BSH 2020 VIRTUAL
9 -14 NOVEMBER
British Society for Haematology
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60 1960–2020

Phase Ib/II Trial of Polatuzumab Vedotin Plus Obinutuzumab and Lenalidomide in Patients with Relapsed/Refractory Follicular Lymphoma: Primary Analysis of the Full Efficacy Population

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INTRODUCTION

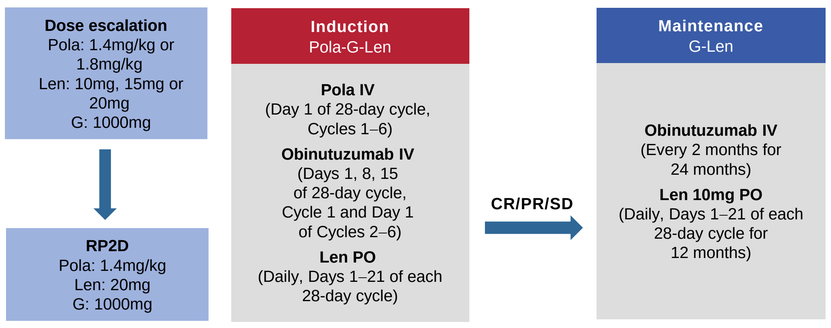
- Polatuzumab vedotin (Pola) is an antibody–drug conjugate targeted to cell-surface CD79b expressed on B-cell receptors; it delivers a potent microtubule-disrupting agent, monomethyl auristatin E (MMAE) directly to tumour cells[1,2]
- Pola combined with obinutuzumab (G) was well tolerated and showed evidence of clinical activity in a Phase Ib/II study in patients with relapsed/refractory (R/R) follicular lymphoma (FL) who were heavily pretreated or refractory to the last prior regimen[3]
- Lenalidomide (Len) in combination with G also showed promising results in a Phase II trial of patients with R/R FL;[4] thus, we hypothesized that addition of Pola to G-Len may further enhance anti-tumour response
- Here, we report the safety and efficacy results from the primary analysis of a Phase Ib/II study (NCT02600897) of this novel triplet combination of Pola-G-Len

METHODS

Study design and treatment (Figure 1)

- This was an open-label, single-arm, Phase Ib/II study in patients with CD20-positive R/R FL (excluding grade 3b), who had previously been treated with anti-CD20-containing therapy
- The recommended Phase II dose (RP2D) was determined during the dose-escalation phase of the study as Pola 1.4mg/kg; Len 20mg; G 1000mg
- In the induction phase, patients received the RP2D of Pola-G-Len for 6 cycles; responders then received Len maintenance for 12 months plus G for up to 24 months

Figure 1. Study design



Primary efficacy endpoint: CR at EOI, as determined by the IRC, on the basis of PET-CT scans (by Modified Lugano 2014 criteria)

CR, complete response; EOI, end of induction; G, obinutuzumab; IRC, independent review committee
IV, intravenous; Len, lenalidomide; PO, by mouth; PR, partial response; RP2D, recommended Phase II dose; SD, stable disease

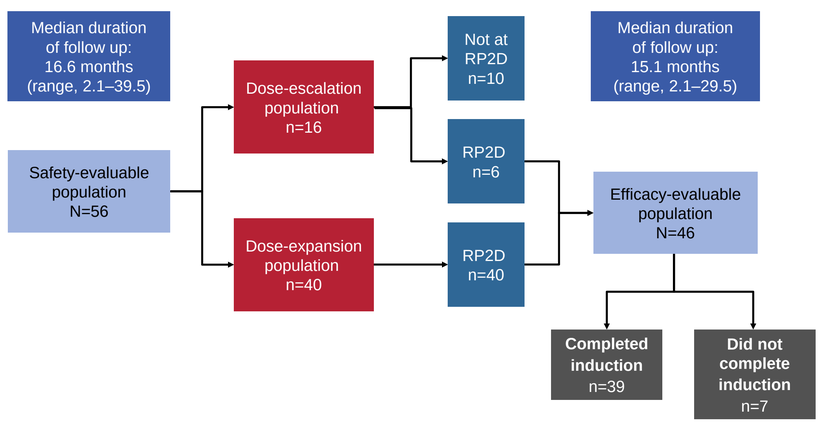
Patient population

- Key inclusion criteria:
  - Age ≥18 years; R/R FL (grade 1, 2, 3a); at least one bi-dimensionally measurable lesion ≥1.5cm in its longest dimension; histologically documented CD20-positive cells; Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2
- Key exclusion criteria:
  - Grade 3b FL; prior allogeneic stem-cell transplant; autologous stem-cell transplant ≤100 days before Cycle 1, Day 1; current grade >1 peripheral neuropathy; history of resistance to lenalidomide; inadequate haematological, renal or liver function; positive test for hepatitis (hepatitis B virus surface antigen or core antibody hepatitis C virus)

Study endpoints

- Primary safety endpoint
  - The maximum tolerated dose of Pola and Len when given in combination with a fixed dose of G
- Primary efficacy endpoint
  - Independent Review Committee (IRC)-assessed complete response (CR) at end of induction (EOI) assessed by modified Lugano 2014 criteria
- Key secondary and exploratory endpoints
  - Overall response rate (ORR), progression-free survival (PFS), overall survival (OS)

Figure 2. Primary analysis population



Safety was evaluated in all patients who received at least one dose of any component of the drug combination. Efficacy was evaluated in all patients entering the dose-expansion phase, as well as those in the dose-escalation phase reaching RP2D

RESULTS

Patients

- 56 patients were enrolled from 23 sites (**Figure 2**)
- Baseline characteristics are shown in **Table 1**

Table 1. Baseline characteristics

Characteristic	Study population (N=56)
Median age, years (range)	62 (32–87)
Male	33 (59)
ECOG PS 0–1	55 (98)
Ann Arbor Stage III/IV	49 (88)
Bulky disease (≥7cm)	9 (16)
Bone marrow involvement	24 (43)
FLIPI high ≥3	31 (55)
No. of prior lines of treatment	
1	13 (23)
2	14 (25)
≥3	29 (52)
Median no. of prior lines (range)	3 (1–7)
Refractory to last prior therapy[1]	33 (59)
Refractory to any line of anti-CD20[2]	40 (71)
POD24 on first-line treatment[3]	14 (25)

Values are n (%) unless otherwise stated; FLIPI, follicular lymphoma international prognostic index; POD24, progression of FL within 24 months of diagnosis
[1]Defined as no response or progression or relapse within 6 months of last anti-lymphoma therapy end date
[2]Defined as no response or progression or relapse within 6 months of therapy with an anti-CD20 agent at any prior line of treatment
[3]Defined as progression of disease within 24 months of initiation of first anti-lymphoma treatment with chemoimmunotherapy

Safety

- The triplet combination had manageable tolerability, with a safety profile that was consistent with the known profiles of the individual drugs (**Tables 2, 3** and **4**)

Table 2. Summary of adverse events

Total number of patients with at least one AE, n (%)	N=56
Any-grade AE	56 (100)
Grade 3–4 AE	47 (84)
Grade 5 AE[1]	1 (2)
Serious AE	32 (57)
AE leading to any dose interruption	43 (77)
AE leading to any dose reduction	19 (34)
AE leading to any drug discontinuations	17 (30)

[1]Grade 5 AE: septic shock after progressive disease and new anti-lymphoma treatment (TAK-659, tyrosine kinase inhibitor)

Efficacy

- High CR rates were observed at EOI in this heavily pre-treated and refractory population (**Table 5**)
- ORR was lower in POD24-positive (vs late relapse), high FLIPI score (vs low FLIPI) and refractory (vs not refractory) patients; the number of prior lines of therapy did not appear to affect response rates (**Figure 2**)
- After a median duration of follow up of 15.1 months, median PFS remained immature (**Figure 3**)
- 12-month INV-assessed PFS was 83.4% (CI: 70.85–95.96)

Table 5. Efficacy summary in the efficacy-evaluable population (N=46)

EOI response, n (%)	Modified Lugano 2014[1]		Lugano 2014	
	INV	IRC	INV	IRC
Objective response	38 (83)	35 (76)	38 (83)	35 (76)
Complete response	28 (61)[2]	29 (63)[2]	34 (74)	33 (72)
Partial response	10 (22)	6 (13)	4 (9)	2 (4)
Stable disease	3 (7)	4 (9)	3 (7)	4 (9)
Disease progression	3 (7)	1 (2)	3 (7)	1 (2)
Missing/not evaluable/not available	2 (4)	6 (13)[3]	2 (4)	6 (13)[3]

INV, investigator assessed; IRC, independent review committee assessed
[1]Modified Lugano requires a negative bone marrow biopsy to confirm PET-CR; PET-PR must also meet CT-PR criteria
[2]CR downgraded to PR due to missing bone marrow biopsy in six patients by INV and four patients by IRC
[3]Three patients experienced early PD, scans were not sent to IRC and therefore were classified as missing

Table 3. Most common all-grade AEs (i.e., occurring in ≥12.5% of patients)

n (%)	N=56
Infections and infestations[1]	42 (75)
Neutropenia	36 (64)
Thrombocytopenia	29 (52)
Diarrhoea	23 (41)
Anaemia	22 (39)
Pyrexia	22 (39)
Infusion-related reaction	19 (34)
Peripheral neuropathy[2]	17 (30)
Cough	15 (27)
Fatigue	14 (25)
Rash[3]	14 (25)
Nausea	12 (21)
ALT increased	11 (20)
Asthenia	10 (18)
Constipation	10 (18)
Decreased appetite	10 (18)
Arthralgias	8 (14)
Blood creatinine increased	8 (14)
Abdominal pain	7 (13)
AST increased	7 (13)
Back pain	7 (13)
Hypokalaemia	7 (13)

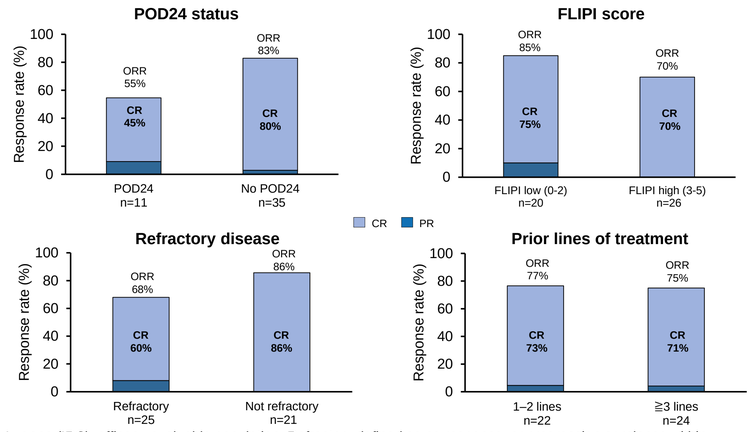
[1]Infections presented as Systems Organ Class terms – all other AEs are reported by 'preferred terms';
[2]Peripheral neuropathy standard MedDRA query included: peripheral motor neuropathy, peripheral sensory neuropathy, neuropathy peripheral, paraesthesia, hypoesthesia, and neuralgia; [3]Rash includes: macula-popular rash and erythematous rash
ALT, alanine aminotransferase AST, aspartate aminotransferase

Table 4. Most common grade 3–4 AEs (i.e., occurring in ≥2 patients) and AEs of special interest

n (%)	N=56
Grade 3–4 AEs	**47 (84)**
Haematological AEs	
Neutropenia	31 (55)
Thrombocytopenia	15 (27)
Anaemia	8 (14)
Febrile neutropenia	6 (11)
Non-haematological AEs	
Infections and infestations[1]	11 (20)
Hypokalaemia	3 (5)
Diarrhoea	2 (4)
Lipase increased	2 (4)
Laboratory tumour lysis syndrome	2 (4)
ALT increased	2 (4)
Syncope	2 (4)
AESIs	**6 (11)**
Neoplasms, benign, malignant, and unspecified	
Tumour flare	4 (7)
Myelodysplastic syndrome	1 (2)
Lung neoplasm malignant	1 (2)

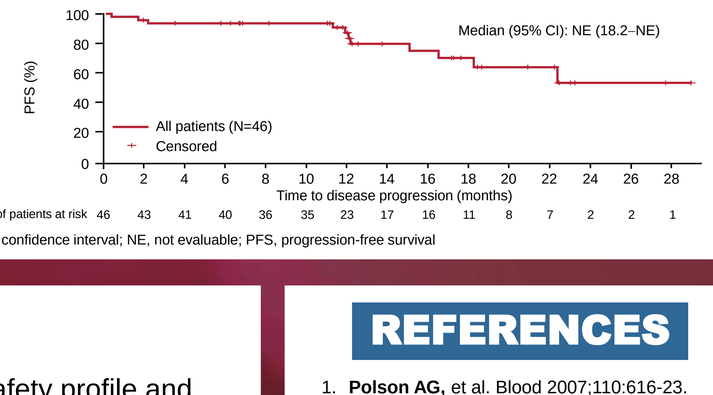
AESI, adverse event of special interest; GCSF, granulocyte colony stimulating factor
[1]Presented as Systems Organ Class term – all other AEs are reported by 'preferred terms'

Figure 3. Subgroup analyses



Lugano (IRC), efficacy-evaluable population. Refractory defined as no response, or progression or relapse within 6 months of last anti-lymphoma therapy end date
ORR, overall response rate

Figure 4. Kaplan-Meier curve of PFS



CI, confidence interval; NE, not evaluable; PFS, progression-free survival

CONCLUSIONS

- The novel triplet combination Pola-G-Len has a manageable safety profile and efficacy that compares favourably with currently available R/R FL therapies
- To determine the median PFS, a longer period of follow-up, through and beyond maintenance treatment, is ongoing
- These compelling findings support further investigation in a larger patient population as this novel triplet combination has a potential place as therapy for patients with R/R FL

ACKNOWLEDGEMENTS

Authors would like to thank the patients and their families, and also the study investigators, coordinators and site personnel at the clinical study sites.

Spain: Clínica Universidad de Navarra, Pamplona; Complejo Hospitalario de Navarra, Pamplona; Fundacion Jimenez Diaz, Madrid; Hospital Clínic Barcelona, Barcelona; Hospital General Universitario Gregorio Marañon, Madrid; Hospital Santa Creu i Sant Pau, Barcelona; Hospital Universitari Vall d'Hebron, Barcelona; Institut Catala d'Oncologia Hospitalet, Barcelona.

USA: Barbara Ann Karmanos Cancer Institute, Detroit, MI; New York University Langone Medical Center - NYU Cancer Institute, NY; Rocky Mountain Cancer Centers, CO; Texas Oncology - San Antonio Medical Center, TX; Washington University School of Medicine in St. Louis, MO.

UK: Maidstone and Tunbridge Wells Hospital, Kent Oncology Center; Nottingham University Hospitals NHS Trust - City Hospital; Sarah Cannon Research UK, London; St. James's University Hospital, Leeds; University Hospitals of Leicester NHS Trust - Leicester Royal Infirmary.

These data were originally presented at the 62nd meeting of the American Society of Hematology, 7–10 December 2019, Orlando, FL, USA. Blood, 2019;134 (Supplement_1):126.

This study was sponsored by F. Hoffmann-La Roche Ltd. Third-party writing assistance was provided by Angela Rogers, PhD, Gardiner-Caldwell Communications, Macclesfield, UK and funded by F. Hoffmann-La Roche Ltd.

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DISCLOSURES

AM declares honoraria from Roche, Celgene, Novartis, MSD, BMS, Sandoz; research funding from Pfizer; speaker's bureau for Roche, Celgene. **CD** declares a consultancy/advisory role with Seattle Genetics, Bayer, Bristol-Myers Squibb, Genentech/Roche, Merck; stock ownership in Gilead Sciences; research funding from Seattle Genetics, Bristol-Myers Squibb, Genentech/Roche, Merck, Incyte, Millenium, MEI Pharma, LAM Therapeutics. **BK** declares a consultancy/advisory role with Roche, Genentech, Celgene, Abbvie, Pharmacyclics, Acerta; research funding from Genentech, Acerta, BeiGene; expert testimony to Genentech. **LB** declares travel/accommodation expenses from Novartis, Takeda, Gilead. **FM** declares honoraria and a consultation/advisory role for Takeda, Roche; travel/accommodation from Takeda, Roche, Janssen. **JB** declares honoraria from Roche, Takeda, Novartis, Gilead; a consultation/advisory role for Takeda, Novartis, Celgene; research funding from Roche; travel/accommodation from Roche, Celne, Jansen, Gilead. **RC** declares a consultation/advisory role for Celgene, Janssen; speakers' bureau for Janssen, Roche, Servier; travel/accommodation from Janssen, Roche, Abbvie. **JH** is employed by and holds stock in Roche. **YC** is employed by and holds stock in Roche. **LM** is employed by and holds stock in Roche. **PA** declares honoraria, a consultation/advisory role and speakers' bureau for Janssen, Abbvie, Roche; travel/accommodation from Janssen, Abbvie.