POST ASCO/EHA/ASH
2016

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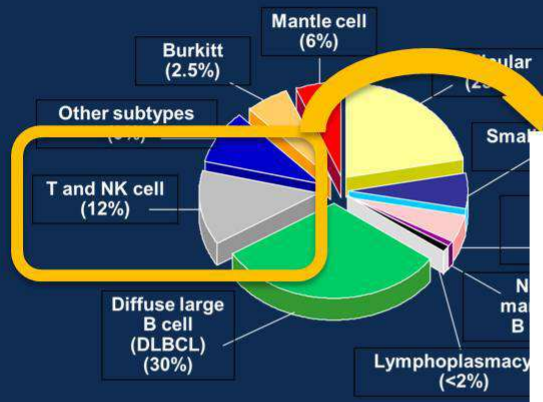
- Lymphomes T périphériques

T-NHL: Rare, heterogeneous and with dismal outcomes



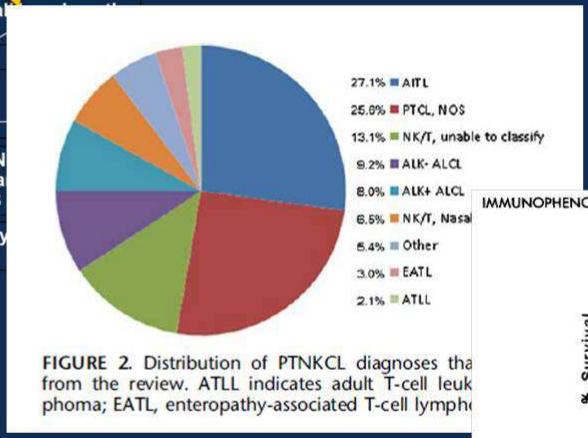
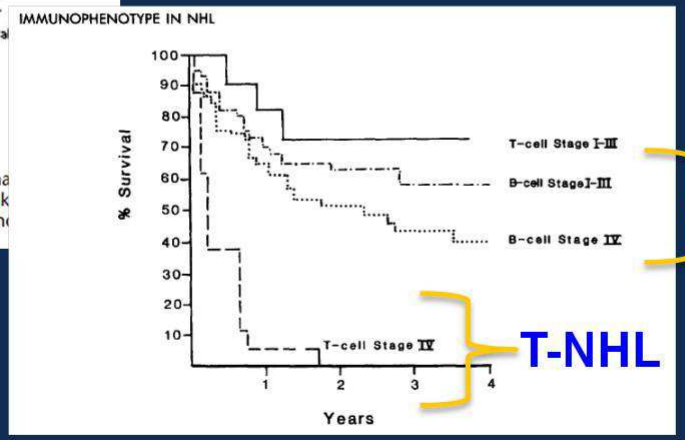


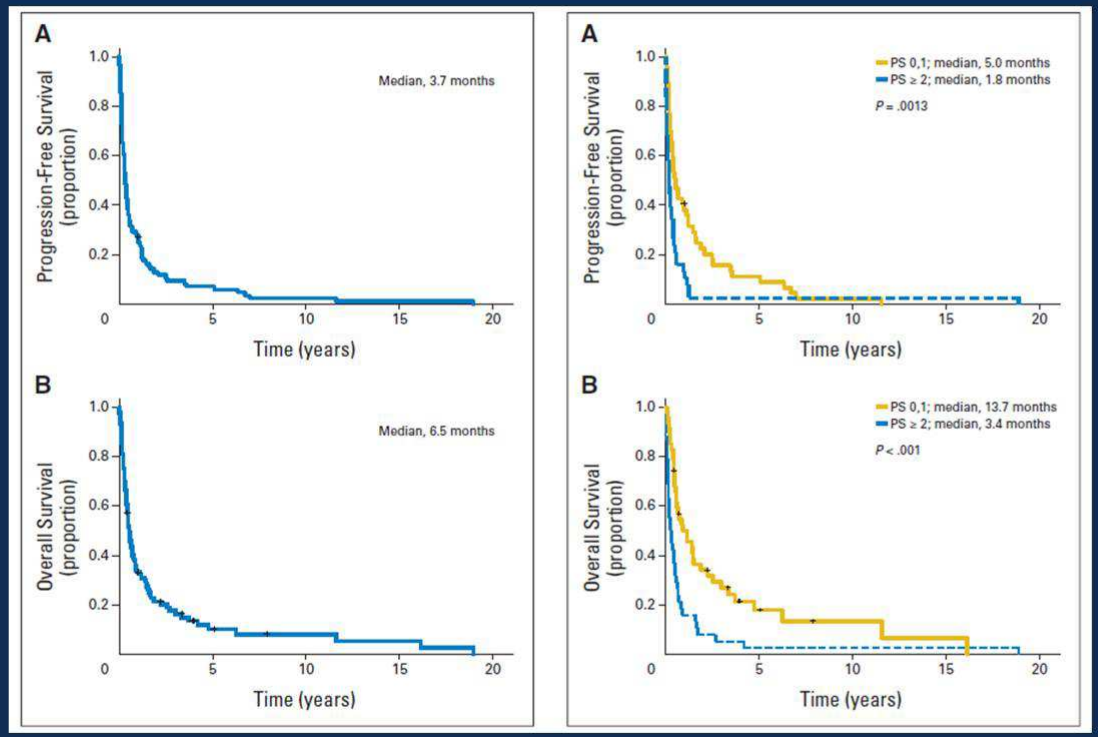
FIGURE 2. Distribution of PTNKCL diagnoses tha
from the review. ATLL indicates adult T-cell leuk
phoma; EATL, enteropathy-associated T-cell lymph



Hsi, et al., Am J Surg Path 38(6), 2014.
Vose JCO 7:1783-1790, 1989

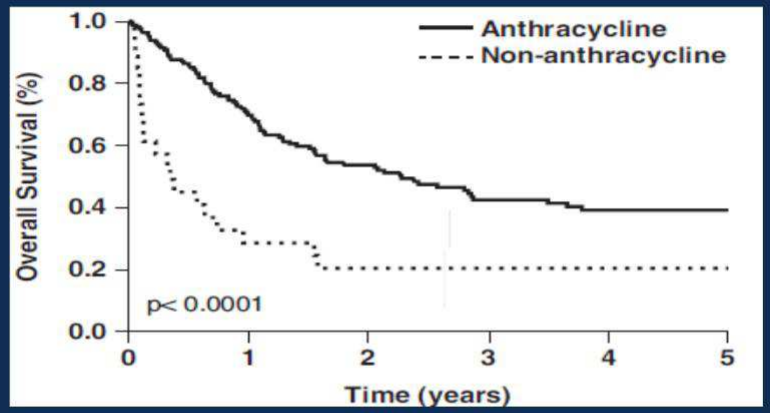
Low expectations after relapse (BCCA Registry Analysis, n=153)

- 48% of patients relapsed within 6 months of initial diagnosis
- 29% of patients had PD to primary therapy
- Median OS after relapse is 6.5 months

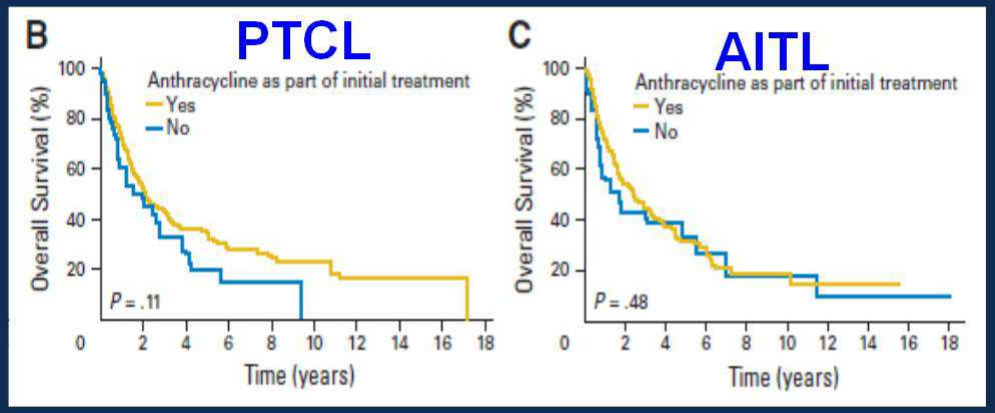


J Clin Oncol. 2013 Jun 1;31(16):1970-6. doi: 10.1200/JCO.2012.44.7524. Epub 2013 Apr 22.

T-NHL: Are we stuck with CHOP?

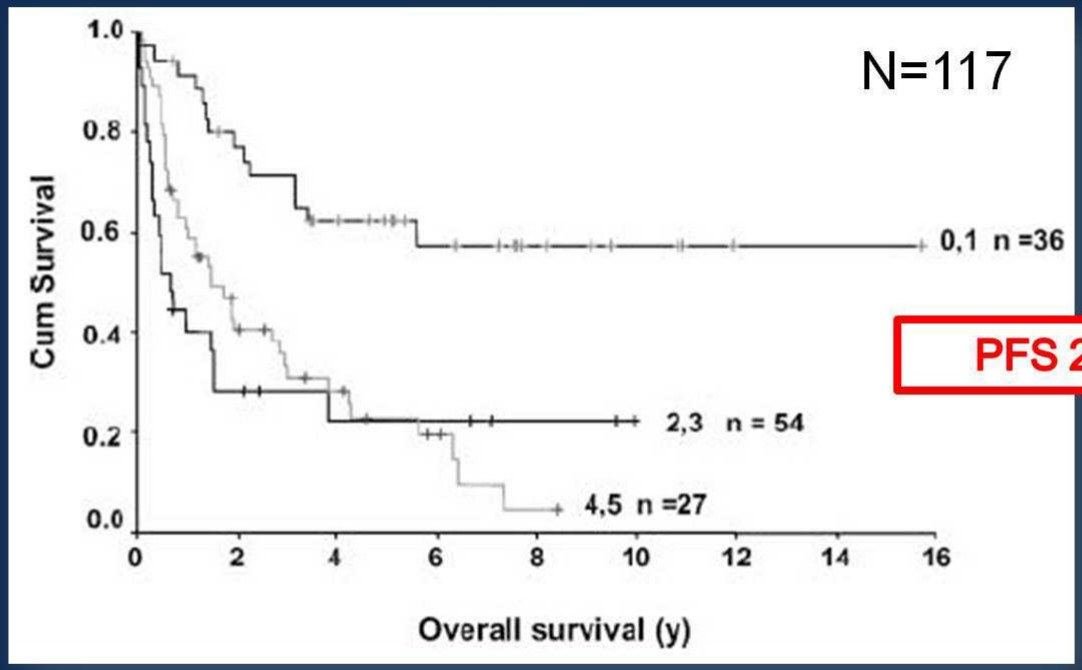


Mayo Clinic 1994-2009; U Michigan 1988-2011
Briski et al., Blood Cancer Journal 2014; 4; e214



Vose International Peripheral T-cell and NKTCL Project
JCO 26(25)2008

BCCA Analysis of CHOP/CHOP-like regimens in T-NHL (Overall survival)



PFS 24%

Savage et al. Annals of Oncology 2004; 15:1467–1475.

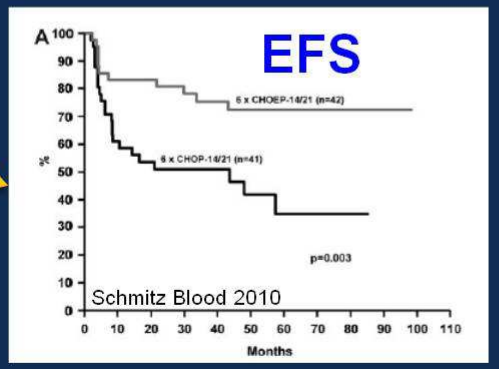
Ongoing or completed trials using CHOP as a backbone in T-NHL

CHOP +

- Romidepsin
- Everolimus
- Belinostat
- Denileukin diftitox
- Vorinostat
- Bortezomib
- Rituximab (AITL)
- Etoposide

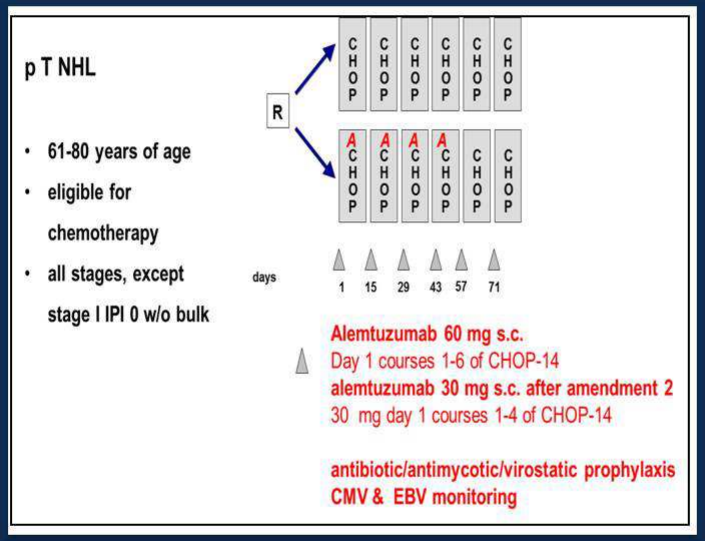
No clear benefit to date, although several trials ongoing

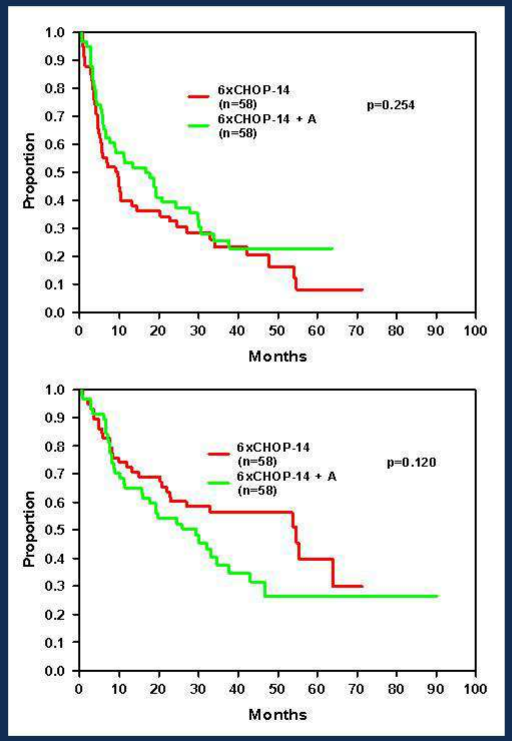
CHOP vs. BV-CHP



- Benefit mostly in ALCL patients, younger patients
- No OS difference
- Not a prospective trial

ACT-2 Results: no difference in EFS or OS





EFS

OS

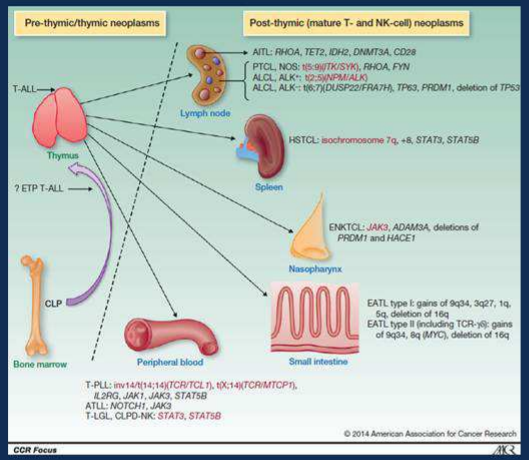
ACT-2 Comments

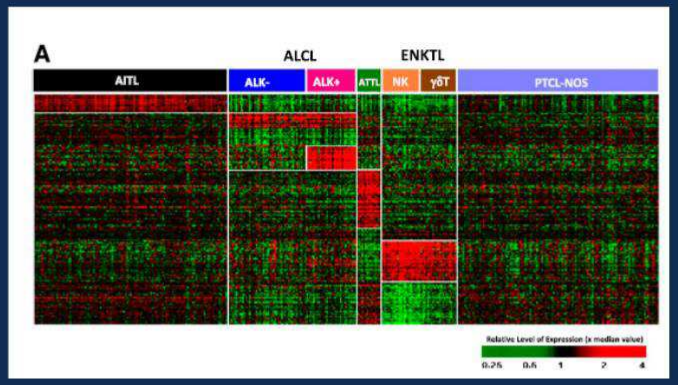
- Initial design with higher dose of alemtuzumab was not feasible
- Reduced dose and schedule of alemtuzumab plus CHOP-14 x 6 was feasible and had a higher response rate (72% vs. 60%)
- BUT…
  - Took 9 years to accrue
  - More leukopenia in A-CHOP arm
  - Viral infections 50% vs. 0% in A-CHOP arm
  - No difference in number of lymphoma-related deaths

The bar has not moved:

- **Failure of CHOP?**
- **Failure of alemtuzumab?**
- **Underlying heterogeneity?**

Approaches to subdivide and classify T-NHL





TFH phenotype as a distinct subset

THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

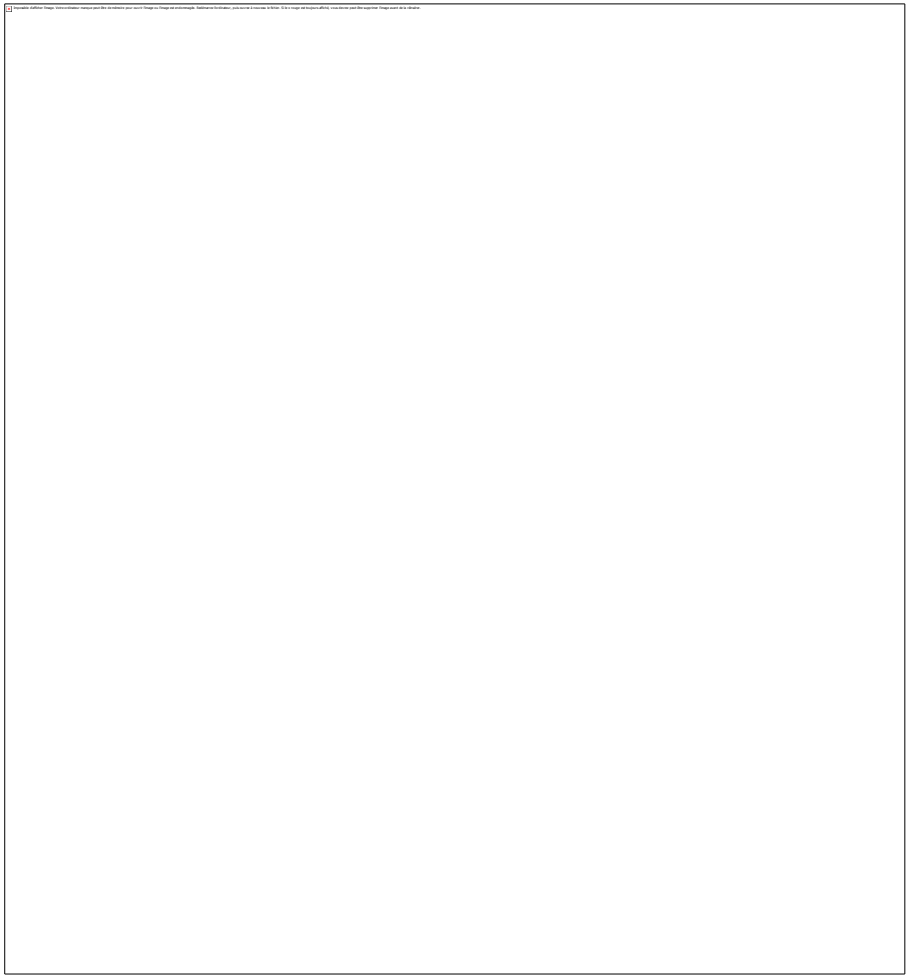
Steven H. Swerdlow,[1] Elias Campo,[2] Stefano A. Pileri,[3] Nancy Lee Harris,[4] Harald Stein,[5] Reiner Siebert,[6] Ranjana Advani,[7] Michele Ghielmini,[8] Gilles A. Salles,[9] Andrew D. Zelenetz,[10] and Elaine S. Jaffe[11]

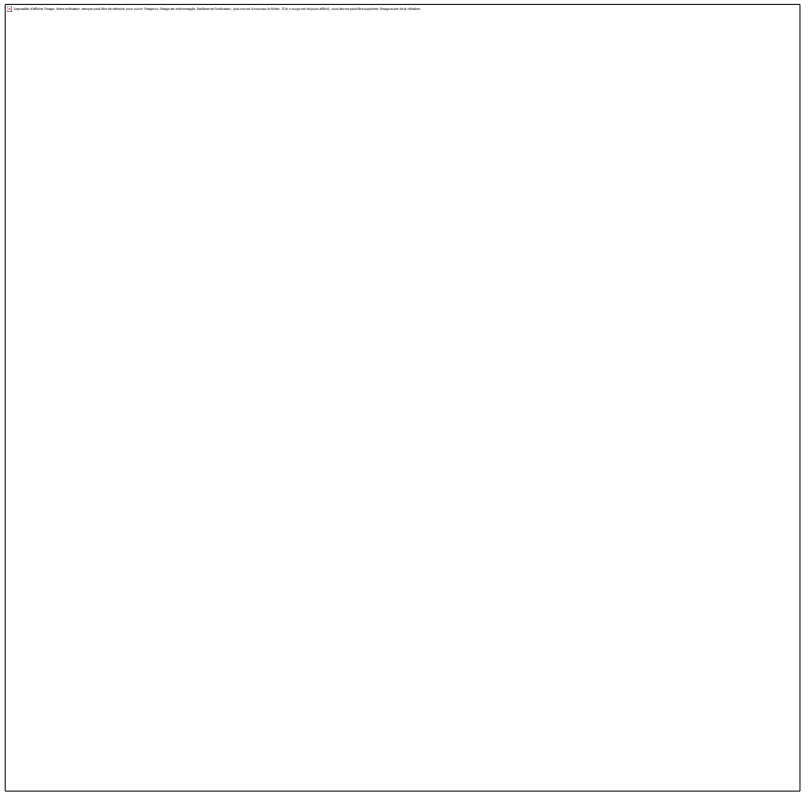
Iqbal, et al., Blood. 2014 May 8;123(19):2915-23. doi: 10.1182/blood-2013-11-536359.
O'Connor, et al., Clin Cancer Res. 2014 Oct 15;20(20):5240-54. doi: 10.1158/1078-0432.CCR-14-2020
Blood. 2016 May 19;127(20):2375-90. doi: 10.1182/blood-2016-01-643569. Epub 2016 Mar 15

Azacytidine in Angioimmunoblastic T-cell lymphoma and related forms of T_{FH} derived lymphomas

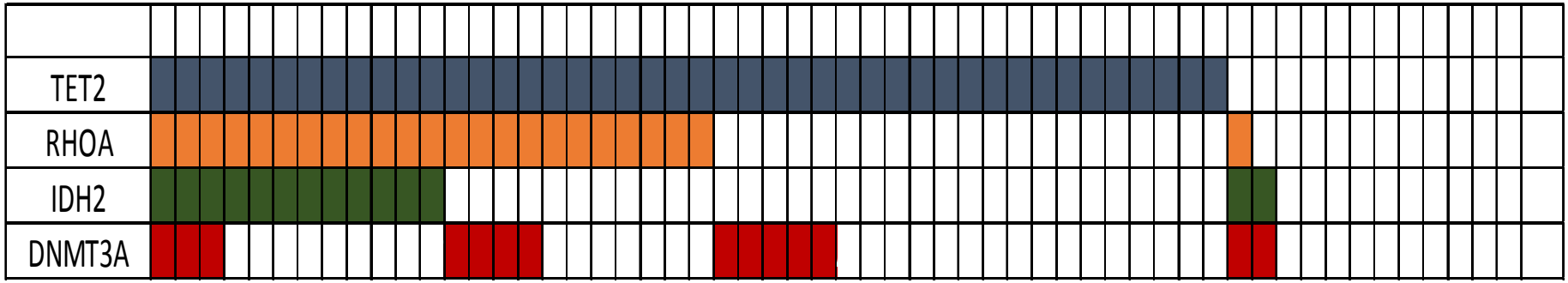
Delarue et al. ASH 2016

Frequent mutations of DNA methylation related genes in AITL

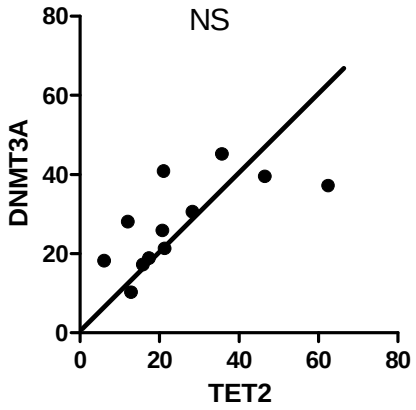


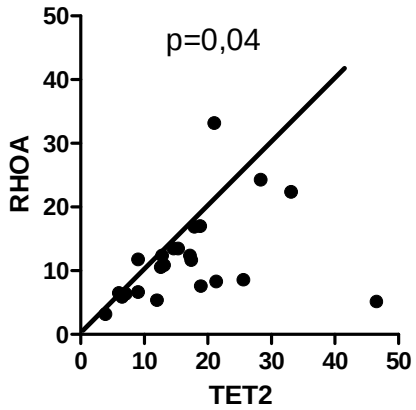


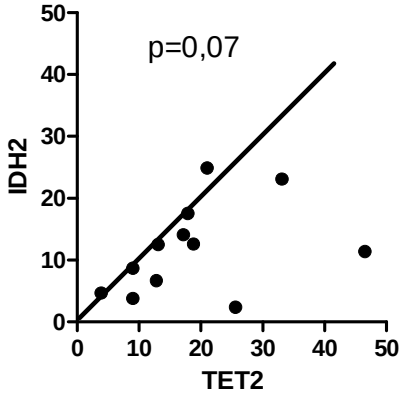
AITL mutational landscape: RAIL/REVAIL experience



VAF analysis of TET2, IDH2, DNMT3A and RHOA mutations in these two series







Two published case reports of patients with concommitant AITL and CMML treated with Azacytidine

Efficacy of 5-Azacytidine in a TET2 mutated angioimmunoblastic T cell lymphoma

British Journal of Haematology, 2015, **168,** 902–919

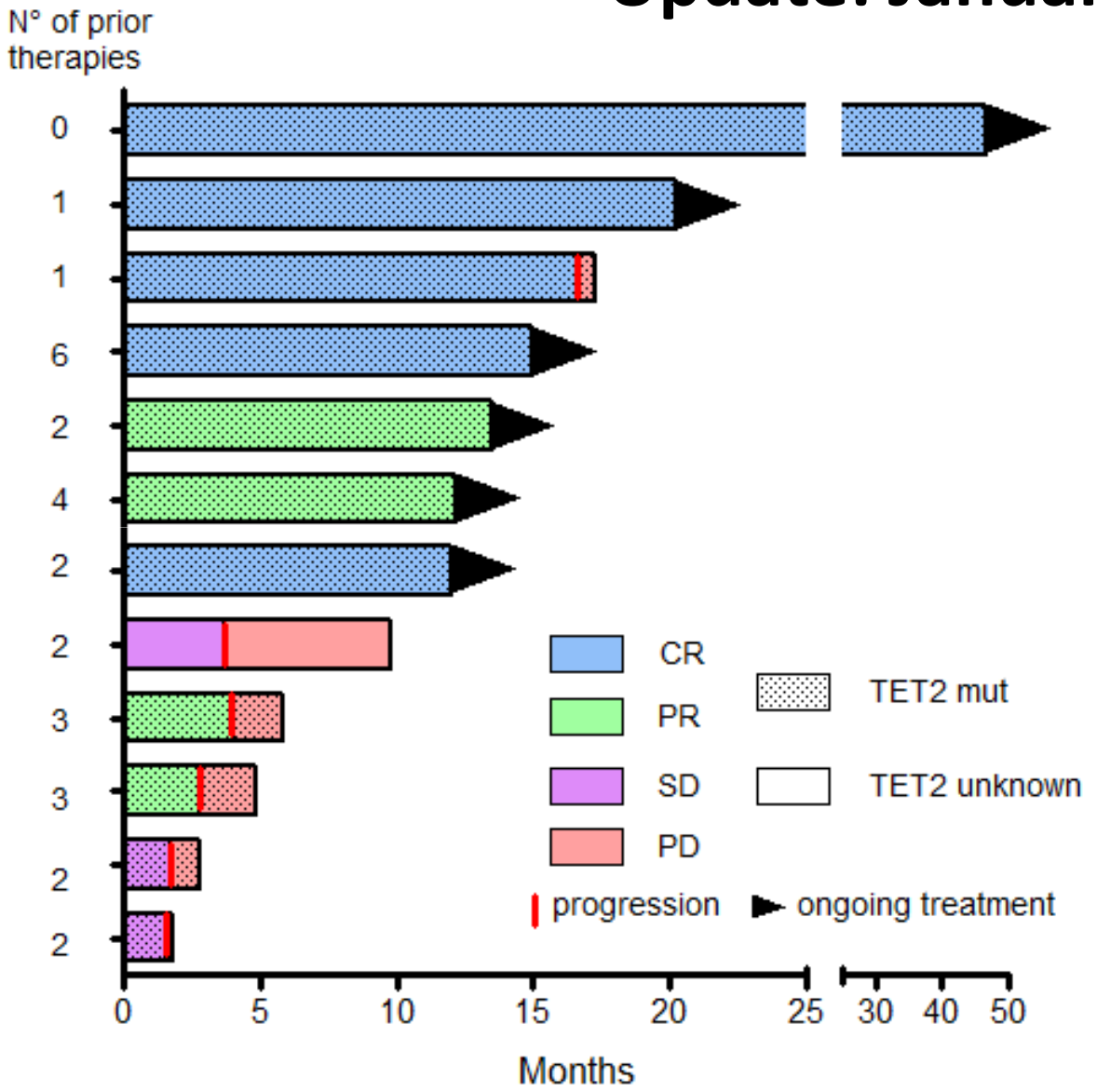
Hematol Oncol. 2016 Jun 29. doi: 10.1002/hon.2319. [Epub ahead of print]

Response to 5-azacytidine in a patient with TET2-mutated angioimmunoblastic T-cell lymphoma and chronic myelomonocytic leukaemia preceded by an EBV-positive large B-cell lymphoma.

Saillard C[1], Guermouche H[2], Derrieux C[3], Bruneau J[4], Frenzel L[1], Couronne L[1,5], Asnafi V[3], Macintyre E[3], Trinquand A[3], Lhermitte L[3], Molina T[4], Suarez F[1,5], Lemonnier F[1], Kosmider O[2], Delarue R[1,5], Hermine O[1,5], Cheminant M[1,5].

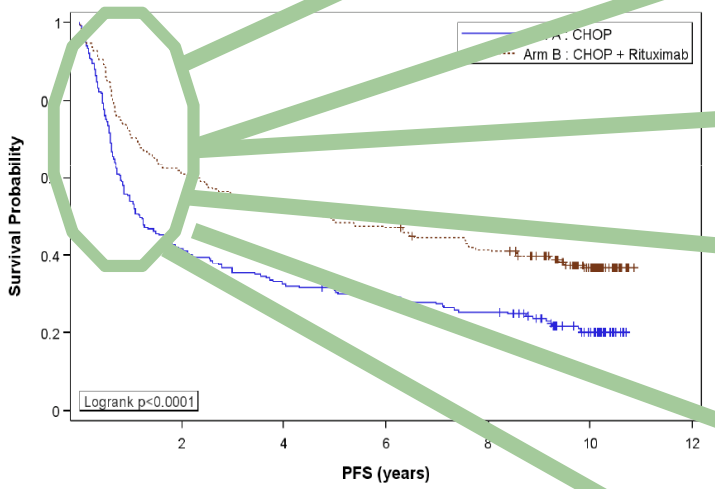
- Long-lasting remissions of > 40 months and >12 months, respectively

Update: January 2017



- Lymphomes diffus à grandes cellules B

DLBCL: Strategies to improve beyond R-CHOP-21



Intensification over R-CHOP-21?

Other MoAB

Combo R-CHOP-21 + X ?

Better predict /evaluate quality of response?

Maintenance after CR/PR

Take into consideration biological diversity of DLBCL

R-CHOP is a standard of care

TT	Phase	Patient status	OS	ref
R-ACVBP vs R-CHOP	III	<60 yr, IPI 1	92 vs 84% @ 3yr	Recher 2011
R-CHOP 21 vs R-CHOP 14	III	>18 yr, stade I bulk-4	80 vs 82% @2yr	Cunningham 2013
R-CHOP 21 vs R-CHOP 14	III	60-80 yr aaIPI>1	72 vs 69%@3yr	Delarue 2013
R-MegaCHOEP Vs R-CHOP	III	<60yr aaIPI>1	77 vs 84% @ 3 yr	Schmitz 2012
R-CHOP 14 vs R highdosechemo + auto	III	<60 yr aaIPi>1	85 vs 82% @ 3 yr	Milpied 2011
R-CHOP + auto vs R-CHOP	III	<60yr, aaIPI>1	74 vs 71% @ 2yr	Stiff 2013
R-dose dense CHOP vs R CHOP + auto	III	18-65 yr, aaIPI> 1	81 vs 78% @ 3yr	Vittolo 2012
DA-EPOCH-R Vs R-CHOP	III	<60 yr	**ASH 2016**	NCI

DA EPOCH: Background

- Characteristics of DA-EPOCH-R
  - Infusional scheduling
  - Etoposide use (topo II inhibition and Bcl-6 down regulation)
  - Pharmacodynamic dose-adjustment based on ANC nadir
- Gene expression subgroups of DLBCL identify patients with distinct biology and clinical outcomes[1, 2]
  - Germinal Center B-cell-like (GCB)
  - Activated B-cell-like (ABC)
    - Less favorable outcome with R-CHOP
- Molecular profiling recognized as a potential tool to identify subgroups of DLBCL that are more susceptible or resistant to specific treatments.

1. Alizadeh, AA, Nature 403:503:2000
2. Lenz, G, NEJM 359: 232:2008

50303 Treatment Regimens

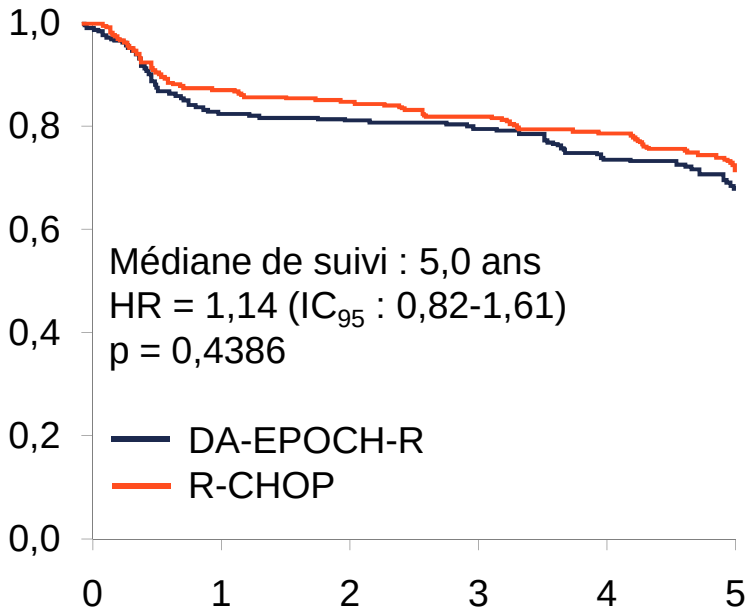
	R-CHOP x 6 (mg/m^2)	DA-EPOCH-R x 6 DL1 (mg/m^2)
Rituximab	375	375
Cyclophosphamide	750	750 *
Doxorubicin	50	10/d CI D1-4*
Etoposide		50/d CI D1-4*
Vincristine	1.4 (2 mg cap)	0.4/d CI D1-4 (no cap)
Prednisone	40 D1-5	60 BID D1-5
GCSF	PRN	Days ≈ 6-12

* Escalated by 20% if nadir ANC >0.5; de-escalated if ANC <0.5 > 3 days

- CI: Continuous infusion
- CNS prophylaxis (IT MTX x 4 doses, D1 of C3-6) required if
  - ≥ 2 extranodal sites AND elevated LDH or bone marrow or testicular involvement
- No RT allowed on either arm

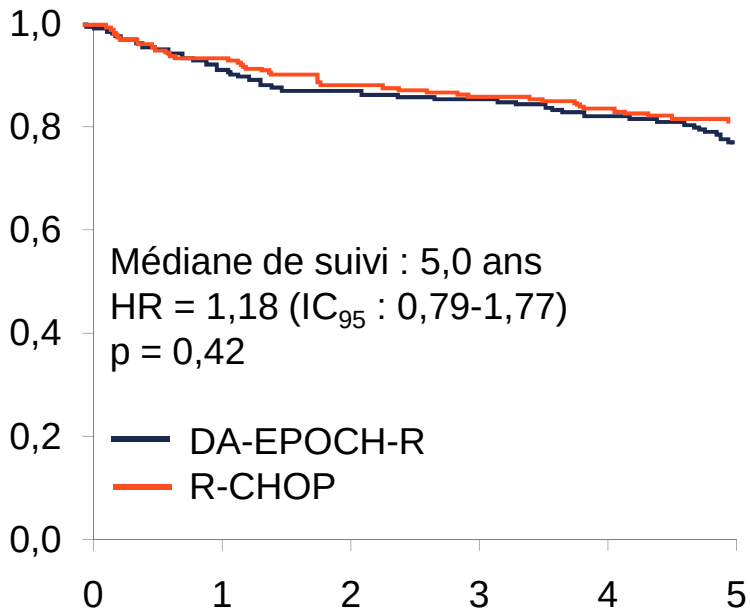
Étude de phase III randomisée : R-CHOP versus DA-EPOCH-R

Survie sans événement



Bras	Patients (n)	Événements	3 ans (IC_{95})
R-CHOP	233	64	0,81 (0,75-0,85)
DA-EPOCH-R	232	70	0,79 (0,73-0,84)

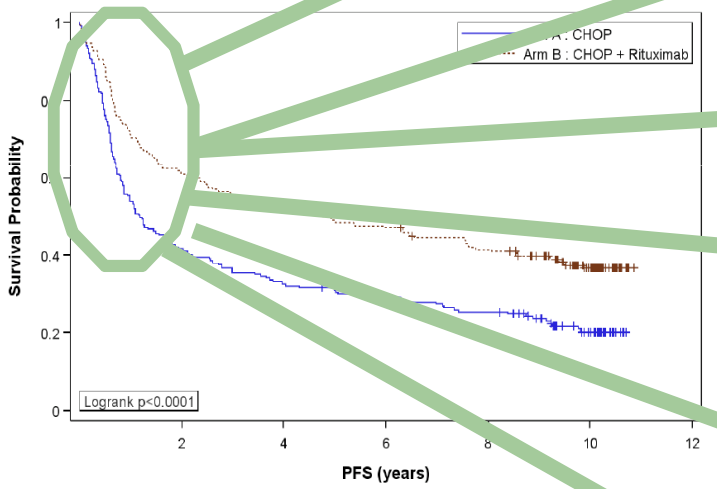
Survie globale



Bras	Patients (n)	Événements	3 ans (IC_{95})
R-CHOP	233	44	0,85 (0,80-0,89)
DA-EPOCH-R	232	50	0,85 (0,79-0,89)

ASH 2016 - D'après Bartlett NL et al., abstr. 469, actualisé

DLBCL: Strategies to improve beyond R-CHOP-21



Intensification over R-CHOP-21?

Other MoAB

Combo R-CHOP-21 + X ?

Better predict /evaluate quality of response?

Maintenance after CR/PR

Take into consideration biological diversity of DLBCL

Obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma: final results from an open-label, randomized Phase III study (GOYA)

Umberto Vitolo,[1] Marek Trněný,[2] David Belada,[3] Angelo Michele Carella,[4] Neil Chua,[5] Pau Abrisqueta,[6] Judit Demeter,[7] Ian Flinn,[8] Xiaonan Hong,[9] Won Seog Kim,[10] Antonio Pinto,[11] John M Burke,[12] Yuan Ki Shi,[13] Yoichi Tatsumi,[14] Mikkel Z Oestergaard,[15] Michael Wenger,[16] Günter Fingerle-Rowson,[15] Olivier Catalani,[15] Tina Nielsen,[15] Maurizio Martelli,[17] Laurie H Sehn[18]

[1]Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; [2]Charles University, Prague, Czech Republic; [3]Charles University Hospital and Medical School, Hradec Kralove, Czech Republic; [4]IRCCS AO University, San Martino-IST, Genoa, Italy; [5]Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [6]University Hospital Vall d'Hebron, Barcelona, Spain; [7]Semmelweiss University, Budapest, Hungary; [8]Sarah Cannon Research Institute, Nashville, TN, USA; [9]Fudan University Shanghai Cancer Center, Shanghai, China; [10]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [11]Istituto Nazionale Tumori, Fondazione G. Pascale, IRCCS, Naples, Italy; [12]Rocky Mountain Cancer Centers, Aurora, CO and US Oncology Research, The Woodlands, TX, USA; [13]National Cancer Center, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China; [14]Kinki University Hospital, Osaka, Japan; [15]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [16]Genentech Inc., South San Francisco, CA, USA; [17]'Sapienza' University, Rome, Italy; [18]Centre for Lymphoid Cancer, British Columbia Cancer Agency and the University of British Columbia, Vancouver, BC, Canada

Background

- Rituximab (R) + CHOP (R-CHOP) is standard of care for previously untreated pts with DLBCL[1]
- Most pts respond to R-CHOP, but 20–40% fail to achieve a remission or relapse[2]
  - Outcomes with salvage therapy remain poor[2,3]
- Obinutuzumab (GA101; G)
  - Glycoengineered type II anti-CD20 mAb
  - Greater direct cell death induction and ADCC/ADCP activity than R[4,5]
- GOYA (NCT01287741) compared the efficacy and safety of G-CHOP with R-CHOP in pts with previously untreated DLBCL

	ADCC / ADCP	CDC	Direct cell death
Type I mAb (rituximab)	+	+	+
Glycoengineered type II mAb (obinutuzumab)	+++	–	+++

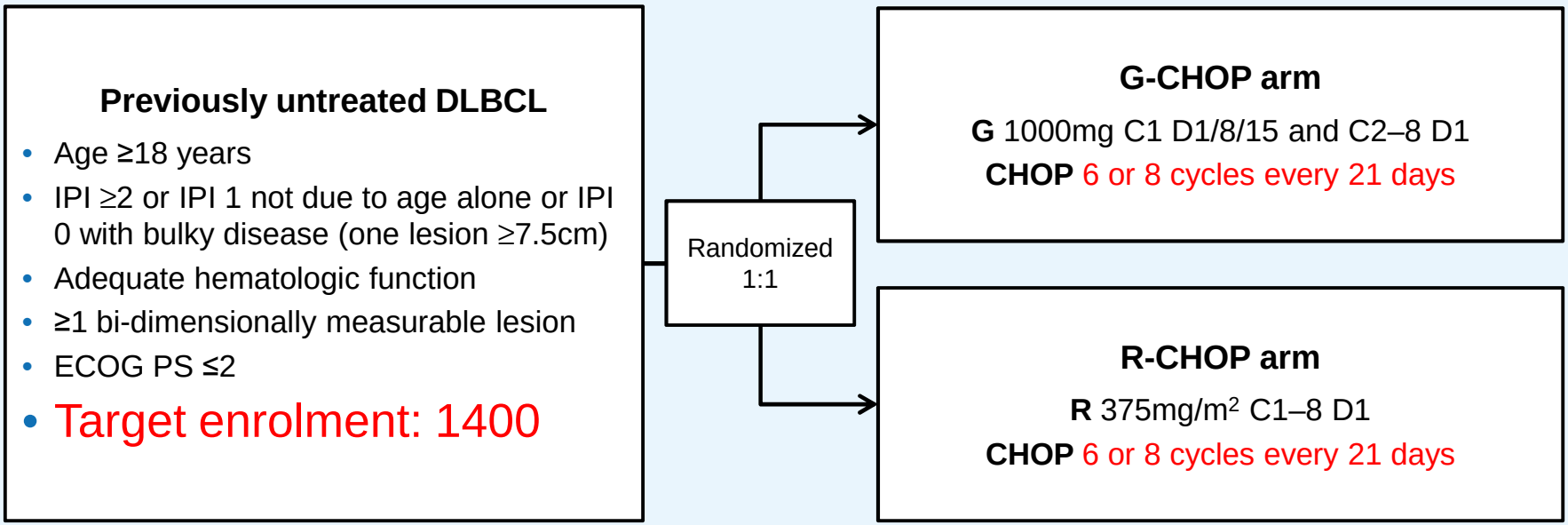
ADCC, antibody-dependent cell-mediated cytotoxicity;
ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity

1. Tilly et al. 2015; 2. Maurer et al. 2014
3. Sehn & Gascoyne 2015; 4. Herter et al. 2013; 5. Mössner et al. 2010

Study design

International, open-label, randomized Phase III study in 1L DLBCL pts

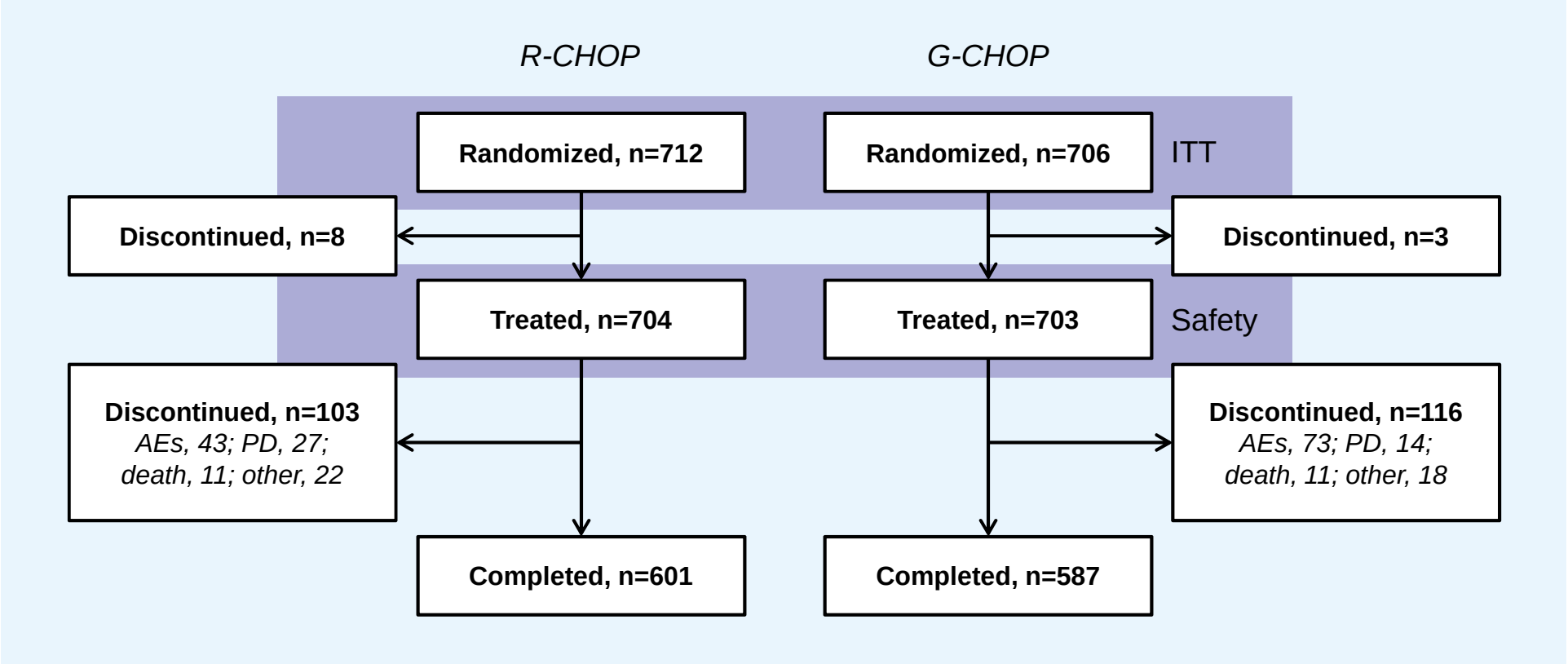
- *Scientific support from the Fondazione Italiana Linfomi*



- Number of CHOP cycles pre-planned in advance for all pts at each site
- Randomization stratification factors: planned number of CHOP cycles, IPI, geographic region

Patient disposition

1418 pts randomized at 207 centers in Western and Eastern Europe, South, Central, and North America, Asia, and other regions*



*29 countries in total; highest recruiters (>50 pts): Italy (259), China (252), Canada (120), Japan (111), USA (96), Thailand (86), Spain (79), Czech Republic (74), Hungary (68), Republic of Korea (59)

Baseline patient and disease characteristics

% (n)	*R-CHOP, n=712*	*G-CHOP, n=706*
Median age, years (range)	62.0 (18–83)	62.0 (18–86)
Female	46.2% (329)	47.7% (337)
Ann Arbor stage at diagnosis		
I–II	24.1% (171)	24.1% (170)
III–IV	75.9% (540)	75.9% (536)
ECOG PS*		
0	46.3% (330)	46.0% (325)
1	39.7% (283)	41.5% (293)
2	13.8% (98)	12.2% (86)
IPI		
Low/low-intermediate	57.4% (409)	53.3% (376)
High-intermediate	27.0% (192)	31.3% (221)
High	15.6% (111)	15.4% (109)
Extranodal involvement (>1 site)	33.7% (240)	37.3% (263)
Bone marrow involvement	10.9% (77)	10.9% (76)
Bulky disease (≥7.5cm)	36.9% (262)	37.1% (261)
COO subtype in evaluable pts (n=933)†		
GCB	**58.2% (269)**	**57.5% (271)**
ABC	**25.5% (118)**	**26.5% (125)**
Unclassified	**16.2% (75)**	**15.9% (75)**

*ECOG PS: 3 R-CHOP, 1 G-CHOP, n=1
†Missing COO classifications due to: restricted Chinese export license, n=252; CD20+ DLBCL not confirmed, n=102; missing/inadequate tissue, n=131

Investigator-assessed response rates at end of treatment*

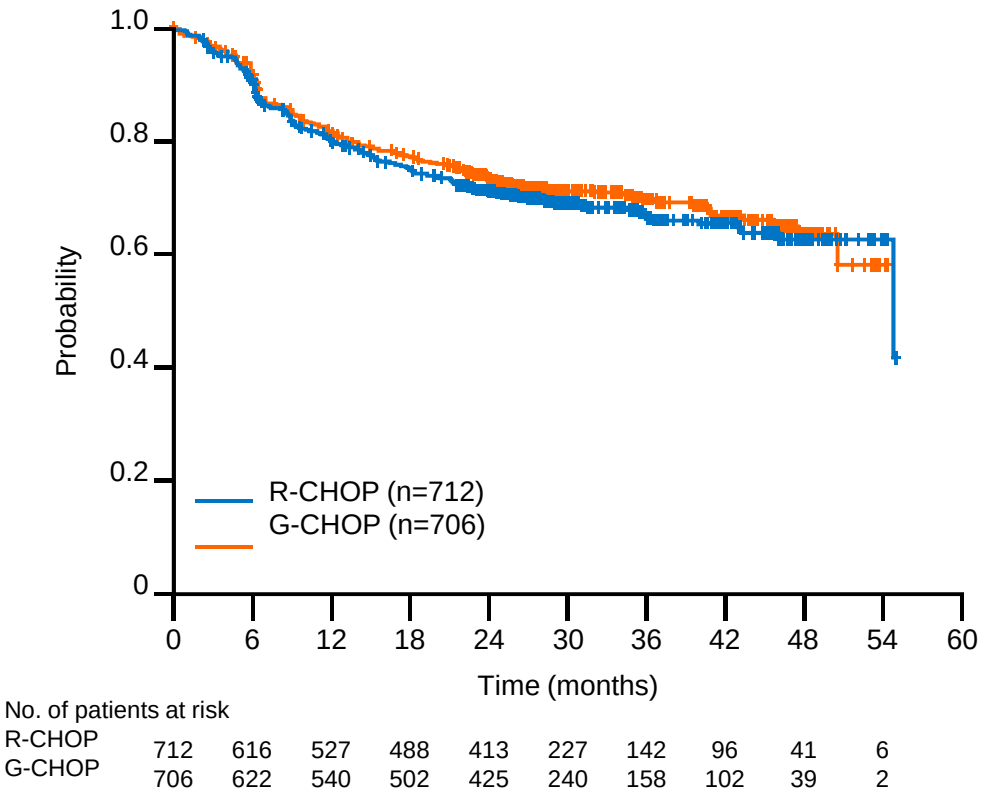
	CT-based		CT + PET-based	
	R-CHOP, n=712	G-CHOP, n=706	R-CHOP, n=665	G-CHOP, n=669
ORR	80.3%	81.7%	77.9%	77.4%
CR	**33.8%**	**35.1%**	**59.5%**	**56.7%**
PR	46.5%	46.6%	18.3%	20.8%
SD	2.0%	1.6%	0.3%	1.2%
PD	9.6%	7.4%	6.5%	5.1%
Not evaluable	2.0%	2.5%	9.6%	9.6%
Missing	6.2%	6.8%	5.7%	6.7%

- INV-assessed and IRC-assessed response rates at EOT were similar

*Assessed using the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007) with and without PET

Investigator-assessed PFS (primary endpoint)

Kaplan-Meier plot of investigator-assessed PFS by treatment arm



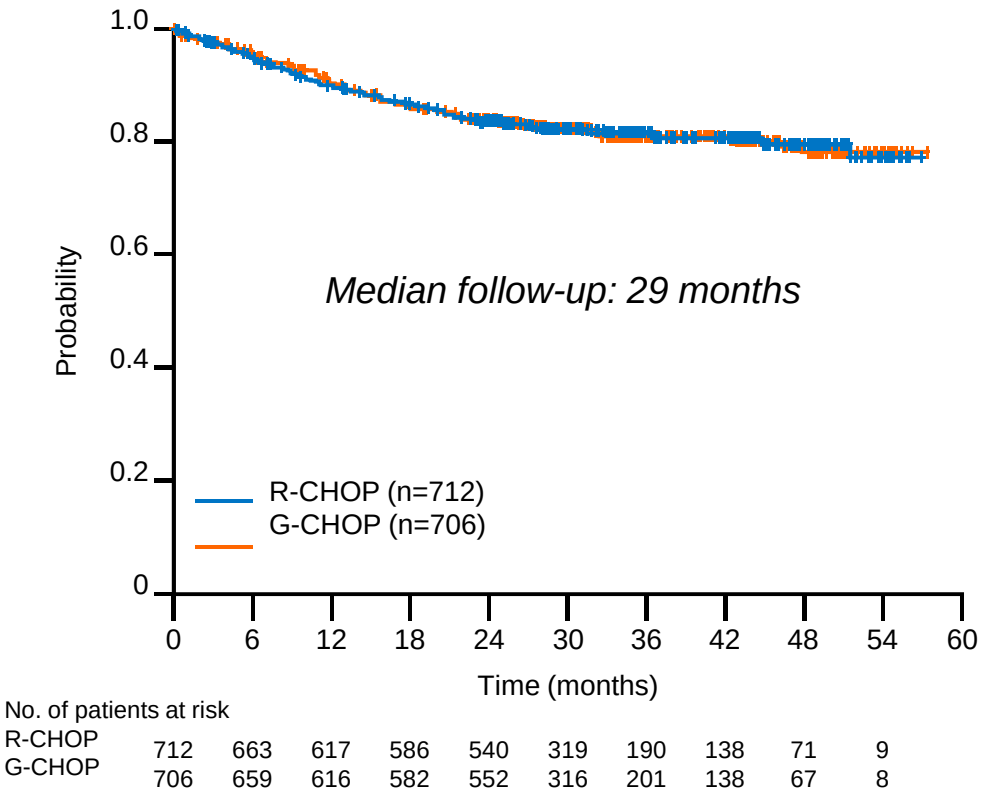
	R-CHOP, n=712	*G-CHOP, n=706*
Pts with event, n (%)	215 (30.2)	201 (28.5)
1-yr PFS, %	79.8	81.6
2-yr PFS, %	71.3	73.4
3-yr PFS, %	66.9	69.6
HR (95% CI), p-value*	0.92 (0.76, 1.11), p=0.3868	

Median follow-up: 29 months

*Stratified analysis; stratification factors: IPI score, number of planned chemotherapy cycles

Overall survival

Kaplan-Meier plot of OS by treatment arm

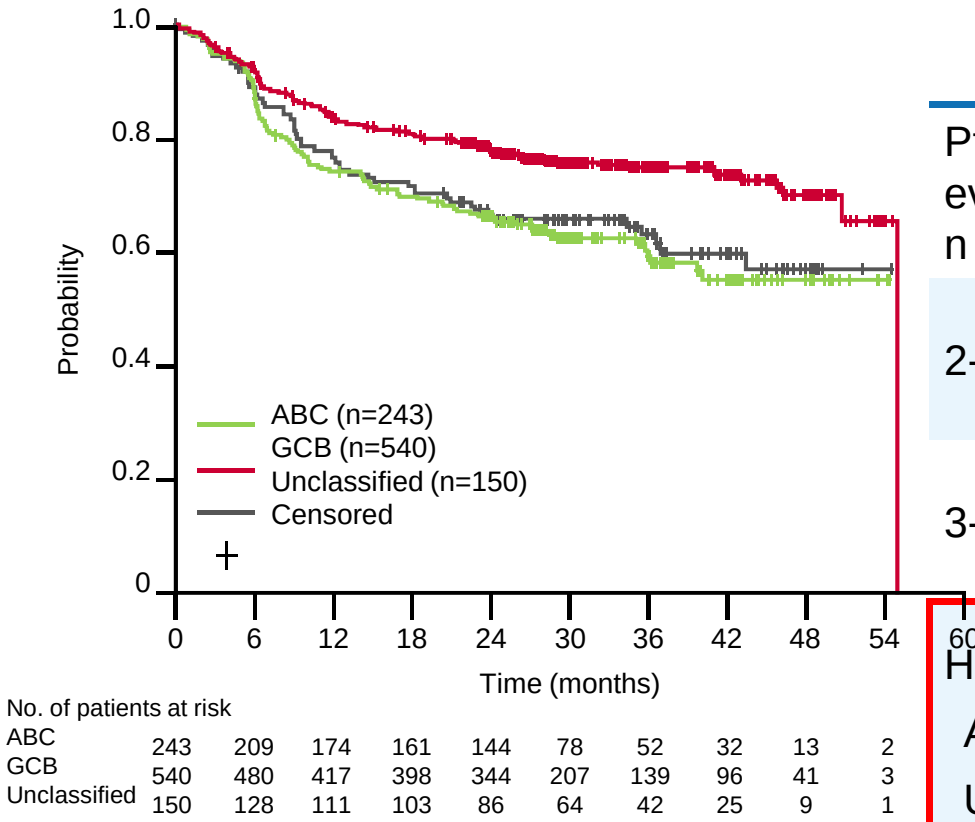


	R-CHOP, n=712	G-CHOP, n=706
Pts with event, n (%)	126 (17.7)	126 (17.8)
1-yr OS, %	89.9	90.7
2-yr OS, %	83.7	83.9
3-yr OS, %	81.4	81.2
HR (95% CI), p-value*	1.00 (0.78, 1.28), p=0.9982	

*Stratified analysis; stratification factors: IPI score, number of planned chemotherapy cycles

Investigator-assessed PFS by cell of origin*

Kaplan-Meier plot of investigator-assessed PFS by COO



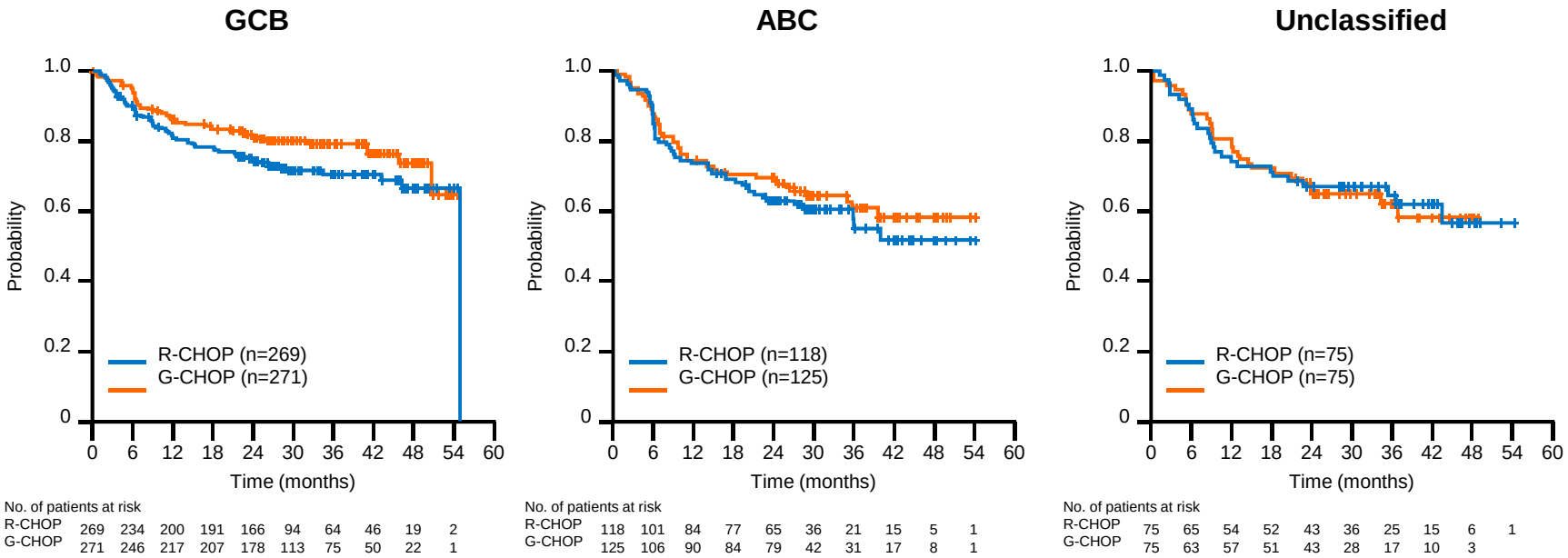
	ABC, n=243	GCB, n=540	Unclassified, n=150
Pts with event, n (%)	92 (37.9)	129 (23.9)	54 (36.0)
2-yr PFS, %	66.4	78.0	65.9
3-yr PFS, %	59.3	75.0	63.2

HR (95% CI)	
ABC vs GCB	1.70 (1.30, 2.23)
Unclassified vs GCB	1.57 (1.14, 2.16)

*Exploratory analysis; COO classification determined for 933 pts by gene expression profiling assay (Nanostring); missing COO classifications due to: restricted Chinese export license, n=252; CD20+ DLBCL not confirmed, n=102; missing/inadequate tissue, n=131; PFS HR=0.82 (0.64, 1.04) in pts with COO classification; PFS HR=1.18 (0.85, 1.64) in pts without COO classification

Investigator-assessed PFS by cell of origin and treatment arm*

Kaplan-Meier plots of investigator-assessed PFS by COO and treatment arm

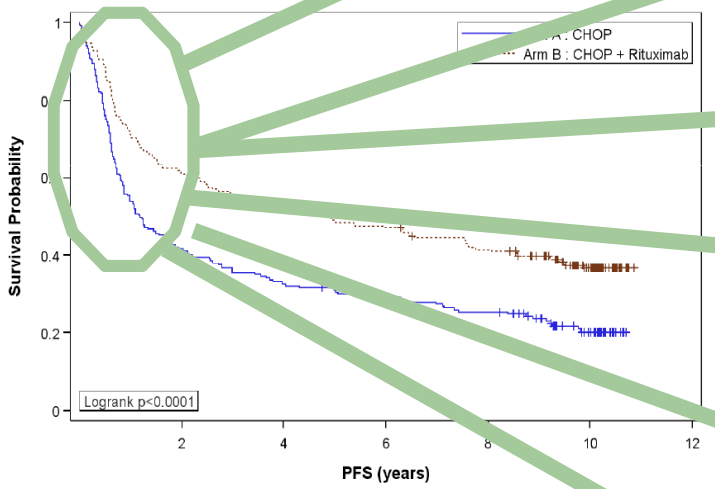


HR (95% CI)†	0.72 (0.50, 1.01)	HR (95% CI)†	0.86 (0.57, 1.29)	HR (95% CI)†	1.02 (0.60, 1.75)
3-yr PFS	71% vs 79%, R-CHOP vs G-CHOP	3-yr PFS	58% vs 61%, R-CHOP vs G-CHOP	3-yr PFS	64% vs 62% R-CHOP vs G-CHOP

*Exploratory analysis: COO classification available in 933 pts; missing COO classifications due to: restricted Chinese export license, n=252; CD20+ DLBCL not confirmed, n=102; missing/inadequate tissue, n=131; PFS HR=0.82 (0.64, 1.04) in pts with COO classification; PFS HR=1.18 (0.85, 1.64) in pts without COO classification

†Unstratified analysis

DLBCL: Strategies to improve beyond R-CHOP-21



Intensification over R-CHOP-21?

Other MoAB

Combo R-CHOP-21 + X ?

Better predict /evaluate quality of response?

Maintenance after CR/PR

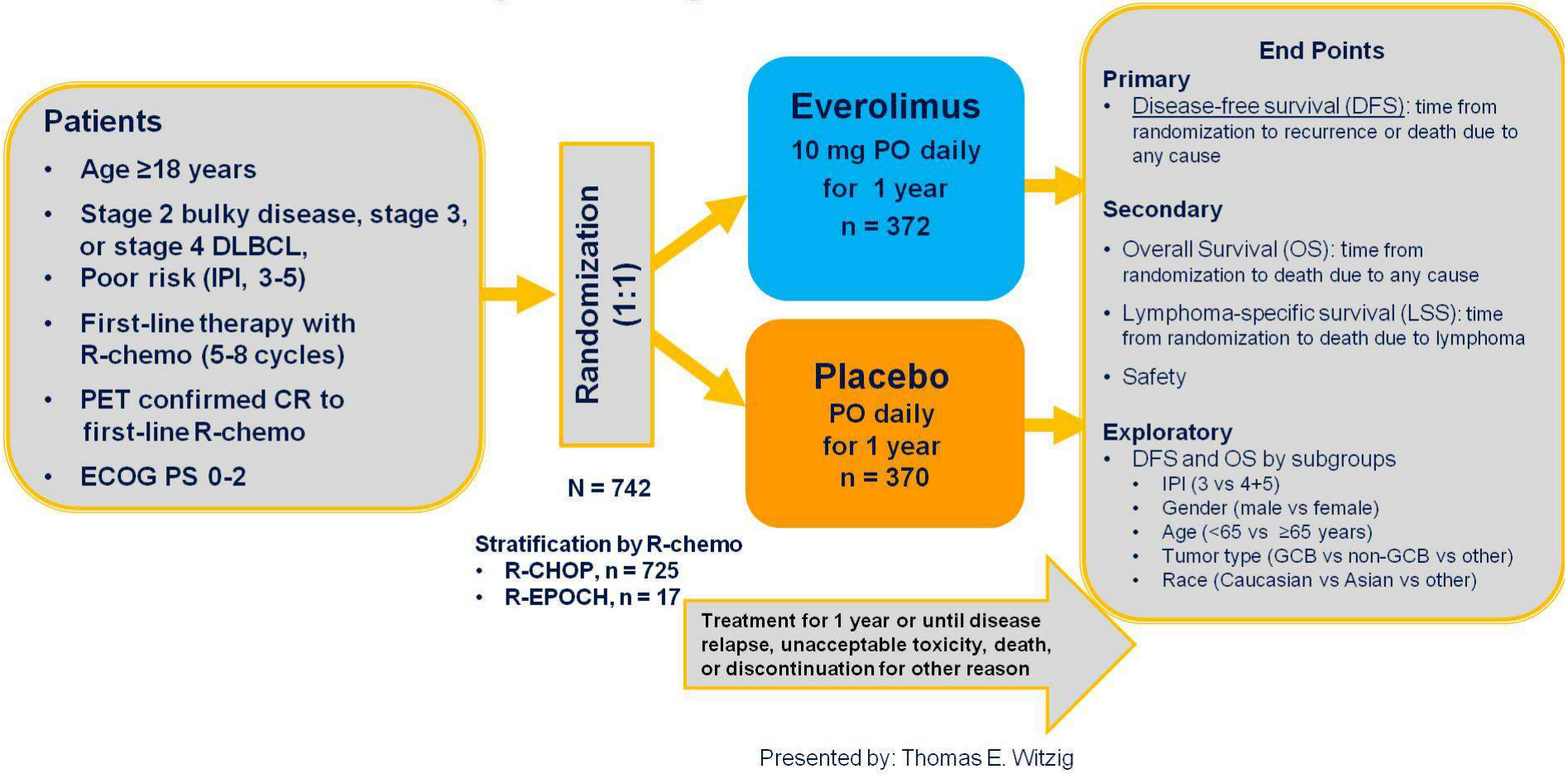
Take into consideration biological diversity of DLBCL

DLBCL: Strategies to improve beyond R-CHOP-21

A role for maintenance treatment ?

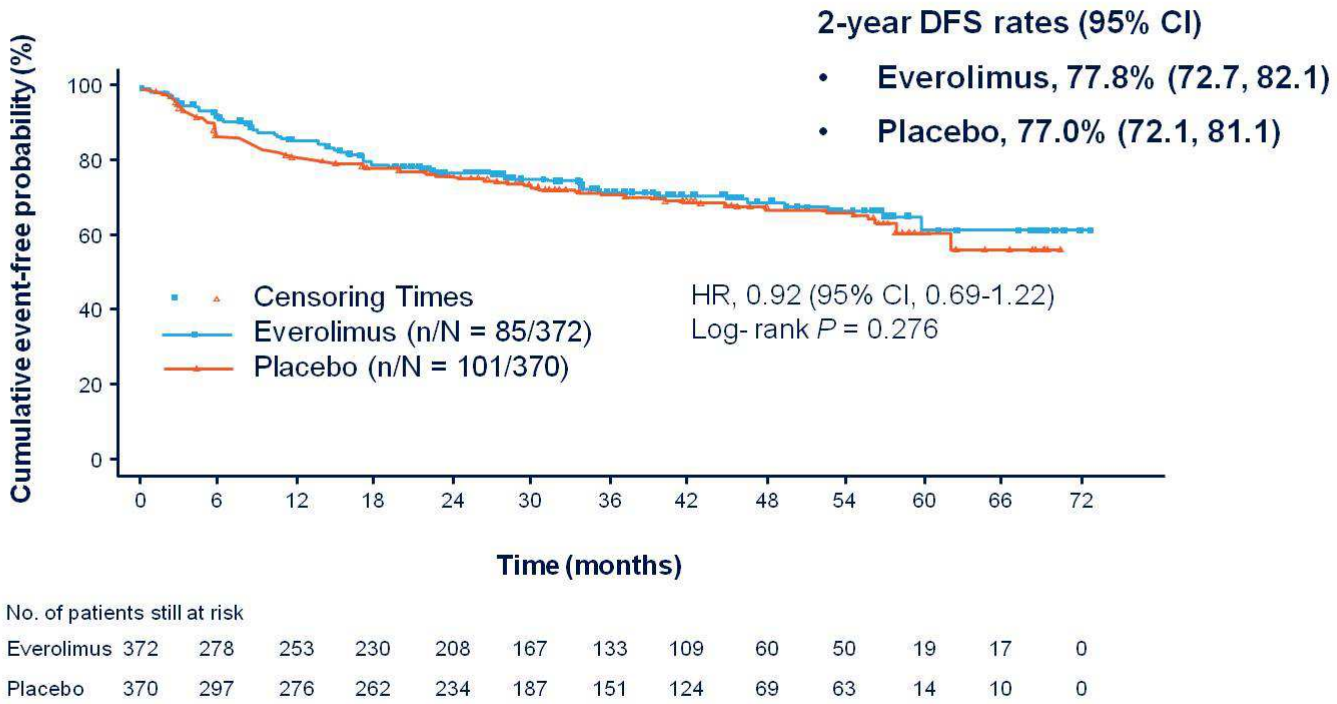
- Rituximab — No
- Enzastaurin — No
- Everolimus — PILLAR
- Lenalinomide — REMARC

PILLAR-2 Study Design



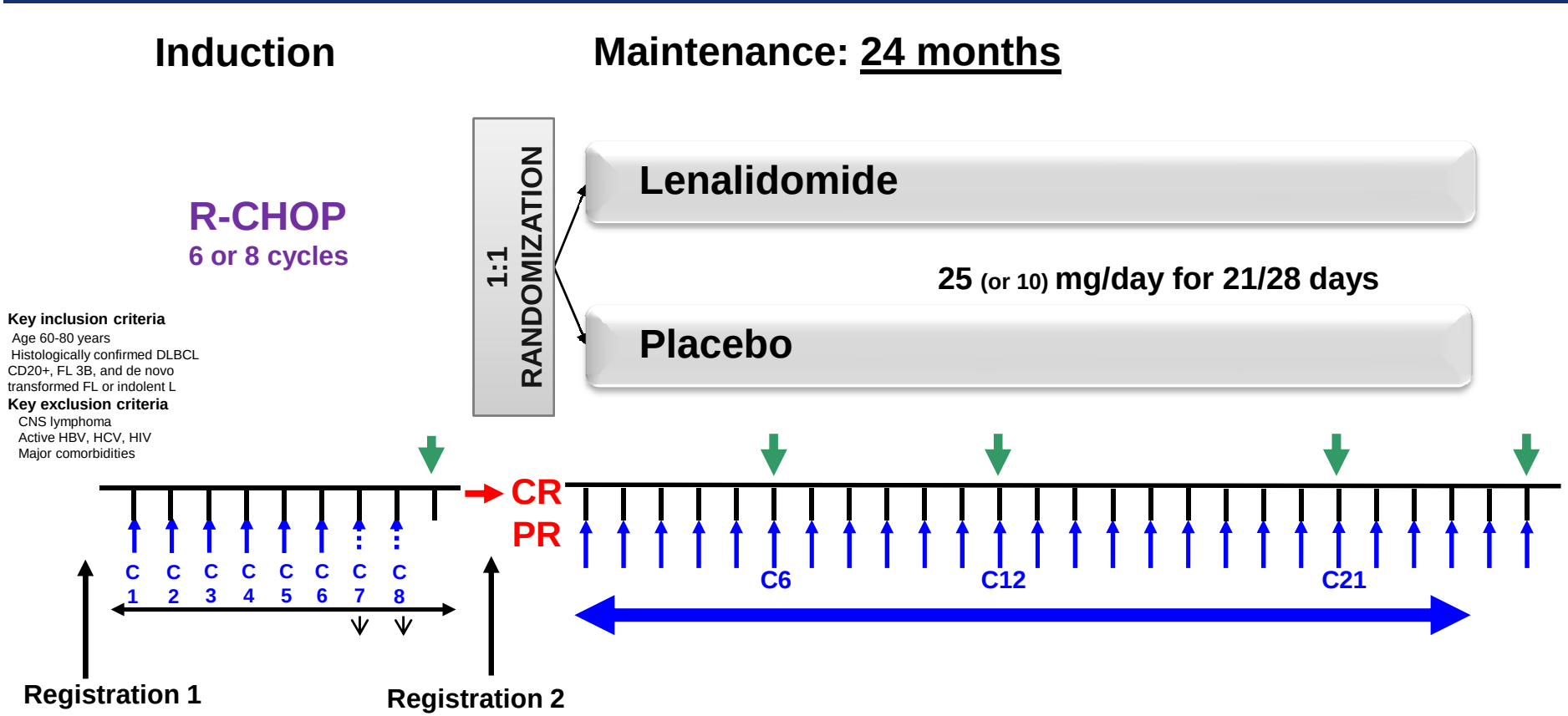
Presented by: Thomas E. Witzig

DFS: No Significant Difference Between Everolimus and Placebo



Presented by: Thomas E. Witzig

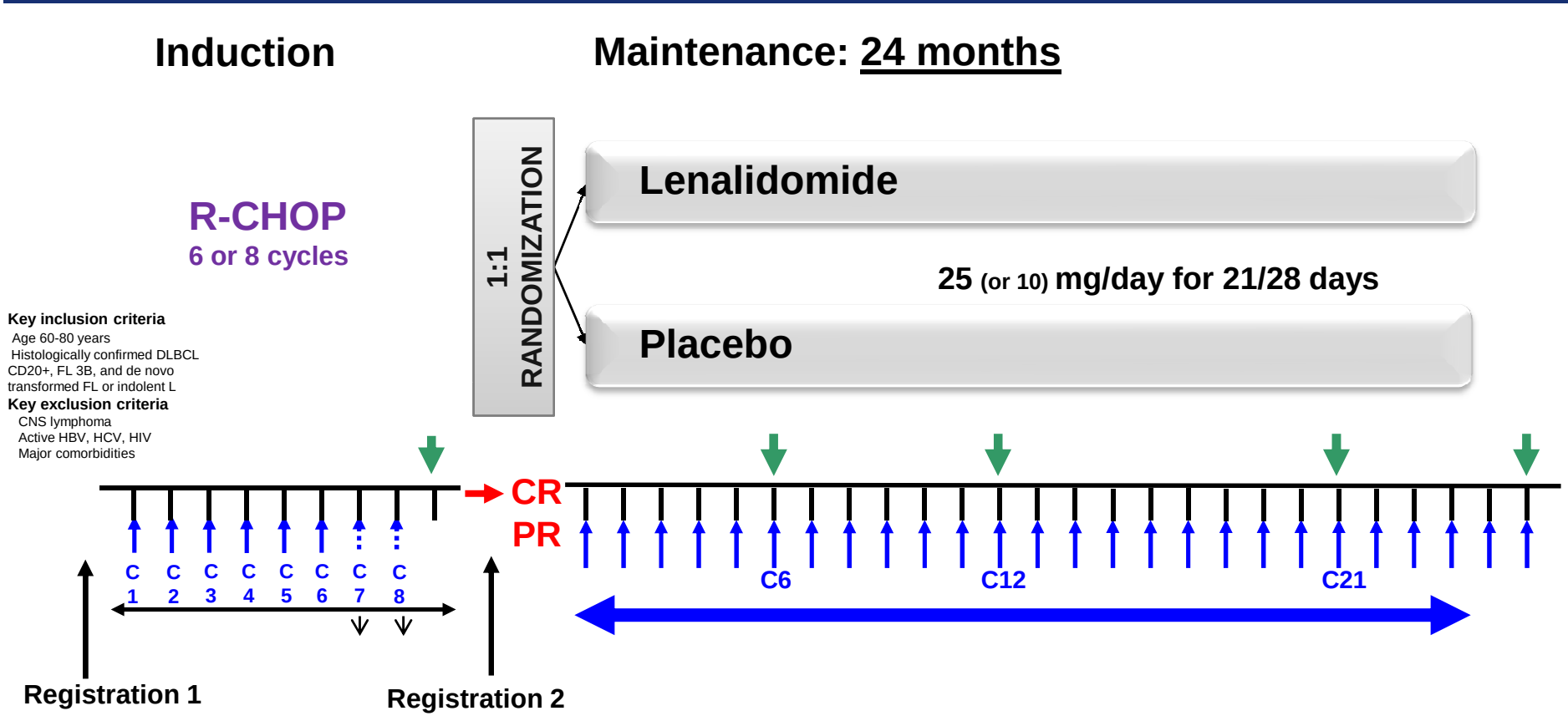
REMARC Study Design



Response evaluation

Available from: https://clinicaltrials.gov NCT01122472

REMARC Study Design



Response evaluation

Available from: https://clinicaltrials.gov NCT01122472

REMARC Study Endpoints

Primary Endpoint

- **Progression-free survival (central review)**

Secondary Endpoints

- **Safety**
- **PR to CR conversion rate**
- **Overall survival**
- **Efficacy according to the response to R-CHOP**

Patient Characteristics At Randomization

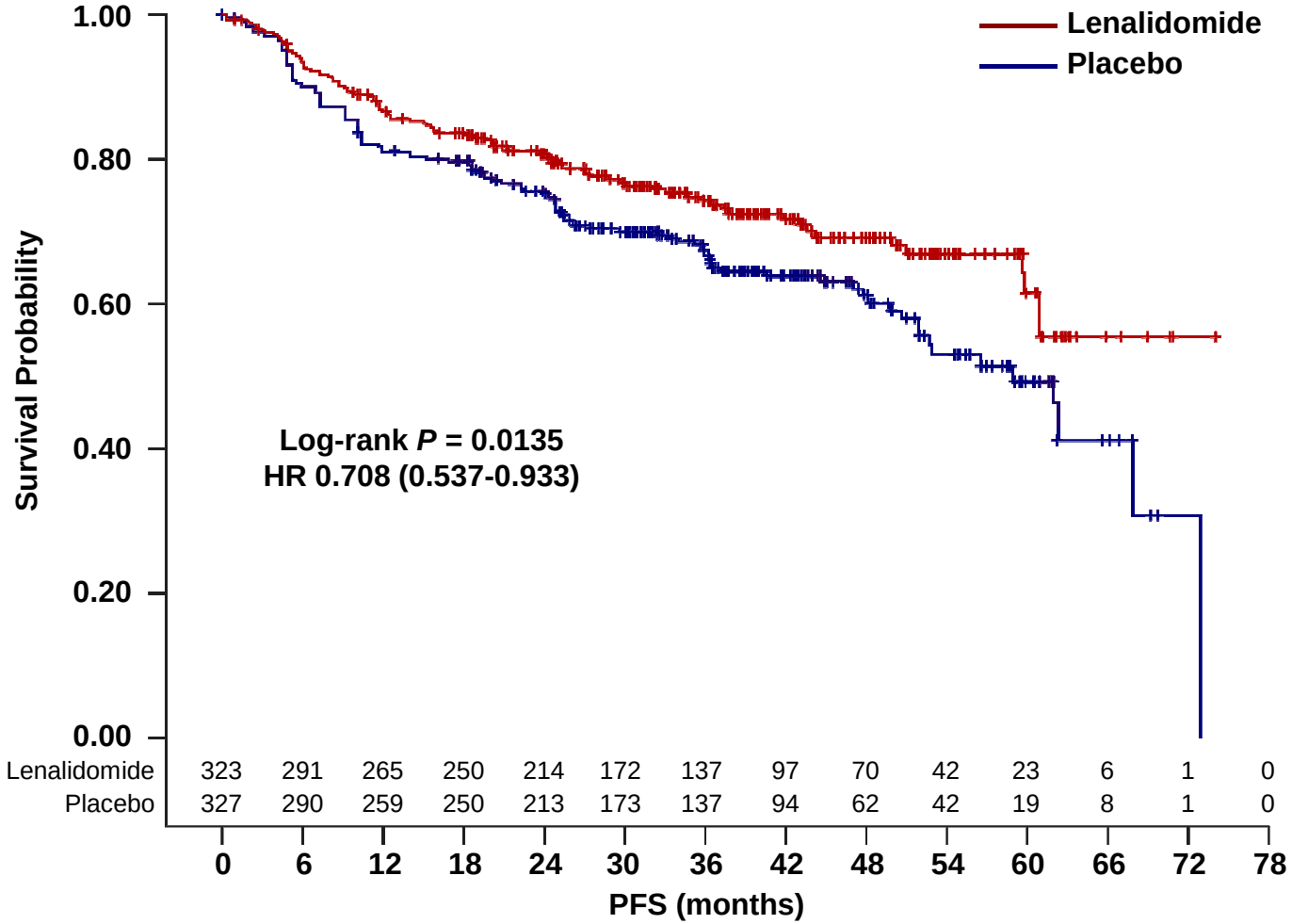
Characteristic, n (%)	Treatment Arm	
	Lenalidomide (n = 323)	Placebo (n =327)
Median age	**69 years**	**68 years**
≥70 years	154 (48)	145 (44)
Sex		
Male	183 (57)	180 (55)
Female	140 (43)	147 (45)
Response after R-CHOP		
CR	251 (78)	244 (75)
PR	69 (21)	83 (25)
ORR	320 (99)	327 (100)

Histology

Characteristic, n (%)	Treatment Arm	
	Lenalidomide (n = 323)	Placebo (n =327)
Histological diagnosis classification (central review)	**n = 290**	**n = 290**
Diffuse large B-cell NOS	225 (78)	233 (80)
Follicular lymphoma grade 3b	2 (1)	3 (1)
De novo transformed	31 (11)	16 (6)
Other*	32 (11)	38 (13)
GCB/ABC profile (NanoString technology) – DLBCL NOS only	**n = 151**	**n = 167**
ABC	**63 (42)**	**58 (35)**
GCB	**59 (39)**	**79 (47)**
Unclassified	24 (16)	25 (15)
N/A	5 (3)	5 (3)

*Other: B-cell lymphoma with intermediate features between DLBCL and Burkitt's; B-cell lymphoma with intermediate features between DLBCL and HD; composite: FL 3b and DLBCL; and composite: DLBCL and HD.

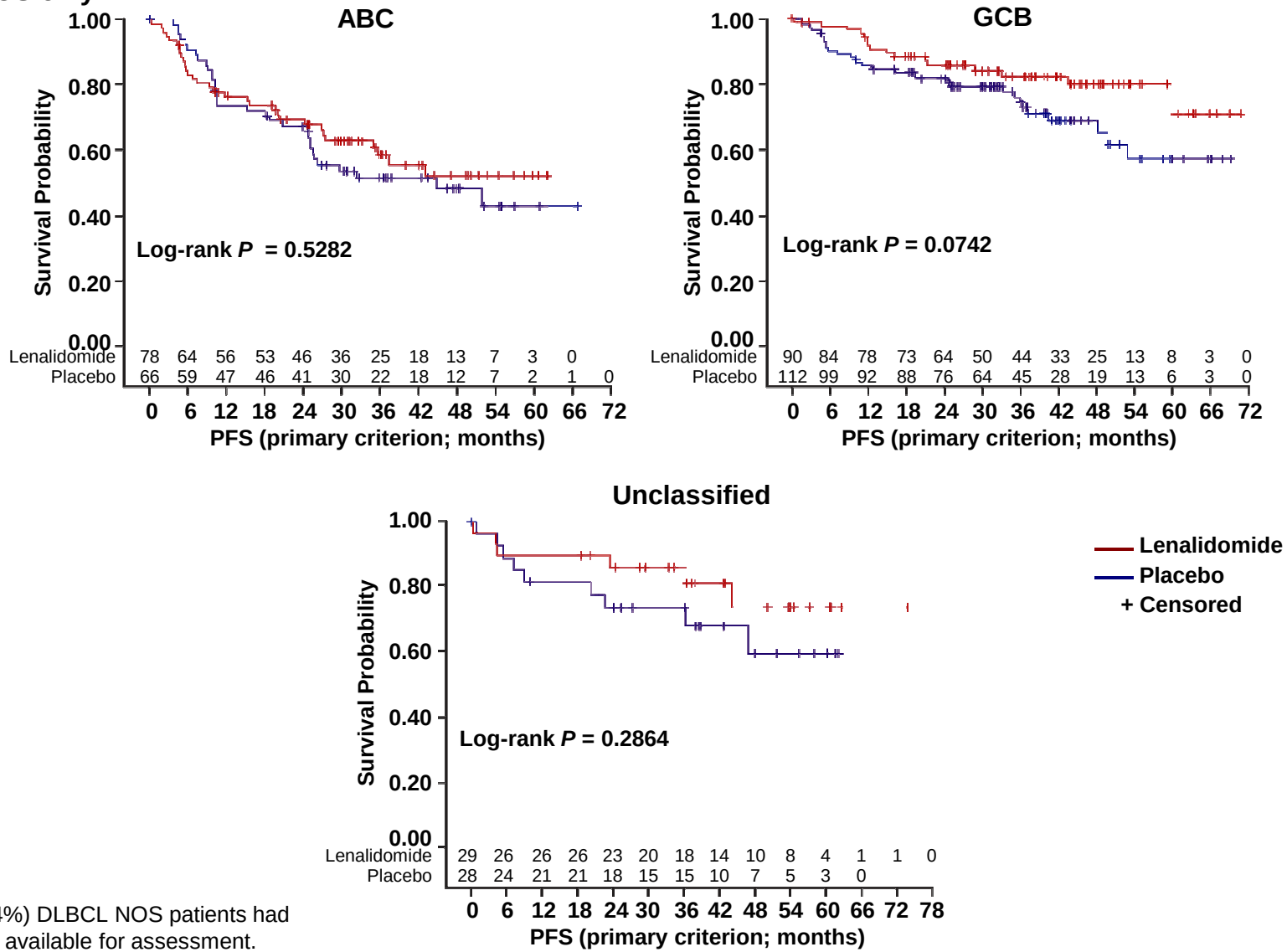
REMARC: Progression-Free Survival (Central Review)



At a median follow-up of 40 months, median PFS was not reached (NR) for Lenalidomide and 58.8 months for Placebo

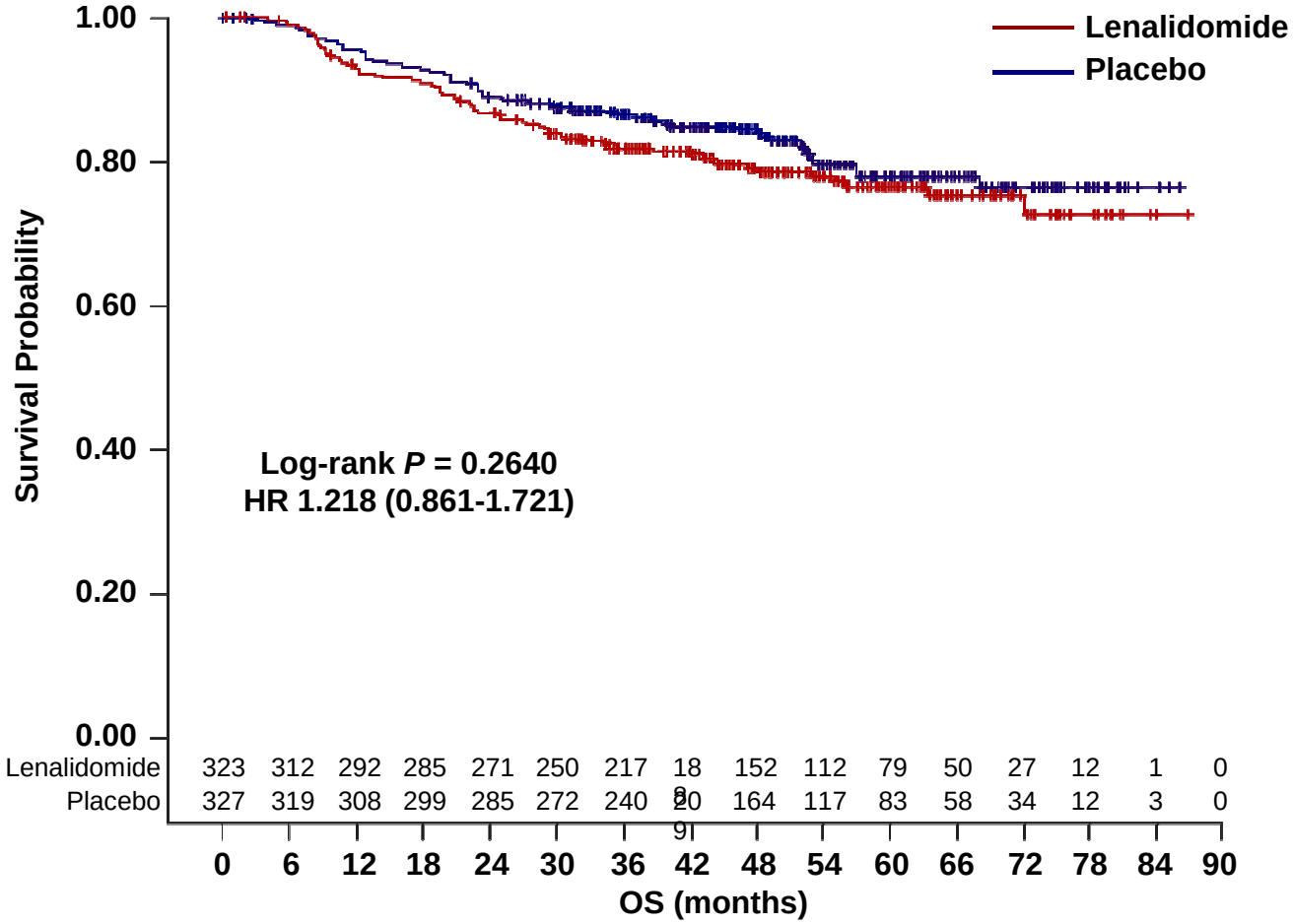
REMARC PFS: GCB vs ABC (GEP)

DLBCL NOS only*



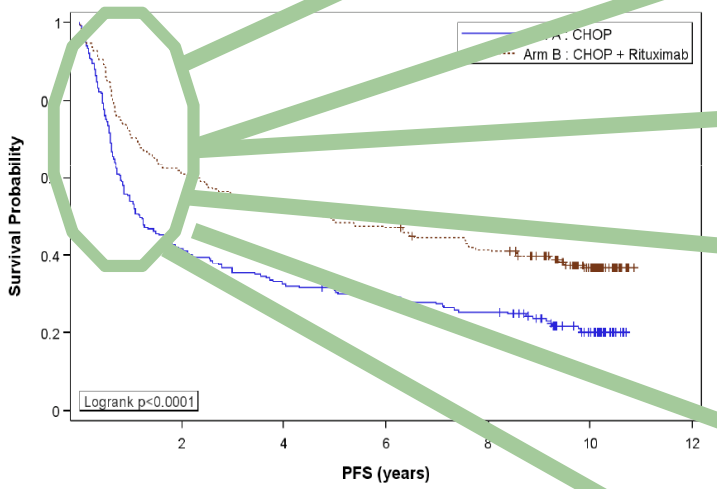
*318/432 (74%) DLBCL NOS patients had COO results available for assessment.

REMARC: Overall Survival



- At a median follow-up of 52 months, there was no statistical difference between arms
- Multivariate analysis showed that treatment arm was not a statically significant factor

DLBCL: Strategies to improve beyond R-CHOP-21



Intensification over R-CHOP-21?

Other MoAB

Combo R-CHOP-21 + X ?

Better predict /evaluate quality of response?

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Take into consideration biological diversity of DLBCL

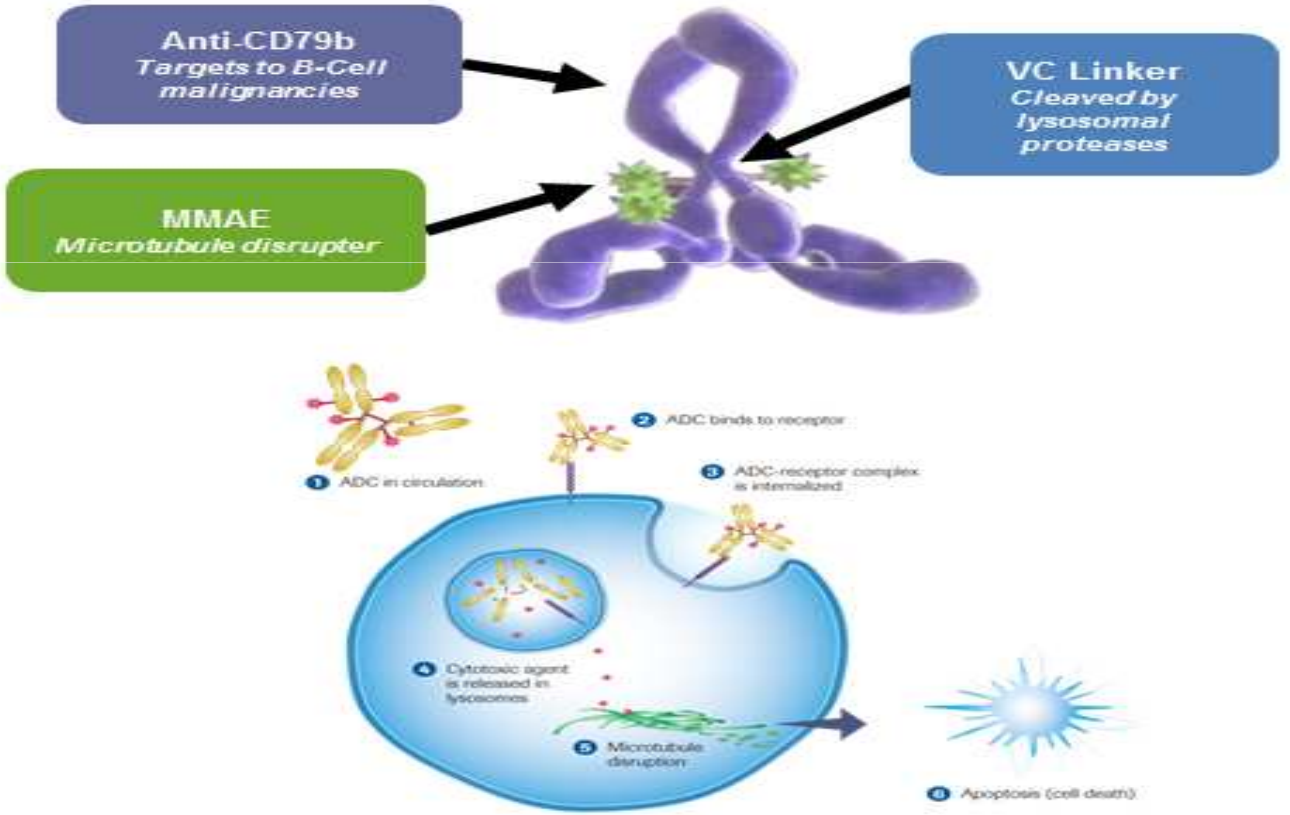
R (G) CHOP + X

- RA-CHOP: stopped because of bevacizumab toxicity
- **R2-CHOP (lenalidomide)**
  - ***phase II published, historical comparison, Phase 3 ongoing (ROBUST)***
- **R-CHOP + bortezomib**
  - ***Phase II : no benefit in non GCB group***
- R-CHOP + enzastaurin: negative
  - ***Phase III: no benefit***
- **R-CHOP + ibrutinib**
  - ***phase II published, Phase 3 results expected (PHOENIX)***
- R-CHOP + idelalisib
- R-CHOP + ABT-199
- R-CHOP + Polatuzumab (phase I/II)

- …

Polatuzumab

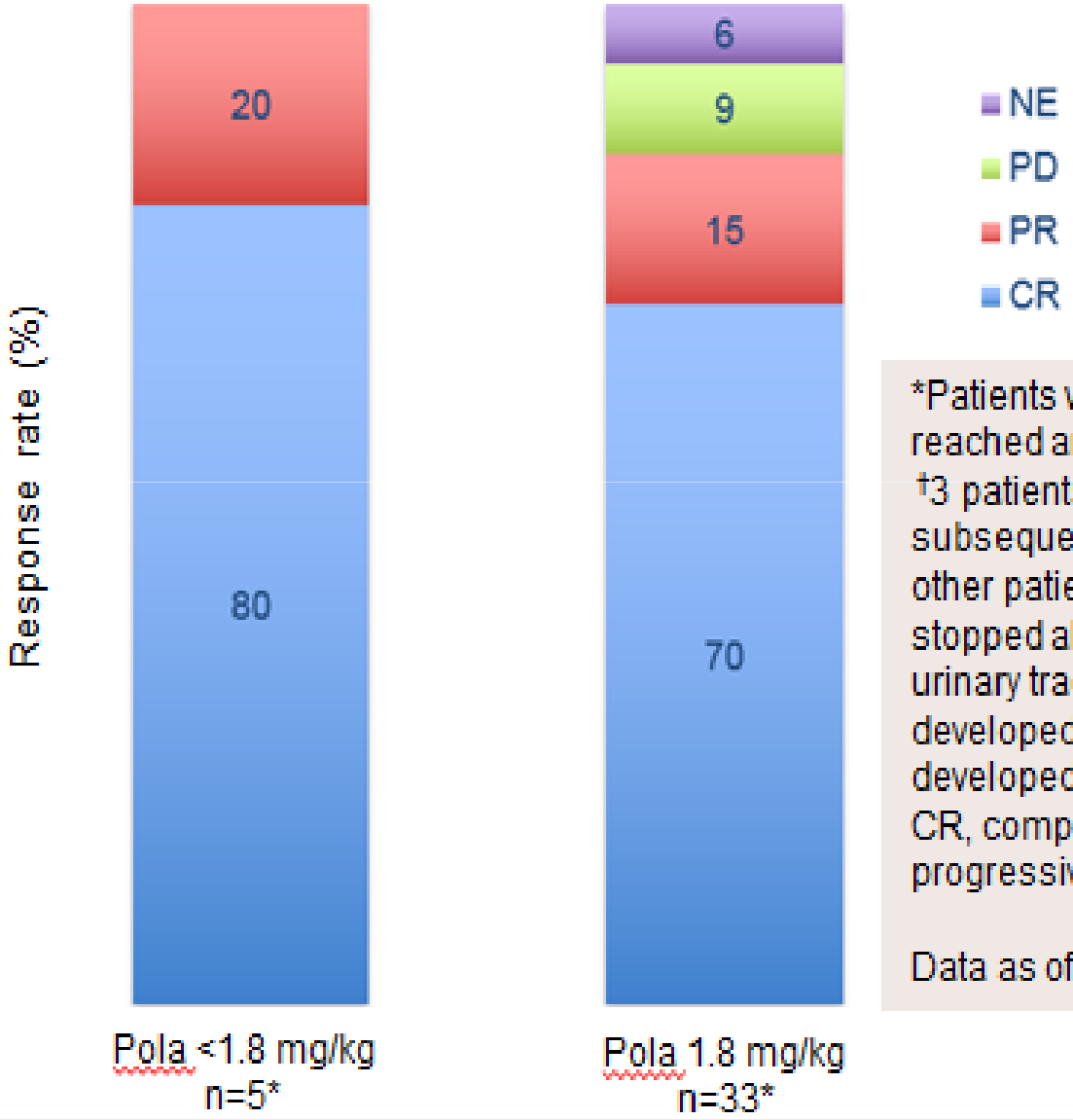
Figure 1: Mode of Action of Polatuzumab Vedotin



ADC, antibody-drug conjugate; MMAE, monomethyl auristatin E; VC, valine-citrulline

Tilly et al. ASH 2016

Figure 3: Efficacy of Pola + R-CHP in DLBCL by PET/CT

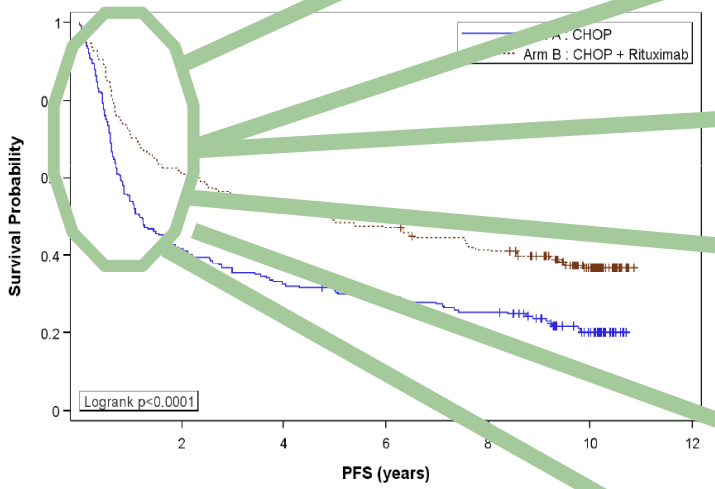


*Patients were only considered evaluable if they reached any defined response point.
†3 patients: one had a new axillary lesion and subsequently died despite salvage treatment; one other patient had a CR) at interim evaluation, but stopped all treatment after 5 cycles due to *E. coli* urinary tract infection (UTI) and subsequently developed recurrent disease; the third patient developed a new pulmonary lesion after two cycles.
CR, complete response; PR, partial response; PD, progressive disease; NE, non-evaluable,

Data as of 24 July 2016

Tilly et al. ASH 2016

DLBCL: Strategies to improve beyond R-CHOP-21



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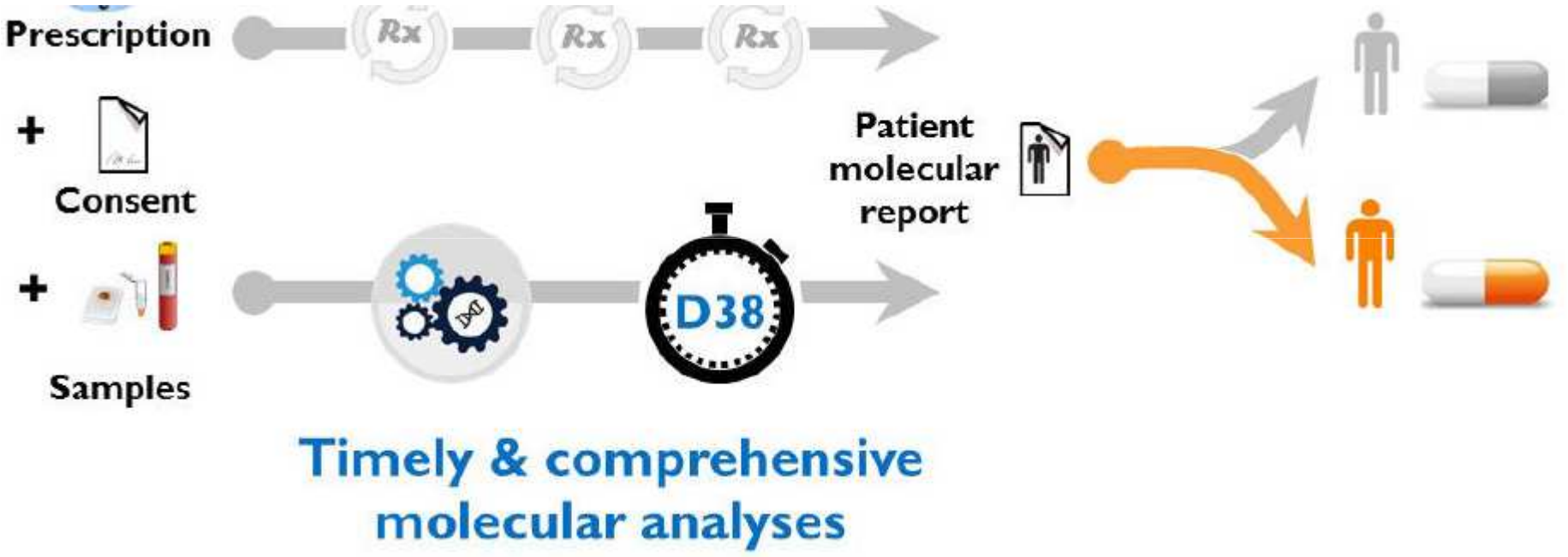
projet RT3 « Real Time Tailored Therapy »



Phenotype, FISH, GEP, NGS

INSTITUT CARNOT CALYM
Lysa
Lysarc

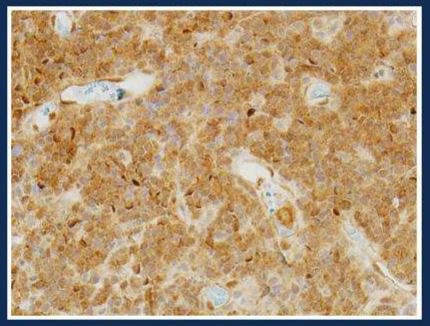
Lymphomes cérébraux

Primary or secondary CNS recurrence is usually a fatal event

- Risk of secondary CNS recurrence is 6.4% in the rituximab era
- Median survival after CNS recurrence is 3-4 months
- Management options
  - High dose methotrexate, cytarabine
  - ASCT with thiotepa or radiation-based regimens
  - WBRT
  - Temozolomide with or without rituximab

Villa, et al., Ann Oncol. 2010 May;21(5):1046-52

Lenalidomide treatment of CNS recurrence: an emerging story



Cereblon is overexpressed in CNS lymphomas

Lenalidomide

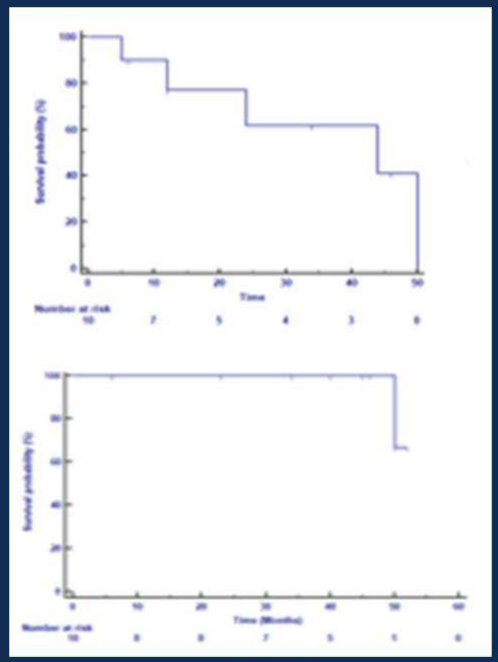
- Targets cereblon in recurrent CNS lymphoma
- Crosses BBB

From Rubeinstein, ASCO 2016 Abstract 7502

Key Results of len for recurrent CNS lymphoma

PFS

OS



From Rubeinstein, ASCO 2016 Abstract 7502

Lenalidomide extended treatment was tolerable and has promising early efficacy

- Med age 70 years
- Heavily pretreated patients
- Emerging biomarkers of response
- Response duration exceeds other treatment modalities (WBRT, ASCT)

Étude PRECIS : radiothérapie ou autogreffe en première ligne ? (1)

Résultats intermédiaires

LOC

Lymphomes du SNC primitifs

Randomisation

Bras A : induction + Rx

S1 → **R-MBVP**

S4 → **R-MBVP**

S8 → **R-AraC**

S11 → **R-AraC**

Recueil

Bras B : induction + autogreffe

40 Gy encéphale

Rituximab	375 mg/m^2	J1
Méthotrexate	3 g/m^2	J1 ; J15
VP16	100 mg/m^2	J2
Carmustine	100 mg/m^2	J3
Prednisone	60 mg/m^2/j	J1-J5

Rituximab	375 mg/m^2	J1
Cytarabine	3 g/m^2	J1 ; J2

Conditionnement greffe :

Thiotépa	250 mg/m^2/j	J9-8-7
Busulfan	8 mg/kg	J6-5-4
Cy	60 mg/kg/j	J3-2
Greffe		J0

Cy : cyclophosphamide.

Critère principal : SSP à 2 ans

Étude PRECIS : radiothérapie ou autogreffe en première ligne ? (2)

Résultats intermédiaires

Population de l'analyse intermédiaire

	Bras A (Rx) [n = 38]	Bras B (auto.) [n = 38]
Hommes/femmes	27/11	24/14
Âge médian	53 (27-60)	55 (25-60)
ECOG, n (%) 0-1 2-4 NA	 24 (63) 13 (34) 1 (3)	 28 (74) 10 (26)
Intra-oculaire, n (%)	5 (13)	3 (8)
LCR, n (%)	6 (16)	5 (13)

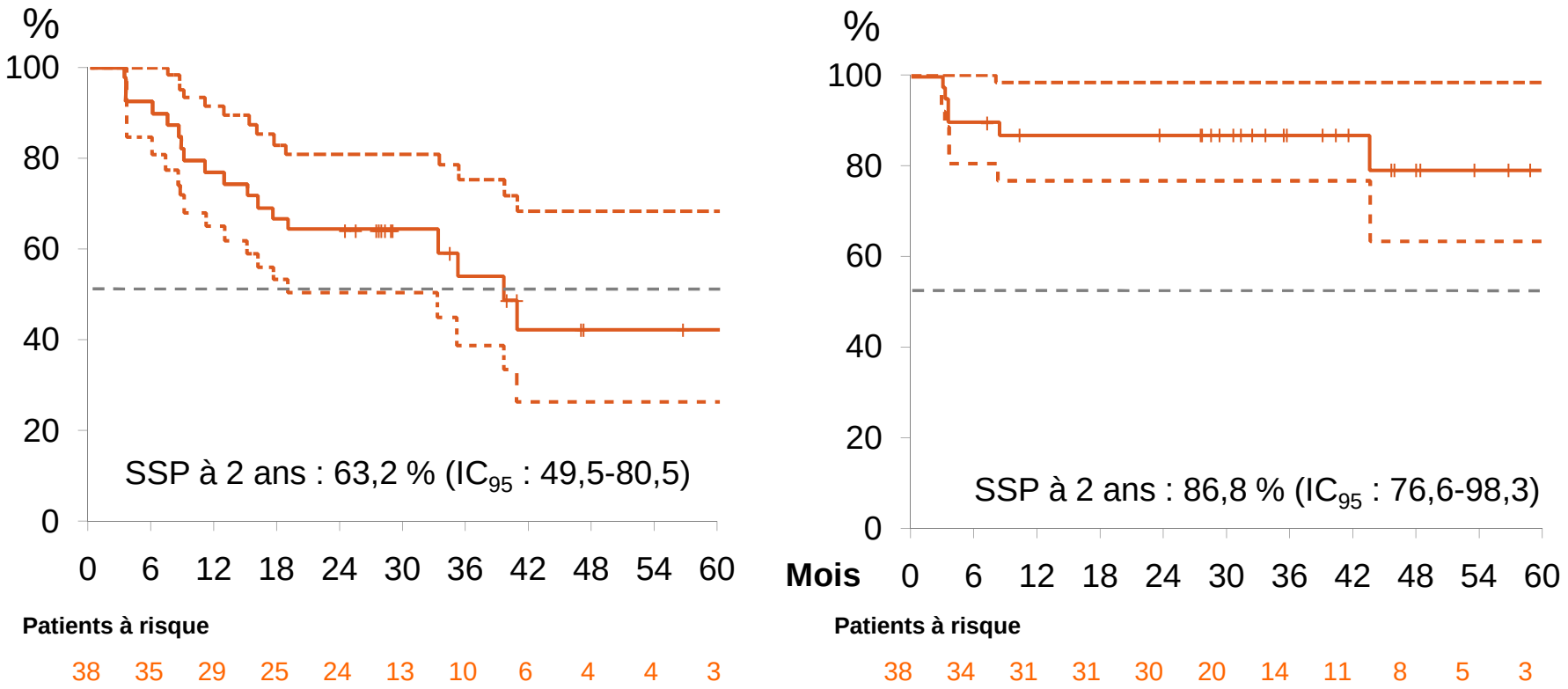
LCR : liquide céphalorachidien ; NA : non applicable.

ASH 2016 - D'après Soussain C et al., abstr. 782, actualisé

Étude PRECIS : radiothérapie ou autogreffe en première ligne ? (4)

Résultats intermédiaires

Critère principal



Étude PRECIS : radiothérapie ou autogreffe en première ligne ? (5)

Résultats intermédiaires

LOC

- Conclusion 1 : la chimiothérapie avant consolidation est décevante
- Conclusion 2 : l'autogreffe de cellules souches est plus efficace que la radiothérapie pour la survie sans progression (survie globale identique)
- Question 1 : quelle est la toxicité neurologique de la radiothérapie (analyse en cours)
- Question 2 : le conditionnement est-il optimal (toxicité+)

ASH 2016 - D'après Soussain C et al., abstr. 782, actualisé

Études REVRI et I-LOC : LNH du SNC en rechute/réfractaire

Résultats intermédiaires

LOC

Justification

- Traitement de première ligne (données LOC, *abstr. 926*)
  - Réponse complète : < 60 ans : 53 %, > 60 ans : 40 %
  - Réfractaires : 26 %
  - Survie sans progression : < 60 ans : 34,6 mois, > 60 ans : 7,9 mois

- Justification lénalidomide
  - Actif dans les LNH B diffus à grandes cellules non-centre germinatif
  - Cas publiés SNC *(Rubenstein JL et al. J Clin Oncol 2011 ; Houillier C et al. Neurology 2015)*

- Justification ibrutinib
  - Mutation Myd88 dans 70 à 80 % des LNH du SNC
  - RC sous ibritunib de LNH à cellules du manteau à localisation cérébrale *(Bernard S et al. Blood 2015)*

ASH 2016 - D'après Soussain C et al., abstr. 784 et 785, actualisés

Études REVRI et I-LOC : LNH du SNC en rechute/réfractaire (2)

Résultats intermédiaires

LOC

Schémas

REVRI

Lénalidomide 20/25 mg*/j 21 j
Rituximab 375 mg/m^2 j1
8 cycles de 28 j

→ *Si réponse*
Lénalidomide
10 mg/j 21 j
12 cycles de 28 j

CP : réponse globale

I-LOC

Ibrutinib 560 mg/j 12 mois

Poursuite possible
après 12 mois

CP : contrôle de la maladie à 2 mois (RC + RP + MS)

* Premier cycle à 20 mg, suivants à 25 mg en cas de bonne tolérance.

CP : critère principal ; RC : rémission complète ; RP : rémission partielle ; MS : maladie stable.

ASH 2016 - D'après Soussain C et al., abstr. 784 et 785, actualisés

Études REVRI et I-LOC : LNH du SNC en rechute/réfractaire (3)

Résultats intermédiaires

Réponses

	I-LOC	REVRI
Nombre (analyse – étude complète)	18 - 52	45
Contrôle à 2 mois (RG-RC) **RG (RC)**	**83% (55%-17%)**	**67% (40%)**
Suivi médian	6,6 mois	19,2 mois
Survie sans progression	8 progressions 8 patients toujours sous traitement	8,1 mois (rechutes pendant entretien : 10/18)
Toxicité	2 aspergilloses	27 % de grade 3-4

ASH 2016 - D'après Soussain C et al., abstr. 784 et 785, actualisés

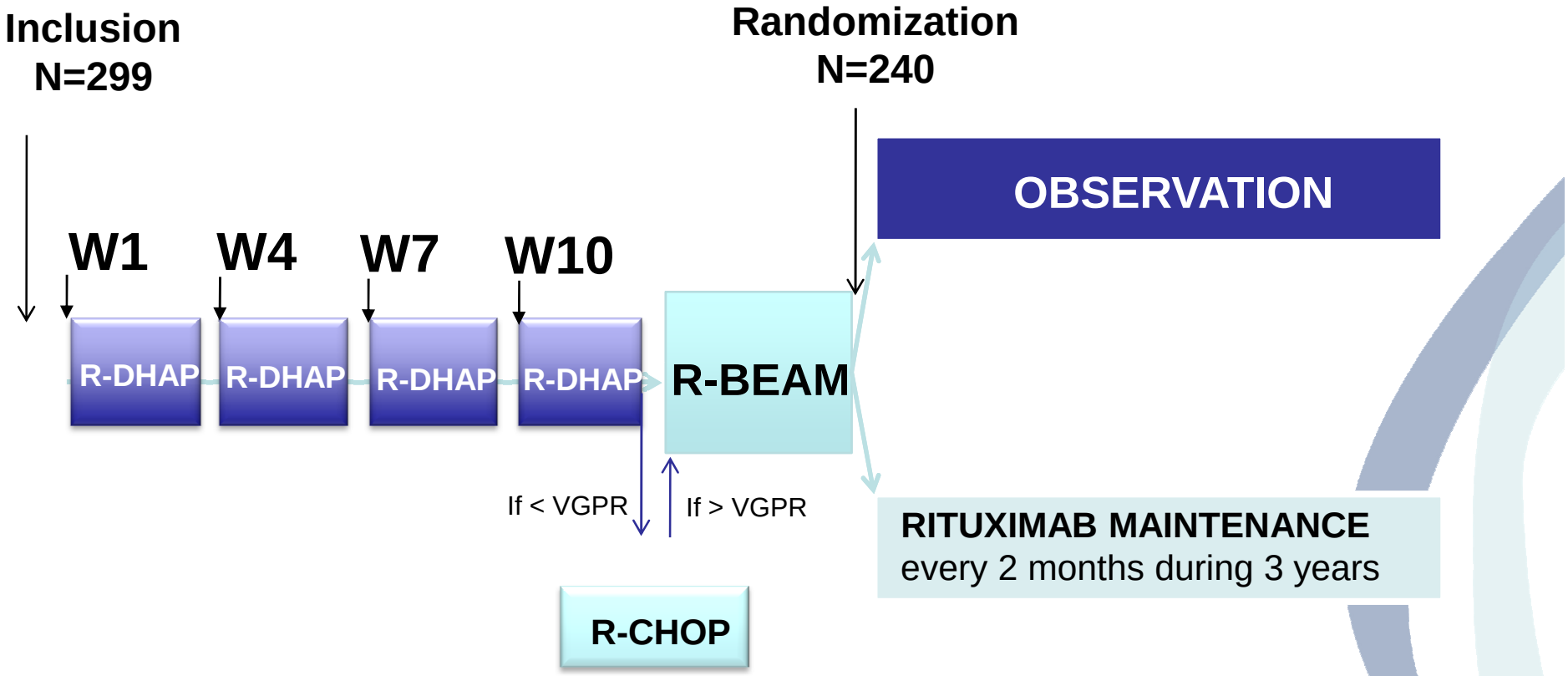
Études REVRI et I-LOC : LNH du SNC en rechute/réfractaire (4)

Résultats intermédiaires

- Conclusion 1 : le lénalidomide et l'ibrutinib sont efficaces dans les LNH du SNC
- Conclusion 2 : rechutes fréquentes (effet-dose du lénalidomide) – suivi court
- Conclusion 3 : aspergilloses sous ibrutinib, à surveiller !
- Conclusion 4 : associations futures ?

Lymphome du manteau

LyMa trial

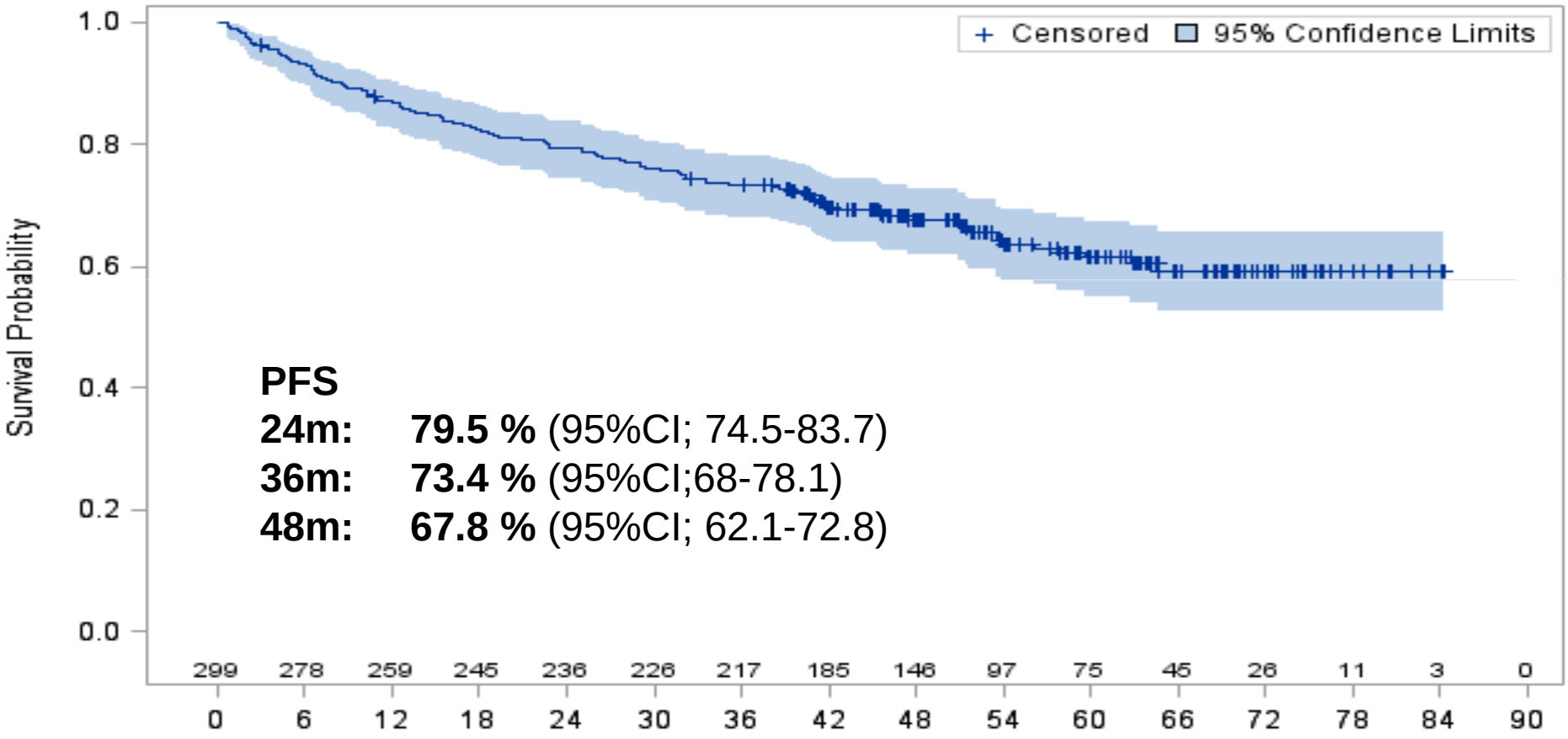


R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or oxaliplatin or carboplatin)

R-BEAM: Rituximab 500mg/m2 d-8; BCNU 300mg/m2 d-7; Etoposide 400mg/m2/d d-6 to -3; aracytine 400mg/m2/d d-6 to d-3; melphalan 140mg/m2 d-2

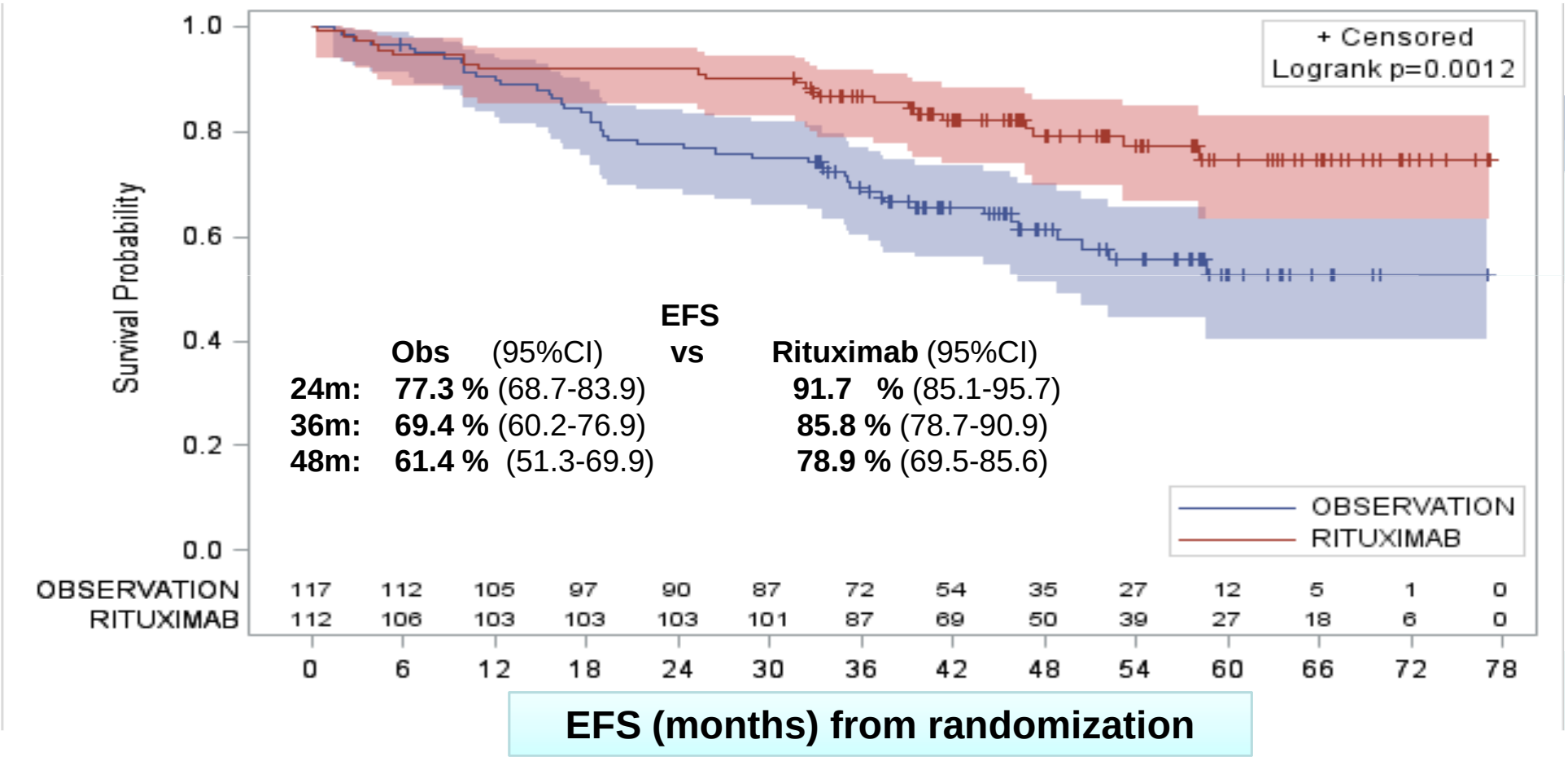
PFS from inclusion

mFU : 54.4m (52.7-59.2)



EFS from Randomization

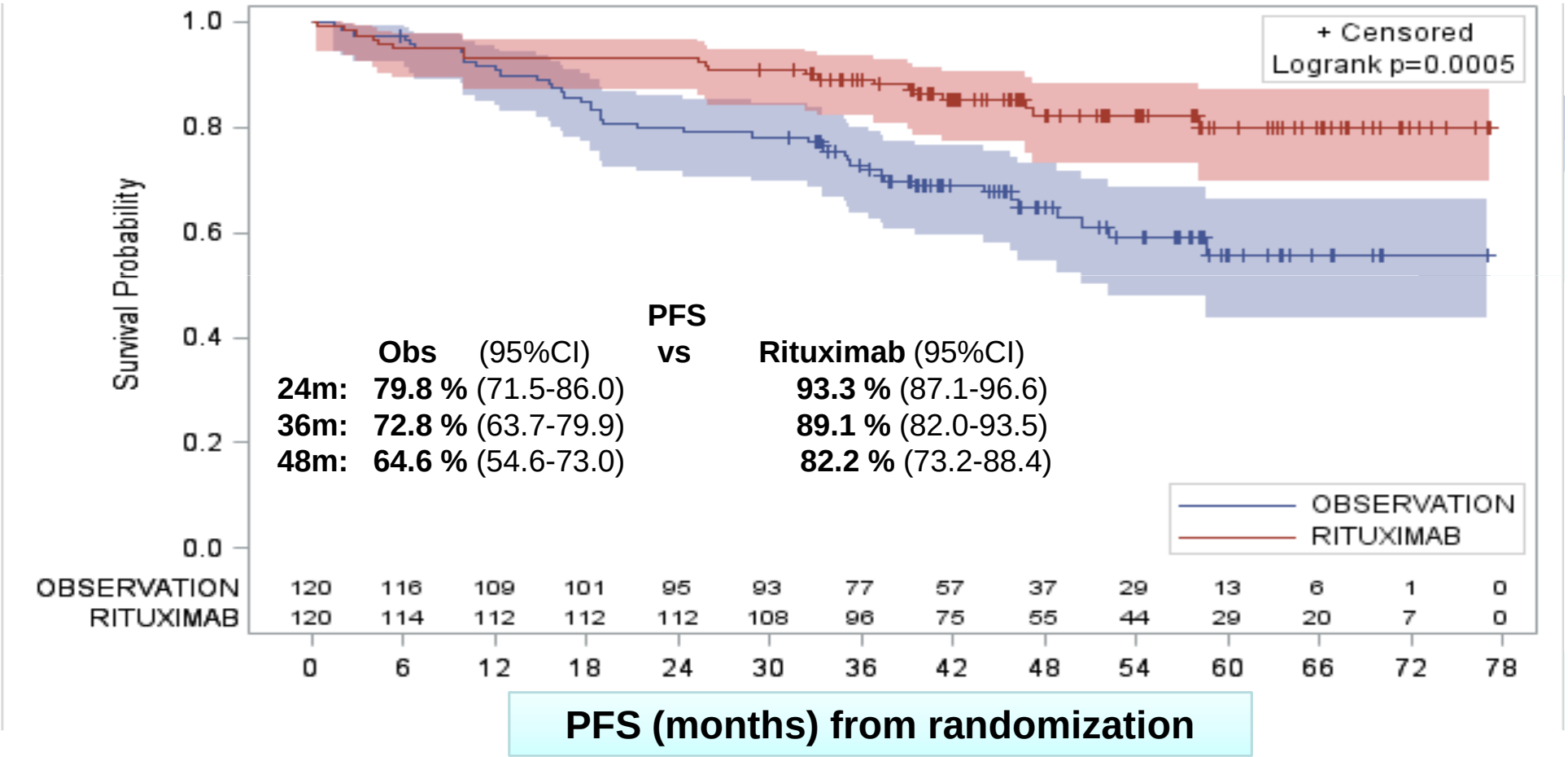
mFU: 50.2m (46.4-54.2)



EFS: Progession, Rechute, Décès, infections grade 4, allergie au Rituximab

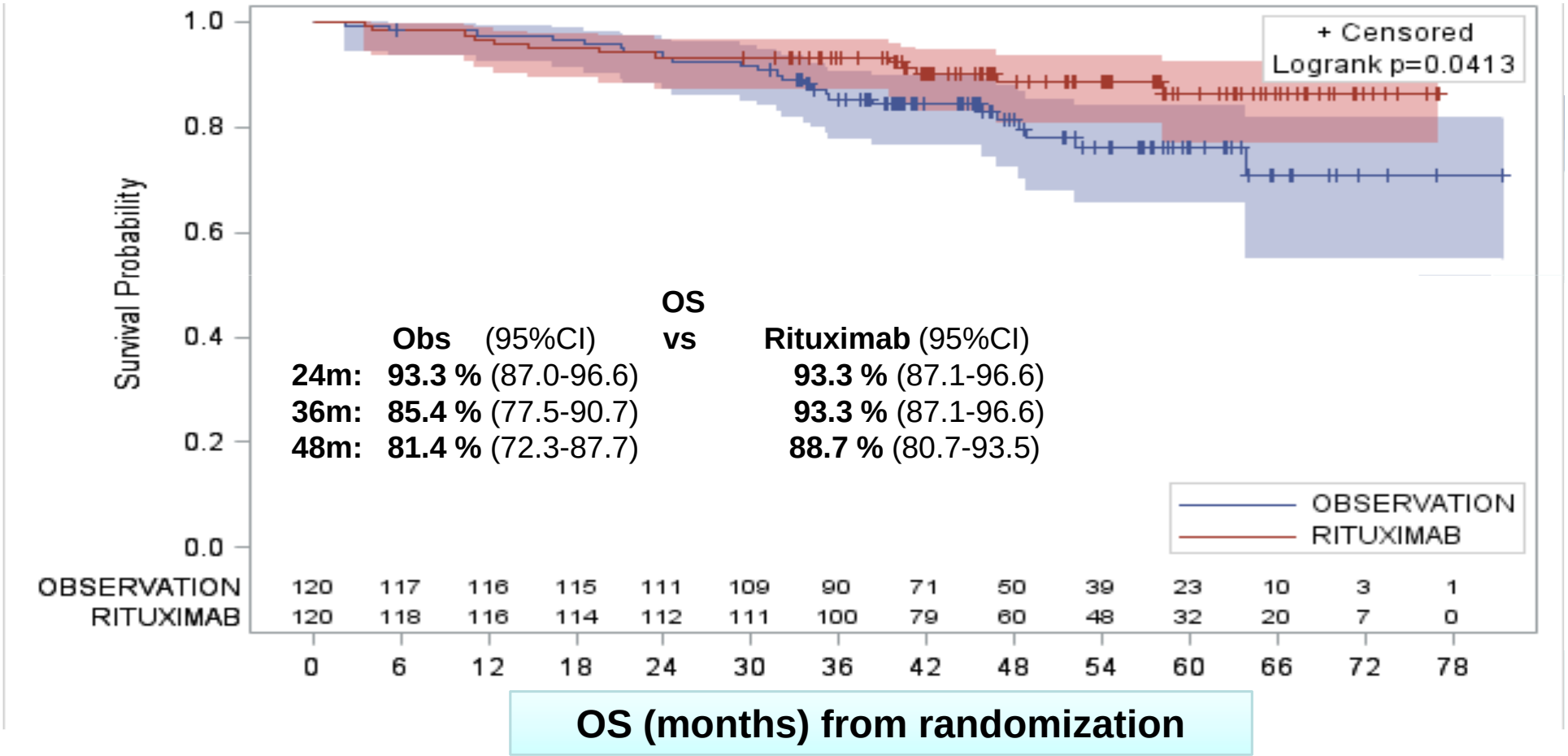
PFS from Randomization

mFU: 50.2m (46.4-54.2)



OS from Randomization

mFU: 50.2m (46.4-54.2)



Merci pour votre attention