A Comparison of Clinical Outcomes from Updated ZUMA-5 (Axicabtagene Ciloleucel) and the International SCHOLAR-5 External Control Cohort in Relapsed/Refractory Follicular Lymphoma (r/r FL)

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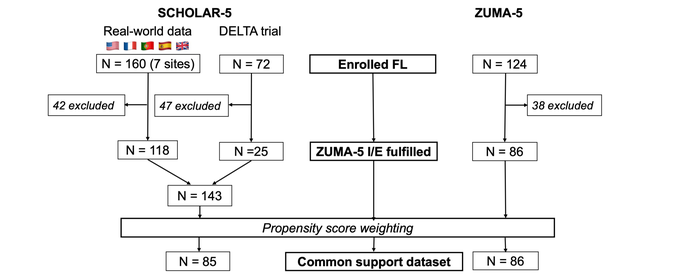
INTRODUCTION

- In the pivotal ZUMA-5 single-arm trial,[1] axicabtagene ciloleucel (axi-cel; an autologous anti-CD19 chimeric antigen receptor T-cell therapy) demonstrated high rates of durable response in r/r FL patients, including those with high-risk disease.
- The international SCHOLAR-5 external cohort was constructed to allow the comparison of ZUMA-5 to alternative available therapies for r/r FL.
- A previous weighted analysis including 18-month ZUMA-5 data, compared to SCHOLAR-5 data, showed a substantial clinical benefit of axi-cel in overall response rate (ORR), complete response (CR), progression-free survival (PFS), and overall survival (OS).[2]
- Here, we present an updated comparative analysis using 24-month ZUMA-5.

METHODS

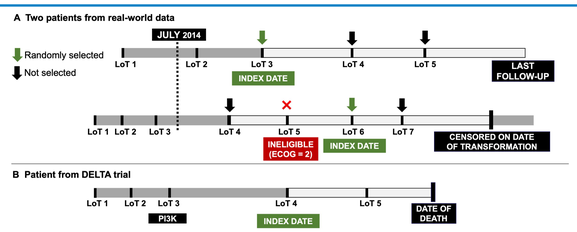
- The international SCHOLAR-5 cohort data were extracted for r/r FL patients who initiated a third or higher line of therapy (LoT) on or after July 2014 **(Figure 1)**. Anti-CD20 monoclonal antibody monotherapy (e.g. rituximab) was not an eligible LoT and did not count towards prior LoTs.

Figure 1. Patient enrollment, selection, and analysis



- For the real-world data, lines that were eligible for inclusion in the analysis were entered into a random selection. A single LoT for each patient was included in the analysis set **(Figure 2)**.

Figure 2. LoT selection for real-world data



- The SCHOLAR-5 and ZUMA-5 cohorts were balanced (standardized mean difference [SMD] <0.1) for patient characteristics through propensity scoring on prespecified prognostic factors and standardized mortality ratio weighting.[3]
- ORR was compared using odds ratio. OS, PFS and next treatment-free survival (NTFS; time to next treatment or death) were evaluated using Kaplan-Meier analysis.
- Subgroup analyses were conducted on patients who initiated ≥4th LoT.

RESULTS

- 143 patients were identified in SCHOLAR-5, reducing to a weighted sum of 85 after applying propensity score weights, versus 86 patients in ZUMA-5 **(Table 1)**.
- Median follow-up time for ZUMA-5 and SCHOLAR-5 were 29.4 and 26.2 months respectively.
- Variables that were successfully balanced (SMD <0.1) included POD24, number of prior LoT, relapsed vs refractory, prior stem cell transplant, size of largest nodal mass, response to prior LoT, time since last therapy and age (**Table 1**).
- ECOG was not balanced, though it was limited to 0-1. We were unable to assess potential imbalance in FLIPI and disease stage due to the extent of missing data

Table 1. Patient characteristics before and after propensity weighting

		SCHOLAR-5 before weighting (n = 143)	ZUMA-5 (n = 86)	SCHOLAR-5 after weighting (n = 85)	SMD (p-value)
Median age (range), years		64 (36 – 89)	62 (34 – 79)	61 (36 – 89)	0.036 (.85)
Male, n (%)		81 (56.6%)	48 (55.8%)	53 (61.9%)	0.123 (.46)
POD24, n (%)		51 (35.7%)	49 (57.0%)	47 (55.9%)	0.022 (.90)
Prior lines of therapy, median (range)		2 (2-8)	3 (2-9)	3 (2-8)	0.047 (.81)
Refractory to prior line, n (%)		87 (60.6%)	63 (73.3%)	65 (76.6%)	0.077 (.61)
Prior SCT, n (%)		31 (21.7%)	21 (24.4%)	24 (28.0%)	0.080 (.64)
Size of largest nodal mass (cm)*		4.16 (2.75 – 6.50)	4.35 (3.27 – 6.43)	4.02 (2.90 – 6.25)	0.094 (.59)
Time since last therapy (months)*		6.76 (1.16 – 22.66)	3.53 (1.77 – 9.01)	2.30 (0.69-7.99)	0.056 (.67)
Time since diagnosis (months)*		84.79 (52.99 – 130.47)	59.86 (35.10– 96.62)	64.55 (40.96 – 115.79)	0.100 (.52)
ECOG, n (%):	0	39 (33.1%)	51 (59.3%)	21 (29.0%)	0.640 (.002)
	1	79 (66.9%)	35 (40.7%)	51 (71.0%)	

* Median and inter-quartile range ; ECOG, Eastern Co-operative Oncology Group performance; POD24: Having progressed within 24 months of first-line anti-CD20 monoclonal antibody and chemotherapy combination; SCT, stem-cell transplant.

Table 2. Comparison of Response outcomes

		SCHOLAR-5	ZUMA-5	Odds ratio	P value
Primary analysis: ≥ 3rd LoT	ORR	42/85 (**49.9%**)	81/86 (**94.2%**)	16.2 (5.6, 46.9)	< .001
	CR	25/85 (**29.9%**)*	68/86 (**79.1%**)**	8.85 (4.3, 18.25)	< .001
Sub-group analysis: ≥ 4th LoT	ORR	24/59 (**40.3%**)	57/60 (**95%**)	28.14 (7.38, 107.33)	< .001
	CR	12/59 (**20.6%**)*	48/60 (**80%**)	15.42 (5.82, 40.83)	< .001

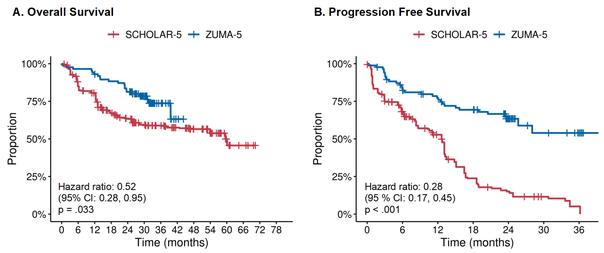
* Response assessment includes CT-based and PET-Based scans with limited confirmatory bone marrow biopsy; **13 patients with imaging CRs did not receive confirmatory bone marrow biopsy
CR, complete response; LoT, line of treatment; ORR, overall response rate.

Table 3. Comparison of time-to-event outcomes

		24 months % (95% CI)		Median months (95% CI)		Hazard ratio (95% CI)	p-value
		SCHOLAR-5	ZUMA-5	SCHOLAR-5	ZUMA-5		
Primary analysis: ≥ 3rd LoT	OS	63.4 (50.3, 76.4)	81.2 (71.2, 88.1)	59.8 (21.9, -)	NR (39.6, -)	0.52 (0.28, 0.95)	.033
	PFS	15.0 (4.8, 25.2)	63.4 (51.6, 73.0)	12.7 (6.2, 14.7)	39.6 (25.7, -)	0.28 (0.17, 0.45)	<0.001
	NTFS	49.5 (36.3, 62.7)	63.8 (52.7, 73.0)	14.4 (6.2, 25.8)	39.6 (28.0, -)	0.58 (0.36, 0.95)	.031
Sub-group analysis: ≥ 4th LoT	OS	51.5 (36.2, 66.8)	79.8 (67.1, 88.0)	28.4 (12.3, -)	NR (39.6, -)	0.43 (0.23, 0.81)	.010
	PFS	5.7 (0, 12.2)	59.0 (44.5, 71.0)	3.5 (1.8, 12.9)	28.0 (20.5, -)	0.20 (0.12, 0.33)	<.001
	NTFS	43.3 (28.0, 58.6)	59.8 (46.2, 70.9)	14.2 (5.8, -)	39.6 (22.8, -)	0.58 (0.33, 1.00)	.051

LoT, line of treatment; NTFS, next treatment-free survival; OS, overall survival; PFS, progression-free survival.

Figure 3. Time-to-event outcomes



Kaplan-Meier curves showing survival outcomes in ZUMA-5 (blue), compared to SCHOLAR-5 (red).

- ORR and CR were higher in ZUMA-5 compared to SCHOLAR-5. In the sub-group analysis of ≥4th LoT patients, which compared 60 patients from ZUMA-5 to 59 patients from SCHOLAR-5, these differences were more pronounced **(Table 2)**.
- The median OS was not reached in ZUMA-5, while median PFS was 39.6 months. In SCHOLAR-5 median OS and PFS were 59.8 months and 12.7 months, respectively **(Table 3)**. The hazard ratios for OS and PFS were both clinically and statistically significant **(Figure 3)**. In the sub-group analysis of ≥4th LoT patients, improvements in OS and PFS outcomes were more pronounced **(Table 3)**.
- Within the real-word cohort of SCHOLAR-5, outcomes were analyzed by LoT **(Table 4).** In line with existing data,[4,5] quality and duration of clinical response decreased with increasing LoTs. Due to sample size, all ≥5 LoT were included in one model. Given that response and progression are line-specific, a repeated-measures analysis with mixed-effects was used (i.e., LoT 5 and 6 were used if a patient was eligible for both). For OS, only the first ≥5 LoT was used because the event, death, is shared by all LoTs.

Table 4. SCHOLAR-5 outcomes by LoT

		3rd LoT	4th LoT	≥ 5th LoT
Response outcomes				
ORR	N responders % (95% CI)	59/89 66.3% (55.5, 76.0)	26/49 53.1% (38.3, 67.5)	13/35 37.4% (22.1, 55.7)
CR	N responders % (95% CI)	38/89 42.7% (32.3, 53.6)	16/49 32.7% (19.9, 47.5)	6/35 17.1% (7.9, 33.3)
Time-to-event outcomes				
		N = 98	N = 52	N = 27
OS	Median months (95% CI)	NR (53.2 – NE)	30.4 (22.3 – NE)	13.1 (12.0 – NE)
	24 months % (95% CI)	79.6 (71.5 – 88.5)	57.3 (44.4 – 73.8)	36.1 (21.7, 60.1)
PFS	Median months (95% CI)	11.0 (8.6, 17.1)	7.4 (5.3, 15.1)	4.0 (3.1, 11.4)
	24 months % (95% CI)	20.4 (11.9 – 35.2)	11.5 (4.6 – 28.5)	3.5 (0.6, 22.6)
NTFS	Median months (95% CI)	21.2 (16.3 – 41.9)	22.9 (9.1 – NE)	8.7 (4.3 – 16.7)
	24 months % (95% CI)	48.3 (38.7 – 60.3)	46.2 (33.7 – 63.3)	22.38 (12.6 – 39.8)

CR, complete response; LoT, line of treatment; NTFS, next treatment-free survival; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

CONCLUSIONS

- Compared to currently available therapies in r/r FL patients, axi-cel demonstrated a clinically and statistically significant improvement in overall response rate and complete response.
- Similarly, axi-cel demonstrated a clinically and statistically significant improvement PFS, NTFS and OS, highlighting the durable treatment effect of axi-cel.
- Analysis of real-world outcomes show poor clinical outcomes that worsen with increasing LoT.
- These findings suggest that axi-cel addresses an important unmet medical need for r/r FL patients.

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DISCLOSURES

MLP, holding individual stocks and stock options from Seres and Notch, receiving consulting fees from Novartis, Kite, PCYC, and BeiGene, research funding from Seres, patents and royalty fees from Seres, Juno, Wolters, and Kluwer; **PG MTR,** reports no conflict of interest; **AP, ASJ, JTS, MN,** current employment at and holding stock and stock options from Kite, a Gilead company; **SB**, receiving fees for serving on a speakers' bureau from Roche and Gilead, consulting fees from Roche; **KD, AJH**, current employment at Delta Hat; **CAJ**, receiving consulting fees and honoraria from AbbVie, Bristol Myers Squibb/Celgene Corporation, Nkarta, Inc., Novartis Pharmaceuticals Corporation, Precision Biosciences, Kite, a Gilead Company, Lonza, Pfizer, Celgene, and Humanigen, honoraria from bluebird bio and Epizyme, travel support from Novartis Pharmaceuticals Corporation, Precision Biosciences, Kite, a Gilead Company, and Lonza, research funding from Kite, a Gilead Company and Pfizer, membership on Board of Directors or advisory committees for Ipsen, fees for serving on the speakers' bureau from Axis and Clinical Care Options, other fees and/or funding from Celgene, Pfizer, and Humanigen; **SK, EHLO**, current employment at RainCity Analytics; **SSN**, receiving honoraria from Kite, Merck, BMS, Novartis, Celgene, Pfizer Allogene Therapeutics, CellMedica/Kuur, Incyte, Precision Biosciences, Legend Biotech, Adicet Bio, Calibr, Unum Therapeutics, and Buebird Bio, patents and royalty fees from Takeda Pharmaceuticals, research funding from Kite, a Gilead Company, Bristol Myers Squibb, Merck, Poseida, Cellectis, Celgene, Karus Therapeutics, Unum Therapeutics (Cogent Biosciences), Allogene, Precision BioSciences, Acerta, and Adicet Bio, personal fees from Kite, a Gilead Company, Merck, Bristol Myers Squibb, Novartis, Celgene, Pfizer, Allogene, Kuur, Incyte, Precision BioSciences, Legend, Adicet Bio, Calibr, and Unum Therapeutics; **HG**, receiving consulting fees from Gilead Science, Celgene, Roche, and Mundipharma, honoraria from Gilead Science, Celgene, Mundipharma, and Janssen; AB has served as a scientific advisor to AbbVie, Amgen, Inc, The Birgham and Women's Hospital, Fibrogen, Genentech, Gilead, Merck, RxAnte, TargetPharma, World Health Informaion Consultants, and holds equity in NoviSci Inc; **JR**, receiving consulting fees from Takeda, ADCT, BMS, and Novartis, honoraria from Takeda, ADCT, and BMS, fees for serving on the speakers' bureau from Takeda and ADCT, research funding from Takeda, holding stocks or other ownerships on ADC Therapeutics and AstraZeneca; **JG**, receiving consulting fees from AbbVie, Acerta Group Limited/AstraZeneca, Bristol Myers Squibb/ Celgene Corporation, Janssenn Karyopharm, Morphosys AG, Novartis, and TG Therapeutics, research funding from Acerta Group Limited/AstraZeneca, Bristol Myers Squibb/ Celgene Corporation, and Janssen. **SWW:** Consultant or advisory role: Kite Pharma, Amgen, Allergan