Abstract #630
Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The Orcharrd Study (OMB110928)

Gustaaf W van Imhoff, Andrew McMillan, Matthew J Matasar, John Radford, Kirit M Ardeshna, Kazimierz Kuliczkowski, WonSeog Kim, Xiaonan Hong, Jette Soenderskov Goerloev, Andrew Davies, María Dolores Caballero Barrigón, Michinori Ogura, Michael Fennessy, Qiming Liao, Bronno van der Holt, Steen Lisby, Thomas S Lin, and Anton Hagenbeek

Disclosures
Gustaaf W van Imhoff, MD, PhD

In compliance with ACCME policy, ASH requires the following disclosures to the session audience:	
Research Support/P.I.	-
Employee	University of Groningen, University Medical School
Consultant	-
Major Stockholder	-
Speakers Bureau	-
Honoraria	-
Membership in Advisory Board	-
Presentation includes a description of the following off-label use of a drug or medical device	Ofatumumab combined with chemotherapy for relapsed diffuse large B-cell lymphoma

Background

- Addition of rituximab (R) to first-line CHOP therapy of DLBCL has improved the outcome such that 60% of patients are cured
- Coinciding with this, the 3-yr EFS following treatment of relapsed/refractory DLBCL with R-chemotherapy followed by ASCT has decreased from 47% to 21% (1)
- This may be due to acquired resistance to R

- The anti-CD20 monoclonal antibody ofatumumab (O) has shown efficacy in R resistant lymphoma cell lines and in patients with relapsed or refractory DLBCL when combined with salvage chemotherapy (2)

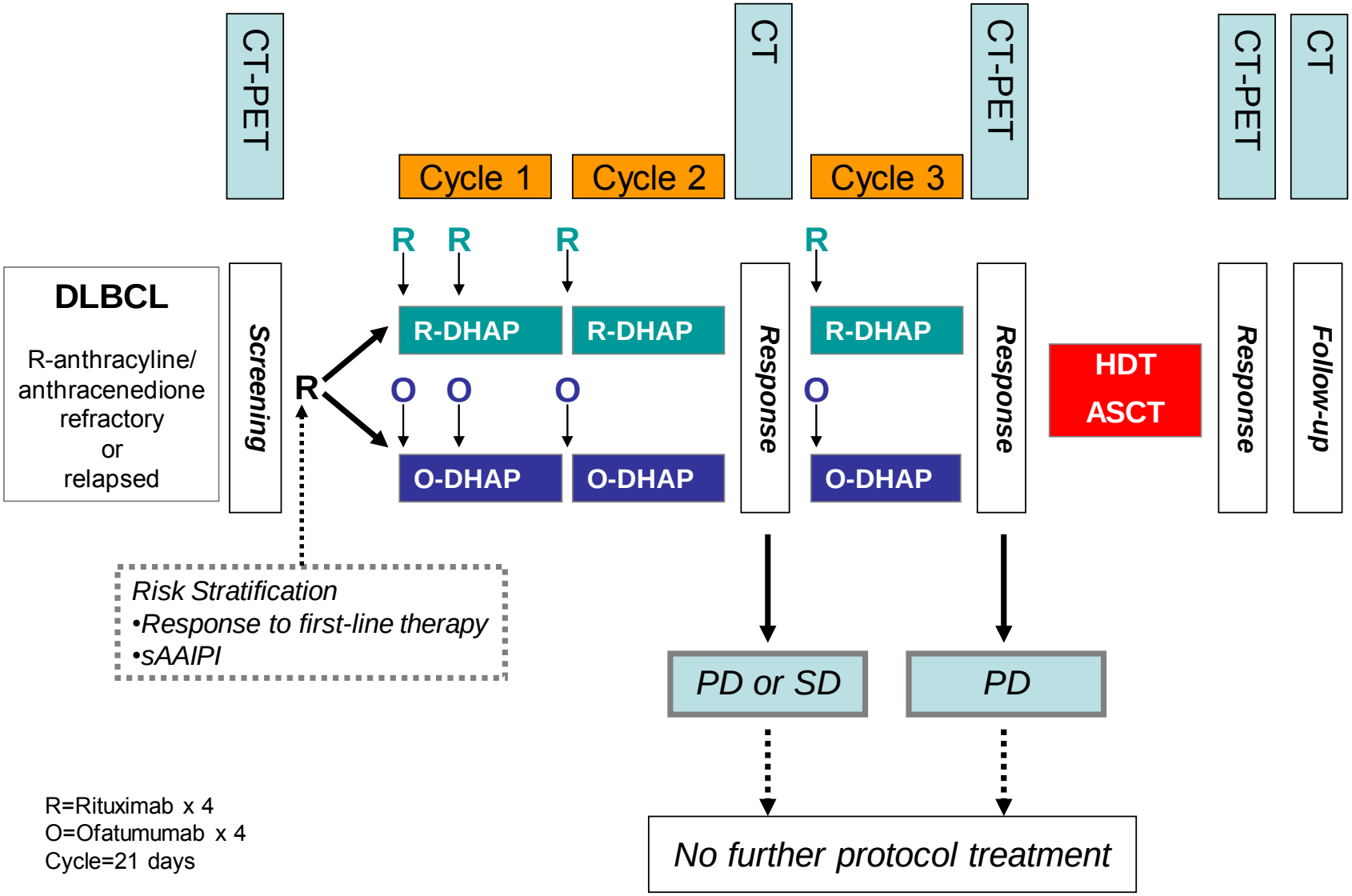
- Hypothesis: O-chemotherapy may overcome R-resistance

1: Gisselbrecht, J Clin Oncol; 2010:28:4184; 2: Matasar, Blood; 2013 122: 499

Aim of the Study

- To compare the efficacy of Ofatumumab versus Rituximab in combination with DHAP (dexamethasone, cytarabine, cisplatin) salvage treatment and ASCT in relapsed/refractory DLBCL

ORCHARRD Study Design



Treatment Regimens

- 21 -day cycles

- **Ofatumumab: 1000 mg** **cycle 1: day 1 and 8; cycles 2 and 3: day 1**
- **Rituximab: 375 mg/m^2** **cycle 1: day 1 and 8; cycles 2 and 3: day 1**

- DHAP
  - Dexamethason: 40 mg days 1-4
  - Cisplatin: 100 mg/m^2/24h day 1
  - Cytarabine: 2 g/m^2 every 12 h on day 2

- BEAM (*recommended*) + ASCT (day 0) 4-6 wks after last cycle of DHAP

Objectives

Primary Objective

- **Progression free survival:**
  - Death any cause,
  - Disease progression,
  - **Stable disease at cycle 2**

Secondary Objectives

- Event free survival; Overal survival
- Response rate: after salvage chemoimmunotherapy & 3 mos. after ASCT.
- Incidence, severity of AE, SAE and other safety parameters.
- Stem cell mobilisation efficacy
- Number of subjects completing ASCT.
- Time to neutrophil and platelet recovery after each cycle of salvage chemotherapy and time to engraftment after HDT/ASCT.

Eligibility

Key Inclusion criteria

- CD20+ DLBCL or FL gr 3b in first relapse or not responding (<CR) to 1st-line R-CHOP-like treatment +/- radiotherapy, if needed
- FDG-PET positive measurable disease
- Age >=18
- ECOG PS 0-2
- Eligible for HDT and ASCT
- Adequate organ and BM function

Key Exclusion criteria

- CNS localisation of lymphoma
- HIV positivity, Hepatitis B or C viraemia
- Major comorbidity

Statistical Considerations and Analysis

- Multicenter, randomised phase III trial
- Power 90% to detect a 15% improvement in 2-year PFS (from 25% to 40%)
- Stratification for: Time to failure of R-CHOP (CR<12 vs >12 months); sAAIPI

- Response evaluation: Independent Central Review

Study start :	March 2010
Study closure:	December 2013
No. Patients Randomised:	447 (started treatment 445)
Database closure :	February 2014

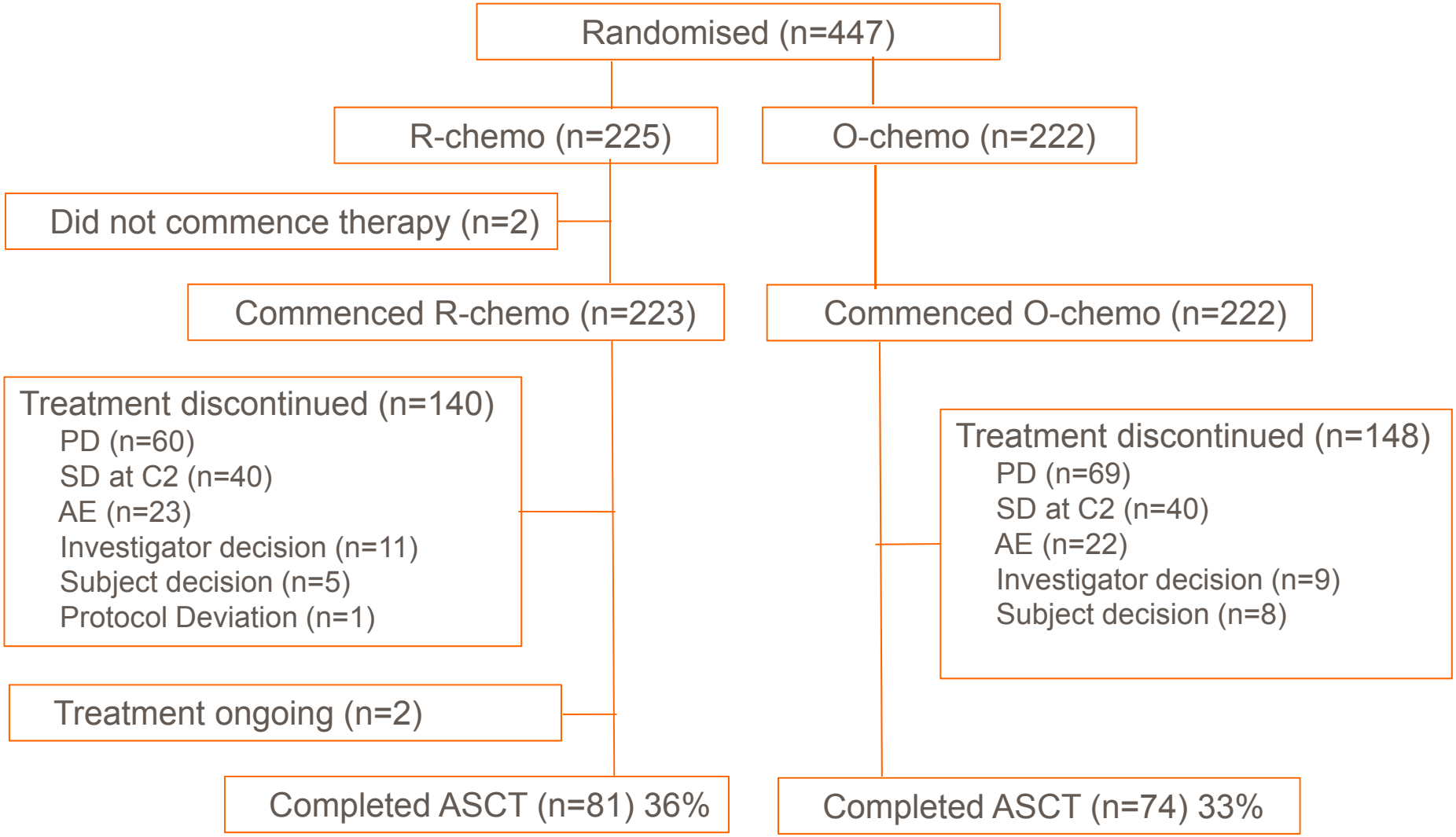
Baseline Characteristics

	R-chemo (n=223)	O-chemo (n=222)
Age Years [median (range)]	56 (18-79)	57.5 (23-83)
Age ≥ 65 years, n (%)	36 (16%)	41 (18%)
Male, n (%)	135 (61%)	137 (62%)
Caucasian	169 (76%)	152 (68%)
Japanese, east Asian	47 (21%)	58 (26%)
Histology, DLBCL	208 (93%)	208 (94%)
LDH (> ULN)	108 (48%)	111 (50%)
Stage III/IV	142 (64%)	139 (63%)
BM involved	12 (5%)	18 (8%)
ECOG PS 0-1	207 (93%)	202 (91%)
sAAIPI 2-3	87 (39%)	89 (40%)

Baseline Characteristics

1st-line treatment	R-chemo n=223	O-chemo n=222
No. cycles R-CHOP		
≥6	185 (83%)	185 (83%)
<6	29 (13%)	35 (16%)
Unknown	8 (4%)	1 (<1%)
Response from 1st-line treatment		
CR >12 months	**66 (30%)**	**63 (28%)**
CR ≤12 months	22 (10%)	28 (13%)
PR	83 (37%)	79 (36%)
SD	15 (7%)	19 (9%)
PD	37 (17%)	32 (14%)
Unknown	0	1 (<1%)

CONSORT (Study Flow)



Response (independent central review)

At completion of R/O-DHAP	R-chemo (n,%) n=223	O-chemo (n,%) n=222	OR (95%CI)	p-value
Overall RR	**94 (42%)**	**84 (38%)**	**0.84 (0.56-1.24)**	**0.41**
CR	48 (22%)	34 (15%)	0.66 (0.39-1.10)	0.12
PR	46 (21%)	50 (23%)		

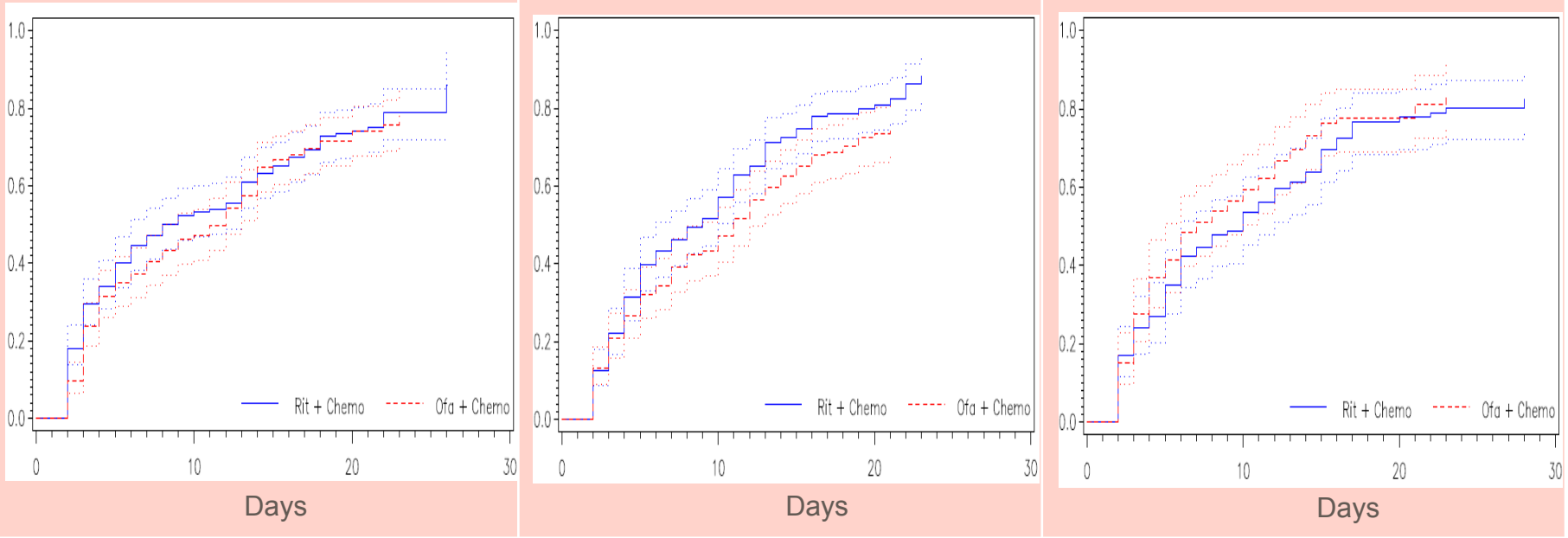
Response 3 months post ASCT	R-chemo (n,%) ASCT n=81 (36%)	O-chemo (n,%) ASCT n=74 (32%)	OR (95%CI)	p-value
Overall RR	**53 (65%)**	**46 (62%)**	**0.87 (0.43-1.76)**	**0.80**
CR	**41 (51%)**	**39 (53%)**	**1.09 (0.55-2.14)**	**0.92**
PR	12 (15%)	7 (9%)		

Summary of Compliance and SAE's

- Compliance with ofatumumab and rituximab treatment was similar
- The proportion of patients receiving < 80% of the planned dose was low, both in ofatumumab-treated (6%) and rituximab-treated (4%) patients.
- Overall compliance with chemotherapy was also similar between treatment groups.
- SAEs incidence was similar between treatment groups. Most frequently reported SAE was: febrile neutropenia, followed by acute renal failure, thrombocytopenia, and vomiting.
- Fatal SAEs were infrequent during the study and reported in a similar proportion of patients in both treatment groups.

Time to Neutrophil Recovery after O/R DHAP Salvage

Cycle 1	Cycle 2	Cycle 3

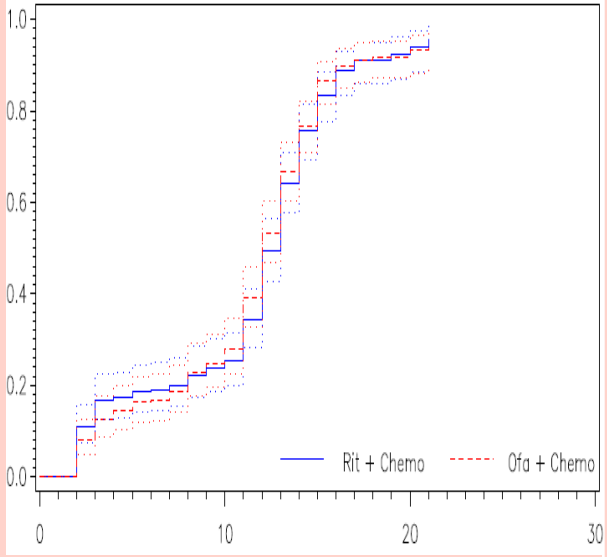
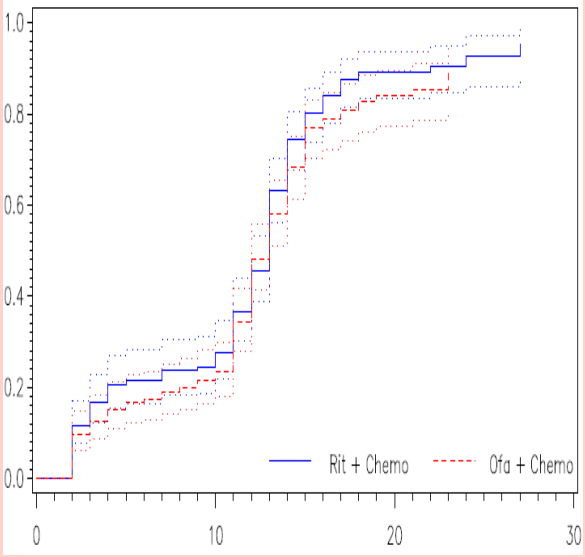
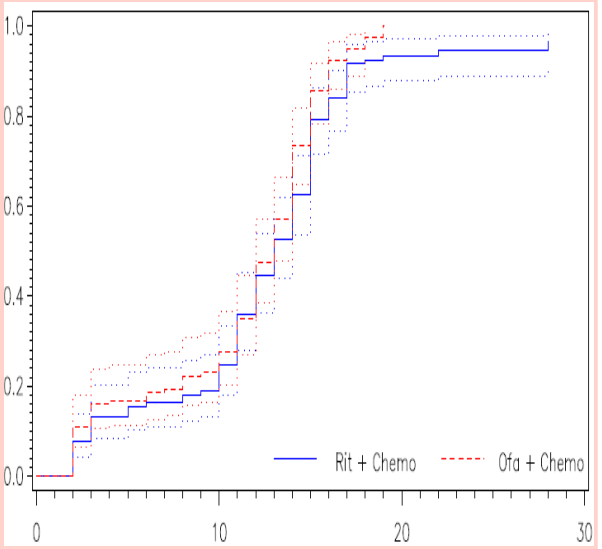


R-DHAP

O-DHAP

Neutrophil recovery is defined as an ANC >0.5x 10^9/L and increasing

Time to Platelet Recovery after O/R DHAP Salvage

Cycle 1	Cycle 2	Cycle 3
		
Days	Days	Days

R-DHAP

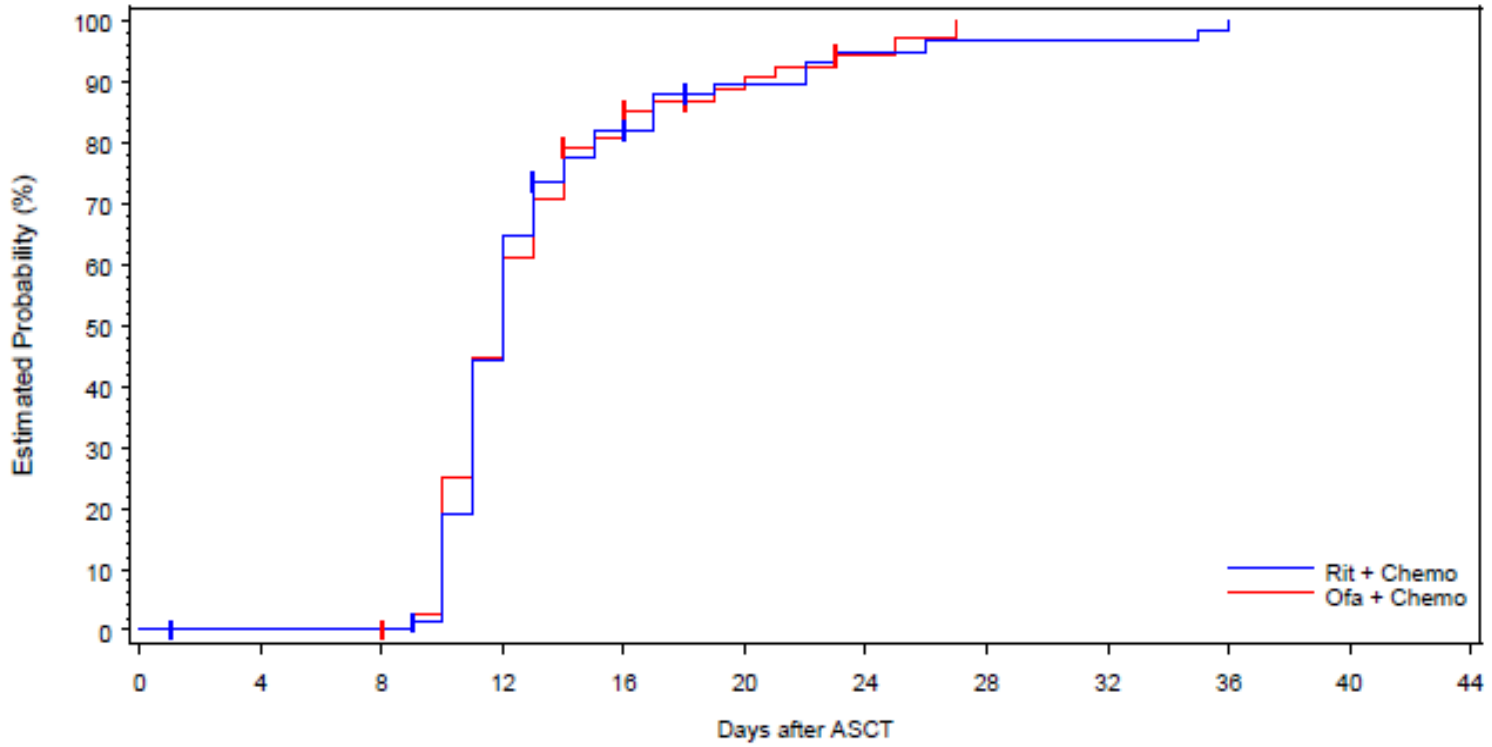
O-DHAP

Platelet recovery is defined as the PLT count >10 x10^9/L and increasing

Peripheral Blood Stem Cell Mobilization

	R-chemo n=223	O-chemo n=222	p-value
Commenced mobilization (n, %)	134 (60%)	125 (56%)	
Mobilized ≥2×10^6 CD34+ cells/kg (n,%)	121 (90%)	120 (96%)	0.074
CD34+ cells collected (x10^6 cells/kg median, range)	4.4 (0-30)	4.1 (0-23)	

Time to Neutrophil Recovery after ASCT



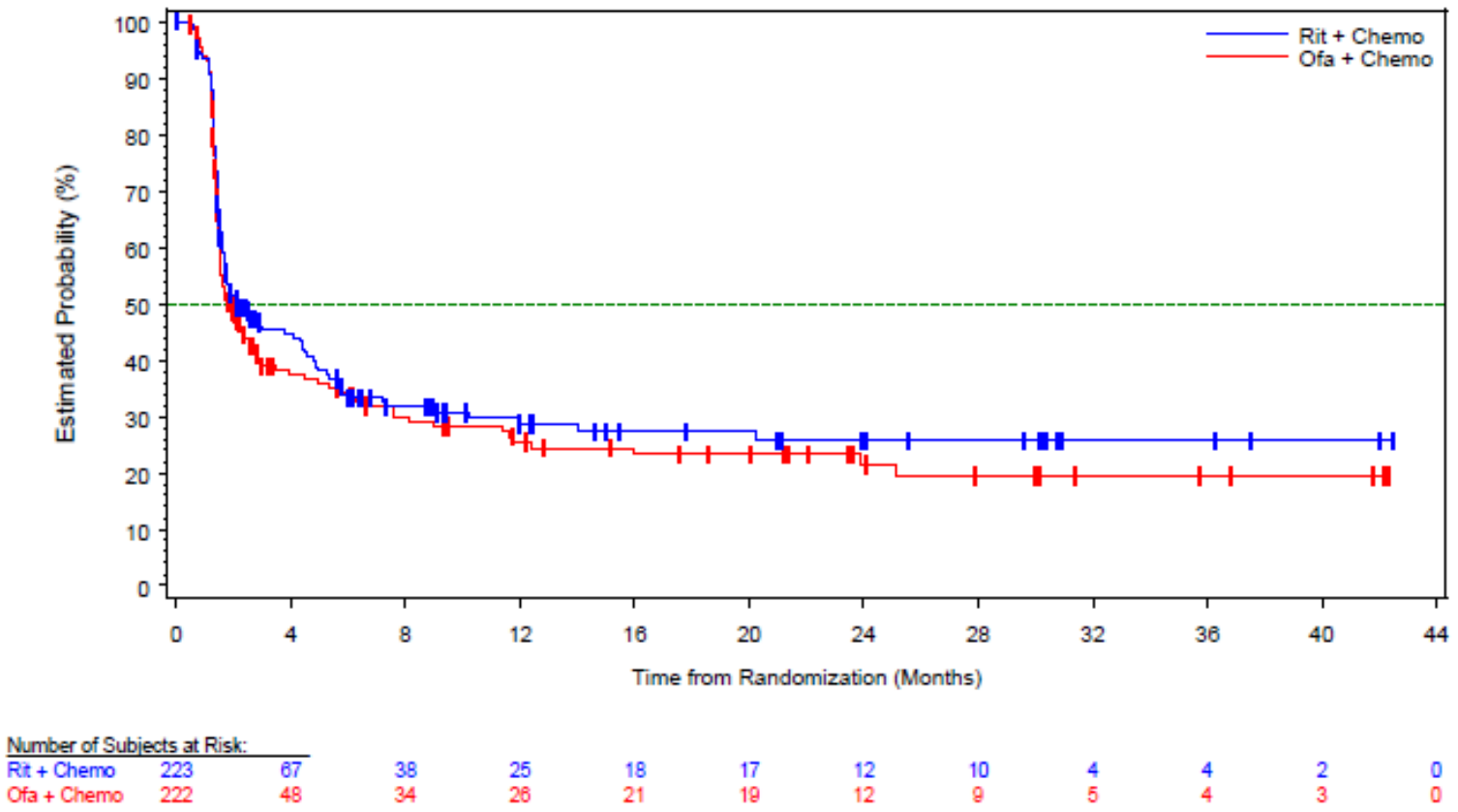
Number of Subjects at Risk:												
Rit + Chemo	81	80	80	44	13	6	3	2	2	1	0	0
Ofa + Chemo	74	73	73	40	13	6	2	0	0	0	0	0

Recovery is defined as 2 consecutive results of ANC >=0.5x10^9/L

Deaths

	R-chemo n=223	O-chemo n=222
Dead, n (%)	113 (51%)	102 (46%)
Primary Cause of Death, n (%)		
Lymphoma	89 (79%)	81 (79%)
Other	24 (21%)	21 (21%)

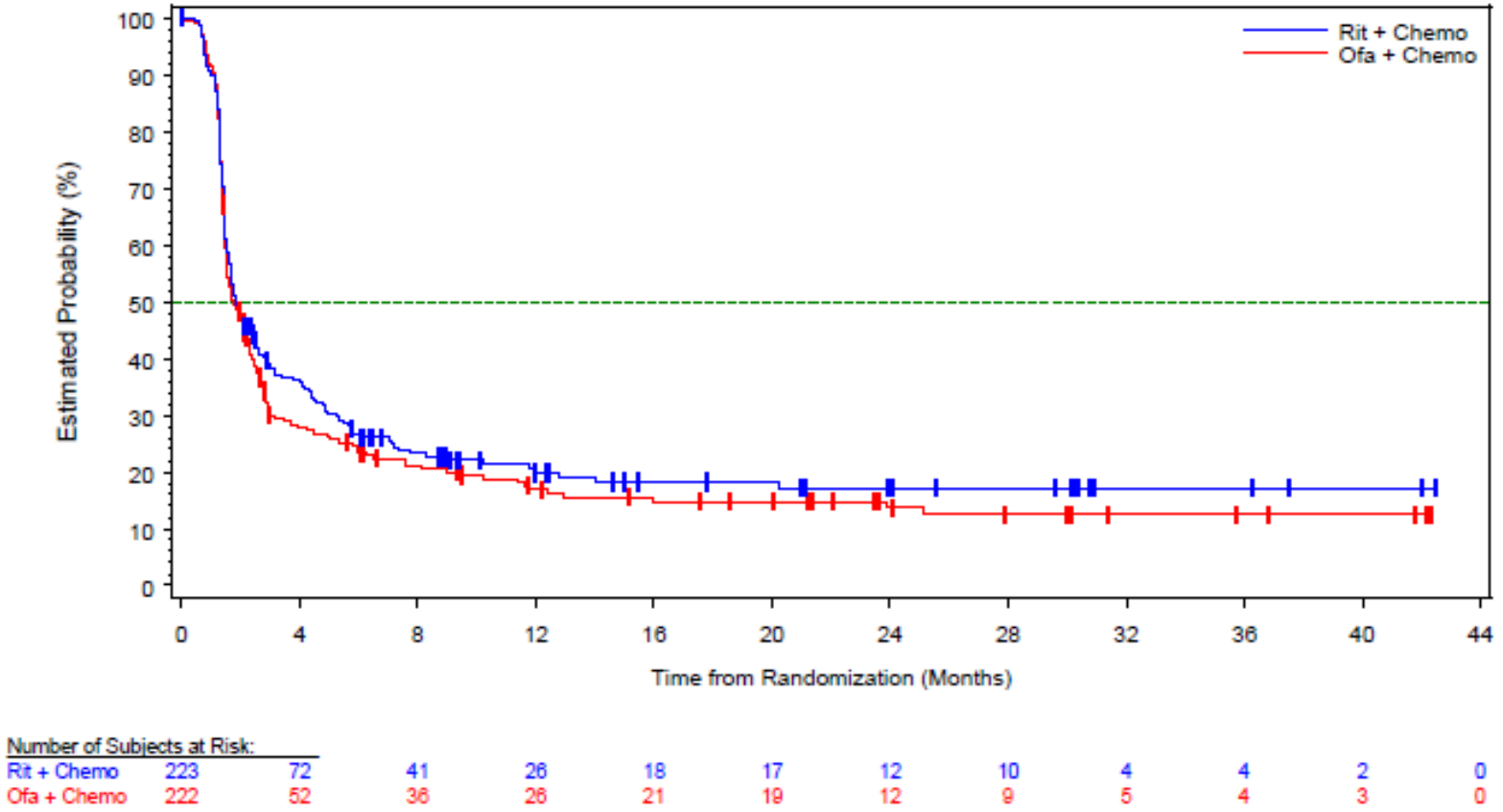
Progression-free survival (IRC)



Median PFS 2.1 months R-chemo vs 1.8 months O-chemo (HR=1.14, p=0.27)

2yr PFS 26% R-chemo vs 21% O-chemo

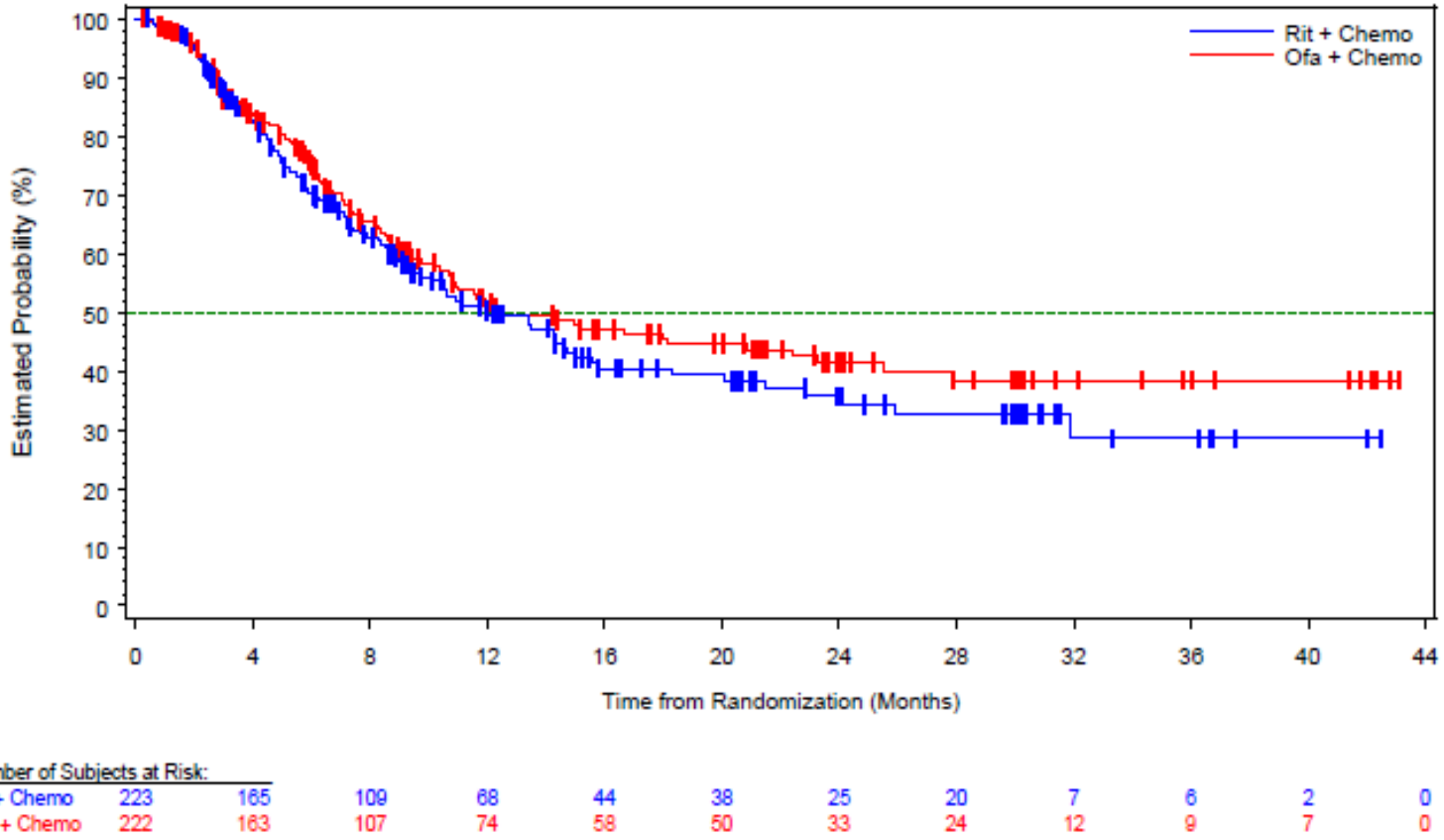
Event-free survival (IRC)



Median EFS 1.8 months R-chemo vs 1.7 months O-chemo (HR=1.12, p=0.27)

2yr EFS 17% R-chemo vs 14% O-chemo

Overall survival



Median OS 12 months R-chemo vs 12.5 months O-chemo (HR=0.86, p=0.25)

2yr OS 36% R-chemo vs 41% O-chemo

Conclusion

- In this large international study no difference in efficacy was found between Ofatumumab and Rituximab in combination with DHAP as salvage treatment for refractory or relapsed DLBCL
- No major differences in clinically relevant toxicity were observed between the study arms
- No differences were found in
  - time to recovery of neutrophil and platelet counts
  - stem cell mobilisation
  - time to neutrophil and platelet recovery post ASCT

➢ Improved salvage treatment for patients failing first-line R-CHOP treatment is urgently needed

Acknowledgments

Thank you to all Investigators who recruited patients:

NCRI: Kirit Ardeshna; George Follows; Eve Gallop-Evans; Chris Hatton; Abraham Jacob; Peter Johnson; Roderick Johnson; Nagesh Kalakonda; Jonathan Lambert; Anne Lennard; Richard Lush; Marian Macheta; Pam McKay; Andrew McMillan; Nick Morley; Christopher Price; John Radford; Fiona Scott. **United States:** Thomas Chauncey; Luciano Costa; Saurabh Chhabra; Stephanie Elkins; Siddhartha Ganguly; Teresa Gentile; Matthew Matasar; Steven Park; David Peach; Fahd Quddus; Stuart Seropian; Sonali Smith. **NLG:** Jette Goerloev; Judit Joergensen; Tuula Lehtinen; Sirpa Leppa; Jenni Peltonen; Harald Holte; Mats Jerkeman; Daniel Molin; Stefan Norin. **HOVON:** Aart Beeker; Lara Böhmer; Jeanette Doorduijn; Anton Hagenbeek; Gustaaf van Imhoff; Maria Leijs; Pieternella Lugtenburg; Willem Marijt; Monique Minnema; Hendricus Schouten; Wendy Stevens; Okke de Weerdt; Johanna Zijlstra-Baalbergen. **Japan:** Masahiro Abe; Kiyoshi Ando; Shigeru Chiba; Shinichiro Fujiwara; Shotaro Hagiwara; Kiyohiko Hatake; Yoshitaka Imaizumi; Fumihiro Ishida; Takayuki Ishikawa; Kenichi Ishizawa; Fumihiko Nakamura; Naoto Takahashi; Yochi Tatsumi; Kensei Tobinai; Naoto Tomita; Toshiki Uchida. **China:** Xiaonan Hong; Ming Hou; Jie Jin; Xiaoyan Ke; Tongyu Lin; Lugui Qiu; Zhixiang Shen; Yuankai Shi; Depei Wu; Wei Xu; Li Yu; Jun Zhu. **PLRG:** Sebastian Grosicki; Kazimierz Kuliczkowski; Jan Walewski; Krzysztof Warzocha. **Korea:** Jin Seok Kim; WonSeog Kim. **GELTAMO:** Aránzazu Alonso Alonso; Reyes Arranz Sáez; María Dolores Caballero Barrigón; José Luis Díez Martín; Jose Antonio García Marco; Carlos Grande García; Jose María Moraleda Jiménez; Carlos Panizo Santos. **Hungary:** Zita Borbényi; Miklós Egyed; Zoltan Gasztonyi; Árpád Illés; András Rosta. **Belgium:** Marc André; Fritz Offner; Koen Theunissen; Eric van den Neste; Gregor Verhoef. **Czech Republic:** David Belada; Jiri Mayer. **Republic of Russian Federation:** Boris Afanasyev; Nadezhda Medvedeva; Natalya Tyurina. **Austria:** Michael Fridrik; Ulrich Jaeger; Ansgar Weltermann; Wolfgang Willenbacher. **Germany:** Antonio Pezzutto; Christoph Schliemann; Andreas Viardot. **ICORG:** Amjad Hayat; Elizabeth Vandenberghe. **Israel:** Amos Cohen; Arnon Nagler. **Thailand:** Suporn Chuncharunee; Noppadol Siritanaratkul. **Greece:** Maria Aggelopoulou; Konstantinos Tsionos. **Estonia:** Jane Lehtmaa; Iige Viigimaa. **Argentina:** Alicia Enrico; Maria Cecilia Foncuberta.

IDMC: Andreas Engert; James Armitage; Nicolas Mounier.

A very big thank you to all of the patients who participated