P1447 INFERIOR OUTCOMES OF EU VS. US PATIENTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA AFTER CD19 CAR T-CELL THERAPY ARE IMPACTED BY BASELINE RISK FACTORS AND CAR PRODUCT CHOICE

**Topic:** Gene therapy, cellular immunotherapy and vaccination - Clinical

**Background:**
CD19 CAR T cells have significantly improved the prognosis of patients with relapsed/refractory (r/r) large B-cell lymphoma (LBCL). Real-world evidence (RWE) in the US has confirmed outcome data from pivotal trials. In contrast, several European consortia reported inferior real-world response rates and survival.

**Aims:**
To understand these divergent outcomes, we sought to characterize differences in patients treated with CD19 CAR T cells in Europe vs. the US.

**Methods:**
In this retrospective observational study, we assessed CAR T cell logistics, patient/disease characteristics, toxicities, response, and survival of r/r LBCL patients treated with Axi-cel or Tisa-cel at five EU and one US CAR T center. We evaluated variables for their association with PFS by univariate and multivariate stepwise Cox regression.

**Results:**
A total of 386 patients were included (EU: 175, USA: 211). Indeed, the objective response rate was lower in the EU (65% vs. 82% in the US, p<0.001). Median PFS (Fig. 1, 3 vs. 8 months, p<0.001) was significantly shorter for EU patients. Tisa-cel was applied more frequently in the EU cohort (74% vs. 14%, p<0.001).

In terms of baseline characteristics, median LDH (321 vs. 272 U/l, p=0.02) and ferritin levels (682 vs. 449 ng/ml, p=0.002) were significantly higher in the EU cohort. EU patients received fewer treatment lines (p=0.004), though the percentage of prior auto-SCT (35% vs. 18%, p<0.001) and active/history of CNS disease (17% vs. 7%, p=0.005) was higher. Analysis of CAR-T logistics revealed longer EU vein-to-vein intervals (43 vs. 28 days, p<0.001). The proportion of patients receiving “holding” therapy, defined as lymphoma treatment between indication-to-CAR and
apheresis, was comparable between EU and US centers (22% vs. 27%, p=0.32). However, significantly more patients were treated with bridging therapy (between apheresis and transfusion) in the EU (89% vs. 69%, p<0.001).

In univariate analyses, shorter PFS was associated (p<0.05) with lack of response to the latest therapy, longer indication-to-CAR intervals, higher ECOG, stage III/IV disease, IPI, extranodal disease (END), higher LDH, ferritin, CRP levels, and Tisa-cel use. On multivariate regression (n=319), ECOG (adjusted HR 1.4), ferritin (HR 1.5), refractory disease (HR 1.5), END (HR 1.4), and Tisa-cel use (HR 1.5) represented independent risk factors.

Of note, the aggregate of these four independent baseline risk factors (ECOG, ferritin, refractory disease, END) did not significantly differ between EU vs. US patients (p=0.18), indicating that product choice likely influenced the observed differences in PFS. Interestingly, although Axi- vs. Tisa-cel did not confer different outcomes for patients with 0-1 risk factors (p=0.47), Axi-cel led to significantly improved PFS compared to Tisa-cel in patients with 2-4 risk factors (p<0.001).

Summary/Conclusion: This is the first analysis to comprehensively compare CAR T cell treatment characteristics in Europe vs. the US in a large real-world cohort. Response rates and PFS were significantly inferior in the EU, potentially due to the use of Tisa-cel in adverse-risk patients. Our data suggest that Tisa- and Axi-cel are equally effective in low-risk patients (≤1 risk factor - ECOG, ferritin, refractory disease, END), but that Axi-cel facilitates improved outcomes in patients with 2-4 risk factors, with a representative toxicity profile.