Results of a UK real world study of polatuzumab vedotin, bendamustine, and rituximab for relapsed/refractory large B-cell lymphoma

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Abstract:
The addition of polatuzumab vedotin to bendamustine and rituximab (Pola-BR) has been shown to improve overall survival (OS) in stem cell transplant (SCT)-ineligible patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). It is also increasingly used as bridging to CAR T-cell therapy (CAR-T). We retrospectively analysed the efficacy of Pola-BR in 133 patients at 28 UK institutions. Treatment intent was bridging to CAR-T for N=40, re-induction with planned SCT for N=13 and stand-alone treatment for N=78. The overall response rate (ORR) was 57.0% (complete response (CR) 32.8%). After median 7.7 months follow-up, median PFS and OS were 4.8 months and 8.2 months respectively. For stand-alone treatment shortened PFS was associated with bulk disease (>7.5cm) (HR 2.32 (95% CI 1.23-4.38), p=0.009), >1 prior treatment (HR 2.17 (95% CI 1.19-3.95), p=0.01) and refractoriness to the last treatment (HR 3.48 (95% CI 1.79-6.76), p<0.001). For CAR-T bridging the ORR was 42.1% (CR 18.4%) and for treatment after CAR-T failure the ORR was 43.8% (CR 18.8%). These data demonstrate efficacy for Pola-BR as a treatment for SCT-ineligible patients with R/R DLBCL, help to delineate which patients may benefit most, and provide preliminary evidence of efficacy as bridging to CAR-T and after CAR-T failure.

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Ten to 15% of patients with diffuse large B-cell lymphoma (DLBCL) have primary refractory disease and 20-30% relapse.\(^1\) For stem cell transplant (SCT)-eligible patients second-line chemotherapy and autologous SCT is curative in around 20%, while third-line anti-CD19 chimeric antigen receptor T-cell therapy (CAR-T) results in durable remissions in up to 40% of treated patients.\(^2\)–\(^4\)

For SCT/CAR-T ineligible patients, and those with progressive disease (PD) after CAR-T, outcomes remain poor and new approaches are required.\(^1\) Where CAR-T is planned, up to 20% of patients do not go on to receive the product, often due to PD, and novel bridging strategies are needed for this largely chemotherapy-refractory group.\(^5\)–\(^8\)

In the randomised phase 2 G029365 trial polatuzumab vedotin (an anti-CD79b monoclonal antibody conjugated to the cytotoxin monomethyl auristatin E) with bendamustine and rituximab (Pola-BR) was compared to bendamustine-rituximab for treatment of relapsed/refractory (R/R) DLBCL in SCT-ineligible patients. For Pola-BR the objective response rate (ORR) was 62.5% (complete response (CR) 50%). Median progression-free survival (PFS) and overall survival (OS), at 9.2 and 12.4 months respectively, were both superior for Pola-BR.\(^9\) A single arm cohort identified primary refractory disease, >1 prior treatment, and refractoriness to the last treatment as predictors of inferior PFS and OS.\(^10\)

Prior to UK regulatory approval Pola-BR was available via the Early Access to Medicines Scheme (EAMS) between June 2019-January 2020 in line with the intended label.\(^11\) Subsequently, interim funding (March-August 2020) was provided via the Cancer Drugs Fund (CDF) for Pola-BR as CAR-T bridging therapy due to potential delays in CAR-T delivery during the Covid-19 pandemic. We analysed outcomes of patients treated on these schemes.

Anonymised data were collected retrospectively from 28 UK hospitals for consecutive patients treated with Pola-BR via EAMS or CDF interim funding. All patients who started Pola-BR treatment via either scheme were eligible (for EAMS: relapsed/refractory (R/R) DLBCL after ≥1 prior treatment and ineligible for SCT; for CDF R/R DLBCL after ≥2 prior treatments and approved to receive CAR-T). Polatuzumab was given on day 1 or 2 of a 28-day cycle at a dose of 1.8mg/kg for a maximum of 6 cycles. Dose reduction/treatment delay due to adverse events was permitted according to physician discretion. Response assessment was performed according to local policy.

The collection and analysis of the data were part of routine NHS service evaluation and did not require ethical review. Full methods, statistical analysis and treatment details are listed in the supplementary materials.

Data were collected from 133 patients (EAMS N=106, CDF N=27) treated June 2019-October 2020. Treatment intent was bridging to CAR-T for 30.1% (N=40), re-induction therapy with planned SCT consolidation for 9.8% (N=13) and stand-alone treatment (no planned CAR-T/SCT) for 58.6% (N=78). Table 1 summarises patient characteristics. Figure 1 shows sub-groups according to treatment intent.

A median of 4 cycles (range 1-6) were given (median 1 for CAR-T bridging versus 4 for stand-alone treatment, and 5 where SCT consolidation was planned). Pola-BR was initiated with full dose bendamustine for N=91 (68.4%) and reduced dose bendamustine for N=24 (18.0%), bendamustine was omitted for N=5 (3.8%) and data were missing for N=13 (9.8%). The investigator-assessed best ORR was 57.0% (CR 31.6%). Response rates for pre-defined subgroups are provided in figure 1. Median follow-up duration was 7.7 months and median PFS and OS were 4.8 months (95% CI 3.7-9.3) and 8.2 months (95% CI 5.9-14.3) respectively (figure 1).
For stand-alone Pola-BR (no planned CAR-T/SCT (N=78)), a majority were SCT-ineligible due to age or comorbidities (55.1% and 21.8% respectively), but for 17.9% this was due to insufficient response to prior therapy. Primary reasons for treatment discontinuation were completion of 6 cycles (N=33, 42.3%), PD (N=25, 32.1%), treatment-related toxicity (N=14, 17.9%), patient death (N=2, 2.6%), achieving CR (N=2, 2.6%), and ‘other’ (N=2, 2.6%).

In the stand-alone group N=26 (33.3%) experienced treatment delay due to adverse events, most commonly infection (N=14, 17.9%) and haematological toxicity (N=11, 14.1%), as well as nausea (N=1), diarrhoea (N=1), fatigue (N=4) and peripheral neuropathy (PN) (N=1). Bendamustine was dose reduced for N=33 (42.3%) and omitted for N=4 (5.1%) in at least 1 cycle. Reported reasons for bendamustine dose reduction or omission were haematological toxicity (N=7), patient age (N=7), infection (N=6), frailty (N=4), diarrhoea (N=3), bilirubin increased (N=2), infusion-related reaction (N=1), co-morbidities (N=1) and unknown (N=6). N=1 (1.3%) discontinued treatment due to PN. Where data were available, 16/59 patients (27.1%) required hospital admission due to Pola-BR-related toxicity during treatment.

The ORR for the stand-alone cohort was 65.8% (CR 39.7%), the median follow-up duration was 8.2 months and median PFS and OS were 5.4 months (95% CI 3.0-10.8) and 10.2 months (95% CI 5.2-14.3) respectively. The 12-month PFS rate was 37% (95% CI 24%-50%). For patients achieving CR, median PFS was 14.0 months and median OS was not reached (figure 1). For this stand-alone group, significant factors by univariate analysis for shortened PFS were bulky disease (>7.5cm) (HR 2.32 (95% CI 1.23-4.38), p=0.009), >1 prior treatment (HR 2.17 (95% CI 1.19-3.95), p=0.01) and refractoriness to the last treatment (HR 3.48 (95% CI 1.79-6.76), p<0.001). Significance was maintained in a multivariate model using these three variables.

Pola-BR was planned as bridging to CAR-T for 40 patients: 31/40 (77.5%) received cell infusion (18 Axicabtagene ciloleucel, 12 Tisagenlecleucel and 1 clinical trial product), 5 died due to PD, 1 died due to infection during bridging, CAR-T infusion was pending for 2 and data were missing for 1. Leukapheresis occurred prior to bridging for 36 patients (90.0%) and after at least 1 cycle of Pola-BR for 3 (10.0%) (of these 2 patients received bendamustine and both underwent successful leukapheresis). The best ORR to Pola-BR bridging was 42.1% (CR 17.5%, partial response (PR) 22.5%, stable disease (SD) 15.0%, PD 40.0%, missing 5.0%). Sixteen patients received Pola-BR having progressed post-CAR-T. The ORR and CR rate were 43.8% and 18.8% respectively and 3/16 subsequently proceeded to allogeneic SCT.

In total 4 patients underwent SCT following Pola-BR (3 allogeneic, 1 autologous). Sixty patients died during follow-up including 48 due to PD and 6 due to infection during Pola-BR treatment.

These outcome data for 133 consecutive patients treated with Pola-BR add substantially to evidence from the registration trial and other studies.\textsuperscript{9,10,12-15} Within its limitations (investigator-reported outcomes and limited toxicity data) this retrospective study supports Pola-BR as a treatment for SCT-ineligible patients with R/R DLBCL and provides preliminary evidence of efficacy for CAR-T bridging and after CAR-T failure.

For stand-alone Pola-BR without planned consolidation the ORR (57.1%, 95% CI 54.0%-76.3%) is comparable to that reported in G029365 (62.5%), although fewer patients attained CR (39.7% versus 50%). Median PFS (5.4 months, 95% CI 3.0-10.8) and OS (10.2 months, 95% CI 5.2-14.3) are shorter than in the trial where they were 9.2 months (95% CI 6.2-13.9) and 12.4 months (95% CI 9-not estimable) respectively.\textsuperscript{9} The short median PFS in this group may reflect the frequency of high-risk features; more were SCT-ineligible due to age, co-morbidities or performance status (PS) than in the trial (78.2% versus 35.0%), and many had bulk disease (28.2%), high IPI (71.8%) or PS ≥2 (39.7%). Just
17.9% of patients in this group were SCT-ineligible due to insufficient response to prior treatment, compared to 30.0% of patients in the trial. Unsurprisingly, PFS was shorter after >1 prior treatment and for patients refractory to the preceding treatment. Bulky disease was also associated with inferior PFS – a finding not previously reported from G029365. For those achieving CR, median PFS was 14.0 months (median OS not reached), but further follow-up is required to have confidence in the durability of CR. The limited toxicity data available for this stand-alone group are overall in keeping with the known safety profile of Pola-BR, however it is of note that as a result of treatment-associated toxicity 17.9% of patients in the stand-alone treatment group stopped Pola-BR before completing 6 cycles and 27.1% required hospital admission.

While response rates for the 16 patients who received Pola-BR for PD post CAR-T were lower than for the whole cohort (ORR 43.8%, CR 18.8%) few other treatments have been tested in this setting, and it is of note that 3/16 were successfully bridged to allogeneic SCT.

A median of 1 cycle was given as bridging to CAR-T. The ORR and CR rate were 42.1% and 18.4% respectively, similar to the post CAR-T group. A majority (31/40 (77.5%)) proceeded to cell infusion, thus Pola-BR appears to be a feasible bridging strategy. Further studies are required to define who is most likely to benefit, and to assess other approaches for this chemotherapy-refractory group.17,18

This is the largest data set of patients treated with Pola-BR to date. Other series report broadly similar outcomes, but this study is unique in its sample size and inclusion of patients at different stages in the DLBCL treatment pathway.12–15 These outcomes support Pola-BR as a treatment for SCT-ineligible patients, help to delineate which groups stand to benefit most, and show efficacy in transformed low-grade lymphoma and double hit lymphoma which were not represented in the G029365 trial. Furthermore, these data offer new insights into its role as CAR-T bridging and as treatment after CAR-T failure. PFS appears shorter in this study than in the G029365 trial possibly reflecting patient characteristics including a higher median age in this study (72 versus 67), a higher proportion with PS ≥2 (30.1% versus 15%) and the inclusion of 16 patients with prior CAR-T. The optimal partner agent(s) for Polatuzumab, and its place in the DLBCL treatment algorithm, remains open questions worthy of further study.
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| Characteristic                                      | All patients (N=133) | Stand-alone therapy (N=78) | Bridge to CAR-T (N=40) |
|----------------------------------------------------|----------------------|---------------------------|------------------------|
| Median age, years (range)                          | 72 (18-88)           | 75 (41-88)                | 66.5 (29-82)           |
| Sex, N(%)                                          |                      |                           |                        |
| Male                                               | 87 (65.4%)           | 54 (69.2%)                | 23 (57.5%)             |
| Female                                             | 46 (34.6%)           | 24 (30.8%)                | 17 (42.5%)             |
| ECOG, N(%)                                         |                      |                           |                        |
| 0-1                                                | 90 (67.7%)           | 46 (59.0%)                | 31 (77.5%)             |
| ≥2                                                 | 40 (30.1%)           | 31 (39.7%)                | 7 (17.5%)              |
| Unknown                                            | 3 (2.3%)             | 1 (1.3%)                  | 2 (5%)                 |
| Diagnosis, N(%)                                    |                      |                           |                        |
| DLBCL (transformed low grade lymphoma)             | 31 (23.3%)           | 17 (21.8%)                | 12 (30%)               |
| DLBCL, not otherwise specified                     | 78 (58.6%)           | 48 (61.5%)                | 23 (57.5%)             |
| Double/triple hit DLBCL                            | 14 (10.5%)           | 9 (11.5%)                 | 4 (10.0%)              |
| Post-transplant lymphoproliferative disorder       | 1 (0.8%)             | 1 (1.3%)                  | 0                      |
| Plasmablastic lymphoma                             | 2 (1.5%)             | 1 (1.3%)                  | 0                      |
| Primary cutaneous DLBCL, leg type                  | 1 (0.8%)             | 1 (1.3%)                  | 0                      |
| Primary mediastinal large B-cell lymphoma          | 4 (3.0%)             | 0                         | 1 (2.5%)               |
| T-cell rich/histiocyte rich large B-cell lymphoma  | 1 (0.8%)             | 1 (1.3%)                  | 0                      |
| IPI, N(%)                                          |                      |                           |                        |
| 0-2                                                | 39 (29.3%)           | 21 (26.9%)                | 10 (25%)               |
| ≥3                                                 | 86 (64.7%)           | 56 (71.8%)                | 25 (62.5%)             |
| Unknown                                            | 8 (6.0%)             | 1 (1.3%)                  | 5 (12.5%)              |
| Bulky disease (>7.5cm), N(%)                       |                      |                           |                        |
| Yes                                                | 29 (21.8%)           | 22 (28.2%)                | 2 (5.0%)               |
| No                                                 | 73 (54.9%)           | 53 (67.9%)                | 10 (25.0%)             |
| Unknown                                            | 31 (23.3%)           | 3 (3.8%)                  | 28 (70.0%)             |
| Cell of origin, N(%)                               |                      |                           |                        |
| Non-germinatcentre                                 | 40 (30.1%)           | 27 (34.6%)                | 7 (17.5%)              |
| Germinal centre B-cell                             | 45 (33.8%)           | 37 (47.4%)                | 4 (10.0%)              |
| Unknown                                            | 48 (36.1%)           | 14 (17.9%)                | 29 (72.5%)             |
| Lines of prior therapy, median (range)             |                      |                           |                        |
| 1                                                  | 45 (33.8%)           | 43 (55.1%)                | 1 (2.5%)               |
| 2                                                  | 25 (18.8%)           | 13 (16.7%)                | 25 (62.5%)             |
| ≥3                                                 | 34 (25.6%)           | 20 (25.6%)                | 14 (35.0%)             |
| Unknown                                            | 2 (1.5%)             | 2 (2.6%)                  | 0                      |
| Duration of response of last treatment, N(%)       |                      |                           |                        |
| <12 months                                         | 103 (77.4%)          | 53 (67.9%)                | 36 (90.0%)             |
| >12 months                                         | 23 (17.3%)           | 20 (25.6%)                | 3 (7.5%)               |
| Unknown                                            | 7 (5.3%)             | 5 (6.4%)                  | 1 (2.5%)               |
| Refractory to last line of treatment, N(%)         |                      |                           |                        |
| Yes                                                | 91 (68.4%)           | 45 (57.7%)                | 33 (82.5%)             |
| No                                                 | 42 (31.6%)           | 33 (42.3%)                | 7 (17.5%)              |
Table 1: Patient and disease characteristics and summary of prior treatment and Pola-BR treatment intent. ECOG – Eastern Cooperative Oncology Group Performance Status; IPI – International Prognostic Index; DLBCL – diffuse large B-cell lymphoma; SCT – Stem cell transplant; CAR-T – chimeric antigen receptor T-cell therapy; Auto-SCT – autologous stem cell transplant; Allo-SCT – allogeneic haematopoietic stem cell transplant.

| Prior SCT, N(%) |       |       |       |
|-----------------|-------|-------|-------|
| Yes             | 6 (4.5%) | 0     | 6 (15.0%) |
| No              | 127 (95.5%) | 78 (100%) | 34 (85.0%) |

| Prior CAR-T, N(%) |       |       |       |
|------------------|-------|-------|-------|
| Yes              | 16 (12.0%) | 6 (7.7%) | 0 |
| No               | 117 (88.0%) | 72 (92.3%) | 40 (100%) |

| Treatment intent, N(%) |       |       |       |
|------------------------|-------|-------|-------|
| Bridge to auto-SCT     | 5 (3.8%) | 0     | 0     |
| Bridge to CAR-T        | 40 (30.1%) | 0     | 40 (100%) |
| Bridge to allo-SCT     | 8 (6.0%) | 0     | 40 (100%) |
| Standalone (no planned SCT/CAR-T) | 78 (58.6%) | 78 (100.0%) | 0 |
| Unknown                | 2 (1.5%) | 0     | 0     |

| Primary reason for SCT ineligibility, N(%) |       |
|--------------------------------------------|-------|
| Age                                        | 43 (55.1%) |
| Co-morbidities                             | 17 (21.8%) |
| Failed prior transplantation               | 1 (1.3%) |
| Insufficient CD34+ cells collected         | 1 (1.3%) |
| Insufficient response to salvage therapy   | 14 (17.9%) |
| Performance Status                         | 1 (1.3%) |
| Unknown                                    | 1 (1.3%) |
**1a: Pola-BR treatment subgroups according to treatment intent**

| Best response to Pola-BR | All patients (N=133) | Prior CAR-T (N=16) | Bridge to CAR-T (N=40) | >1 prior lines of treatment (N=86) | Refractory to most recent (N=91) | Bulk (N=36) |
|--------------------------|----------------------|-------------------|-----------------------|-----------------------------------|---------------------------------|------------|
| CR                       | 42 (31.6%)           | 3 (18.8%)         | 3 (21.4%)             | 31 (39.7%)                        | 21 (24.4%)                      | 16 (25.0%) |
| PR                       | 31 (23.3%)           | 4 (25.0%)         | 2 (14.3%)             | 2 (24.4%)                         | 9 (22.1%)                       | 5 (8.3%)   |
| SD                       | 13 (9.8%)            | 3 (18.8%)         | 2 (14.3%)             | 5 (6.4%)                          | 11 (12.8%)                      | 6 (16.7%)  |
| PD                       | 42 (31.6%)           | 6 (37.5%)         | 6 (42.9%)             | 7 (22.6%)                         | 16 (40.0%)                      | 32 (41.7%) |
| Missing                  | 5 (3.8%)             | 0 (0.0%)          | 1 (7.1%)              | 1 (3.2%)                          | 2 (2.6%)                        | 3 (5.5%)   |

**1b: Response rates to Pola-BR.** *p*-values are from a chi-squared test comparing ORR in the following subgroups: Prior CAR-T vs No prior CAR-T; Double/triple hit vs No double/triple hit; Stand-alone treatment vs all other treatment intention; Bridge to CAR-T vs all other treatment intention; >1 prior lines of treatment vs 1 prior line; Refractory to most recent vs Not refractory to most recent; Bulk vs No bulk. Patients with missing information on a subgroup are excluded from that comparison.

**1c: Progression-free survival and overall survival**

- **A:** Progression-free survival for all patients
- **B:** Overall survival for all patients
- **C:** Progression-free survival for patients in the ‘stand-alone’ Pola-BR cohort (no planned stem cell transplant or CAR T-cell therapy) according to treatment response. CR=complete response, PR=partial response, HR=hazard ratio, CI=confidence interval.
- **D:** Overall survival for patients in the ‘stand-alone’ Pola-BR cohort (no planned stem cell transplant or CAR T-cell therapy) according to treatment response.