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LETTER

Real-world resource utilization, toxicity management, and efficacy outcomes of CD20 × CD3 bispecific antibodies in B-cell lymphoma: A study from the GELTAMO network

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The introduction of CD20 × CD3 bispecific antibodies (BsAbs) has reshaped the treatment landscape of relapsed/refractory (R/R) B-cell lymphomas by providing an effective, off-the-shelf immunotherapy approach capable of redirecting T cells against malignant B cells across various histologic subtypes.[1–3] Pivotal trials have demonstrated high response rates and a manageable safety profile.[4–7] However, real-world evidence remains limited, particularly in healthcare systems where this treatment modality is delivered within routine clinical practice, not restricted to large, academic centers with experience in clinical trials.

Initial BsAb cycles are frequently administered inpatient to safely deliver step-up dosing, mitigate cytokine release syndrome (CRS) risk, and provide close patient monitoring. While effective, this model entails repeated hospital admissions, straining healthcare resources, and impacting patients' quality of life. As BsAbs are increasingly implemented, real-world data are warranted to guide safe execution strategies and identify opportunities to transition toward scalable outpatient care.

We conducted a nationwide retrospective study within the GELTAMO (Spanish lymphoma group) network, in which affiliated centers were invited to participate, including all consecutive adult patients with R/R B-cell lymphoma treated with commercially available BsAbs between November 2023 and March 2025. The study was conducted across 38 centers, including high-volume tertiary hospitals (n = 21) and smaller regional hospitals (n = 17), using a cut-off of approximately 800 beds; notably, 16 of the participating centers were accredited for chimeric antigen receptor (CAR) T-cell therapy. Subcutaneous (sc) epcoritamab for large B-cell lymphoma (LBCL) and intravenous (iv) mosunetuzumab for follicular lymphoma (FL) were administered according to national reimbursement policies; however, sc epcoritamab for FL and iv glofitamab for LBCL were provided through early access programs, as they were not yet reimbursed in Spain. Baseline characteristics, toxicity, resource utilization, and efficacy outcomes were collected as part of standard clinical care. This represents one of the largest European real-world BsAbs cohorts, outside of clinical trials. Accordingly, the primary objective of this study was to characterize real-world safety, toxicity management, and resource utilization, with efficacy outcomes assessed as secondary, descriptive endpoints.

A total of 168 patients were included in this study. Median age was 64 years (range 26–86), 58% were diagnosed with LBCL, and 42% FL. Notably, 29% of the patients would not have met eligibility criteria for pivotal trials, with significant differences across histologies (35% in LBCL and 20% in FL [P = 0.04]). Ineligibility also varied across the different BsAbs (35% with epcoritamab, 21% with glofitamab, and 14% with mosunetuzumab [P = 0.05]) and was predominantly due to comorbidities (67%) and cytopenias (33%) (Table S1). The impact of trial eligibility on outcomes differed by histology, with ineligible patients showing inferior progression-free survival (PFS) in LBCL (2.38 [95% CI 1.33–4.17]; P = 0.003), while no significant differences were observed in FL. Although this pattern varied between FL and LBCL, formal interaction testing was not performed due to the limited number of events within each subgroup. Patients had received a median of three prior lines of therapy (range 2–7), and prior exposure to CAR-T-cell therapy was frequent, particularly in LBCL (54%). High-risk features were common, including primary refractory disease in LBCL (59%) and progression of disease within 24 months (POD24) in FL (52%). Detailed baseline characteristics are shown in Table S2.

During the step-up dosing phase, 86% of patients had a scheduled hospital admission due to the potential risk of CRS and neurotoxicity, with a median duration of scheduled inpatient stay of 4 days (range 1–20). Among them, 88 patients (61%) remained hospitalized throughout the entire step-up dosing phase, whereas the remaining 39% were hospitalized only for the administration of the full dose. Overall, unplanned hospitalizations occurred in 32% of patients. Among patients requiring urgent hospitalization (Table S3), the median time from initiation of BsAb therapy to admission was 25.5 days (range, 10.3–98.5). The main causes were infection (26 patients, 50%), disease-related complications (12 patients, 23%), CRS/neurotoxicity (9 patients, 17%), and other (5 patients, 10%). Factors associated with unplanned hospital admission included LBCL/high-grade histology, poorer performance status, shorter bendamustine washout, and higher extranodal disease burden. Inpatient treatment was almost universal in LBCL patients (98%), while mosunetuzumab in FL was administered outpatient more often (20%), although this rate still remained higher than expected. These patterns reflect the structured inpatient-to-outpatient transition currently adopted to ensure a safe ramp-up. The high proportion of hospitalizations throughout the entire step-up phase likely reflects a cautious approach during early implementation and appears higher than expected based on the known safety profile of BsAbs, suggesting that hospitalization strategies could be safely reduced as experience increases.

The safety profile was consistent with pivotal trial results and real-world data. CRS occurred in 42% of patients (45% epcoritamab, 45% glofitamab, and 48% mosunetuzumab), predominantly during Cycle 1 (97% [3% and 2% in Cycles 2 and 3, respectively]), and was Grade ≥3 in 2% (0% epcoritamab, 4% glofitamab, and 2% mosunetuzumab) (Table S4). Tocilizumab was administered in 31% of patients (median of 1 dose; no patient required more than 1) and corticosteroids in 37%, with a median duration of 3 days (range 1–12) (excluding the corticosteroid premedication required for step-up dosing). No cases of CRS were reported beyond Cycle 3, except for a single event occurring in Cycle 4.

Immune effector cell–associated neurotoxicity syndrome (ICANS) occurred in 4% of patients, almost exclusively Grade 1 (98%), with only one Grade 2 and one Grade 3 event. Half of the ICANS cases occurred in patients with prior CAR-T therapy, although all higher grade events were observed in CAR-T–naïve patients. This safety profile closely mirrors trial and real-world data, with frequent but mainly low-grade CRS and uncommon neurotoxicity.[8–10] Key adverse events, inpatient patterns, cumulative hospital stay, and intensive care unit (ICU) admission are presented in Table 1. Subgroup analyses of CRS and ICANS are provided in Figure S1 and show consistent toxicity rates across patient subsets.

Cytopenias and infections represented the main ongoing toxicities. Cytopenias occurred in 40% of patients (Grade ≥3 in 30%), and infections in 27% (Grade ≥3 in 10%), predominantly respiratory (60%) and mainly limited to the first cycles (74% in Cycles 1–2, 21% in

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TABLE 1 Summary of adverse events, supportive care, and healthcare resource utilization.

Category	Description	Full cohort (*N* = 167)
Cytopenias	Global, *n* (%)	66 (41)
	Global neutropenia *n* (%)	29 (18)
	Grade ≥3, neutropenia *n* (%)	21 (13)
	Global thrombocytopenia *n* (%)	31 (19)
	Grade ≥3 thrombocytopenia, *n* (%)	31 (19)
Infections	Global, *n* (%)	43 (27)
	Grade ≥3, *n* (%)	4 (10)
	Type of infection, %	
	Respiratory	80%
	Skin and mucose	12%
	Urinary	7%
	Others	5%
	Timing of infection onset, %	
	Cycles 1–2	74%
	Cycles 3–4	21%
	≥Cycle 5	5%
Supportive care	Tocilizumab use, *n* (%)	15 (31)
	Median number of doses, range	1 (1–1)
	Corticosteroid use, *n* (%)	22 (38)
	Median number of days, range	3 (1–12)
Healthcare utilization	Scheduled hospitalization, *n* (%)	142 (86)
	Median days, range	12 (1–92)
	Urgent hospitalization, *n* (%)	51 (32)
	ICU admission, *n* (%)	13 (8)
Mortality	Non-relapse mortality, *n* (%)	8 (6)

Note: No Grade 5 cytokine release syndrome (CRS) events and no Grade 4–5 immune effector cell–associated neurotoxicity syndrome (ICANS) were reported.

Abbreviation: ICU, intensive care unit.

Cycles 3–4, and 5% in Cycle 5 and beyond). These rates are comparable to reports describing neutropenia in up to 40% of patients and severe infections in 23%.[11–13] ICU admission occurred in 13 patients (8%), due to infections (*n* = 5), CRS (*n* = 5), or cardiac events (*n* = 1); 2 patients had an elective ICU admission for preventive monitoring during glofitamab administration. Non-relapse mortality (NRM) was 5.9%, largely driven by infections (80%), in line with pooled estimates (~4%–5%).[12,14] Taken together, immune-mediated toxicities were generally predictable and manageable, whereas infections and cytopenias represented the predominant clinical challenge, supporting structured prophylaxis, immunoglobulin replacement strategies, and vaccination.

In terms of efficacy, LBCL patients had an overall response rate (ORR) and complete response rate (CRR) of 43% and 23%, respectively (Figure 1). These outcomes are consistent with other real-world reports, including a recent US study (CRR 23%–30%, median PFS 2.6 months)[8] and the German–Austrian–Swiss effort, which showed comparable efficacy (ORR 47%, CRR 27%) and a median PFS of 3.6 months.[15] Similar to those analyses, our outcomes likely reflect a high-risk patient population, with a significant proportion of patients with primary refractory disease and prior CAR-T exposure. The median time from CAR-T therapy to BsAb initiation was 6.67 months (interquartile range [IQR] 3.09–11.57; range 1.38–48.10). Among the subset of LBCL patients previously treated with CAR-T (*N* = 52, 53%), ORR and CRR were 45% and 22%, confirming clinically meaningful activity in this subgroup. Patients with a time interval between CAR-T-cell infusion and bispecific start that was longer than the median showed a numerically higher CRR than those treated earlier after CAR-T failure (30% vs. 13%, P = 0.28). These findings are consistent with previously published data and further support the concept that early CAR-T failures are associated with a particularly poor prognosis, underscoring the need to prioritize these patients for clinical trial enrollment whenever feasible.

In FL, the response rate was higher (75% ORR, 49% CRR), in line with pivotal trials (5,5,7) showing ≈80% ORR and ≈60%–70% CRR. Among patients with previous CAR-T exposure (*n* = 7, 10%), ORR and CR rates were comparable to those observed in the overall FL population (67% and 50%), but should be interpreted with caution in light of the limited sample size. Response rates according to individual BsAbs are reported in Table S5.

After a median follow-up of 8.8 months, median PFS and overall survival (OS) in LBCL versus FL were 4 and 11 months versus 17 months and not reached, respectively. These findings reflect disease biology, with encouraging results in FL and more limited benefit in LBCL when BsAbs are used after multiple prior lines of treatment, supporting their current evaluation in earlier lines. Notably, HGBCL patients (*N* = 19) seemed to derive similar benefit from BsAbs compared to DLBCL, and in contrast to pivotal trial results, which usually presented poor outcomes in this high-risk subset.[4,6] Both response rates and survival outcomes are represented in Figures 1 and S2.

Risk factor analyses for PFS and OS are shown in Figures S3–S5 and demonstrate broadly consistent benefit across subgroups, including prior CAR-T exposure. Variables included in multivariable models were selected a priori based on clinical relevance rather than statistical significance. Given the exploratory nature and limited sample size, no formal variable selection was performed, and results should be interpreted with caution. Additional sensitivity analyses using more parsimonious model specifications showed consistent estimates across models (Table S7). Focusing on LBCL, older age was associated with longer PFS and OS in the multivariate analysis (hazard ratio [HR] 0.97 [95% CI 0.94–1], P = 0.031 and HR 0.96 [95% CI 0.95–0.98], P = 0.001), potentially reflecting a more stringent selection process for elderly patients in real-world practice. Prior bendamustine exposure did not influence outcomes in LBCL nor FL, similar to other BsAbs reports[16] and in contrast with the CAR-T setting, where prior exposure to this alkylating agent is associated with impaired efficacy.[17] Importantly, as shown in Table S2, most LBCL patients with prior bendamustine had received it within the last 9 months (75%), whereas this was the case for only 16% of FL patients. For FL, extranodal involvement showed a significant impact on PFS in the univariable analysis (HR 1.94 [95% CI 1.07–3.53], P = 0.003), confirmed in the multivariable model (HR 4.54 [95% CI 1.72–11.95], P = 0.002). Patients with ≥2 extranodal sites had a median PFS of 6.0 months (95% CI 5.1–NR), whereas median PFS was not reached in those with 0–1 extranodal sites (HR 3.40 [95% CI 1.52–7.54], P = 0.003; Figure S6). Table S6 shows the number and location of extranodal sites in FL patients. In contrast to LBCL, older age was associated with inferior PFS in the FL cohort (HR 1.39 [95% CI 1.06–1.92], P = 0.017), underscoring biological and clinical differences between indolent and aggressive lymphomas. Finally, POD24 did not influence BsAb outcomes, consistent with findings from the pivotal trial, suggesting that this T-cell-redirecting strategy may overcome traditional adverse prognostic features.

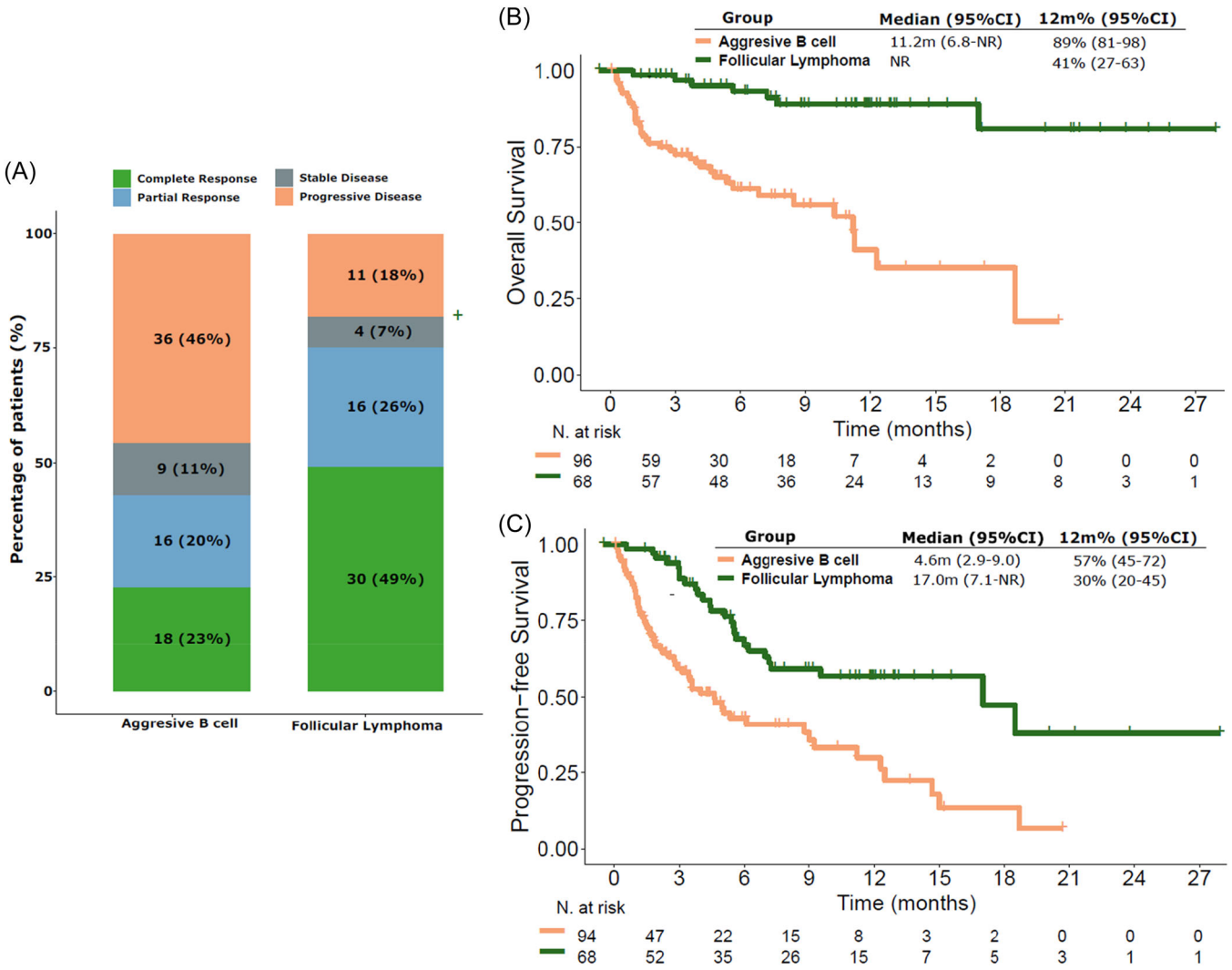

FIGURE 1 **Response and survival outcomes by histology in patients treated with bispecific antibodies. (A)** Response rates in large B-cell lymphoma (LBCL) and follicular lymphoma (FL). **(B)** Overall survival in LBCL and FL. **(C)** Progression-free survival in LBCL and FL.

As a real-world retrospective analysis, this study may be subject to under-reporting of adverse events, and response assessments were performed locally according to routine practice, without centralized radiologic review. On the other hand, although antiviral and *Pneumocystis jirovecii* prophylaxis and seasonal vaccination are recommended as standard of care in Spain, adherence to these measures could not be systematically verified at the individual patient or center level, which represents a limitation of this study and may have influenced infection-related outcomes.

In summary, this nationwide real-world study confirms that BsAbs are feasible in routine clinical practice, even outside academic centers. The safety and efficacy results were consistent with clinical trial and published real-world reports, with encouraging results in refractory and CAR-T-exposed subgroups. Notably, outcomes were particularly favorable in patents with FL, supporting the role of BsAbs as an effective treatment option in advanced lines. These findings also support the feasibility of BsAbs in a broader real-world population, including patients who would not meet eligibility criteria for pivotal trials, who represent a substantial proportion of those treated in routine practice. While in many healthcare systems the optimal sequencing of BsAbs versus CAR-T-cell therapy in FL remains an open clinical question, in Spain this decision is largely defined by reimbursement criteria, with BsAbs available in the third-line setting and CAR-T-cell therapy in the fourth line. Importantly, this analysis provides a detailed characterization of resource utilization and healthcare burden associated with BsAb therapy in routine clinical practice, an aspect that has not been thoroughly addressed in prior real-world studies. In this regard, the proportion of patients hospitalized throughout the entire step-up phase was high and likely reflects a cautious approach during early implementation. Based on both the known safety profile of BsAbs and the findings from our cohort, this rate appears higher than necessary for many patients and supports the development of more selective, outpatient-oriented strategies as experience grows.

The main clinical challenge did not seem to be immune-mediated events—largely predictable and manageable with structured step-up dosing—but cytopenias and infectious complications, supporting systematic prophylaxis, immunoglobulin monitoring, and coordinated multidisciplinary care.

Despite the high rate of planned hospitalization during the step-up phase, the incidence and severity of early immune toxicities suggest that inpatient use could be reduced. These findings support the

development of standardized outpatient pathways with early-intervention protocols, remote monitoring strategies, and predefined escalation criteria to safely minimize hospitalization during initial cycles.

Looking ahead, ongoing Phase III studies in first-line DLBCL and the recent approval of epcoritamab-based combinations in second-line and beyond FL[18,19] are expected to further redefine treatment algorithms in the coming years.

As BsAbs expand to earlier treatment lines and are administered outside of large, tertiary centers, real-world data such as these will remain essential to refine supportive care, optimize resource allocation, and ensure safe and equitable access to this transformative therapy.

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AUTHOR CONTRIBUTIONS

Mariana Bastos-Oreiro: Conceptualization; investigation; writing—original draft; methodology; writing—review and editing; data curation. **Gloria Iacoboni**: Conceptualization; investigation; writing—original draft; methodology; writing—review and editing; data curation. **Victor Navarro**: Formal analysis; visualization; data curation; methodology; software. **Carolina Martínez**: Investigation; writing—review and editing. **Pablo Manresa**: Investigation; writing—review and editing. **Laura Magnano**: Investigation; writing—review and editing. **Ana Jiménez-Ubieto**: Investigation; writing—review and editing. **Sofia Vázquez**: Investigation; writing—review and editing. **María Jose Rodriguez**: Investigation; writing—review and editing. **Maria Teresa Busnego**: Investigation; writing—review and editing. **Raquel Del Campo**: Investigation; writing—review and editing. **Pedro José Paúl**: Investigation; writing—review and editing. **Ilda Murillo**: Investigation; writing—review and editing. **Eva María Donato**: Investigation; writing—review and editing. **Angel Serna**: Investigation; writing—review and editing. **Hugo Luzardo**: Investigation; writing—review and editing. **Pilar Gómez**: Investigation; writing—review and editing. **Elena Pérez**: Investigation; writing—review and editing. **Begoña Mendibil**: Investigation; writing—review and editing. **Sergio Ramos**: Investigation; writing—review and editing. **Ana García-Noblejas**: Investigation; writing—review and editing. **Sonia Gonzalez de Villambrosia**: Investigation; writing—review and editing. **Francisco Javier Díaz**: Investigation; writing—review and editing. **Javier López**: Investigation; writing—review and editing. **Fernando Martín-Moro**: Investigation; writing—review and editing. **Paula Fernandez-Caldas**: Investigation; writing—review and editing. **Ruben Fernandez**: Investigation; writing—review and editing. **Antonio Gutierrez**: Investigation; writing—review and editing. **Blanca Sánchez**: Investigation; writing—review and editing. **Nazaret Domínguez**: Investigation; writing—review and editing. **María Civeira**: Investigation; writing—review and editing. **Paola Villafuerte**: Investigation; writing—review and editing. **Iñigo Olazabal**: Investigation; writing—review and editing. **Izaskun Zeberio**: Investigation; writing—review and editing. **Cristina Barrenetxea**: Investigation; writing—review and editing. **Norma Gutierrez**: Investigation; writing—review and editing. **Samuel Romero**: Investigation; writing—review and editing. **Sofía Martín-Consuegra**: Writing—review and editing; investigation. **Sofia Huerga**: Investigation; writing—review and editing. **Nuria Golbano**: Investigation; writing—review and editing. **Rosaía Riaza**: Investigation; writing—review and editing. **Jose Antonio Hueso**: Investigation; writing—review and editing. **Pilar Martinez-Barranco**: Writing—review and editing; investigation. **Belen Navarro**: Investigation; writing—review and editing. **Lucía Villalón**: Writing—review and editing; investigation. **Paula Ortega**: Writing—review and editing; investigation. **Ana Torres**: Writing—review and editing; investigation. **Iñigo Ormenazabal**: Writing—review and editing; investigation. **María Piva Sanchez Anton**: Investigation; writing—review and editing. **Maria Angeles Goñi**: Writing—review and editing; investigation. **Pau Abrisqueta**: Supervision; writing—original draft; writing—review and editing; conceptualization. **Alejandro Martín García-Sancho**: Writing—original draft; supervision; writing—review and editing; conceptualization.

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Mariana Bastos-Oreiro: Honoraria and/or consulting fees: AbbVie, AstraZeneca, Bristol Myers Squibb (BMS), Incyte, Kite/Gilead, and Roche. Research support: AbbVie, Incyte, Kite/Gilead, and Roche; this research funding is unrelated to the present study.

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All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This retrospective study was approved by the Ethics Committee of Vall d'Hebron University Hospital and conducted in accordance with the Declaration of Helsinki.

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Additional supporting information can be found in the online version of this article.

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