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UPDATE ON FOLLICULAR LYMPHOMA

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DISCOVERY AND VALIDATION OF A SIMPLIFIED SCORING SYSTEM (THE PRIMA-PROGNOSTIC INDEX) IN *DE NOVO* FL TREATED INITIALLY WITH IMMUNOCHEMOTHERAPY

Bachy E, et al. Blood 2017;130(S1):413

FL, Follicular Lymphoma

PRIMA-PI
INTRODUCTION

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- In FL, no Prognostic Index (PI) had been developed that was based on patients treated only with initial immunochemotherapy
- This led to the development of the PRIMA-PI[1] which included:
  - Model building using PFS as the primary endpoint
  - Data from the PRIMA trial[2] cohort of 1,135 patients for the discovery component
- For the validation component, patients with FL from the FL2000 trial[3] and MER-SPORE[4] were included; EFS was the primary endpoint
- **The aim of the investigation was to develop an easy-to-compute and reliable PI that could aid in trial stratification and routine clinical evaluation**

EFS, event-free survival; FL, follicular lymphoma; FL2000, follicular lymphoma trail with start date 2000: MER, Molecular Epidemiology Resource; PI, prognostic index; PFS, progression free survival; PRIMA, PRIMA; Primary RItuximab and MAintenance trial; SPORE, Specialized Program of Research Excellence

1. Bachy E et al. Blood 2017;130(S1):413; 2. Salles G et al. Lancet. 2011; 377:42-51; 3. Salles G et al Blood 2008; 112:4824-4831; 4. Mayo Clinic Molecular Epidemiology Resource, website accessed 28 Jan 2019, https://www.mayo.edu/research/labs/lymphoma-epidemiology/research/molecular-epidemiology-resource

PRIMA-PI
RESULTS (1)

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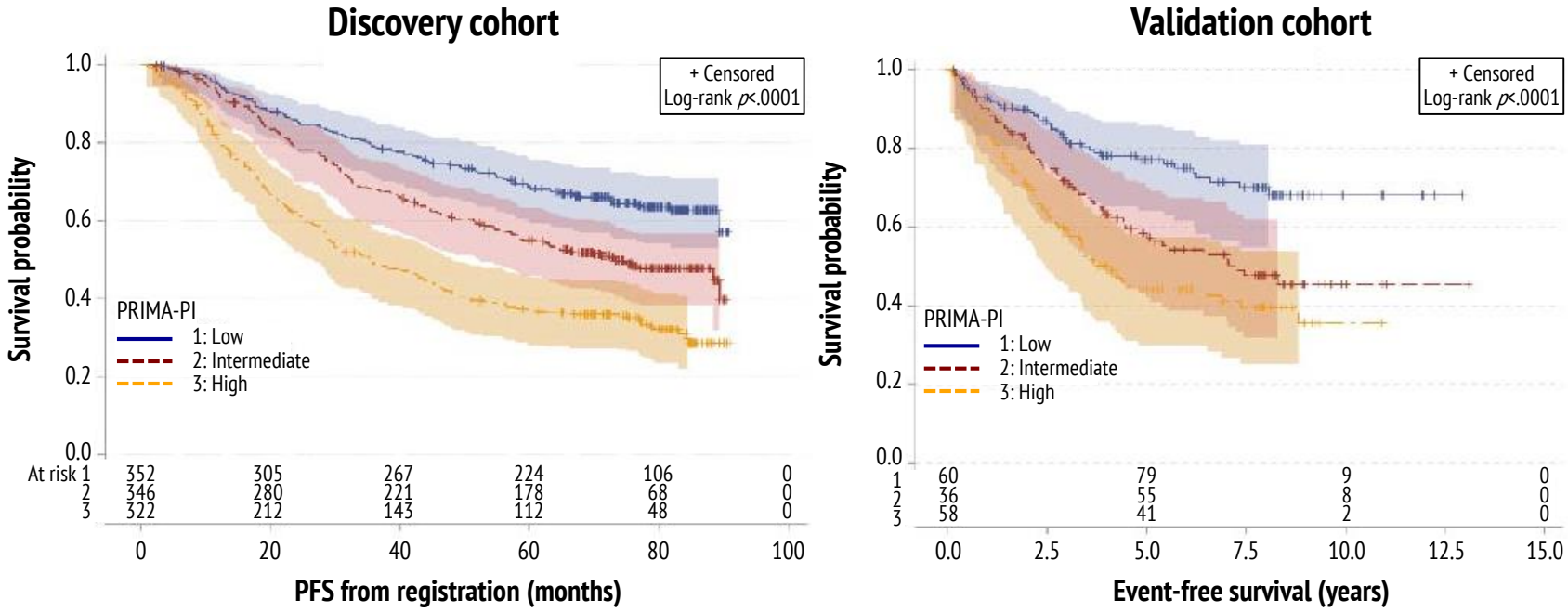
- PRIMA-PI features included:
  - It is a two-factor model consisting of B2M and BM involvement
  - With 3 risk categories based on B2M and BM involvement
    - Low: Neither
    - Intermediate: Either
    - High: Both
- PFS24 was a strong post-treatment prognostic parameter for subsequent OS in the discovery cohort
- **PRIMA-PI was highly discriminatory** for predicting outcome for the 3 risk categories in the validation cohort

B2M; beta-2 microglobulin; BM, bone marrow; PFS24; progression free survival at 24 months; PI, prognostic index; PRIMA, Primary RItuximab and MAintenance trial
Bachy E et al. Blood 2017;130(S1):413

PRIMA-PI
RESULTS (2)



P, probability; PFS, progression free survival; PI, prognostic index; PRIMA, Primary RItuximab and MAintenance trial

Bachy E et al. Blood 2017;130(S1):413

PRIMA-PI
CONCLUSIONS

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- PRIMA-PI is an **easy-to-compute prognostic index** for patients with FL treated upfront with Immunochemotherapy

FL, follicular lymphoma; PI, prognostic index; PRIMA; PRImary rituximab and MAintenance trial
Bachy E et al. Blood 2017;130(S1):413

PROGNOSTIC VALUE OF PET-CT AFTER 1ST-LINE THERAPY IN PATIENTS WITH FL: A POOLED ANALYSIS OF CENTRAL SCAN REVIEW IN THREE MULTICENTRE STUDIES

Trotman J et al. Lancet Haematol 2014;1(1):e17-e27

FL, Follicular Lymphoma; PET-CT , Positron Emission Tomography and Computed Tomography Scan

PET-CT AFTER FRONTLINE THERAPY FOR FL
INTRODUCTION

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- ^{18}F-fluorodeoxyglucose (FDG) PET-CT imaging has been shown to be useful for assessing treatment response following 1L rituximab chemotherapy of FL[1]
- This study analysed the application of the five-point Deauville scale (5PS), used to score FDG uptake on PET images, in a large cohort derived from three studies[2]
- The aim was to assess the **correlation between post-induction PET status and survival** in patients with FL, and confirm the primary role of PET response assessment

1L, first line; 5PS, 5-point Deauville scale; ^{18}F, fluorine-18 radioisotope; FDG, ^{18}F-fluorodeoxyglucose; FL, follicular lymphoma; PET-CT , Positron Emission Tomography and Computed Tomography Scan

1. Trotman J et al. J Clin Oncol 2011; 29:3194–200; 2. Trotman J et al. Lancet Haematol 2014;1(1):e17-e27

PET-CT AFTER FRONTLINE THERAPY FOR FL
RESULTS: ALL PATIENTS

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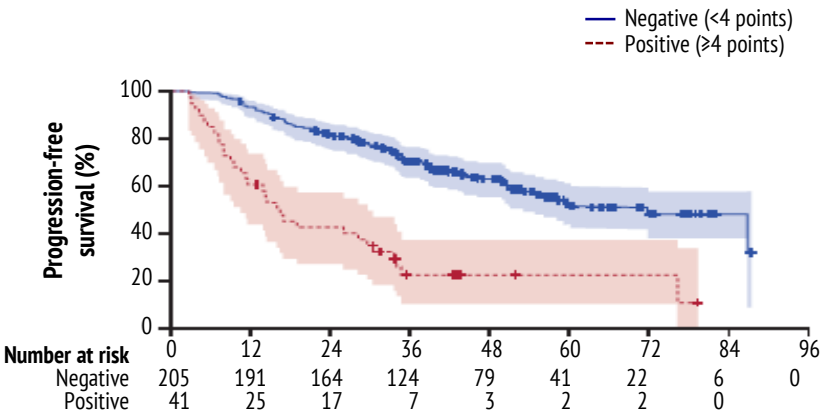
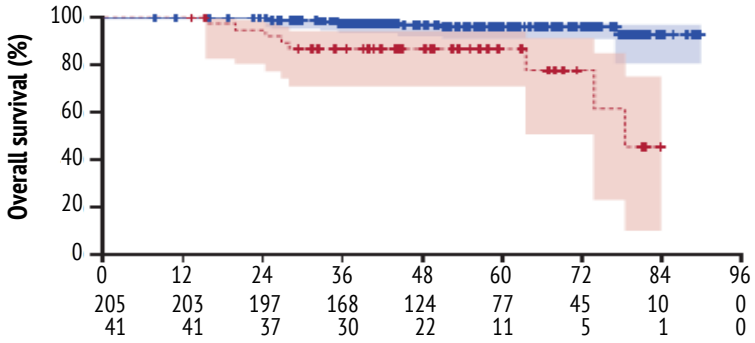
FL PATIENTS WITH A POSITIVE PET-CT SCAN (> 4 POINTS) HAD SIGNIFICANTLY SHORTER PFS AND OS COMPARED WITH THOSE WITH A NEGATIVE SCAN (< 4 POINTS)

A **Progression-free survival according to PET scan score (cutoff ≥4)**



	Events	Censored	Median survival (95% CI), months	Log-rank *p* value
Negative (n=205)	81 (40%)	124 (60%)	74 (54.7–NA)	<0.0001
Positive (n=41)	31 (76%)	10 (24%)	16.9 (10.8–31.4)	

B **Overall survival according to PET scan score (cutoff ≥4)**



	Events	Censored	Median survival (95% CI), months	Log-rank *p* value
Negative (n=205)	7 (3%)	198 (97%)	NA (NA–NA)	<0.0001
Positive (n=41)	8 (20%)	33 (80%)	78.7 (74.1–NA)	

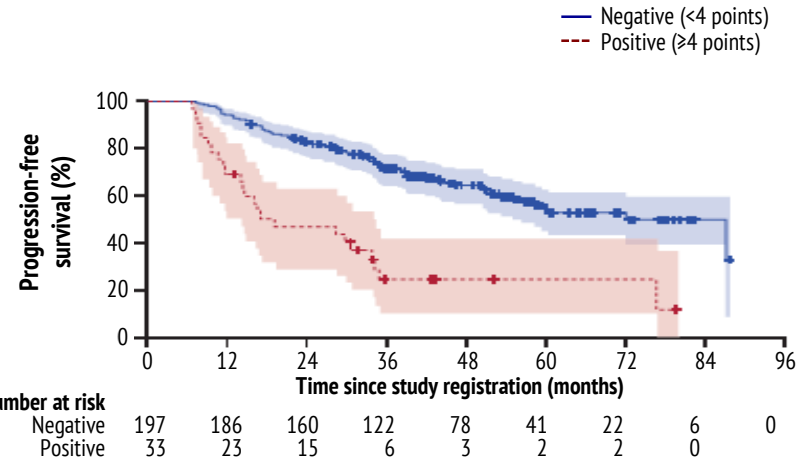
1L, first line; FL, follicular lymphoma; OS, overall survival; PET-CT, Positron Emission Tomography and Computed Tomography Scan; PFS, progression free survival

Trotman J et al. Lancet Haematol 2014;1(1):e17-e27

PET-CT AFTER FRONTLINE THERAPY FOR FL
RESULTS: IWC RESPONDERS

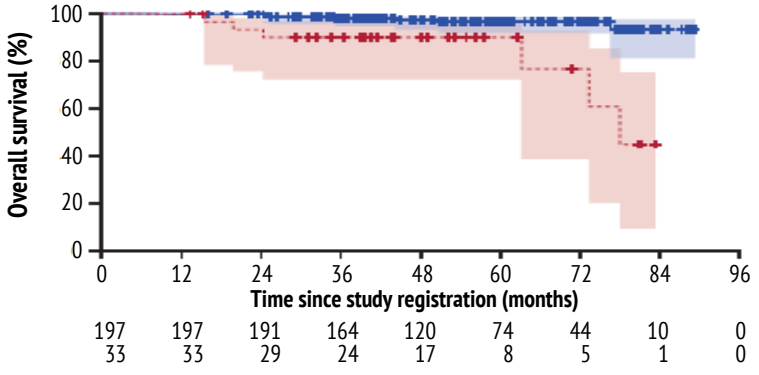
FL PATIENTS WITH A POSITIVE PET-CT SCAN (> 4 POINTS) HAD SIGNIFICANTLY SHORTER PFS AND OS COMPARED WITH THOSE WITH A NEGATIVE SCAN (< 4 POINTS)

C Progression-free survival according to PET scan score (cutoff ≥4) in IWC responders



	Events	Censored	Median survival (95% CI), months	Log-rank *p* value
Negative (n=197)	75 (38%)	122 (62%)	89.5 (57.9–NA)	<0.0001
Positive (n=33)	24 (73%)	9 (27%)	19.6 (14.3–35.1)	

D Overall survival according to PET scan score (cutoff ≥4) in IWC responders



	Events	Censored	Median survival (95% CI), months	Log-rank *p* value
Negative (n=197)	6 (3%)	191 (97%)	NA (NA–NA)	<0.0001
Positive (n=33)	6 (18%)	27 (82%)	78.7 (63.7–NA)	

1L, first line; FL, follicular lymphoma; IWC, International Workshop Criteria (1999); OS, overall survival; PET-CT, Positron Emission Tomography and Computed Tomography Scan; PFS, progression free survival

Trotman J et al. Lancet Haematol 2014;1(1):e17-e27

PET-CT AFTER FRONTLINE THERAPY FOR FL
CONCLUSIONS

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- Post-induction PET status according to 5PS was a **significant predictor of both PFS and OS**
- PET-CT should be considered as a new standard for assessing treatment response for FL in clinical practice

1L, first line; 5PS, 5-point Deauville scale; FL, follicular lymphoma; OS, overall survival; PET-CT, Positron Emission Tomography and Computed Tomography Scan; PFS, progression free survival

Trotman J et al. Lancet Haematol 2014;1(1):e17-e27

VALIDATION OF POD24 AS A ROBUST EARLY CLINICAL ENDPOINT OF POOR SURVIVAL IN FL: RESULTS FROM THE FL ANALYSIS OF SURROGACY HYPOTHESIS (FLASH)

Casulo C et al. Blood 2017; 130:412

FL, Follicular Lymphoma; POD24, progression of disease within 24 months of diagnosis

POD24 IN FL
INTRODUCTION

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- FL is the most common indolent lymphoma[1] with prolonged survival[2]
- However, there is significant clinical heterogeneity with a subset of patients experiencing transformation, early recurrence or refractory disease[3]
- Using the FLASH data, the aims of this investigation[4] was to
  - evaluate the association between FLIPI and other baseline factors on PFS24
  - **validate POD24** as an early clinical endpoint in FL
  - Investigate individual data from 5,453 patients on 13 clinical trials

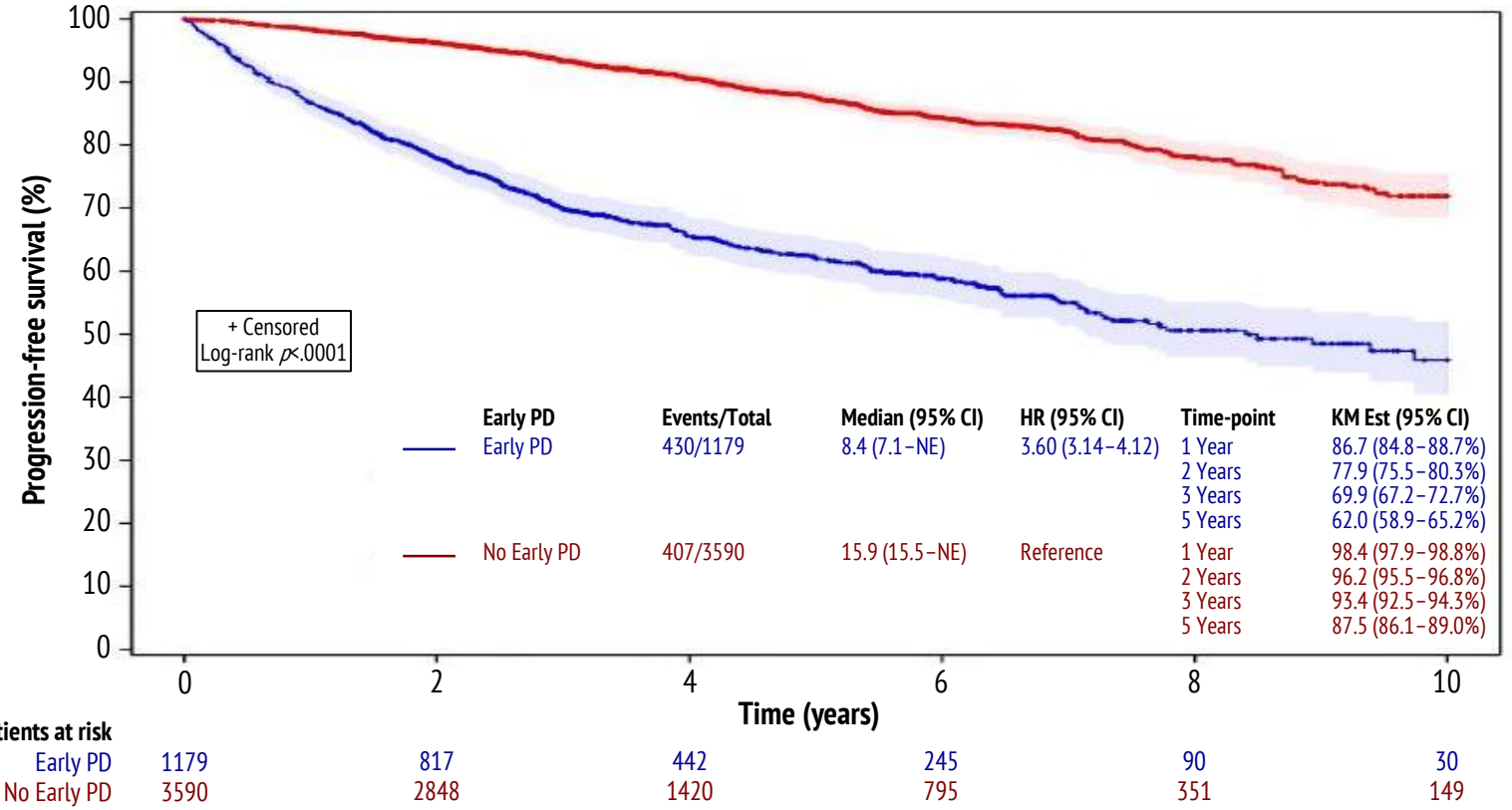
FL, follicular lymphoma; FLASH, follicular lymphoma analysis of surrogacy hypothesis; FLIPI, follicular lymphoma international prognostic index; PFS24, progression-free survival within 24 months of trial enrolment; POD24, progression of disease within 24 months of diagnosis

1. No authors, Blood 1997; 89(11):3909-18; 2. NIH, SEER datahttps://seer.cancer.gov/statfacts/html/follicular.html; 3. Dreyling M et al. Annals of Oncology 2016; 27(S5): v83–v90; 4. Casulo C et al. Blood 2017; 130:412

POD24 IN FL

RESULTS

LANDMARK OS OF FL PATIENTS WITH EARLY POD (STARTING AT 2 YEARS AFTER REGISTRATION)



CI, confidence interval; Est, estimate; FL, follicular lymphoma; HR, hazard ratio; KM, Kaplan Meier; OS, overall survival; PD, progressive disease; POD, progression of disease; POD24, progression of disease within 24 months of diagnosis

Casulo C et al. Blood 2017; 130:412

POD24 IN FL
CONCLUSIONS

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- These results **confirm POD24 as an early clinical endpoint of poor survival in FL** that should be utilised to identify patients for prospective clinical trials

FL, follicular lymphoma; POD24, progression of disease within 24 months of diagnosis
Casulo C et al. Blood 2017; 130:412

OBINUTUZUMAB FOR THE 1ST-LINE TREATMENT OF FL (GALLIUM TRIAL)

Marcus R et al. N Engl J Med 2017;377(14):1331-1344

FL, Follicular Lymphoma

GALLIUM TRIAL: 1ST-LINE FL, MZL

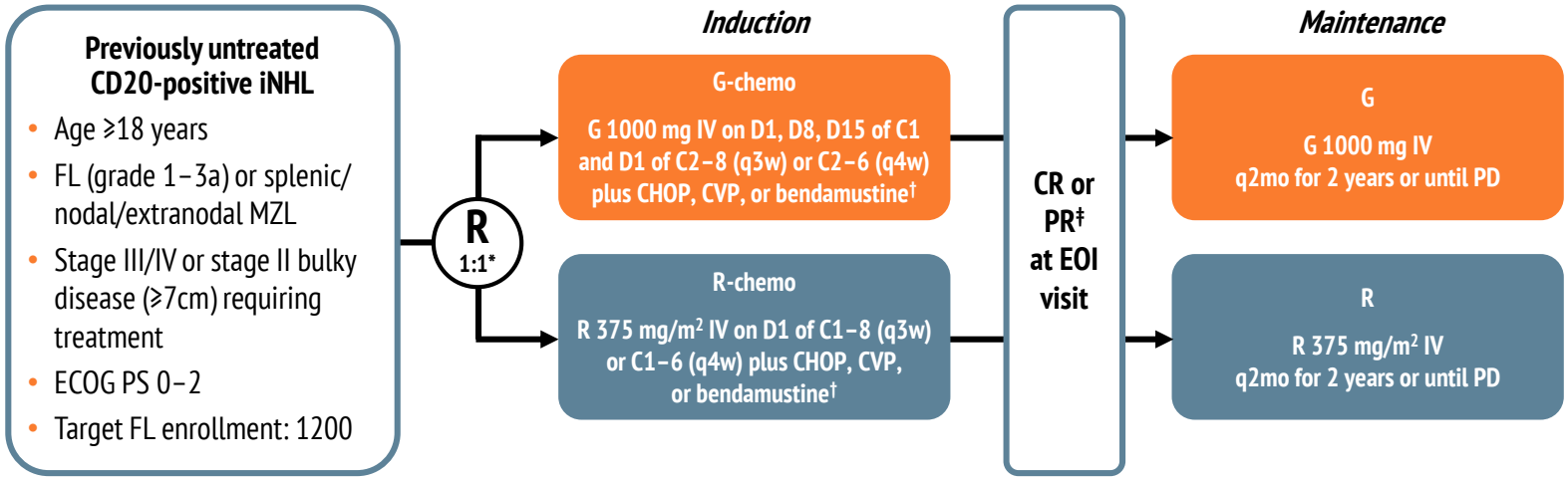
INTRODUCTION

- The aim of the GALLIUM trial was to compare the efficacy and safety of **induction** with **obinutuzumab**, as compared with **rituximab**, each combined with **chemotherapy**, followed by **maintenance** therapy with the same monoclonal antibody, in patients with previously untreated indolent non-Hodgkin's lymphoma (FL or MZL)

FL, follicular lymphoma; MZL, marginal-zone lymphoma

Marcus R et al. N Engl J Med 2017;377(14):1331-1344; NCT01332968, Clinicaltrials.gov

GALLIUM TRIAL: 1ST-LINE FL AND MZL DESIGN



Primary endpoint	Secondary and other endpoints	
• PFS (INV-assessed in FL)	• PFS (IRC-assessed)§ • OS, EFS, DFS, DoR, TTNT	• CR/ORR at EOI (+/– FDG-PET) • Safety

*FL and MZL pts were randomized separately; stratification factors: chemotherapy, FLIPI (FL) or IPI (MZL) risk group, geographic region; †CHOP q3w × 6 cycles, CVP q3w × 8 cycles, bendamustine q4w × 6 cycles; choice by site (FL) or by pt (MZL); ‡Pts with SD at EOI were followed for PD for up to 2 years; §Confirmatory endpoint

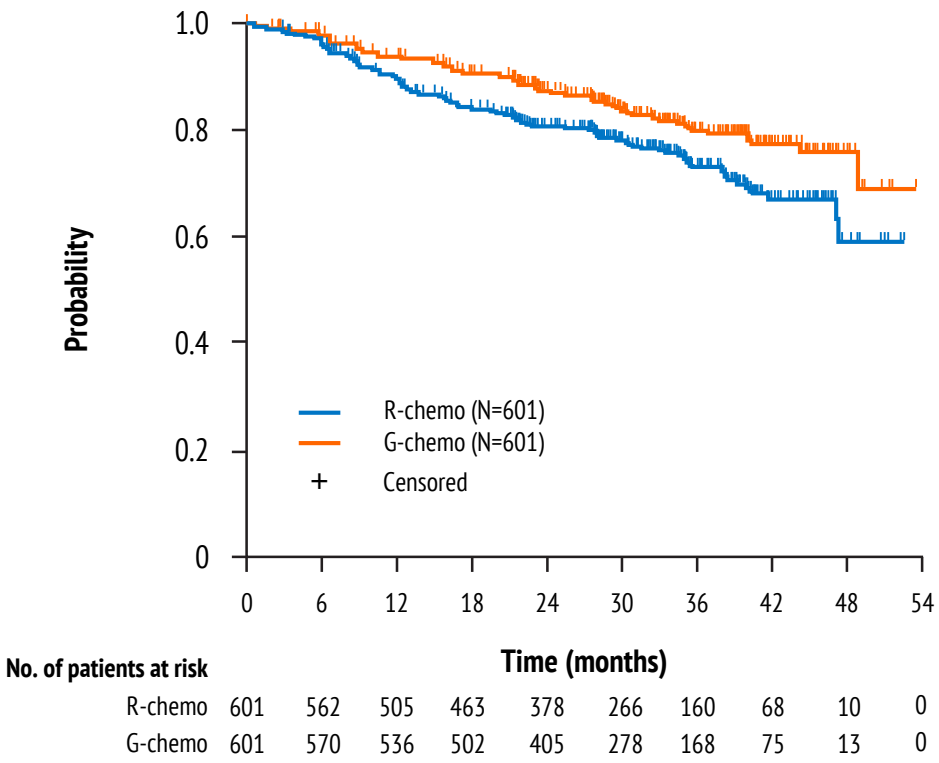
CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CR, complete response; CVP, cyclophosphamide, vincristine and prednisone; DFS, disease free survival; DoR, duration of response; EFS, event free survival; EOI, end of induction; FDG-PET, 18F-fluorodeoxyglucose–positron-emission tomography; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; G, obinutuzumab; IPI, International Prognostic Index; IRC, independent review committee; MZL marginal-zone lymphoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; R, rituximab; SD, stable disease; TTNT, time to new anti-lymphoma treatment.

Marcus R et al. N Engl J Med 2017;377(14):1331-1344; NCT01332968, Clinicaltrials.gov

GALLIUM TRIAL: 1ST-LINE FL†

RESULTS: PFS

PFS SIGNIFICANTLY LONGER WITH G-CHEMO COMPARED WITH THE R-CHEMO



	R-chemo n=601	G-chemo n=601
Pts with event, n (%)	144 (24.0)	101 (16.8)
3-yr PFS, % (95% CI)	73.3 (68.8, 77.2)	80.0 (75.9, 83.6)
HR (95% CI), *P*-value*	0.66 (0.51, 0.85), *P*=.001	

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

† results are for the FL cohort of patients

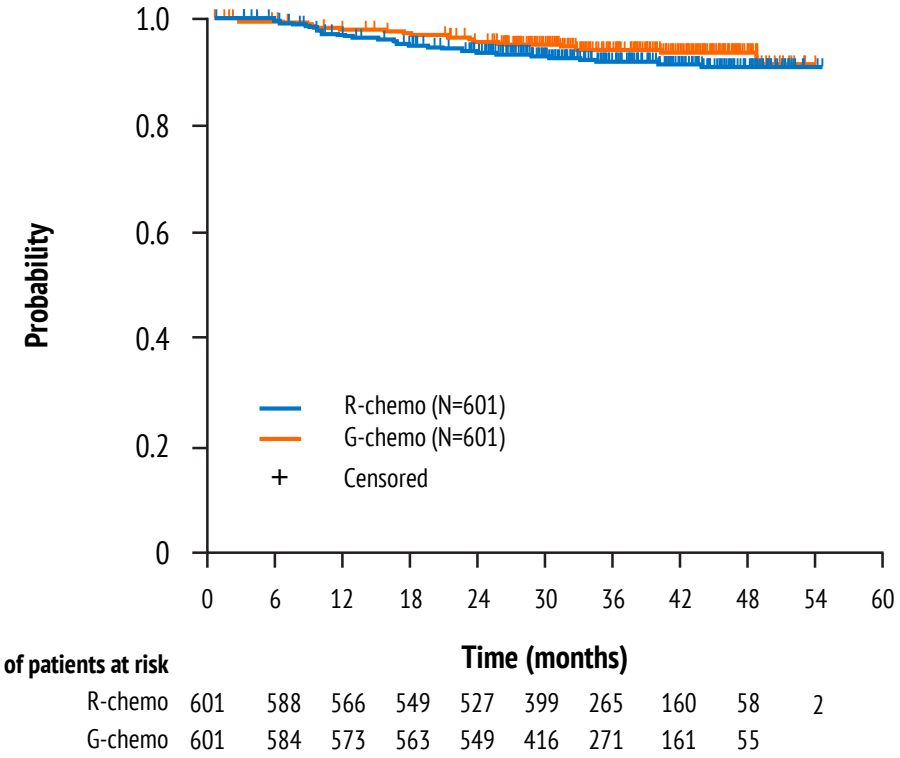
CI, confidence interval; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; G, obinutuzumab; HR, hazard ratio; n, number of patients; No., number; P, probability; PFS, progression free survival; Pts, patients; R, rituximab; yr, year;

Marcus R et al. N Engl J Med 2017;377(14):1331-1344; NCT01332968, Clinicaltrials.gov

GALLIUM TRIAL: 1ST-LINE FL†

RESULTS: OS

OS SIMILAR WITH G-CHEMO AND R-CHEMO



	R-chemo n=601	G-chemo n=601
Pts with event, n (%)	46 (7.7)	35 (5.8)
3-yr OS, % (95% CI)	92.1 (89.5, 94.1)	94.0 (91.6, 95.7)
HR (95% CI), *P*-value*	0.75 (0.49, 1.17), *P*=.21	

Median follow-up: 34.5 months

*Stratified analysis; stratification factors: chemotherapy regimen, FLIPI risk group, geographic region

† results are for the FL cohort of patients

CI, confidence interval; FLIPI, Follicular Lymphoma International Prognostic Index; G, obinutuzumab; HR, hazard ratio; n, number of patients; No., number; P, probability; Pts, patients; OS, overall survival; R, rituximab; yr, year;

Marcus R et al. N Engl J Med 2017;377(14):1331-1344; NCT01332968, Clinicaltrials.gov

GALLIUM TRIAL: 1ST-LINE FL†
CONCLUSIONS

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- Obinutuzumab-based immunochemotherapy and maintenance therapy **resulted in longer PFS** than rituximab-based therapy

† based on the results for the FL cohort of patients

FL, follicular lymphoma; PFS, progression free survival
Marcus R et al. N Engl J Med 2017;377(14):1331-1344; NCT01332968, Clinicaltrials.gov

RITUXIMAB PLUS LENALIDOMIDE IN ADVANCED UNTREATED FL (RELEVANCE TRIAL)

Morschhauser F et al. N Engl J Med 2018;379(10):934-947

FL, Follicular Lymphoma; RELEVANCE, Rituximab Lenalidomide versus Any Chemotherapy trial

RELEVANCE TRIAL: R^2 IN 1L FL

INTRODUCTION

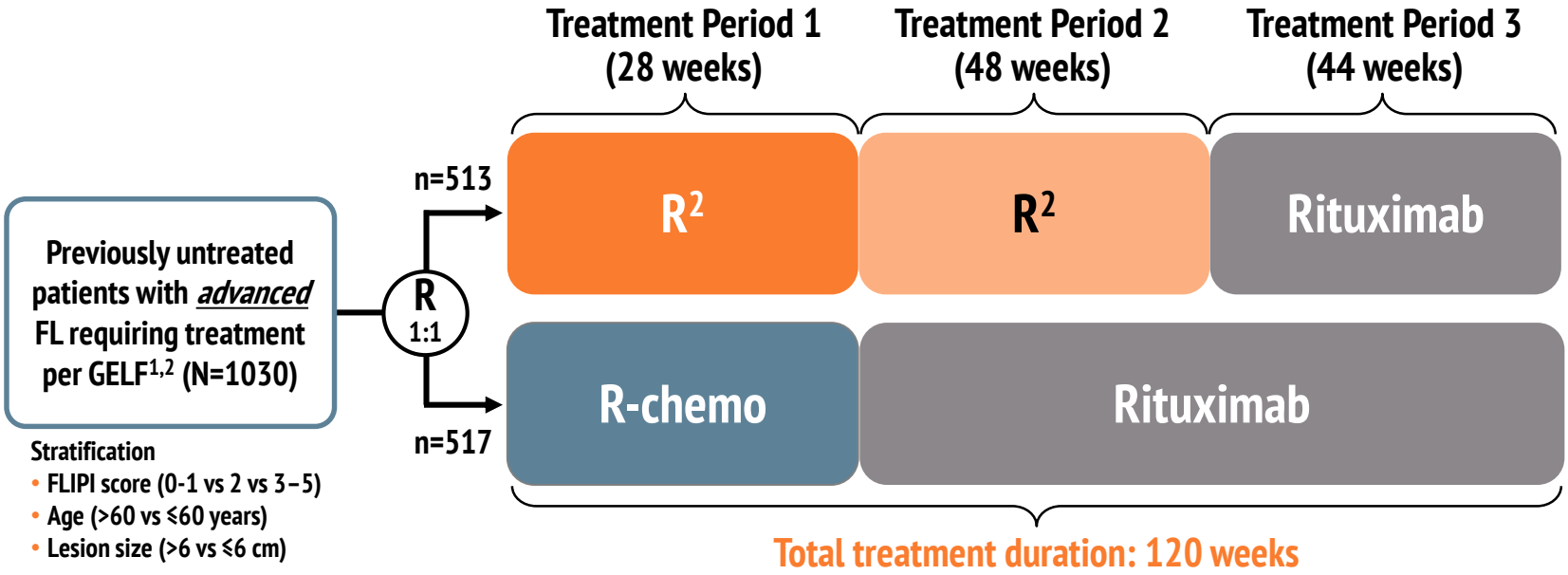
- The RELEVANCE trial was a randomized, phase 3 trial that compared the efficacy and safety of **R^2 with those of R+chemo**, with both regimens followed by maintenance therapy with R, in patients with previously untreated, advanced FL

1L, first line; FL, follicular lymphoma; R, rituximab; R^2, lenalidomide and rituximab; RELEVANCE, Rituximab Lenalidomide versus Any Chemotherapy trial;

Morschhauser F et al. N Engl J Med 2018;379(10):934-947

RELEVANCE TRIAL[3]: R² IN 1L FL

DESIGN



Co-primary endpoints per 1999 IWG criteria*

- CR/CRu at 120 weeks
- PFS (first interim analysis at ~50% of targeted events)

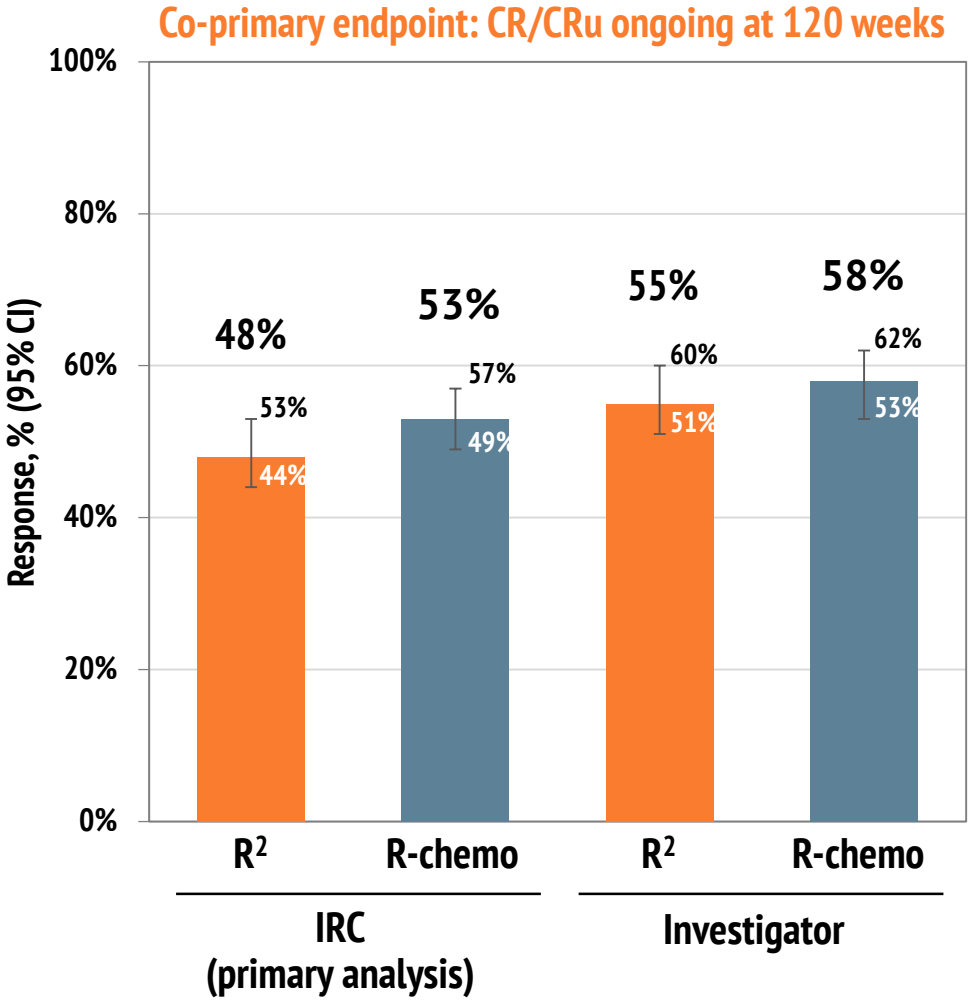
NCT01476787; NCT01650701; EUDRA 2011-002792-42.
*Per central (IRC) review by 1999 IWG with CT

Dosing schedule

- **R²:** Lenalidomide 20 mg/d, d2-22/28 until CR/CRu at 6, 9, or 12 cycles, then 10 mg/d (total 18 cycles) and rituximab 375 mg/m²/wk c1 and d1 c2-6; continued in responders q8wk for 12 cycles
- **R-chemo:** 3 options (R-CHOP, R-B, R-CVP) plus 2 years rituximab maintenance
  - R-chemo regimen selected pre-randomization by investigators
  - Included 72% R-CHOP, 23% R-B, and 5% R-CVP

1L, first line; CR, complete response; CRu, complete response unconfirmed; CT, computed tomography; FLIPI, Follicular Lymphoma International Prognostic Index; GELF Groupe d'Etude des Lymphomes Folliculaires criteria; IWG, International Working Group; PFS, progression free survival; R, rituximab; R², lenalidomide and rituximab; R-B, rituximab, bendamustine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; 1. Salles G et al. Lancet. 2011;377:42-51.; 2. Brice P et al. J Clin Oncol. 1997;15:1110-1117; 3. Morschhauser F et al. N Engl J Med. 2018;379(10):934-947

RELEVANCE TRIAL: R^2 IN 1L FL
RESULTS: RESPONSE (ITT)



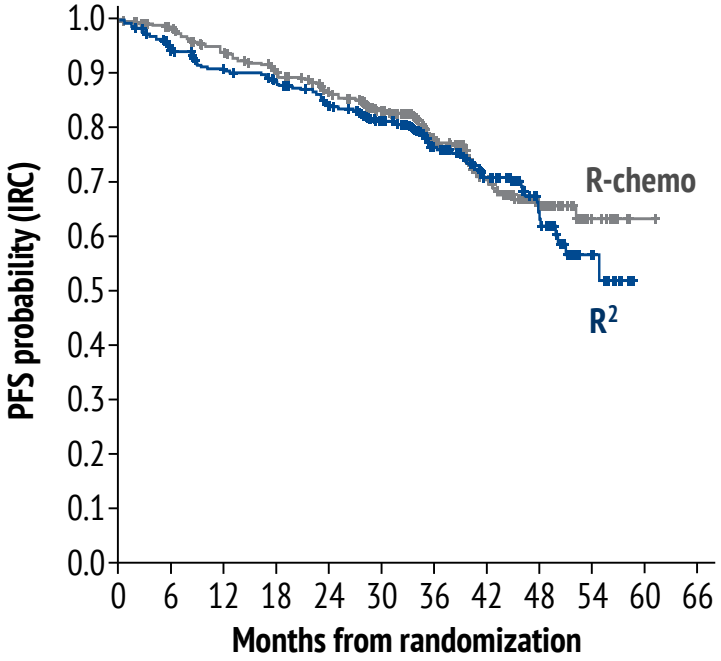
- Best overall response (CR+CRu+PR)
  - 84% R^2 vs 89% R-chemo (IRC)
  - 86% R^2 vs 92% R-chemo (investigator)
- SPD reduction of ⩾50% at 12 weeks was 81% for R^2 and 90% for R-chemo
- ORR ongoing at 120 weeks
  - 61% R^2 vs 65% R-chemo (IRC)
  - 65% R^2 vs 68% R-chemo (investigator)
- Probability of maintaining response (CR/CRu/PR) for ⩾3 years for R^2 vs R-chemo, respectively
  - 77% vs 74% (IRC)
  - 82% vs 77% (investigator)
- Data cut-off 31 May 2017

1L, first line; CI, confidence interval; CR, complete response; CRu, complete response unconfirmed; FL, follicular lymphoma; IRC, independent review committee; ITT, intention to treat; ORR, overall response rate; PR, partial response; R, rituximab; R^2, lenalidomide and rituximab; SPD, sum of the products of the diameters. Morschhauser F, *et al.* N Engl J Med. 2018;379(10):934-947

RELEVANCE TRIAL: R^2 IN 1L FL

RESULTS: PFS

AT A MEDIAN FOLLOW-UP OF 37.9 MO, INTERIM PFS (50% EVENTS) WAS SIMILAR IN BOTH ARMS



Number of patients at risk

R^2	513	435	409	393	364	282	174	107	49	13	0	
R-chemo	517	474	446	417	387	287	175	109	51	14	1	0

Interim PFS By IRC (Co-Primary Endpoint)

	R^2 (n=513)	R-chemo (n=517)
Events, n (%)	119 (23)	111 (21)
3-year PFS (95% CI)	77% (72%-80%)	78% (74%-82%)
HR (95% CI)	1.10 (0.85-1.43)	
P value	0.48	

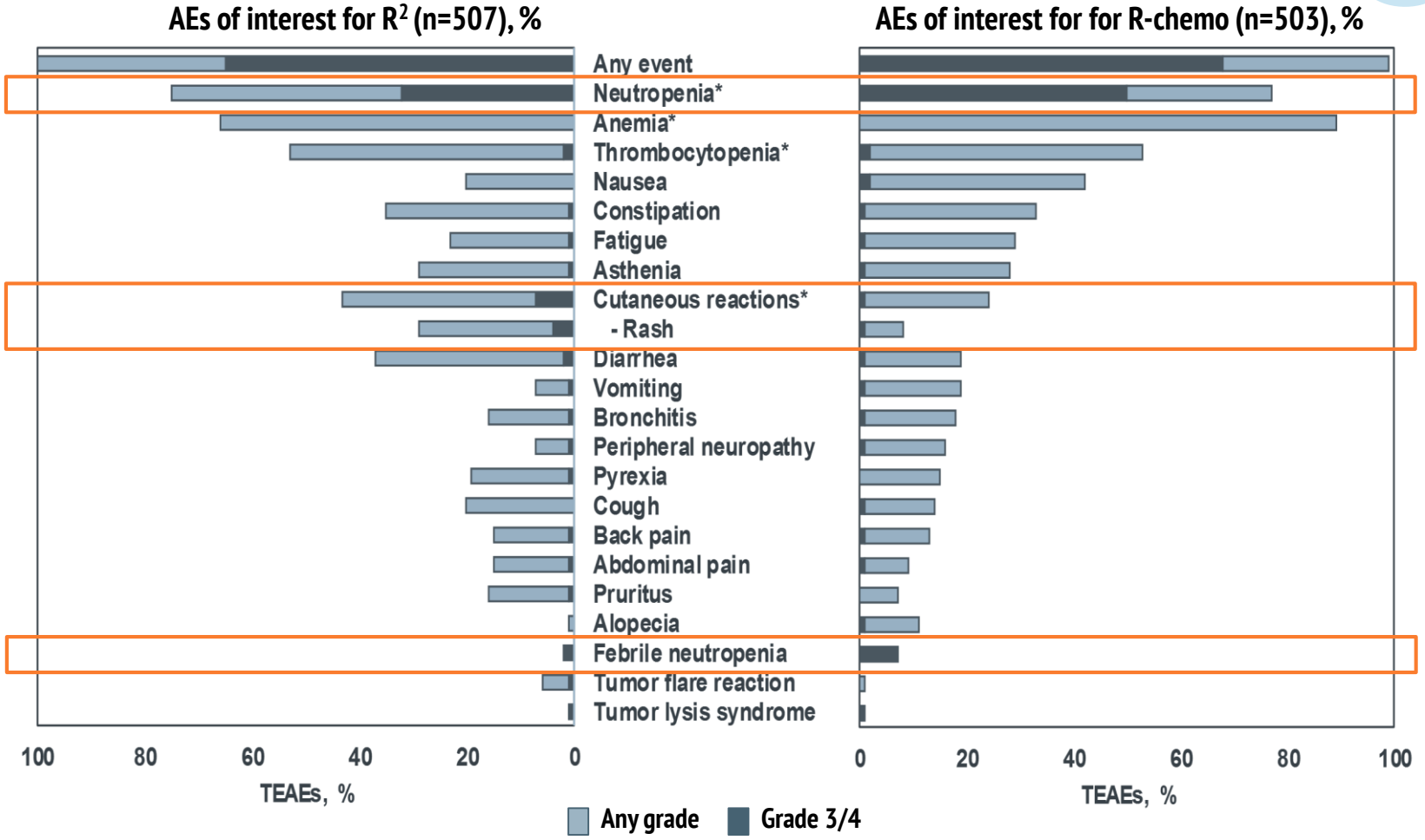
Data cut-off 31 May 2017

1L, first line; CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; IRC, independent review committee; n, number of patients; mo, months; PFS, progression free survival; R, rituximab; R^2, lenalidomide and rituximab.

Morschhauser F, *et al.* N Engl J Med. 2018;379(10):934-947

RELEVANCE TRIAL: R^2 IN 1L FL

RESULTS: AEs



Data cut-off 31 May 2017. Includes any-grade TEAEs (≥15%) and select AEs of interest as assessed per NCI CTCAE v4.03.
*Hematologic AEs were based on laboratory tests; all anemia events were grade 1. *Cutaneous reactions included preferred terms from skin and subcutaneous tissue disorders (including rash), gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and reproductive system and breast disorders

1L, first line; AEs, adverse events; CATAE, common terminology criteria for adverse events; Chemo, chemotherapy; FL, follicular lymphoma; n, number of patients; NCI, National Cancer Institute; R, rituximab; R^2, lenalidomide and rituximab; RELEVANCE, Rituximab Lenalidomide versus Any Chemotherapy trial

Morschhauser F, *et al.* N Engl J Med. 2018;379(10):934-947

RELEVANCE TRIAL: R^2 IN 1L FL

CONCLUSIONS

- In previously untreated FL, the efficacy of R^2 was similar to that of R+chemo
- The **safety profile differed in the two groups**, with a;
  - higher incidence of grade 3-4 neutropenia and febrile neutropenia of any grade with R+chemo
  - higher incidence of grade 3-4 cutaneous reactions with R^2

1L, first line; Chemo, chemotherapy; FL, follicular lymphoma; R, rituximab; R^2, lenalidomide and rituximab; RELEVANCE, Rituximab Lenalidomide versus Any Chemotherapy trial

Morschhauser F et al. N Engl J Med 2018;379(10):934-947

PHOSPHATIDYLINOSITOL 3-KINASE INHIBITION BY COPANLISIB IN RELAPSED OR REFRACTORY INDOLENT LYMPHOMA

Dreyling M et al. J Clin Oncol 2017; 35(35):3898-3905

CHRONOS-1 TRIAL: COPANLISIB IN R/R iNHL

INTRODUCTION

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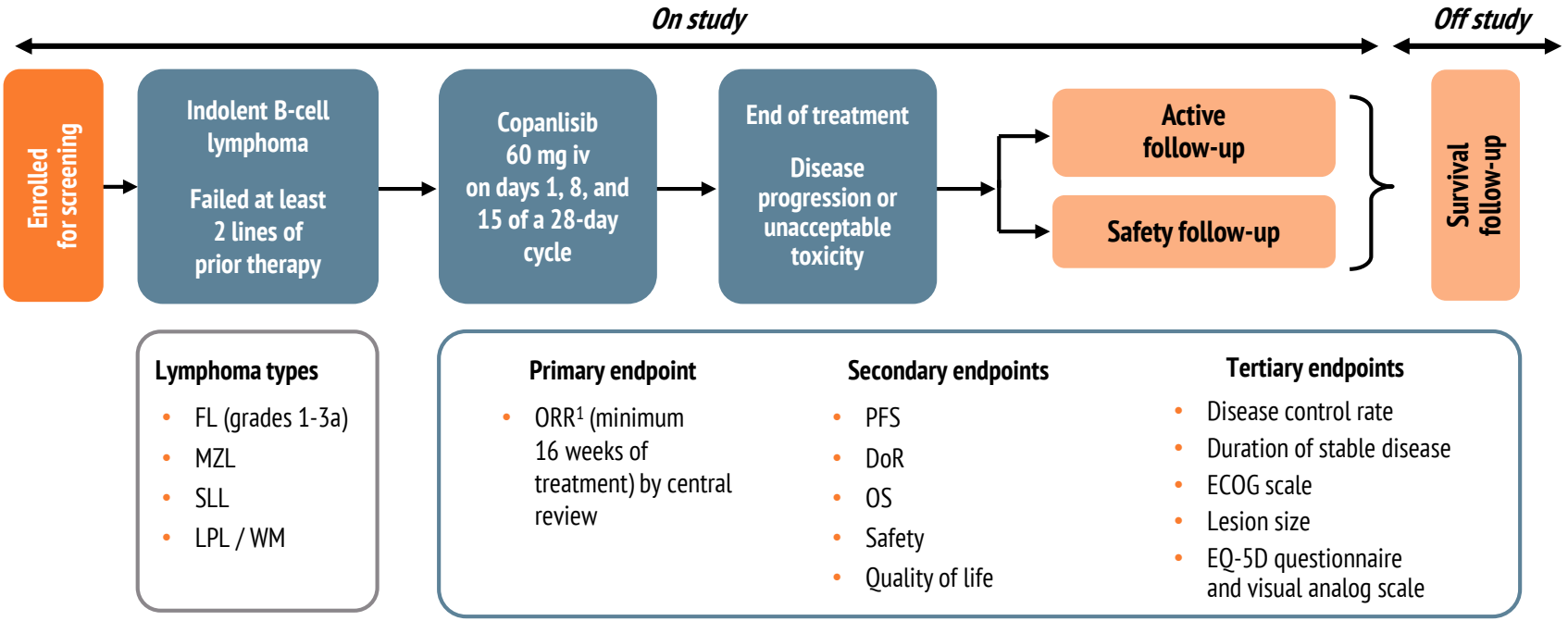
- Copanlisib is an IV pan-class I PI3K inhibitor with predominant activity against the PI3K-α and PI3K-δ isoforms[1,2]
- It is approved by the US FDA for the treatment of patients with relapsed FL who have received at least two prior systemic therapies
- The aim of this open-label phase II study was to evaluate the efficacy and safety of copanlisib in patients with relapsed or refractory indolent B-cell lymphoma[3]

FDA, Food and Drug Administration; FL, follicular lymphoma; iNHL, indolent non-Hodgkin's lymphoma; IV, intravenous; PI3K, phosphatidylinositol 3-kinase; R/R, relapsed or refractory. 1. Liu N et al. Mol Cancer Ther 2013; 12:2319-2330; 2. Scott WJ et al. Chem Med Chem 2016; 11:1517-1530; 3. Dreyling M et al. J Clin Oncol 2017; 35(35):3898-3905; Clinicaltrials.gov NCT01660451 part B, CHRONOS-1

CHRONOS-1 TRIAL: COPANLISIB IN R/R iNHL

DESIGN



DoR, duration of response; ECOG, ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; EQ-5D, European Quality of Life Five Dimension Five Level Scale Questionnaire; iNHL, indolent non-Hodgkin's lymphoma; LPL, Lymphoplasmacytoid lymphoma; MZL, marginal zone lymphoma; ORR, objective tumour response rate; OS, overall survival; PFS, progression free survival; R/R, relapsed or refractory; SLL, small lymphocytic lymphoma; WM, Waldenström;

Dreyling M et al. J Clin Oncol 2017; 35(35):3898-3905; NCT01660451 part B, CHRONOS-1

CHRONOS-1 TRIAL: COPANLISIB IN R/R iNHL

RESULTS: EFFICACY

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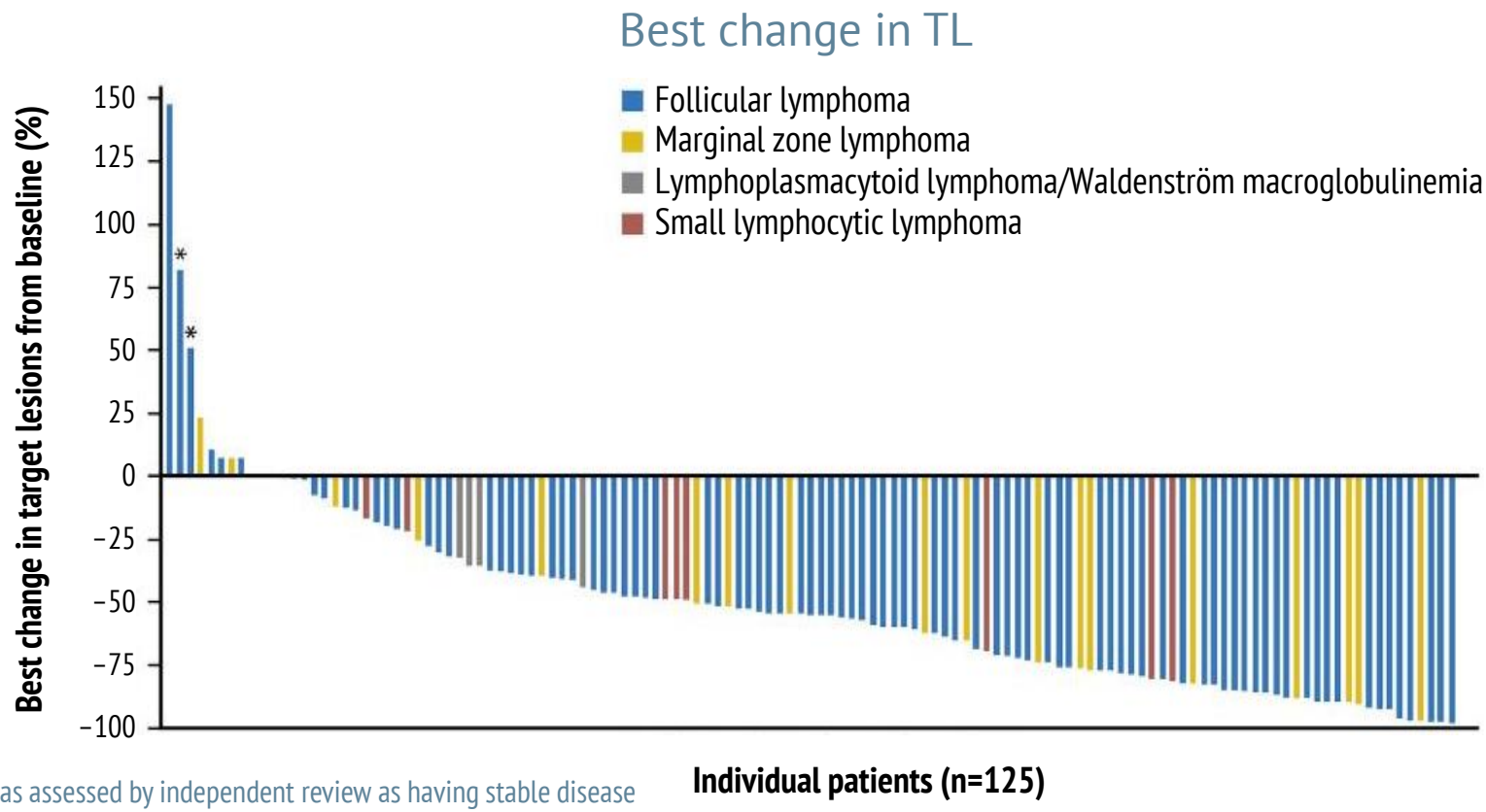
ORR 59%; CR 12%; MEDIAN TTR, 53 DAYS; MEDIAN DOR, 22.6 MONTHS; MEDIAN PFS 11.2 MONTHS, AND MEDIAN OS NOT YET BEEN REACHED



* Patient was assessed by independent review as having stable disease

CR, complete response; DOR, duration of response; iNHL, indolent non-Hodgkin's lymphoma; ORR, objective tumour response rate; PFS, progression free survival; OS, overall survival; R/R, relapsed or refractory; TTR, time to response

Dreyling M et al. J Clin Oncol 2017; 35(35):3898-3905; NCT01660451 part B, CHRONOS-1

CHRONOS-1 TRIAL: COPANLISIB IN R/R iNHL

RESULTS: SAFETY

- The most frequent TEAEs:
  - transient hyperglycemia
    - all grades, 50%; grade 3 or 4, 41%
  - transient hypertension
    - all grades, 30%; grade 3, 24%
  - other grade ≥3 events included decreased neutrophil count (24%) and lung infection (15%)

iNHL, indolent non-Hodgkin's lymphoma; R/R, relapsed or refractory; TEAEs, treatment emergent adverse events

Dreyling M et al. J Clin Oncol 2017; 35(35):3898-3905; NCT01660451 part B, CHRONOS-1

CHRONOS-1 TRIAL: COPANLISIB IN R/R iNHL

CONCLUSIONS

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- Copanlisib demonstrated **significant efficacy and a manageable safety profile** in heavily pre-treated patients with R/R indolent lymphoma

iNHL, indolent non-Hodgkin's lymphoma; R/R, relapsed or refractory
Dreyling M et al. J Clin Oncol 2017; 35(35):3898-3905; NCT01660451 part B, CHRONOS-1

DYNAMO: A PHASE 2 STUDY DEMONSTRATING THE CLINICAL ACTIVITY OF DUVELISIB IN PATIENTS WITH DOUBLE-REFRACTORY (DR) iNHL

Zinzani P et al. Hematol Oncol 2017; 35(S2):69-70

iNHL, indolent non-Hodgkin's lymphoma

DYNAMO TRIAL: DUVELISIB IN DR iNHL

INTRODUCTION

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- Duvelisib is an oral, dual inhibitor of PI3K-δ,γ[1]
- It is approved by the FDA[1] for;
  - R/R CLL or SLL
  - R/R FL after at least two prior systemic therapies

CLL, chronic lymphocytic lymphoma; DR, double refractory; FDA, Food and Drug Administration; FL, follicular lymphoma; iNHL, indolent non-Hodgkin's lymphoma; PI3K, phosphatidylinositol 3-kinase; R/R, relapse or refractory; SLL, small lymphocytic lymphoma

1. Duvelisib, US PI accessed 29 Jan 2019 http://www.verastem.com/wp-content/uploads/2018/08/prescribing-information.pdf;
2. Zinzani P, *et al.*, Hematol Oncol. 2017; 35(S2):69-70; NCT01882803, DYNAMO trial, clinicaltrials.gov

DYNAMO TRIAL: DUVELISIB IN DR iNHL

DESIGN

A PHASE 2 STUDY OF DUVELISIB MONOTHERAPY IN DOUBLE REFRACTORY iNHL POPULATIONS

Double refractory* iNHL patients
N=129

*Heavily pretreated patient population:

- Median number of prior treatments = 3
- Inclusion criteria: Refractory to both rituximab and a chemotherapy regimen or radioimmunotherapy

Duvelisib
25 mg PO BID

Treatment continued until progression or unacceptable toxicity

Response assessments were conducted per revised IWG Criteria (Cheson 2007) at baseline, Cycles 3, 5, 7, 10 and every 4 months thereafter
(1 cycle = 28 days)

PHASE 2 STUDY, FINAL ANALYSIS COMPLETED

Study Endpoints

Primary: ORR by Independent Review Committee

Key secondary:

- Safety
- DOR
- PFS
- OS

- ✓ Accrual complete November 2015
- ✓ Final analysis (April 2016) presented at ASH 2016
- ✓ Mature follow up (March 2017) presented at EHA 2017
- ✓ Pending publication in peer reviewed journal

BID, bis in die, twice daily; DR, double refractory; DOR, duration of response; iNHL, indolent non-Hodgkin's lymphoma; IWG, International Working Group; N, number of patients; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PO, per os (oral route of administration)

Cheson BD et al. J Clin Oncol 2007; 25:579-586; Zinzani P, *et al.*, Hematol Oncol. 2017; 35(S2):69-70; NCT01882803, DYNAMO trial, clinicaltrials.gov

DYNAMO TRIAL: DUVELISIB IN DR iNHL

RESULTS: ORR

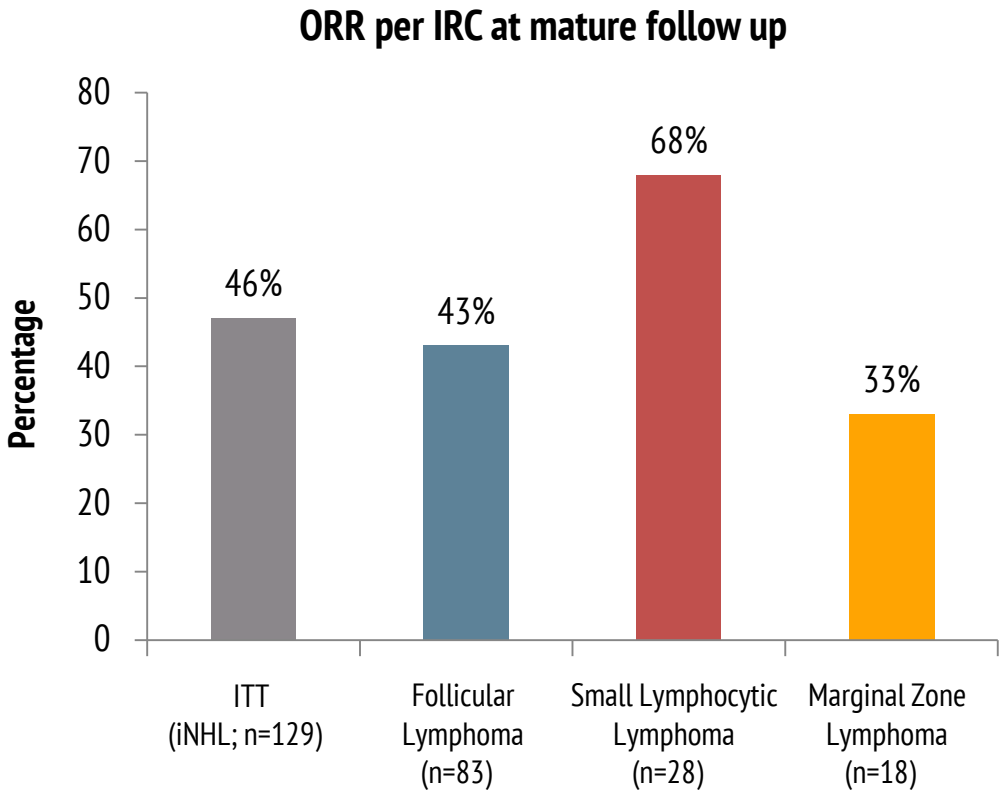
MET PRIMARY ENDPOINT OF ORR BY IRC IN DOUBLE REFRACTORY iNHL PATIENTS AT FINAL ANALYSIS

Primary endpoint:

- ORR by IRC at per-protocol final analysis: (p=0.0001)

Secondary endpoints:

- Median PFS on duvelisib: 8.3 months
- Median DOR: 9.9 months



DOR, duration of response; DR, double refractory; iNHL, indolent non-Hodgkin's lymphoma; IRC, independent review committee; ITT, intention to treat; ORR, overall response rate; P, probability; PFS, progression free survival

Zinzani P, *et al.*, Hematol Oncol. 2017; 35(S2):69-70; Zinzani PL *et al.*, Blood 2018; 132:4167; NCT01882803, DYNAMO trial, clinicaltrials.gov

DYNAMO TRIAL: DUVELISIB IN DR iNHL

RESULTS: PFS AND OS PER IRC

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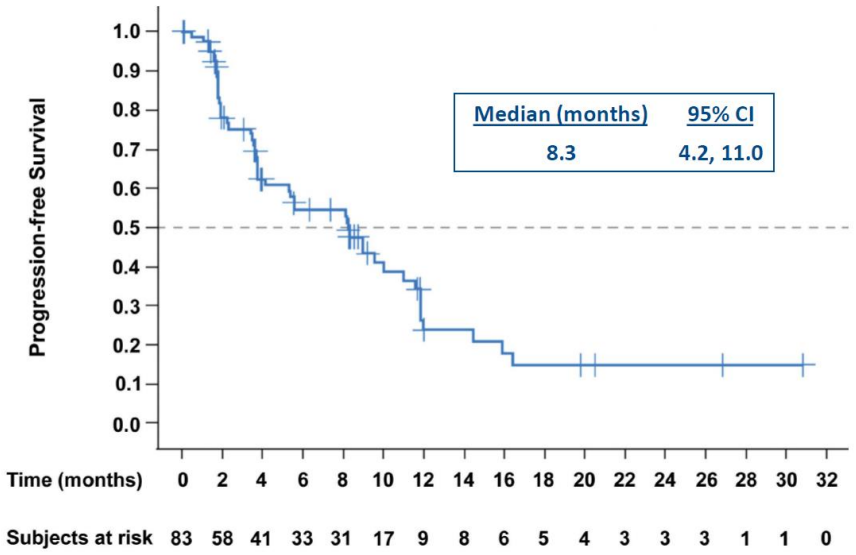
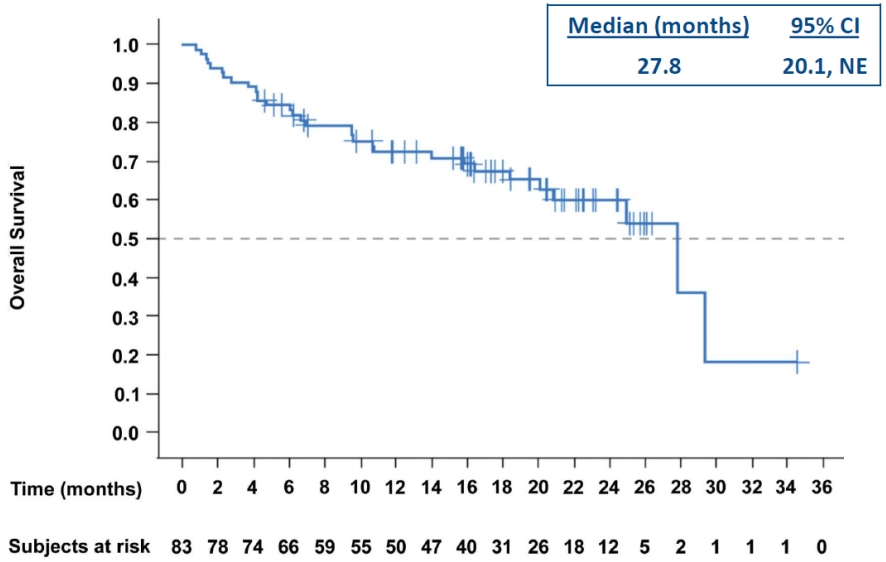
PFS per IRC



OS



CI, confidence interval; DR, double refractory; iNHL, indolent non-Hodgkin's lymphoma; IRC, independent review committee; NE, not evaluable; PFS, progression free survival

Zinzani P, *et al.*, Hematol Oncol. 2017; 35(S2):69-70; NCT01882803, DYNAMO trial, clinicaltrials.gov

DYNAMO TRIAL: DUVELISIB IN DR iNHL

RESULTS: SAFETY

- Most common AEs ⩾ Grade 3 were:
  - transient cytopenia, including neutropenia (23%), anaemia (12%), thrombocytopenia (10%)
  - diarrhoea (15%)
- Opportunistic infections occurred in <5% of patients, none fatal
- Six patients had an AE with outcome of death

AEs, adverse events; iNHL, indolent non-Hodgkin's lymphoma

Zinzani P, *et al.*, Hematol Oncol. 2017; 35(S2):69-70; NCT01882803, DYNAMO trial, clinicaltrials.gov

DYNAMO TRIAL: DUVELISIB IN DR iNHL

CONCLUSIONS

- The DYNAMO trial met its primary endpoint, with duvelisib achieving an **ORR of 46%**, significantly greater that null hypothesis that the ORR would be ≤ 30% (p=0.0001)
- Duvelisib was generally well tolerated

iNHL, indolent non-Hodgkin's lymphoma; ORR, overall response rate; p, probability

Zinzani P, *et al.*, Hematol Oncol. 2017; 35(S2):69-70; NCT01882803, DYNAMO trial, clinicaltrials.gov

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