ABCL-102

# A SEER-Medicare analysis of the cost of disease progression after frontline (1L) R-CHOP in diffuse large B-cell lymphoma (DLBCL)

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## Summary

R-CHOP is the current standard of care for treatment of DLBCL; however, **30–40%** of patients **relapse** or are **refractory** to R-CHOP.[1]

The incremental per patient per month cost for patients with disease progression was **$8,026 higher** than for patients with no progression.

Effective treatments in 1L DLBCL could reduce the **economic burden** associated with disease progression.

The cost of disease progression per patient per month was five times higher among patients with disease progression who received **SCT/CAR-T ($15,075)** than for patients with no progression ($2,902).

## Background

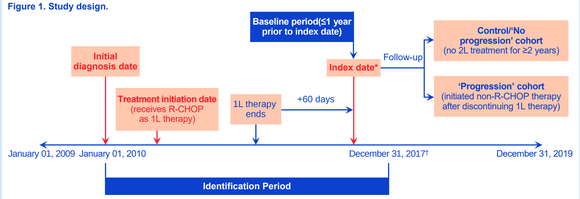
- Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is the current standard of care for the treatment of DLBCL; however, 30–40% of patients are refractory to, or relapse following treatment.[1]
- In the Phase 3 POLARIX study (NCT03274492), polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (Pola-R-CHP) significantly improved progression-free survival (hazard ratio: 0.73; 95% confidence interval [CI]: 0.57–0.95; p=0.02) vs R-CHOP in patients with previously untreated DLBCL and had an equivalent safety profile[2]
  - Pola-R-CHP has since been approved for this patient population in Europe,[3] which may change the treatment landscape in 1L DLBCL.
- Previous studies estimating the cost of disease progression following R-CHOP are outdated,[4–6] and do not account for current therapies for relapsed/refractory (R/R) DLBCL that are associated with considerable treatment costs, such as chimeric antigen receptor T-cell therapy (CAR-T).
- The primary objectives of this study were to estimate the incremental and cumulative costs for patients with DLBCL who experienced disease progression after 1L R-CHOP therapy vs those who did not, and to determine the drivers of disease progression costs, including treatments, pharmacy costs, hospitalizations, emergency department, and outpatient visits.
- Exploratory objectives were to estimate disease progression costs associated with novel therapies by assessing receipt of stem cell transplant (SCT) or CAR-T in later lines, and receipt of multiple lines of therapy.

## Methods

### Study design

- This was a retrospective cohort study using data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry from January 2009–December 2017, and the Medicare claims database from January 2009–December 2019.
- Patients aged ≥66 years who received 1L R-CHOP after initial DLBCL diagnosis from January 2010–December 2017 were included.
- The index date was defined as either 60 days after the end of 1L treatment, or the initiation of second-line (2L) treatment, whichever occurred first.[5] Using this definition as a proxy for progression, patients not receiving 2L treatments for ≥2 years were assigned to the 'no progression' cohort, and those who initiated non-R-CHOP therapy within 2 years after the end of 1L therapy were assigned to the 'progression' cohort (**Figure 1**).
- All patients were required to have continuous enrollment in Medicare Part A/B/D 1 year before and 2 years after the index date, allowing time for post-1L relapse.
- Patients who survived for ≥6 months after index and died within 2 years were included.
- Patient follow-up occurred until death, disenrollment, or the end of the study period.
- The primary analyses used data from patients who survived for ≥6 months from the index date. Sensitivity analyses were performed on data from patients who survived for ≥1 month from the index date.

**Figure 1. Study design.**




*The index date was defined as either 60 days after the end of 1L treatment, or the initiation of 2L treatment, whichever occurred first; †Patients with ≥2 years of follow-up from the index date were considered; patients who survived ≥6 months from the index date but who died within 2 years from the index date were included.
1L, frontline; 2L, second-line; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

### Study outcomes

- During the baseline period (≤1 year before index date), sex, age at index, race/ethnicity, US region, urban/rural status of residence, census tract median income, census tract education level, Ann Arbor stage at diagnosis, Charlson Comorbidity Index (CCI), and baseline total cost of care were assessed.
- Direct medical expenditure (cost) was measured based on payments (reimbursement amount plus total pass through amount) and beneficiary responsibility (co-payments and deductibles).
- Per patient per month (PPPM) cost was measured for individual patients to account for differences in follow-up time.
- PPPM cost and 4-year cumulative all-cause costs were compared between cohorts. All costs were adjusted to 2021 US dollars based on the 2021 Consumer Price Index for health services.

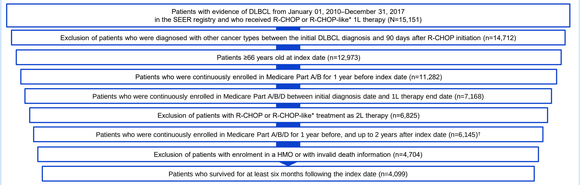
### Statistical analysis

- Descriptive statistics were used to describe unadjusted PPPM and 4-year cumulative costs.
- Generalized linear models (gamma distribution with log link) were performed to adjust for baseline characteristics and evaluate adjusted mean costs.[6]
- To understand the association between costs and 1) SCT and CAR-T and 2) number of subsequent lines of therapy, patients in the progression cohort were split into subgroups based on whether SCT or CAR-T was received, and by the number of lines of systemic therapy that were received following 1L R-CHOP.

## Results

- Overall, 4,099 patients with DLBCL who initiated R-CHOP or R-CHOP-like therapy were identified and included (**Figure 2**).
- Compared with patients in the 'no progression' cohort (n=3,389), patients in the 'progression' cohort (n=710) were slightly younger and had higher baseline total cost of care; the 'progression' cohort also included a greater proportion of patients diagnosed with later stage (or advanced stage) disease (**Table 1**).
- The overall mean duration of follow-up was 49.9 months.

**Figure 2. Inclusion and exclusion criteria.**




*R-CHOP or R-CHOP-like therapies were defined as regimens including rituximab and cyclophosphamide; †Patients who died within 2 years were included.
1L, frontline; DLBCL, diffuse large B-cell lymphoma; HMO, health maintenance organization; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; SEER, surveillance, epidemiology, and end results.

**Table 1. Patient characteristics.**

| | Overall (N=4,099) | 'No progression' cohort (n=3,389) | 'Progression' cohort' (n=710) | P-value* |
|---|---|---|---|---|
| **Female, n (%)** | 2,076 (51) | 1,731 (51) | 345 (49) | 0.2 |
| **Mean age at index, years (SD)** | 76.31 (6) | 76.42 (6) | 75.77 (6) | 0.01 |
| **Age category, n (%)** | | | | |
| 66–75 years | 1,980 (48) | 1,612 (48) | 368 (52) | 0.1 |
| 76–85 years | 1,754 (43) | 1,465 (43) | 289 (41) | |
| ≥86 years | 365 (9) | 312 (9) | 53 (7) | |
| **Race/ethnicity, n (%)** | | | | |
| Non-Hispanic white | 3,529 (86) | 2,926 (86) | 603 (85) | 0.6 |
| Non-Hispanic black | 100 (2) | 78 (2) | 22 (3) | |
| Non-Hispanic American Indian/Alaskan native | <11 | <11 | <11 | |
| Non-Hispanic Asia or Pacific Islander | 190 (5) | 153 (5) | 37 (5) | |
| Hispanic | 258 (6) | 212 (6) | 46 (7) | |
| Unknown | <11 | <11 | <11 | |
| **US Region, n (%)** | | | | 0.1 |
| Midwest | 435 (11) | 374 (11) | 61 (9) | |
| Northwest | 1,491 (36) | 1,215 (36) | 276 (39) | |
| South | 667 (16) | 560 (17) | 107 (15) | |
| West | 1,506 (37) | 1,240 (37) | 266 (37) | |
| **Ann Arbor stage, n (%)** | | | | <0.001 |
| Stage I/II | 1,878 (46) | 1,658 (49) | 220 (31) | |
| Stage III/IV | 2,054 (50) | 1,601 (47) | 453 (64) | |
| Unknown | 167 (4) | 130 (4) | 37 (5) | |
| **Urban/rural status, n (%)** | | | | 0.08 |
| Big metro | 2,367 (58) | 1,927 (57) | 440 (62) | |
| Metro | 1,090 (27) | 914 (27) | 176 (25) | |
| Urban | 226 (6) | 197 (6) | 29 (4) | |
| Less urban | 346 (8) | 294 (9) | 52 (7) | |
| Rural | 70 (2) | 57 (2) | 13 (2) | |
| **Census tract median income, mean USD (SD)** | 71,407 (34,399) | 71,270 (34,599) | 72,054 (33,456) | 0.3 |
| **Census tract % college education, mean (SD)** | 35.12 (20) | 34.96 (20) | 35.87 (21) | 0.4 |
| **Non-cancer CCI, mean (SD)** | 2.82 (2) | 2.80 (2) | 2.95 (2) | 0.09 |
| **Baseline total cost of care†, mean USD (SD)** | 124,531 (51,952) | 123,169 (52,252) | 131,033 (50,023) | <0.001 |

*Chi-square test of independence and Wilcoxon rank-sum tests were performed to estimate p-values for the progression vs no progression cohorts; †Total cost of care 1 year prior to index date to account for comorbidities that are not captured by CCI and access to care.
CCI, Charlson Comorbidity Index; SD, standard deviation; USD, US dollars.

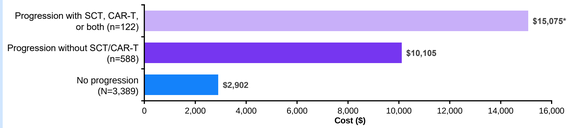
- Disease progression was associated with an incremental PPPM cost increase of $8,026 (**Table 2**)
  - For both cohorts, inpatient costs accounted for the largest proportion of total unadjusted costs (35% for progressors and 43% for non-progressors)
  - A cost driver for patients with progression vs those without was outpatient costs (27% for progressors vs 17% for non-progressors).
- Using change-in-therapy as a proxy for relapse, approximately half (n=360; 51%) of the patients in the 'progression' cohort had multiple relapse events (i.e. received ≥3 lines of anti-lymphoma therapy)
  - Cost of progression associated with multiple relapse events was >20% higher than that associated with a single relapse event (unadjusted mean PPPM cost: $11,940 vs $9,887; adjusted mean total cost: $12,197 vs $9,668, p<0.001; **Table 2**).
- In the 'progression' cohort, 119 (17%) patients received SCT, 12 (2%) received CAR-T.
- The cost for patients receiving SCT and/or CAR-T after disease progression following 1L R-CHOP was approximately five times greater than the cost for patients without progression (**Figures 3 and 4**).

**Table 2. Incremental PPPM cost associated with disease progression.**

| | 'No progression' cohort (n=3,389) | 'Progression' cohort (n=710) | Progression with 2 lines of therapy (n=350) | Progression with ≥3 lines of therapy (n=360) |
|---|---|---|---|---|
| **Unadjusted mean PPPM cost, USD (SD)** | 2,899 (3,852) | 10,928 (8,720) | 9,887 (8,276) | 11,940 (9,028) |
| Inpatient mean cost, USD (%) | 1,238 (43) | 3,817 (35) | 3,681 (37) | 3,950 (33) |
| Outpatient mean cost, USD (%) | 485 (17) | 2,921 (27) | 2,323 (24) | 3,502 (29) |
| Pharmacy mean cost, USD (%) | 273 (9) | 1,074 (10) | 811 (8) | 1,329 (11) |
| Physician services mean cost, USD (%) | 684 (24) | 2,715 (25) | 2,656 (27) | 2,773 (23) |
| Other cost, USD (%) | 218 (8) | 401 (4) | 416 (4) | 386 (3) |
| Paid out of pocket, USD (%) | 388 (13) | 1,388 (13) | 1,246 (13) | 1,526 (13) |
| Paid by Medicare, USD (%) | 2,511 (87) | 9,540 (87) | 8,641 (87) | 10,415 (87) |
| **Adjusted mean total costs, USD (95% CI)*** | 2,902 (2,372–3,561) | 10,928 (8,804–13,601) | 9,668 (7,654–12,242) | 12,197 (9,661–15,438) |
| **Difference in adjusted mean costs, USD (P-value†)** | N/A | 8,026 (p<0.001) | 6,766 (p<0.001) | 9,295 (p<0.001) |

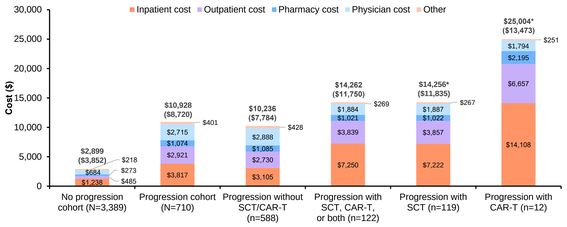
*Costs adjusted according to the following covariates: age, sex, US geographic region, urban/rural status, marital status, census tract median income, census tract % college education, Ann Arbor stage, CCI, and baseline total cost of care 1 year before index date (as a proxy for non-CCI comorbidities and/or access to care); †'Progression' vs 'No progression' cohort.
CCI, Charlson Comorbidity Index; CI, confidence interval; PPPM, per patient per month; SD, standard deviation; USD, US dollars.

**Figure 3. Adjusted incremental PPPM cost associated with SCT or CAR-T.**




Mean cost (SD) was reported; *Patients who received CAR-T were grouped with patients who received SCT; Covariate list: age, sex, US geographic region, urban/rural status, marital status, census tract median income, census tract % of college education, Ann Arbor stage, CCI, and baseline total cost of care 1 year before index date (as a proxy for non-CCI comorbidities and/or access to care).
CAR-T, chimeric antigen receptor T-cell therapy; CCI, Charlson Comorbidity Index; PPPM, per patient per month; SD, standard deviation; SCT, stem cell transplant.

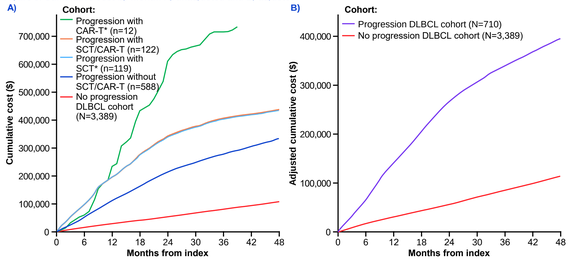
**Figure 4. Unadjusted incremental PPPM cost of disease progression with SCT or CAR-T.**




Mean cost (SD) was reported; *patients who received both SCT and CAR-T were included in both subgroups.
CAR-T, chimeric antigen receptor T-cell therapy; PPPM, per patient per month; SD, standard deviation; SCT, stem cell transplant.

- Similar trends in unadjusted and adjusted 4-year cumulative costs based on month of disease progression for patients in the no progression, progression, and SCT, CAR-T subgroups were observed (**Figures 5A and 5B**).

**Figure 5. Cumulative cost by month: A) unadjusted and B) adjusted.**




Cost was based on data from patients who had enrollment in the month and survived the month; *patients who received both SCT and CAR-T were included in both subgroups.
CAR-T, chimeric antigen receptor T-cell therapy; DLBCL, diffuse large B-cell lymphoma; SCT, stem cell transplant.

- In a sensitivity analysis including patients who survived ≥1 month after index date, unadjusted mean PPPM cost (USD [standard deviation]) was $4,406 ($8,162) vs $13,880 ($11,727) for patients with no progression vs patients with progression, respectively.
- Adjusted mean PPPM cost (USD [95% CI]) in the sensitivity analysis was $4,404 (3,419–5,699) vs $14,322 (10,940–18,823) for patients with no progression vs patients with progression, respectively (difference progression vs no progression: $9,918; p<0.001).

## Study limitations

- Findings may only be applicable to the Medicare insured population.
- There was a lack of additional clinical variables to control for in the multivariate model; unobserved variables could not be controlled for during the analysis.
- The differences in baseline characteristics (e.g. higher Ann Arbor stage and slightly higher baseline costs in the progression cohort) may overestimate the cost of disease progression; however, these variables were controlled for in the multivariate analysis.
- Limited CAR-T use is included in this dataset, which may change in future analyses.

## Conclusions

- The cost of disease progression in DLBCL is considerable, particularly among patients receiving SCT, CAR-T, or ≥3 lines of therapy.
- Future use of CAR-T and other novel agents in earlier lines of therapy may increase the cost of disease progression further; additional analyses are required to evaluate the economic impact of such therapies.
- More effective treatments in 1L DLBCL may reduce the economic burden associated with disease progression.
- Cost analyses of 1L treatment options should incorporate up-to-date estimates of the cost of disease progression, including costs associated with SCT and CAR-T.
- Future analyses including younger patients are required to determine the cost of disease progression among this patient population, which may be higher than the cost of progression presented in the current analysis.

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