POLARGO: Randomized phase III study of polatuzumab vedotin plus rituximab, gemcitabine, and oxaliplatin (R-GemOx) in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL)

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Background

• The antibody-drug conjugate (ADC) polatuzumab vedotin (pola) targets CD79b on B-cell malignancies (Figure 1).
• In the phase II G020505 study (NCT02257567) pola plus bendamustine and rituximab (BR) improved complete response rate, CR; by position emission tomography-computed tomography (PET-CT) at six weeks of treatment; and overall survival (OS) in patients with R/R DLBCL, compared with BR alone (CR rate: 40% vs 18%, respectively, p=0.002; median OS: 14.4 v 4.7 months, respectively; p=0.003).1
• As a result, pola-BR was approved by the US Food and Drug Administration for patients with R/R DLBCL after 22 prior therapies. In January 2020, pola-BR was granted conditional European marketing authorization in patients with transplant-incompatible R/R DLBCL.2

A range of therapies are used for R/R DLBCL and one recommended option is pola in addition to BR. In the POLARGO study (NCT040598; NCT43412204), the safety and efficacy of pola-R-GemOx vs pola-R alone will be assessed in patients with R/R DLBCL.

Figure 1: Pola mode of action1–4,11

Polatuzumab vedotin
• ADC targeted to CD79b expressed on malignant B cells
• Designed to deliver a potent microtubule-disrupting agent, MMAE, directly to tumor cells.1–6,7

MMAE2
• Highly potent
• Non-immunogenic

Microtubule disrupter

MMAE-linked vedotin-Polymer

Figure 2: Study design

The study comprises a safety run-in and a randomized controlled trial (RCT) stage (Figure 2).

Patient inclusion criteria

• Confirmed availability of archival or freshly collected tumor tissue prior to enrollment
• Relapse defined as disease that recurs following a response lasting 6 months from completion of the last line of therapy
• Refractory defined as disease that progressed during previous therapy or stable disease for up to 6 months from completion of the last line of therapy.
• Eastern Cooperative Oncology Group performance status 0–2
• Adequate hematologic function.

Safety and efficacy will be assessed with up to 2 years of follow-up

• Safety will be assessed by recording the incidence, nature, and severity of AEs (NCI CTCAE v5.0).
• Dose interruptions, reductions, and intensity will be used to manage toxicities.
• PET-CT and CT scans will be obtained at screening, during, and after the treatment period; 28 days after the last dose of study drug, and then every 2 months (PET-CT), and 6 (CT) months during follow-up for up to 2 years.

The RCT stage primary endpoint is overall survival
• Safety run-in stage primary endpoint: safety and tolerability of pola-R-GemOx, with a focus on PN.
• RCT stage primary endpoint: OS.
• Secondary endpoints: investigator- and independent review committee-assessed best overall response, progression-free survival, duration of objective response, event-free survival, CR rate and objective response rate (Lugano 2014 criteria); safety with a focus on PN.

Patients will receive up to eight cycles of pola-R-GemOx or R-GemOx (Table 1)

• Patients in the safety run-in stage will receive pola (1.8mg/kg) + R-GemOx (R, 375mg/m²; Gem, 1000mg/m²; Ox, 100mg/m²) administered in 21-day cycles.
• If pola + R-GemOx is tolerable in the safety run-in stage, patients will be randomized 1:1 to receive up to eight 21-day cycles of either pola + R-GemOx or R-GemOx alone.

Table 1: Treatment schedule

Cycles 1–8

<table>
<thead>
<tr>
<th>Drug order</th>
<th>Dose</th>
<th>D1</th>
<th>D2</th>
<th>D3–21</th>
</tr>
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<tbody>
<tr>
<td>Rituximab</td>
<td>375mg/m²</td>
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<td>●</td>
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<tr>
<td>Pola</td>
<td>1.8mg/kg</td>
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<tr>
<td>Gemcitabine</td>
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<tr>
<td>Oxaliplatin</td>
<td>100mg/m²</td>
<td>●</td>
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</tbody>
</table>

Safety and efficacy will be assessed with up to 2 years of follow-up

• Safety will be assessed by recording the incidence, nature, and severity of AEs (NCI CTCAE v5.0).
• Dose interruptions, reductions, and intensity will be used to determine tolerability.
• Health-related quality of life will be assessed.
• PET-CT and CT scans will be obtained at screening, during, and after the treatment period; 28 days after the last dose of study drug; and then every 2 months (PET-CT), and 6 (CT) months during follow-up for up to 2 years.

Key exclusion criteria

• Previous autologous stem-cell transplantation (SCT) and/or planned autologous allogeneic SCT.
• Baseline peripheral neuropathy (PN) grade >1 (as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)).

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