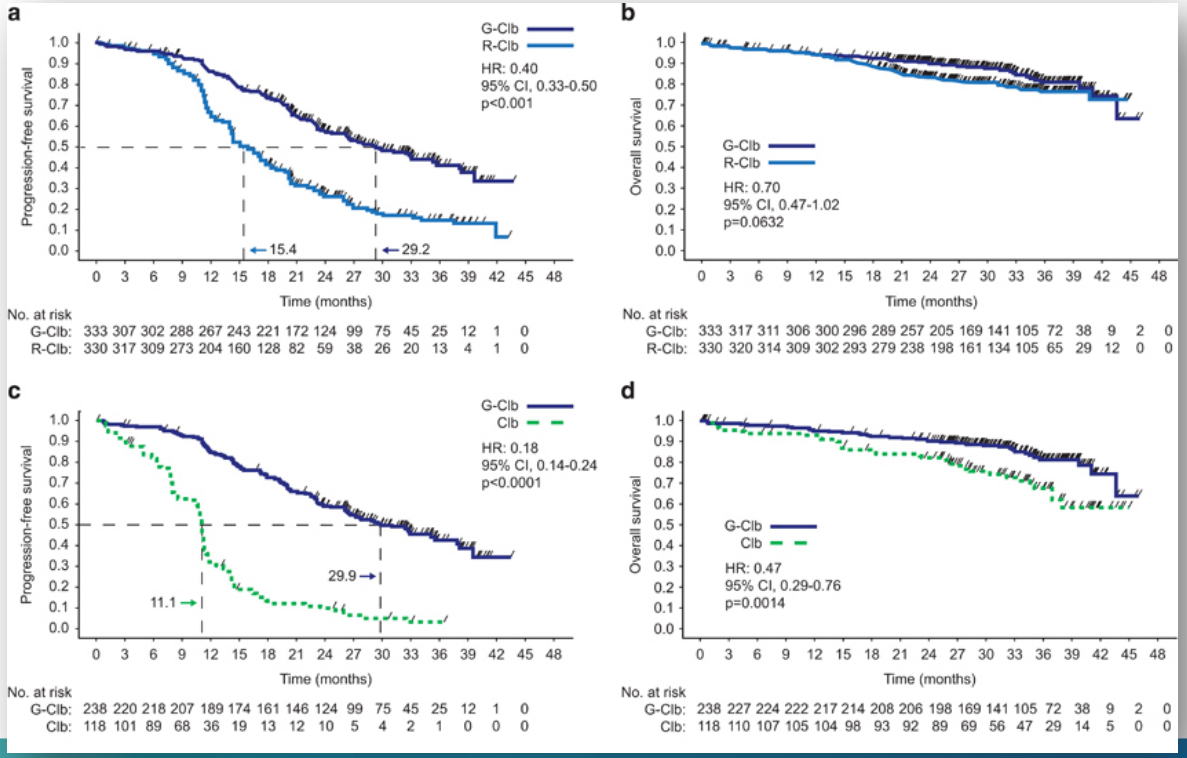


Obrien. Lancet Oncol 2016.

Treatment Options for “Unfit” Patients

CLL11: Chlorambucil + Obinutuzumab

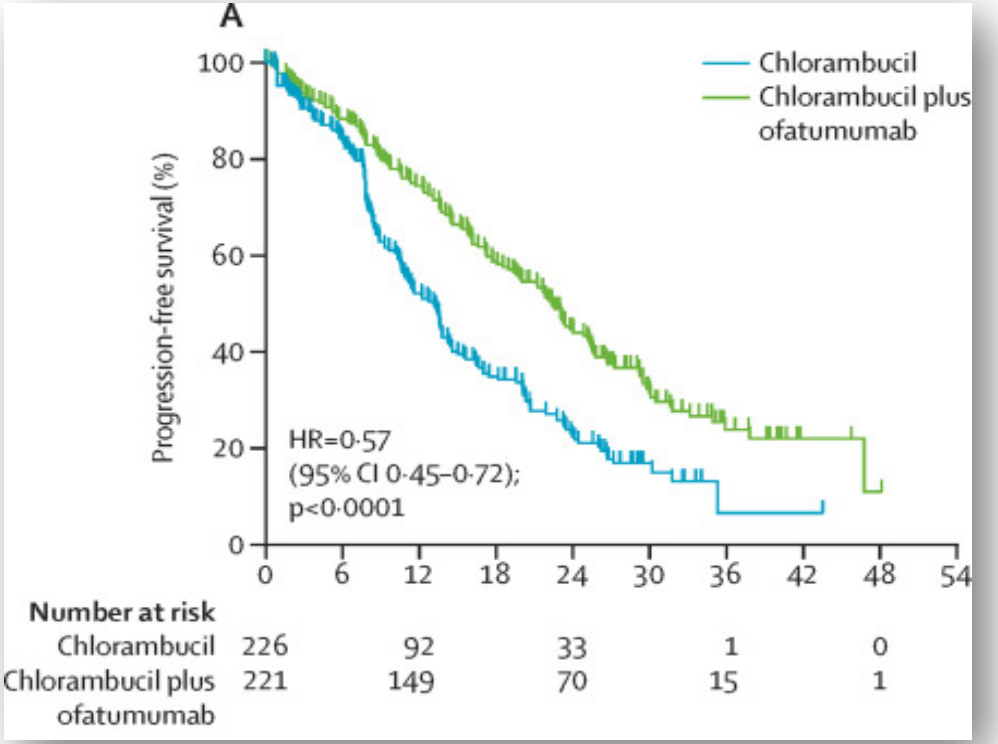
- Eligibility: CIRS >6 (median 8) or eGFR <70 (median 62)
- Median age 73



Goede. N Engl J Med 2014.

COMPLEMENT 1: Chlorambucil + Ofatumumab

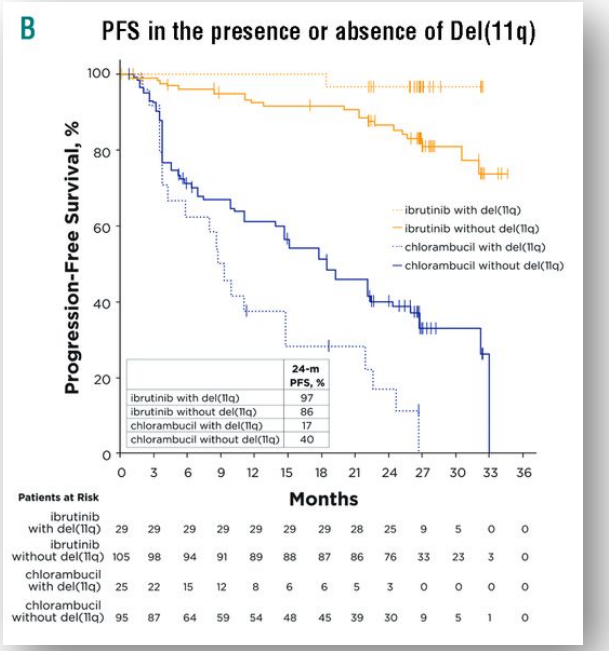
- Eligibility: fludarabine-based treatment "inappropriate" (investigator judgement)
- Median age 69

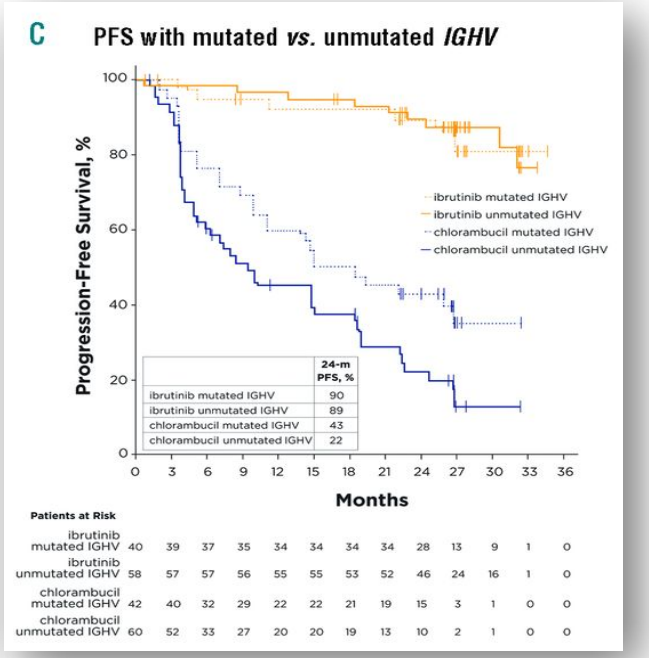


Hillmen P, et al. Lancet 2015

RESONATE II: Ibrutinib vs. Chlorambucil

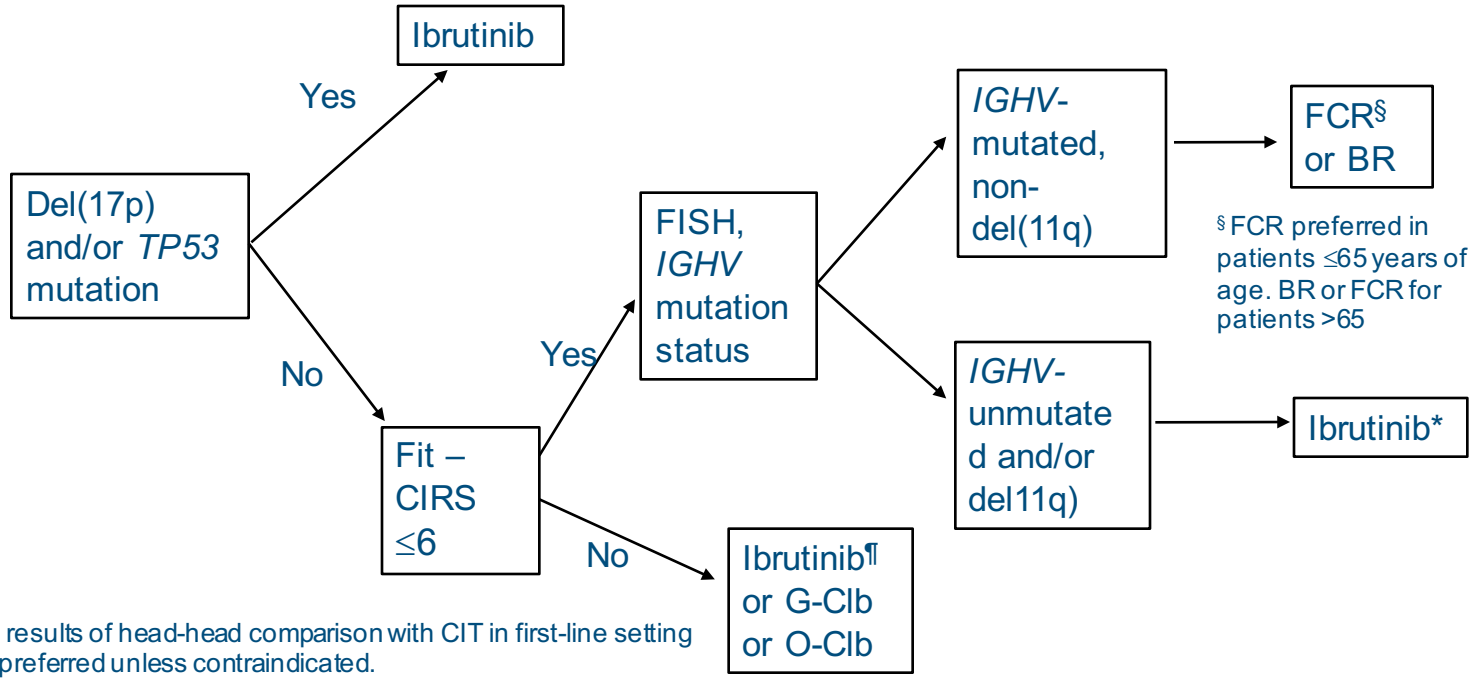
- Eligibility: patients ≥65 (median 73)
- 2-year PFS 89%; compare to median PFS of 29 months with G-Clb





Barr. Haematologica 2018.

A Suggested First-Line Treatment Algorithm



*Note, no results of head-head comparison with CIT in first-line setting
¶Ibrutinib preferred unless contraindicated.

Adapted from Jain et al. ASCO Education Book 2018.

Key Ongoing Studies in "Fit" First-Line Treatment of CLL

Study	Age Range, Fitness	CIT Regimen	Comparator Regimen(s)
ECOG E1912 (NCT02048813)	Fit; 18–70 yr; ECOG PS ≤2	FCR × 6	Ibr + R × 6, then Ibr
UK FLAIR study	Fit; 18–75 yr, ECOG PS ≤ 2	FCR × 6	Ibr + R × 6, then Ibr until U-MRD (max 6 y)
CLL13 (NCT02950051)	Fit; ≥18 yr; CIRS score ≤ 6; no individual organ score ≥ 4	FCR × 6 cycles if ≤65, BR × 6 cycles if > 65 year	1. V+R × 6 then V × 6 2. V+G x 6 then V × 6 3. Ibr+V+G × 6, then Ibr + V x 6

Key Ongoing Studies in First-Line CLL "Unfit" Patients

Study	Age Range, Fitness	CIT Regimen	Comparator Regimen(s)
Elevate CLL TN (NCT02475681)	Unfit; ≥65 yr **or** CrCl 30–69 **or** CIRS score >6	G-Clb × 6	1. Acalabrutinib 2. Acalabrutinib + G × 6, then acalabrutinib
iLLUMINATE (NCT02264574)	≥ 65 yr or CrCl 30–69 or CIRS score >6	G-Clb x 6	Ibr + G x 6 cycles then Ibr monotherapy
CLL14 (NCT02242942)	Unfit; ≥ 18 yr; CIRS score > 6	G-Clb × 6	V+G × 6 then V × 6
UNITY (NCT02612311)	≥ 18 yr, ECOG 0-2	G-Clb x 6	TGR-1202 (umbralisib) + ublituximab

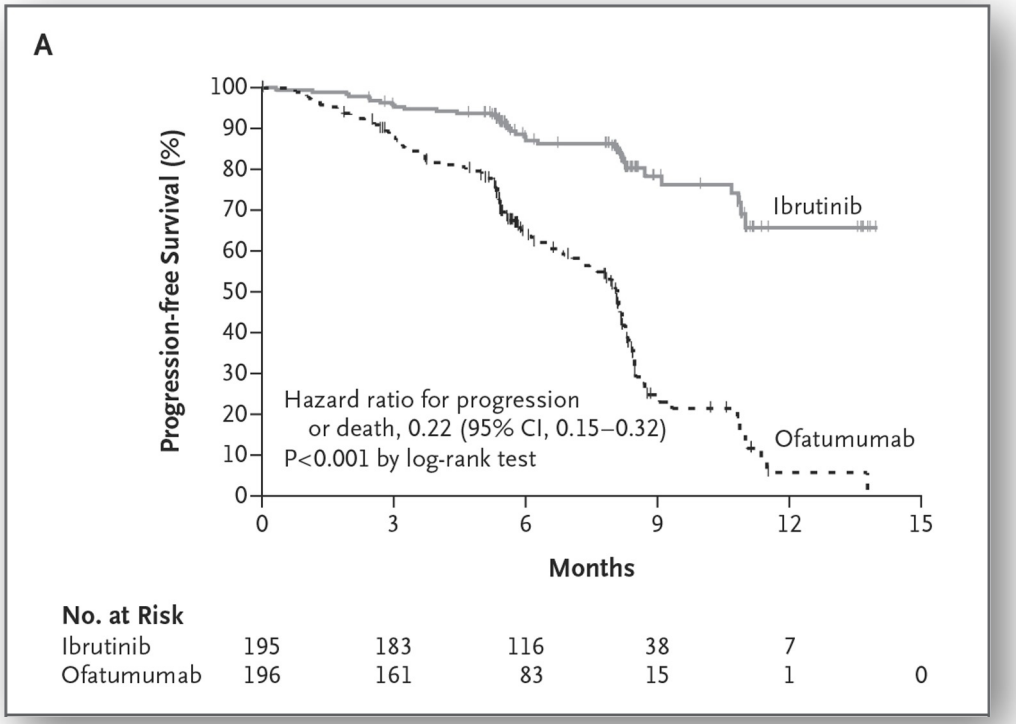
Potential First-Line Approvals

- Ibrutinib + rituximab
- Ibrutinib + obinutuzumab
- Acalabrutinib +/- obinutuzumab
- Venetoclax + …
  - Rituximab
  - Obinutuzumab
  - Ibrutinib + obinutuzumab
- Umbralisib + ublituximab

Targeted Therapies in R/R CLL

- 4 approved agents in 3 classes:
  - BTK inhibitors: ibrutinib
  - PI3K inhibitors: idelalisib, duvelisib
  - Bcl-2 inhibitor: venetoclax
- No head-to-head data to guide which to use or which order to use them
- Data to show venetoclax is effective after failure of ibrutinib or idelalisib but no high-quality data to demonstrate the reverse

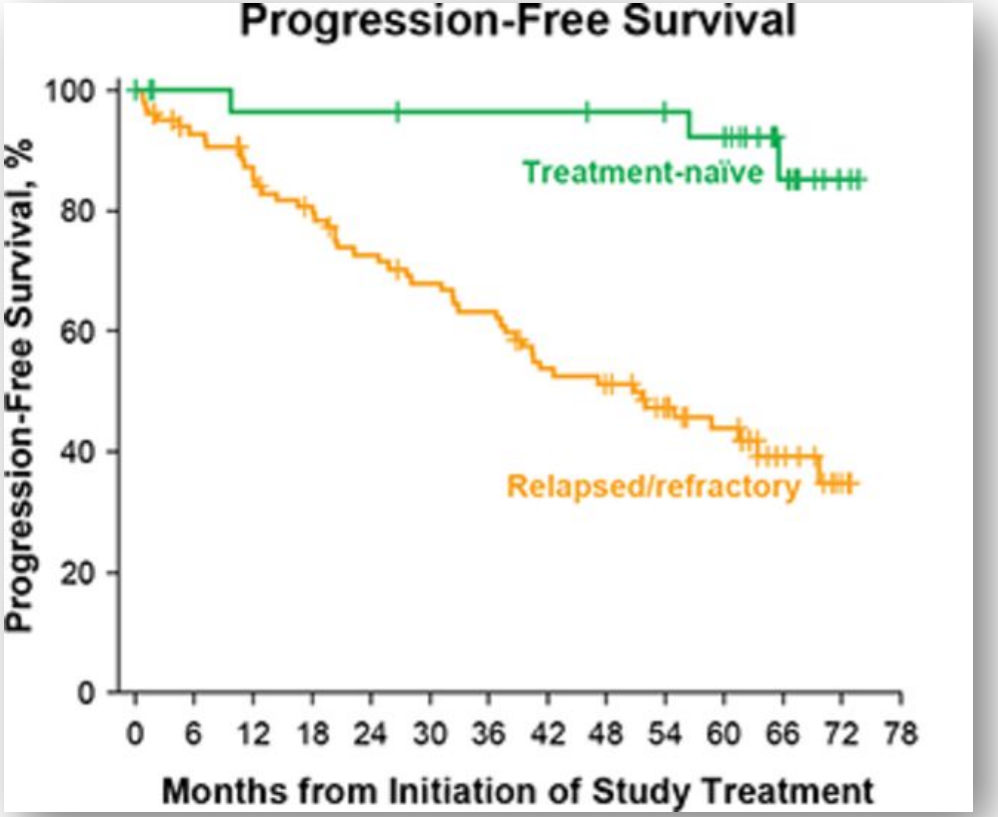
RESONATE I: R/R CLL



Byrd. N Engl J Med 2014.

Long-Term Ibrutinib Phase II PFS Data

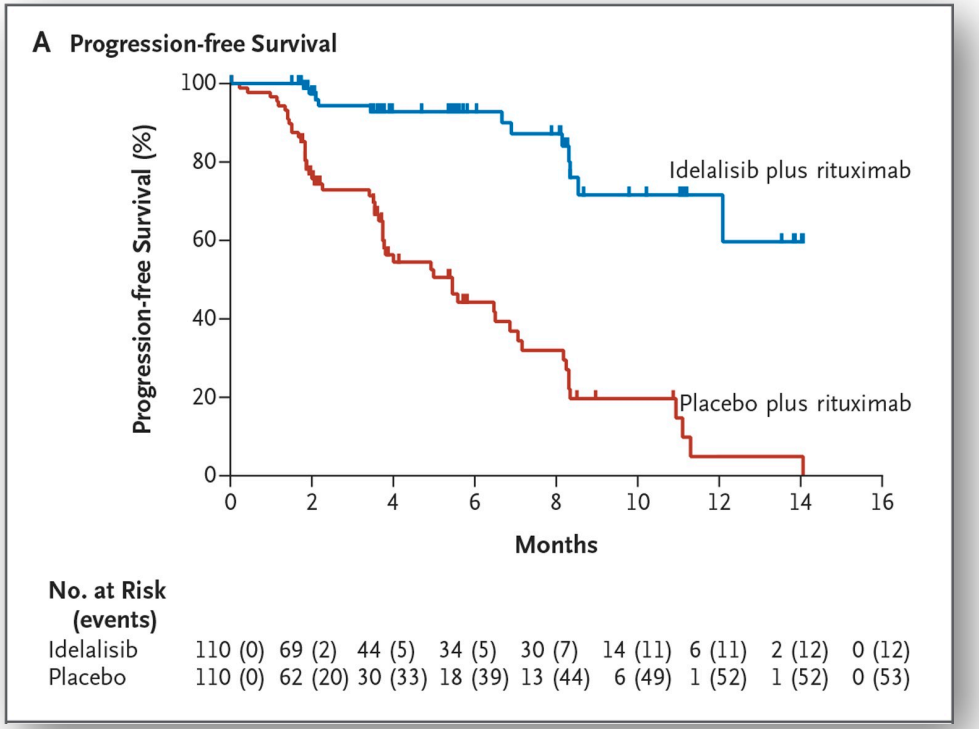
- R/R cohort median PFS 51 months (43 months for UM-CLL)



Obrien. Blood 2018.

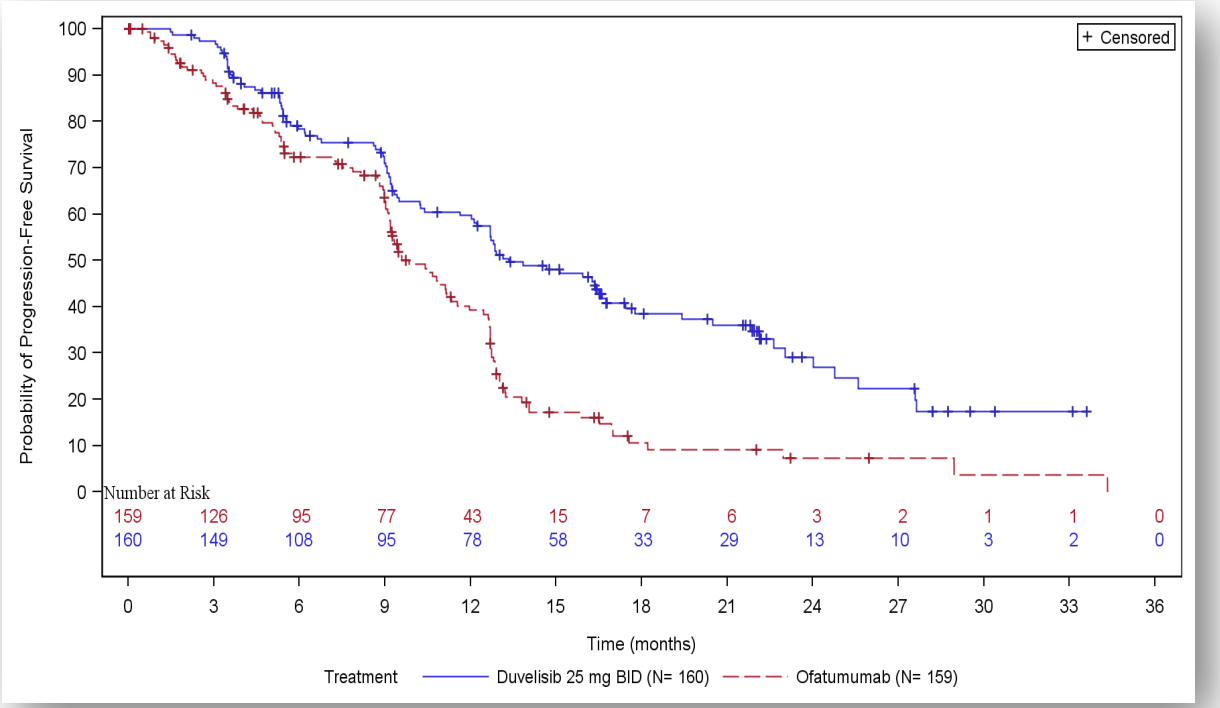
Idelalisib + Rituximab in R/R CLL

- Durable responses in R/R CLL
- Toxicity management more complex than Bcl-2 inhibitors and BTK inhibitors



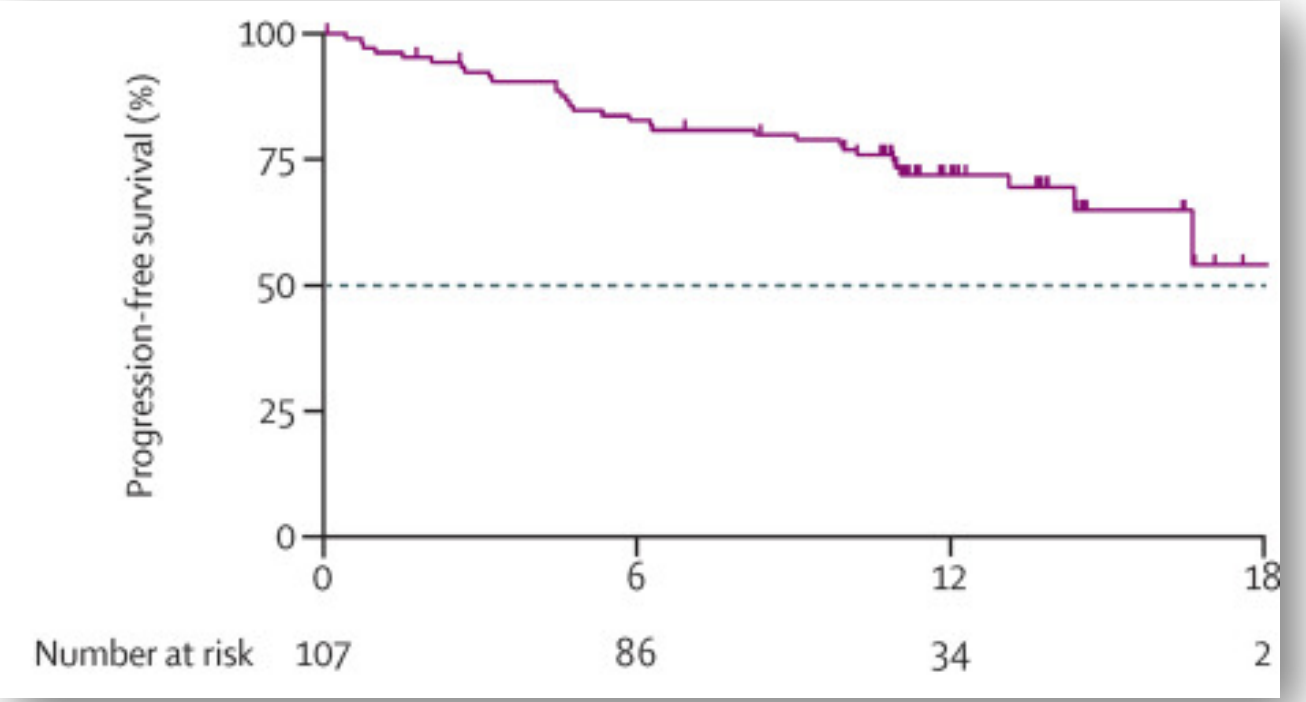
Furman. N Engl J Med 2014.

Duvelisib vs. Ofatumumab (DUO)



Flinn I, et al. Blood 2017;130: Abstract 493.

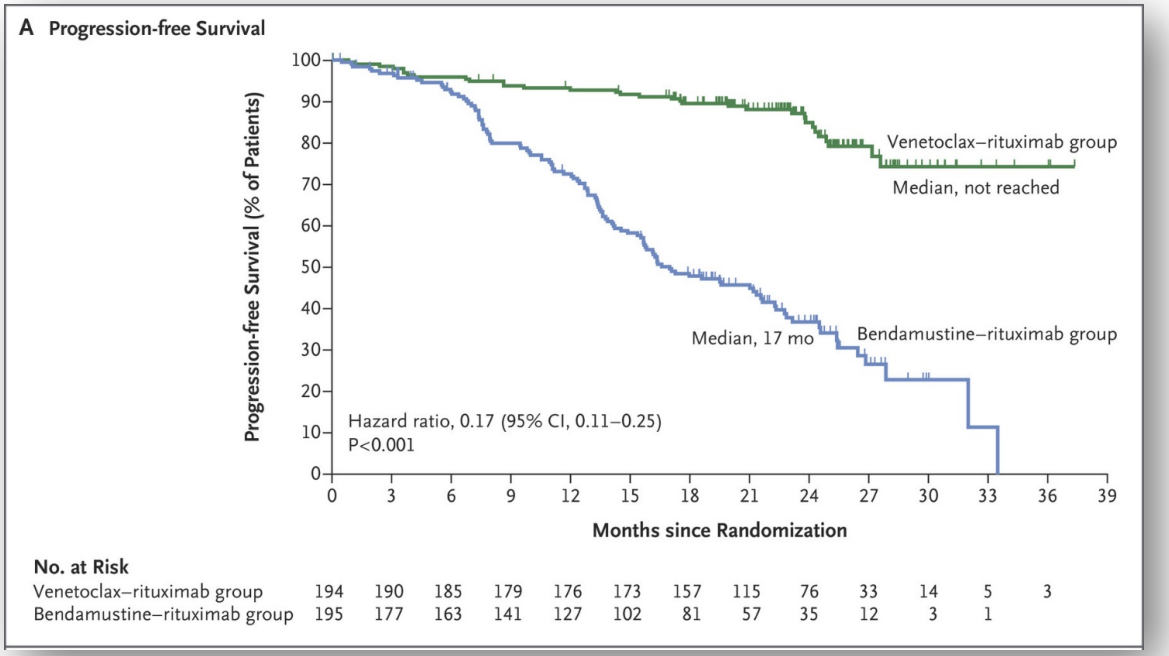
Venetoclax in R/R Patients With del(17p)



Stilgenbauer et al. Lancet Oncol 2016.

Venetoclax + Rituximab in First Relapse

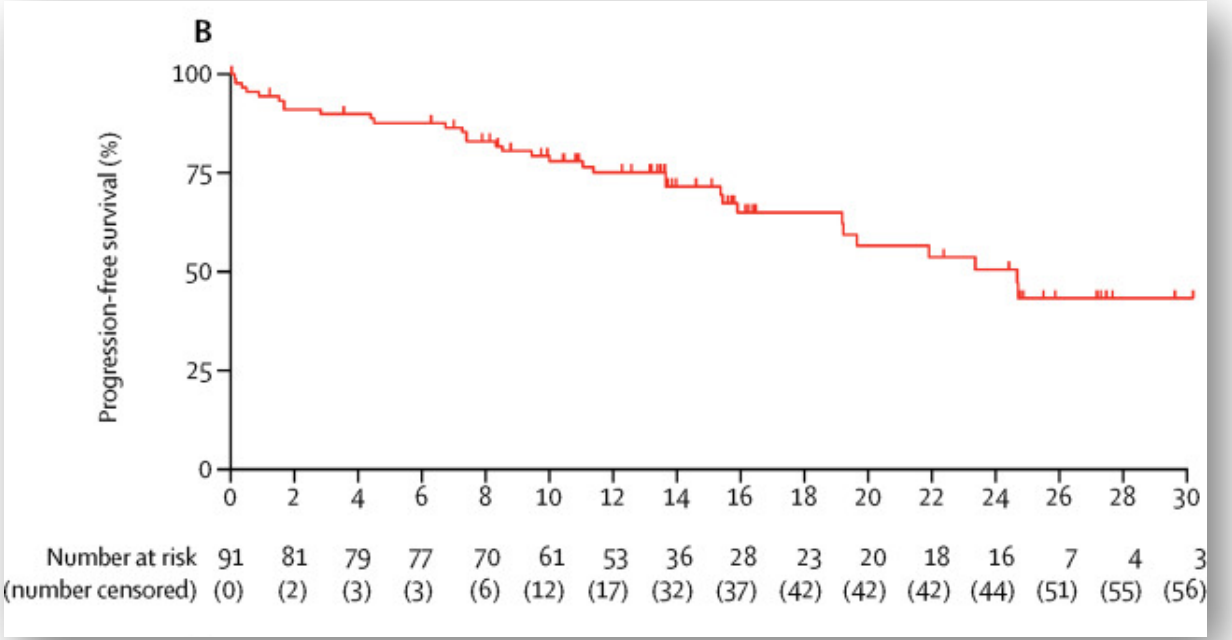
- U-MRD in PB 62%; not affected by pre-treatment genomic characteristics
- 90% with U-MRD in PB had U-MRD in BM
- Now approved for R/R CLL regardless of del(17p)



Seymour. N Engl J Med 2018.

Venetoclax Post-Ibrutinib/Idelalisib Failure

- Median PFS 2 years in very high-risk patient group

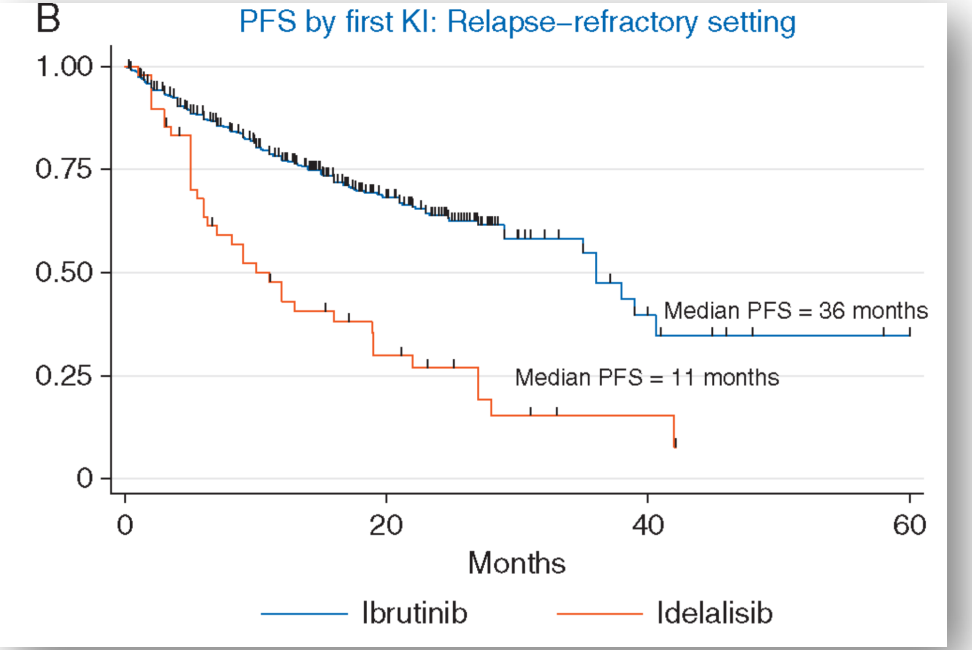


Jones J, et al. Lancet Oncol 2018.

How to Sequence Therapies in Relapsed CLL

Which Treatment to Give at Relapse

- No randomized data
- Nonrandomized data suggest superior PFS for ibrutinib compared to idelalisib
- No comparative data for ibrutinib vs. venetoclax or venetoclax + R



Mato A, et al. Ann Oncol 2017;28(5):1050-1056.

Approach to Treatment of R/R CLL

- BTKi and BCL-2 inhibitor naive → either ibrutinib or venetoclax +/- rituximab; no comparative data
- BTKi intolerant/refractory → venetoclax +/- rituximab; if BTKi intolerant, idelalisib + R or duvelisib could also be tried
- Venetoclax-refractory → limited data; trial of ibrutinib
- Double-refractory → clinical trials (e.g., CAR-T)
- Patients who are refractory to BTKi or venetoclax should be considered for allogeneic stem cell transplant if otherwise eligible

Part II: Recognition and Management of Toxicities From Targeted Agents in CLL

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Ofatumumab

- First fully humanized anti-CD20 mAb[1]
- FDA approved indications:
  - 2009: refractory to fludarabine and alemtuzumab[2]
  - 2014 COMPLEMENT 1: with chlorambucil in treatment naive[3]
  - 2016 COMPLEMENT 2: with fludarabine and cyclophosphamide[4]
  - 2016 PROLONG: maintenance therapy after two lines of therapy[5]
- Black box warning[1]
  - Hepatitis B virus reactivation
  - Progressive multifocal leukoencephalopathy

1. Arzerra® PI 2018; 2. Wierda WG, et al. J Clin Oncol 2010;28(10):1749-1755; 3. Hillmen P, et al. Blood 2013;122 (21):528; 4. Robak T, et al. Leuk Lymphoma 2017;58(5):1084-1093; 5. van Oers MH, et al. Lancet Oncol 2015;16:1370-1379.

Obinutuzumab

- Humanized anti-CD20 mAb with greater ADCC than rituximab[1]
- FDA approved in 2013 for treatment naive CLL in combination with chlorambucil[2]
- Black box warning[3]
  - Hepatitis B virus reactivation
  - Progressive multifocal leukoencephalopathy

1. Mossner E, et al. Blood 2010;115(22):4393-4402; 2. Goede V, et al. N Engl J Med 2014;370:1101-1110; 3. Gazyva® PI 2018.

Anti-CD20 mAb-Related Toxicities

- Tumor lysis syndrome
- Infusion related reactions
  - Grade 3 ≥: obinutuzumab 21-31%[1] and ofatumumab 10%[2]
  - High tumor burden and/or ALC >25,000: ↑ risk
  - Hypotension, rigors, pyrexia, hypoxia, urticaria, bronchospasms, etc.
  - Premedication protocol per institution: acetaminophen, steroid and antihistamine
  - Frequently monitor patients with preexisting pulmonary/cardiac conditions
- Neutropenia: grade 3 ≥ 26%
- Bacterial, fungal, and reactivated viral infections (e.g., CMV, HSV, VZV)

1. Gazyva® PI 2018; 2. Arzerra® PI 2018.

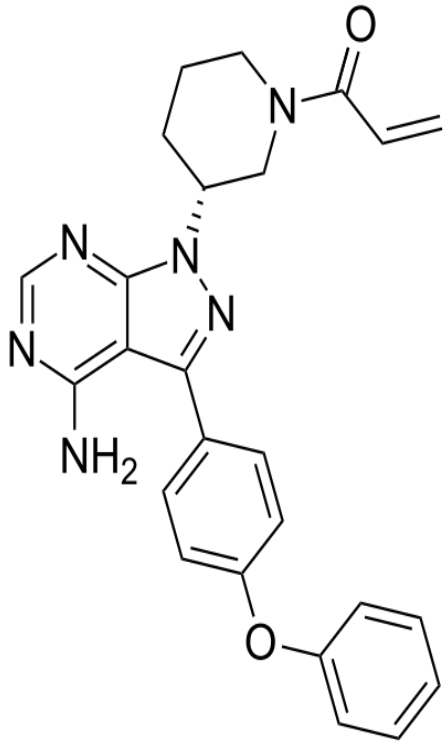
Oral Targeted Therapies in CLL

- Ibrutinib inhibits BTK[1]
  - RESONATE (2014) and RESONATE-2 (2016): broad approval regardless of Del 17p
- Idelalisib inhibits PI3K delta kinase[2]
  - FDA approved in 2014 for R/R CLL in combination with rituximab or SLL after 2 prior therapies
- Duvelisib is a dual inhibitor of PI3K delta and gamma kinases[3]
  - FDA approved in 2018 for R/R CLL after 2 prior therapies
- Venetoclax inhibits BCL-2[4]
  - FDA approved in 2016 for R/R CLL harboring Del 17p and 2018 for R/R CLL with rituximab

1. Imbruvica® PI 2018; 2. Idelalisib® PI 2018; 3. Copiktra ® PI 2018; 4. Venclexta™ PI 2018.

Ibrutinib

- Binds covalently to BTK cysteine 481 with an initial half-life of 4-6 hours and 24-hour target inhibition
- Promotes apoptosis by inhibiting B-cell proliferation, migration and adhesion
  - Rapid reduction in lymphadenopathy
  - Redistribution lymphocytosis (class effect)
- Testing for BTK and PLCγ2 mutations in suspected progression



RESONATE and RESONATE-2
AEs of Interest in the Integrated Analysis

- Median 29 mos. of ibrutinib with 47 mos. follow-up
- 29% discontinued for AEs and 12% dose reductions, > first year
- Notable interest: atrial fibrillation, bleeding, hypertension, and infection (30%)

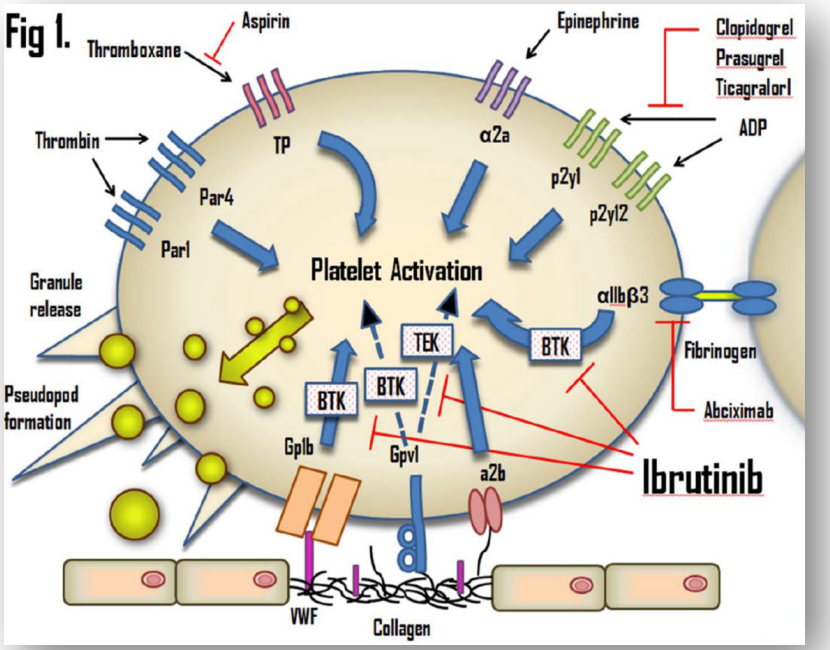
Integrated Analysis (N=330)	Diarrhea	Arthralgia	HT	Rash[a]	Bleeding[a]	Fatigue	AFib
AEs of interest, n (%)	174 (53)	74 (22)	68 (21)	119 (36)	182 (55)	120 (36)	36 (11)
Grade 1	116 (35)	45 (14)	11 (3)	72 (22)	130 (39)	66 (20)	5 (2)
Grade 2	43 (13)	22 (7)	33 (10)	35 (11)	35 (11)	44 (13)	15 (5)
Grade 3	15 (5)	7 (2)	24 (7)	12 (4)	14 (4)	10 (3)	16 (5)
Grade 4	0	0	0	0	2 (1)	0	0
Grade 5	0	0	0	0	1 (<1)	0	0
Dose reductions due to AEs of interest, n/N (%)	5/174 (3)	3/74 (4)	0	3/119 (3)	4/182 (2)	2/120 (2)	4/36 (11)
Discontinuation due to AEs of interest, n (%)	2/174 (1)	0	1/68 (1)	2/119 (2)	6/182 (3)	1/120 (1)	3/36 (8)

[a]Pooled terms.

Coutre S, et al. Blood 2016;128(22):4383.

Ibrutinib-Associated Bleeding

- BTK and TEC kinases play key roles in glycoprotein VI signaling necessary for collagen-mediated platelet aggregation
- Impact partially reversed after 2.5 days of withholding Ibrutinib and reversible within 1 week of discontinuation



Shatzel JJ, et al. J Thromb Haemost 2017;15:835-847.

Ibrutinib: Atrial Fibrillation

- Activation of PI3K-Akt pathway is a critical regulator of atrial rhythm under stress[1]
  - Regulated by BTK and TEC kinases
- Standard rate/rhythm management
  - Avoid CYP3A4 inhibitors
  - Referral to cardio-oncologist
- CHA2DS2-VASc system based on risk: score of ≥2 recommend direct oral anticoagulant[2]

1. McMullen JR, et al. Blood 2014;124(25):3829-3830; 2. Shatzel JJ, et al. J Thromb Haemost 2017;15:835-847.

Ibrutinib-Associated Bleeding: Patient Management

- Avoid vitamin K antagonists due to limited safety data[1]
- Caution against concomitant NSAIDs, fish oils, vitamin E, and aspirin-containing products
- Direct oral anticoagulants may increase risk
  - Assess risks and benefits individually when making treatment decisions (e.g., CHA2DS2-VAS c and HAS-BLED)
  - Caution with CYP3A4 interacting therapy
- Hold pre/post surgical procedures for 3 days (minor) and 7 days (major)
- Transfuse platelets for serious bleeding events

1. Shatzel JJ, et al. J Thromb Haemost 2017;15:835-847.

Ibrutinib: Hypertension

- Mechanism under investigation
- Incidence of grade ≥3 hypertension increased over time to 26% after 46 months[1]
- Standard management
  - Avoid CYP3A4 inhibitors and inducers
- Monitor blood pressure regularly as hypertension may be co-causal for the development of atrial fibrillation and cerebral hemorrhage

1. O'Brien SM, et al. Blood 2016;128:233.

Idelalisib

- Inhibitor of PI3K delta kinase isoform unique to leukocytes[1]
- Inhibition of T regulatory cells increases risk for immune-mediated toxicities[2]
  - Not indicated for treatment naive CLL/SLL
- Black box warning: fatal and serious toxicities (hepatic, diarrhea, colitis, pneumonitis, infections and intestinal perforation)[3]

1. Cheah CY, et al. Blood 2016;128(3):331-336; 2. Lampson BL, et al. Blood 2016;128(2):195-203; 3. Zydelig® PI 2018.

Idelalisib Study 116: Select AEs in ≥20%

SAFETY		Group; any Grade/Grade ≥3, %	
Category	Term	IDELA+R	PBO+R
Selected AEs	Diarrhea/Colitis	★ 21/5	15/0
	Bleeding[c]	14/1	19/1
	Pneumonia	★ 10/8	13/9
	Rash	10/1	5/0
	Pneumonitis	★ 6/4	1/1
Selected lab values, abnormal	ALT/AST elevation	★ 40/8	20/1
	Neutropenia	60/37	51/27
	Anemia	29/7	32/17
	Thrombocytopenia	19/11	32/18

Sharman,JP, et al. Blood 2014;124(21):330.

Idelalisib: Diarrhea

- Exclude infectious etiology
- Early onset: median time 8 weeks
  - Typically grade 1-2
  - Supportive care and anti-motility agents
- Late onset: median time 8 months
  - Typically grade ≥ 3
  - Characteristic of immune-mediated colitis (assess for CMV-colonoscopy/biopsy)
  - Drug holding and corticosteroids (enteric, PO or IV)
    - Duration based on clinical response
    - Mean time to resolution with budesonide 9mg was 12.1 days versus 1 month for drug holding
  - 67% rechallenged and 58% without recurrence

Coutre S, et al. Leuk Lymphoma 2015;56(10):2779-2786

Idelalisib: Pneumonitis vs. Pneumonia

Pneumonitis

- Rare, 4%[1]
- Pulmonary symptoms (cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or >5% decline in oxygen saturation)
  - Hold Idelalisib
  - Bronchoscopy with BAL?
- Time to onset < 1 to 15 months[1]
- Corticosteroids and permanently discontinue[1,2]

Pneumonia

- 8% grade 3[1]
- Acute inflammation of lung caused by infection
- Bronchoscopy with BAL?
- *Pneumocystis jirovecii* pneumonia
  - Rare, 3%[1]
  - Occurred in patients not receiving prophylaxis
  - NCCN recommends prophylaxis[3]

1. Coutre S, et al. Leuk Lymphoma 2015;56(10):2779-2786; 2. Zydelig® PI 2018; 3. NCCN. CLL/SLL Guidelines. Version 5.2018.

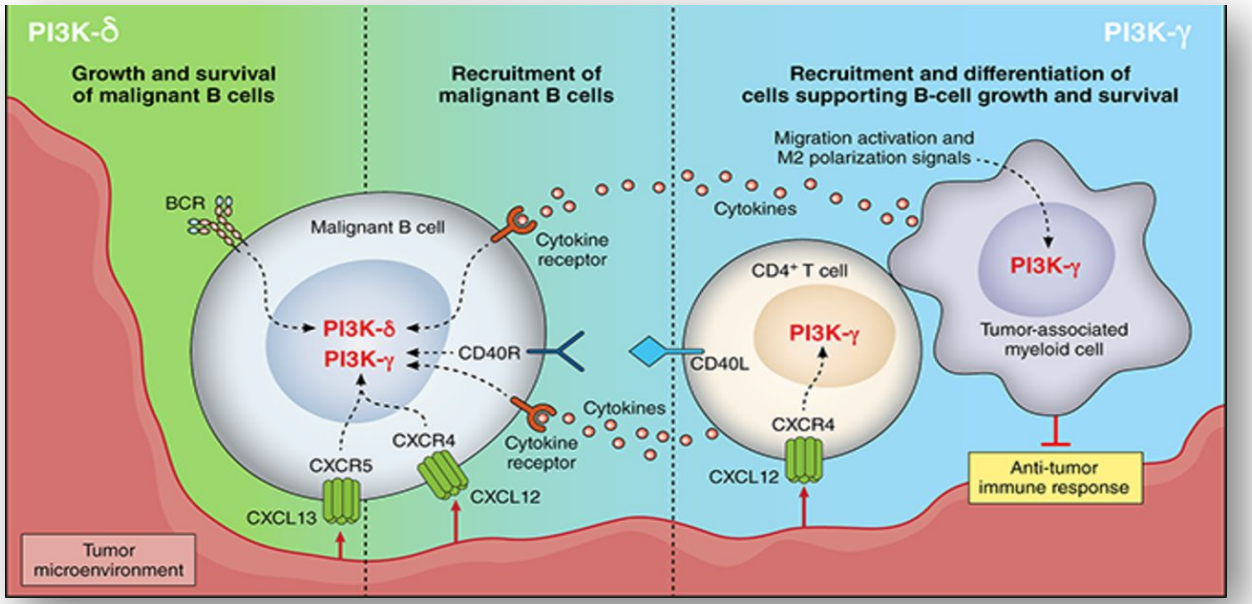
Idelalisib: Hepatotoxicity

- Typically occurs <12 weeks of initiation and reversible with dose interruption[1]
- 74% of patients requiring treatment interruptions successfully resumed without recurrence[2]
- Avoidance of hepatotoxic agents
- Monitor for viral reactivation (HSV, CMV, Hep)[1-3]

1. Coutre S, et al. Leuk Lymphoma 2015;56(10):2779-2786; 2. Zydelig® PI 2018; 3. NCCN. CLL/SLL Guidelines. Version 5.2018.

Duvelisib

- Dual inhibitor of PI3K delta and gamma kinases[1,2]
- Black box warnings: fatal and serious toxicities (infections, diarrhea or colitis, cutaneous reactions and pneumonitis)[2]



1. Flinn I, et al. Blood 2018; doi: 10.1182/blood-2018-05-850461; 2. Copiktra ® PI 2018.

DUO Study: Select AEs

- Median exposure: duvelisib 50 wks and ofa 12 doses (6 mos)
- Severe opportunistic infections (6%): bronchopulmonary aspergillosis (n=4), fungal (n=2), PJP (n=3), and CMV colitis (n=1)

Select AEs ≥ 10%		All Grades (%)		≥ Grade 3 (%)	
		Duv (N=158)	Ofa (N=155)	Duv (N=158)	Ofa (N=155)
Hematologic	Neutropenia	33	21	★ 30	17
	Anemia	23	10	13	5
	Thrombocytopenia	15	6	8	2
Nonhematologic	Diarrhea	51	12	★ 15	1
	Colitis	13	1	★ 12	1
	Pneumonia	18	6	★ 14	1
	Rash	10	12	2	1
	Pneumonitis	-	-	3	-
	URTI	16	8	0	0

Flinn I, et al. Blood 2018; doi: 10.1182/blood-2018-05-850461.

Venetoclax

- Selective BCL-2 inhibitor that directly induces apoptosis independent of TP53 pathway[1,2]
- FDA approved indications[3]:
  - 2016: monotherapy for R/R CLL with Del 17p[4]
  - 2018 MURANO trial: +rituximab for R/R CLL[5]
- Concomitant use with strong CYP3A inhibitors during ramp-up contraindicated[3]

1. Souers AJ, et al. Nat Med 2013;19:202-208; 2. Anderson MA, et al. Blood 2013;122(suppl; abstr):1304; 3. Venclexta™ PI 2018; 4. Stilgenbauer S, et al. Lancet Oncol 2016; 17(6):768-778; 5. Seymour JF, et al. N Eng J Med 2018; 378:1107-1120.

Venetoclax: AEs of Special Interest

- AIHA 7% as monotherapy[1]
- Myelosuppression: managed with dose interruption/reduction
  - Grade ≥ 3 neutropenia 64% (+rituximab)[1] and 63% (monotherapy);[2] consider G-CSF and/or antibiotics
  - Thrombocytopenia 29% (any grade): monotherapy
- GI: Any grade, diarrhea 43% and nausea 42% in both trials[1,2]
- Infection[1,2]
  - Upper respiratory infection most common in ≥ 20% across both trials
  - Pneumonia 9% (grade 3) across both trials
- Grade ≥3 laboratory tumor lysis syndrome: 3% (+rituximab)[1] and 6% (monotherapy)[2]

1. Stilgenbauer S, et al. Lancet Oncol 2016; 17(6):768-778; 2. Seymour JF, et al. N Engl J Med 2018; 378:1107-1120.

Measures to Mitigate Tumor Lysis Risk

- Disease burden + anti-hyperuricemic agent + hydration
- Low-risk: nodal mass <5 cm AND ALC ≤25,000
  - Outpatient dosing at all levels
  - Post dose labs: 6-8 and 24 hours for first dose of 20 mg and 50 mg
- Medium risk: nodal mass 5 to <10 cm OR ALC ≥ 25,000
  - Outpatient. Consider hospitalization if CrCl <80 mL/min.
  - Post dose labs: 6-8 and 24 hours for first dose of 20 mg and 50 mg
- High risk: nodal mass ≥10 cm OR ALC ≥25,000 AND any node ≥5 cm
  - Hospitalized for first dose of 20 mg and 50 mg
  - Post dose labs: 4, 8, 12, and 24 hours for first dose of 20 mg and 50 mg then outpatient for ramp-up doses with post dose labs at 6-8 hours and 24 hours

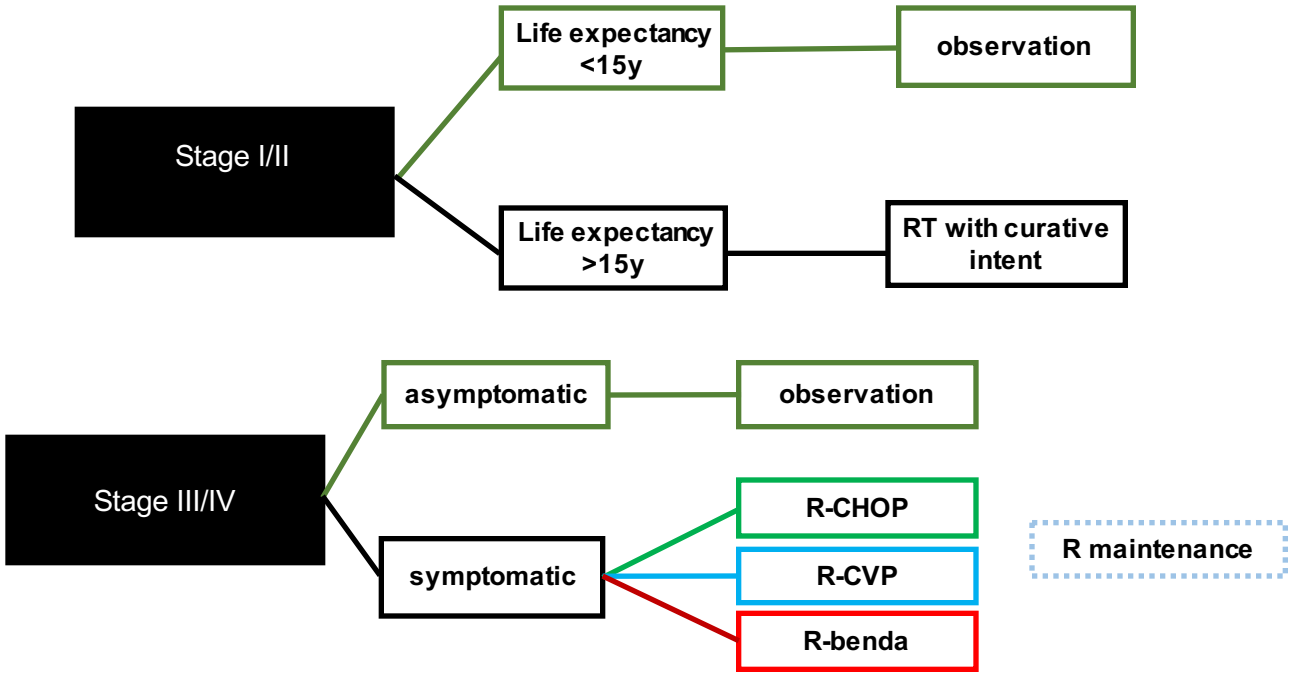
Part II: Summary

- Infusion-related reactions are manageable events inherent to ofatumumab and obinutuzumab
- Patients receiving ibrutinib should be counseled and monitored for bleeding and cardiac-related events. Consider referral to cardio-oncologist
- Counsel patients receiving Idelalisib regarding diarrhea, infections, and hepatic toxicities
- Venetoclax has a favorable risk-benefit profile. Patient profiling required to mitigate risk of tumor lysis
- Concomitant medication monitoring with oral oncolytics

Part III: Treatment of FL

Philip A. Thompson, MB, BS (Hons.)
Assistant Professor, Department of Leukemia
University of Texas MD Anderson Cancer Center

Part III: Initial Treatment of Follicular Lymphoma



Watch and Wait vs. Immediate Treatment for Stage III/IV FL

- No survival benefit for early treatment in asymptomatic patients[1-3]
- GELF criteria for high disease burden suggesting need for treatment:
  1. Any nodal or extranodal tumor mass >7 cm in diameter
  2. Involvement of at least 3 nodal sites, each with diameter >3 cm
  3. Presence of systemic or B symptoms
  4. Splenic enlargement with inferior margin below the umbilical line
  5. Compression syndrome (ureteral, orbital, gastrointestinal)
  6. Pleural or peritoneal serous effusion (irrespective of cell content)
  7. Leukemic phase (>5.0 x 10^9/L circulating malignant cells)
  8. Cytopenia (granulocyte count < 1.0x10^9/L and/or platelets <100x10^9/L)

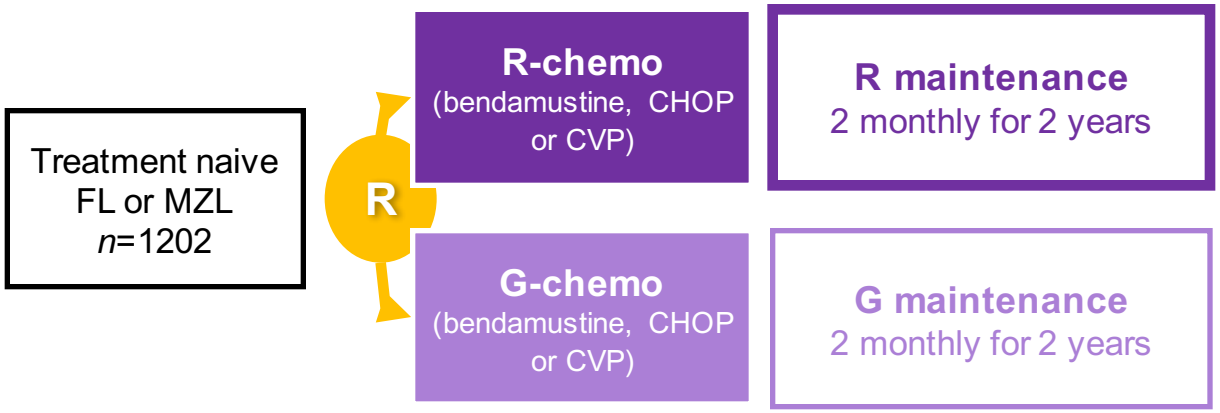
1. Brice PJ. Clin Oncol 1997; 2. Ardeshna KM. Lancet 2003; 3. Solal-Celigny. J Clin Oncol 2012.

Choice of CIT

- STiL study[1] (BR vs R-CHOP in indolent and mantle cell lymphoma) showed:
  1. Superior PFS for BR vs R-CHOP, including when only FL analyzed
  2. BR associated with lower grade 3/4 neutropenia, infection rates, peripheral neuropathy and no alopecia
- Value of maintenance R more uncertain after BR therapy
- Additionally, post-hoc analysis of GALLIUM study showed higher rates of fatal AEs in older adults (>70) receiving bendamustine (in both R- and G-containing arms)
- Either remains a reasonable choice; R-CVP or R monotherapy for very elderly/unfit patients

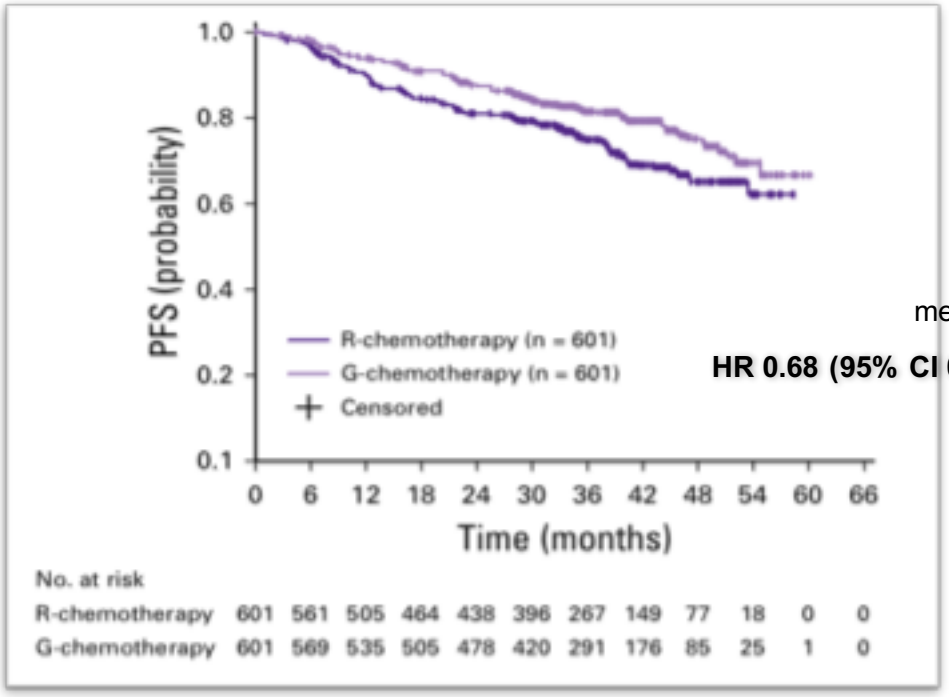
1. Rummel, Lancet Oncol 2013.

R vs. G: GALLIUM STUDY



Marcus, et al. N Engl J Med 2017.

Obinutuzumab Improves PFS Compared With Rituximab



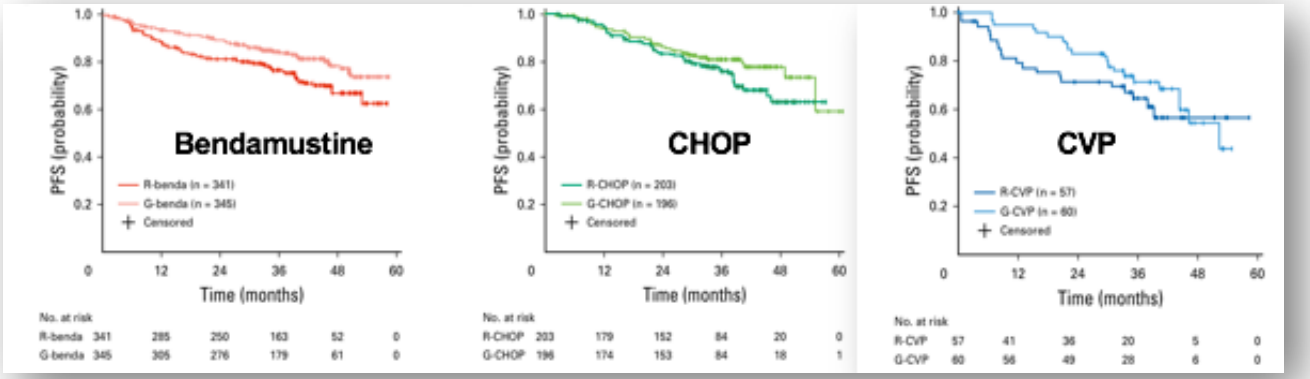
median follow-up 41 months

HR 0.68 (95% CI 0.54 to 0.87, *P*=0.0016)

Hiddeman, et al. J Clin Oncol 2018.

G Superior PFS to R in Both Bendamustine and CHOP Groups

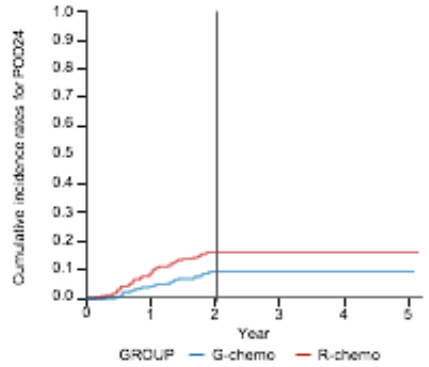
- Obinutuzumab arm associated with higher:
  1. IRRs (59 vs 49%)
  2. Febrile neutropenia per cycle (6.9 vs. 4.9%)
  3. Cumulative incidence of grade 3-4 infections (20 vs. 15.6%).
- Bendamustine arm associated with highest # fatal AEs; CHOP with highest # grade 3-5 AEs (esp. cytopenias)



Hiddeman, et al. J Clin Oncol 2018.

GALLIUM: Risk of a POD24 Event by Treatment Arm

- POD24 an important milestone as patients who progress within 2 years have very poor outcomes



	R-chemo, N=601	G-chemo, N=601	Risk reduction G-chemo vs R-chemo
POD24 events*, %	16.7	9.7	41.5%†
POD24 events, n	72	43	

- G-chemo reduced the relative risk of a POD24 event by 42% compared with R-chemo

*Cumulative incidence rates
†Following further analysis, the data value has been revised to 46% as of November 2017

Laurenen A et al. Poster presentation, ASH 2017

Factors Influencing Choice of Monoclonal Antibody

Rituximab

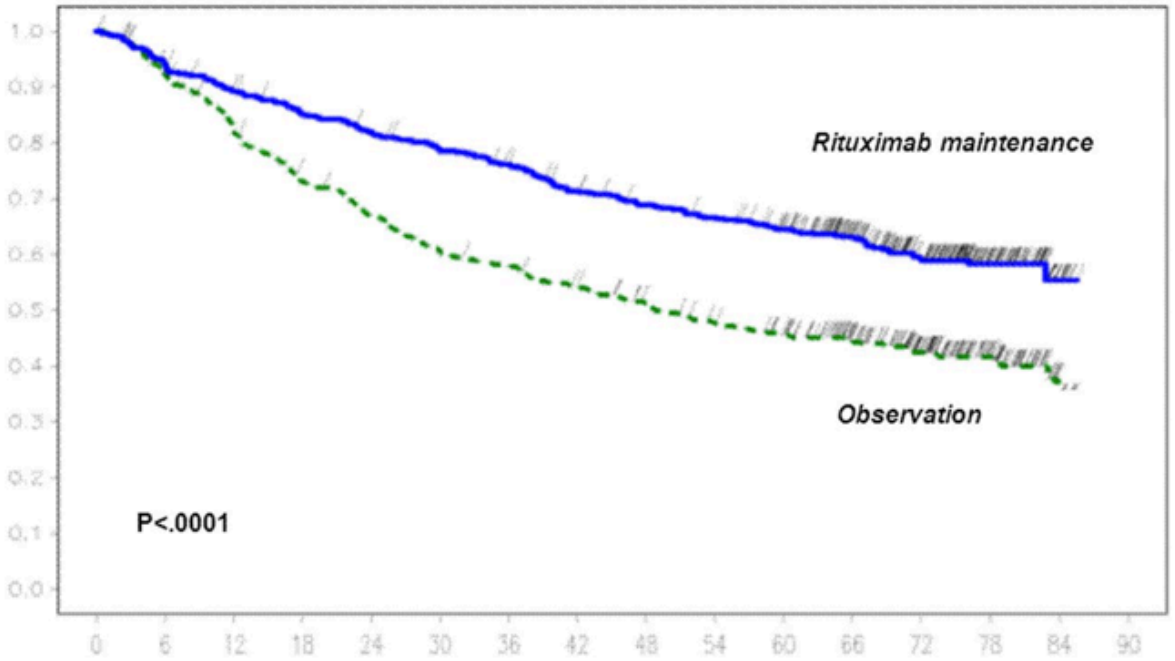
- Less grade ≥3 toxicity (infections/IRRs)
- Lower cost
- No OS advantage
- Can use G if rituximab refractory

Obinutuzumab

- More potent, more MRD negative patients
- Superior PFS
- 5% absolute reduction in POD24 events

PRIMA Study: PFS

- 2-year rituximab maintenance post-CIT (R-CHOP, R-CVP or R-FCM)
- No OS benefit

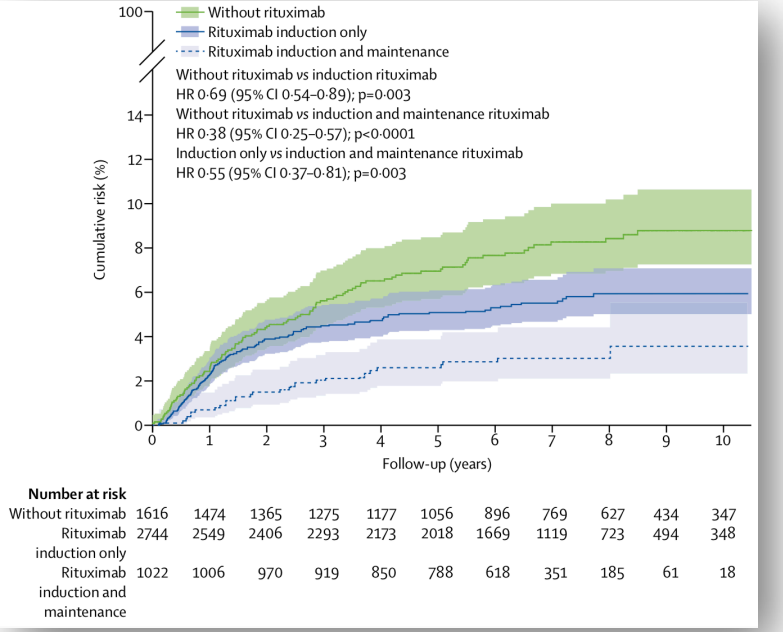


Seymour J, et al. Blood 2013;122:509.

R Maintenance May Be Associated With Reduced Risk of Transformation

- Multi-center, retrospective analysis
- 2.6% absolute risk reduction for transformation at 10 years

10-year cumulative risk of histologic transformation



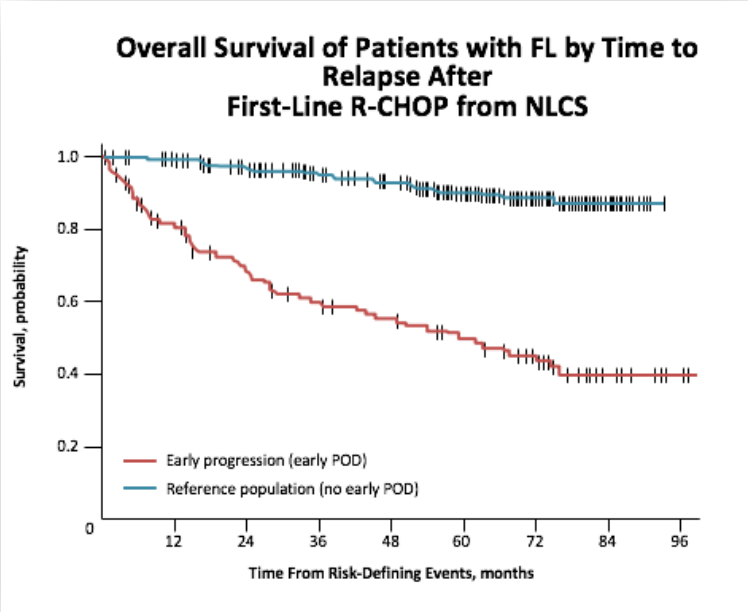
Federico, et al. Lancet Haem 2018.

Factors Influencing Decision to Give Maintenance

- Chemotherapy backbone: PRIMA study used R maintenance after R-CHOP or R-CVP; unclear if beneficial after BR
- Tolerability of induction
- Reduced risk of histologic transformation
- NB. No survival benefit from R maintenance

Approach to Relapsed/Refractory Follicular Lymphoma

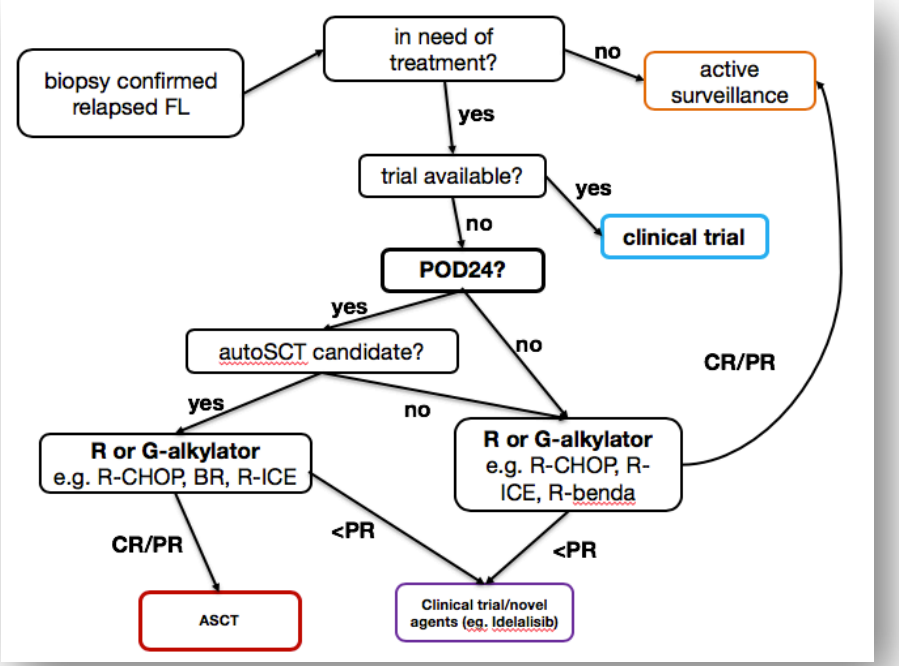
Early Relapse Within 2 Years of R-CHOP Is Associated With Poor Outcome



Time to Relapse	2-Year OS (95% CI), %	5-Year OS (95% CI), %
Reference (no early POD) n = 420	97 (94.6-98.1)	90 (86.2-92.4)
Early progression (early POD) n = 110	68 (58.2-76.3)	50 (39.4-59.2)

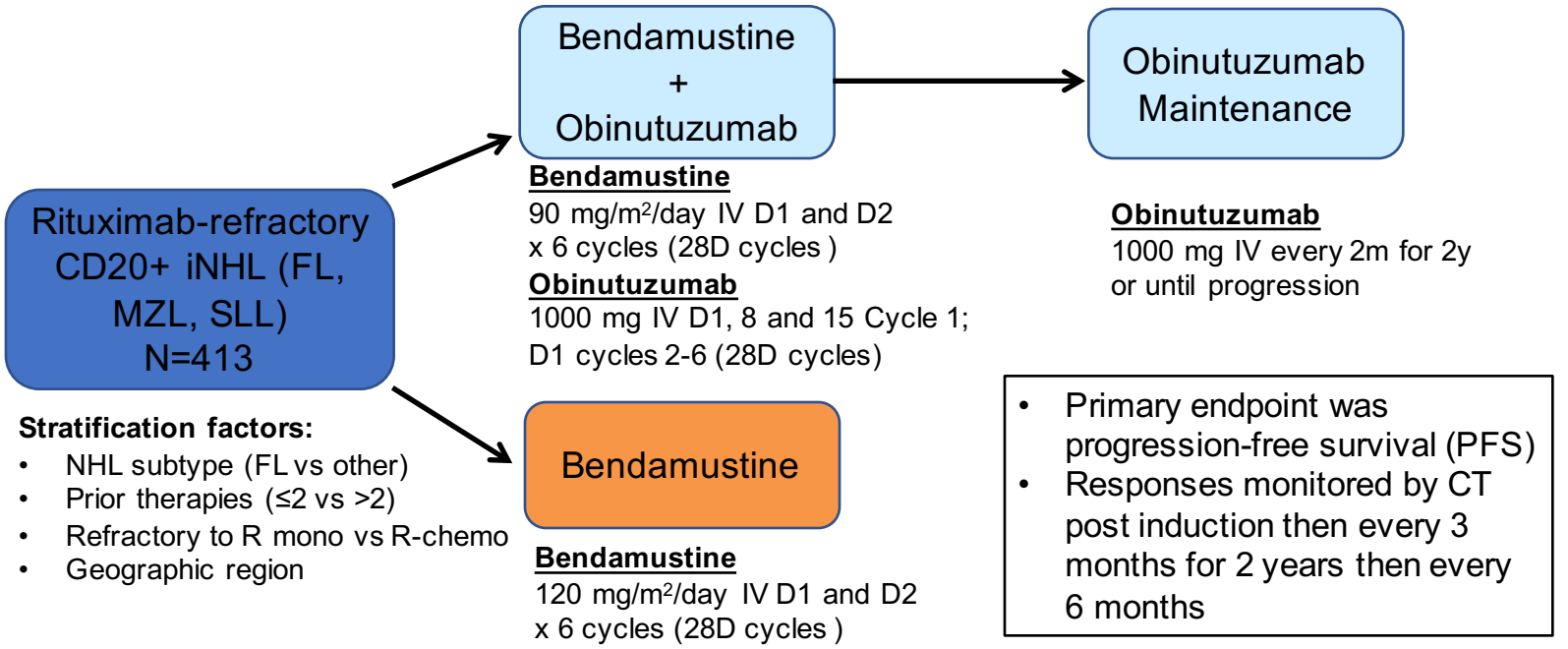
Casulo C, et al. J Clin Oncol. 2015;33:2516-2522.

Approach to First Relapse of Follicular Lymphoma



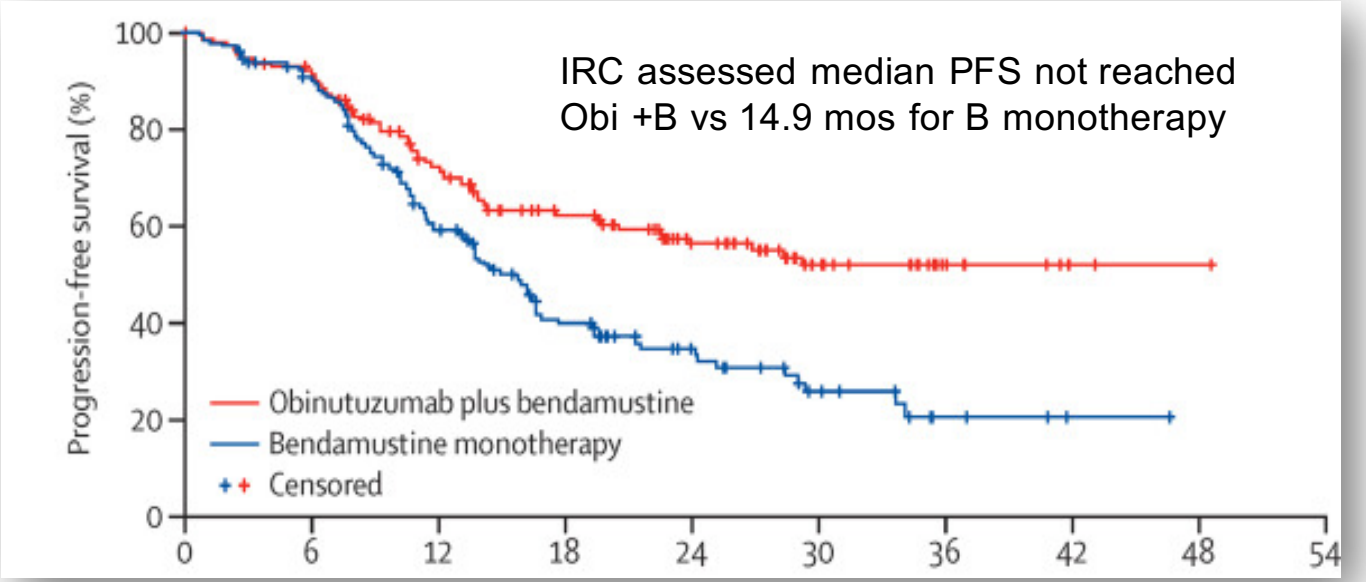
Courtesy of Dr. Chan Cheah

Phase III GADOLIN Study: Obinutuzumab + Bendamustine vs. Bendamustine



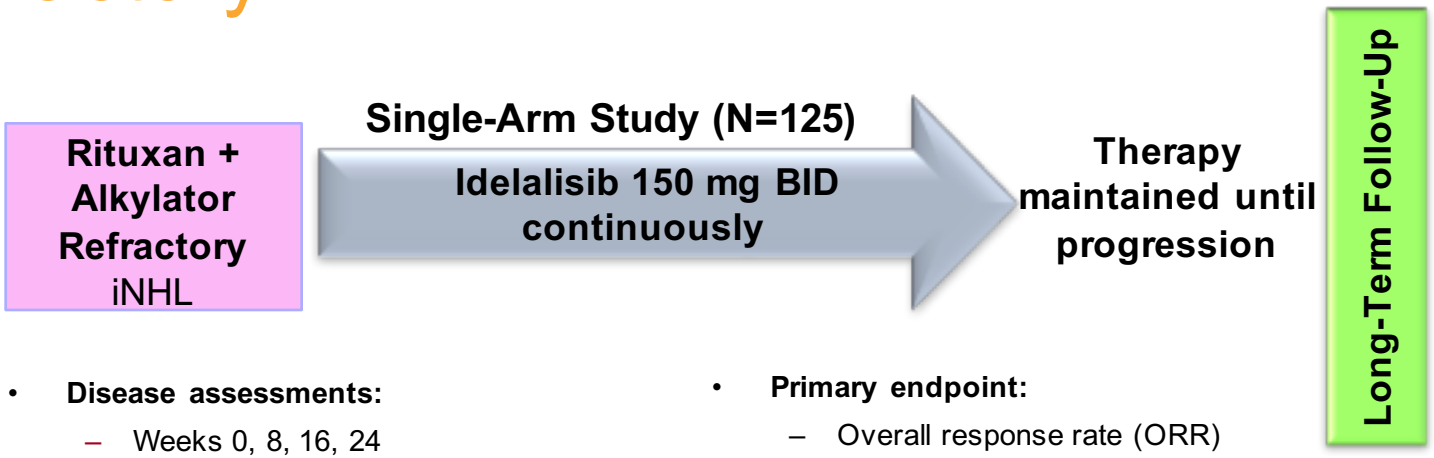
Sehn L, et al. Lancet Oncol. 2016;17(8):1081-1093.

GADOLIN: Obinutuzumab Improves Progression-Free Survival



Sehn L, et al. Lancet Oncol. 2016;17(8):1081-1093.

Phase II 101-09: Idelalisib Monotherapy in Refractory iNHL



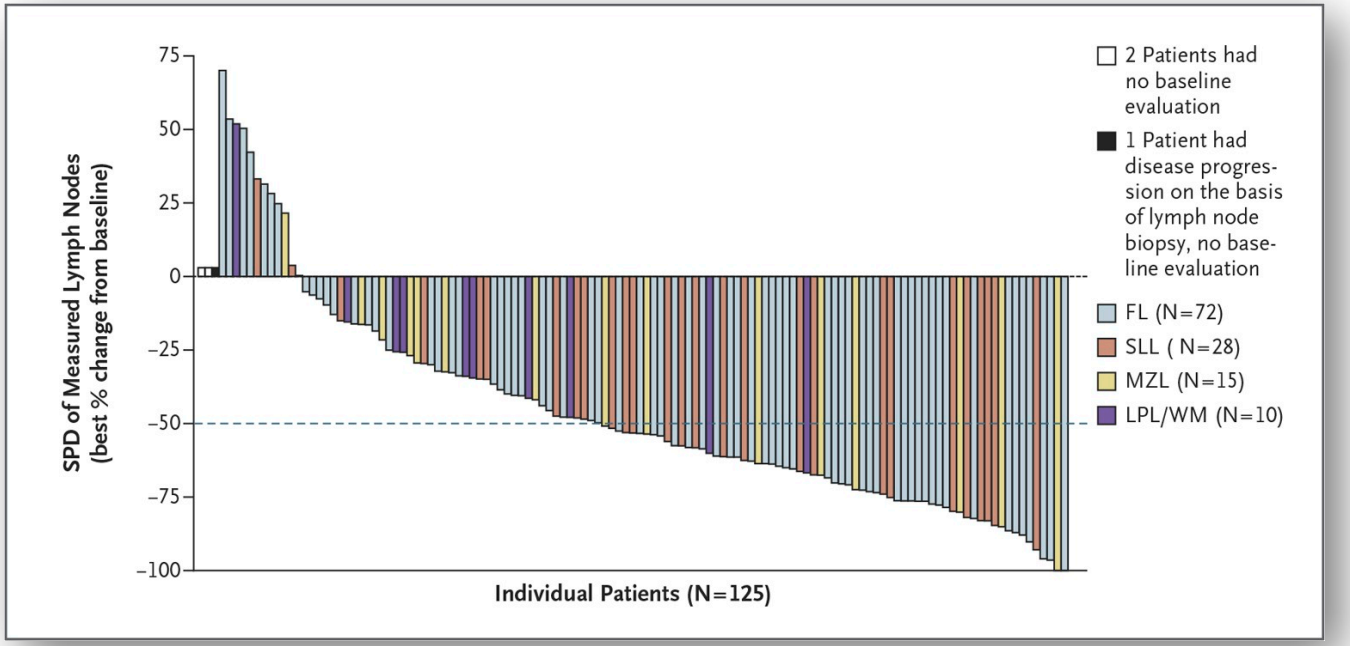
- **Disease assessments:**
  - Weeks 0, 8, 16, 24
  - Every 12 weeks thereafter
  - Evaluated by Independent Review Committee

- **Primary endpoint:**
  - Overall response rate (ORR)
- **Secondary endpoints:**
  - Duration of response (DOR)
  - PFS
  - Overall survival (OS)
  - Safety
  - Quality of life

Gopal AK, et al. N Engl J Med. 2014;370:1008-1018.

Tumor Response

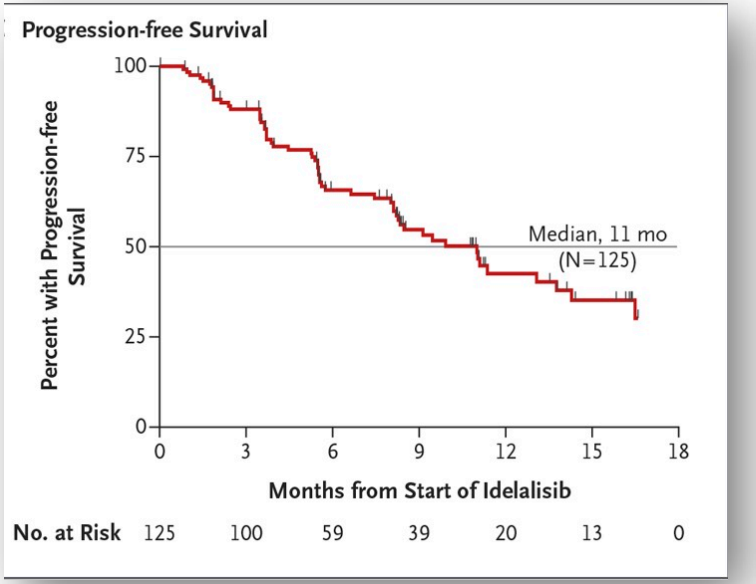
- Follicular lymphoma (N=72): ORR 56%, 42% PR, and 14% CR



Gopal AK, et al. N Engl J Med. 2014;370:1008-1018.

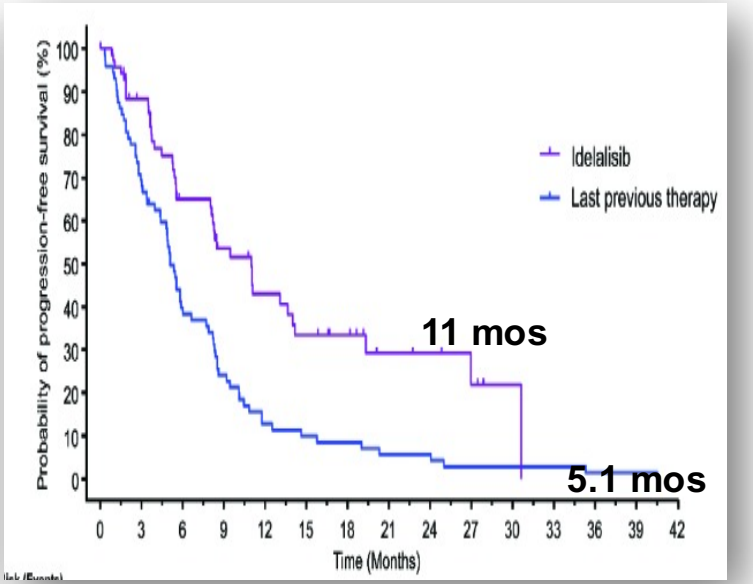
Idelalisib: PFS

Median PFS = 11 months[1]



Time from Start of Idelalisib (Months)

PFS: Idelalisib vs last prior therapy[2]

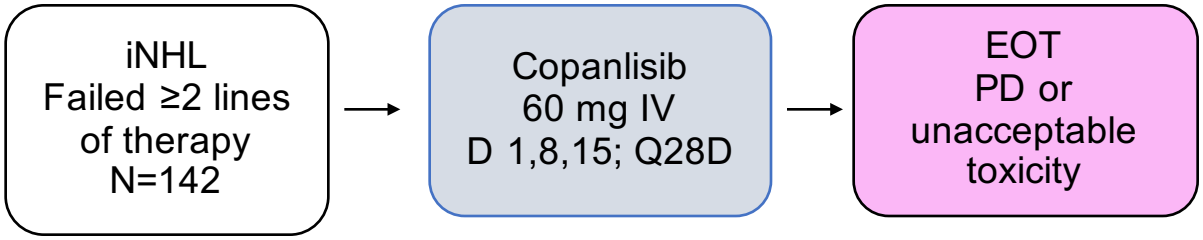


Time from Start of Idelalisib (Months)

1. Gopal AK, et al. N Engl J Med. 2014;370:1008-1018; 2. Salles G, et al. Haematologica 2017;156-159.

Phase II CHRONOS-1: Copanlisib in Relapsed/Refractory Follicular Lymphoma

- Inhibitor of PI3K alpha and delta isoforms



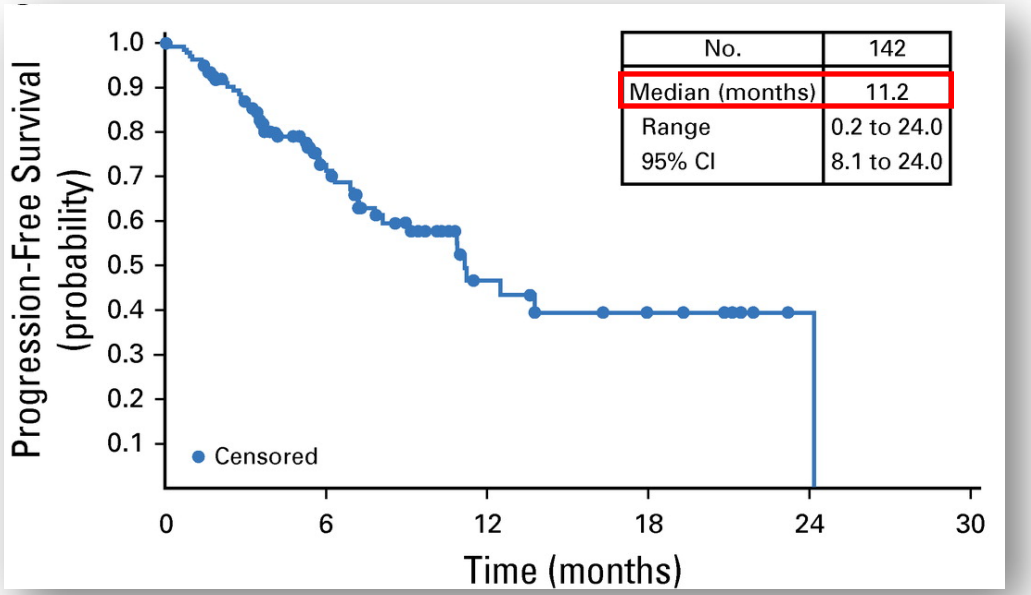
Patient Characteristics

- Prior treatment, n (range): 3 (2-8)
- Median time from last therapy until PD: 8.5m
- Prior Rituximab: 100%
- Refractory to last regimen: n (%)
  - Rituximab: 59 (56.7)
  - Alkylating agent: 39 (37.5)
  - Rituximab and alkylating agent: 43 (41.3)

Primary endpoint: ORR

Dreyling, M, et al *J Clin Oncol* 2017;35:3898-3905.

Phase II CHRONOS-1: PFS



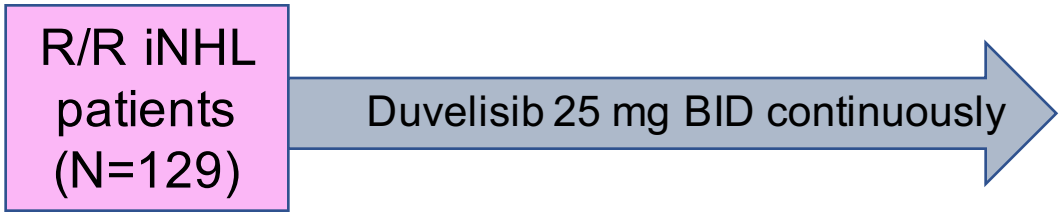
Results (N=104 FL):

- ORR 59%
  - 14% CR
  - 44% PR
- Median DOR 12.2 mos (range, 0-22.6)

Dreyling, M, et al *J Clin Oncol* 2017;35:3898-3905.

Phase II DYNAMO Study: Duvelisib in Relapsed/Refractory iNHL

- Inhibitor of PI3K delta and gamma isoforms



Study Endpoints
- **Primary**: ORR
- **Secondary**:
  - Safety
  - DOR
  - PFS
  - OS

Inclusion Criteria:
- 3 iNHL disease subtypes
  - follicular lymphoma (FL)
  - small lymphocytic lymphoma (SLL)
  - marginal zone lymphoma (MZL)
- Double refractory to rituximab (monotherapy or in combination) and to chemotherapy or radioimmunotherapy
- No eligibility restrictions for cytopenias

Flinn IW, et al. Blood 2016;128:1218.

Phase II DYNAMO Study: Duvelisib in Relapsed/Refractory iNHL

	FL N=83	SLL N=28	MZL N=18	Overall N=129
ORR, %	41	68	33	46
DoR (months), median	9.2	9.9	NE	9.9
PFS (months), median	8.3	11.3	NE	8.4
TTR (months), median	1.9	1.9	3.6	1.9
OS (months), median	18.4	NE	NE	18.4

Flinn IW, et al. Blood 2016;128:1218.

Part III: Summary

- Approximately 20% of FL patients relapse within two years and are refractory to therapy resulting in 5-year OS <50%
- Patients refractory to or relapsed with two years after rituximab and alkylating agents have limited treatment options and should be enrolled in clinical trials or treated with novel agents
- Limited efficacy of BCL-2 inhibitors or BTK inhibitors (unlike CLL). Novel therapies (e.g., CAR-T) urgently needed

Part IV: Recognition and Management of AEs of Novel Agents in FL

Copanlisib: AEs of Special Interest

Adverse Event	Grade, No. (%) All	3	4	5
Any treatment-emergent adverse event	140 (99)	75 (53)	38 (27)	6 (4)
Nonhematologic toxicities				
Hyperglycemia	71 (50)	48 (34)	10 (7)	0
Diarrhea	48 (34)	7 (5)	0	0
Fatigue	43 (30)	3 (2)	0	0
Hypertension	43 (30)	34 (24)	0	0
Fever	36 (25)	6 (4)	0	0
Nausea	33 (23)	1 (1)	0	0
Lung infection	30 (21)	18 (13)	3 (2)	2 (1)
Oral mucositis	28 (20)	4 (3)	0	0
Upper respiratory infection	26 (18)	4 (3)	0	0
Cough	23 (16)	0	0	0
Maculopapular rash	18 (13)	1 (1)	0	0
Constipation	17 (12)	0	0	0
Bronchial infection	16 (11)	2 (1)	0	0
Flu-like symptoms	16 (11)	1 (1)	0	0
Anorexia	15 (11)	0	0	0
Skin infection	15 (11)	1 (1)	0	0
Hematologic toxicities				
Decreased neutrophil count	42 (30)	11 (8)	23 (16)	0
Decreased platelet count	29 (20)	9 (6)	1 (1)	0
Anemia	22 (15)	6 (4)	0	0
Adverse events of special interest				
Pneumonitis (noninfectious)	11 (8)	2 (1)	0	0
Colitis	1 (1)	0	1 (1)	0
Laboratory toxicities				
Elevated AST*	39 (28)	1 (1)	1 (1)	0
Elevated ALT*	32 (23)	1 (1)	1 (1)	0

- Hyperglycemia: 50%; grade ≥3 41%
- Hypertension: 30%; grade ≥3 24%
- Elevated AST: 28%
- Elevated ALT: 23%
- Other grade ≥3 events:
  - Decreased ANC 30%
  - Lung infection 21%; grade ≥3 13%

Acknowledgements

- Dr. Chan Cheah – follicular lymphoma insights and slides

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SMARTIE

This has been a SMARTIE presentation.

SMARTIE participants, you can now go to smartie2018.com or visit the SMARTIE booth to answer the post-session questions for this presentation.

If you would like more information about this program, please ask a conference staff member or visit the SMARTIE booth.