NCCN 10th Annual Congress:
Hematologic Malignancies™

Evolving Therapies for Follicular Lymphoma

Andrew D. Zelenetz, MD, PhD
Memorial Sloan Kettering Cancer Center
Weill Cornell Medicine

NCCN National Comprehensive Cancer Network®

NCCN.org

Summary

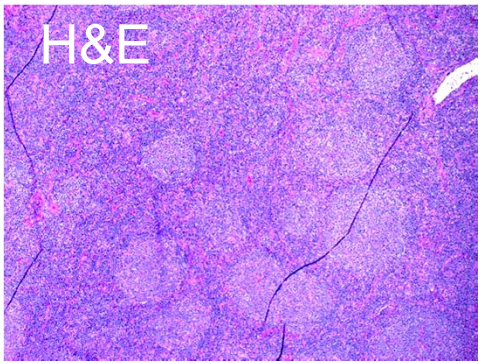
- Overall survival for patients with FL only slightly inferior to aged-matched controls
  - Patients event-free at 12-24 months have survival equivalent to age-matched general population
- Observation remains appropriate for asymptomatic patients with low tumor bulk
- For patients needing therapy, addition of rituximab to chemotherapy improves overall survival
- A number of agents are emerging for therapy of FL including:
  - Kinase inhibitors
  - IMIDs
  - BCL2 inhibitors
  - Checkpoint inhibitors

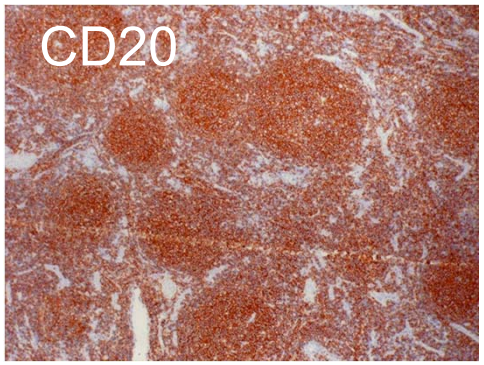
Memorial Sloan Kettering Cancer Center

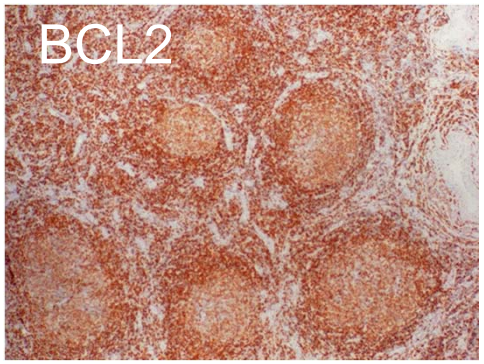
Memorial Sloan Kettering Cancer Center

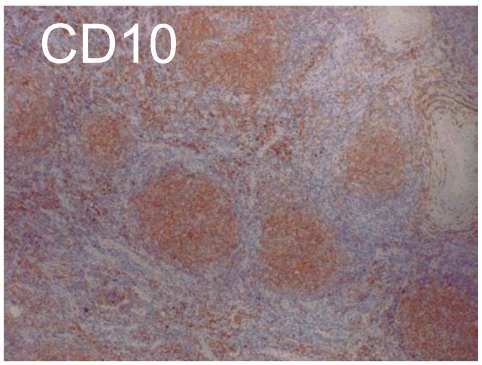
Pathology and Natural History

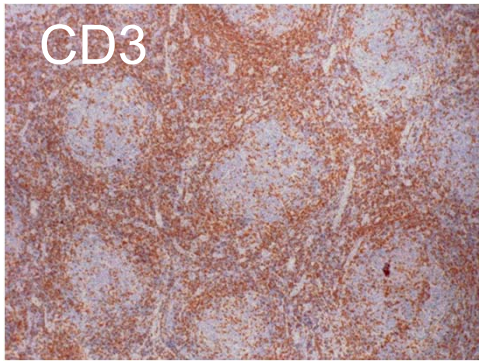
Follicular Lymphoma: Immunophenotype

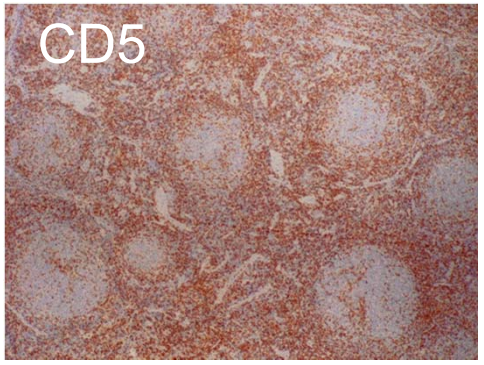








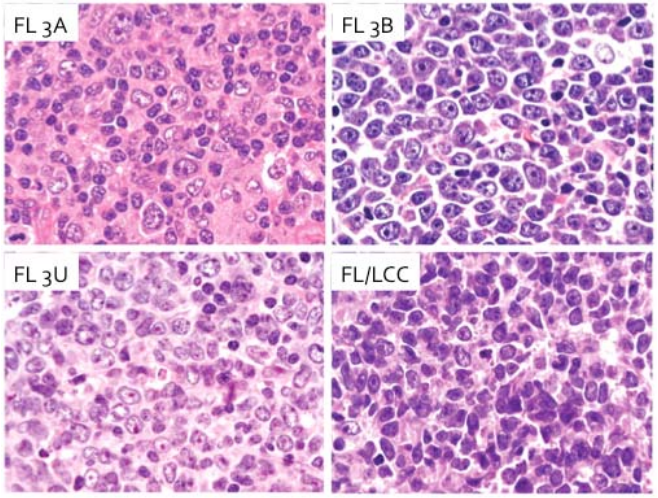


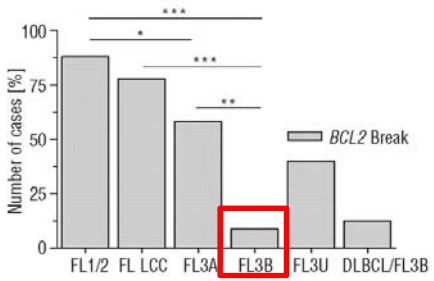


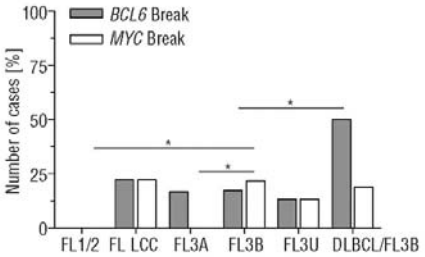
- CD 10+, CD 19+, CD 20+, CD 22+, LCA+, κ/λ clonal excess
- CD 3 -, CD 5 -, CD 15 -, CD 30 -

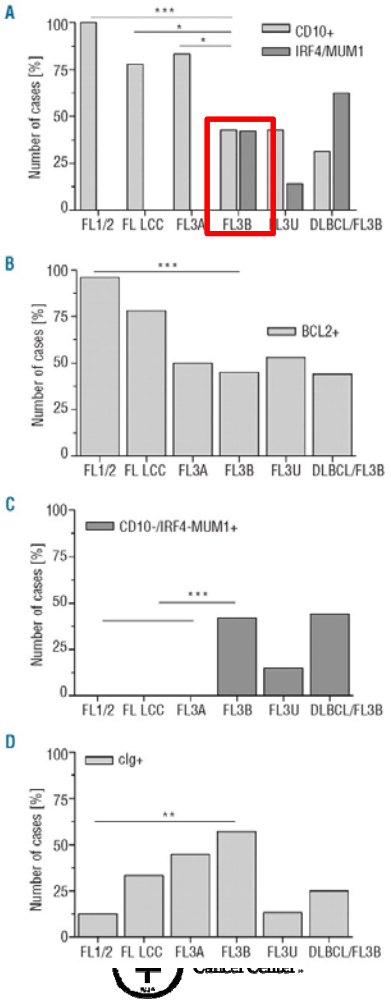
Memorial Sloan Kettering Cancer Center

FL, Grade 3B is a distinct entity







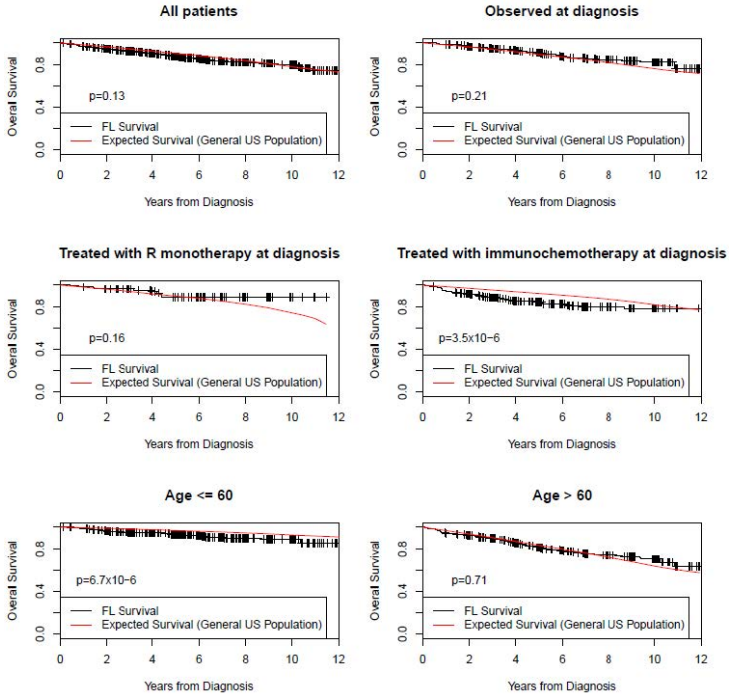


- FL 3A is composed of an admixture of centrocytes and centroblasts
- FL 3B is composed of homogeneous blastic cells
- FL3U can be difficult to clear distinguish A and B
- FL/LCC is grade 1/2 with large cells with blastic features
- FL 3B is more likely to express CD10 and MUM1/IRF4 and NOT have a t(14;18) translocation

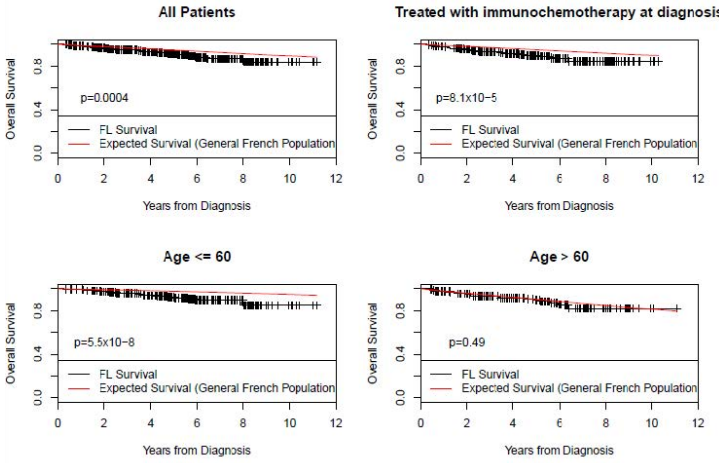
Horn H et al. Haematologica 2011;96:1327-1334

Natural History of Follicular Lymphoma

Mayo/Iowa Spore Molecular Epidemiology Resource (MER)



Lyon Validation

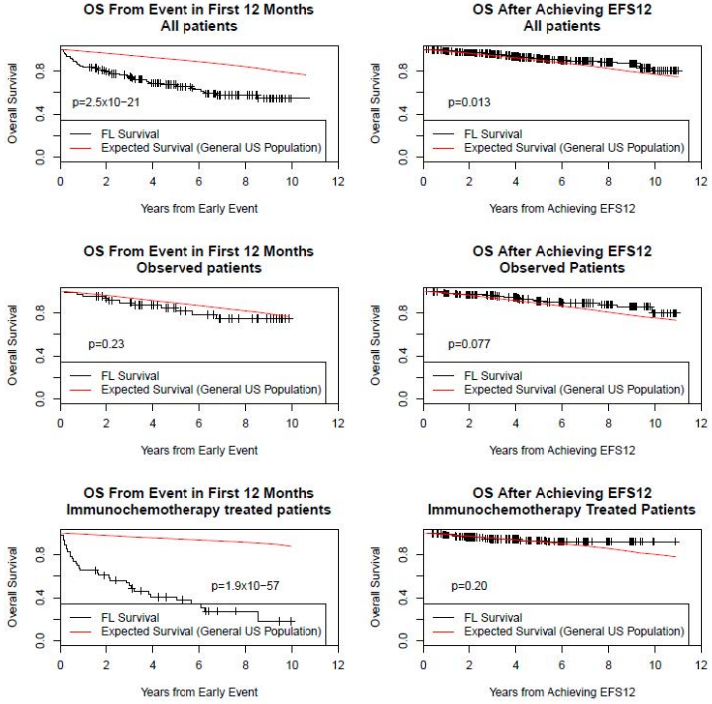


Maurer et al. ASH 2014; Abstract 1664

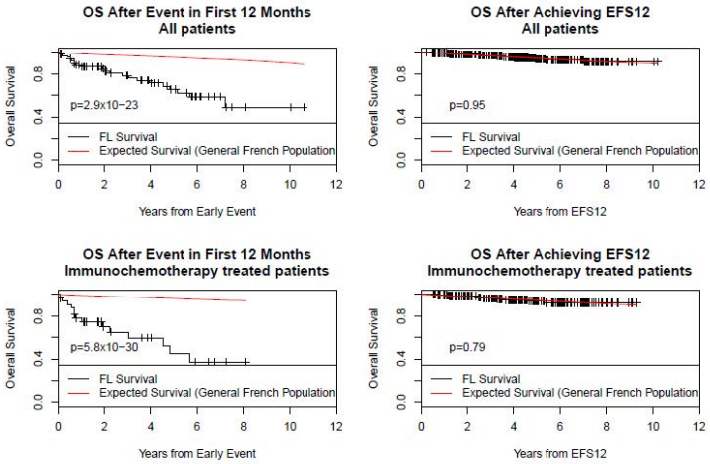
Memorial Sloan Kettering Cancer Center

Follicular Lymphoma Outcomes: EFS12

Mayo/Iowa Spore Molecular Epidemiology Resource (MER)



Lyon Validation

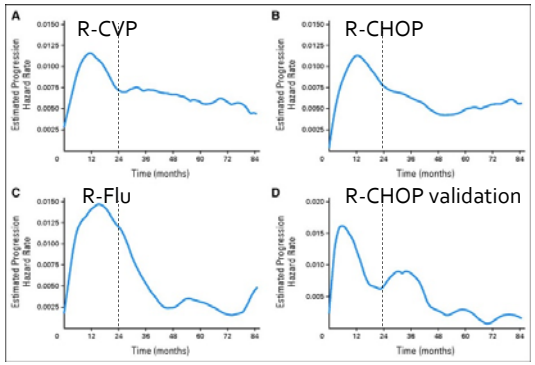


Maurer et al. ASH 2014; Abstract 1664

Memorial Sloan Kettering Cancer Center

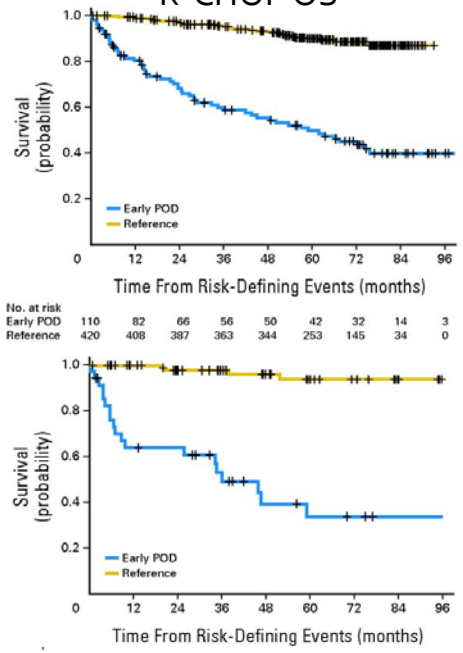
2 Years defines a group with high risk of relapse and poor outcome

Hazard for Progression



- For R-CHOP treated patients at median follow up of 7 years:
  - Early progressors: 19%
  - Reference group: 76%
  - Lost to follow up: 5%
- 110 R-CHOP treated patients were classified as early progressors

R-CHOP OS

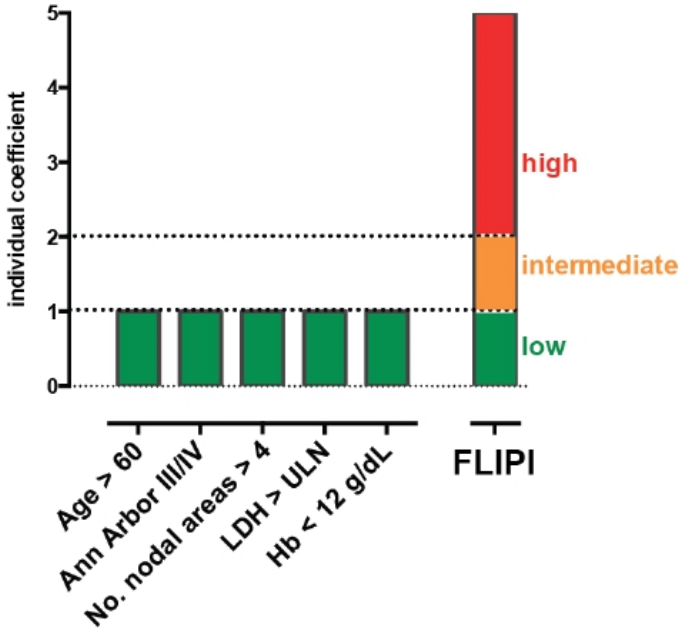


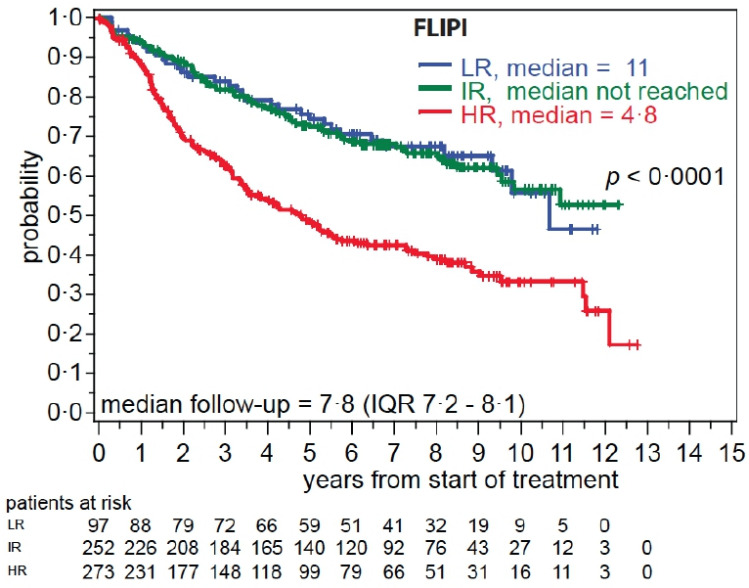
Group	R-CHOP Total No.	R-CHOP No. of Deaths	R-CHOP HR	R-CHOP 95% CI	R-CVP Total No.	R-CVP No. of Deaths	R-CVP HR	R-CVP 95% CI	R-Flu Total No.	R-Flu No. of Deaths	R-Flu HR	R-Flu 95% CI
Reference	420	44			184	34			131	17		
Early POD	110	57										
FLIPI adjusted	110	57	6.44	4.33 to 9.58	53	31	3.66	2.20 to 6.09	53	27	4.86	2.60 to 9.10
Unadjusted	420	44	7.17	4.83 to 10.65	53	31	4.91	3.00 to 8.01	53	27	5.87	3.17 to 10.87

Memorial Sloan Kettering Cancer Center

Casulo et al. J Clin Oncol. 2015;33(23):2516-22

Follicular Lymphoma Prognostic Model: FLIPI





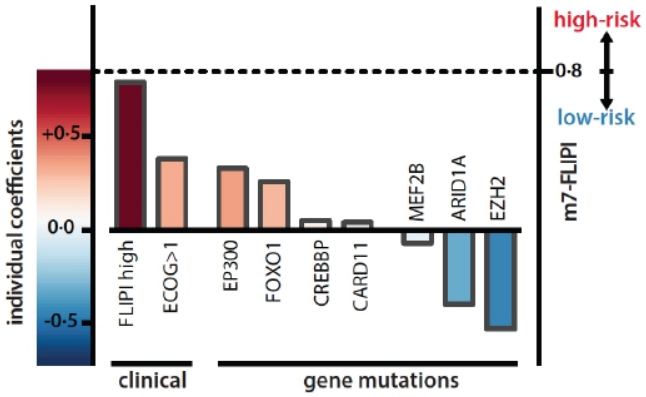
patients at risk

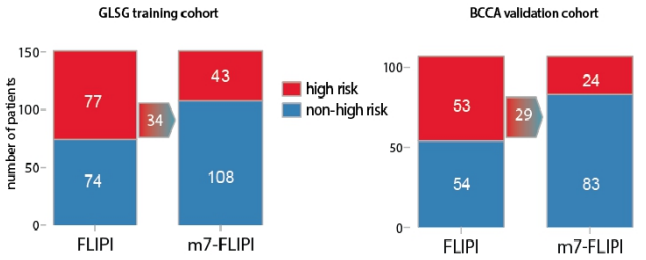
LR	97	88	79	72	66	59	51	41	32	19	9	5	0
IR	252	226	208	184	165	140	120	92	76	43	27	12	3	0
HR	273	231	177	148	118	99	79	66	51	31	16	11	3	0

Memorial Sloan Kettering Cancer Center

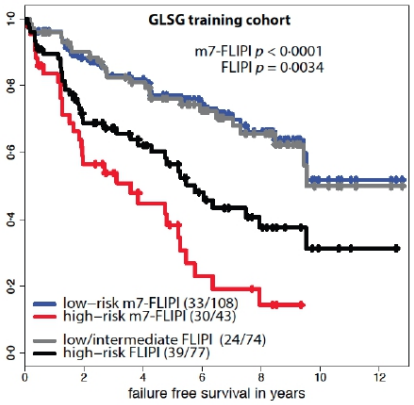
Weigert et al. 13-ICML 2015

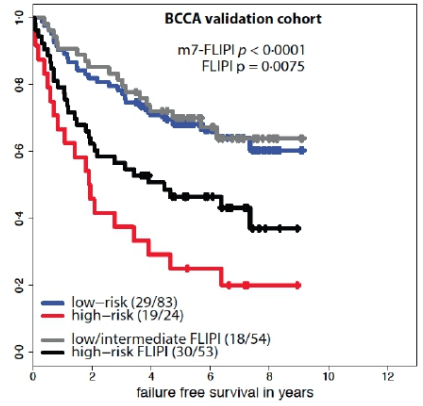
Clinicogenomic Risk Model, m7-FLIPI: Clinical Impact



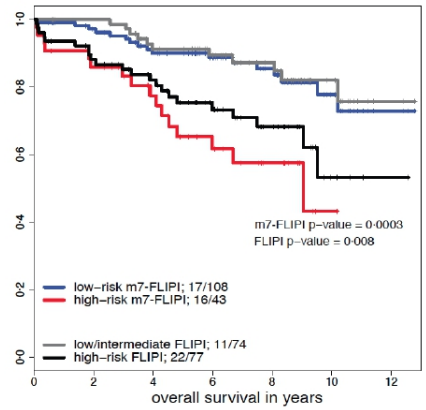


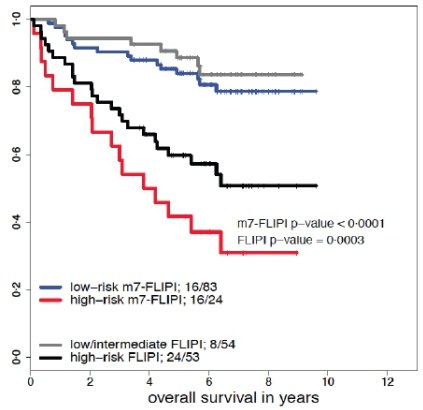
FFS





OS





Memorial Sloan Kettering Cancer Center

Weigert et al. 13-ICML 2015

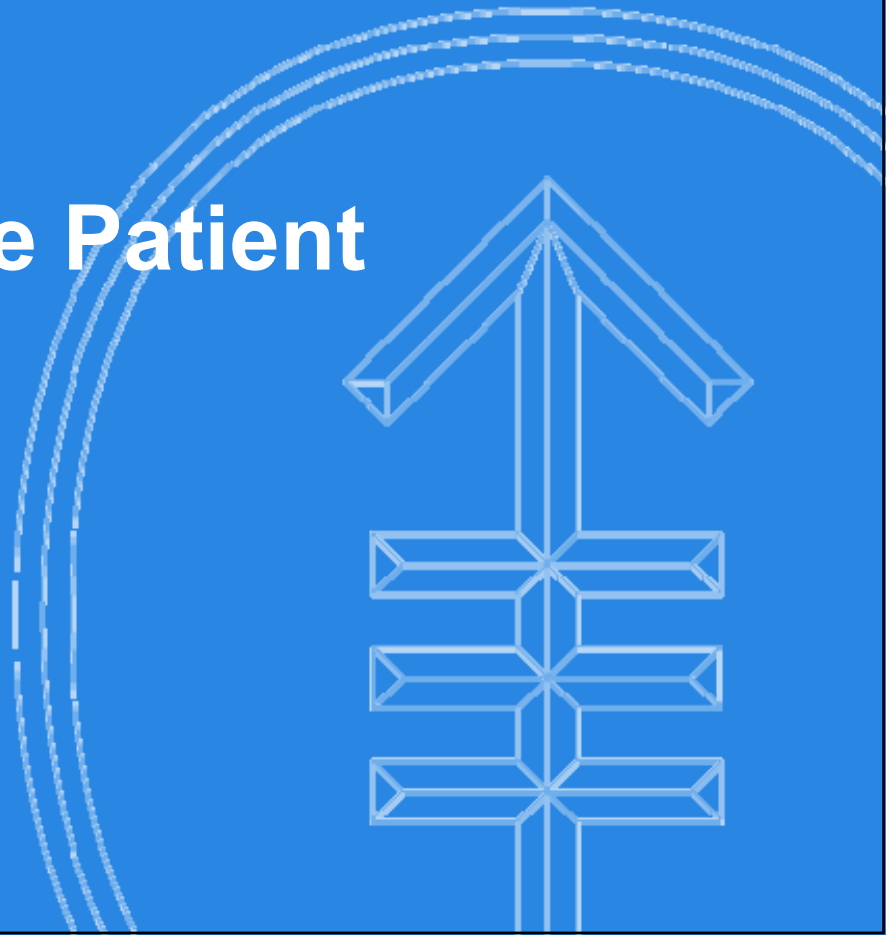
Natural History of Follicular Lymphoma

- The impact of the diagnosis on overall survival in minimal for
  - Patients suitable for observation
- Patient needing therapy at initial diagnosis have an inferior OS compared to the general population
  - However, if they remain Event-Free after 12 months survival is similar to general populations controls
  - Observation validated in a French cohort.
- Patients with a PSF event in the first 24 months have an markedly inferior overall survival
- CR 30 has been validated as a surrogate for PFS
- M7-FLIPI (or a variant) may help identify high risk patients at diagnosis

Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

Approach to the Patient



Follicular Lymphoma:
Individualized Treatment Planning

- Follicular lymphoma is a disease of paradoxes
  - Incurable but a long natural history
  - Highly responsive to therapy but relapse inevitable
  - Current potentially curative therapy (alloSCT) is associated with a high risk of treatment related mortality

- Patient Characteristics
  - Age
  - Symptoms
  - Short & long term goals
  - Co-morbidity
  - Preserve future options
  - Reimbursement

- Disease Characteristics
  - Stage
  - FL IPI
  - Transformation
  - Sites of involvement
  - Prior therapy
  - Time from prior therapy

Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

Advanced Stage: Low Tumor Bulk

NCCN Indications for Therapy in Advanced Disease: Modified GELF Criteria

- **Symptoms attributable to disease**
- Bulk: 3 masses > 3 cm, 1 mass > 7 cm
- Splenomegaly
- Cytopenias secondary to BM infiltration
- Threatened end-organ function
- Presentation with concurrent histologic transformation
- Rapid progression: >50% increase in 6 months
- **Appropriate clinical trial**

Solal-Celigny et al. J Clin Oncol 1998;16:2332-2338.

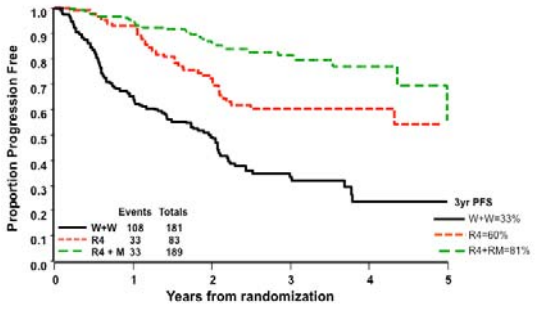
Memorial Sloan Kettering Cancer Center

Watch & Wait versus Chemotherapy: Key Observations

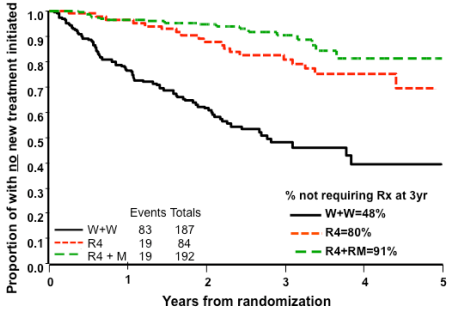
- The overall chance of not requiring chemotherapy or dying of lymphoma is 19% at 10 years
- Chance of not requiring chemotherapy > 70yr = 40%
- Median delay in requiring chemotherapy is 2.6 years

- **What about rituximab versus observation?**
  - **Three arm study (R x4, R x4+M, Observation)**

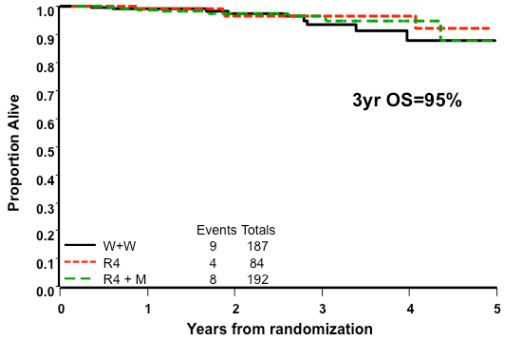
PFS



TTINT



OS



Memorial Sloan Kettering Cancer Center

Ardeshna KM, *et al. Lancet* 2003; 362:516–522; Ardeshna et al. Blood 116: Abstract 6, 2010

Memorial Sloan Kettering Cancer Center

Advanced Stage: Requiring Therapy

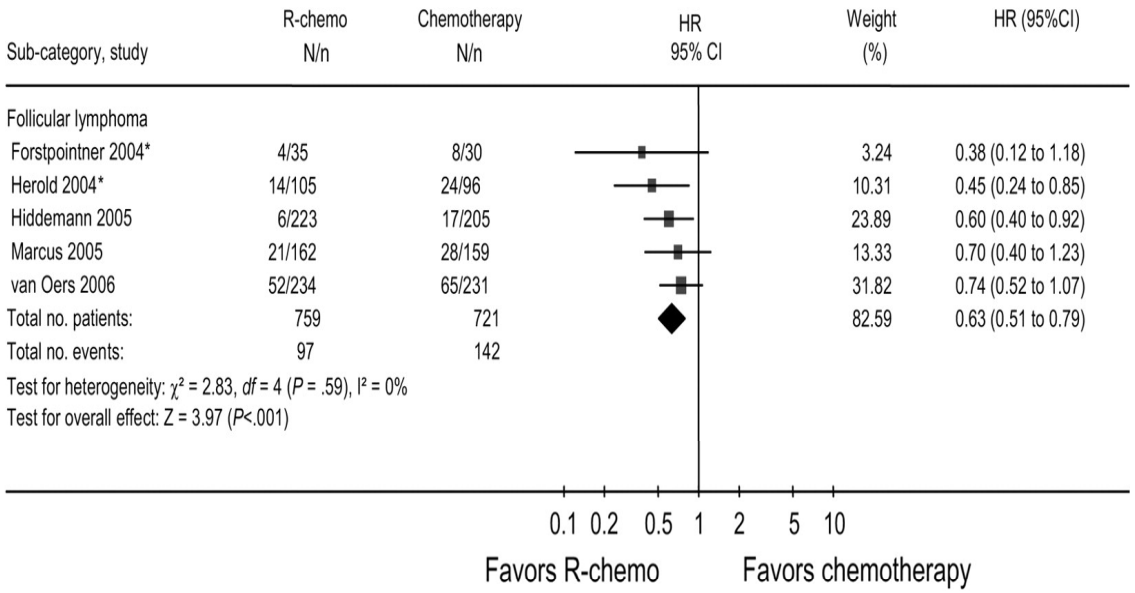
Appropriate Treatment Options for Initial Therapy of FL

Regimen	Comments
R-CHOP	vs CVP PFS superior (PRIMA, FOLL05) , OS = vs BR PFS = (BRIGHT), inferior (STIL) , OS = anthracycline not available for transformed disease
R-CVP	Preserves anthracycline for later vs BR PFS = (BRIGHT), OS =
BR	Different results in two phase III trials (STIL v BRIGHT), No OS advantage
Rituximab	Inferior CR, ORR, PFS to R-chemo, appropriate in selected patients

Emerging Option	
Rituximab-Len	Phase II only, RELEVANCE phase III accrual complete

Memorial Sloan Kettering Cancer Center

Meta-analysis Demonstrates an Overall Survival Advantage Among Patient Treated with R-chemo vs Chemo alone



Based on the results of this meta-analysis and the supporting phase III trials, rituximab in combination with chemotherapy is the STANDARD OF CARE for patients requiring therapy. (CATEGORY 1)

The optimal R-CHEMO regimen remains undefined.

Memorial Sloan Kettering Cancer Center

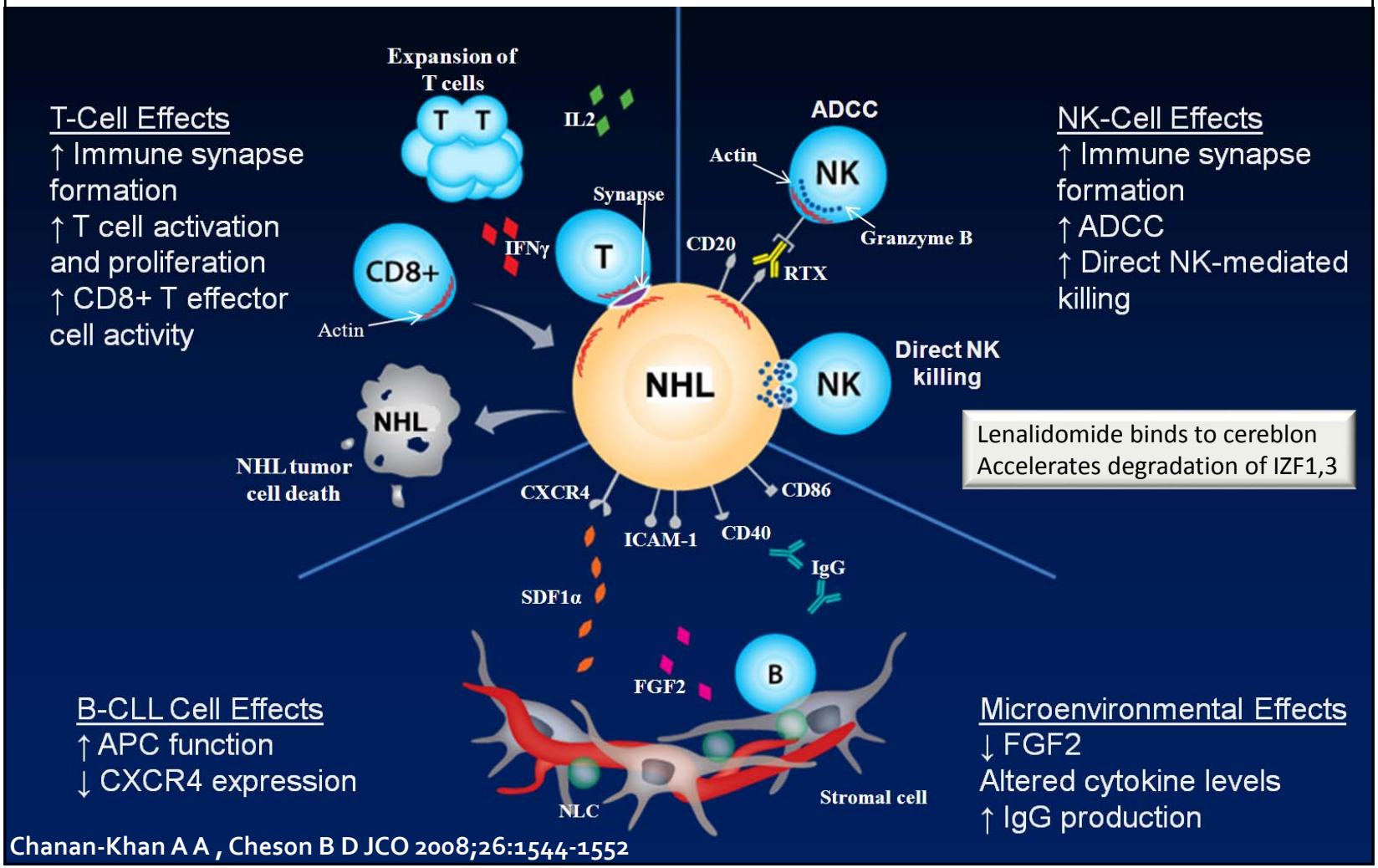
Schulz H et al. JNCI J Natl Cancer Inst 2007;99:706-714

Initial Selection of R-chemotherapy

- Response (CR/PR) has not reliably predicted PFS (or OS)
- PFS is:
  - Superior for patients treated with R-CHOP or R-FMD compared to R-CVP
  - Equivalent for patients treated with R-Bendamustine compared to R-CHOP or R-CVP (two differing results)
- At clinical meaningful follow-up (~4 years)
  - No differences have emerged in overall survival
  - Note when rituximab was added to chemotherapy, OS advantages emerged by 24 months

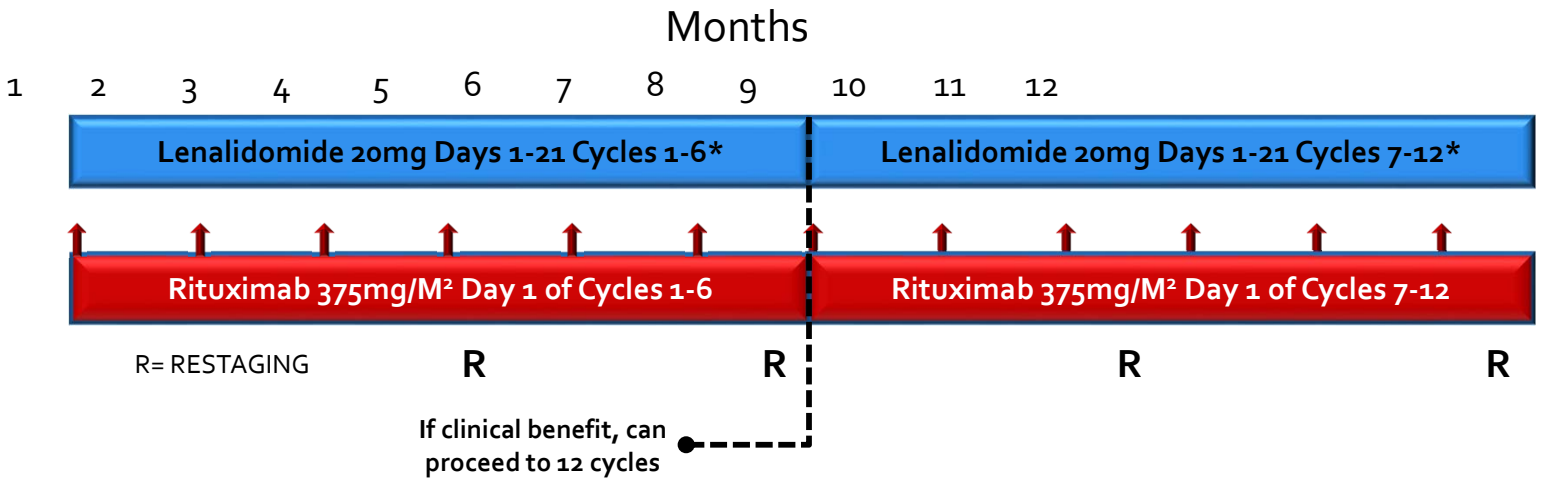
Memorial Sloan Kettering Cancer Center

Lenalidomide: Mechanism of Action in Lymphoma



Chanan-Khan A A , Cheson B D JCO 2008;26:1544-1552

Rituximab-Lenalidomide for untreated FL: Study Design



- Phase II, single institution
- Planned Enrollment
  - N= 50 Follicular lymphoma (grade I/II)
  - N=30 Small lymphocytic lymphoma*
  - N=30 Marginal zone lymphoma
- Groups analyzed independently for response and toxicity

*SLL patients: Dose escalation of lenalidomide starting with cycle 1: (10mg, 15mg, 20mg)

Memorial Sloan Kettering Cancer Center

Fowler et al, The Lancet Oncology 2014;15:1311-1318.

Rituximab-Lenalidomide for untreated FL: Response Rates

	SLL (N=30)	Marginal (N=27)*	Follicular (N=46)*	All Patients	
				Eval (N=103)	ITT (N=110)
ORR, n (%)	24 (80)	24(89)	45(98)	93(90)	93(85)
CR/Cru	8(27)	18(67)	40(87)	66(64)	66(60)
PR	16(53)	6(22)	5(11)	27(26)	27(25)
SD, n (%)	4(13)	3(11)	1(2)	8(8)	8(7)
PD, n (%)	2(7)	0	0	2(2)	2(2)

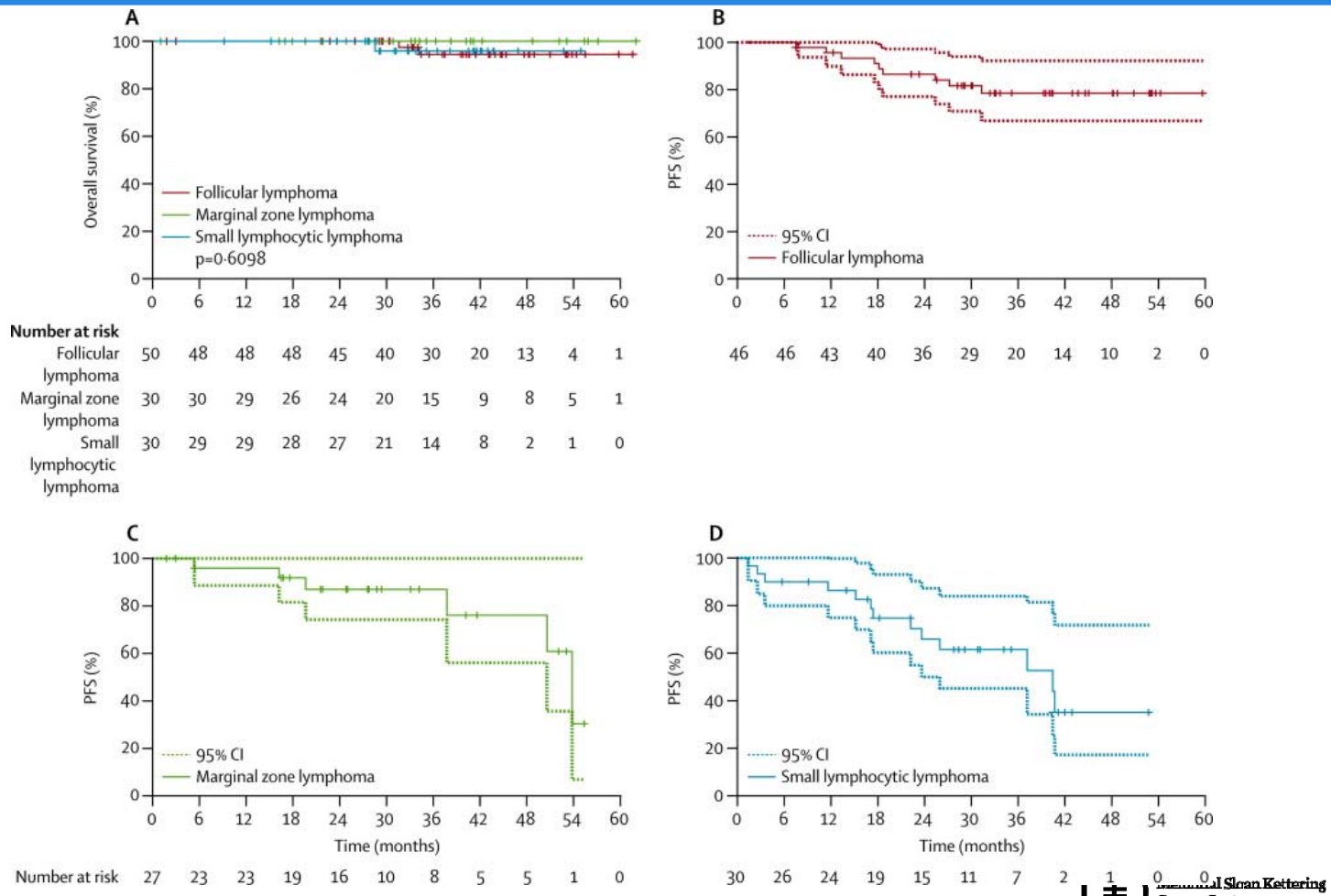
*7 pts not evaluable for response:

- 5 due to adverse event in cycle 1
- 1 due to non-compliance
- 1 due to withdrawal of consent

Fowler et al, The Lancet Oncology 2014;15:1311-1318

Memorial Sloan Kettering Cancer Center

Rituximab-Lenalidomide for FL: OS and PFS



Fowler et al, The Lancet Oncology 2014;15:1311-1318

Memorial Sloan Kettering Cancer Center

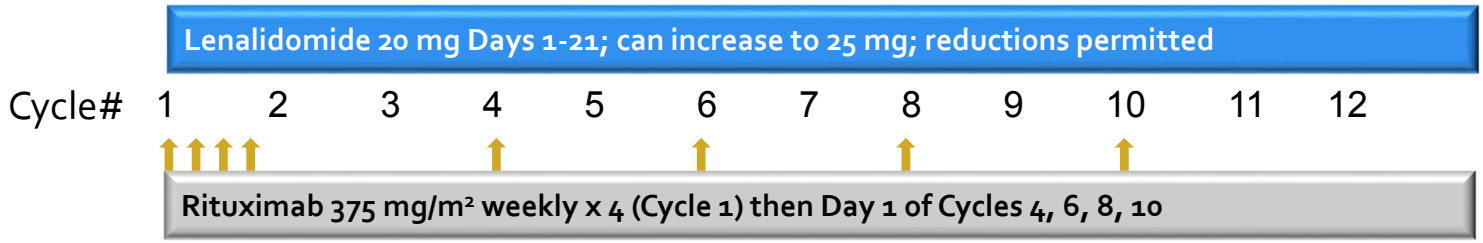
Rituximab-Lenalidomide for FL: Safety

	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Hematological					
Anemia	61 (55%)	8 (7%)	0	0	69 (63%)
Neutropenia	14 (13%)	32 (29%)	27 (25%)	11 (10%)	84 (76%)
Thrombocytopenia	48 (44%)	4 (4%)	3 (3%)	1 (<1%)	56 (51%)
Non-hematological					
Constipation	31 (28%)	26 (24%)	0	0	57 (52%)
Cough, dyspnea, pulmonary (other)	32 (29%)	17 (15%)	4 (4%)	1 (1%)	54 (49%)
Infusion reaction	6 (5%)	9 (8%)	2 (2%)	0	17 (15%)
Diarrhea	35 (32%)	20 (18%)	0	0	55 (50%)
Dizziness	33 (30%)	14 (13%)	1 (<1%)	0	48 (44%)
Edema	39 (35%)	7 (6%)	1 (<1%)	1 (<1%)	48 (44%)
Eye irritation	54 (49%)	11 (10%)	0	0	65 (59%)
Fatigue	45 (41%)	49 (45%)	4 (4%)	1 (<1%)	99 (90%)
Fever	34 (31%)	5 (5%)	1 (<1%)	0	40 (36%)
Memory impairment	27 (25%)	9 (8%)	1 (<1%)	0	37 (34%)
Mucositis	36 (33%)	1 (<1%)	0	0	37 (34%)
Nausea or vomiting	40 (36%)	27 (25%)	0	0	67 (61%)
Pain or myalgia	38 (35%)	40 (36%)	10 (9%)	0	90 (82%)
Peripheral neuropathy	32 (29%)	8 (7%)	1 (<1%)	0	41 (37%)
Rash	33 (30%)	23 (21%)	8 (7%)	0	64 (58%)
Thyroid abnormalities	15 (14%)	10 (9%)	0	0	25 (23%)
Upper respiratory infection	0	23 (21%)	2 (2%)	0	25 (23%)

Memorial Sloan Kettering Cancer Center

Fowler et al, The Lancet Oncology 2014;15:1311-1318

Alliance/CALGB 50803: Lenalidomide plus rituximab in untreated follicular lymphoma: Study Design



1 cycle = 28 days, 12 cycles planned

- **Evaluation:**
  - PET/CT at baseline, weeks 10, 24, 52
  - Then CT/MRI chest/abdomen/pelvis every 4 months x 2 years, then every 6 months until progression for up to 10 years
  - Response assessed by investigator according to IHP criteria – no central review of PET imaging
  - Monitored for toxicity weekly during cycle 1, then monthly during lenalidomide, then at restaging.

Memorial Sloan Kettering Cancer Center

Martin et al., ICML 2013

Alliance 50803: Best Response

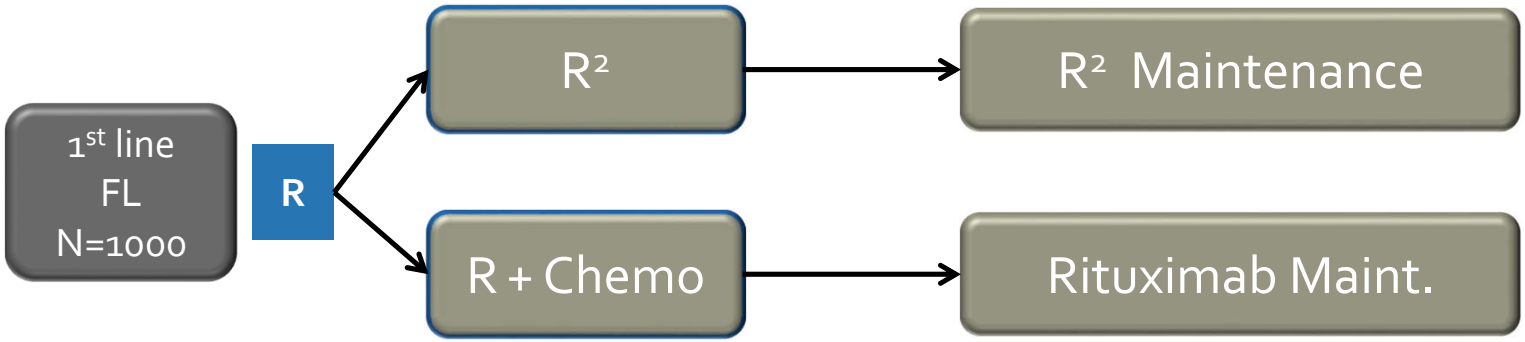
	Overall N =57	FLIPI 0-1 N = 17	FLIPI 2 N = 36	FLIPI 3 N = 2
ORR	53 (93%)	16 (94%)	33 (92%)	2 (100%)
CR	41 (72%)	13 (77%)	25 (70%)	2 (100%)
PR	12 (21%)	3 (18%)	8 (22%)	-
SD	2 (4%)	0 (0%)	2 (6%)	-
Inevaluable	2 (4%)	1 (6%)	1 (3%)	-

- 4 additional patients in PET- CR but not confirmed by BMBx.
- No significant association between CR rate and FLIPI score, presence of bulky disease, or grade.
- Median FU = 1.6 years (0.4 – 2.5 years)
- Median time to first response = 10 weeks
- Median time to complete response = 10 weeks
- 92% of PET-negative CRs occurred by 24 weeks
- 7/57 evaluable patients have progressed so far

Martin et al., ICML 2013

Memorial Sloan Kettering Cancer Center

RELEVANCE Study Design
(Rituximab and LEnalidomide Versus ANy ChEmotherapy)



- Treatment Arms
  - R + Chemo
    - Investigator's choice of R-CHOP, R-CVP, BR
  - R + Lenalidomide 20mg for 6 cycles, then 10mg if CR
- Groups:
  - LYSA (PI: Morschhauser) + North America (PI: Fowler)
- Accrual completed 10/2014

Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

Relapsed-Refractory Disease

Options for Treatment at Relapse

Established

- Radioimmunotherapy
- Rituximab
- Conventional chemotherapy:
  - Fludarabine-based
  - Bendamustine-based
  - Including repeating prior therapy
  - With rituximab maintenance
- HDT/ASCR
- Allogeneic SCT
- Idelalisib

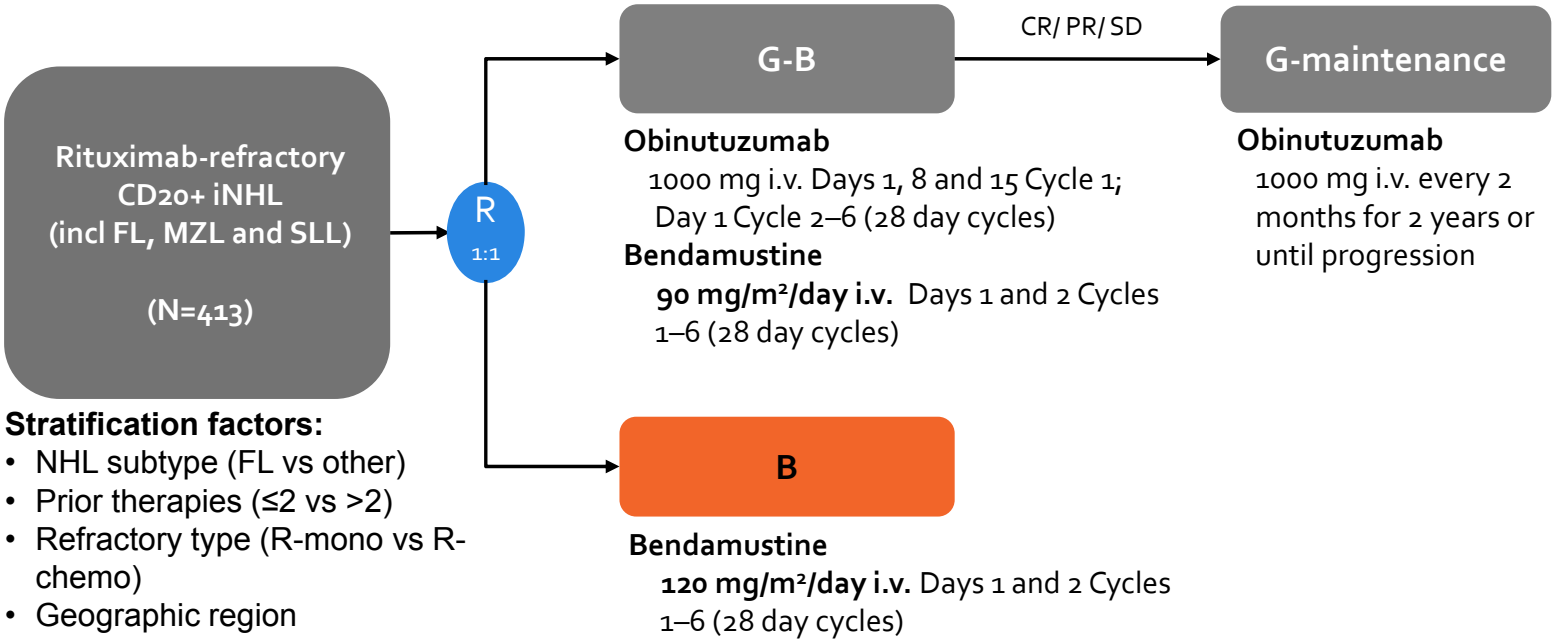
Investigational

- Bortezomib alone or in combination
- Lenalidomide alone or in combination
- BCL2 inhibitors
- BCR kinase inhibitors (SYK, BTK)
- Novel antibodies (naked and conjugates)
- Obinutuzumab

- Consider clinical trials prior to development of refractory disease

Memorial Sloan Kettering Cancer Center

GADOLIN: Study design (NCT01059630)



Stratification factors:

- NHL subtype (FL vs other)
- Prior therapies (≤2 vs >2)
- Refractory type (R-mono vs R-chemo)
- Geographic region

- **Primary endpoint:** PFS as assessed by an Independent Radiology Facility (IRF)
- **Secondary endpoints:** PFS as assessed by investigator; OS; End of induction response; Best overall response; Duration of response, EFS, DFS, Pharmacokinetic profile; Pharmacoeconomics; Patient-reported outcomes

Memorial Sloan Kettering Cancer Center

Sehn et al. ASCO 2015; Abstract LBA8502. Cheson 13-ICML 2015

GADOLIN: Adverse Events Grade 3–4

Hematological AEs

AE, n (%)*	G-B (n=194)	B (n=198)
Neutropenia	64 (33.0)	52 (26.3)
Thrombocytopenia	21 (10.8)	32 (16.2)
Anemia	15 (7.7)	20 (10.1)
FN	9 (4.6)	7 (3.5)
Leukopenia	2 (1.0)	3 (1.5)

* Multiple occurrences of same AE in an individual were only counted once

Non-hematological AEs**

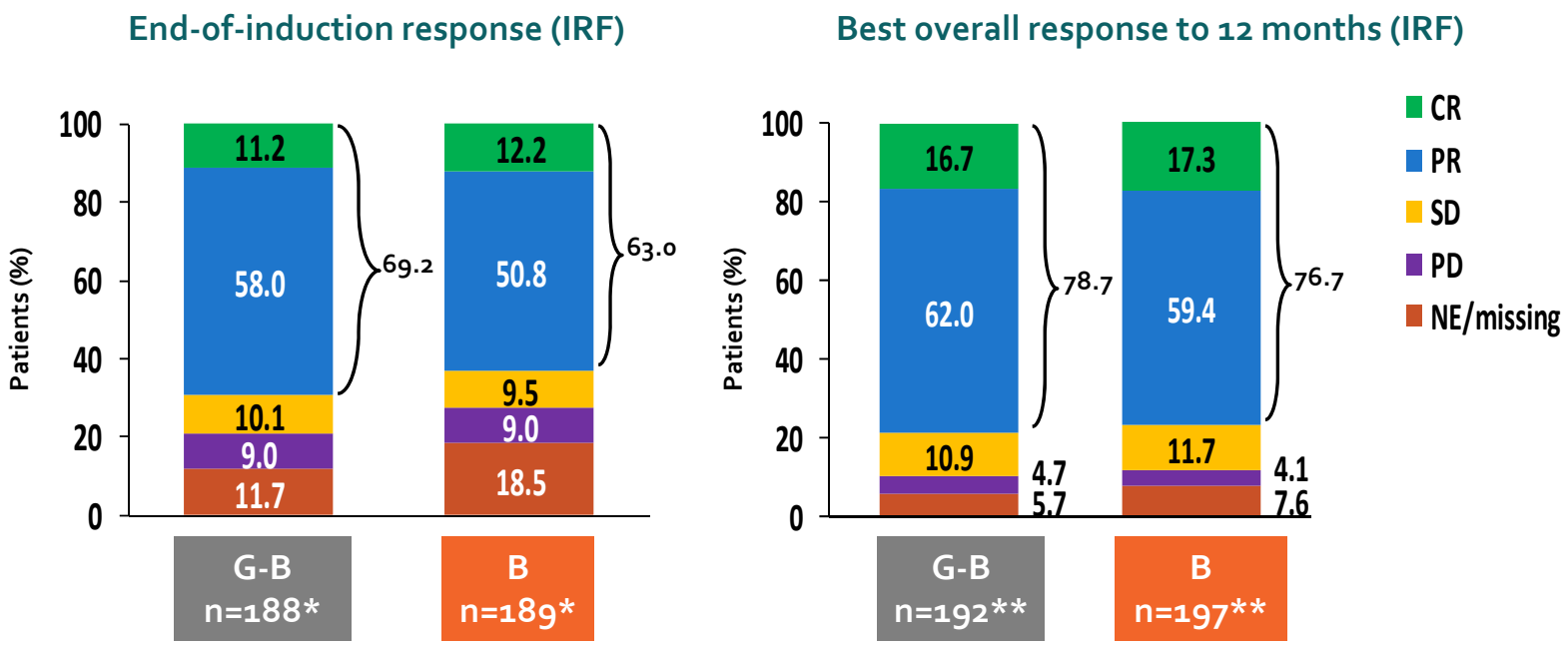
AE, n (%)*	G-B (n=194)	B (n=198)
IRR***	21 (10.8)	11 (5.6)
Vomiting	4 (2.1)	2 (1.0)
Decreased appetite	3 (1.5)	2 (1.0)
Fatigue	3 (1.5)	5 (2.5)
Nausea	2 (1.0)	6 (3.0)
Diarrhea	2 (1.0)	5 (2.5)
Pyrexia	2 (1.0)	0
Headache	1 (0.5)	2 (1.0)

* Multiple occurrences of same AE in an individual were only counted once
** Adverse events with≥15% incidence across all grades
*** AEs occurring during or within 24 hours after an infusion and considered to be related to any study drug

Memorial Sloan Kettering Cancer Center

Sehn et al. ASCO 2015; Abstract LBA8502. Cheson 13-ICML 2015

GADOLIN: Response to therapy



19 patients still in induction (G-B, n=6; B, n=13)

* Patients ongoing in induction therapy are excluded from analysis. Patients with end of induction response assessment performed >60 days after last induction dose shown as missing.

** Best overall response excludes ongoing patients who have not yet reached the first response assessment.

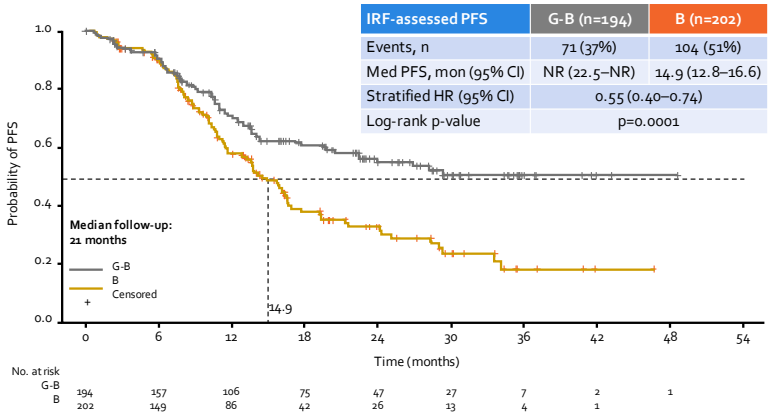
IRF, independent radiology facility

Sehn et al. ASCO 2015; Abstract LBA8502. Cheson 13-ICML 2015

Memorial Sloan Kettering Cancer Center

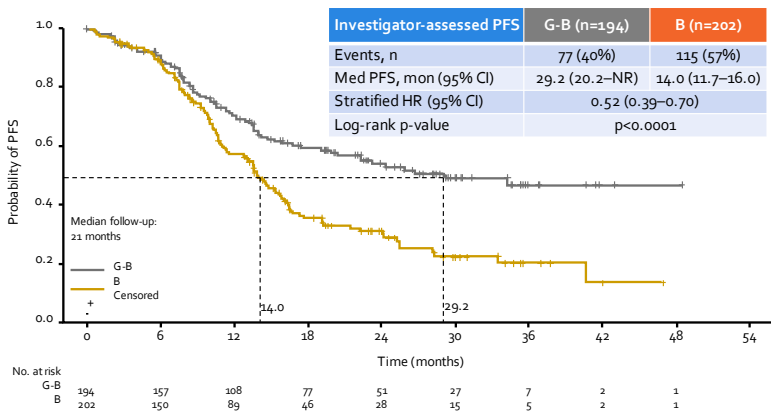
GADOLIN: Outcomes

IRF-assessed



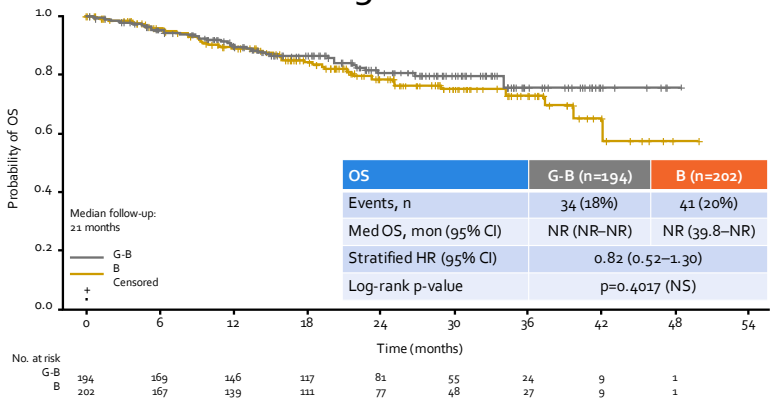
IRF-assessed PFS	G-B (n=194)	B (n=202)
Events, n	71 (37%)	104 (51%)
Med PFS, mon (95% CI)	NR (22.5–NR)	14.9 (12.8–16.6)
Stratified HR (95% CI)	0.55 (0.40–0.74)	
Log-rank p-value	p=0.0001	

Investigator-assessed



Investigator-assessed PFS	G-B (n=194)	B (n=202)
Events, n	77 (40%)	115 (57%)
Med PFS, mon (95% CI)	29.2 (20.2–NR)	14.0 (11.7–16.0)
Stratified HR (95% CI)	0.52 (0.39–0.70)	
Log-rank p-value	p<0.0001	

OS Investigator-assessed



OS	G-B (n=194)	B (n=202)
Events, n	34 (18%)	41 (20%)
Med OS, mon (95% CI)	NR (NR–NR)	NR (39.8–NR)
Stratified HR (95% CI)	0.82 (0.52–1.30)	
Log-rank p-value	p=0.4017 (NS)	

Memorial Sloan Kettering Cancer Center

Sehn et al. ASCO 2015; Abstract LBA8502. Cheson 13-ICML 2015

Summary

- Obinutuzumab plus bendamustine followed by obinutuzumab maintenance resulted in a statistically significant and clinically meaningful PFS benefit compared with bendamustine monotherapy
  - IRF-assessed median PFS: not reached in G-B arm vs 14.9 months in B arm (HR=0.55)
  - Consistent findings across the majority of subgroups tested
- No difference in response rates between treatment arms
  - Bendamustine dose was higher in the B monotherapy arm
- No new safety signals were observed

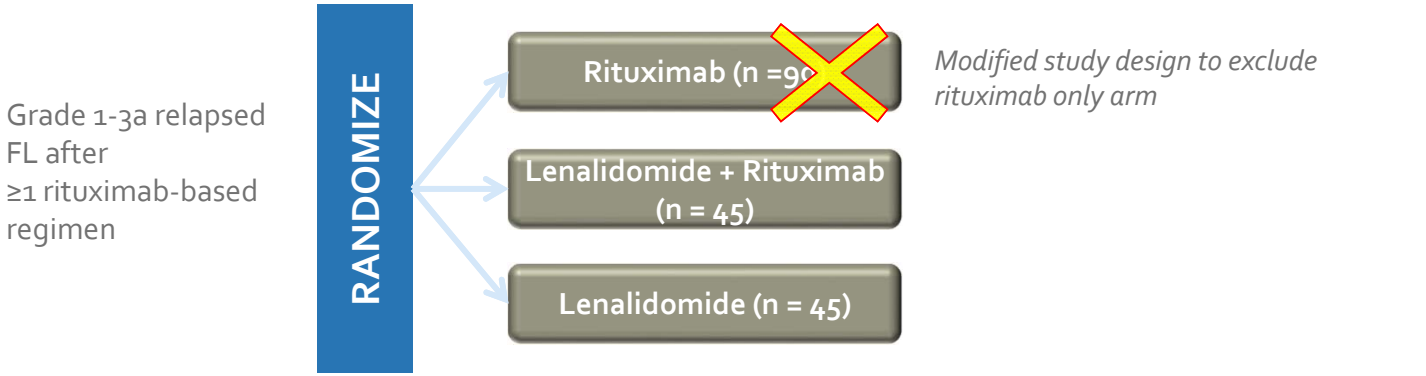
- Curves separate only after start of obinutuzumab maintenance
- Bendamustine has become a major therapy in first line limiting applicability of obinutuzumab-bendamustine
- Suggests a benefit of obinutuzumab maintenance in rituximab-refractory patients

Memorial Sloan Kettering Cancer Center

Sehn et al. ASCO 2015; Abstract LBA8502. Cheson 13-ICML 2015

Lenalidomide vs. Lenalidomide + Rituximab (R2) in Recurrent FL: Study Design

- Phase II safety and efficacy of lenalidomide vs. lenalidomide + rituximab (R2) in patients with recurrent follicular lymphoma
- Key eligibility criteria
  - Grade 1, 2, or 3a recurrent FL
  - Prior rituximab alone or in combination
  - Time to progression ≥6 months since last rituximab dose
  - No history within 3 months of deep vein thrombosis (DVT) or pulmonary embolism (PE)
- Primary endpoint: overall response rate (ORR)
  - Secondary endpoints: complete response (CR), event-free survival (EFS), safety
- Study design



Lenalidomide: 15 mg/d d1-21/28 cycle 1, then d20 and 25 if tolerated; 12 cycles
Rituximab: 375 mg/m² d8, 15, 22, 29 of cycle 1

Memorial Sloan Kettering Cancer Center

Leonard et al. J Clin Oncol (ASCO Annual Meeting Abstracts). 2012;30. Abstract 8000.

Lenalidomide vs. Rituximab Lenalidomide in Recurrent FL: Efficacy

Efficacy	Lenalidomide (n = 45)	R-Len (n = 44)
ORR, % (95% CI)	51% (36%–66%)	73% (52%–85%)
CR	13%	36%
PR	38%	36%
Median EFS	1.2 years	2.0 years
2-year EFS	27%	44%

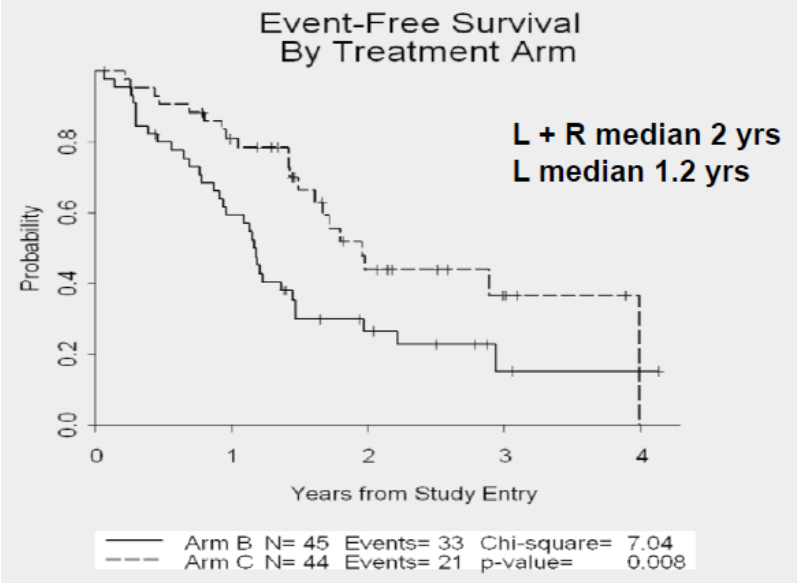
- At a median follow-up of 1.7 years (0.1–4.1), ORR was higher with R2 compared with REV alone (73% vs. 51%, respectively)
- Median EFS and 2-year EFS were also improved with R2 compared with REV alone
- EFS for REV vs. R2
  - Unadjusted HR = 2.1 (P = 0.010)
  - Adjusted for FLIPI HR = 1.9 (P = 0.061)
- No significant difference in OS (P = 0.4201)

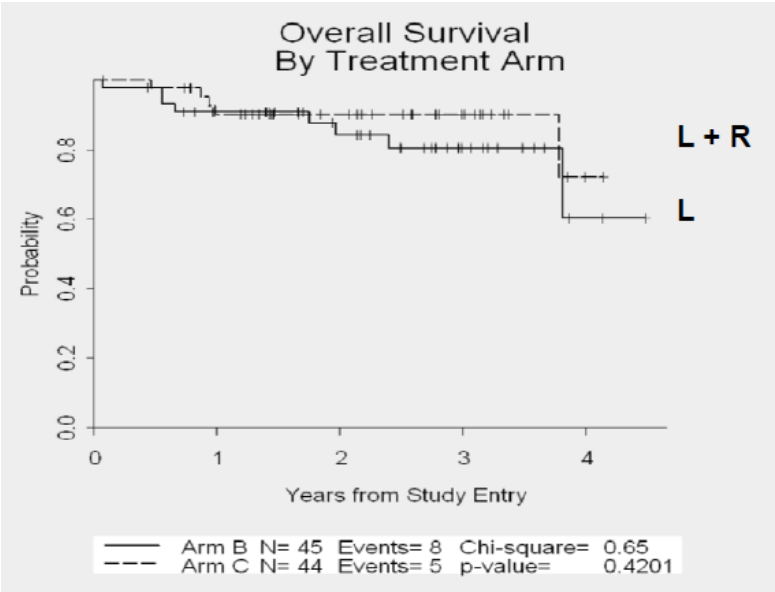
CI, confidence interval; HR, hazard ratio; PR, partial response; OS, overall survival.

Leonard et al. J Clin Oncol (ASCO Annual Meeting Abstracts). 2012;30. Abstract 8000.

Memorial Sloan Kettering Cancer Center

Lenalidomide vs. Rituximab Lenalidomide: Efficacy Data





Leonard et al. J Clin Oncol (ASCO Annual Meeting Abstracts). 2012;30. Abstract 8000.

Memorial Sloan Kettering Cancer Center

Idelalisib for "double refractory" iNHL Phase II: Schema

iNHL Alkylator And Rituximab Refractory

→ **Idelalisib** 150 mg oral twice daily until POD or intolerance

Eligibility	• **iNHL with measurable disease** • **Refractory to both rituximab and alkylating agent** - Refractory defined as lack of response or progression of lymphoma within 6 months of completion of therapy, documented by imaging
Disease assessment	• **Independent review committee** • **Cheson, 2007**
Endpoints	• **Primary: ORR** • **Secondary: DOR, PFS**

Memorial Sloan Kettering Cancer Center

Gopal et al. ASH 2013, Abstract 85; NEJM (2014) 370:1008-18

Idelalisib for "double refractory" iNHL Phase II: Patient Characteristics, n=125

Characteristics	N (%)
Age median (range)	64 (33-87)
FL	72 (58%)
SLL	28 (22%)
MZL	15 (12%)
WM	10 (8%)
Prior therapy median (range)	4 (2-12)
Elevated LDH	30%
Bulk >7 cm	26%
Refractory to last regimen	112 (90%)
Refractory to ≥2 regimens	99 (79%)
Anemia ≥ grade 1	51%
Neutropenia ≥ grade 1	24%
Thrombocytopenia	34%

Memorial Sloan Kettering Cancer Center

Gopal et al. ASH 2013, Abstract 85; NEJM (2014) 370:1008-18

Idelalisib for "double refractory" iNHL Phase II: Toxicity

Adverse Event*	Total (%)/≥Grade 3 (%)
Diarrhea	43/13
Fatigue	30/2
Nausea	30/2
Cough	29/0
Pyrexia	28/2
Rash	13/2
Pneumonia	11/7
AST/ALT elevations**	-/13%
Neutropenia	-/27%
Thrombocytopenia	-/6%
Anemia	-/2%

*20% of pts have discontinued therapy due to adverse events.

**Drug was held for these pts, and 11/14 pts (79%) were re-treated without recurrence of ALT/AST elevation.

Memorial Sloan Kettering Cancer Center

Gopal et al. ASH 2013, Abstract 85; NEJM (2014) 370:1008-18

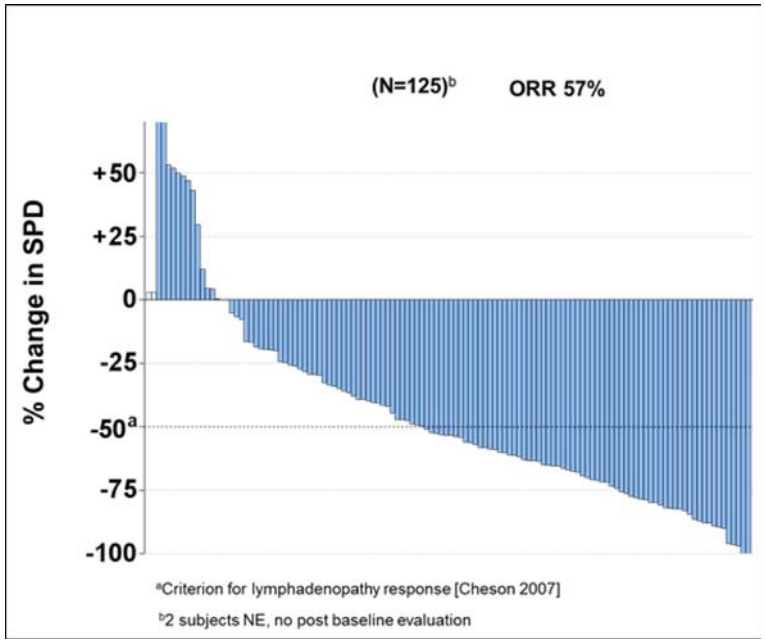
Idelalisib for "double refractory" iNHL Phase II: Response @median follow up 9.4 months

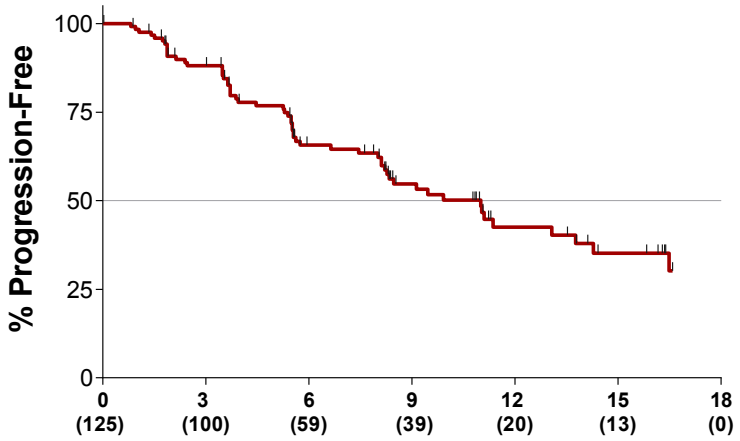
ORR	57% (47.6-65.6)
CR	6%
PR	50%
Median time to response	1.9 months (1.6-8.3)
Median time to CR	3.7 months (1.9-12)
Subtype	
FL	54%
SLL	61%
MZL	47%
WM	80%
Bendamustine refractory	59%
Prior therapy <4/≥4	50%/62%
Bulk <7≥/7	57%/57%
DOR	12.5 months
PFS	11 months
OS	20.4 months

Memorial Sloan Kettering Cancer Center

Gopal et al. ASH 2013, Abstract 85; NEJM (2014) 370:1008-18

Idelalisib for iNHL Phase II: Response and PFS

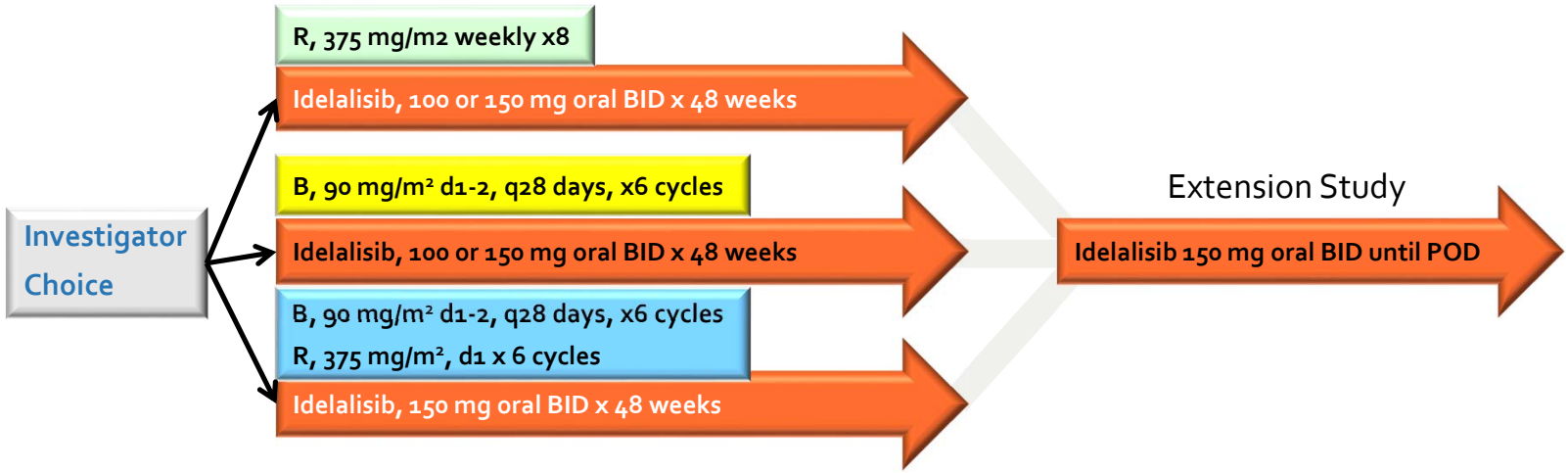




Memorial Sloan Kettering Cancer Center

Gopal et al. ASH 2013, Abstract 85; NEJM (2014) 370:1008-18

Idelalisib Combinations in iNHL: Study Design



Disease Assessments

- Weeks 0, 8, 16, 24
- Thereafter every 12 weeks
- Investigator determined

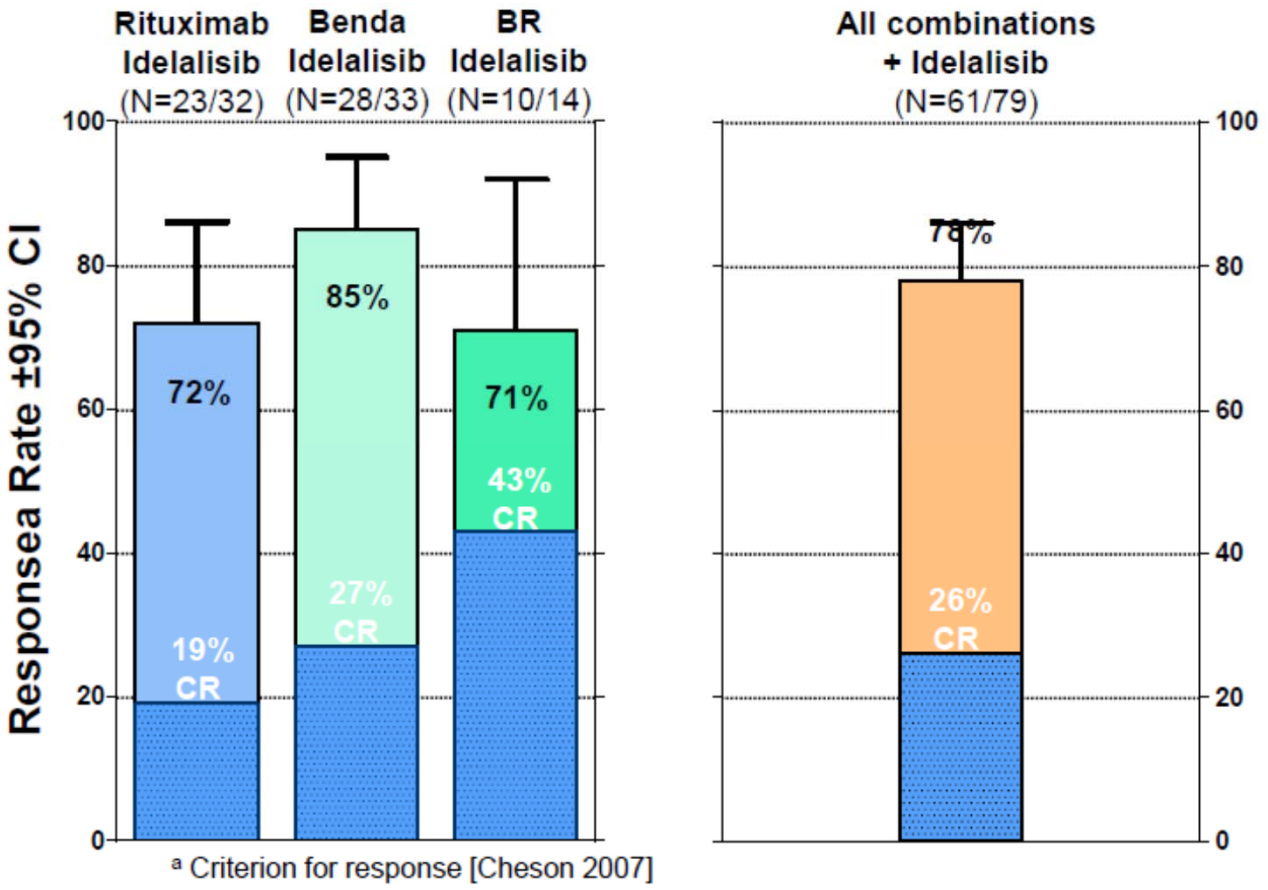
Endpoints

- Safety (Primary)
- Dose selection
- Pharmacokinetics
- Pharmacodynamics
- Efficacy

Memorial Sloan Kettering Cancer Center

de Vos et al. ASH 2014; Abstract 3063

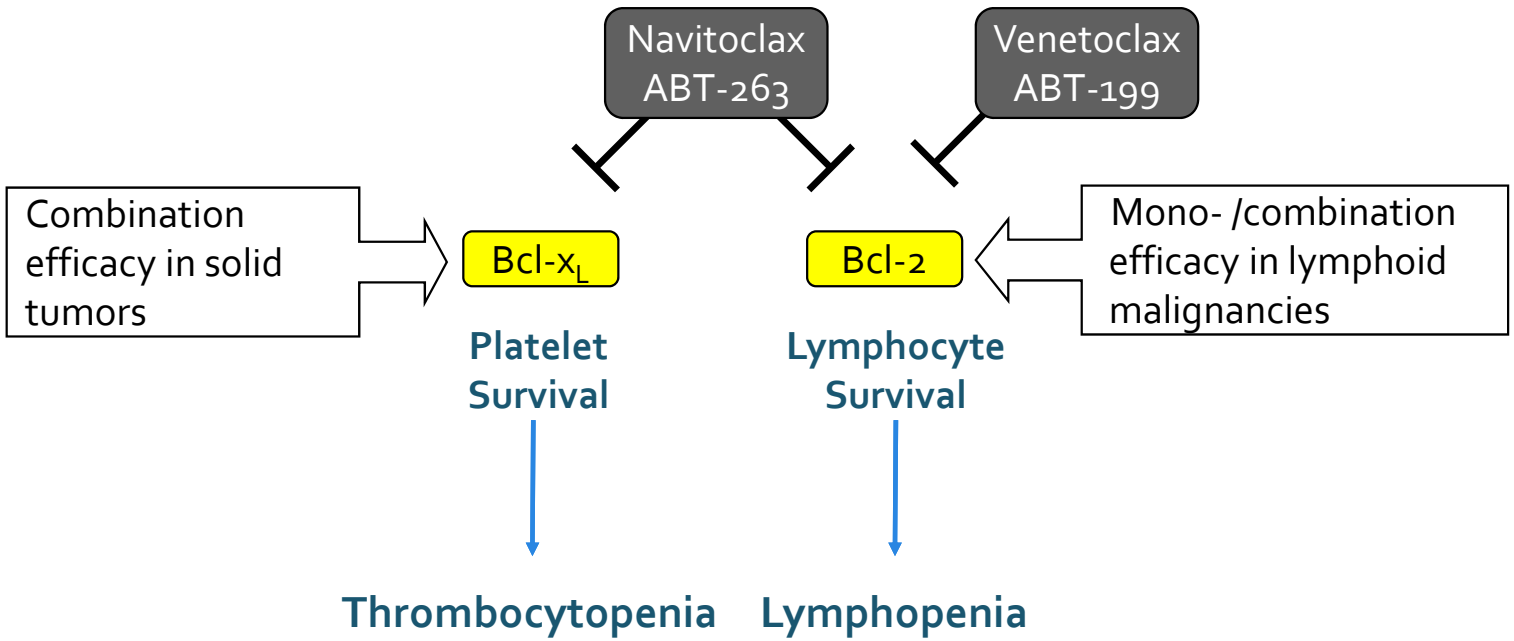
Idelalisib Combinations: Responses



de Vos et al. ASH 2014; Abstract 3063

Memorial Sloan Kettering Cancer Center

Venetoclax (ABT-199) is a Second Generation BCL-2 inhibitor



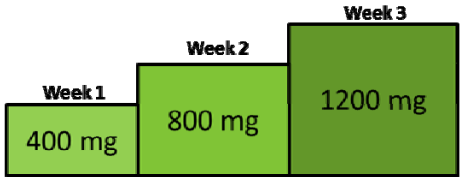
- Dual Bcl-2 / Bcl-xL Inhibition Dictates Efficacy / Toxicity of Navitoclax
- Venetoclax (ABT-199) is specific Bcl-2 inhibitor

Memorial Sloan Kettering Cancer Center

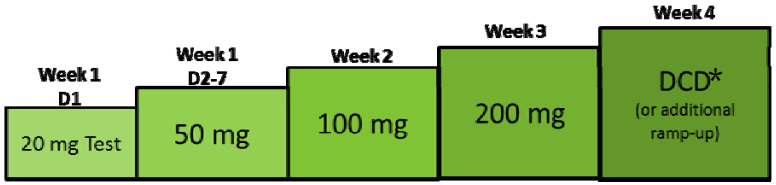
ABT-199 Dosing Schema

- Initial Ramp-Up Dosing of ABT-199 to Designated Cohort Dose (DCD)
  - Starting doses ranging from 50 to 400 mg
  - Modified Fibonacci design
  - Single initial dose for PK on Day -7
  - Amended Ramp-Up Dosing for ABT-199

Non-MCL NHL Patients: Last Dose Escalation/ Expanded Safety Schematic



MCL Patients: Current Dose Escalation Schematic



*DCD 400 or 800 mg

Davis et al. EHA 2015

Memorial Sloan Kettering Cancer Center

Safety Profile of ABT-199 in NHL Patients

Adverse Events

All Grades ≥20% of Patients	N=62 n (%)
Nausea	23 (37)
Diarrhea	18 (29)
Anemia	14 (23)
Fatigue	14 (23)

Grade 3/4 ≥5% of Patients	N=62 n (%)
Anemia	12 (19)
Neutropenia	6 (10)
Thrombocytopenia	4 (7)

Dose Limiting Toxicities (DLTs)

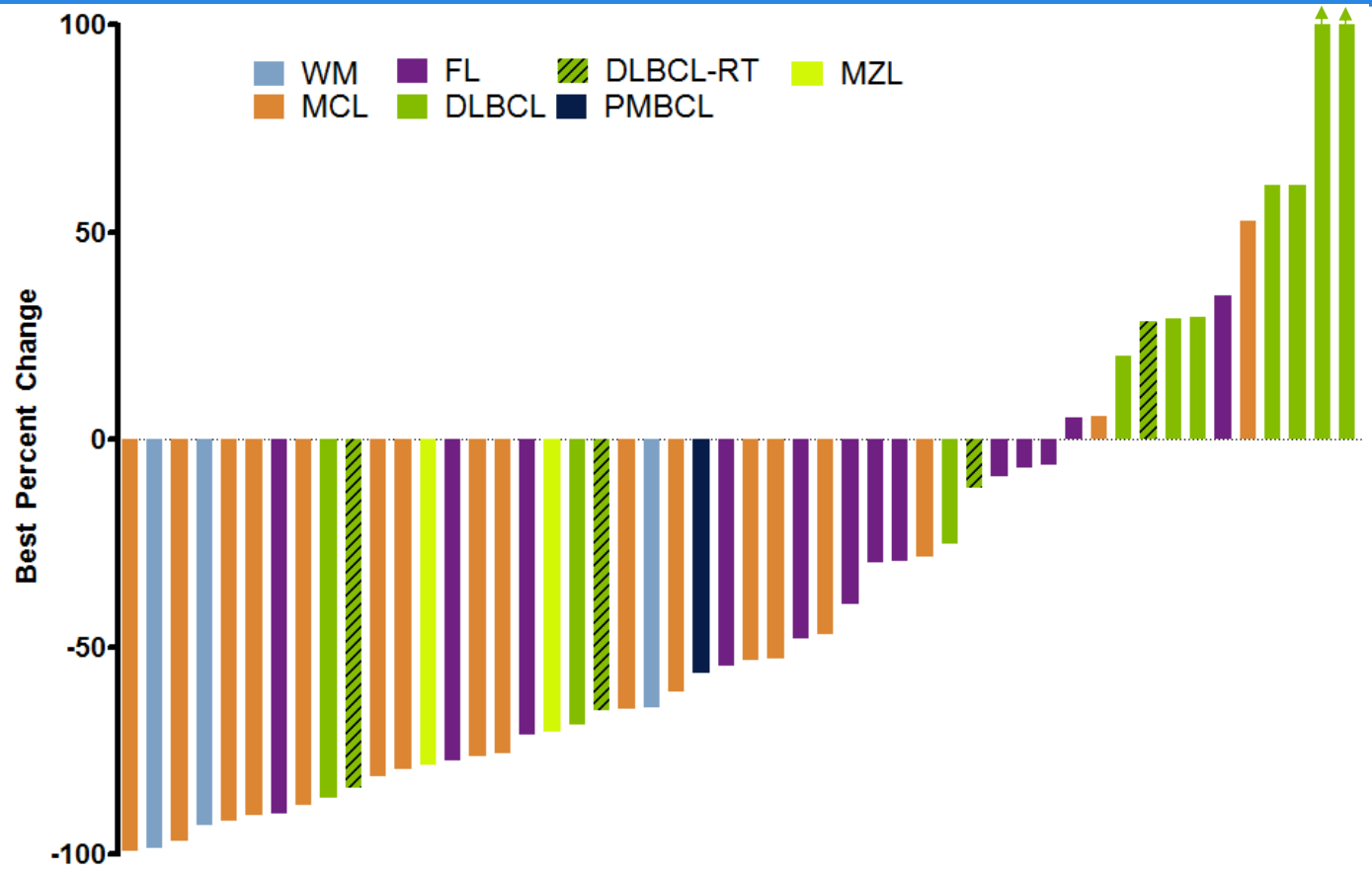
Two DLTs in Cohort 5 at 600 mg:

- Grade 4 neutropenia
- Grade 3 febrile neutropenia

Davis et al. EHA 2015

Memorial Sloan Kettering Cancer Center

Best Percent Change from Baseline in Nodal Mass by CT Scan (n=50)



- 27/50 (54%) of patients had 50% reduction in nodal size

RT = Richter's Transformation

Davis et al. EHA 2015

Memorial Sloan Kettering Cancer Center

Overall Reponses in ABT-199 Treated NHL Patients

Histology	Overall Response (CR + PR)	Complete Response n (%)	Partial Response n (%)	Stable Disease n (%)	Progressive Disease n (%)	D/C Prior to Response n (%)
Total evaluable (n=59)	48%	3 (5)	25 (42)	15 (26)	12 (20)	4 (7)
MCL (n=19)	68%	1 (5)	12 (63)	4 (21)	1 (5)	1 (5)
DLBCL (n=18)	28%	1 (6)	4 (22)	1 (6)	9 (50)	3 (5)
FL (n=13)	31%	1 (8)	3 (23)	9 (69)	-	-
WM (n=4)	75%	-	3 (75)	1 (25)	-	-
MZL (n=3)	67%	-	2 (67)		1 (33)	-
MM (n=1)	-	-	-	-	1 (100)	-
PMBCL (n=1)	100%	-	1 (100)	-	-	-

- FL = All responses occurred at doses ≥ 600 (4/8 pts, 50%)
- DLBCL = 3 responses at 600 mg (1 RT), 2 responses at 400 mg (2 RT)
- MCL and WM responses observed across dose cohorts

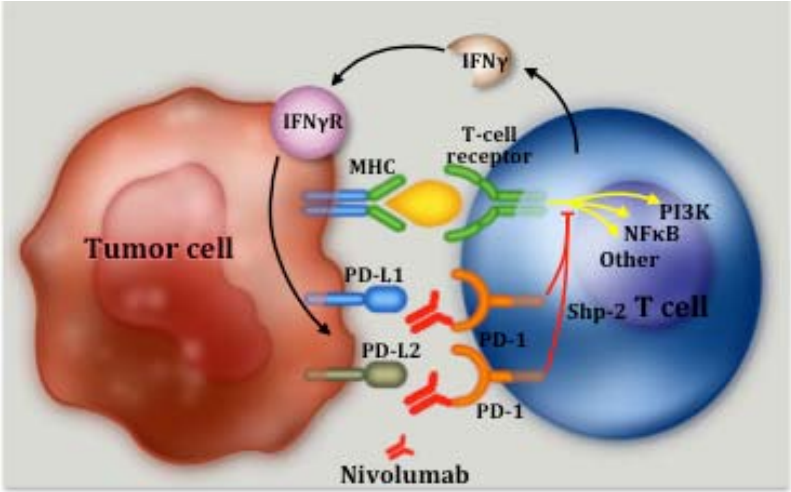
RT = Richter's Transformation

Davis et al. EHA 2015

Memorial Sloan Kettering Cancer Center

Nivolumab – PD-1 Immune Check Point Inhibitor

- PD-1 ligands are overexpressed in inflammatory environments and attenuate the immune response via PD-1 on immune effector cells.[1]
- PD-L1 expressed on malignant cells and/or in the tumor microenvironment suppresses tumor infiltrating lymphocyte activity and interferes with host antitumor immunity.[2]

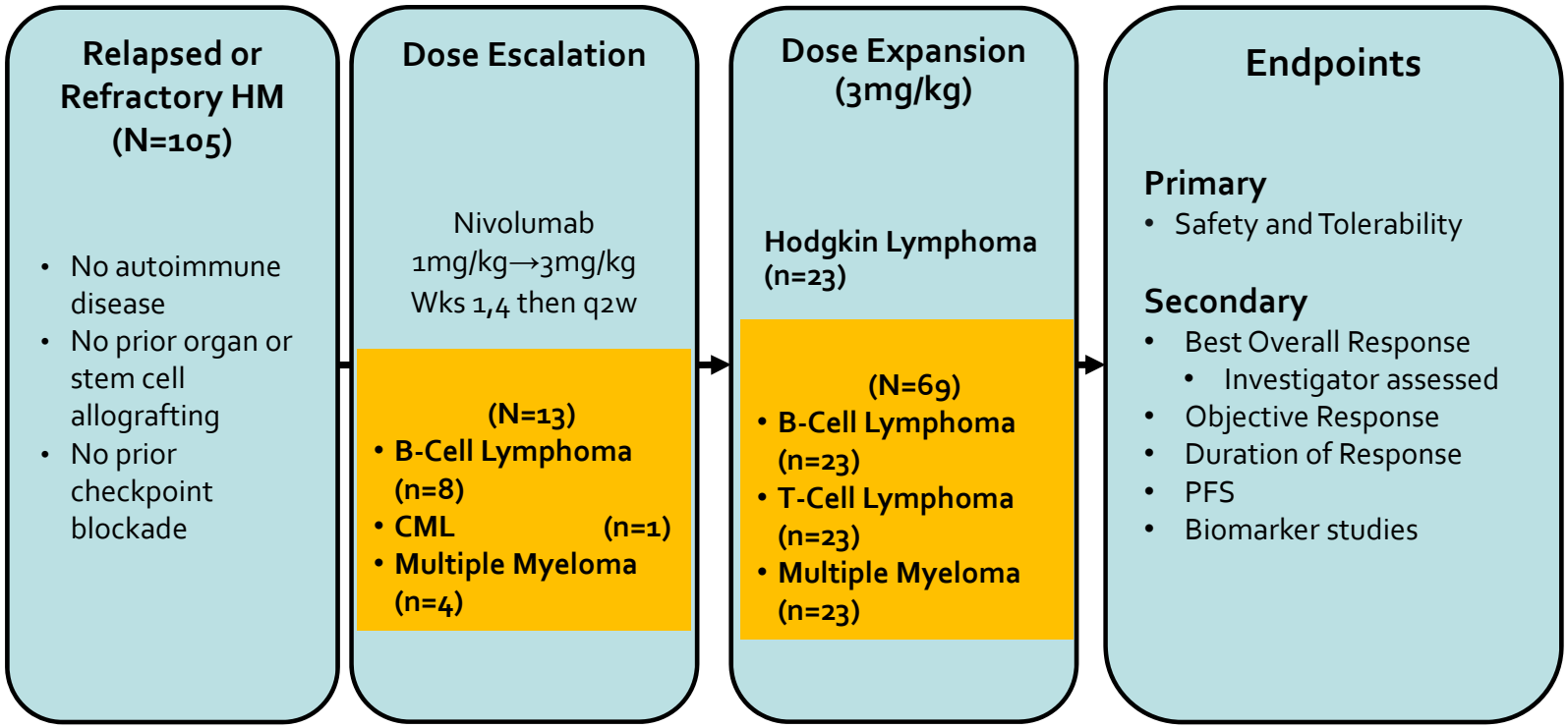


- Nivolumab is a fully human IgG4 monoclonal antibody with anti-PD-1 activity.

[1]Francisco LM et al. J Exp Med 2009;206:3015-29.
[2]Andorsky DJ et al. Clin Cancer Res 2011;17:4232-44

Memorial Sloan Kettering Cancer Center

Nivolumab for Relapsed/Refractory Hematologic Malignancies: Phase I Study Design



Lesokhin et al., ASH 2014; Abstract 291.

Memorial Sloan Kettering Cancer Center

Nivolumab for R/R HM: Drug-related Adverse Events (AEs) Overview

Nivolumab (N=82)	n (%)
Any Grade Related AE	51 (62)
Any Grade Drug-related AE Occurring in ≥ 5% of Patients	**n (%)**
Fatigue	11 (13)
Pneumonitis	9 (11)
Pruritus	7 (9)
Rash	7 (9)
Pyrexia	6 (7)
Anemia	5 (6)
Diarrhea	5 (6)
Decreased appetite	5 (6)
Hypocalcemia	5 (6)

- Safety profile similar to other nivolumab trials
- The majority of pneumonitis cases were Grade 1 or 2
- No clear association between pneumonitis and prior radiation (28 patients), brentuximab vedotin (9 patients) or gemcitabine

Memorial Sloan Kettering Cancer Center

Lesokhin et al., ASH 2014; Abstract 291.

Nivolumab for R/R HM: Best Overall Response

	Objective Response Rate, n (%)	Complete Responses, n (%)	Partial Responses, n (%)	Stable Disease n (%)
B-Cell Lymphoma* (n=29)	8 (28)	2 (7)	6 (21)	14 (48)
Follicular Lymphoma (n=10)	4 (40)	1 (10)	3 (30)	6 (60)
Diffuse Large B-Cell Lymphoma (n=11)	4 (36)	1 (9)	3 (27)	3 (27)
T-Cell Lymphoma† (n=23)	4 (17)	0 (0)	4 (17)	10 (43)
Mycosis Fungoides (n=13)	2 (15)	0 (0)	2 (15)	9 (69)
Peripheral T-Cell Lymphoma (n=5)	2 (40)	0 (0)	2 (40)	0 (0)
Multiple Myeloma (n=27)	0 (0)	0 (0)	0 (0)	18 (67)
Primary Mediastinal B-Cell Lymphoma (n=2)	0 (0)	0 (0)	0 (0)	2 (100)

†includes other cutaneous T-cell lymphoma (n=3) and other non-cutaneous T-cell lymphoma (n=2)

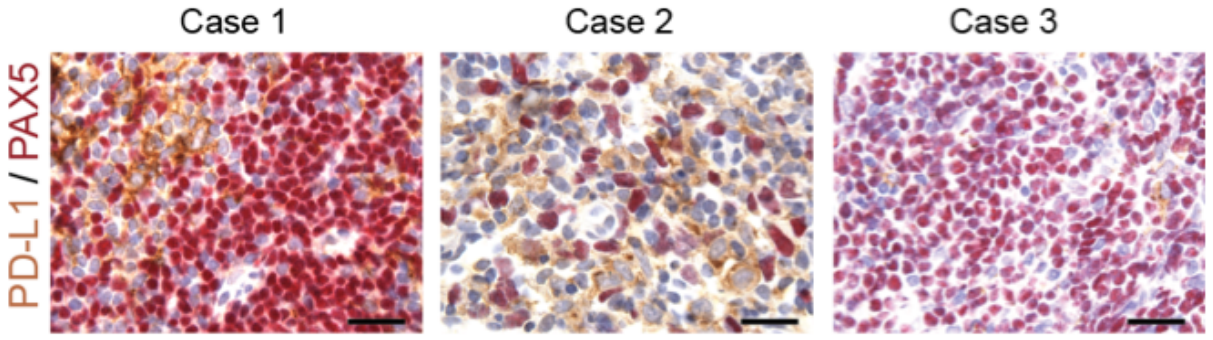
Memorial Sloan Kettering Cancer Center

Lesokhin et al., ASH 2014; Abstract 291.

Nivolumab: PD-L1 Expression

Tumor	Cytogenetics 9p Alteration	Immunohistochemistry PD-L1 Positive
Diffuse Large B-Cell (n=6)	1/6	1/6
Follicular (n=6)	1/6	1/5*
Other B-Cell Lymphoma (n=7)	0/7	1/7
Mycosis Fungoides (n=4)	1/4	1/4
Peripheral T-Cell (n=3)	0/3	0/3
T-Cell Lymphoma (n=2)	0/2	0/2
Unknown (n=2)	0/2	0/2

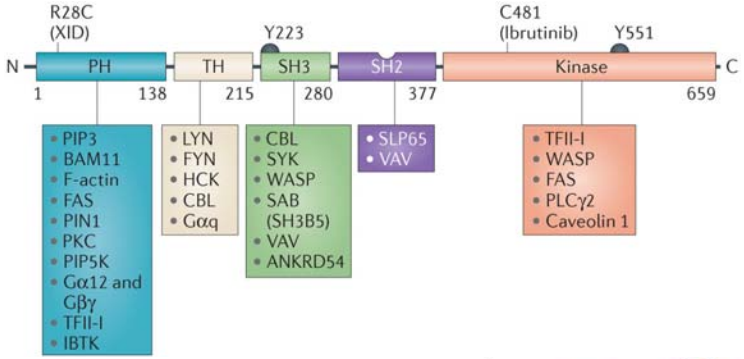
PD-L1 In FL



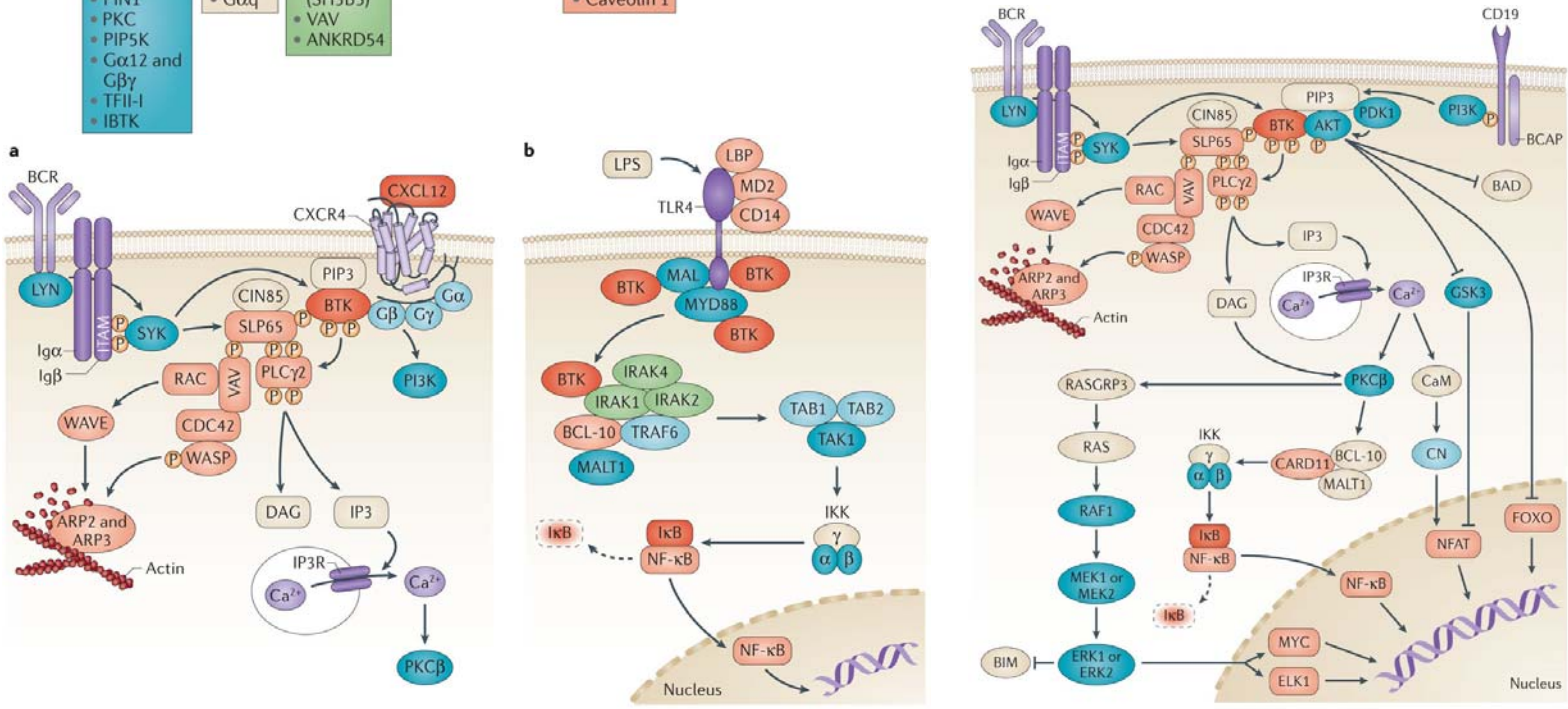
Memorial Sloan Kettering Cancer Center

Lesokhin et al., ASH 2014; Abstract 291.

BTK is Involved in BCR and Other Key Signaling Pathways



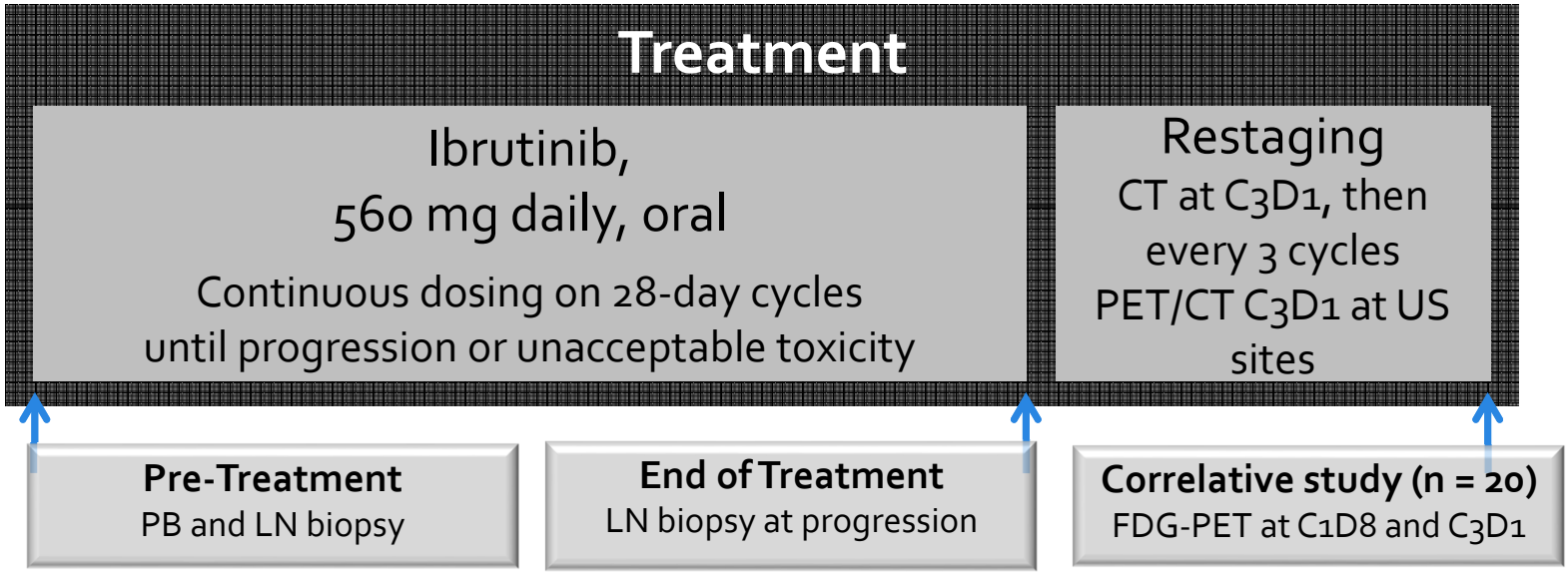
Laboratory studies have also demonstrated that BTK is activated by MyD88 via unmapped domain



Memorial Sloan Kettering Cancer Center

Hendriks et al. Nature Reviews Cancer 14, 219–232 (2014)

Ibrutinib for FL P2C Phase 2 Study: Study Design



- **Primary endpoint: ORR [CR + PR]**
  - PET/CT not included in formal response analysis
- **Secondary endpoints:**
  - Safety and tolerability
  - OS, PFS, time to response, duration of response, time to treatment failure, time to subsequent treatment

Memorial Sloan Kettering Cancer Center

Bartlett et al. ASH 2014; Abstract 800.

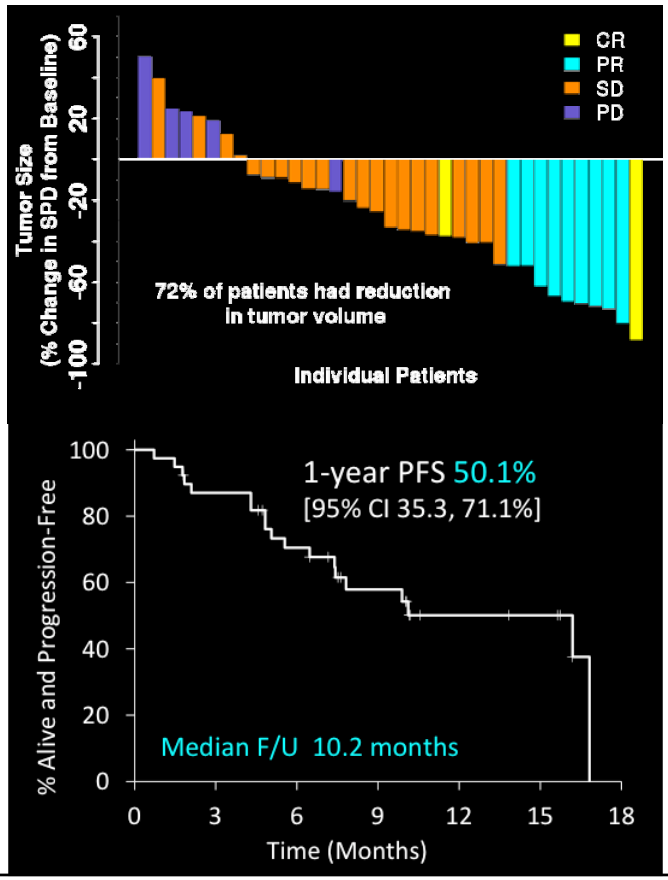
Ibrutinib for FL P2C Phase 2 Study: Outcomes

FL
Grade 1-3a,R/R

→ Ibrutinib 560 mg oral daily
Until POD or intolerance

Primary endpoint: ORR
Secondary endpoints: safety, OS, time to response, TTTF, DOR, PFS

	No.
Overall response rate (ORR)	28% [CI 15-44%]
CR	2 (5%)
PR	9 (23%)
SD	22 (55%)
PD/NE	5 (12%) /2
Response based on prior rituximab therapy	
Rituximab-refractory	1/18 (6%)
Rituximab-sensitive	8/19 (42%)
Rituximab-naïve (2/3 prior ofatumumab)	2/3 (67%)



Bartlett et al. ASH 2014; Abstract 800.

Living with Follicular Lymphoma

- Survival in follicular lymphoma = ∑
  - Time with active disease but without indication for therapy
    - Includes periods of observation both at diagnosis and at disease progression
    - In absence of symptoms living with disease is similar to being in remission
  - Time on active therapy
    - Side effects of therapy are an investment for a period of disease-free (or less disease) remission
  - Time in remission
  - Clinical experience suggests that quality of life for patients in remission is often similar to patients alive with low tumor burden disease
    - Prospective data is limited

Memorial Sloan Kettering Cancer Center

NCCN Member Institutions