Monoclonal antibodies alone and in combination

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Disclosure slide

- I have nothing to disclose for this presentation.

Agenda

- **mAb monotherapy**
- **mAb + X**
- **Our experience**

Agenda

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- mAb + X
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Annals of Oncology 25 (Supplement 3): iii76–iii82, 2014
doi:10.1093/annonc/mdu200
Published online 13 August 2014

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. Dreyling[1], M. Ghielmini[2], R. Marcus[3], G. Salles[4], U. Vitolo[5] & M. Ladetto[6] on behalf of the ESMO Guidelines Working Group*

[1]*Department of Medicine III, University of Munich, Munich, Germany;* [2]*Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland;* [3]*Haematology, Kings College Hospital, London, UK;* [4]*Service D'Hématologie, Centre Hospitalier Lyon-Sud, Pierre-Benite, France;* [5]*Haematology II, Centro Universitario Ricerca Oncologica Ospedale Molinette, Turin;* [6]*Divisione di Ematologia, Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy*

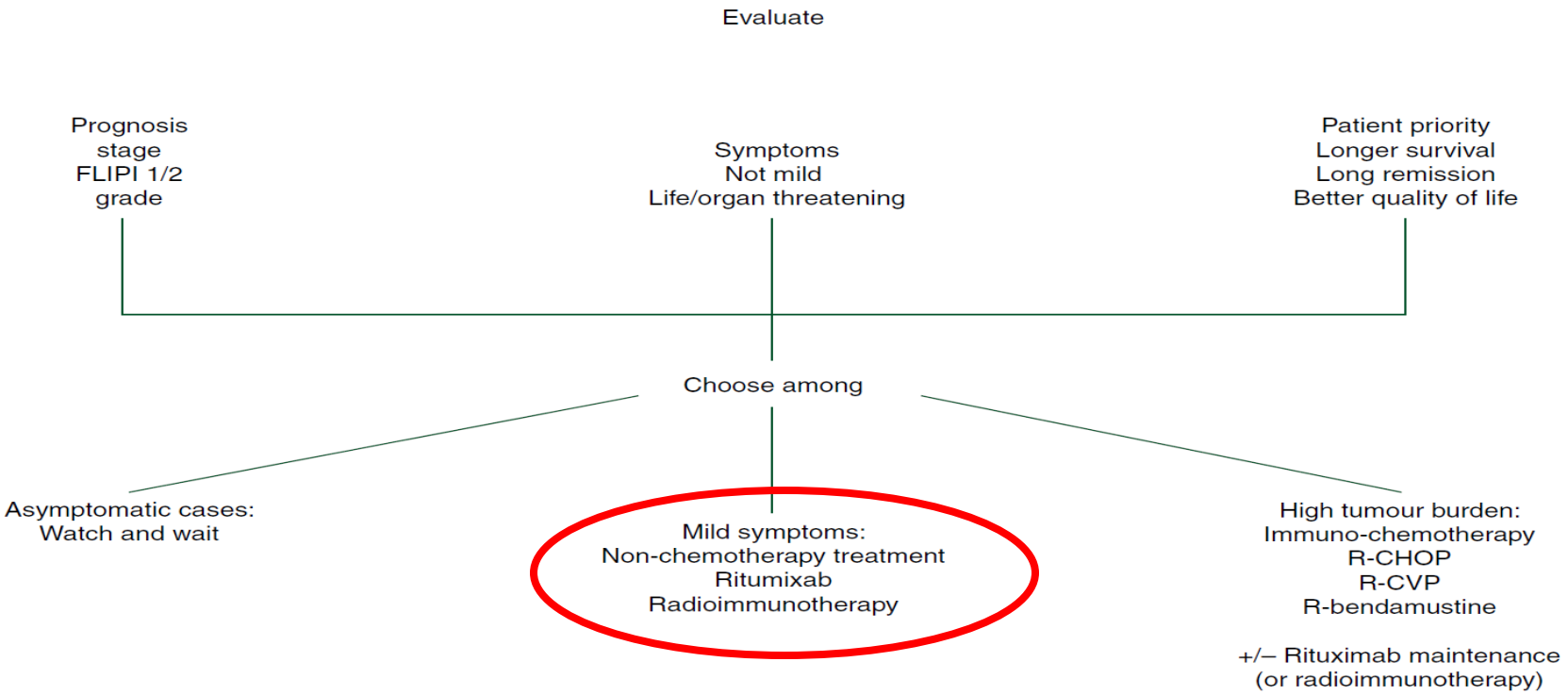

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Table 7. Consensus-driven recommendations outside clinical studies

Low tumour burden		High tumour burden	
Stage I/II	Stage III/IV	Stage III/IV (<65 years[a])	Stage III/IV (>65 years[a])
Front line			
Radiotherapy (involved field) 24–36 Gy In selected cases, watchful waiting	Watch and wait In symptomatic cases, consider rituximab monotherapy	Chemoimmunotherapy (e.g. R-CHOP, R-CVP, BR) In selected cases, rituximab monotherapy	Chemoimmunotherapy (e.g. R-CVP, BR, R-CHOP) or brief chemoimmunotherapy In selected cases, rituximab–chlorambucil rituximab monotherapy
–	–	CR/PR Rituximab maintenance (every 2 months, up to 2 years)	CR/PR Rituximab maintenance (every 2 months, up to 2 years)
Relapse/progress			
Watch and wait Rituximab monotherapy In selected cases, palliative radiation (e.g. 2 × 2 Gy)	Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) In selected cases, rituximab monotherapy	Dependent on first-line regimen and remission duration • Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) • Discuss high-dose consolidation with ASCT • Rituximab maintenance (every 3 months, up to 2 years) • Alternatively, radioimmunotherapy • In selected cases, discuss allogeneic transplantation	Dependent on first-line regimen and remission duration • Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) • Rituximab maintenance (every 3 months, up to 2 years) • Alternatively, radioimmunotherapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Follicular Lymphoma (grade 1-2)

NCCN Guidelines Index
NHL Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a,b]
(in preference order)

First-line Therapy[c]
- Bendamustine + rituximab (category 1)
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- Rituximab (375 mg/m² weekly for 4 doses)
- Lenalidomide + rituximab (category 3)

First-line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable in the opinion of treating physician)
- Rituximab (preferred) (375 mg/m² weekly for 4 doses)
- Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab
- Radioimmunotherapy[d,e] (category 2B)

First-line Consolidation or Extended Dosing (optional)
- Rituximab maintenance 375 mg/m² one dose every 8 wks for 12 doses for patients initially presenting with high tumor burden (category 1)
- If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m² one dose every 8 weeks for 4 doses
- Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)[d,e,f]

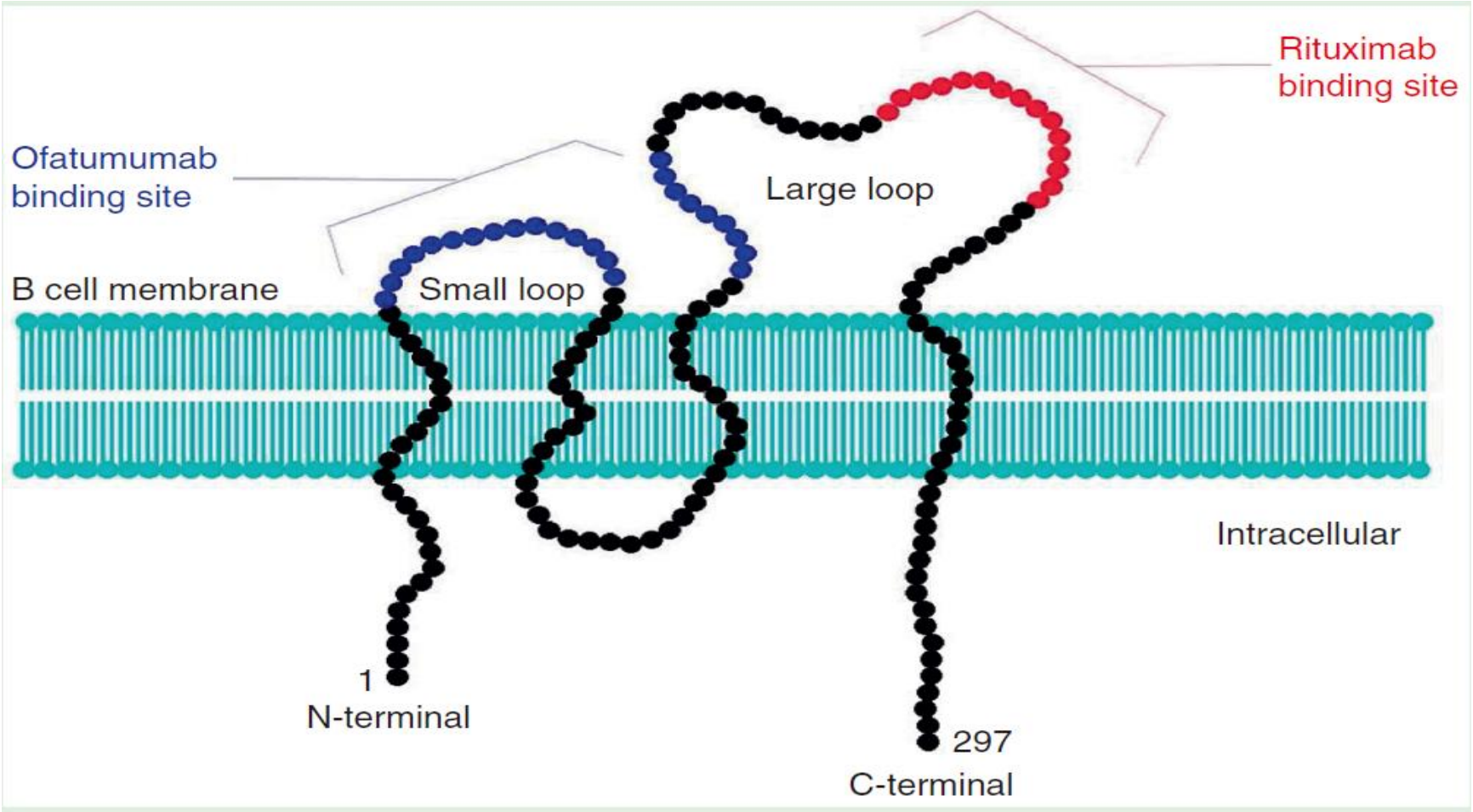
Second-line and Subsequent Therapy
- Chemoimmunotherapy (as listed under first-line therapy)
- Rituximab
- Lenalidomide ± rituximab
- Radioimmunotherapy[d,e] (category 1)
- Idelalisib[g]
- Fludarabine[h] + rituximab
- RFND[h,i] (rituximab, fludarabine, mitoxantrone, dexamethasone)
- See Second-line Therapy for DLBCL (BCEL-C 2 of 4) without regard to transplantability

Second-line Consolidation or Extended Dosing
- Rituximab maintenance 375 mg/m² one dose every 12 wks for 2 years (category 1) (optional)
- High-dose therapy with autologous stem cell rescue
- Allogeneic stem cell transplant for highly selected patients
- Obinutuzumab maintenance for rituximab-refractory disease (category 2B) (1 g every 8 wks for total of 12 doses)

For patients with locally bulky or locally symptomatic disease, consider ISRT 4–30 Gy ± additional systemic therapy.

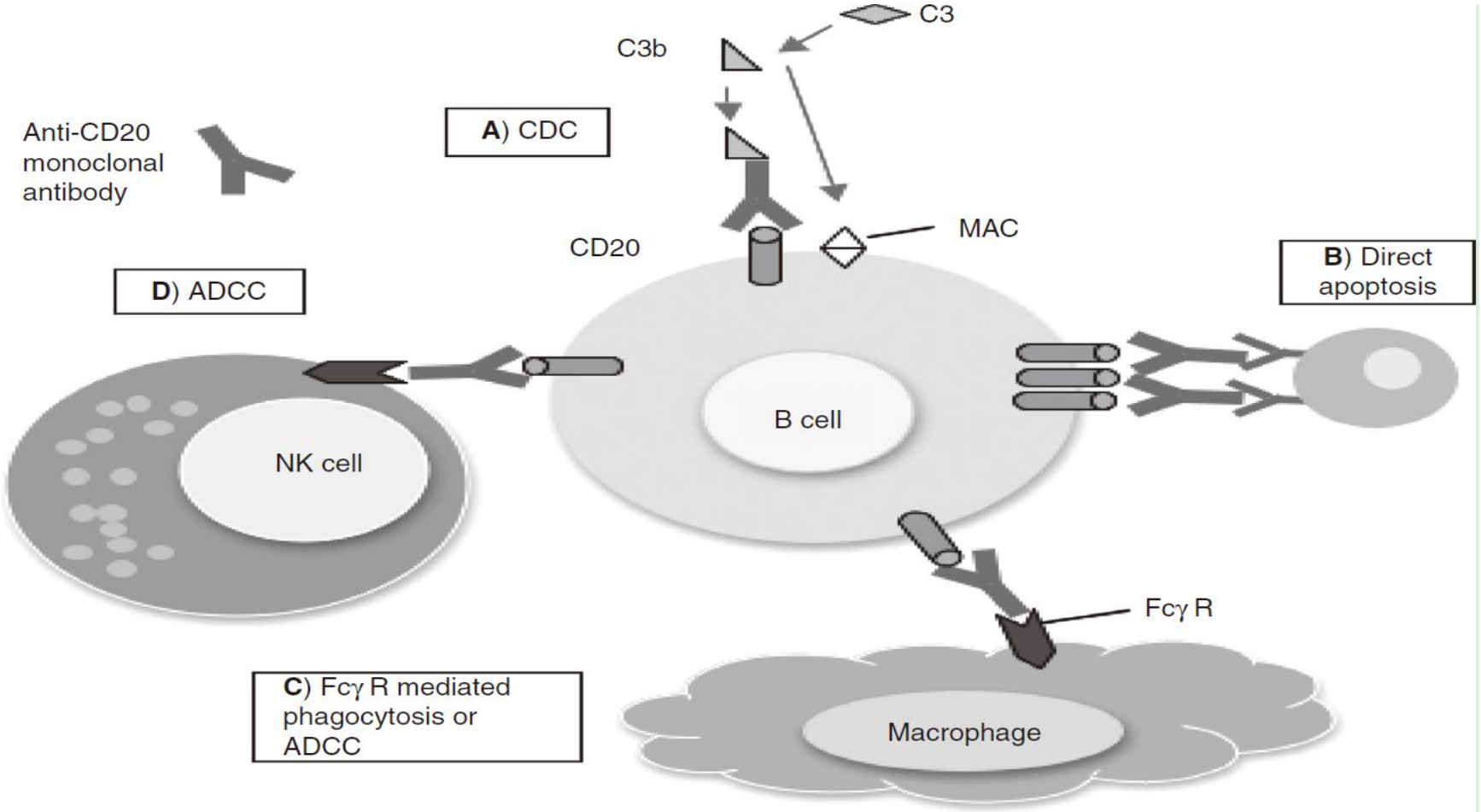
Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

Structure of CD20 molecule



Chaudhry M, et al. Expert Rev. Hematol. 2015,8(6),33–42

Mechanism of action of anti-CD20 mAb



Chaudhry M, et al. Expert Rev. Hematol. 2015,8(6),33–42

Rituximab Chimeric Anti-CD20 Monoclonal Antibody Therapy for Relapsed Indolent Lymphoma: Half of Patients Respond to a Four-Dose Treatment Program

Table 1. Patient Features and Response

Feature	No. of Patients	% CR + PR	P
All patients	166	48	—
Assessable patients*	151	50	—
Age ≥ 60 years	67	51	NS
Sex: male	95	48	NS
Histology			
Small lymphocytic	30	13	< .011
Follicular small cleaved	60	60	
Follicular mixed	48	60	
Follicular large cell	10	60	
Other‡	3	33	
Elevated LDH§	46	43	NS
Elevated β_2-microglobulin§	41	56	NS
Bulk§			
< 5 cm	88	56	NS
≥ 5 cm	61	43	
Marrow§			
Negative	66	61	.03
Positive	83	42	
bcl-2 in peripheral blood¶			
Negative	62	52	.04
Positive	55	71	
bcl-2 in bone marrow¶			
Negative	60	52	.05
Positive	52	71	
≥ 2 extranodal sites	75	39	.01

Table 3. Adverse Events During Therapy

Event	NCI Grade 1-2	NCI Grade 3	NCI Grade 4	% of Patients
Any	599	18	2	84
General				
Fever	84	—	—	43
Chills	51	2	—	28
Headache	26	1	—	14
Asthenia	25	—	—	13
Pain	22	—	—	11
Pruritus	21	1	—	13
Rash	16	—	—	10
Urticaria	9	1	—	6
Angioedema	27	1	—	14
Dizziness	11	—	—	6
Digestive				
Nausea	34	1	—	18
Vomiting	13	1	—	8
Diarrhea	10	—	—	4
Respiratory				
Bronchospasm	15	1	—	8
Dyspnea	1	1	—	1
Rhinitis	14	1	—	7
Cough increase	4	1	—	3
Cardiovascular				
Hypotension	18	1	—	10
Arrhythmia	5	2	1	2
Hematologic				
Anemia	1	1	—	1
Thrombocytopenia	5	1	—	3
Leukopenia	12	1	—	7
Neutropenia	6	—	1	4

McLaughlin P J Clin Oncol 1998 Aug;16(8):2825-33

Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly × 4 schedule

Michele Ghielmini, Shu-Fang Hsu Schmitz, Sergio B. Cogliatti, Gabriella Pichert, Jörg Hummerjohann, Ursula Waltzer, Martin F. Fey, Daniel C. Betticher, Giovanni Martinelli, Fedro Peccatori, Urs Hess, Emanuele Zucca, Roger Stupp, Tibor Kovacsovics, Claudine Helg, Andreas Lohri, Mario Bargetzi, Daniel Vorobiof, and Thomas Cerny, for the Swiss Group for Clinical Cancer Research (SAKK)

Standard schedule (R qW × 4)

R/S

R

Prolonged schedule (R q2M × 4)

Obs

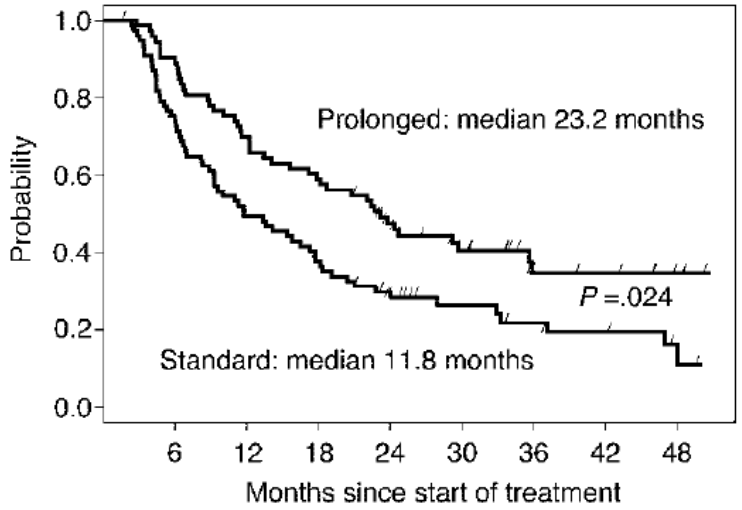


Figure 3. EFS of all randomized patients according to study arm. The curves are parallel, suggesting that the gain acquired during the 9 months of prolonged treatment is maintained over time.

Ghielmini M, et al. Blood, 2004;103:4416-4423

Long-Term Follow-Up of Patients With Follicular Lymphoma Receiving Single-Agent Rituximab at Two Different Schedules in Trial SAKK 35/98

Giovanni Martinelli, Shu-Fang Hsu Schmitz, Urs Utiger, Thomas Cerny, Urs Hess, Simona Bassi, Emmie Okkinga, Roger Stupp, Rolf Stahel, Marc Heizmann, Daniel Vorobiof, Andreas Lohri, Pierre-Yves Dietrich, Emanuele Zucca, and Michele Ghielmini

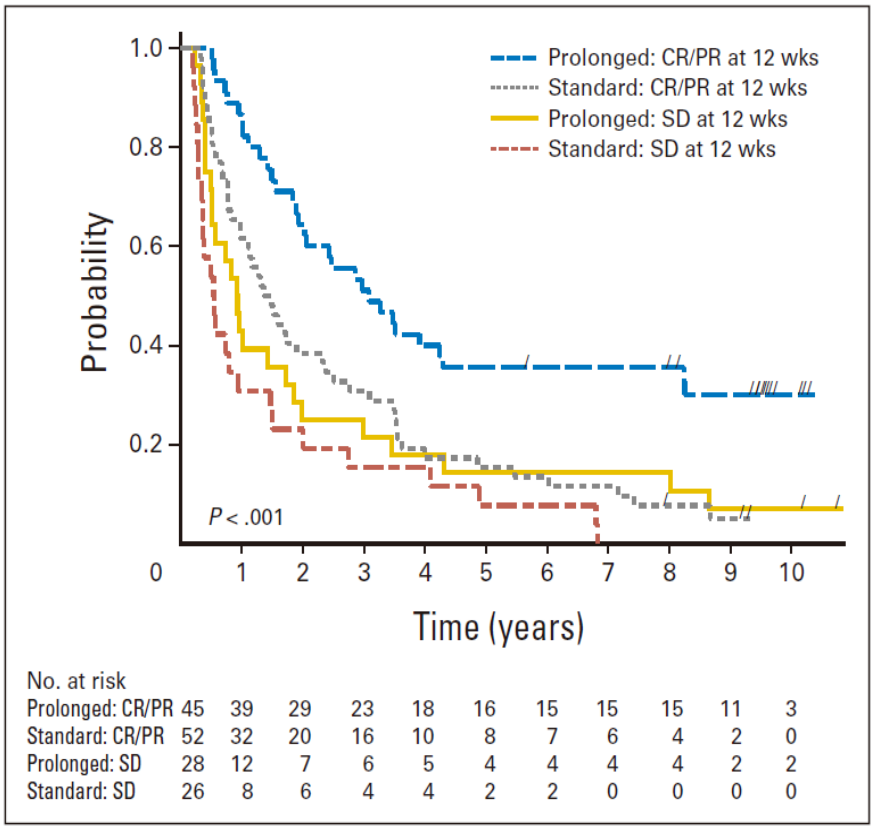


Fig 2. Event-free survival by treatment arm according to response to the induction treatment (complete response [CR]/partial response [PR] or stable disease [SD]).

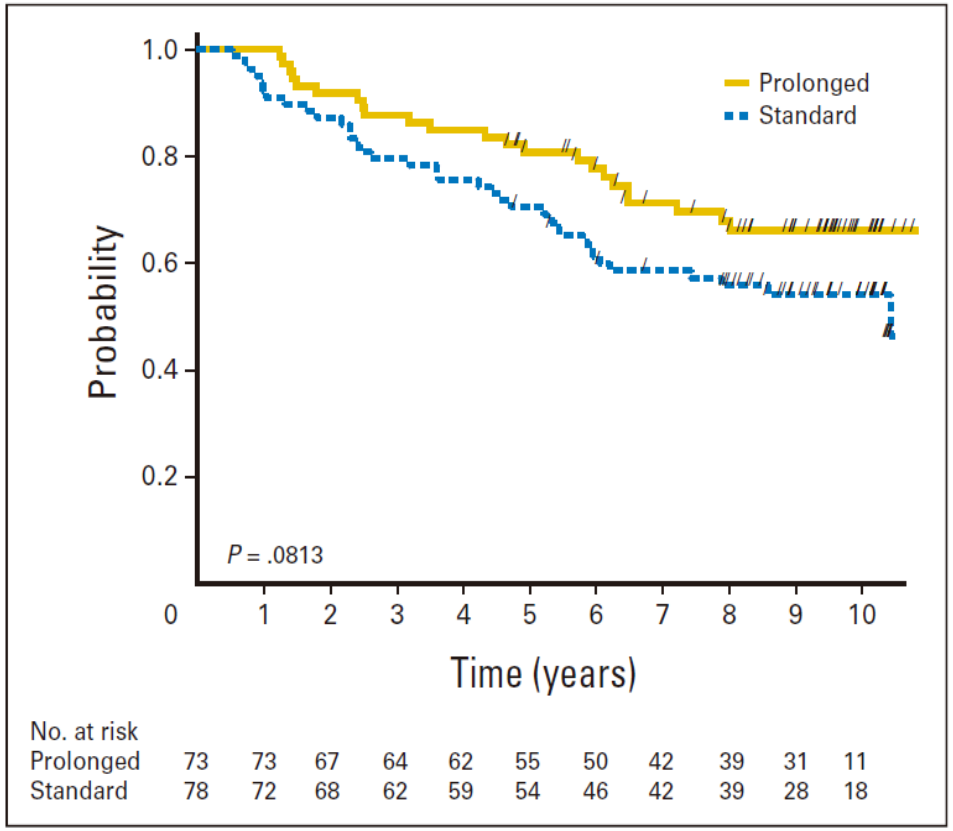


Fig 4. Overall survival by treatment arm.

Martinelli G, et al. Clin Oncol, 2010, 28:4480-4484

Rituximab as First-Line and Maintenance Therapy for Patients With Indolent Non-Hodgkin's Lymphoma

By John D. Hainsworth, Sharlene Litchy, Howard A. Burris III, Daniel C. Scullin, Jr, Steven W. Corso, Denise A. Yardley, Lisa Morrissey, and F. Anthony Greco

Table 2. Response to Treatment (60 assessable patients)

Response	At Week 6		Best Response (after one or more maintenance courses)	
	No. of Patients	%	No. of Patients	%
Complete	4	7	22	37
Partial	24	40	22	37
Stable	27	45	11	18
Progression	5	8	5	8

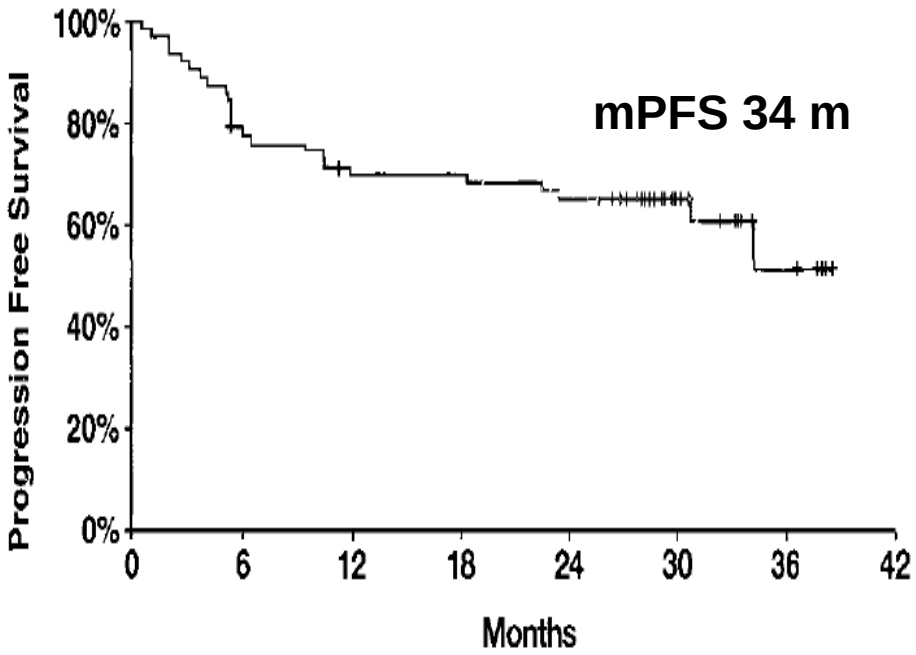


Fig 1. Progression-free survival for all patients.

Hainsworth JD, et al. J Clin Oncol, 2002, 20:4261-4267

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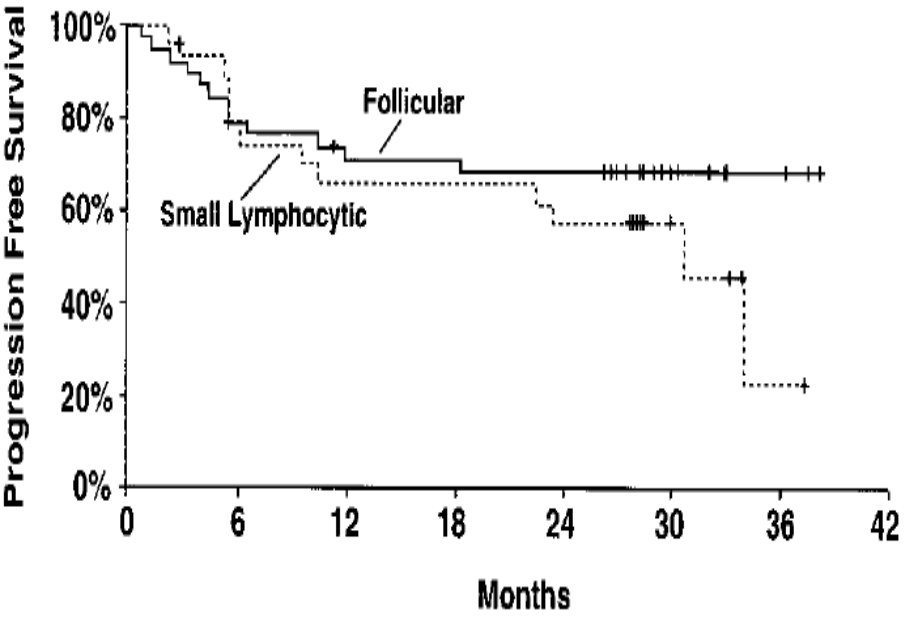

Fig 2. Survival comparisons of patient subsets.

Table 3. Treatment-Related Toxicity, First Course of Rituximab (62 patients/245 doses)

	Grade 1/2		Grade 3/4	
Toxicity	No. of Patients	%	No. of Patients	%
Infusion related				
Chills/rigors	16	26	1	2*
Fever	11	18		
Nausea/vomiting	13	21		
Flushing	5	8	1	2
Hypotension	3	5		
Headache	3	5		
Chest pain	1	2	1	2*
Angioedema	1	2		
Bronchospasm	1	2		
Other				
Fatigue	18	29		
Anemia	4	6		
Leukopenia	2	3		

*Both toxicities experienced by the same patient during the first rituximab infusion, resulting in removal from study.

Hainsworth JD, et al. J Clin Oncol, 2002, 20:4261-4267

Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial

Kirit M Ardeshna, Wendi Qian, Paul Smith, Nivette Braganca, Lisa Lowry, Pip Patrick, June Warden, Lindsey Stevens, Christopher F E Pocock, Fiona Miall, David Cunningham, John Davies, Andrew Jack, Richard Stephens, Jan Walewski, Burhan Ferhanoglu, Ken Bradstock, David C Linch

	Watch and wait (n=187)	Rituximab induction (n=84)	Maintenance rituximab (n=192)
Age (years)	60 (28–82)	60 (33–86)	60 (27–87)
Sex			
Men	79 (42%)	34 (40%)	99 (52%)
Women	108 (58%)	50 (60%)	93 (48%)
Eastern Cooperative Oncology Group performance status			
0	169 (90%)	77 (92%)	174 (91%)
1	18 (10%)	7 (8%)	18 (9%)
Follicular lymphoma grade			
1	89 (48%)	37 (44%)	92 (48%)
2	80 (43%)	35 (42%)	81 (42%)
3a	18 (10%)	12 (14%)	19 (10%)
Stage			
I	0 (0%)	1 (1%)	0 (0%)
II	36 (19%)	19 (23%)	41 (21%)
III	67 (36%)	31 (37%)	72 (38%)
IV	84 (45%)	33 (39%)	79 (41%)
Bone marrow trephine			
Normal	100/182 (55%)	52/83 (63%)	109/188 (58%)
Abnormal	82/182 (45%)	31/83 (37%)	79/188 (42%)
Lactate dehydrogenase concentration			
Normal	178 (95%)	80/83 (96%)	183 (95%)
Abnormal	9 (5%)	3/83 (4%)	9 (5%)
Follicular Lymphoma International Prognostic Index score			
0	16 (9%)	8/83 (10%)	19 (10%)
1	52 (28%)	28/83 (34%)	47 (24%)
2	67 (36%)	32/83 (39%)	85 (44%)
3	50 (27%)	13/83 (16%)	38 (20%)
4	2 (1%)	2/83 (2%)	3 (2%)
β2 microglobulin			
≤2·4 mg/L	117/150 (78%)	50/65 (77%)	118/159 (74%)
>2·4 mg/L	33/150 (22%)	15/65 (23%)	41/159 (26%)

Ardeshna KM Lancet Oncol 2014;15(4):424-35

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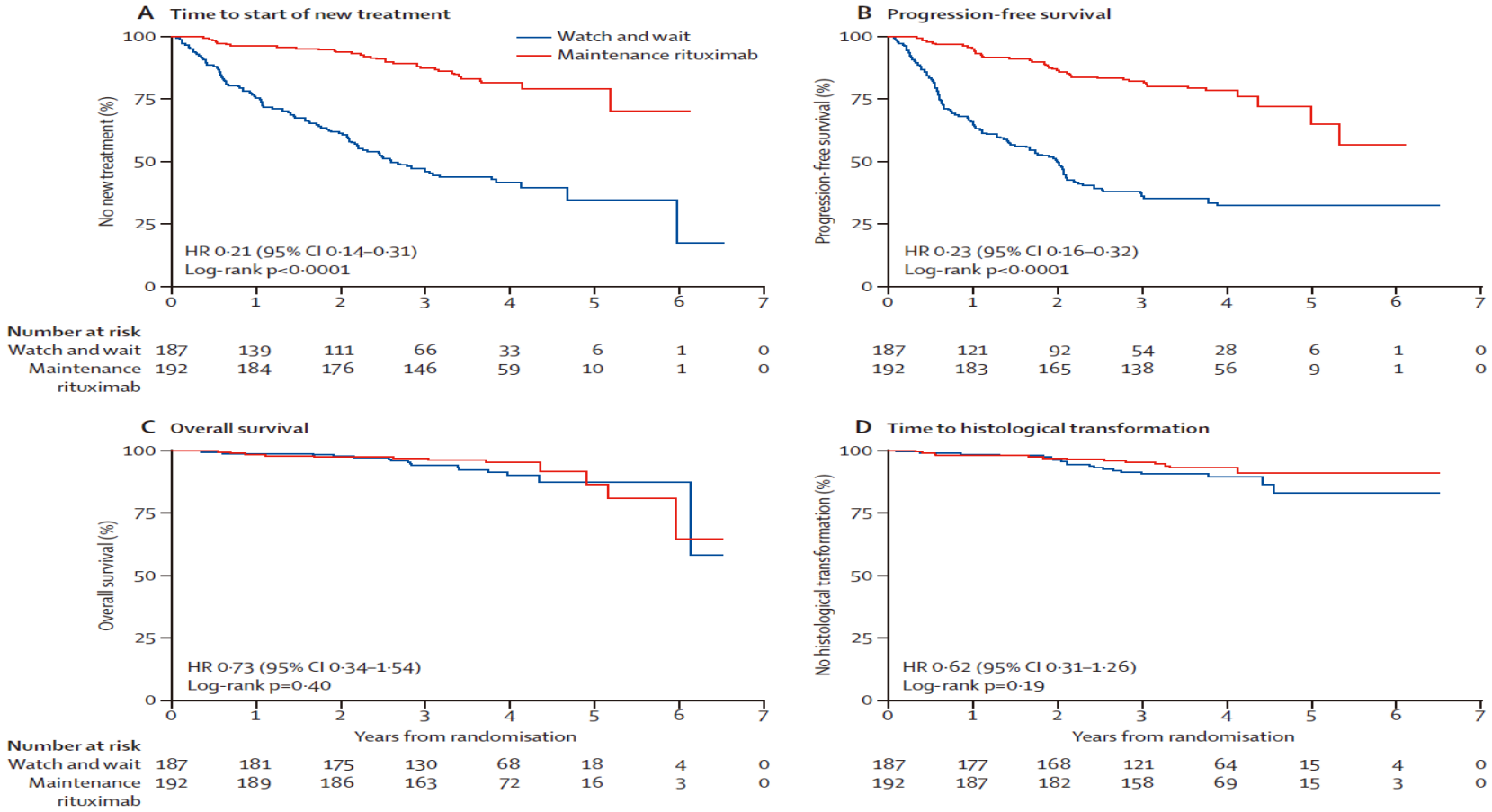

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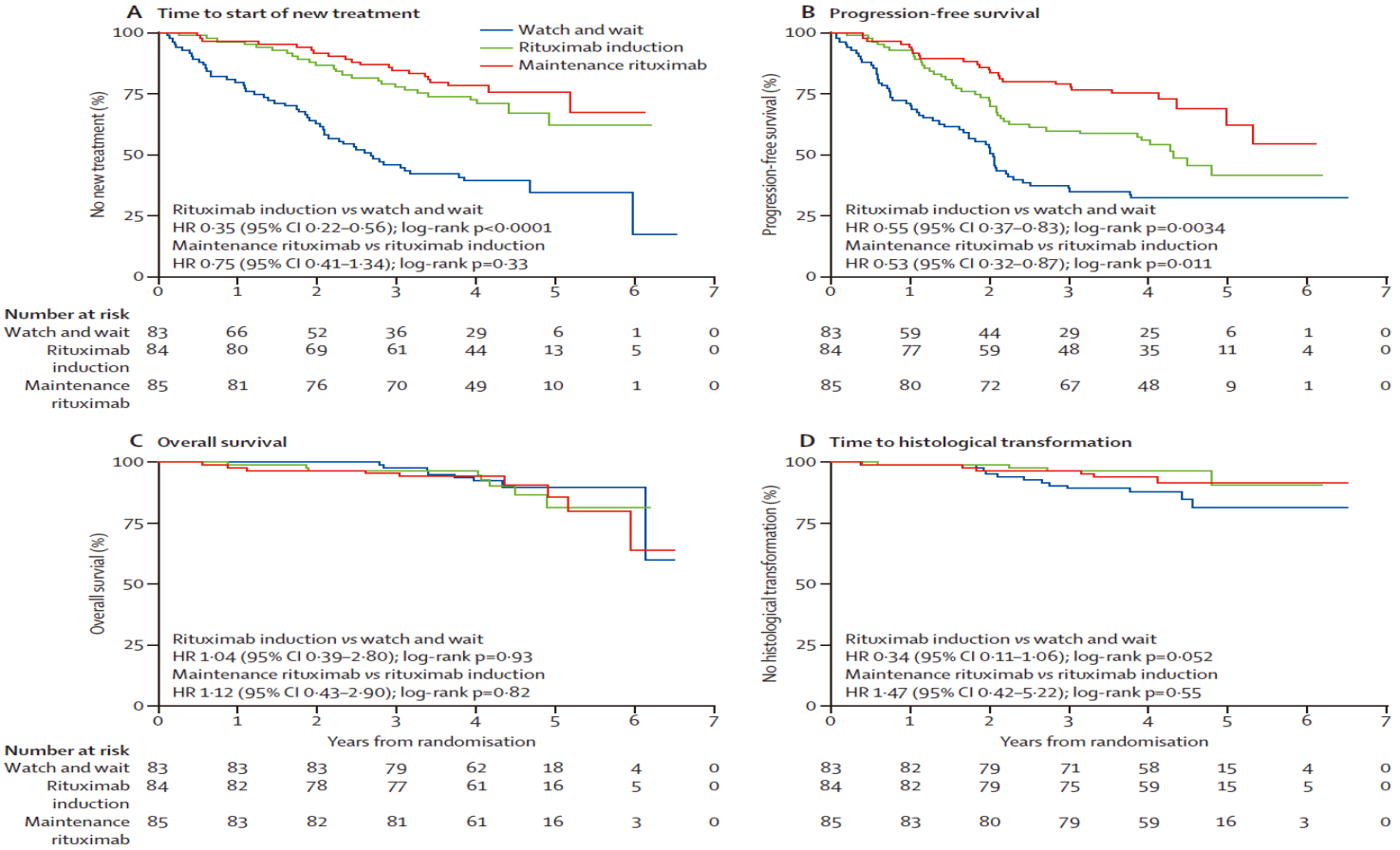

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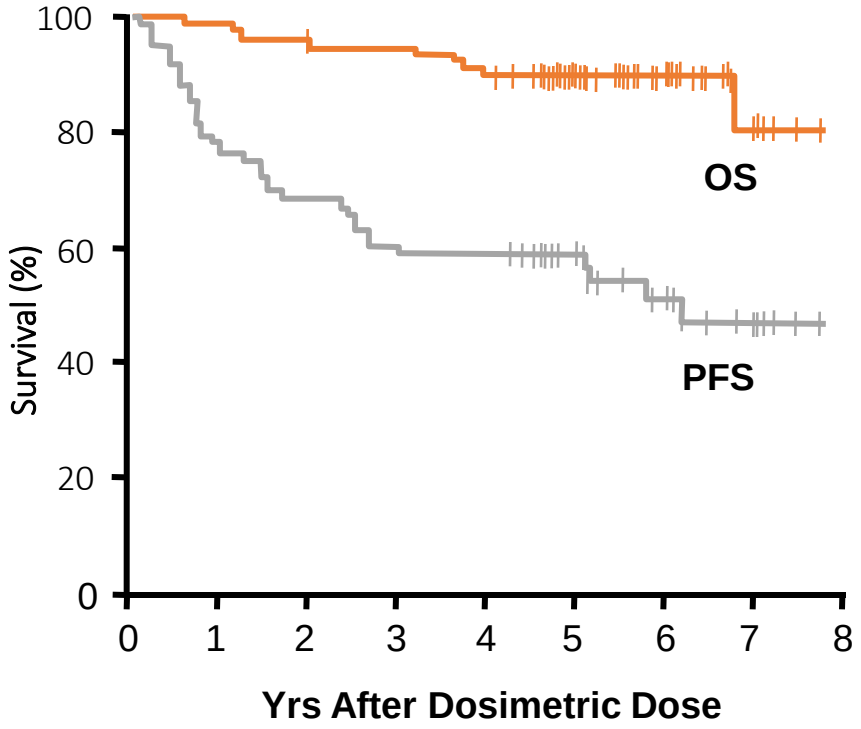
- **MR vs WW: QoLsignificant improvements (Mental adjustment to Cancer scale score and Illness Coping Style score)**
- **R induction vs WW: QoL no difference**
- **SAE: R 18 (R induction 4, MR 14; G3/4: five infections, three allergic reactions, and four cases of neutropenia), all of which fully resolved.**
- **Rituximab monotherapy should be considered as a treatment option.**

Ardeshna KM Lancet Oncol 2014;15(4):424-35

Frontline Therapy With ^{131}I-Tositumomab

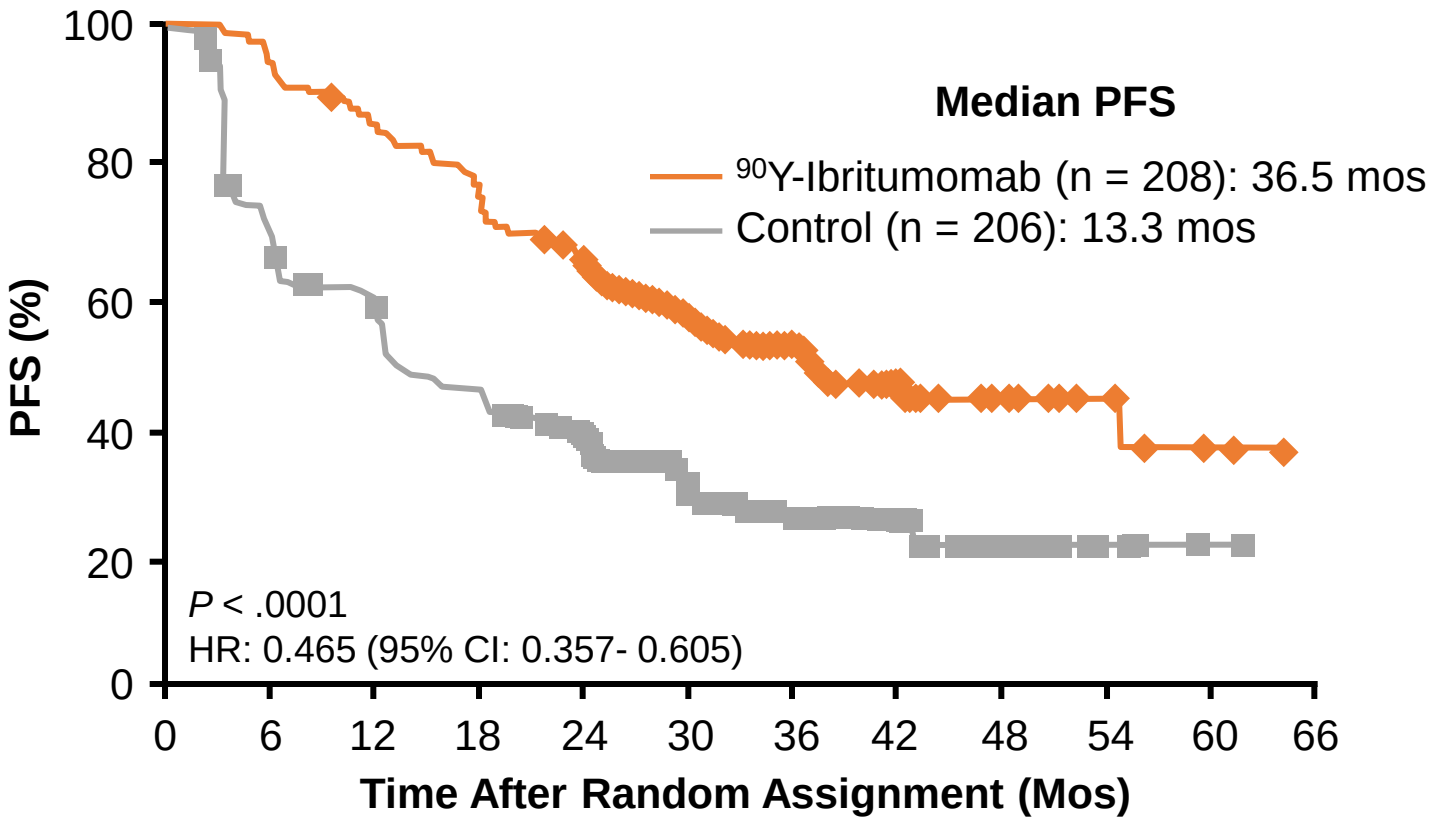
- N = 76 patients with stage III/IV untreated FL (phase II study)
  - Median follow-up: 5.1 yrs

Outcome	Result
ORR, %	95
Median DOR	NR
Complete response, %	75
Median PFS, yrs	6.1
5-yr PFS, %	59



Kaminski MS, et al. N Engl J Med. 2005;352:441-449.

^{90}Y-Ibritumomab in Advanced FL: PFS (Phase III FIT Study)



Median observation time: 3.5 yrs

Morschhauser F, et al. J Clin Oncol. 2008;26:5156-5164

Ofatumumab

Table 3. Clinical trials evaluating ofatumumab in indolent lymphomas.

Study	Number of patients (histotypes)	Population	Treatment schedule	ORR% (CR)	PFS (months)
Hagenbeek *et al.* [2008]	40 (FL)	Rel/Ref	Ofatumumab (300 to 1000 mg x4, q7)	43	8.8
Czuczman *et al.* [2012a]	116 (FL)	Rituximab-Ref	Ofatumumab (500 or 1000 mg x8, q7)	13 *versus* 10	5.8
Czuczman *et al.* [2012b]	58 (FL)	1st-line	Ofatumumab (500 *versus* 1000 mg + CHOP x6, q21)	90 (24) *versus* 100 (38)	

Obinutuzumab

Table 4. Clinical trials evaluating obinutuzumab (GA-101) in indolent lymphomas.

Study	Number of patients (histotypes)	Population	Treatment schedule	ORR% (CR)	PFS (months)
Salles *et al.* [2012]	21 (13 FL, 2 LPL, 1 SLL, 4 MCL, 1 DLBCL)	Rel/Ref	Obinutuzumab (50 to 2000 mg x9, q7)	43	
Salles *et al.* [2011]	40 (34 FL, 6 iNFL)	Rel/Ref	Obinutuzumab (1600/800 *versus* 400/400 mg x9, q7)	60 (20) *versus* 35 (7)	11.8 *versus* 6
Sehn *et al.* [2012]	22 (10 FL, 2 SLL, 5 CLL, 1 MCL, 4 DLBCL)	Rel/Ref	Obinutuzumab (100 to 2000 mg x4 q7 + 8 q12)	22	
Sehn *et al.* [2011]	175 (149 FL, 26 iNFL)	Rel/Ref	Obinutuzumab (1000 mg) *versus* Rituximab 375 mg/m^2) x4, q7	43 *versus* 28	
Radford *et al.* [2011]	56 (FL)	Rel/Ref	[G-CHOP] *versus* [G-FC] (Obinutuzumab 1600/800 *versus* 400/400 mg)	96.4 (39) *versus* 92.9 (50)	

Brentuximab vedotin

Table 1. Selected studies of BV for HL after auto-SCT

Study	Year reported	Disease state	Treatment	Study type	Patients, *n*	Key results
Younes et al[7]	2010	Relapse (after auto-SCT)*	BV for 3 weeks (dose escalation)	Phase 1	42*	86% tumor regression
Younes et al[12]	2012	Relapse after auto-SCT	BV 1.8 mg/kg for 3 weeks (max 16 cycles)	Phase 2	102	ORR 75%; CR 34%; PFS 5.6 months
Moskowitz et al[19]	2014†	Maintenance after auto-SCT	BV 1.8 mg/kg for 3 weeks (max 16 cycles) versus placebo	Phase 3	327	Median 15 cycles administered
Chen et al[22]	2012	Bridge to allo-SCT	BV, dosing not reported	Retrospective	17	1 year post-SCT PFS 92%
Anderlini et al[23]	2013	Bridge to allo-SCT	BV, dosing not reported	Retrospective	14	1.5 year post-SCT PFS 80%
Gopal et al[28]	2012	Relapse after allo-SCT	BV 1.2 or 1.8 mg/kg for 3 weeks (1–16, 8)	Retrospective	25	ORR 50%; CR 38%; PFS 7.8 months
Bartlett et al[17]	2014	Relapsed after BV‡	BV 1.8 mg/kg for 3 weeks	Phase 2	21	ORR 60%; CR 30%; PFS 9.9 months

Graf SA, et al. Hematology Am Soc Hematol Educ Program. 2014;2014(1):151-7

Brentuximab vedotin

Table 3 Overall Response Rates (ORRs) Reported for FDA-Approved Agents, by Common Peripheral T-Cell Lymphoma (PTCL) Subtypes

PTCL Subtype	Pralatrexate (2009)[28]	Brentuximab Vedotin (2011)[16,30]	Romidepsin (2011)[29]	Belinostat (2014)[32,33]
PTCL-NOS	32%	33%[a]	29%	23%
AITL	8%	54%[a]	30%	46%
ALCL	29%	86%	24%	15%

[a]Not FDA-approved for this subtype of PTCL.

AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large-cell lymphoma; FDA = US Food and Drug Administration; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified.

ORR data are from Horwitz SM et al. Blood. 2014.[31]

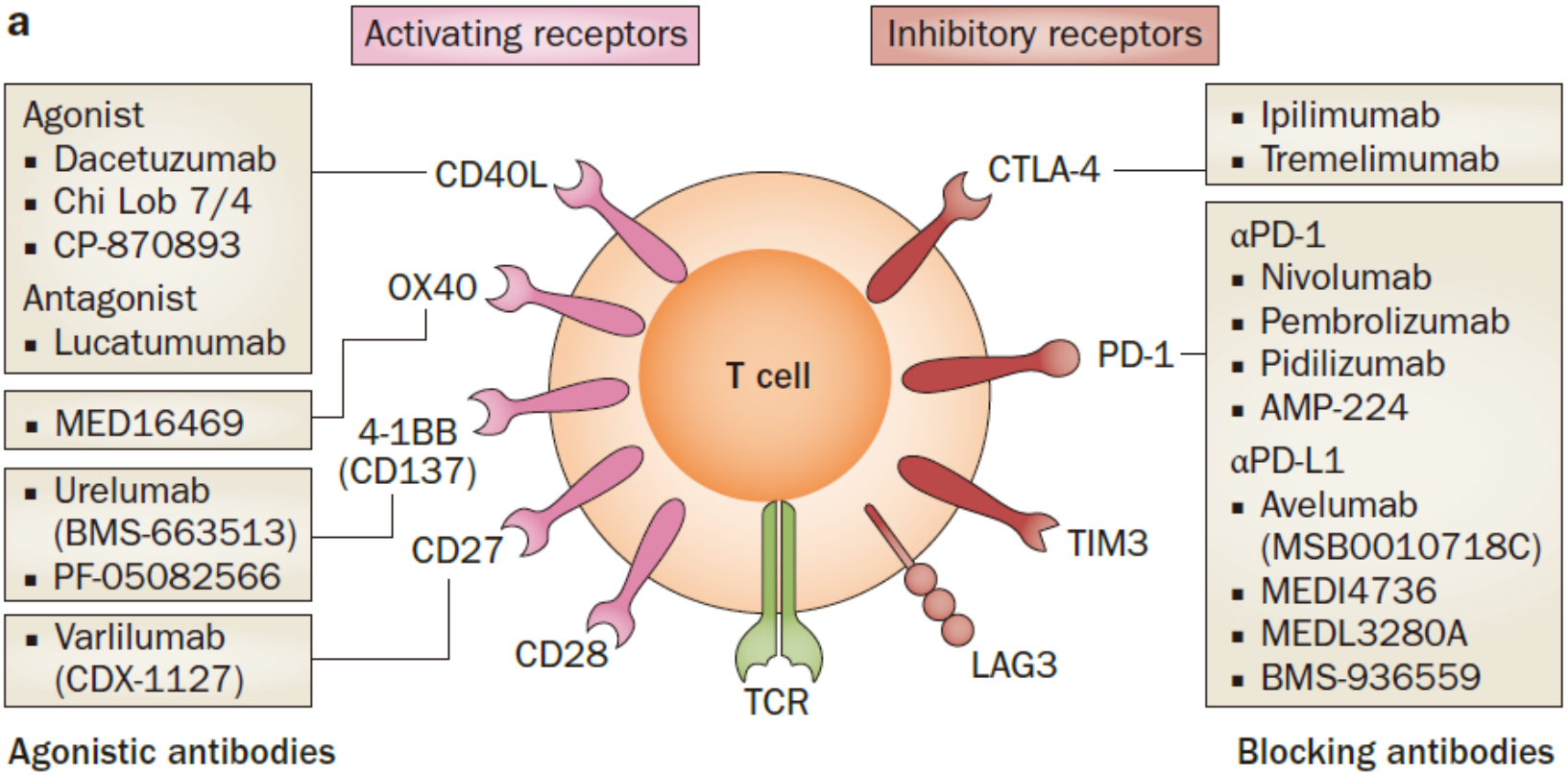
Lunning MA.Oncology (Williston Park). 2015;29(8):545-50

mAbs

Regimen	Pts	N	ORR (%)	CRR (%)	PFS (%)	OS (%)	G3/4 AE (%)
Ofatumumab (Ramdomized Phase II)	FL (1st line)	15 vs 36	500 mg: 60 vs 1000 mg: 86.6	13.3 vs 13.3	85.1 vs 96.6 @1y	-	G3: N 1 case IRE 25
Pembrolizumab (Phase II)	R/R cHL (after SGN-35 failure)	31	65 (transplant failure 73, transplant ineligibity 44)	16	69 @24w	-	16

Pitcher B, et al. ASH 2015, Abstract 2741
Armand P, et al. ASH 2015. Abstract 584

Immune-checkpoint axis



Batlevi, C. L. et al. Nat. Rev. Clin. Oncol. advance online publication 3 November 2015

Checkpoint inhibitors and lymphoma

Table 3 | Clinical efficacy of immune-checkpoint inhibitors

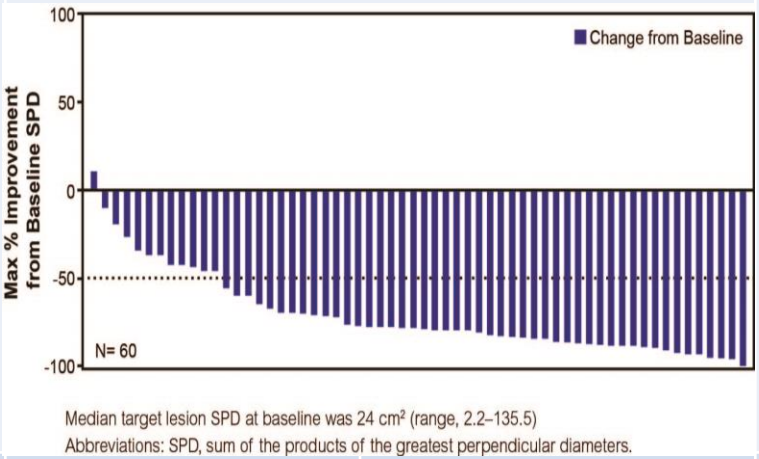
Drug (manufacturer) and disease	Number of patients	Treatment schedule	Response rate				Median duration of response (range)	Survival outcomes
			ORR (%)	CR (%)	PR (%)	SD (%)		
Nivolumab (BMS, USA)								
B-NHL[145]*	31‡	1 mg/kg or 3 mg/kg week 1, week 4, and every 2 weeks thereafter	26	10	16	52	NA	NA
DLBCL[145]*	11‡	1 mg/kg or 3 mg/kg week 1, week 4, and every 2 weeks thereafter	36	18	18	27	22 weeks (6–77 weeks)	NA
Follicular lymphoma[145]*	10‡	1 mg/kg or 3 mg/kg week 1, week 4, and every 2 weeks thereafter	40	10	30	60	Not reached (27–82 weeks)	NA
T-NHL[145]	23‡	3 mg/kg week 1, week 4, and every 2 weeks thereafter	17	0	17	43	NA	NA
Hodgkin lymphoma[145,148]	23§	1 mg/kg or 3 mg/kg week 1 and 4, and every 2 weeks thereafter	87	26	61	13	NA	PFS: 86% at 24 weeks OS: median not reached
Pembrolizumab (Merck, USA)								
Hodgkin lymphoma[150]	29‡	10 mg/kg every 2 weeks	66	21	45	21	Not reached (1–185 days)	NA
Ipilimumab (BMS, USA)								
B-NHL[154]	18	3 mg/kg → 1 mg/kg×3 doses (or 3 mg/kg×4 doses in 6 patients)	11.1	5.6	5.6	NA	NA	NA
Hodgkin lymphoma (post allo SCT)[172]	14§	0.1–3.0 mg/kg	14.3	14.3	0	14.3	NA	NA

Batlevi, C. L. et al. Nat. Rev. Clin. Oncol. advance online publication 3 November 2015

Agenda

- mAb monotherapy
- **mAb + X**
- Our experience

mAbs + X

Regimen	Pts	N	ORR (%)	CRR (%)	PFS (%)	OS (%)	G3/4 AE (%)
Rituximab + Venetoclax (Phase I)	R/R CLL	49	86	47	83 @2y	94 @2y	76
Rituxiamb+ Ibrutinib (Phase II)	FL (1st line)	60	82  Median target lesion SPD at baseline was 24 cm² (range, 2.2–135.5) Abbreviations: SPD, sum of the products of the greatest perpendicular diameters.	30	86 @12m	98 @12m	48
Rituximab + Bortezomib vs Rituximab (Phase III)	R RN/ RS FL	676	63 vs 49 (P<0.004)	25 vs 18 (NS)	mPFS* 12.8m vs 11.0 m	1y OS: 90.1 Vs 90.5	46 vs 21**

*** P<0.039, without clinical benefit**

*** *N 11% vs 4%, I 11% vs 4%, D 7% vs 0, HZ 4% vs <1%, N/V 3% vs <1%, T 3% vs <1%**

Ma S, et al. ASH 2015. Abstract 830.
Fowler NH, et al. ASH 2015. Abstract 470.
Coiffier B, et al. Lancet Oncol 2011;12(8):773-84

mAbs + X

Regimen	Pts	N	ORR (%)	CRR (%)	PFS (%)	OS (%)	G3/4 AE (%)
R^2 (Phase II)	R/R DLBCL FLG3 TL	32 4 9	28.1 25.0 55.6	22.2	mPFS 3.7 m 22.5 @ 6 m 11.3 @ 12m	43.5 @ 1 y 38.9 @ 2 y 15.4 @ 5 y mOS 10.8 m Responders: 50.3 m Non-responders: 6.6m	-
R^2 (Phase II)	iNHL (1st line)	110 50FL 30MZL 30CLL	90 FL:98	63 FL:87	mPFS 53.8 m FL: 78.5 @ 3 y	96.1 @3 y	N 35, MP 9, R 7%, C/D 7, F 5, T 5, T 4
R^2 (Phase II)	MCL (1st line)	38	92	64	mPFS NR 85 @2 y	97 @2 y	N 50, R 29, T 13, TF 11, A 11, SS 8, F 8

Wang Y, et al. ASH 2015, Abstract 3969
Fowler N, et al. Lancet Oncol, 2014;15(12):1311-8
Ruan J, et al. N Engl J Med. 2015;373(19):1835-44

mAbs + X

Regimen	Pts	N	ORR (%)	CRR (%)	PFS (%)	OS (%)	G3/4 AE (%)
Obinutuzumab + Lenalidomide (Phase I)	R/R iNHL	15	93	27	-	-	N 20, I 13, T 6, IRI 13

mAbs + X + Y

Regimen	Pts	N	ORR (%)	CRR (%)	PFS (%)	OS (%)	G3/4 AE (%)
R^2 + Ibrutinib (Phase I)	FL (1^{st} line)	22	91	63	84 @ 12 m	86 @ 12 m	No DLT G3/4: N 18.2, T 4.5, A 4.5; G3: R 32, AF/CP (n=1), D (n=1), FN (n=1)

Fowler NH, et al. ASH 2015. Abstract 2742
Ujjani CS, et al. ASH 2015, Abstract 471

mAbs + X + Y

Regimen	Pts	N	ORR (%)	CRR (%)	PFS (%)	OS (%)	G3/4 AE (%)
Rituximab + Bendamustine + Temsirolimus (Phase I)	R/R MCL FL	34 25 9	94 88 93	N=7 N=1 31	mPFS: 22 m NR 18.6 m	-	G3/4: L 32, N 24, T 21; 4 events: angioedema, hypopotassaemia, infection, and metabolic
Rituximab + Bendamustine + Bortezomib (Phase II)	1st line: FL MZL LPL SLL	55 38 8 5 4	94 94	65 67	75 73 @ 36 m	88 89 @36 m	G 3/4: leukopenia (29%), neutropenia (29%) and lymphopenia (16%); neuropathy (9%), diarrhea (7%), and fatigue (7%)

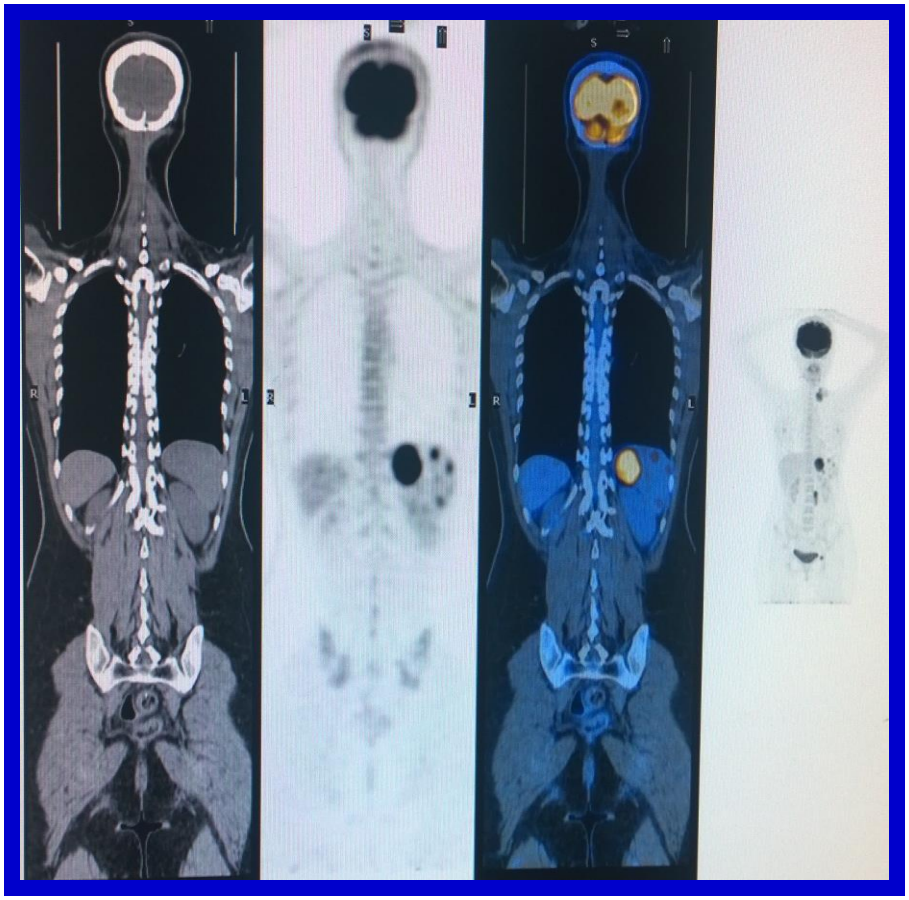
Hess G, et al. ASH 2015, Abstract 3930
Flinn IW, et al. ASH 2015, Abstract 1492

Agenda

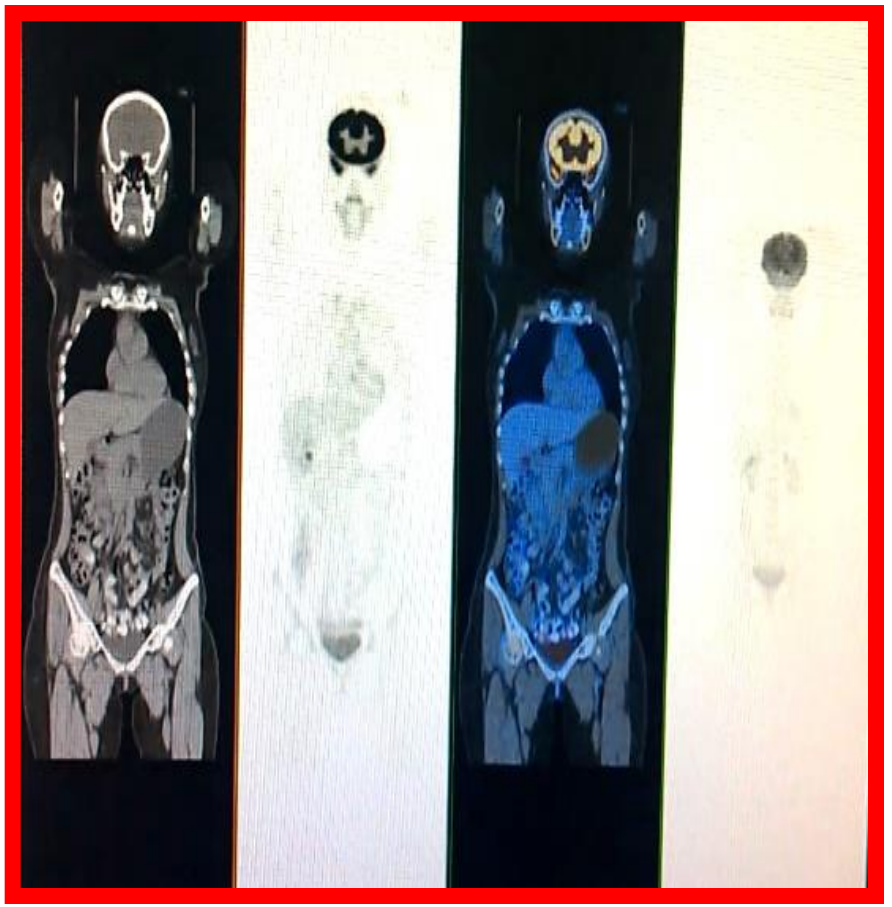
- mAb monotherapy
- mAb + X
- **Our experience**

Case 1

38 yo female, stage III, asymptomatic, non-bulky, FL (G1-2)



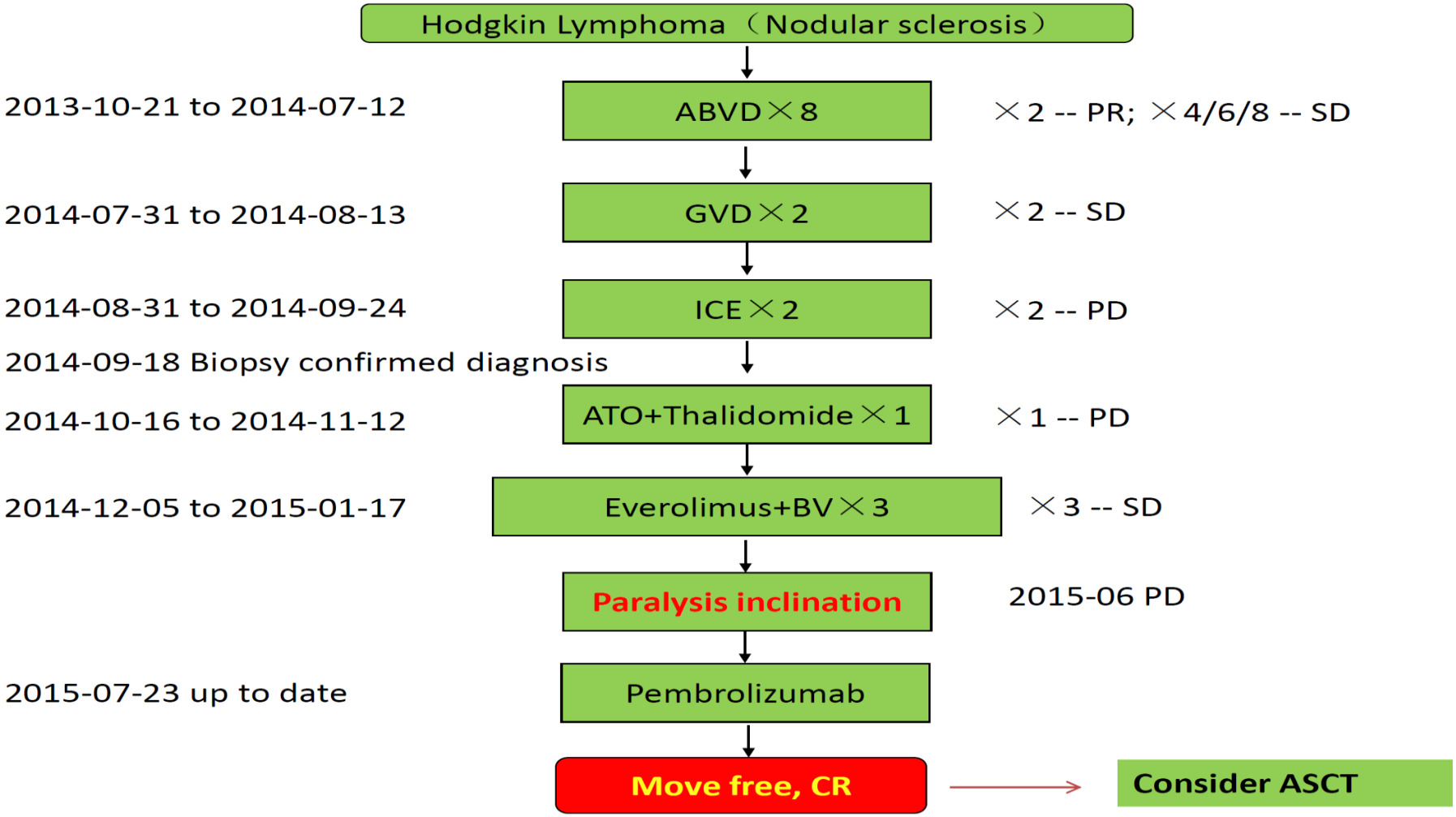
Before R



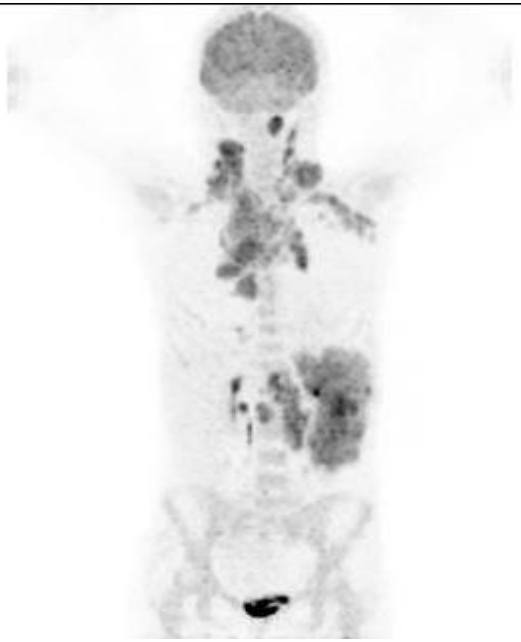
R qw×4 → MR

Case 2

21 yo female, R/R HL



2013-10-23



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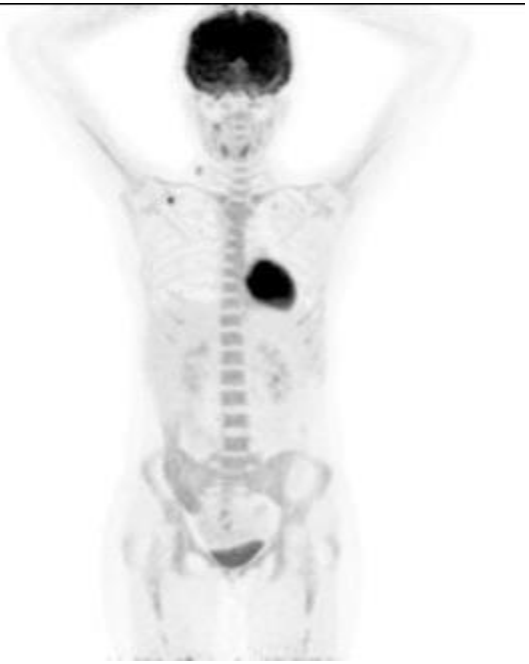

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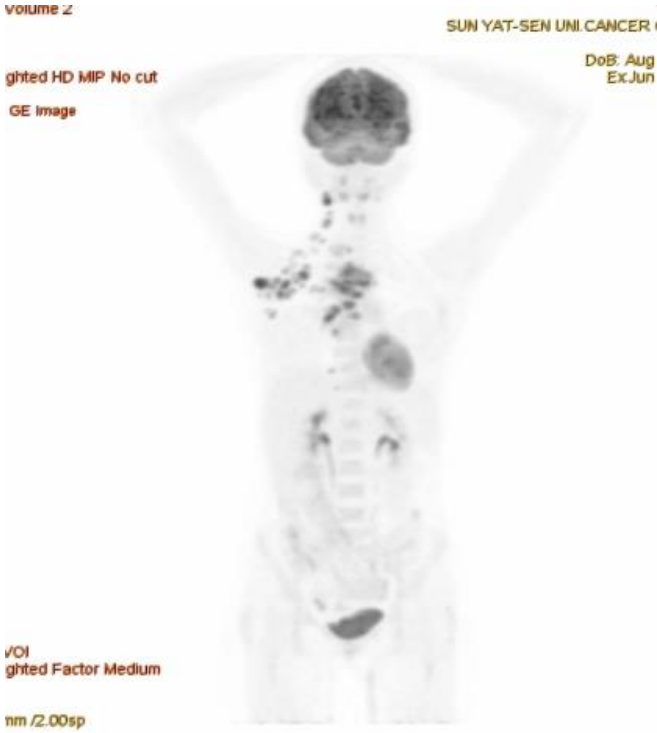

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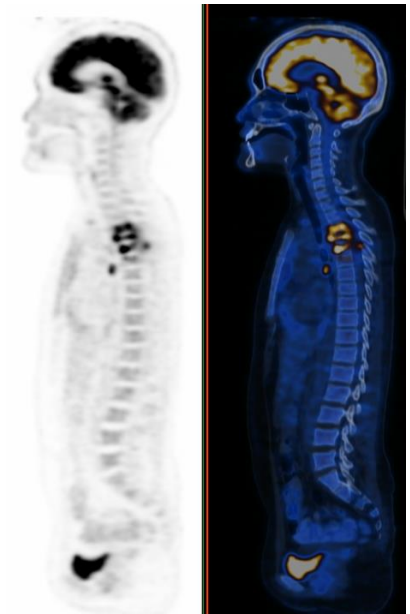

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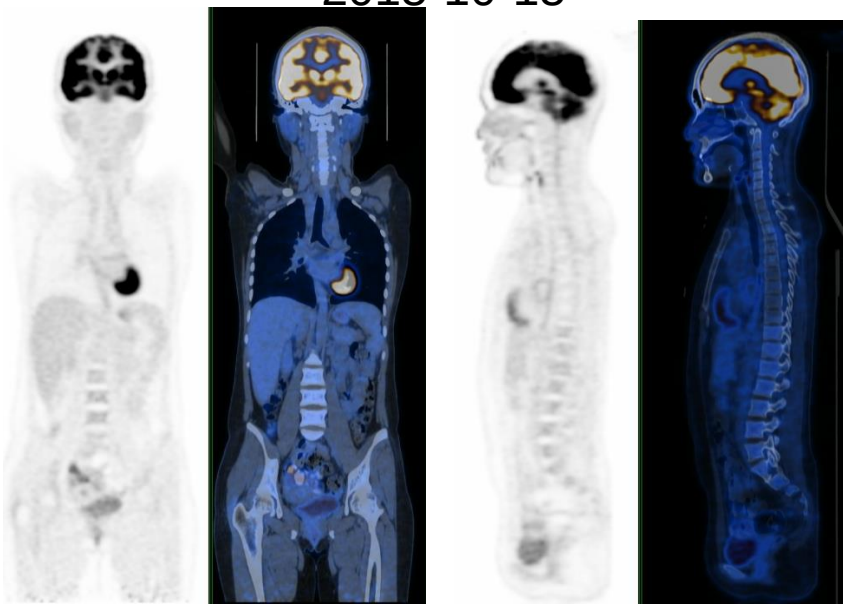


Effect of rituximab on adult Burkitt's lymphoma: a systematic review and meta-analysis

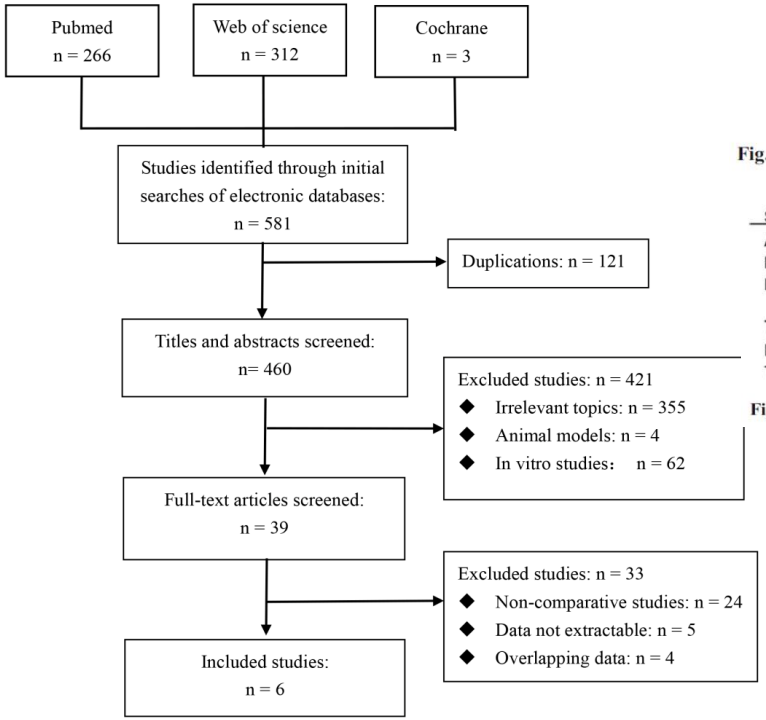


Fig 1
Flow diagram of studies identified, included and excluded

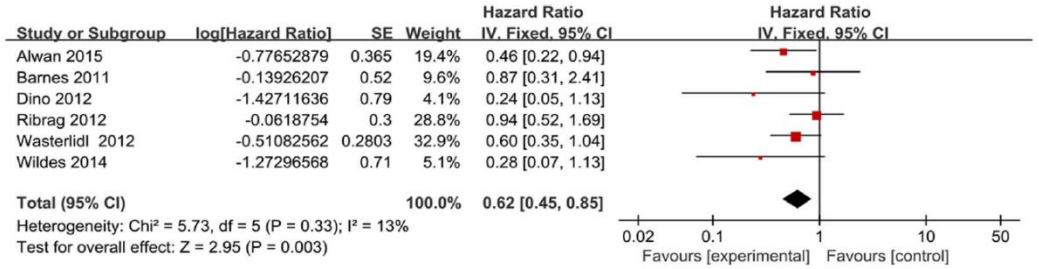


Fig. 2 Forest plot meta-analysis of 2-year OS between chemotherapy with rituximab group and chemotherapy-alone group

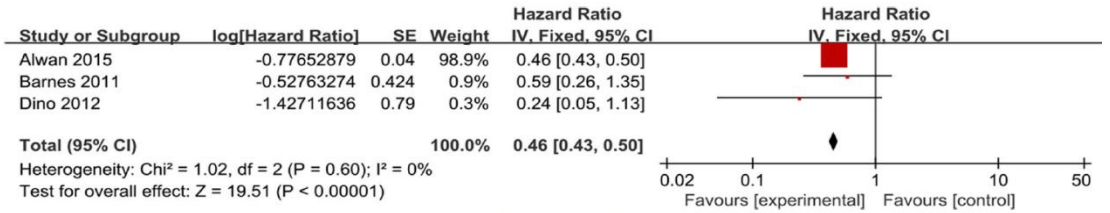


Fig. 3 Forest plot meta-analysis of 2-year OS PFS between chemotherapy with rituximab group and chemotherapy-alone group

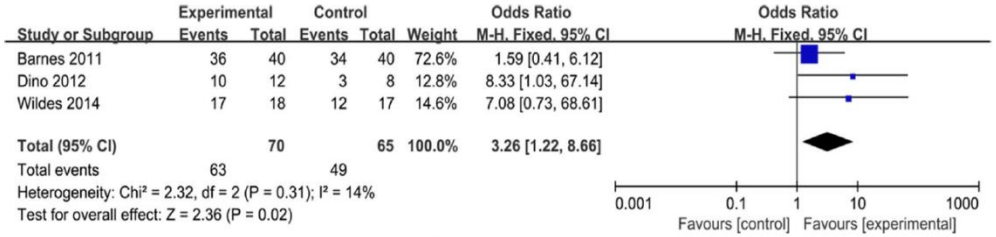


Fig. 4 Forest plot meta-analysis of CR between chemotherapy with rituximab group and chemotherapy-alone group

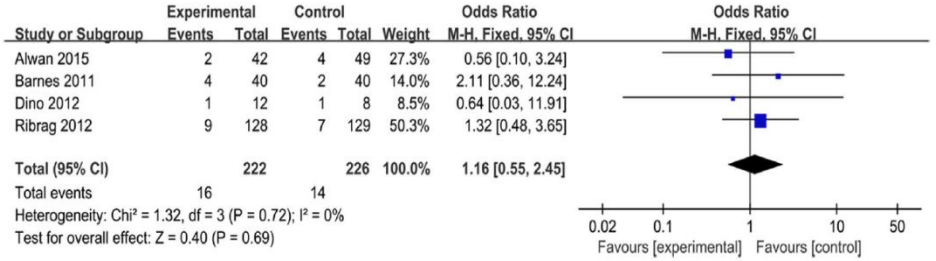
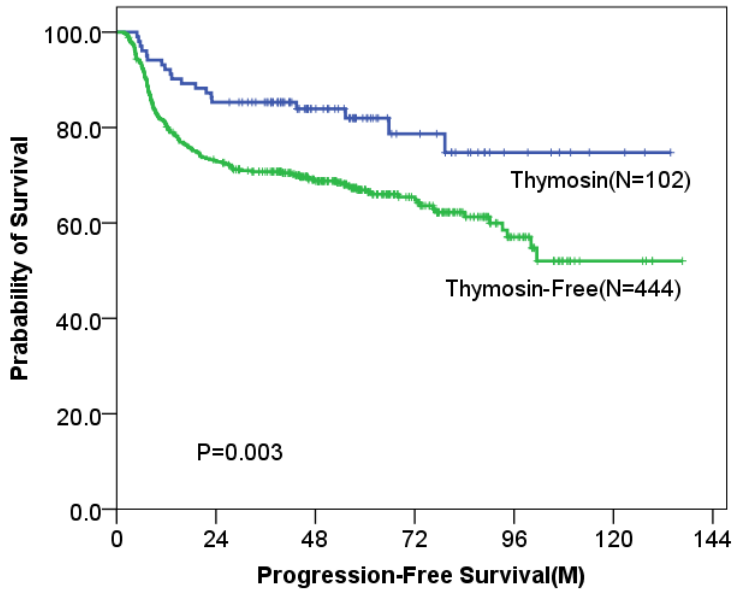
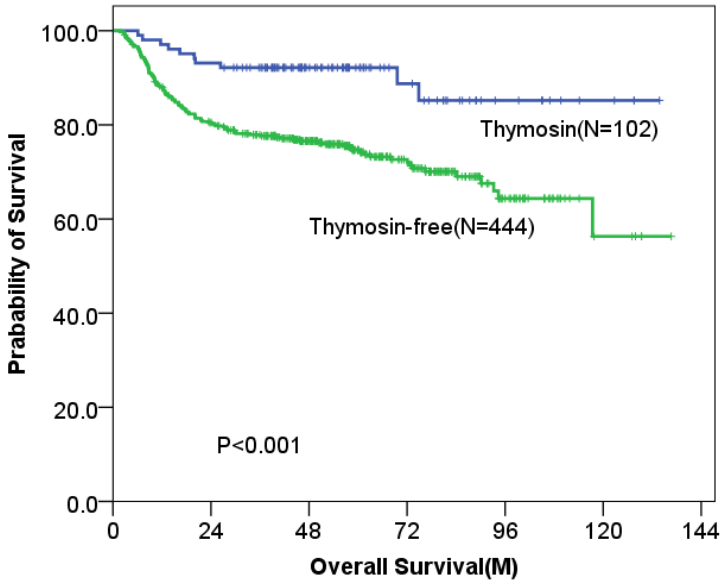


Fig. 5 Forest plot meta-analysis of treatment-related mortality between chemotherapy with rituximab group and chemotherapy-alone group

Nie M, et al. ESMO-ASIA 2015, 297P

R-CHOP+Thymosine vs R-CHOP



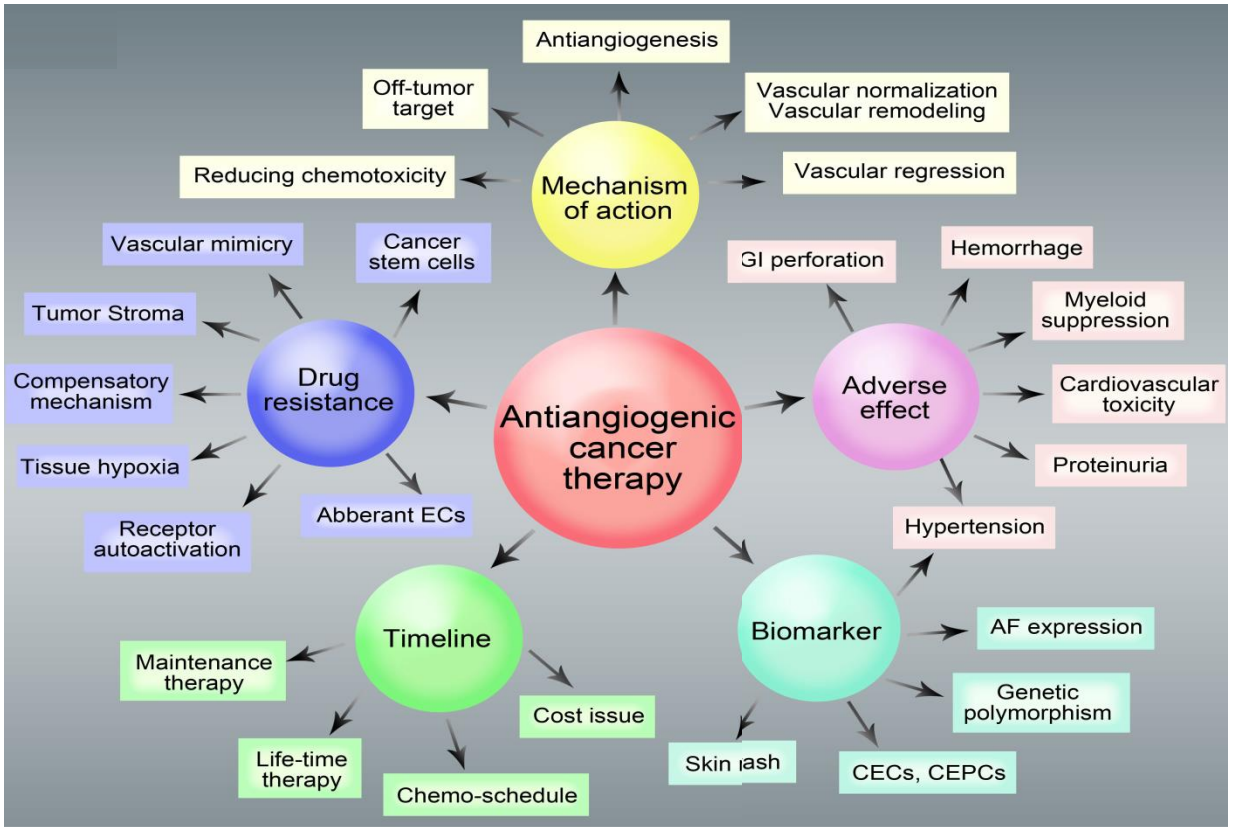


Impact of Thymosin on HBV Reactivation ,R-CHOP

	R-CHOP + Thymosin (N=102)	R-CHOP (N=444)	P value
HBV infection	30（29.4%）	115（25.9%）	P=0.469
HBV reactivation	0	12（2.7%）	
HBV reactivation related death	0	1（0.2%）	

Huang H, et al. ESMO-ASIA 2015, 290P

Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)



Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

- **Inclusion Criteria**
  - Histologic diagnosis of NK/T Cell Lymphoma
  - Age:18-80 years
  - ECOG status 0-3
  - Estimated survival time > 3months
  - No previous antilymphoma treatments
  - ≥1 poor prognostic factors

Unpublished data

Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

- **Avastin+P-Gemox regimen**

- Avastin 7.5mg/kg Day 1
- Pegaspargase 2500U/m^2 Day 1
- Gemcitabine 1000mg/m^2 Day 1,8
- Oxaliplatin 130mg/m^2 Day 1,8
- Dexamethasone 20mg/d Day 1-3

Q21 days for 6 cycles

Early stage: sandwich A-chemoradiation

Advancced stage: A-Chemotherapy

Unpublished data

Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

- **Baseline Character**
  - 31 patients enrolled

Characteristics	Number of assessable patients	(%)
Age (years)		
Range (Median)	18~66 (36)	
≦60	28	90.3
Gender		
male to female	26:5	93.9:16.1

Unpublished data

Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

- **Baseline Character**

- 31 patients enrolled

Characteristics	Number of assessable patients	(%)
B symptoms	18	58.1
ECOG PS≧2	2	6.5
LDH> ULN	11	35.5
Ann Arbor stages		
Stage Ⅰ	13	41.9
Stage Ⅱ	7	22.6
Stage Ⅲ	1	3.2
Stage Ⅳ	10	32.3

Unpublished data

Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

- **Baseline Character**

  - 31 patients enrolled

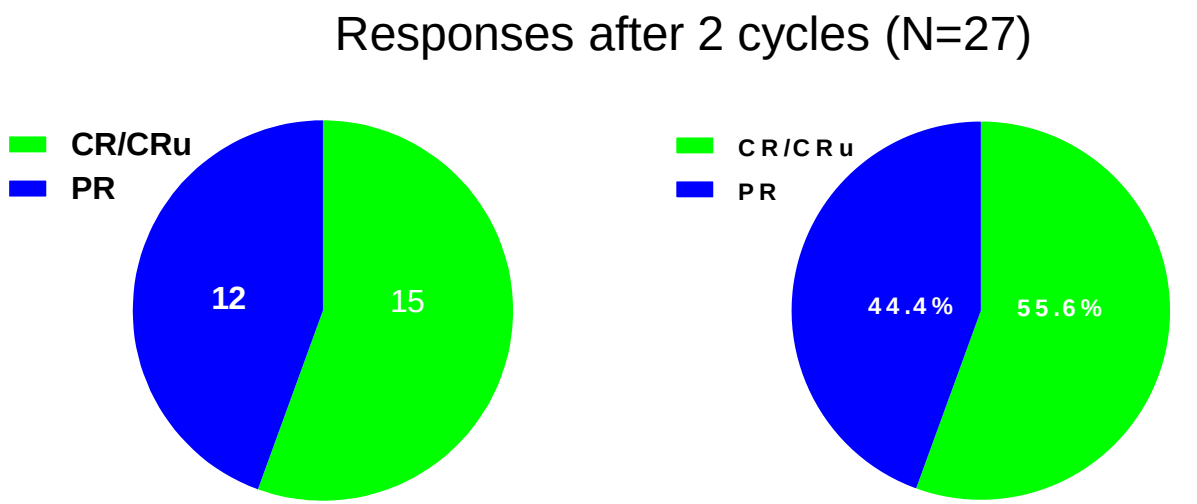
Characteristics	Number of assessable patients	(%)
Primary involvement		
nasal cavity	24	77.4
waldeyer ' s ring	3	9.7
skin	3	9.7
bone	1	3.2
Bone marrow involvement	2	6.5
EBV DNA copy>10^3copy/ml	13	41.9

Unpublished data

Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

- **Efficacy Analysis**

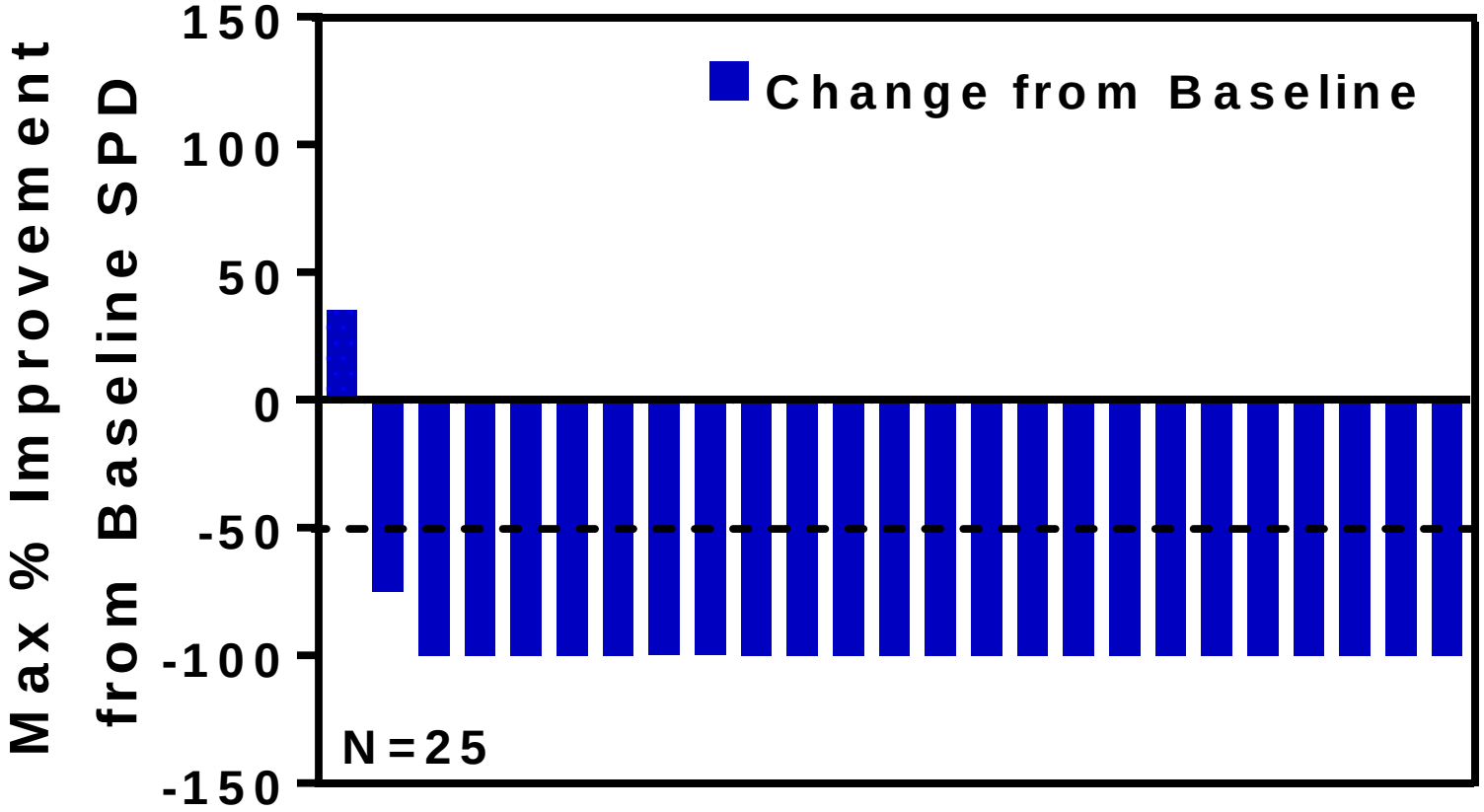
Responses after 2 cycles (n=27)	% (n)
ORR	100(27)
CR/CRu	55.6(15)
PR	44.4(12)



Unpublished data

Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

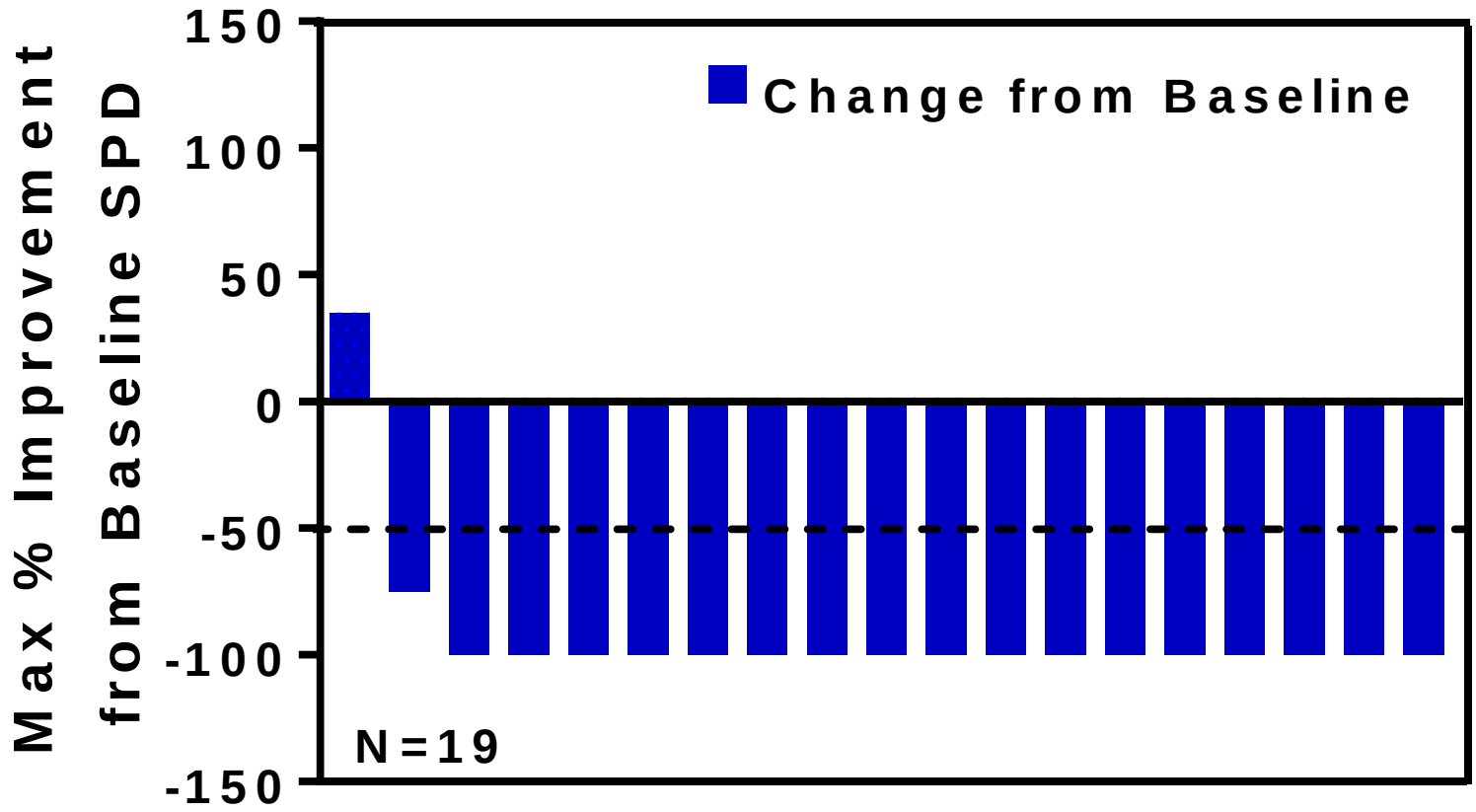
- **Efficacy Analysis for ITT(n=25, finish treatment)**



Unpublished data

Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

- **Efficacy Analysis for PP(n=19)**



Unpublished data

SPD: sum of the products of the greatest perpendicular diameters

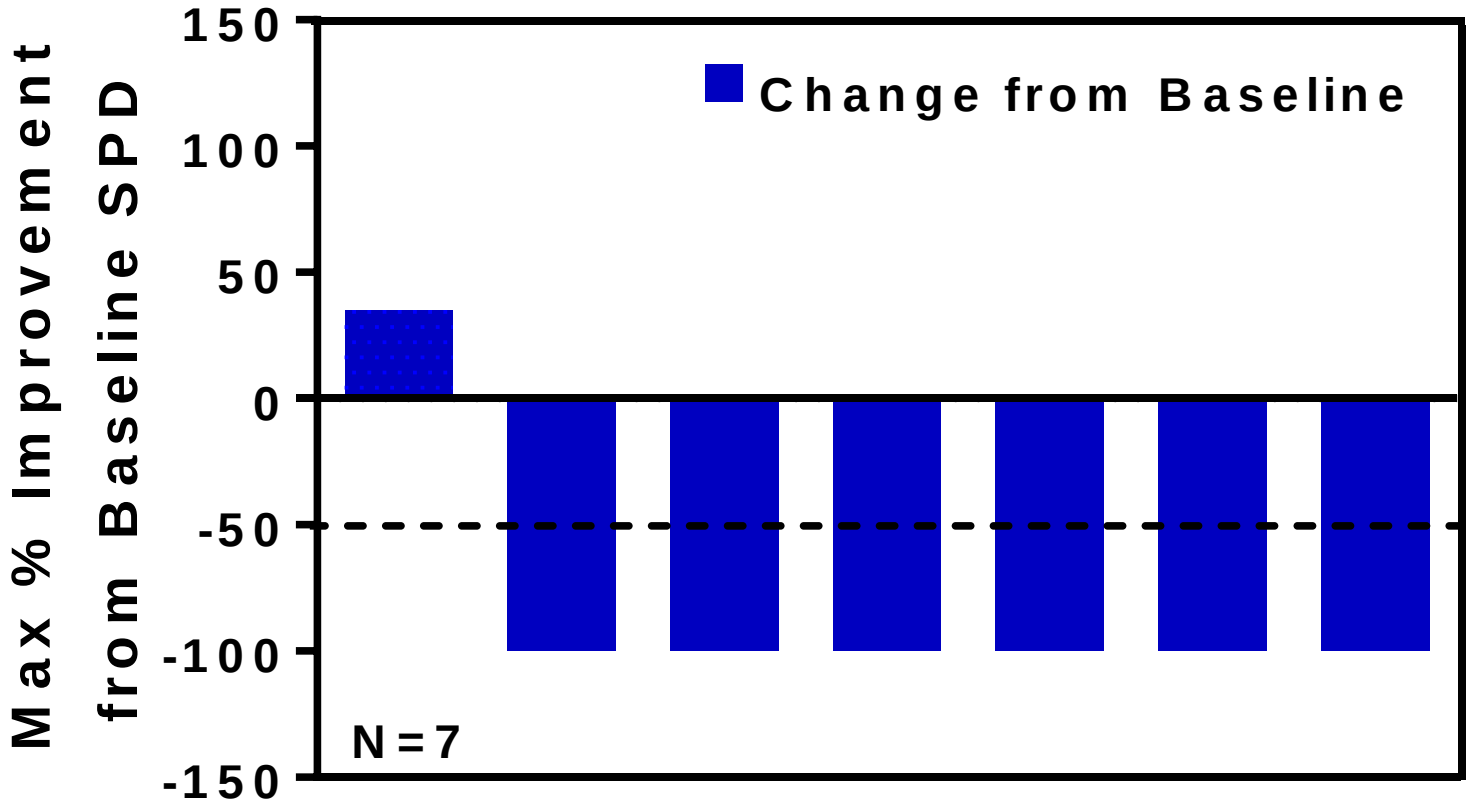
Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

- **Efficacy Analysis for advanced stage**
  - **10 patients in stage Ⅳ were enrolled**
  - **7 of 10 patients finish the treatment**
    - **6 patients finish 6 cycles for the treatment**
    - **1 patient was dead due to PD after 4th cycle**
  - **3 patients were going on the treatment**

Unpublished data

Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

- **Efficacy Analysis for Stage IV pts**



Unpublished data

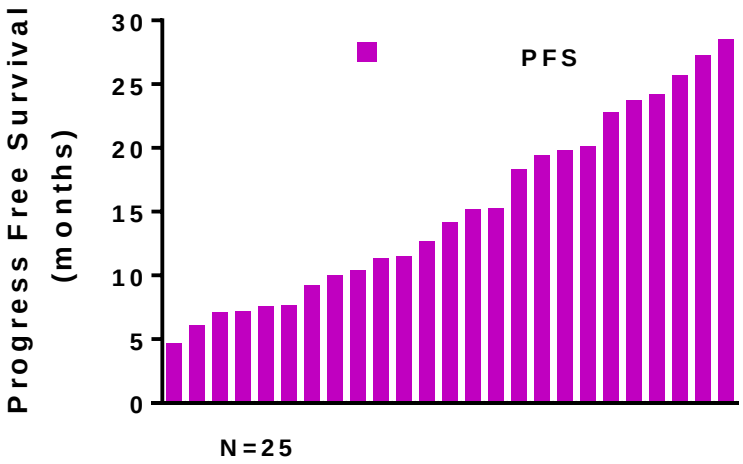
Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

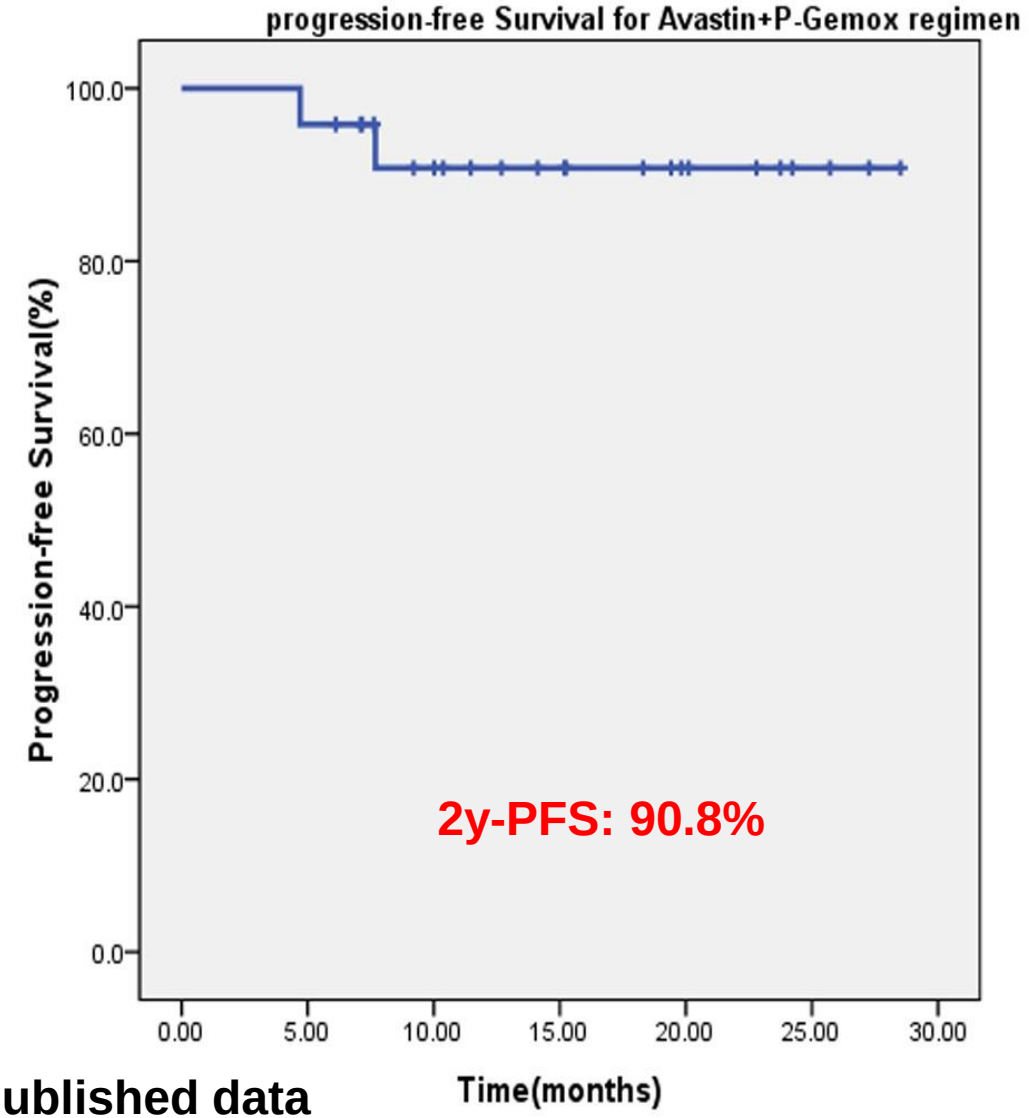
- **Efficacy Analysis**

  - Median follow up: 11.46mos

    [range 1.12~28.52]

  - Just only 1 patients were PD after the treatment till the last follow up(Nov 20th 2015)





Unpublished data

Phase 2 trial A-PGemox in newly diagnosed ENKTL (NCT01921790)

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  [range 1.12~28.52]

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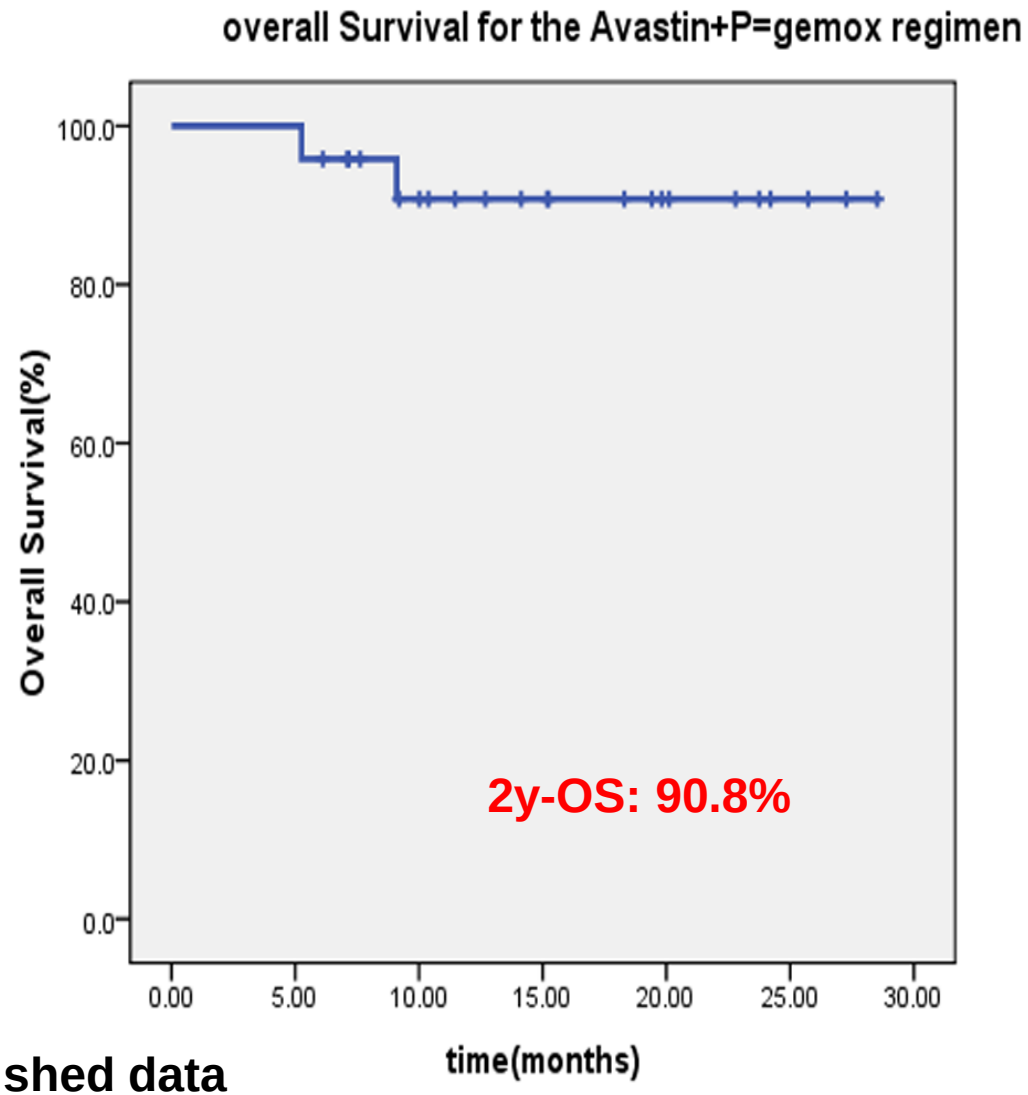

Unpublished data

Conlusion

- **Monoclonal antibody alone and in the combination of other novel targeted drugs may be a new option for lymphoma treatment**
- **The chemotherapy-free approaches would avoid chemotherapy-related toxicity but preserve the antilymphoma activity in selected patients.**

Acknowledgement


Спасибо
RUSSIAN
Gracias
SPANISH
ありがとう
ございました。
JAPANESE
CÁM ƠN
VIETNAMESE
Thank You!
ENGLISH
Merci
FRENCH
Ευχαριστώ
GREEK
شكرًا
ARABIC
고맙습니다
KOREAN
谢谢
CHINESE