Clinical Outcomes of Solid Organ Transplant Patients With EBV⁺ PTLD Who Fail First-line Rituximab or Rituximab Plus Chemotherapy: An Analysis of German PTLD Registry

Abstract # PF719

Heiner Zimmermann[1], Hairong Xu[2], Arie Barlev[3], Amy Feng[4], Xiaoming Li[4], Willis Navarro[5], Ralf Ulrich Trappe[1]

[1]Internal Medicine II: Haematology and Oncology, Diako Hospital, Bremen, Germany; [2]Health Economics and Market Access Research, Atara Biotherapeutics, Thousand Oaks; [3]Health Economics and Market Access Research, Atara Biotherapeutics, South San Francisco; [4]Biostatistics, Atara Biotherapeutics, Thousand Oaks, United States; [5]Clinical Development, Atara Biotherapeutics, Thousand Oaks, United States

BACKGROUND

- Post-transplant lymphoproliferative disorder (PTLD) is a rare complication that occurs as a consequence of immunosuppression after solid organ transplantation (SOT).
- Most cases of PTLD are associated with Epstein-Barr virus (EBV) infection of B cells, either due to reactivation of the virus after transplantation, or from primary EBV infection.
- The optimal management of patients (pts) with PTLD after solid organ transplant failing initial therapy is not established.
- The PTLD-1 trials showed that risk-stratified sequential treatment with 4 doses of rituximab induction followed by rituximab consolidation or 4 cycles of CHOP or R-CHOP chemotherapy (CT) yields favorable treatment outcomes and tolerable treatment-related mortality[1].
- Outcomes for those pts failing the PTLD-1 treatment scheme remain unclear.

AIMS

- To characterize outcomes for patients (pts) diagnosed with EBV⁺ PTLD post-SOT who are refractory to or relapsed after first line rituximab or rituximab plus chemotherapy in a real-world setting in Germany.

METHODS

- The German PTLD registry database was screened for pts with EBV⁺ PTLD post-SOT who received rituximab or rituximab plus CT during 2000-2015 and who were refractory (failed to achieve complete-CR or partial remission-PR) to rituximab or rituximab plus CT or relapsed at any point after such therapy.
- Patients with CNS PTLD at diagnosis were excluded.
- Medical charts were reviewed by an experienced physician and response to therapy was determined by computed tomography staging.
- Kaplan-Meier (KM) method was used to estimate the distribution of overall survival (OS) in this cohort and for the subgroup of patients who failed to respond to the first CT. The index date was defined as the date of last dose of first chemotherapy course.

RESULTS

- A total of 36 EBV⁺ PTLD patients were identified during the study period and included in the analysis with a median follow up time of 23.4 months (mos) from the date of PTLD diagnosis. Median age at PTLD diagnosis was 47.5 years (yrs) (range 18-75); median time to PTLD onset from transplant was 2.4 yrs (range 0.2-28). Patient characteristics are summarized in **Table 1**.
- Among the 36 patients, 24 (66.7%) died with a median overall survival (mOS) of 24.8 months (95% CI: 10.3-67.6) from PTLD diagnosis.
- 31 out of 36 patients received first CT regimen following rituximab (29 CHOP/R-CHOP, 2 other) and 5 pts did not receive first CT. Eighty percent of patients died among those who did not receive first CT compared to 64.5% among those who received first CT regimen following rituximab (**Figure 1**).
- Of the 31 patients who received first CT, 19 responded to CT with a mOS of 63 months; for the other 12 who failed to respond to first CT, mOS was 3.3 months (**Table 3; Figure 2**). For the 5 pts who did not receive first CT, mOS was less than 2 months from the date of disease progression.

RESULTS *(continued)*

Table 1: Patient Characteristics

Characteristics	Total cohort (N = 36)
Age at PTLD diagnosis (yrs), median (range)	47.5 (18–75)
Age at transplant (yrs), median (range)	39.7 (4–66)
Follow up from PTLD diagnosis (mos), median (range)	23.4 (2.7–155.5)
Female, n (%)	8 (22.2)
Transplant type, n (%)	
Kidney	18 (50)
Liver	8 (22)
Heart	4 (11)
Lung	3 (8.3)
Intestine	1 (2.8)
Multiple organs	2 (5.6)
PTLD histology type, n (%)	
DLBCL	22 (61.1)
Polymorphic	6 (16.7)
Burkitt	3 (8.3)
Other*	5 (13.9)
PTLD onset time from transplant (yrs), median (range)	2.4 (0.2–28)
CD 20 negative at diagnosis	2 (5.6)
N of extra nodal sites ≥ 3	10 (27.8)

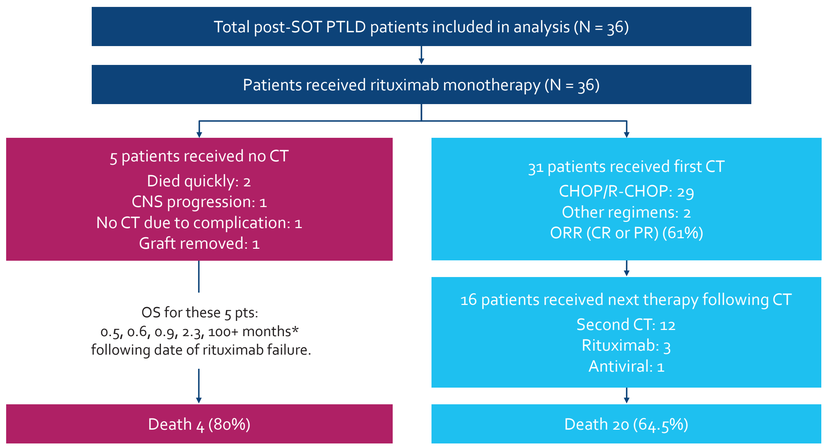
*Other histology type includes: High grade B cell lymphoma 2, Hodgkin lymphoma 2, Plasmablastic lymphoma 1.

Table 2: Death and Causes of Death

	No. of patients, n (%)
Total n of death	24 (66.7)
Causes of death, n (%)	
PTLD disease progression	12 (50)
Treatment related	6 (25)
Organ failure	2 (8.3)
Other causes*	4 (16.7)

*Other causes of death include: Sepsis/Infection 1, Diabetes 1, Unknown cause 1, Complication of surgery 1.

Figure 1: Post-SOT PTLD Treatment Patterns



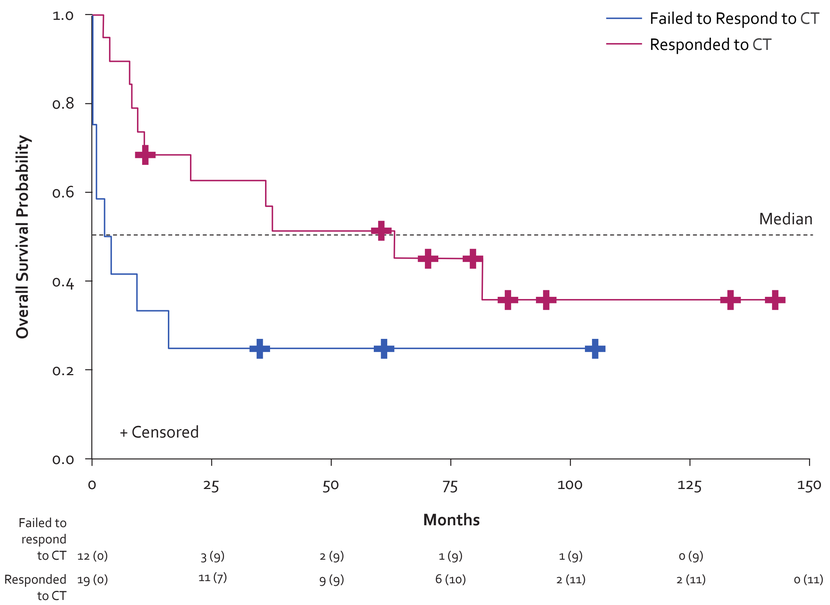
*Patient with 100+ months survival had kidney graft was removed and re-initiated back dialysis.

Table 3: OS by Responders vs Non-responders to First Course of Chemotherapy (N = 31)

	Responders (N = 19)	Non-Responders (N = 12)	Total (N = 31)
Death – n (%)	11 (57.9)	9 (75)	20 (64.5)
OS KM estimator – Median (95% CI)	63.2 (9.3, NE)	3.3 (0.3, NE)	20.5 (7.7–81.4)
OS Rate (%)			
At 12 months	68.4 (42.8, 84.4)	33.3 (10.3, 58.8)	54.8 (36.0, 70.3)
At 24 months	62.7 (37.2, 80.2)	25.0 (6.0, 50.5)	48.0 (29.7, 64.1)

Index date: The date of last dose of first chemotherapy course. NE = not evaluable.

Figure 2: Kaplan-Meier Analysis of EBV⁺ PTLD Post-SOT Patients Receiving Rituximab Plus CT (N = 31)



CONCLUSIONS

- **Patients who failed to respond or did not receive first CT had a mOS of < 3 months.**
- **Two-thirds of rituximab failure patients ultimately died; half of the deaths were from PTLD and 25% were from treatment-related causes.**
- **There remains a significant unmet medical need for EBV⁺ PTLD pts who fail to respond to initial treatment with rituximab.**

REFERENCES

1. Trappe, et al. Response to Rituximab Induction Is a Predictive Marker in B-Cell Post-Transplant Lymphoproliferative Disorder and Allows Successful Stratification Into Rituximab or R-CHOP Consolidation in an International, Prospective, Multicenter Phase II Trial. *J Clin Oncol.* 35:536-543.