Treatment
Nodal Marginal Zone Lymphoma

Catherine Thieblemont
Hôpital Saint-Louis, Paris - France

Bologna 16th, 2017

Treatment

- **No standardized treatment**
- **Similarly treated as FL**

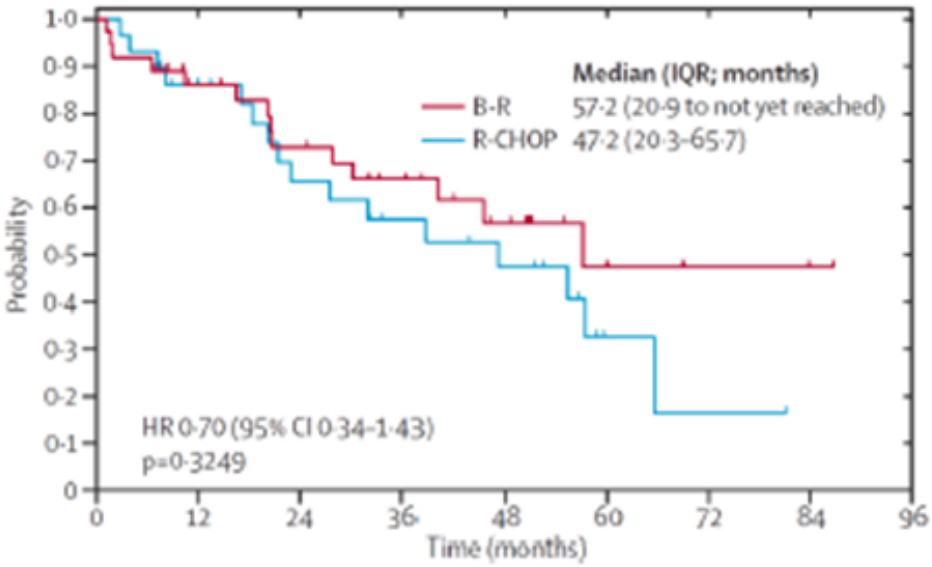
Localized disease	**Disseminated Disease**	
	Low tumor burden	**High tumor burden**
Radiotherapy	Watchful waiting	Recommended first-line treatment: - R-bendamustine* OR - R-fludarabine or R-fludarabine-cyclophosphamide for patients < 70 years**

Thieblemont C et al. Blood 2016

Immuno- chemotherapy

STIL trial

67 patients
with MZL



R-bendamustine > R-CHOP : median PFS, 57.2 vs 47.2 months

Immuno- chemotherapy in NMZL

- **Rare localized cases: *Radiation Therapy***

- **Stage II to IV**
  - **R – Anthracyclin based-regimen (CHOP, CHOP like)**
  - **R – Bendamustine**
  - **Because of the toxicity profile, R-fludarabine or R-fludarabine-cyclophosphamide should only be proposed to patients <70 years**

- **No evidence for recommanding rituximab maintenance**

- **No evidence for recommanding intensive chemotherapy plus ASCT in first line**

What is next ?

Improving on standard therapy

GOALS

- **Improving PFS**
- **Cure?**
- **Same results with no toxicity**

DRUGS

- **Alternative antiCD20**
  - Obinutuzumab GA101 : GAUSS GAUGUIN
  - Antibody Drug Conjugate (ADC) antiCD22, antiCD79
- **Newer agents**

  Bortezomid (Velcade)

  Lenalidomide (revlimid)

  Targeting Pi3K/mTOR :

  Everolimus, Idelalisib, Copanlisib

  Targeting BCR : Ibrutinib

  Targeting bcl2 : ABT199

Obinutuzumab (GA101)

Table 2. Response Rates

Responders	Obinutuzumab (GA101) 400/400 mg (n = 18) No.	%	Obinutuzumab (GA101) 1,600/800 mg (n = 22) No.	%
End-of-treatment response				
ORR	3	16.7	12	54.5
CR/CRu	0	0	2	9.1
PR	3	16.7	10	45.5
ORR in patients with FL	3/14	21.4	10/20	50.0
ORR in rituximab-refractory patients	1/12	8.3	5/10	50.0
Best response				
BORR	6	33.3	14	63.6
CR/CRu	2	11.1	5	22.7
PR	4	22.2	9	40.9
BORR in patients with FL	5/14	35.7	12/20	60.0

Abbreviations: BORR, best overall response rate; CR, complete response; CRu, unconfirmed complete response; FL, follicular lymphoma; ORR, overall response rate; PR, partial response.

GAUGUIN
Salles, JCO 2013

MZL :
n=2 (400/400mg)
n=1 (1600/800mg)

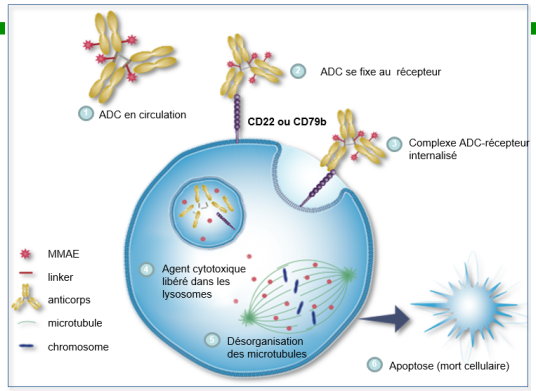
GAUSS
(Sehn, ASH 2011)

Phase II randomised
GA101 vs R
4 perfusions hebdo

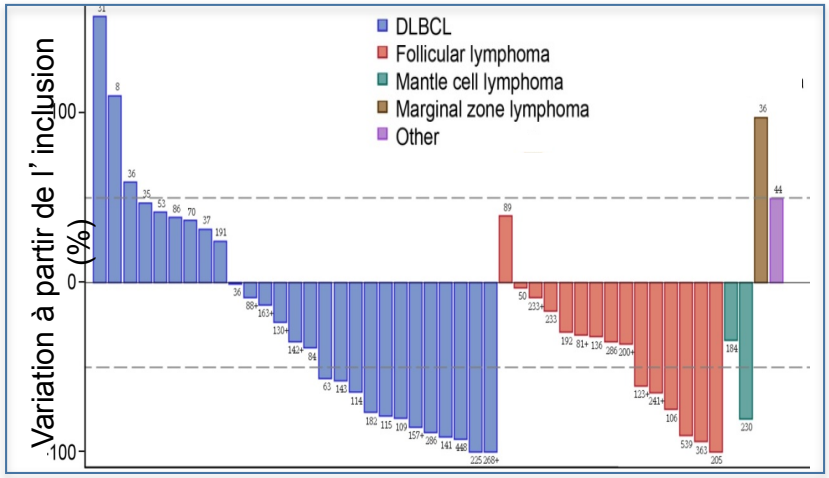
175 patients (26 non-FL), R/R

ORR=42 vs 24.1

Antibody drug conjugate in MZL

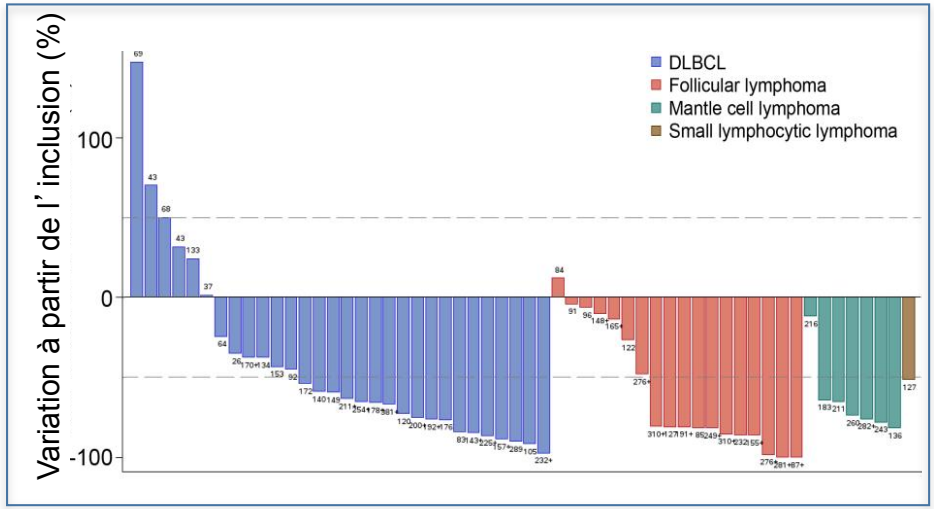


- Phase I : **anti-CD22 ADC**
  +/- Rituximab
  - **n = 65 patients**
  - **39 DLBCL, 19 FL, 3 MCL, 1 SLL, 2 MZL, 1 gray zone**



DCDT2980S

- Phase I : **anti-CD79B ADC**
  +/- Rituximab
  - **n = 60 pts**
  - **32 DLBCL, 18 FL, 7 MCL, 1 SLL,1 MZL, 1 Richter**



DCDS4501A

R. ADVANI, Abstract # 39, ICML 2013

Bortezomib

Rationale : To target NFKB activation

Gastric and non-gastric cases

Relapsed MALT lymphoma

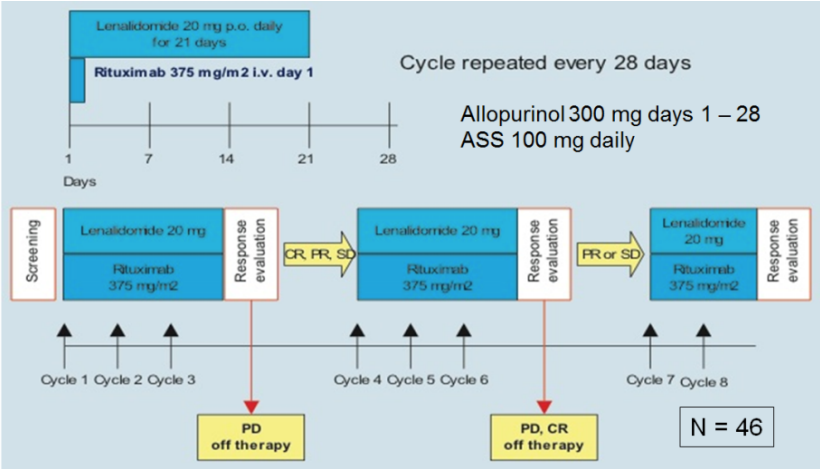
Authors	n	dose	Response	Survival	Toxicity
Troch 2009	16	1.5 mg/m2 i.v., on days 1, 4, 8, and 11 , for up to six 21-day cycles	**ORR : 80%** **CR : 43%**	4 relapses (median F-up=23 mo)	Neuropathy : 44% Diarrhea : 50%
Conconi 2011	32	1.3 mg/m2 i.v., on days 1, 4, 8, and 11 , for up to six 21-day cycles	**ORR : 48%** **CR : 28%**	2-y PFS = 50%	Neuropathy : 65%

High rate of toxicity

Troch M et al. Haematologica 2009; Conconi AR et al. Ann Oncol 2011

R-Lenalidomide

Pretreated: 9 / 40



End of treatment

N = 28

– 6 cycles: n = 24

– 8 cycles: n = 4

ORR:	24 / 28	(86%)	
CR:	18 / 28	(65%)	+ 7
PR:	6 / 28	(21%)	+ 1

Dose reductions:

To 15 mg 8 pts
To 10 mg 2 pts

Drop-outs: 4 pts

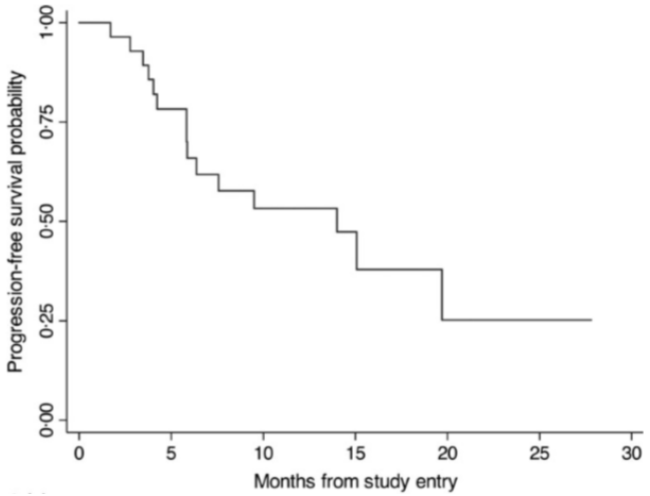
Hematologic AE	WHO I/ II	WHO III/ IV
Leucopenia	10	1
Neutropenia	8	3
Thrombopenia	5	
Anemia	4	2

Raderer M et al, EHA 2014

EVEROLIMUS (RAD001) (mTOR inh)

- **n=30 relapsed/refractory MZL**
- **24 evaluable patients : 16 MALT L, 4 SMZL, 4 NMZL**
- **Median number of prior lines : 2 (1-5)**
- **Phase II – Max 6 cycles**

Response	All patients ($N = 30$)	Evaluable patients ($N = 24$)
Complete remission	1 (3%)	1 (4%)
Partial remission	5 (17%)	5 (21%)
Stable disease	11 (37%)	11 (46%)
Disease progression	7 (23%)	7 (29%)



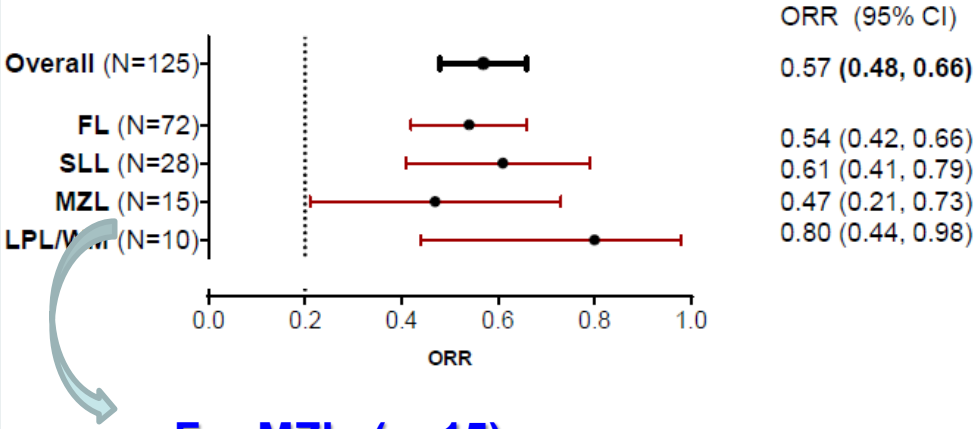
Conconi A. et al. Br J Haematol 2014

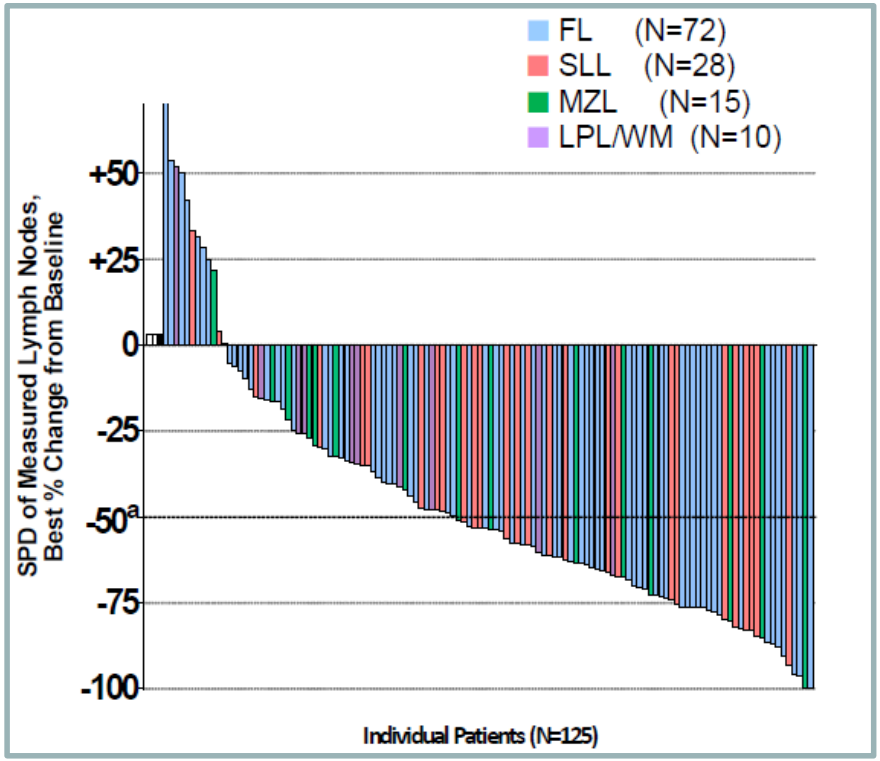
Toxicity	G1	G2	G3	G4
Thrombocytopenia	16	7	5	–
Neutropenia	6	4	4	1
Leucopenia	3	3	2	–
Anaemia	6	–	1	–
Lymphopenia	1	1	–	–
Stomatitis	11	8	3	1
Infection†	1	2	4	1
Cutaneous rash	8	3	1	–
Asthenia	6	2	–	–
Hypercolesterolaemia	7	1	–	–
Hypertriglyceridaemia	4	2	–	–
Interstitial pneumonia	2	2	1	–
Arthromyalgia	3	1	1	–
Anorexia	3	–	1	–
Oedema	1	3	–	–
Diarrhoea	–	3	–	–
Transaminase	2	1	–	–
Gamma-glutamyl transferase	2	1	–	–
Cutaneous ulcers	–	–	2	–
Hyperglicaemia	–	1	1	–
Dyspnea	–	2	–	–
Fever	1	1	–	–
Pleural effusion	–	1	–	–
Atrial fibrillation	–	1	–	–
Acute renal failure	–	1	–	–
Eye disorder	–	1	–	–
Flebitis	–	1	–	–
Constipation	–	1	–	–
Thoracic pain	–	1	–	–
Nausea	–	1	–	–
Nosebleed	1	–	–	–
Heartburn	1	–	–	–

High level of toxicity +++++
Not acceptable for indolent lymphoma

Idelalisib in iNHL (PI3K –d)

- n=125 (72 FL, 28 SLL, 10 LPL/WM, 15 MZL)
- 4 prior lines
- Phase II





For MZL (n=15):

Efficacy
ORR 47%,
mDOR 11,9 mos

Toxicities
10% diarrhea gr3

Idelalisib Treatment	Months
Mean (SD)	8.1 (5.7)
Median	6.6
Range	0.6-23.9

Gopal, NEJM 2014

Copanlisib (PI3K-d and PI3K-α inhibitor)

141 **patients**. Indolent lymphoma
23 MZL : 4 EMZL, 4 SMZL, 15 NMZL

MZL : Overall response rate (CR+PR) : 70%

- CR : 8.7%

- PR : 61%

- **Median Duration of response : not reached range : 15 – 100 days**

- hyperglycemia (70%)
- hypertension (70%)
- Fatigue (64%)
- diarrhea (36%)
- neutropenia (36%)
- anemia (33%).
- Grade 3-4 AEs occurring in >10% of patients included: hypertension (49% grade 3), neutropenia (30%), hyperglycemia (30% grade 3), and anemia (15%).

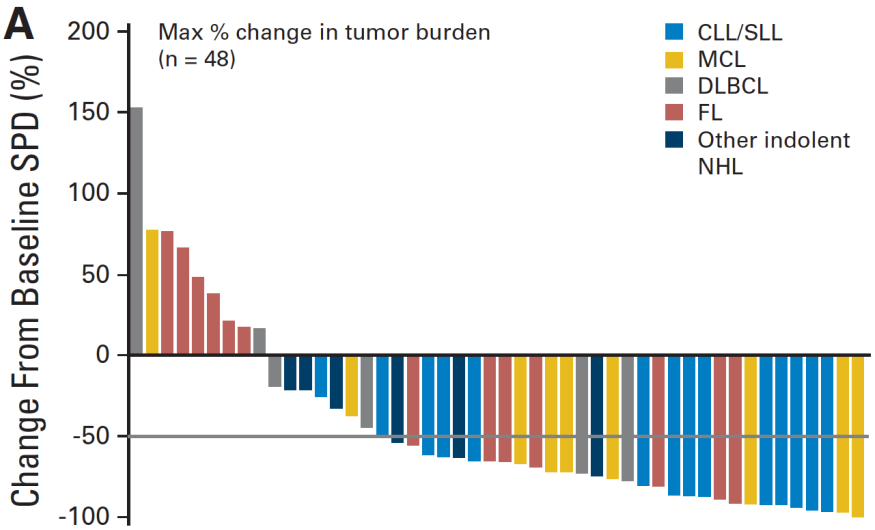
Dreyling M , AACR 2017

Ibrutinib (BTK inhibitor)

Table 1. Baseline Patient Characteristics (N = 56)

Characteristic	No.	%
Age, years		
Median	65	
Range	41-82	
Sex		
Male	38	68
Female	18	32
Histologic subtype		
Follicular lymphoma	16	29
CLL/SLL	16	29
Mantle-cell lymphoma	9	16
DLBCL	7	13
Marginal zone/mucosal-associated lymphoid tissue lymphoma	4	7
Waldenström macroglobulinemia	4	7
Prior therapy		
Median No.	3	
Range	1-10	
Rituximab	52	93
Alkylator based	47	84
Anthracycline based	25	45
Radiotherapy	15	27
Autologous stem-cell transplantation	3	5

Abbreviations: CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; SLL, small lymphocytic lymphoma.

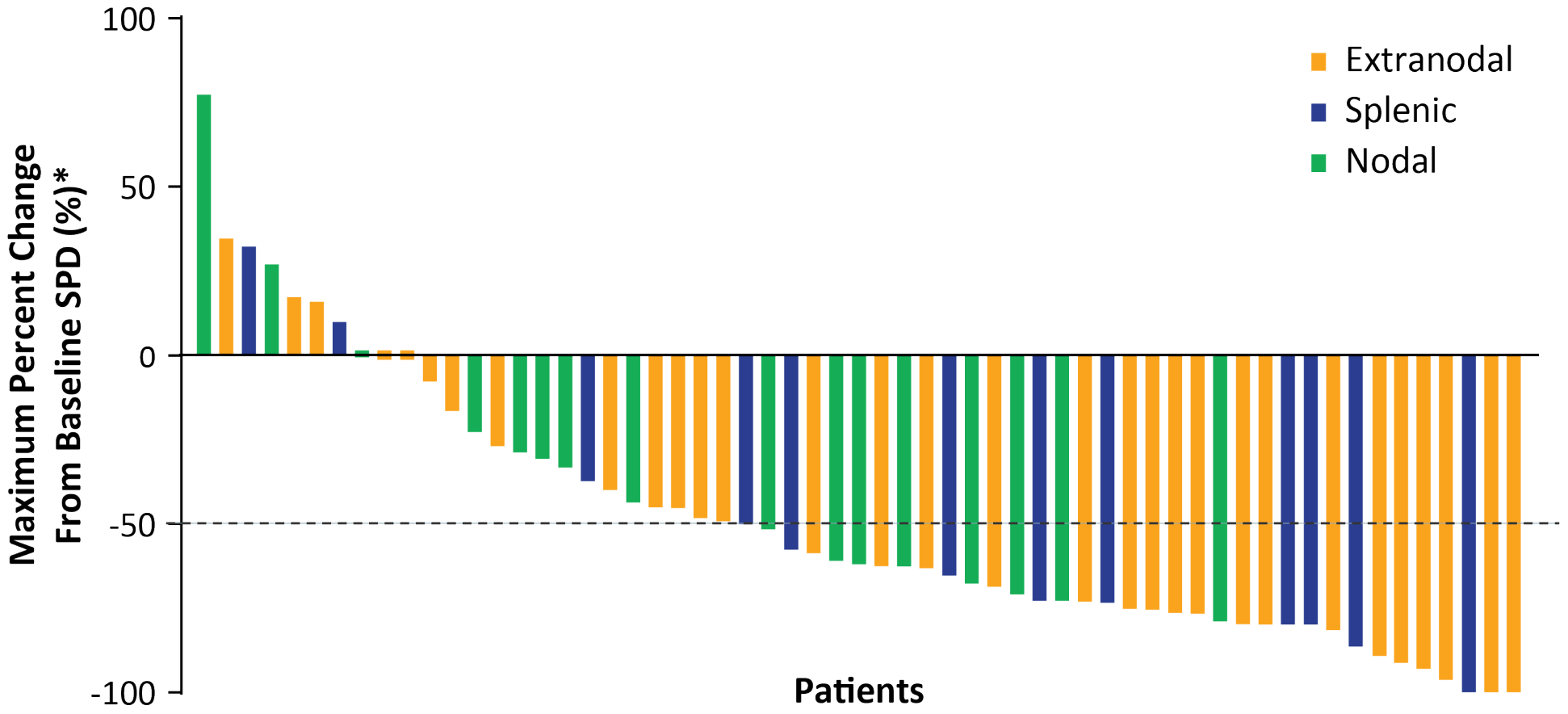


ORR MZL : 1/4

Advani, JCO 2013

→ PCYC1121 Ibrutinib in R/R MZL
65 patients –ASH 2016

Majority of Patients With R/R MZL Had Tumor Reduction With Ibrutinib

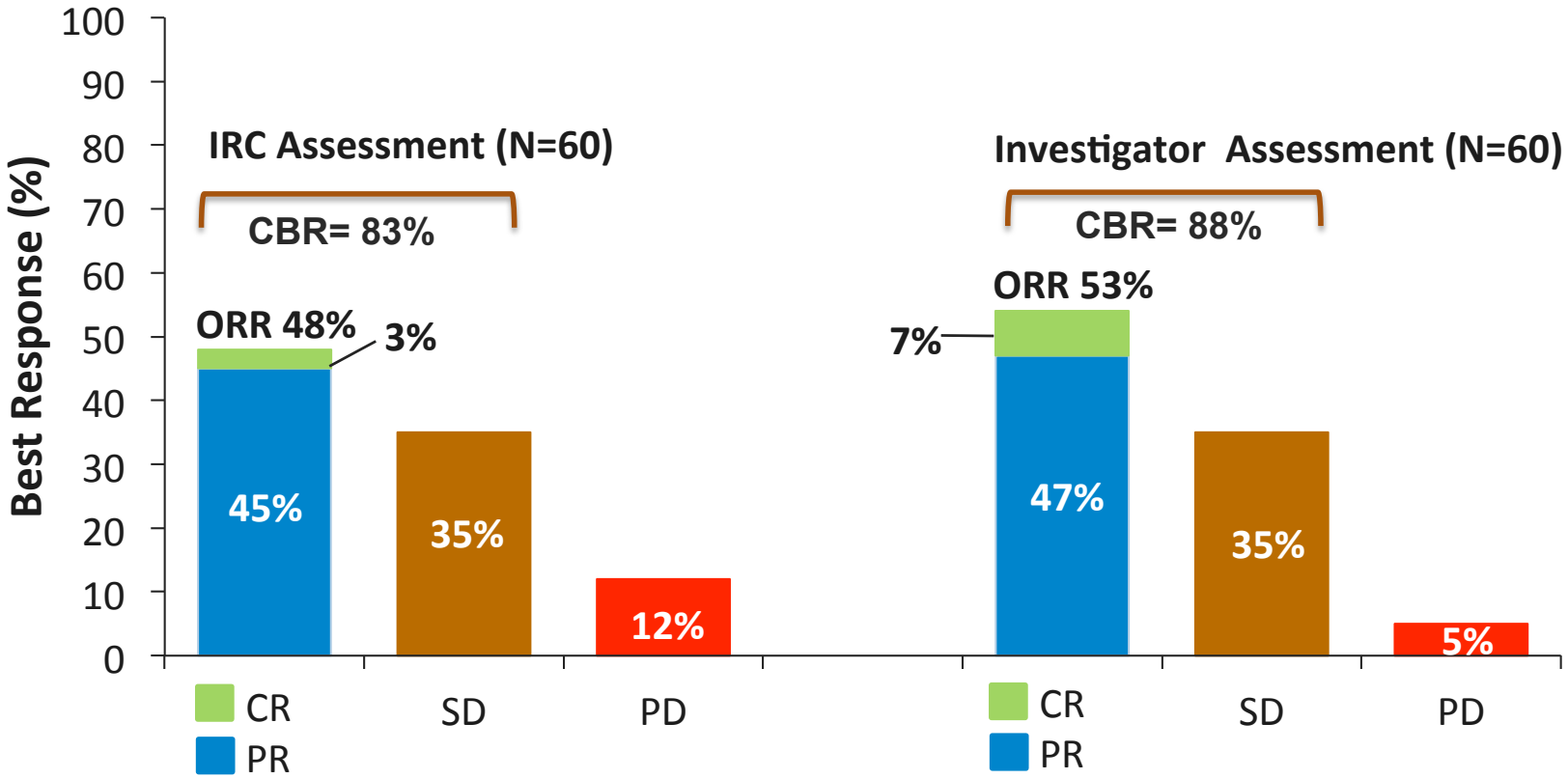


- Tumor shrinkage was seen in 79% (50/63) patients, implying BTK signaling as an important growth and survival factor in MZL.

*Data based on investigator assessment for 60 patients; 3 patients who discontinued treatment prior to first response assessment were not evaluable. Investigator-assessed data were used given that IRC assessment included 2 separate sets of SPD data due to readings by 2 radiologists

ASH 2016, PCYC-1121, Noy et al.

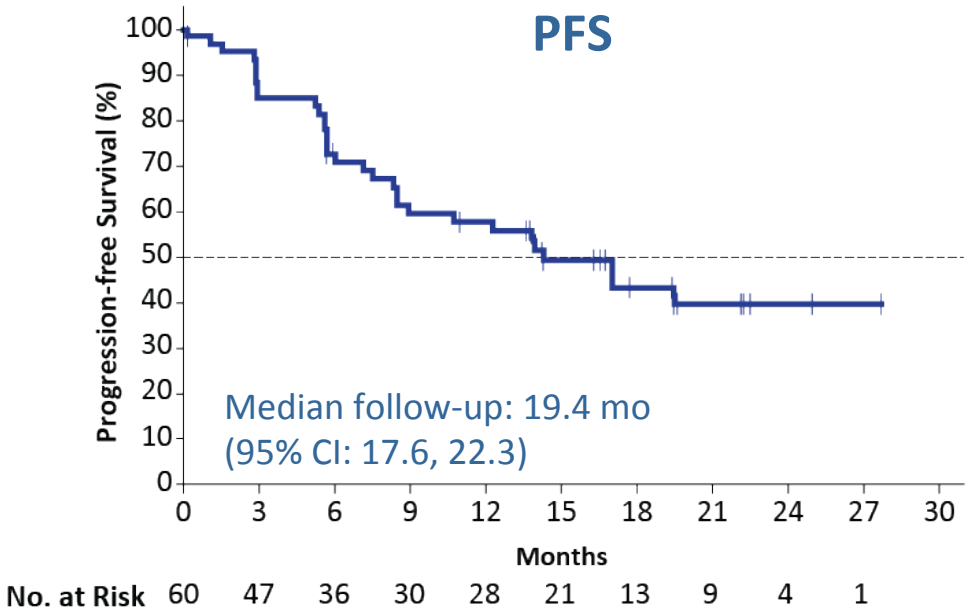
Best Response Results in Clinical Benefit in the Majority of Patients With R/R MZL

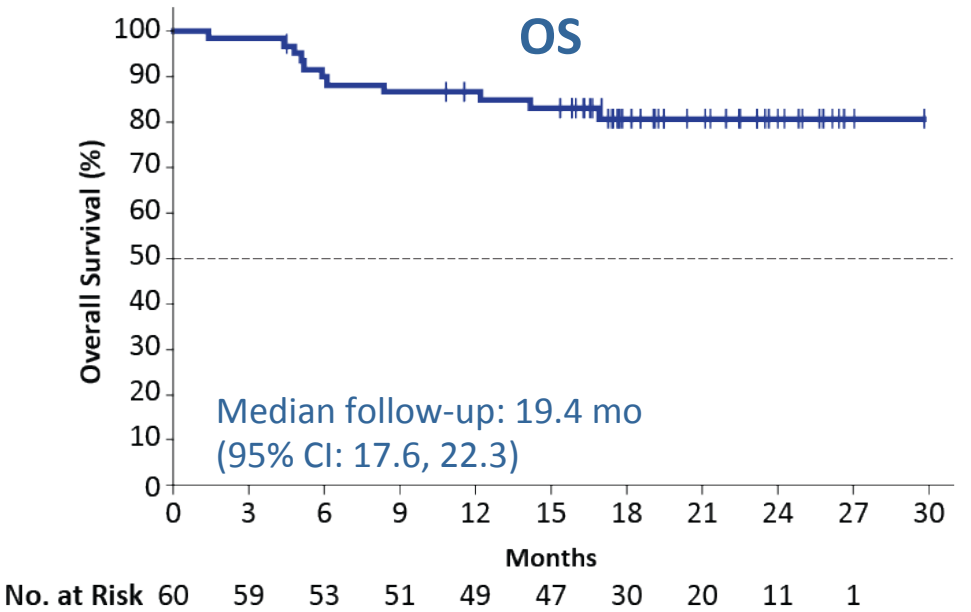


- Clinical efficacy (IRC assessment) as judged by ORR was 48%, and clinical benefit rate (CBR = PR+CR+SD) was 83%.
- Concordance rate for ORR between IRC and investigator assessment was 85%.
- Median time to initial response: 4.5 months and to best response: 5.2 months.

ASH 2016, PCYC-1121, Noy et al.

Progression-Free Survival and Overall Survival





	IRC	Investigator
Median PFS (95% CI)	14.2 (8.3, NR)	15.7 (12.0, NR)
18-mo PFS rate	45%	49%

	Investigator
Median OS (95% CI)	NR (NR, NR)
18-mo OS rate	81%

- Median PFS by MZL subtype was 19.4 months (95% CI, 8.2-NR) for splenic, 13.8 months (95% CI, 8.3-NR) for extranodal, and 8.3 months (95% CI, 2.8-NR) for nodal MZL.

NR, not reached

ASH 2016, PCYC-1121, Noy et al.

Anti - BCL2 (ABT-199) +BR

26 **patients**. 15 FL, 8 DLBCL
3 MZL

CR : 5 (19.2%)

PR : 11 (42.3%)

Overall response rate (CR+PR) for ABT-199+BR :

- **61.5% (16/26) for all patients**
- **73.3% (11/15) for FL**
- **37.5% (3/8) for DLBCL**

Sven de Vos, ASH 2014 – abstract 1722

Targeted therapies in MZL

Pathway	Drug	Target	Nber of pts	response
PI3K/AKT/mTOR	*Everolimus* Toxicity +++	mTOR	24	CR 4% - ORR 28%
	Idelalisib	PI3K-d	15	CR 6% - ORR 57%
	Copanlisib	PI3K-d and PI3K-α	3	ORR : 2/3
BCR	Ibrutinib	Btk	4	ORR : 1/4
Apoptosis	ABT-199	BCL2	3	Result unknown for MZL
Microenv.	Lenalidomide (+R)	immunomodulator	40	CR 65% - ORR 86%
Proteasome	*Bortezomib* Toxicity +++	Proteasome	48	CR 35% - 0RR 64%

Ongoing trials

Compound	Clinical setting	Class	Target	Ongoing Trials				
				Phase	N patients	Comparator	Primary endpoint	Trial status
Obinutuzumab	Rituximab-refractory MZL (among iNHL)	mAb	CD20	III (combo with bendamustine)	414	Bendamustine	PFS	Complete
	Relapsed MZL (among iNHL)			I/II (combo with lenalidomide)	72		MTD, DLT	Recruiting (est. 05/2016)
Ublituximab	r/r MZL (among B cell NHL)	mAb	CD20	I/II	60		MTD, safety	Complete
Ibrutinib	r/r MZL (among iNHL)	iTK	BTK, ITK	III (combo with BR or rituximab only)	400	R-CHOP	PFS	Active (est. completion 08/2012)
	r/r MZL			II	60		ORR	Active, not recruiting (est. 12/2017)
	Relapsed MZL (among B-cell NHL)			I (combo with lenalidomide)	34		DLT, MTD, safety	12/2015 (primary outcome measure)
Lenalidomide	r/r MZL (among iNHL)	Small molecule IMiDs	Immuno-modulatory	I (combo with rituximab and bendamustine)	26		MTD	Active, non- recruiting (est. 11/2016)
	r/r MZL (among B-cell NHL)			I/II (combo with romidepsin and rituximab)	56		MTD, ORR	Not yet recruiting (est. completion 10/2020)
	r/r MZL (together with FL)			III (combo with rituximab)	350	Rituximab + placebo	PFS	12/2016
Idelalisib	Rituximab and alkylating agents-ref MZL (among iNHL)	Small molecule	PI3K	II	125 (15 MZL)		ORR	Active, non-recruiting (est completion 12/2015)
	r/r MZL (among iNHL)			III (combo with rituximab)	375	Rituximab + placebo	PFS	Recruiting (est. 06/2022)
Idelalisib + GS-9973	r/r hematologic malignancies	Small molecules	PI3K Syk	II	66		ORR	Active, non- recruiting (est. completion 09/2015)
Duvelisib	Rituximab and CT or RIT-refractory MZL (among iNHL)	Small molecule	PI3K	II	120		ORR	Recruiting (est. completion 01/2018)

Thieblemont C et al, 2016 for review

Take home messages

- **No standard treatment**
- **CLINICAL TRIAL !!**
- **New drugs**
  - **Inhibitors of signaling pathways : TLR, BCR, NOTCH, NFKB, Jak/stat**