15–ICML

15th International Conference on Malignant Lymphoma
Palazzo dei Congressi, Lugano, Switzerland, June 18-22, 2019

DLBCL a Lugano

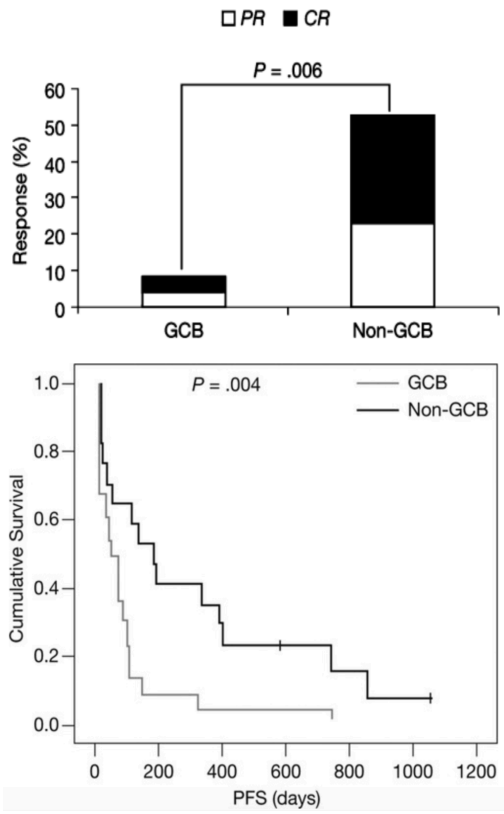
Annalisa Chiappella

14:00 – 15:25 Room A, B, Marquee, Cinema Corso, Auditorium and Aula Magna (USI Università)		**PLENARY SESSION** Co-chairs: J.O. Armitage, Omaha, NE (USA) and F. Cavalli, Bellinzona (Switzerland)
14:00	004	IDENTIFYING MUTATIONS ENRICHED IN RELAPSED-REFRACTORY DLBCL TO DERIVE GENETIC FACTORS UNDERLYING TREATMENT RESISTANCE C. Rushton, Burnaby, B.C (Canada)
14:15	005	ROBUST: FIRST REPORT OF PHASE III RANDOMIZED STUDY OF LENALIDOMIDE/R-CHOP (R2-CHOP) VS PLACEBO/R-CHOP IN PREVIOUSLY UNTREATED ABC-TYPE DIFFUSE LARGE B-CELL LYMPHOMA U. Vitolo, Turin (Italy)

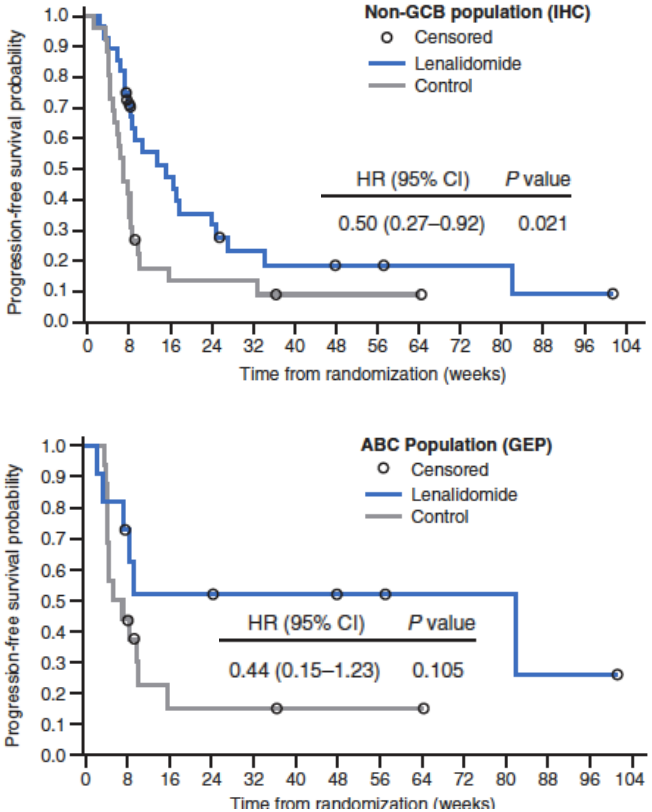
14:30	006	ADDITION OF LENALIDOMIDE TO R-CHOP (R2CHOP) IMPROVES OUTCOMES IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): FIRST REPORT OF ECOG-ACRIN1412 A RANDOMIZED PHASE 2 US INTERGROUP STUDY OF R2CHOP VS R-CHOP G.S. Nowakowski, Rochester, MN (USA)
14:45		Discussant for presentations 004, 005 and 006: M.A. Shipp, Boston, MA (USA)

Lenalidomide in DLBCL: Predominantly Active in Non-GCB or ABC DLBCL

Lenalidomide as single agent in R/R DLBCL

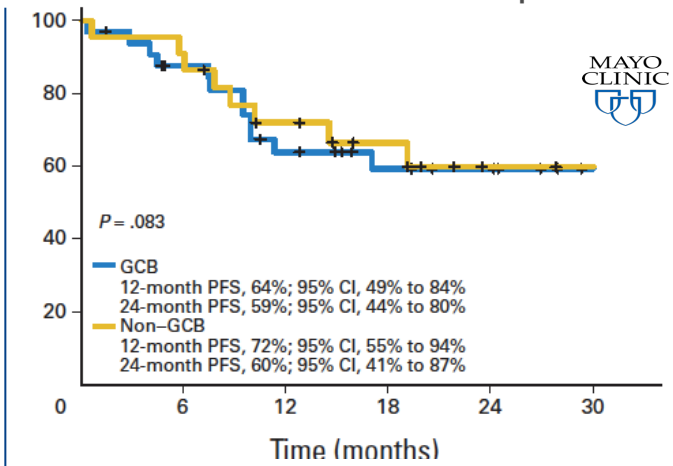


Hernandez-Ilizaliturri FJ, et al. *Cancer.* 2011;117(22):5058-66.

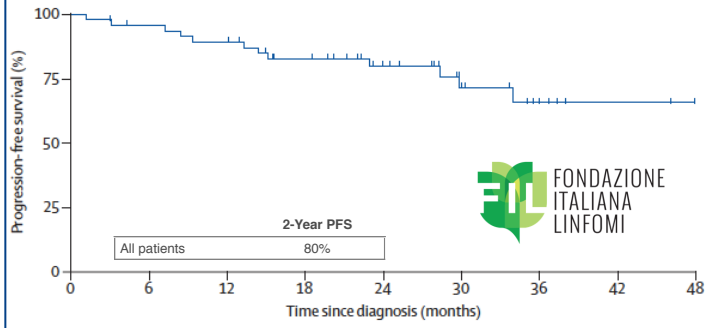


Czuczman M, et al. *Clin Cancer Res.* 2017;23:4127-4137.

R²-CHOP in 64 first line DLBCL patients



R²-CHOP in 49 first line DLBCL elderly patients

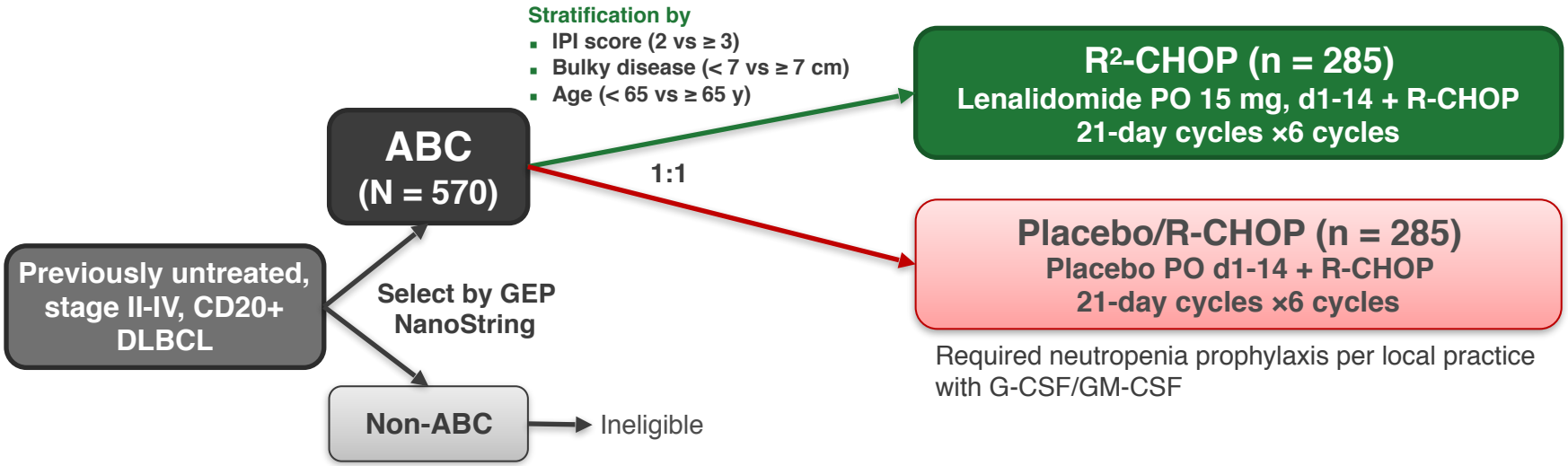


Nowakowski et al. *J Clin Oncol.* 2015;33:251–257.
Vitolo et al. *Lancet Oncol.* 2014;15:730–737.

ROBUST (DLC-002) Phase III Study Design

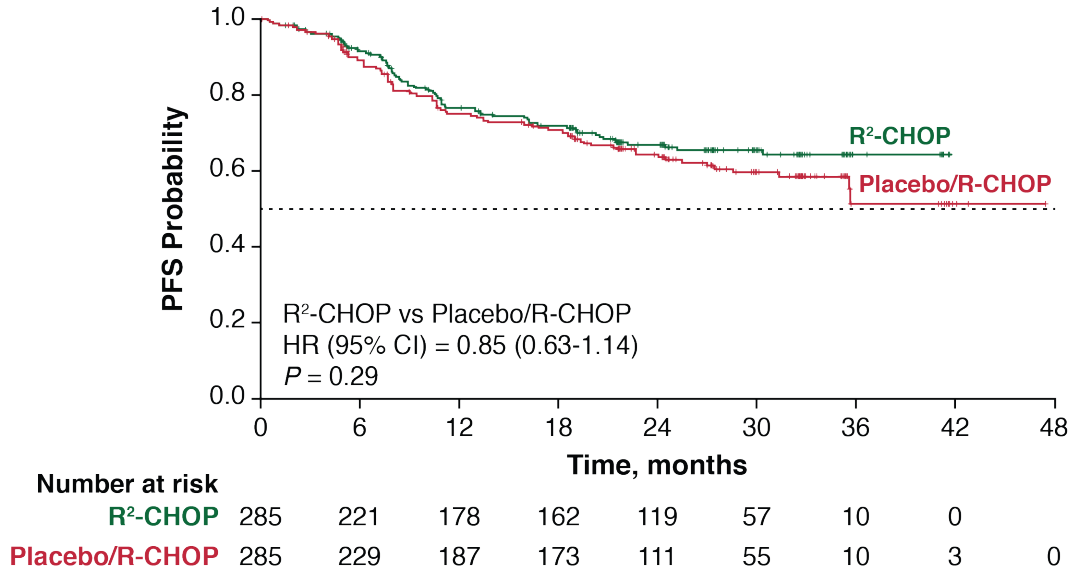
Vitolo U et al.

- ROBUST was a multicenter, international, randomized, double-blind, placebo-controlled, phase III study
- Primary endpoint: PFS by central review (per 2014 IWG)[1]
  - PFS improvement from 24 mo with R-CHOP to 38 mo with R^2-CHOP (192 events with 90% power; HR = 0.625)
- Secondary endpoints: EFS (key secondary), OS, ORR, CR rate, DOR, and safety

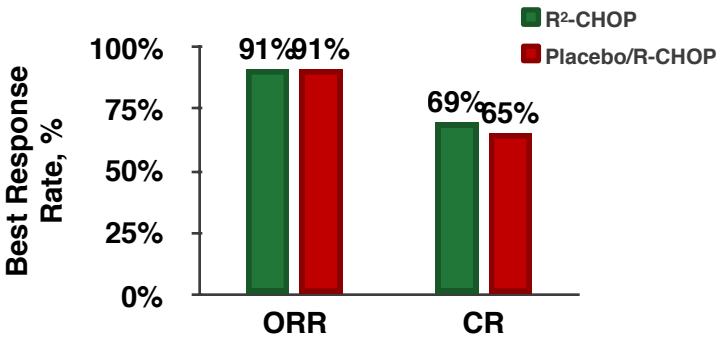


NCT02285062; EudraCT 2013-004054-21. 1. Cheson et al. *J Clin Oncol.* 2014;32:3059-3068.

Primary Endpoint: Progression-Free Survival (ITT, IRAC)



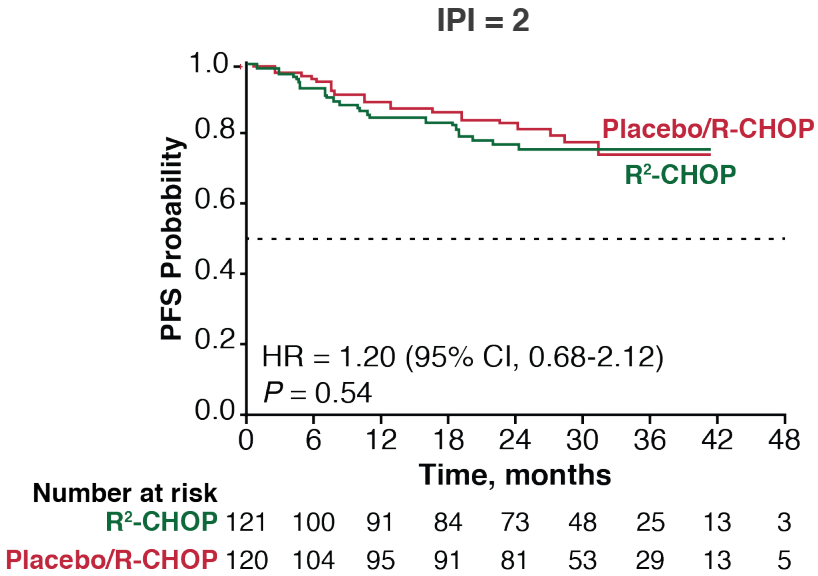
PFS Rates	R²-CHOP (n = 285)	Placebo/R-CHOP (n = 285)
1-y	77%	75%
2-y	67%	64%

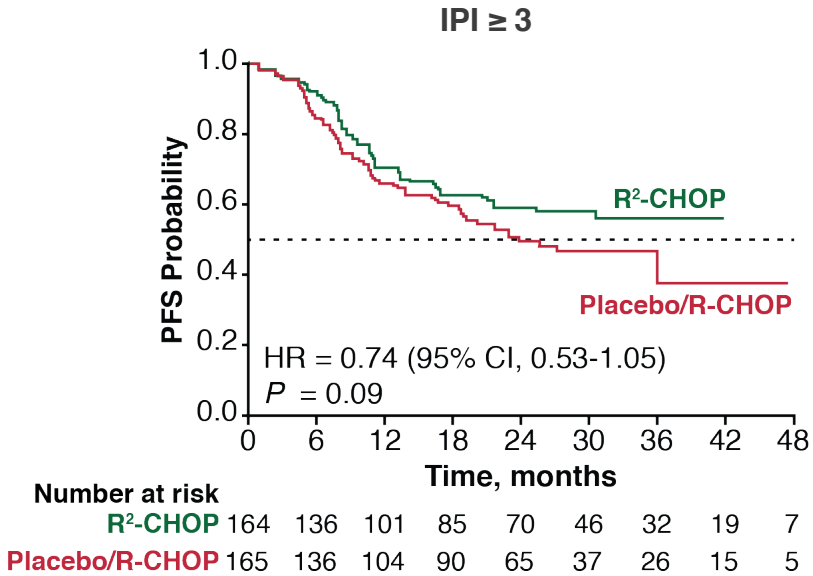


- At a median follow-up of 27.1 mo (range, 0-47), the primary endpoint of PFS was not met (medians not reached)
- ORR and CR rates were high in both arms
- Median time from diagnosis to treatment was 31 days for each arm

Data cut-off 15Mar2019. IRAC, Independent Radiology Adjudication Committee; ITT, intention-to-treat; ORR, overall response rate; PFS, progression-free survival. Complete response (CR) was assessed by 2014 IWG criteria with CT-PET (Cheson et al. *J Clin Oncol.* 2014;32:3059-3068).

PFS Based on International Prognostic Index Score (ITT)





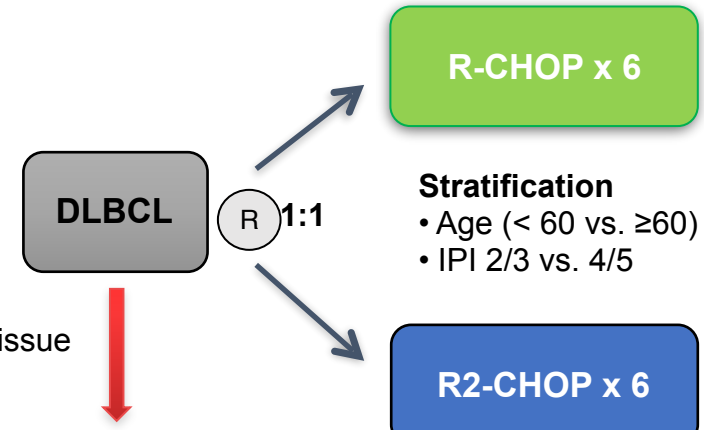
- Positive trends for PFS favoring R²-CHOP over placebo/R-CHOP were observed in patients with IPI score ≥ 3

Data cut-off 15Mar2019.

E1412: US Multicenter Randomized Phase 2 of R2CHOP vs RCHOP

Nowakowski G et al.

ECOG
SWOG
Alliance



Stratification
- Age (< 60 vs. ≥60)
- IPI 2/3 vs. 4/5

Pathology review and COO tissue analysis:
- GEP – NanoString – Predefined Analysis in ABC DLBCL
- IHC - Hans algorithm

R2CHOP:
Len 25 mg/day day 1-10
with R-CHOP21
Mandatory G-CSF

Primary endpoint:
- PFS in all comers DLBCL, and within ABC DLBCL (co-primary)

Secondary endpoints:
- ORR, PET CR, EFS and OS,
- PFS in ABC DLBCL

Statistical assumptions:
- 282 eligible patients , 89% power, one-sided alfa 0.1 for HR - 0.59 for **all comers**
- 102 eligible **ABC DLBCL**, 81% power, one-sided alfa 0.125, HR- 0.52

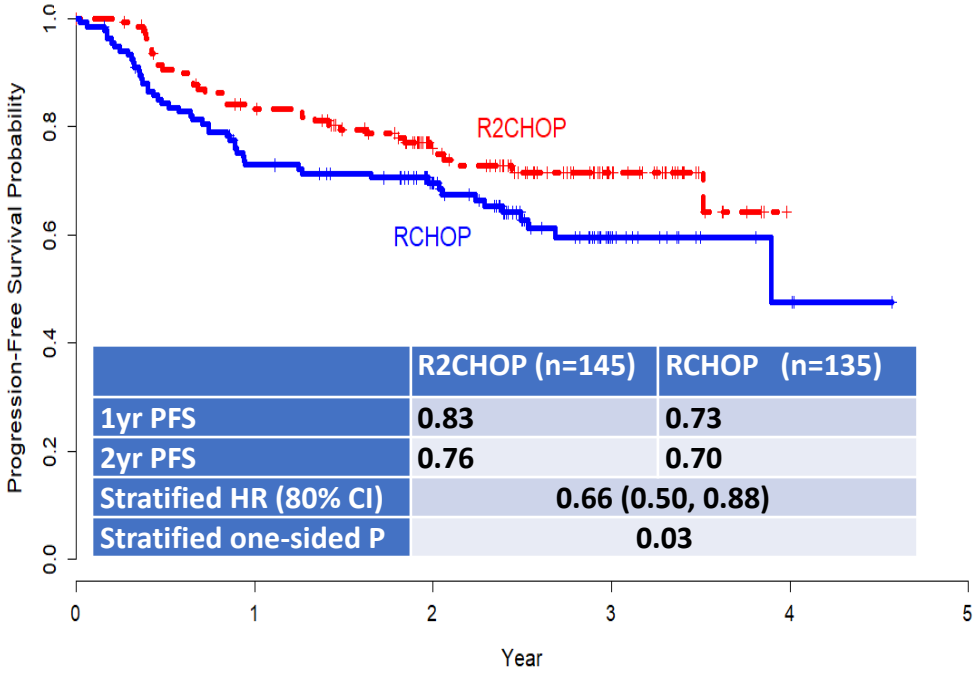
ClinicalTrials.gov Identifier: NCT01856192.

MAYO CLINIC

E1412: Survival

MAYO CLINIC

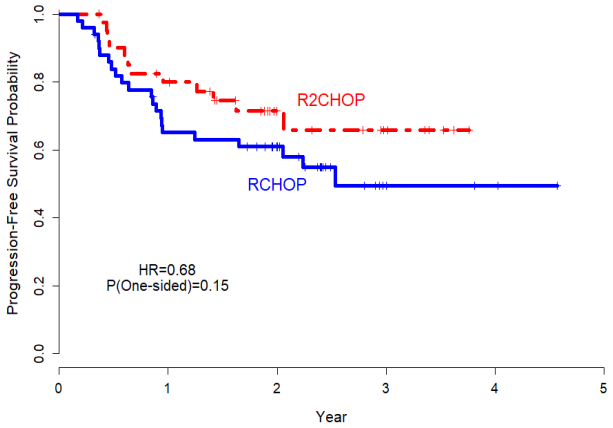
R2CHOP was associated with 34% reduction in risk of progression or death



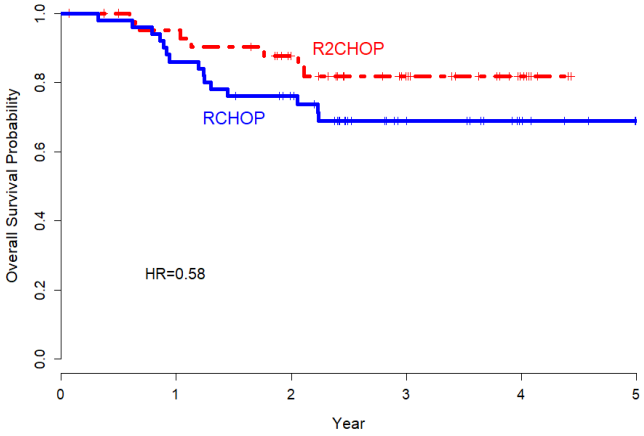
	R2CHOP (n=145)	RCHOP (n=135)
1yr PFS	0.83	0.73
2yr PFS	0.76	0.70
Stratified HR (80% CI)	0.66 (0.50, 0.88)	
Stratified one-sided P	0.03	

Median follow up 2.5 years

PFS ABC DLBCL n=94



OS ABC DLBCL n= 122



Trial Comparison

Shipp M

ROBUST

- ABC only by Nanostring
- Phase 3 (570 patients)
- Global, Worldwide
- LEN 15 mg days 1-14
- Prednisone 100 mg flat
- Double blinded with placebo study
- Diagnosis to treatment (days) was 31 days

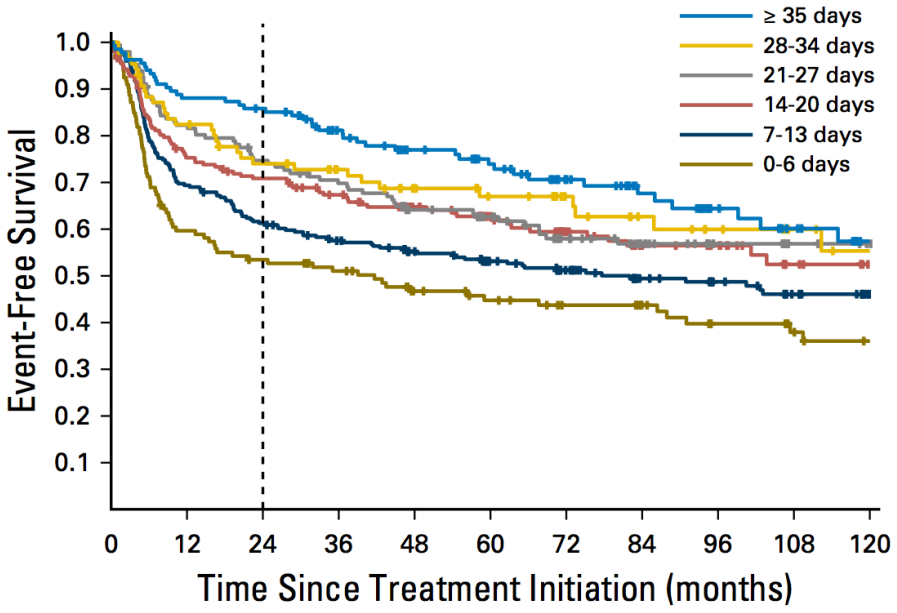
E1412

- GCB and ABC and Unclassified by Nanostring
- Randomized Ph 2 (280 pts)
- United States
- LEN 25 mg days 1-10
- Prednisone 100 mg/m^2
- Open label study
- Diagnosis to treatment (days) was 22 days

Impact of Time from Diagnosis to Treatment

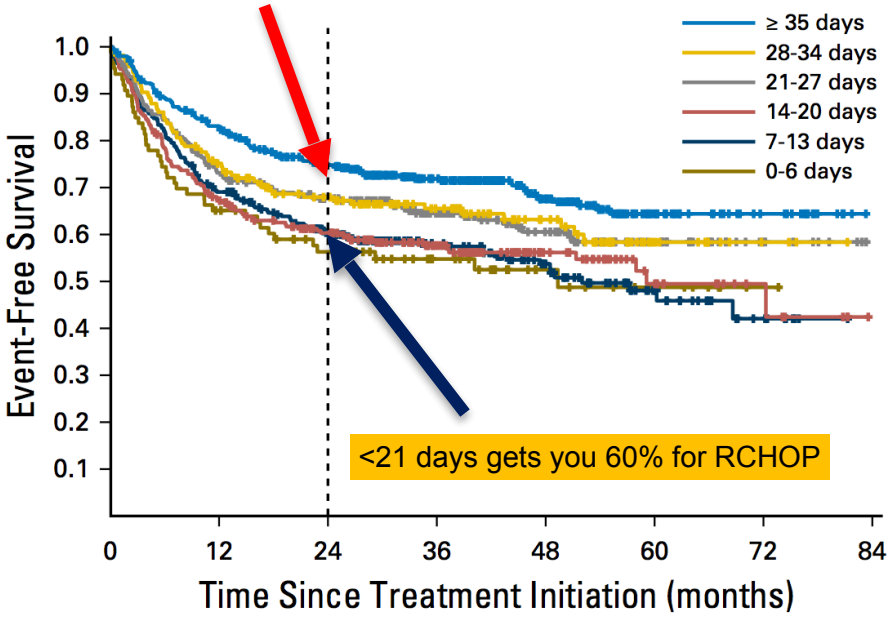
the worst prognosis groups (≤ 3 weeks) are often excluded by clinical trials

MER - United States



LYSA - France

>28 days gets you 75% for RCHOP



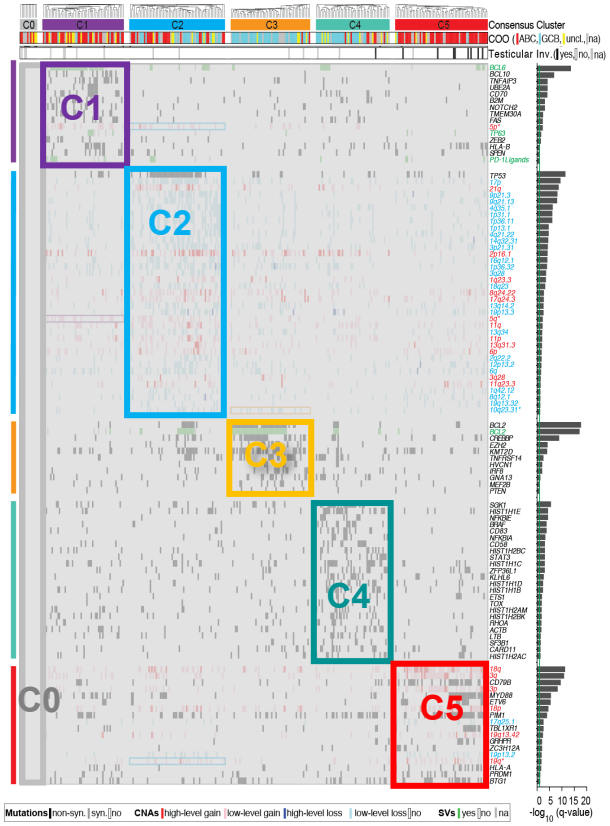
Mauer M, et al *J Clin Oncol*. 2018;36:1603-10.

Should We Still Care About COO?

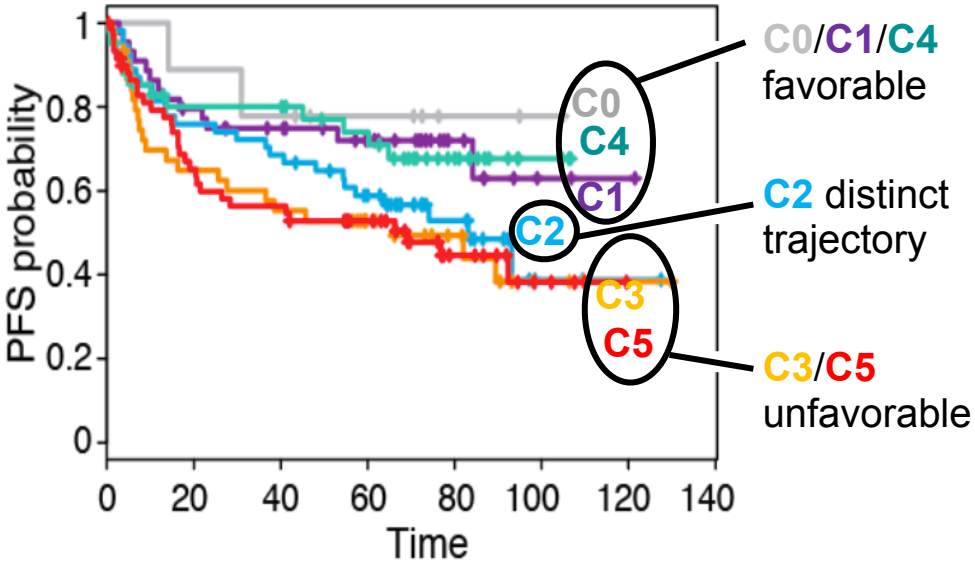
- Yes: the prognosis of ABC is still unsatisfactory
- Yes: subgroups of ABC patients benefit from the addition of specific drugs as ibrutinib in young and lenalidomide in high risk
- No: ABC *alone* is not the best target; DLBCLs are more heterogenous, mutational alterations, etc
- Maybe: ibrutinib or lenalidomide are not the best drugs, we need better drugs, novel-novel combinations

Genetically-distinct DLBCL Subsets are Predictive for Outcome

Genetically-distinct DLBCLs



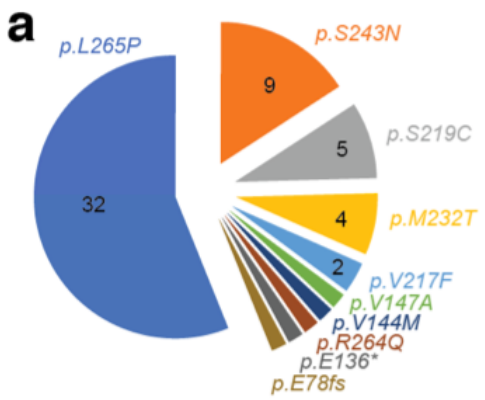
Predictive for Outcome

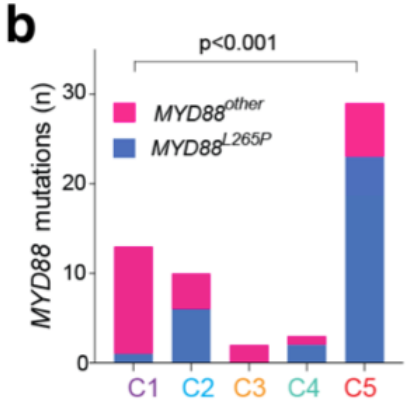


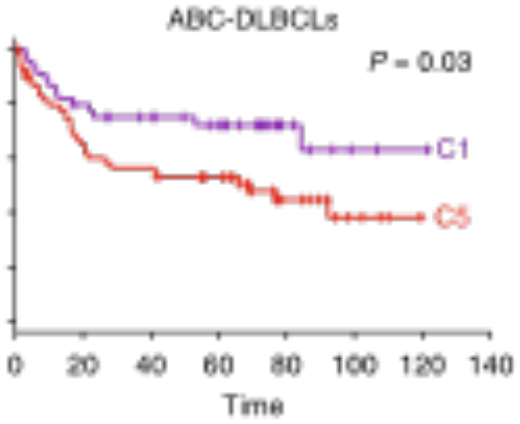
- **Genetic signatures comprised of**
  - Mutations
  - Somatic copy number alterations (SCNAs)
  - Structural Variants (SVs)

Chapuy B, et al. *Nat Med;* 2018; 24(5):679-690.

C1 vs. C5 DLBCLs – Two Genetically Distinct ABC-DLBCLs







c	C1 DLBCLs	C5 DLBCLs
MYD88 mutations	23%(13/56)	44%[28/64]
Type of *MYD88* mutations	non-L265P	L265P
Concordant *CD79B* mutations	no	frequent

- Different types and incidences of *MYD88* mutations

C5 DLBCLs - highest cAID activity
- tumors passaged through the GC

C1 DLBCLs - low to absent cAID activity
- suggestive of extrafollicular origin

➔ C1 and C5 ABC-type DLBCLs arise by distinct pathogenetic mechanisms.

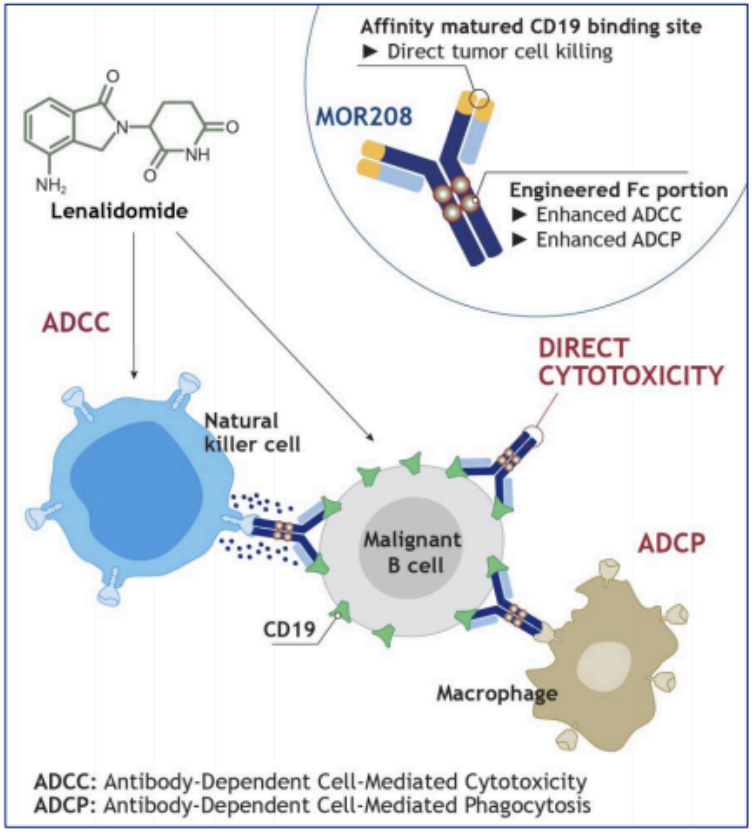
Chapuy B, et al. *Nat Med;* 2018; 24(5):679-690.

Tafasitamab in Combination With Lenalidomide

Salles G et al.

MOR208

- ADCC ↑
- ADCP ↑
- Direct cell death
- Encouraging single agent activity in r/r DLBCL & iNHL patients

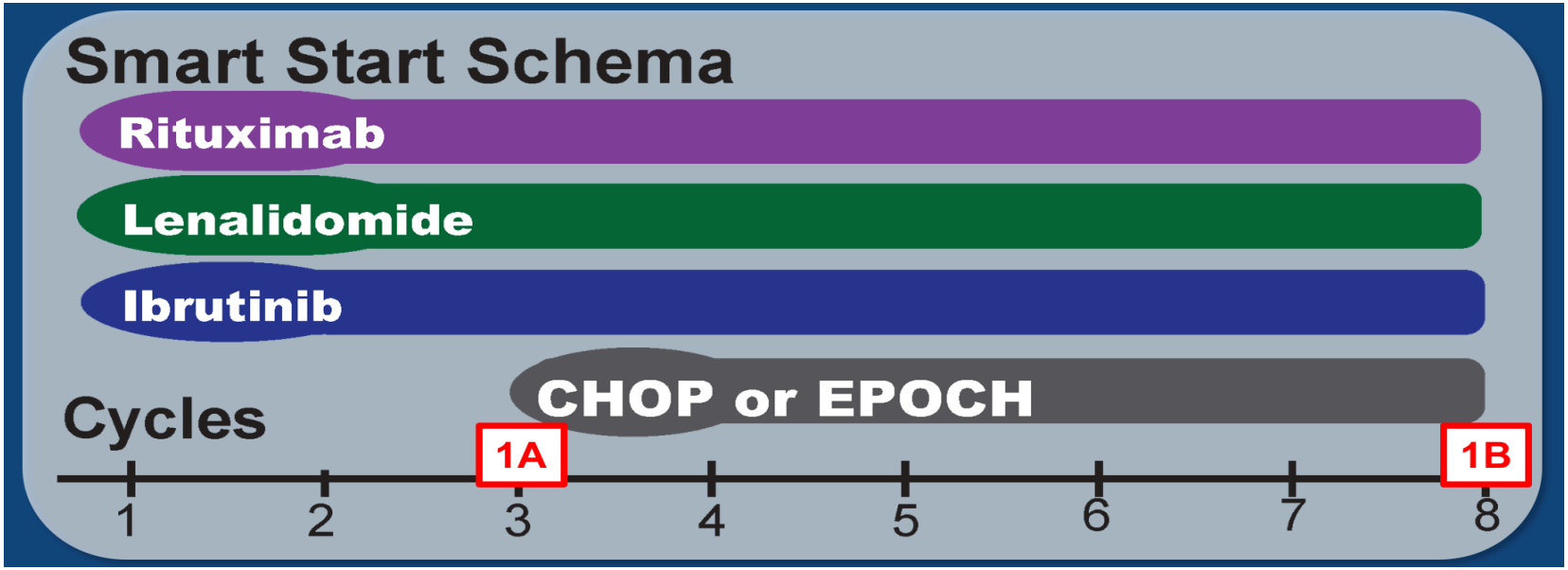


Lenalidomide

- T and NK Cell activation/expansion
- Direct cell death
- Well studied as an anti-lymphoma agent, alone or in combination

Smart Start: R+Len+Ibrutinib Lead-in Prior to Addition of Chemotherapy for Newly Diagnosed DLBCL

Westin et al.



- Primary Objectives
  - 1A: To determine the ORR at the end of 2 cycles of RLI alone
  - 1B: To determine the CR rate at the end of RLI x 2 + RLI combined

Smart Start: Results

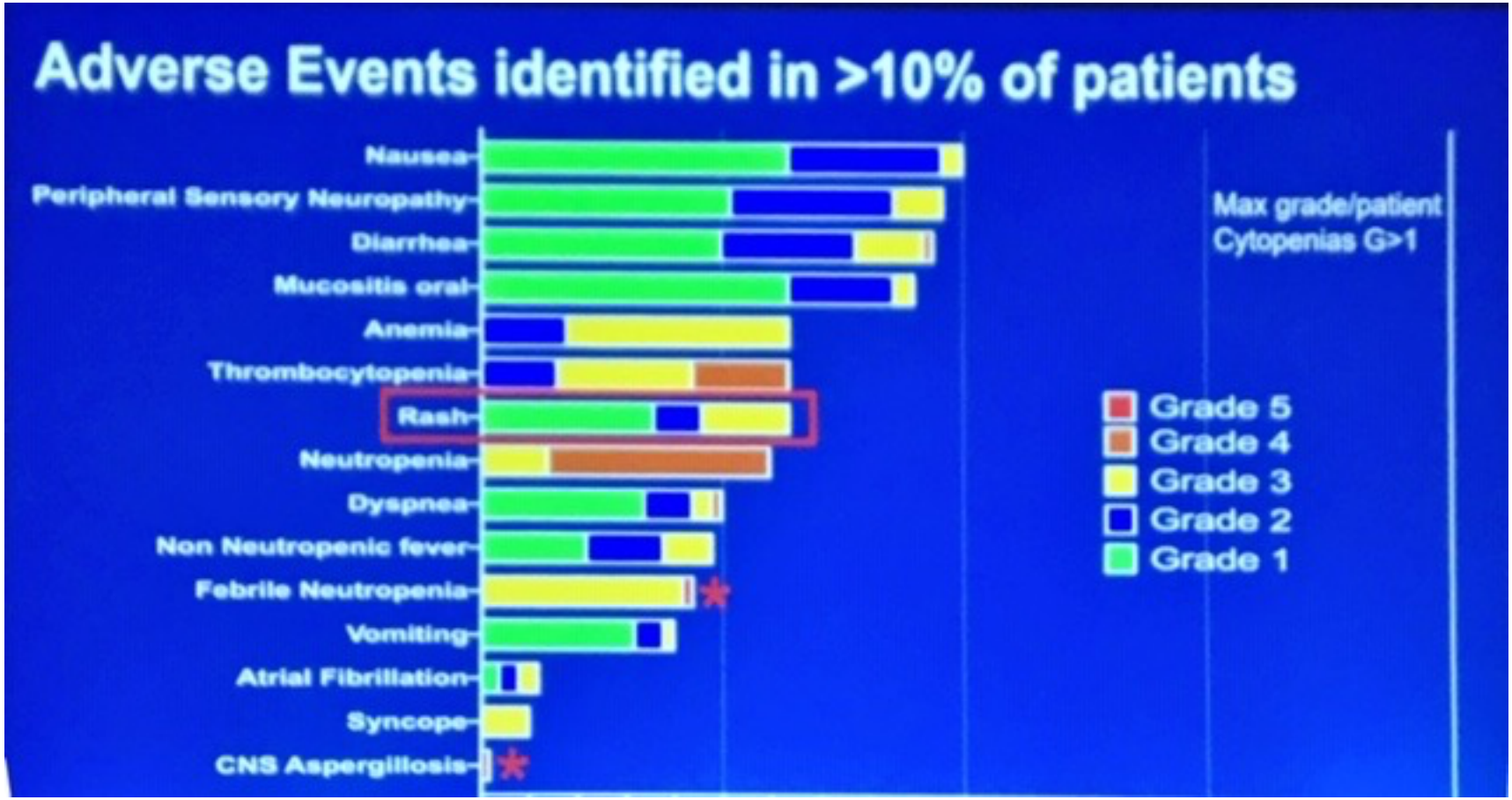
Results

		N = 60
Age, years	Median (range)	63.5 (29 – 83)
	> 65	48%
	> 70	28%
Gender	Female	50%
R-IPI	Median	3
	Very Good (0-1)	16.7%
	Good (2)	31.7%
	Poor (3-5)	51.7%
Ki-67	>80%	77%
	>90%	49%
Stage	III - IV	65%
Double Expressor	MYC & BCL2 + IHC	54% (n=19/35)
Double Hit	MYC & BCL6 FISH	2.7% (n=1/37)
Biopsy to Treatment	Median	24 days

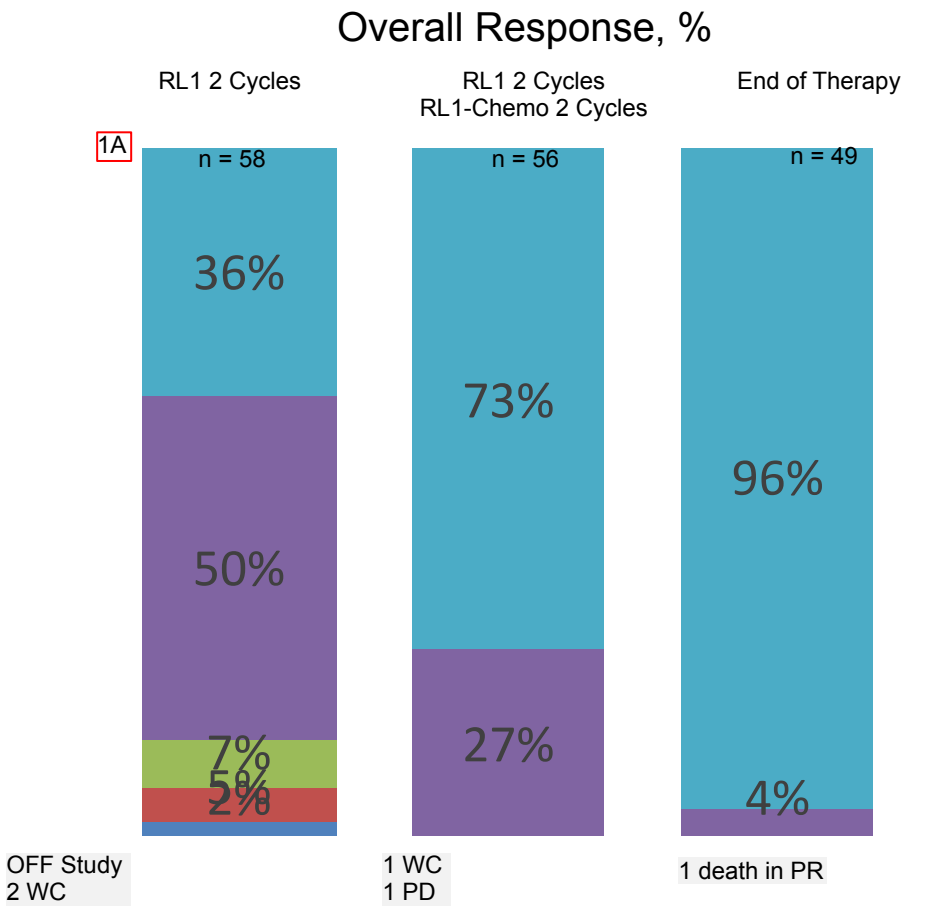
Smart Start

		N = 58
Chemotherapy	CHOP	25 (43%)
	EPOCH	32 (55%)
	None	1 (2%)
Dose Intensity	Ibrutinib	95.4%
	Lenalidomide	90.1%
< 6 cycles of chemotherapy	Patients receiving only 5 cycles chemotherapy	N = 7
	Patients receiving only 4 cycles chemotherapy	N = 4

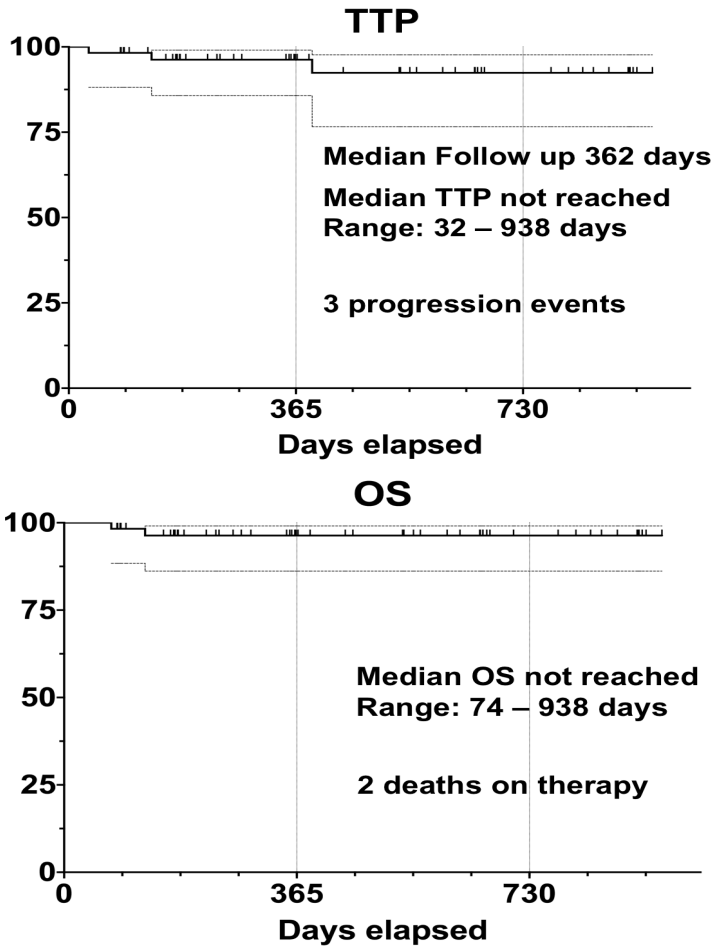
Smart Start


Adverse Events identified in >10% of patients
Nausea
Peripheral Sensory Neuropathy
Diarrhea
Mucositis oral
Anemia
Thrombocytopenia
Rash
Neutropenia
Dyspnea
Non Neutropenic fever
Febrile Neutropenia
Vomiting
Atrial Fibrillation
Syncope
CNS Aspergillosis
Max grade/patient
Cytopenias G>1
Grade 5
Grade 4
Grade 3
Grade 2
Grade 1

Smart Start: Responses

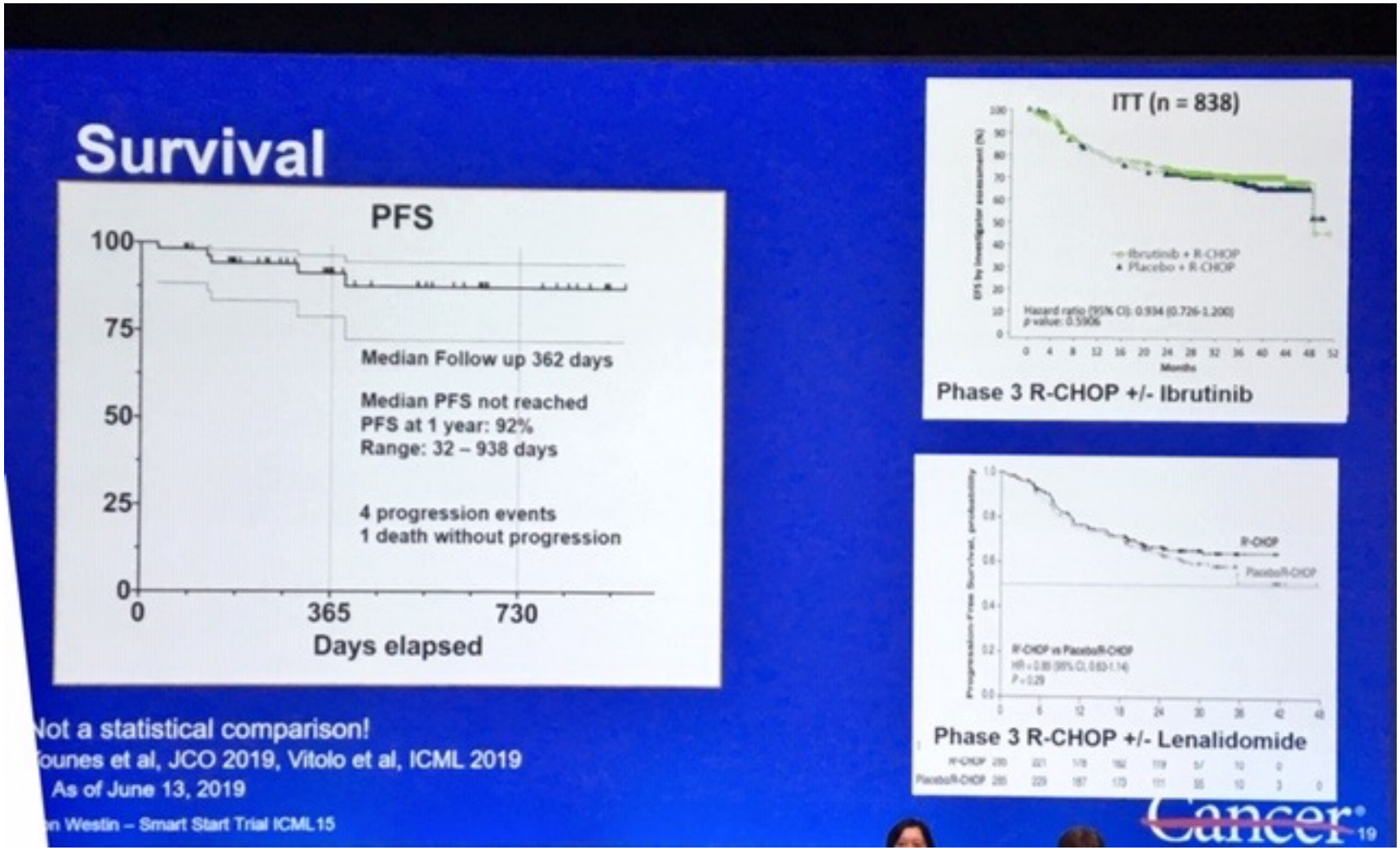


1B

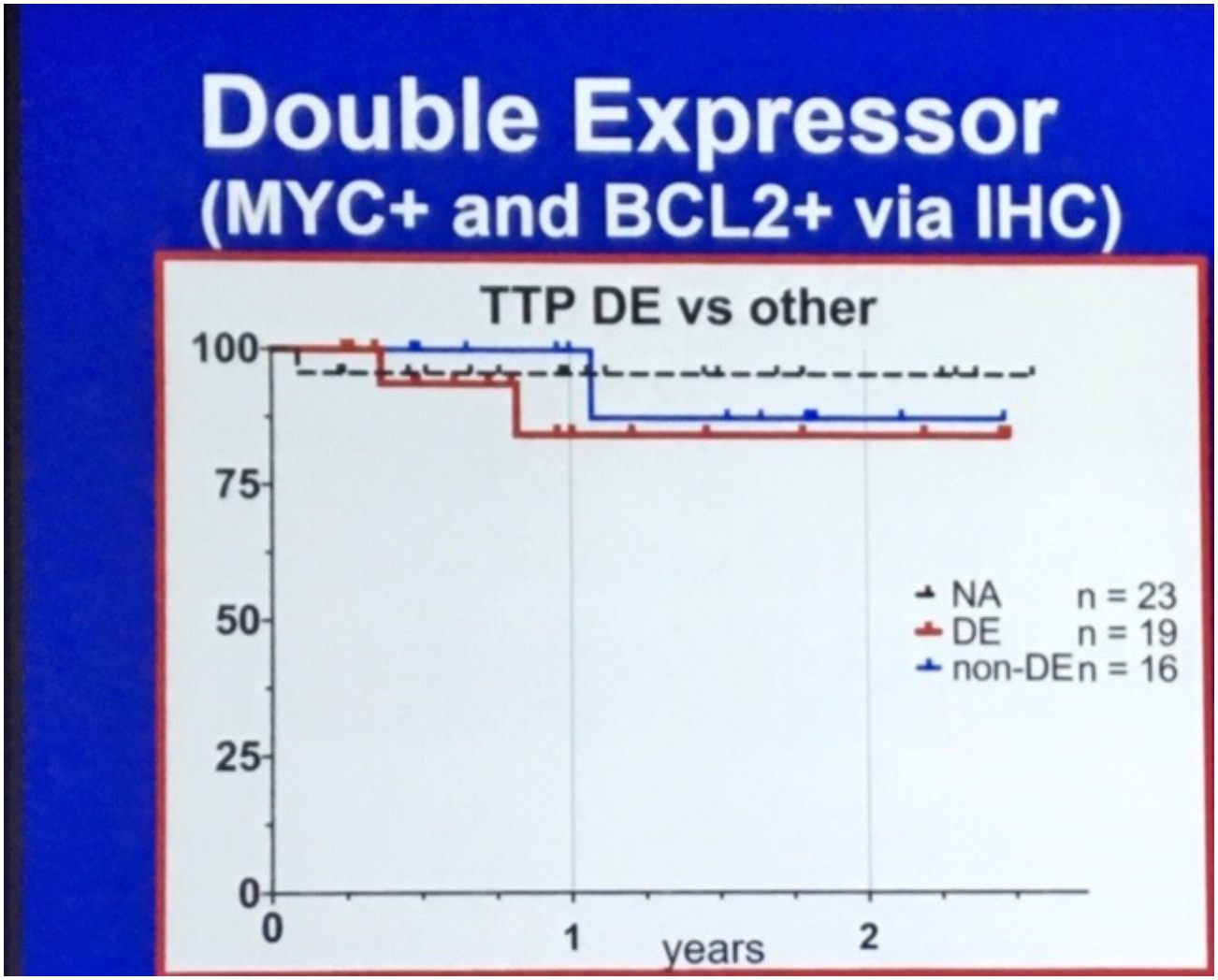


ITT ORR 98%
1 scan and off therapy
CR 92.3% (n=48)
PR 5.8% (n=3)
PD 1.9% (n=1)

Smart Start

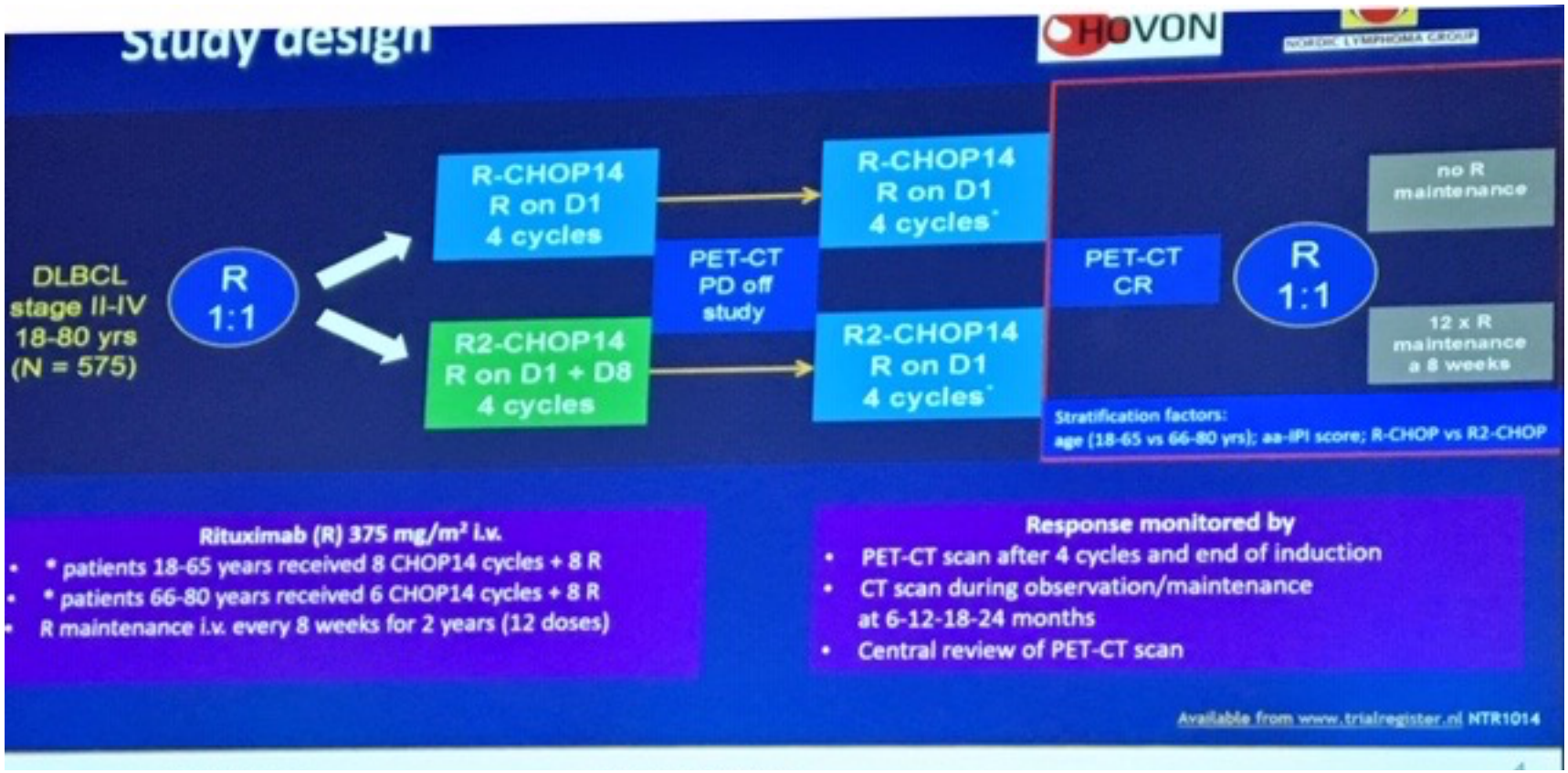

Survival
PFS
100
75
50
25
0
0
365
730
Days elapsed
Median Follow up 362 days
Median PFS not reached
PFS at 1 year: 92%
Range: 32 – 938 days
4 progression events
1 death without progression
ITT (n = 838)
Ibrutinib + R-CHOP
Placebo + R-CHOP
Phase 3 R-CHOP +/- Ibrutinib
R-CHOP
Placebo/R-CHOP
Phase 3 R-CHOP +/- Lenalidomide
Not a statistical comparison!
Younes et al, JCO 2019, Vitolo et al, ICML 2019
As of June 13, 2019
Westin – Smart Start Trial ICML15
Cancer
19

Smart Start


Double Expressor
(MYC+ and BCL2+ via IHC)
TTP DE vs other
100
75
50
25
0
0
1
years
2
NA n = 23
DE n = 19
non-DE n = 16

Hovon phase III, R maintenance after RCHOP14

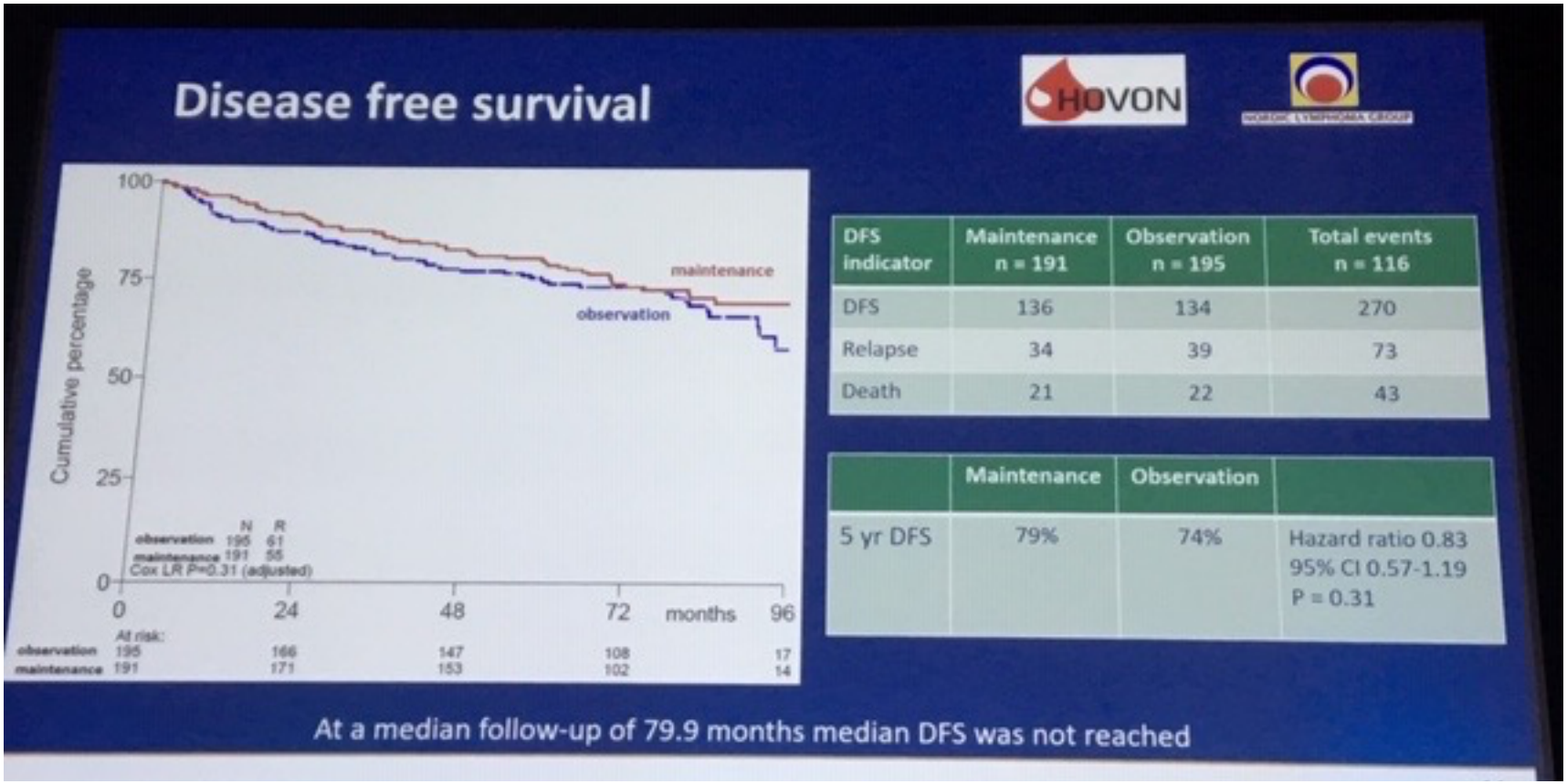
Lugtenburg et al.



Primary endpoint: DFS

Hovon phase III, R maintenance after RCHOP14

Lugtenburg et al.



DFS indicator	Maintenance n = 191	Observation n = 195	Total events n = 116
DFS	136	134	270
Relapse	34	39	73
Death	21	22	43

	Maintenance	Observation	
5 yr DFS	79%	74%	Hazard ratio 0.83 95% CI 0.57-1.19 P = 0.31

No advantage adding R maintenance