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Epcoritamab plus GemOx in transplant-ineligible relapsed/refractory DLBCL: results from the EPCORE NHL-2 trial

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Abstract:

Patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) have poor outcomes. Gemcitabine + oxaliplatin (GemOx) with rituximab, a standard salvage therapy, yields complete response (CR) rates of approximately 30% and median overall survival (OS) of 10-13 months. Patients with refractory disease fare worse, with a CR rate of 7% for subsequent therapies and median OS of 6 months. Epcoritamab, a CD3xCD20 bispecific antibody approved for the treatment of R/R DLBCL after ≥ 2 therapy lines, has shown promising safety and efficacy in various combinations. We report results from the phase 1b/2 EPCORE[®] NHL-2 trial evaluating epcoritamab + GemOx in patients with R/R DLBCL who were ineligible for or had failed autologous stem cell transplant (ASCT). Patients received 48-mg subcutaneous epcoritamab after 2 step-up doses until progression or unacceptable toxicity; GemOx was given Q2W for 8 doses. The primary endpoint was overall response rate (ORR). As of December 15, 2023, 103 patients were enrolled (median follow-up, 13.2 months). Patients had a median age of 72 years and challenging-to-treat disease: ≥ 2 prior therapy lines, 62%; prior CAR T, 28%; primary refractory disease, 52%; refractory to last therapy, 70%. ORR/CR rates were 85%/61%. Median duration of CR and OS were 23.6 and 21.6 months. Common treatment-emergent adverse events were cytopenias and cytokine release syndrome (CRS). CRS events had predictable timing, were primarily low grade (52% overall, 1% grade 3), and resolved without leading to discontinuation. Epcoritamab + GemOx yielded deep, durable responses and favorable long-term outcomes in ASCT-ineligible R/R DLBCL. NCT04663347

Conflict of interest: COI declared - see note

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Agreement to Share Publication-Related Data and Data Sharing Statement: Documents such as the study protocol, statistical analysis plan, informed consent form and others will be made available upon request for further analyses by external independent researchers. However, de-identified individual participant data collected during the trial will not be available. Aggregated clinical trial data from the trial is provided via publicly accessible study registries/databases as required by law. For more information, please contact ClinicalTrials@genmab.com.

Clinical trial registration information (if any): NCT04663347;
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2
3 **Epcoritamab plus GemOx in transplant-ineligible relapsed/refractory DLBCL:**
4 **results from the EPCORE NHL-2 trial**

5
6 **Short Title (Right Running Head): Epcoritamab in transplant-ineligible R/R DLBCL**

7
8 **Left Running Head:** Brody J.D., *et al*

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40 Documents such as the study protocol, statistical analysis plan, informed consent form
41 and others will be made available upon request for further analyses by external
42 independent researchers. However, de-identified individual participant data collected
43 during the trial will not be available. Aggregated clinical trial data from the trial is
44 provided via publicly accessible study registries/databases as required by law. For more
45 information, please contact ClinicalTrials@genmab.com.

46

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52 **KEY POINTS**

- 53 • Epcoritamab, a CD3xCD20 bispecific antibody, plus GemOx yields deep, durable
54 responses in second-line or later ASCT-ineligible R/R DLBCL
- 55 • Higher ORR/CR rates in second-line and in CAR T–naive patients suggest that
56 this regimen may improve outcomes as an earlier treatment

57

58 **ABSTRACT**

59 Patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) have
60 poor outcomes. Gemcitabine + oxaliplatin (GemOx) with rituximab, a standard salvage
61 therapy, yields complete response (CR) rates of approximately 30% and median overall
62 survival (OS) of 10–13 months. Patients with refractory disease fare worse, with a CR
63 rate of 7% for subsequent therapies and median OS of 6 months. Epcoritamab, a
64 CD3xCD20 bispecific antibody approved for the treatment of R/R DLBCL after ≥ 2
65 therapy lines, has shown promising safety and efficacy in various combinations. We
66 report results from the phase 1b/2 EPCORE[®] NHL-2 trial evaluating epcoritamab +
67 GemOx in patients with R/R DLBCL who were ineligible for or had failed autologous
68 stem cell transplant (ASCT). Patients received 48-mg subcutaneous epcoritamab after 2
69 step-up doses until progression or unacceptable toxicity; GemOx was given Q2W for 8
70 doses. The primary endpoint was overall response rate (ORR). As of December 15,
71 2023, 103 patients were enrolled (median follow-up, 13.2 months). Patients had a
72 median age of 72 years and challenging-to-treat disease: ≥ 2 prior therapy lines, 62%;
73 prior CAR T, 28%; primary refractory disease, 52%; refractory to last therapy, 70%.
74 ORR/CR rates were 85%/61%. Median duration of CR and OS were 23.6 and 21.6
75 months. Common treatment-emergent adverse events were cytopenias and cytokine
76 release syndrome (CRS). CRS events had predictable timing, were primarily low grade
77 (52% overall, 1% grade 3), and resolved without leading to discontinuation.
78 Epcoritamab + GemOx yielded deep, durable responses and favorable long-term
79 outcomes in ASCT-ineligible R/R DLBCL. NCT04663347

80 **Keywords:** Non-Hodgkin lymphoma; B-cell lymphoma; diffuse large B-cell lymphoma;
81 bispecific antibody therapy
82

83 INTRODUCTION

84 Diffuse large B-cell lymphoma (DLBCL), an aggressive subtype of lymphoma, is the
85 most frequently diagnosed non-Hodgkin lymphoma (NHL), accounting for approximately
86 30% of NHL.¹ Patients with relapsed or refractory (R/R) disease after first-line treatment
87 who are unable to undergo high-dose therapy followed by autologous stem cell
88 transplant (ASCT) and those for whom ASCT has failed have dismal outcomes and
89 limited treatment options²; treatment-refractory patients do especially poorly, with overall
90 response rates (ORRs) and complete response (CR) rates of 26% and 7% to
91 subsequent therapies and a median overall survival (OS) of 6 months.²

92 Gemcitabine + oxaliplatin (GemOx) is commonly used with rituximab (R-GemOx)
93 as an immunochemotherapy regimen in patients who are ineligible for ASCT.³ However,
94 outcomes are suboptimal, with a CR rate of 33%, median progression-free survival
95 (PFS) of 5 months, and median OS of 10 months (7 months in older patient
96 populations).³ In recently published data, R-GemOx treatment resulted in a median PFS
97 of 3.6 months and median OS of 12.9 months.⁴

98 Current outcomes are suboptimal in R/R DLBCL irrespective of treatment
99 modality. Durable remissions can be achieved with first-line therapy by combining
100 mechanistically distinct therapies to overcome cross-resistance, and similar approaches
101 are needed to achieve durable remissions with salvage therapy. While CAR T-cell
102 therapies have shown long-term efficacy in R/R DLBCL,⁵ their utility is limited by
103 manufacturing timelines, accessibility, logistical challenges, and the need for relatively
104 fit patients.⁶⁻⁹ T-cell-engaging antibodies are an emerging treatment class that offers an

105 off-the-shelf option with promising efficacy and reduced cytokine release syndrome
106 (CRS) and neurotoxicity.⁹

107 Epcoritamab, a CD3xCD20 bispecific antibody, is approved for the treatment of
108 adults with R/R DLBCL or follicular lymphoma after ≥ 2 lines of systemic therapy.¹⁰⁻¹³
109 The pivotal EPCORE NHL-1 phase 2 trial showed that epcoritamab demonstrated deep,
110 durable responses with manageable safety in patients with third-line or later R/R large
111 B-cell lymphoma (LBCL).¹⁴ Long-term follow-up beyond 2.5 years showed ORR and CR
112 rates of 59% and 41% for patients with LBCL. CRs were durable, with 62% of patients
113 with CR remaining in remission at 24 months.¹⁵ Epcoritamab is a distinct bispecific
114 antibody because it is administered as a low-volume subcutaneous injection and does
115 not require bridging therapy or debulking prior to treatment initiation; this allows for rapid
116 T-cell engagement and killing of malignant CD20⁺ B cells.^{16,17} In clinical trials,
117 epcoritamab has shown encouraging efficacy and manageable safety in combination
118 with standard treatments, including chemotherapies.¹⁸⁻²⁰

119 EPCORE[®] NHL-2 is a phase 1b/2 trial of epcoritamab treatment in combination
120 with standard therapies in patients with CD20⁺ NHL. Here, we report efficacy and safety
121 results from arm 5 of the EPCORE NHL-2 trial, which evaluated epcoritamab + GemOx
122 in patients with R/R DLBCL who were not eligible for ASCT due to age, performance
123 status, comorbidities, or failure of prior ASCT.

124

125 **METHODS**

126 **Study design and patients**

127 EPCORE NHL-2 is a phase 1b/2, open-label, multicenter trial in patients with CD20⁺
128 NHL (EPCORE NHL-2; GCT3013-02; ClinicalTrials.gov identifier: NCT04663347). The
129 trial has 2 parts: dose escalation and expansion.

130 In arm 5, adult patients were enrolled with the following key inclusion criteria:
131 Eastern Cooperative Oncology Group performance status of 0 to 2; documented CD20⁺
132 DLBCL that was R/R to ≥ 1 prior therapy and *de novo* or histologically transformed from
133 follicular or nodal marginal zone lymphoma according to 2016 WHO classification²¹
134 (DLBCL, not otherwise specified; double- or triple-hit lymphoma with DLBCL
135 morphology [high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6*
136 translocations]; follicular lymphoma grade 3B; or T-cell/histiocyte-rich DLBCL); and
137 previous ASCT failure or ineligibility for ASCT due to age, performance status,
138 comorbidities, or insufficient response to prior treatment. Eligible patients had
139 measurable disease, had adequate organ function, and were eligible to receive GemOx.
140 Patients were not enrolled if they had active infections requiring systemic therapy;
141 COVID-19 tests were not required at screening. Patients were considered to have
142 relapsed disease if they had an initial response and experienced progression at least 6
143 months after last treatment. Patients were considered to have refractory disease if they
144 experienced progression or stable disease as best overall response during therapy or
145 progression within 6 months of completion of therapy.

146 Patients were treated with subcutaneous epcoritamab in 28-day cycles as
147 follows: once weekly in cycles 1 to 3, once every 2 weeks in cycles 4 to 9, and once
148 every 4 weeks in cycles 10 and beyond until disease progression or unacceptable
149 toxicity.

150 Step-up dosing, given in cycle 1, included 2 step-up doses (0.16 mg on day 1,
151 0.8 mg on day 8), followed by full doses on days 15 and beyond. In the dose-escalation
152 part, patients were treated with either 24-mg or 48-mg full doses. In the expansion part,
153 all patients were treated with the recommended phase 2 dose of 48 mg.²² Patients were
154 required to have ≥ 7 days between epcoritamab administrations. A full repriming cycle
155 (weekly schedule of priming, intermediate, and 2 full doses) was required if an
156 intermediate dose was delayed >1 day, a first full dose was delayed >7 days, or the
157 interval between full doses was >6 weeks. Once repriming was completed, dosing
158 resumed at day 1 of the next planned cycle.

159 GemOx (intravenous gemcitabine 1000 mg/m²; intravenous oxaliplatin 100
160 mg/m²) was administered every 2 weeks for the first 4 cycles (28 days each; 8 total
161 doses, 2 per cycle). Herein, we describe results from patients in the 48-mg epcoritamab
162 treatment groups of dose escalation and expansion.

163 Prophylaxis for CRS in cycle 1 included prednisolone 100 mg or equivalent (oral
164 or intravenous) 30 to 120 minutes prior to epcoritamab dosing (once daily on days 1 to 4
165 for the priming dose; once daily on days 8 to 11 for the intermediate dose; once daily on
166 days 15 to 18 for the first full dose; and once daily on days 22 to 25 for the second full
167 dose). Additionally, oral or intravenous diphenhydramine 50 mg (or equivalent) and oral
168 acetaminophen 650 to 1000 mg were administered once daily on days 1, 8, 15, and 22

169 of cycle 1. Patients were required to be hospitalized for the first full dose of epcoritamab
170 (on cycle 1 day 15 and during repriming cycles) and for 24 hours following
171 administration.

172

173 **Endpoints and assessments**

174 The protocol-specified primary endpoint of the expansion part was ORR in accordance
175 with Lugano criteria.²³ Key secondary endpoints included CR rate, time to response,
176 PFS, duration of response (DOR), and duration of CR (DOCR), all assessed by
177 independent review committee (IRC) per Lugano criteria, and OS. Safety endpoints
178 included adverse events (AEs) and laboratory values, including immunoglobulin levels.

179 Efficacy was evaluated by positron emission tomography–computed tomography
180 imaging obtained at screening and 6, 12, 18, 24, 36, and 48 weeks, and every 24 weeks
181 thereafter, until disease progression. Exploratory minimal residual disease (MRD)
182 analyses were performed with plasma circulating tumor DNA samples, including a cycle
183 3 day 1 landmark analysis, using the AVENIO Oncology Assay Non-Hodgkin
184 Lymphoma Test (AVENIO; Roche Sequencing Solutions, Pleasanton, CA, USA).

185 AEs were classified using Medical Dictionary for Regulatory Activities version
186 26.1, and severity was graded using National Cancer Institute Common Terminology
187 Criteria for Adverse Events version 5.0. CRS and immune effector cell–associated
188 neurotoxicity syndrome (ICANS) were graded using American Society for
189 Transplantation and Cellular Therapy criteria,²⁴ and clinical tumor lysis syndrome was
190 graded using Cairo–Bishop criteria.²⁵ The relationship between AEs and treatment was
191 determined by the investigator. Tumor biopsy was assessed at screening. Blood

192 immunophenotyping and plasma cytokines were measured using flow cytometry and
193 the Meso Scale Discovery assay (Rockville, MD, USA), respectively. Immunoglobulin
194 levels were assessed locally at screening and day 1 of each cycle (predose).

195

196 **Statistical analysis**

197 There was no formal hypothesis testing in this single-arm trial. A sample size of 100
198 patients receiving epcoritamab 48 mg provided at least an 82% chance of detecting a
199 15% improvement in ORR in patients with R/R DLBCL when epcoritamab is added to
200 GemOx, assuming the ORR is 46% for GemOx alone and the 2-sided alpha is 5%.

201 Efficacy and safety analyses were conducted in the full analysis population,
202 comprising patients who received at least 1 dose of trial drug. Efficacy assessments
203 were also performed in prespecified subgroups based on best overall response and
204 characteristics. MRD analyses were conducted in the MRD-evaluable population,
205 comprising patients with at least 1 baseline or on-treatment MRD result and MRD not
206 negative at baseline. Continuous data were summarized descriptively, categorical data
207 were summarized using frequency and percentage, and time-to-event data were
208 summarized using the Kaplan–Meier method. Data were analyzed using SAS software
209 version 9.4 or higher (SAS Institute, Inc, Cary, NC, USA).

210 ORR, based on response by IRC and investigator assessments, was defined as
211 the percentage of patients with a best overall response of CR or partial response (PR).
212 Corresponding exact 95% confidence intervals (CIs) for ORR and CR rates were
213 calculated using the Clopper–Pearson method.

214 PFS was defined as time from cycle 1 day 1 to first documented progression or
215 death due to any cause. OS was defined as time from cycle 1 day 1 to death due to any
216 cause. DOR was defined as time from first CR or PR to first documented progression or
217 death due to any cause. DOCR was defined as time from first CR to first documented
218 progression or death due to any cause. Date of disease progression was defined as the
219 earliest date of documented progression after which there was no CR or PR. PFS and
220 DOR were censored at the date of last disease assessment or prior to the date of
221 subsequent antilymphoma therapy for patients who did not have progression and
222 remained alive. If a patient was not known to have died, then OS was censored at the
223 latest date that the patient was known to be alive. A sensitivity analysis for OS censored
224 patients at the date of last disease assessment prior to death due to confirmed COVID-
225 19.

226

227 **Ethics**

228 Site-specific institutional review boards or institutional or central ethics committees
229 approved the protocol prior to study initiation. The study was conducted in accordance
230 with the International Council for Harmonisation E6(R2) guidelines on good clinical
231 practice and the principles of the Declaration of Helsinki. Before enrollment, all patients
232 reviewed and signed informed consent forms.

233

234 RESULTS

235 Study population and exposure

236 From January 25, 2021, to December 15, 2023, 103 patients with ASCT-ineligible R/R
237 DLBCL were treated with epcoritamab + GemOx (**Supplemental Figure 1**).

238 The median age was 72 years, with 35% of patients ≥ 75 years. Patients had a
239 median of 2 prior lines of therapy (pLOT; range, 1–6), 38% of patients had 1 pLOT, and
240 62% had ≥ 2 pLOT. Overall, 19% had bulky disease (>10 cm) by IRC assessment, 23%
241 had transformed DLBCL, 6 (10%) of 58 patients with evaluable tissue had double- or
242 triple-hit lymphoma by central laboratory, 61% had Ann Arbor stage IV disease, 52%
243 had primary refractory disease, 70% had disease refractory to their last systemic
244 therapy, 10% had prior ASCT, and 28% had prior CAR T. Almost all patients enrolled
245 were from Europe (72%) or North America (27%). Demographic and baseline clinical
246 characteristics in the overall population are shown in **Table 1** (see **Supplemental Table**
247 **1** for patients with CR and patients with 1 pLOT). The primary reasons patients were
248 ineligible for ASCT were age (56%), performance status (8%), prior transplant (8%),
249 comorbidities (5%), and other reasons (22%, most of which were inadequate response
250 to prior therapy).

251 Treatment was ongoing in 44 patients (43%) at the time of data cutoff
252 (**Supplemental Table 2**). A total of 59 patients (57%) discontinued trial treatment; 32
253 (31%) discontinued due to progressive disease; at the time of progressive disease, all
254 but 2 patients were on epcoritamab treatment. There were 20 patients (19%) who
255 discontinued due to AEs (COVID-19/COVID-19 pneumonia in 6 patients; pneumonia in
256 2 patients; aspergillosis, enterocolitis, *Escherichia coli* sepsis, hydrocephalus, ICANS,

257 multiple organ dysfunction syndrome, small intestinal perforation, and subarachnoid
258 hemorrhage in 1 patient each; 1 patient with myelitis, hemiparesis, urinary tract
259 infection, and fall; 1 patient with pneumonia, chronic sinusitis, and respiratory tract
260 infection; 1 patient with pneumonia and hypoxia; and 1 patient with an unspecified AE).
261 Two patients discontinued treatment due to AEs (ICANS and pneumonia, n = 1 each)
262 while in CR and remained in remission at data cutoff (duration of CRs following
263 treatment discontinuation: 18 and 32 weeks). All but 1 patient received at least 1 full
264 dose. Patients initiated a median of 8 epcoritamab cycles (range, 1–37) and 4 GemOx
265 cycles (range, 1–4). Median duration of epcoritamab treatment was 8.3 months (range,
266 0.3–33.2). Median relative dose intensities of gemcitabine and oxaliplatin were 80% and
267 78%, respectively (previous studies reported medians ranging from 73%–93%)^{3,26};
268 treatment-emergent AEs (TEAEs) led to GemOx dose modification in 88 patients (85%).
269

270 **Efficacy**

271 Median study follow-up was 13.2 months (range, 1.0–34.6). Best overall response was
272 consistent between IRC and investigator assessments; ORR and CR rates were 85%
273 and 61% by IRC assessment and 80% and 58% by investigator assessment. Three
274 patients had PRs that converted to CRs after week 24, and 3 patients with stable
275 disease had a PR or CR after week 12. A summary of response in the overall
276 population by IRC and investigator assessments is shown in **Table 2**.

277 Efficacy results by IRC assessment in the overall population, in patients with CR,
278 and by pLOT are shown in **Table 3**. Median PFS in the overall population and among
279 patients with CR was 11.2 (95% CI, 8.0–14.7) and 26.7 (95% CI, 11.7–not reached

280 [NR]) months, respectively (**Figure 1A; Supplemental Figure 2A**). PFS was greater in
281 patients with 1 pLOT compared with ≥ 2 pLOT. Among patients with CR and patients
282 with 1 pLOT, an estimated 68% and 63%, respectively, remained progression free at 12
283 months. There were minimal differences in PFS for patients who had *de novo* vs
284 transformed DLBCL, with an estimated 44% of patients remaining progression free at
285 12 months, regardless of DLBCL type.

286 Median OS was 21.6 months (95% CI, 11.6–NR) in the overall population and
287 NR (95% CI, NR–NR) in patients with CR (**Figure 1B; Supplemental Figure 2B**).
288 Among patients with CR and patients with 1 pLOT, an estimated 84% and 69%,
289 respectively, remained alive at 12 months. Kaplan–Meier curves by IRC assessment for
290 PFS and OS in patients with CR overall and by pLOT are shown in **Supplemental**
291 **Figure 2**.

292 Median time to response and CR were 1.5 and 2.6 months, respectively, in the
293 overall population (**Table 3**). Median DOR in the overall population was 11.7 months
294 (**Figure 1C**). A higher percentage of responders with 1 pLOT remained in response at
295 12 months compared with patients with ≥ 2 pLOT (**Table 3**). Median DOCR was 23.6
296 months (95% CI, 11.7–NR) overall (**Figure 1D**). Twelve-month estimates showed that
297 approximately 60% of complete responders remained in CR regardless of whether they
298 had 1 pLOT, ≥ 2 pLOT, *de novo* DLBCL, or transformed DLBCL.

299 Subgroup analyses showed high CR rates: 74% in patients with 1 pLOT vs 53%
300 in patients with ≥ 2 pLOT and 68% in CAR T–naive patients vs 45% in patients with prior
301 CAR T. Among 6 patients with double- or triple-hit lymphoma, 3 (50%) had a CR and
302 median DOCR was NR (95% CI, NR–NR). High CR rates were seen regardless of

303 whether patients had transformed or *de novo* disease. ORRs and CR rates in
304 subgroups are shown in **Figure 2**.

305 An analysis of PFS, OS, and DOCR by region showed consistent PFS, OS, and
306 DOCR in patients from North America and patients from Europe; 12-month estimates
307 were: 59% vs 40%, PFS; 59% vs 55%, OS; and 62% vs 66%, DOCR (**Supplemental**
308 **Figure 3**).

309 A total of 30 of 62 MRD-evaluable patients (48%) had MRD negativity at any time
310 point (cycle 3 day 1 landmark analysis shown in **Supplemental Figure 4**). By cycle 3
311 day 1, there was a decrease in circulating tumor DNA (median log₁₀-fold decrease,
312 2.04), and MRD-negativity rates were 55% in patients with 1 pLOT and 49% in patients
313 with ≥2 pLOT. Overall, MRD-negativity rates were 50% among patients with primary
314 refractory disease and 47% among patients without primary refractory disease.

315

316 **Safety**

317 The most common TEAEs of any grade in the full analysis population were hematologic
318 AEs, infections, and CRS; 73% of patients had thrombocytopenia, 65% had
319 neutropenia, 59% had anemia, 72% had infections, and 52% had CRS. The most
320 common grade ≥3 TEAEs were thrombocytopenia (59%), neutropenia (57%), and
321 anemia (43%). Febrile neutropenia occurred in 7 patients (7%); all events were grade 3
322 and resolved. ICANS was reported in 3 patients (grade 1–3, n = 1 each). All ICANS
323 events resolved, and 1 patient discontinued treatment due to ICANS. An overview of
324 TEAEs is shown in **Table 4**.

325 Overall, 13 patients (13%) had grade 5 TEAEs. Of these, 5 events were due to
326 COVID-19. The study was largely enrolled during the COVID-19 pandemic. Further
327 descriptions are provided in the **Supplemental Results**.

328 CRS was primarily low grade (52% overall incidence; 28% grade 1, 23% grade
329 2); only 1 patient experienced grade 3 CRS. CRS events mostly occurred in cycle 1
330 (84% of CRS events), and more specifically, following the first full dose (63% of CRS
331 events). All events resolved and none led to epcoritamab discontinuation. Tocilizumab
332 was used in 24 patients (23%) and corticosteroids beyond those for prophylaxis were
333 used in 17 (17%). An overview of CRS is shown in **Supplemental Table 3**.

334 The rate of infections was 72%; most were COVID-19 (29%), upper respiratory
335 tract infection (14%), pneumonia (10%), and urinary tract infection (10%). Overall, 32%
336 of patients experienced serious infections, the majority of which were COVID-19 and
337 pneumonia. Grade 3 or 4 infections were reported in 21% of patients. In the first 12
338 weeks of the trial, during which patients received epcoritamab + GemOx, the incidence
339 of infections was 56% and the incidence of grade 3 or 4 cytopenias was 76%; these
340 rates decreased substantially in subsequent 12-week intervals up to week 60, to 22%–
341 28% for infections overall and 3%–39% for grade 3 or 4 cytopenias. Four patients
342 experienced secondary malignancies: 2 patients had basal cell carcinoma, 1 had
343 pancreatic adenocarcinoma, and 1 had squamous cell carcinoma.

344

345 **Immunoglobulin levels**

346 Immunoglobulin levels decreased from baseline after treatment initiation and remained
347 relatively stable up to cycle 18, with no larger mean decreases from baseline in

348 immunoglobulin G levels over time (**Supplemental Figure 5**). Overall, 22% received
349 supplemental immunoglobulin therapy.

350

351 **DISCUSSION**

352 In EPCORE NHL-2 arm 5, epcoritamab + GemOx treatment resulted in complete
353 remissions in a majority patients with R/R DLBCL who were ineligible for ASCT or for
354 whom ASCT had failed. ORR and CR rates were high at 85% and 61%, respectively.
355 High CR rates were seen in patients with 1 pLOT (74%) and patients with no prior CAR
356 T-cell therapy (68%). Responses were observed early and were deep and durable,
357 translating to sustained CRs and favorable PFS; median OS was NR in patients with
358 CR. Three patients with stable disease had a PR or CR after week 12, suggesting the
359 potential for a later response. MRD negativity was observed in around half of evaluable
360 patients; MRD-negativity rates by cycle 3 day 1 were slightly higher in patients with 1
361 pLOT compared with patients in later lines of therapy. Safety was in line with GemOx
362 therapy and epcoritamab monotherapy and was generally manageable^{3,14,26}; CRS
363 events were low grade, comparable to single-agent epcoritamab data,²⁷ and all
364 resolved. These results demonstrate that the addition of epcoritamab to GemOx was
365 feasible and follow several other studies assessing epcoritamab in combination with
366 immunochemotherapy (R-CHOP and R-DHAX/C) in DLBCL, which collectively show the
367 versatility and combinability of epcoritamab with chemotherapies.^{20,28}

368 Responses to epcoritamab + GemOx were similar to or compared favorably to
369 those observed with other approved therapies, including historical R-GemOx data.^{3,26}
370 However, cross-study comparisons should be interpreted with caution due to

394 patients with double- or triple-hit lymphoma (EPCORE NHL-2 arm 5: n = 6; CR rate,
395 50%) and patients with recent COVID-19 (≤ 6 months of the first study dose).
396 Additionally, EPCORE NHL-2 arm 5 included more patients with ≥ 2 pLOT (62% vs 37%)
397 and prior CAR T (28% vs 7%) relative to STARGLO,⁴ and had minimal regional
398 differences in OS. In another bispecific antibody combination approach, a phase 1b/2
399 trial evaluated mosunetuzumab with the antibody–drug conjugate polatuzumab vedotin
400 for patients with R/R LBCL.³¹ The safety was manageable, with low rates of ICANS
401 (5%) and grade 3 CRS (3%). Although the majority of patients in the dose-expansion
402 cohort did not have a CR, efficacy was promising, with ORR and CR rates of 59% and
403 46% per IRC; however, treatment with epcoritamab + GemOx has yielded higher
404 response rates (85% and 61%). Notably, the mosunetuzumab study excluded patients
405 with prior polatuzumab therapy, so it will be important to assess the efficacy of the
406 approach given the recent approval of polatuzumab with first-line chemotherapy.³²

407 The safety profile of epcoritamab + GemOx was generally similar to that of other
408 chemotherapy combinations in LBCL. High rates of neutropenia, including 73% of
409 patients with grade ≥ 3 neutropenia, have been reported in patients with R/R DLBCL
410 ineligible for high-dose therapy who received R-GemOx.²⁶ In EPCORE NHL-2 arm 5,
411 57% of patients experienced grade ≥ 3 neutropenia (febrile neutropenia, 7%). CRS was
412 primarily low grade (52% overall, 1% grade 3); rates were comparable to single-agent
413 epcoritamab data.²⁷ Three patients experienced ICANS (3% overall, 1% grade 3).
414 Additionally, in this trial, 21% of patients experienced infections that were grade 3 or 4
415 at worst, which is comparable to historical R-GemOx studies (22%).²⁶ Overall, 13% of
416 patients experienced fatal TEAEs, most of which were due to COVID-19 or other

417 infections. Of note, there is a well-documented increased risk of morbidity and mortality
418 due to infections for patients with hematologic malignancies being treated with B-cell–
419 depleting therapies, and this study overlapped with the COVID-19 pandemic.^{33,34}
420 Furthermore, in this trial, patients received GemOx more frequently (every 2 weeks)
421 compared with the less frequent dosing strategy (every 3 weeks) used in the STARGLO
422 study⁴; whereas less frequent administration may be less burdensome for patients, it
423 may yield a greater risk of early kinetic failure, as dose density has been correlated with
424 improved outcomes in lymphoma.³⁵ It is promising that epcoritamab could be safely
425 combined with a dose-dense chemotherapy regimen (GemOx) and that this
426 combination therapy was sufficiently well tolerated.

427 Epcoritamab is a subcutaneous therapy that can offer off-the-shelf convenience
428 compared with other available options. CAR T-cell therapies, such as axicabtagene
429 ciloleucel, lisocabtagene maraleucel, and tisagenlecleucel, demonstrate long-term
430 efficacy but may not be accessible to all patients and are not immediately available to
431 patients with an urgent need for treatment due to requirements for lymphodepletion,
432 access to specialized treatment centers, and manufacturing time.^{8,9,36-40} Of particular
433 importance, the median age of patients in seminal CAR T trials was 56–60 years and
434 trials lacked elderly patients (aged ≥ 75 years [highest age, 76 years]), compared with
435 the current study, in which median age was 72 years and more than one-third of
436 patients were aged ≥ 75 years (highest age, 87 years), highlighting the relative
437 accessibility and safety of this combination therapy.^{7,36,39} Notably, real-world analyses
438 have demonstrated that CAR T therapies have significantly shorter event-free survival in
439 patients aged ≥ 75 years.⁴¹ The combination of epcoritamab and chemotherapy, like

440 GemOx, offers an effective treatment option to improve outcomes for these patients with
441 an unmet need. Like other open-label, single-arm studies, EPCORE NHL-2 is limited by
442 its lack of a comparator or control group. Additional limitations are a lack of racial and
443 ethnic diversity in patients enrolled and missing race and ethnicity data due to regional
444 guidelines. Longer follow-up is needed to better understand long-term outcomes.

445 In conclusion, results from EPCORE NHL-2 arm 5 demonstrated deep and
446 durable responses with epcoritamab + GemOx in a population of patients with
447 ASCT-ineligible R/R DLBCL, the majority of whom had high-risk features. Epcoritamab
448 + GemOx treatment resulted in high response rates across subgroups, especially
449 among patients with 1 pLDT. The addition of epcoritamab to GemOx demonstrated
450 significantly improved outcomes compared with historical data for R-GemOx. These
451 encouraging results support the combinability and versatility of epcoritamab in R/R
452 DLBCL.

453

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461

462 **AUTHORSHIP**

463 **Contributions:**

464 R.Cor. helped design the trial.

465 J.D.B., J.J., D.B., R.Cos., M.T., U.V., D.J.L., Y.H.K., A.S., M.A., B.E.W., P.J.L., and
466 R.Cor. were study investigators and provided patients or study materials.

467 J.D.B., J.J., D.B., R.Cos., M.T., U.V., D.J.L., Y.H.K., A.S., M.A., B.E.W., P.J.L., and
468 R.Cor. collected and assembled data.

469 K.K., A.J.S., A.A., L.W., and M.R. analyzed the data.

470 All authors interpreted the data, prepared the manuscript, participated in the critical
471 review and revision of the manuscript, and provided approval of the manuscript for
472 submission.

473

474 **Conflict of interest disclosures:**

475 J.D.B. reports advisory role for ADC Therapeutics, Epizyme, and Seagen; and research
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491 D.J.L. reports advisory and consultancy roles for Janssen, Lilly, Roche, BeiGene, and
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517

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645

Table 1. Demographic and baseline clinical characteristics in the overall population

Characteristic	Overall N = 103
Age, years, median (range)	72 (20–87)
Age group, years, n (%)	
<65	28 (27.2)
65 to <75	39 (37.9)
≥75	36 (35.0)
Sex at birth, n (%)	
Male	57 (55.3)
Female	46 (44.7)
Race	
White	78 (75.7)
Black or African American	4 (3.9)
Asian	4 (3.9)
Other	1 (1.0)
Not reported	16 (15.5)
Ethnicity*	
Hispanic or Latino	3 (2.9)
Not Hispanic or Latino	22 (21.4)
Not reported	3 (2.9)
Missing	75 (72.8)
Region, n (%)	
Europe	74 (71.8)
North America	28 (27.2)
Australia	1 (1.0)

646

ECOG performance status, n (%)	
0	33 (32.0)
1	57 (55.3)
2	13 (12.6)
IPI, n (%)	
<3	38 (36.9)
≥3	65 (63.1)
Bulky disease by IRC assessment, [†] n (%)	
<7 cm (non-bulky disease)	62 (60.2)
7 to 10 cm	18 (17.5)
>10 cm	20 (19.4)
DLBCL type, [‡] n (%)	
<i>De novo</i>	75 (72.8)
Transformed	24 (23.3)
Double- or triple-hit lymphoma (<i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> rearrangement) by central laboratory, [§] n/n (%)	6/58 (10.3)
DLBCL cell of origin, n (%)	
Activated B-cell/non-germinal center B-cell	43 (41.7)
Germinal center B-cell	41 (39.8)
Unknown	19 (18.4)
Ann Arbor stage, n (%)	
I or II	22 (21.4)
III	18 (17.5)
IV	63 (61.2)
Time from initial diagnosis to first dose of epcoritamab, months, median (range)	13.2 (0.6–177.7)
Time from end of last therapy to first dose of epcoritamab, months, median (range)	4.6 (0.6–98.9)
Prior lines of antilymphoma therapy, median (range)	2 (1–6)

Prior lines of antilymphoma therapy, n (%)	
1	39 (37.9)
2	27 (26.2)
≥3	37 (35.9)
Primary refractory disease, ^{¶#} n (%)	54 (52.4)
Refractory to last systemic therapy, [#] n (%)	72 (69.9)
Refractory to ≥2 consecutive lines of therapy, [#] n (%)	38 (36.9)
Prior ASCT, n (%)	10 (9.7)
Relapsed ≤12 months after ASCT, n/n (%)	5/10 (50.0)
Prior CAR T-cell therapy, n (%)	29 (28.2)

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ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; IRC, independent review committee.

*Ethnicity was not reported for patients enrolled outside of the USA.

[†]A total of 12 patients had bulky disease >10 cm by investigator assessment. Bulky disease status by IRC was missing for 3 patients.

[‡]*De novo* vs transformed status was missing for 4 patients.

[§]*MYC* and *BCL2* and/or *BCL6* rearrangement by central laboratory was not assessed in 45 patients.

^{||}DLBCL cell of origin was determined by local laboratory.

[¶]Primary refractory disease is defined as disease that is refractory to first-line antilymphoma therapy.

[#]Refractory disease is defined as disease progression or stable disease as best overall response during therapy or progression within 6 months of completion of therapy.

660 **Table 2. Summary of response in the overall population by IRC and investigator**
 661 **assessments**
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	IRC assessment N = 103	Investigator assessment N = 103
Overall response rate, n (%)	88 (85.4)	82 (79.6)
CR	63 (61.2)	60 (58.3)
PR	25 (24.3)	22 (21.4)
Stable disease, n (%)	3 (2.9)	7 (6.8)
Progressive disease, n (%)	8 (7.8)	9 (8.7)
Not evaluable, n (%)	4 (3.9)	5 (4.9)
Time to response, months, median (range)	1.5 (0.9–3.0)	1.5 (0.9–11.1)
Time to CR, months, median (range)	2.6 (1.3–22.1)	1.7 (1.3–10.7)

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 664 CR, complete response; IRC, independent review committee; PR, partial response.
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666 **Table 3. Summary of efficacy results by IRC assessment in the overall population,**
 667 **in patients with CR, and by pLOT**
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	Overall N = 103	Patients with CR by IRC n = 63	Patients with 1 pLOT n = 39	Patients with ≥2 pLOT n = 64
Time to response, months, median (range)	1.5 (0.9–3.0)	1.4 (0.9–3.0)	1.5 (1.1–2.8)	1.4 (0.9–3.0)
Time to CR, months, median (range)	2.6 (1.3–22.1)	2.6 (1.3–22.1)	1.6 (1.3–22.1)	2.8 (1.4–11.2)
Patients remaining in response at 12 months,* %	47.6 (32.8–61.1)	63.5 (43.5–78.1)	58.9 (29.5–79.5)	40.4 (23.9–56.3)
Patients remaining in CR at 12 months,* %	62.6 (42.3–77.5)	62.6 (42.3–77.5)	61.7 (24.5–84.7)	62.1 (39.9–78.1)
Progression-free survival at 12 months,* %	44.0 (31.7–55.5)	68.5 (50.0–81.3)	63.2 (40.1–79.4)	32.8 (19.0–47.2)
Overall survival at 12 months,* %	56.6 (45.5–66.3)	84.4 (70.8–92.0)	69.1 (49.3–82.4)	49.6 (36.0–61.8)

669 CR, complete response; IRC, independent review committee; pLOT, prior line(s) of therapy.
 670 *Kaplan–Meier estimates are shown with 95% confidence intervals.
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Table 4. Overview of treatment-emergent adverse events in the overall population (N = 103)

	Any grade n (%)	Grade \geq3 n (%)
Any adverse event	103 (100.0)	97 (94.2)
Serious adverse event	76 (73.8)	54 (52.4)
Adverse event leading to treatment discontinuation	36 (35.0)	30 (29.1)
Adverse events in \geq 15% of patients		
Hematologic adverse events		
Thrombocytopenia*	75 (72.8)	61 (59.2)
Neutropenia [†]	67 (65.0)	59 (57.3)
Anemia [‡]	61 (59.2)	44 (42.7)
Infections [§]	74 (71.8)	30 (29.1)
COVID-19	30 (29.1)	11 (10.7)
Cytokine release syndrome [¶]	54 (52.4)	1 (1.0)
Diarrhea	48 (46.6)	5 (4.9)
Nausea	41 (39.8)	2 (1.9)
Fatigue	36 (35.0)	7 (6.8)
Hypokalemia	32 (31.1)	9 (8.7)
Pyrexia	30 (29.1)	0
Increased alanine aminotransferase	29 (28.2)	10 (9.7)
Increased aspartate aminotransferase	26 (25.2)	6 (5.8)
Peripheral neuropathy	26 (25.2)	1 (1.0)
Cough	21 (20.4)	0
Hypomagnesemia	20 (19.4)	0
Decreased appetite	19 (18.4)	3 (2.9)
Increased lipase	19 (18.4)	6 (5.8)
Injection-site reaction [#]	18 (17.5)	0

	Any grade n (%)	Grade ≥3 n (%)
Dyspnea	17 (16.5)	2 (1.9)
Constipation	16 (15.5)	0
Adverse events of special interest		
Cytokine release syndrome [¶]	54 (52.4)	1 (1.0)
Immune effector cell–associated neurotoxicity syndrome	3 (2.9)	1 (1.0)
Clinical tumor lysis syndrome	0	0

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SMQ, Standardised Medical Dictionary for Regulatory Activities Query.

*Thrombocytopenia includes hematopoietic thrombocytopenia using SMQ narrow search.

†Neutropenia includes neutropenia and decreased neutrophil count.

‡Anemia includes anemia, decreased hematocrit, decreased hemoglobin, decreased red blood cell count, and decreased serum ferritin.

§Infections and infestations by System Organ Class.

||COVID-19 includes COVID-19, COVID-19 pneumonia, and post-acute COVID-19 syndrome.

¶Cytokine release syndrome is shown twice (as an adverse event in ≥15% of patients and as an adverse event of special interest).

#Injection-site reaction includes injection-site reactions as high-level group terms.

686 **FIGURE LEGENDS**

687 **Figure 1. Kaplan–Meier curves by IRC assessment for PFS (A), OS (B), DOR (C),**
688 **and DOCR (D) in the overall population and by pLOT.** PFS was defined as time from
689 cycle 1 day 1 to first documented progression or death due to any cause. OS was
690 defined as time from cycle 1 day 1 to death due to any cause. A sensitivity analysis for
691 OS censored patients at the date of last disease assessment prior to death due to
692 confirmed COVID-19. DOR was defined as time from first CR or PR to first documented
693 progression or death due to any cause. DOCR was defined as time from first CR to first
694 documented progression or death due to any cause. CR, complete response; DOCR,
695 duration of complete response; DOR, duration of response; IRC, independent review
696 committee; OS, overall survival; PFS, progression-free survival; pLOT, prior line(s) of
697 therapy; PR, partial response.

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699 **Figure 2. ORRs (A) and CR rates (B) by IRC assessment in subgroups.** ASCT,
700 autologous stem cell transplant; CAR, chimeric antigen receptor; CI, confidence interval;
701 CR, complete response; DLBCL, diffuse large B-cell lymphoma; IPI, International
702 Prognostic Index; IRC, independent review committee; ORR, overall response rate;
703 pLOT, prior line(s) of therapy.

Epcoritamab Plus GemOx in Transplant-Ineligible Relapsed/Refractory DLBCL: Results From the EPCORE NHL-2 Trial

Context of Research

- Patients with R/R DLBCL who are ineligible for ASCT have poor outcomes
- Epcoritamab, a CD3xCD20 bispecific antibody, was approved as monotherapy for the treatment of 3L+ DLBCL based on the results of the EPCORE NHL-1 trial (median follow-up, 25.1 months)¹

Objective

- EPCORE NHL-2 (Arm 5) evaluated the efficacy and safety results of epcoritamab SC + GemOx in patients with R/R DLBCL who were not eligible for ASCT

1. Thieblemont C, et al. *Leukemia*. 2024;doi:10.1038/s41375-024-02410-8.

Study Design

Phase 1b/2 EPCORE[®] NHL-2 Arm 5

Key Inclusion Criteria

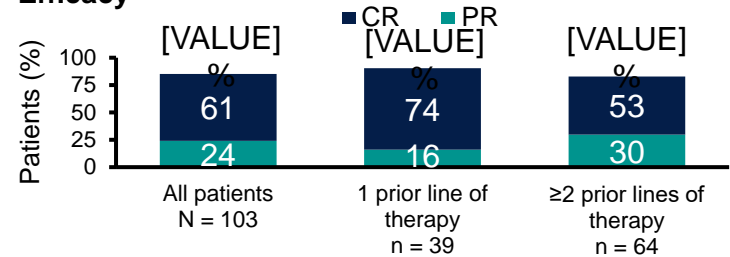
- R/R CD20⁺ DLBCL^a
 - DLBCL, NOS
 - Double-hit or triple-hit DLBCL
 - FL grade 3B
 - T-cell/histiocyte-rich DLBCL
- Ineligible for ASCT (due to age, performance status, or failure of prior ASCT)

^aDe novo or histologically transformed from FL or nodal marginal zone lymphoma based on World Health Organization 2016 classification.

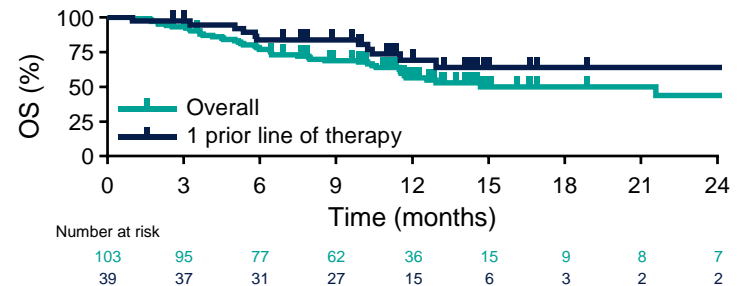
Treatment regimen: Epcoritamab SC 48 mg + GemOx IV						
Agent	C1	C2	C3	C4	C5–9	C10+
Epcoritamab	QW	QW	QW	Q2W	Q2W	Q4W
Gemcitabine				Q2W		
Oxaliplatin						

Key Results

Efficacy



- Median DOCR was 23.6 months



- Median OS was 21.6 months overall and not reached in patients with CR
 - 12-month OS estimate in patients with 1 prior line of therapy was 69%

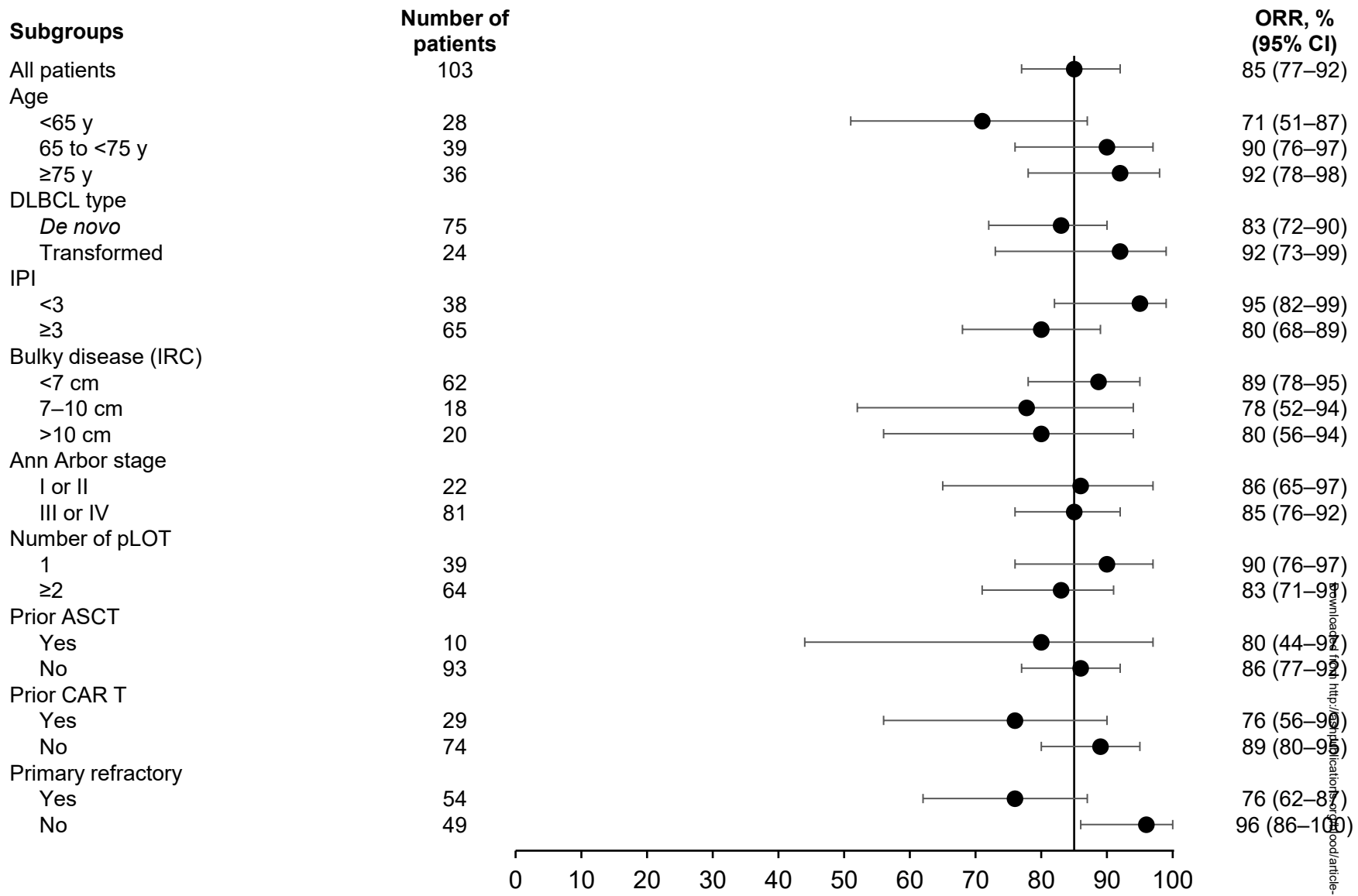
Safety

- Common TEAEs were cytopenias and CRS; CRS events were primarily low grade (52% any grade, 1% grade 3), and all resolved

Conclusions: Epcoritamab + GemOx yielded deep, durable responses in patients with R/R DLBCL. The benefit–risk profile of this combination therapy supports the combinability of epcoritamab in R/R DLBCL.

Brody et al. DOI

Figure 1



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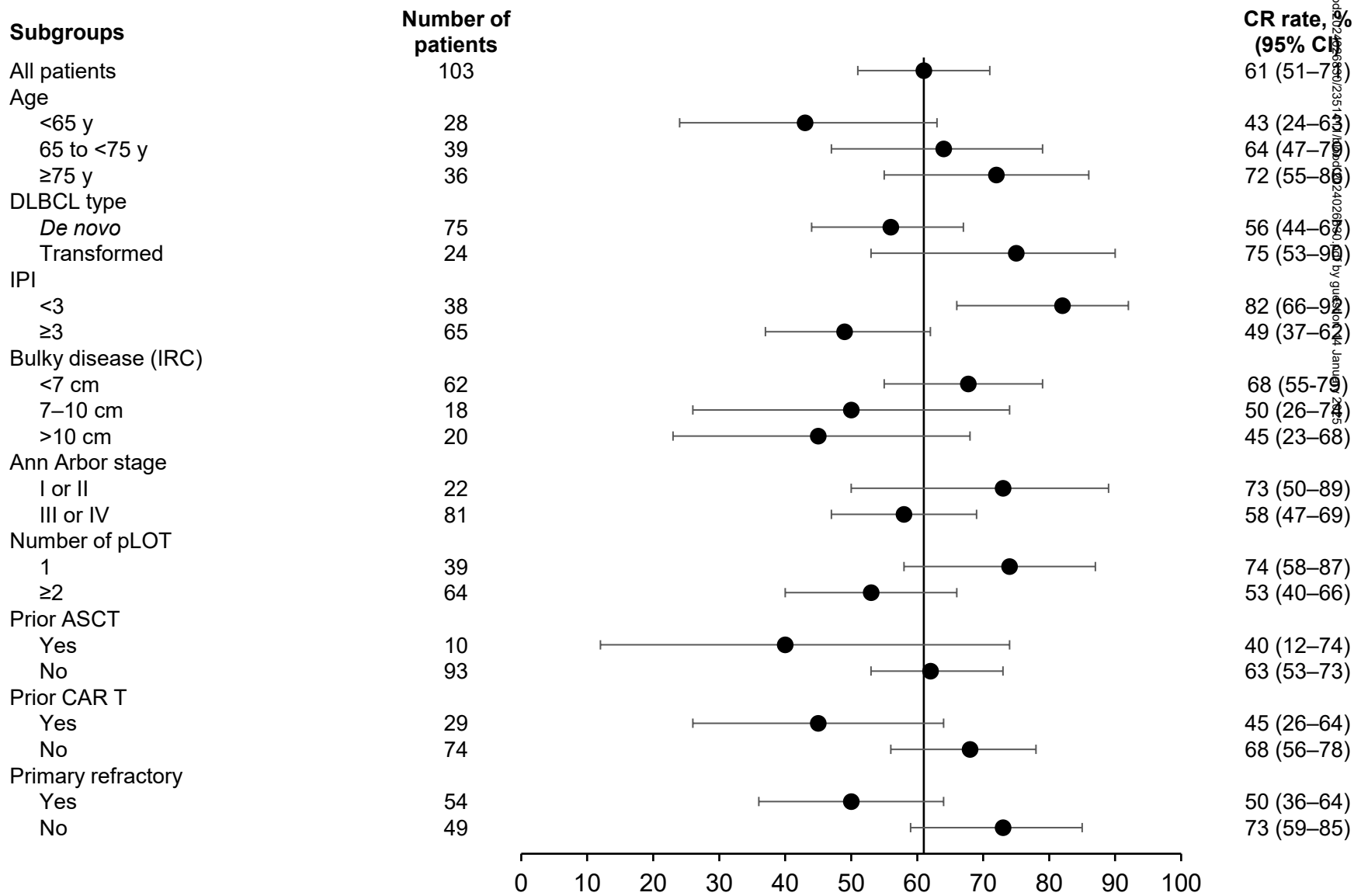


Figure 2

