

Efficacy, Safety, and Patient-Reported Outcomes (PROs) of Treatments for Relapsed/Refractory Follicular Lymphoma (R/R FL) in the Third-Line or Later (3L+) Setting: A Systematic Literature Review (SLR)

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Background

FL is the second most common non-Hodgkin lymphoma (NHL) and the most common indolent NHL subtype, accounting for 70% of low-grade diagnoses^{1,2}

- Approximately 20% of patients will relapse within 24 months after first-line treatment^{1,3}
- Upon relapse, there is no well-defined standard of care, particularly in the 3L+ setting. Novel treatments evaluated in trials or recently approved by regulators in this space include chimeric antigen receptor T-cell therapy (CAR-T), EZH2 inhibitors (EZH2), and PI3K inhibitors (PI3K). Rituximab (R), an anti-CD20 monoclonal antibody, has traditionally been a treatment option for R/R FL patients as well¹⁻³
- There is no well-defined standard of care in 3L+ R/R FL, and systematic literature reviews (SLRs) in this population are currently lacking. It is important to evaluate the literature to appropriately assess currently available treatments⁴⁻⁶

Objective

- To conduct a SLR evaluating the efficacy, safety, and PROs of treatments for 3L+ R/R FL

Materials & Methods

Data sources

- The following electronic databases were searched in November 2020
 - MEDLINE® and MEDLINE® In-Process
 - Embase®
 - Cochrane
- Conference proceedings were hand-searched for the last 3 years (2018–2020) to identify abstracts of interest
 - American Society of Clinical Oncology
 - European Society for Medical Oncology
 - American Society of Hematology
 - European Hematology Association

Study eligibility

- All studies in R/R FL were included at the title/abstract screening stage, regardless of line of therapy
- During the full text screening phase, only studies in patients who have relapsed or are refractory to at least 2 prior lines of therapy, including an anti-CD20 antibody or an alkylating agent, were included
- Intervention/comparator: systemic therapies with/without control arm
 - In this poster, only interventions of interest are presented
- Study design: randomized and non-randomized clinical trials, single-arm trials
- Outcomes: response, survival, safety, PROs
- Only materials published in English were eligible
- Only studies in the 3L+ setting were included for data extraction

Results

- After screening of 7,330 records, 78 publications inclusive of 24 unique studies were identified. Following screening, studies were characterized by line of treatment and the observed response/survival rates, safety, and PROs from the studies were summarized
- Seven studies of 3L+ R/R FL reported interventions of interest (Figure 1) including anti-CD20 monoclonal antibodies (R: 1 study), PI3K (4 studies), EZH2 (1 study), and CAR T cell therapy (1 study)
- Efficacy outcomes
 - Efficacy outcomes and categories reported varied by drug class. Commonly reported efficacy outcomes categories included objective response rates (ORR; Figure 2), median duration of response (mDOR), median progression-free survival, and median overall survival (mPFS, mOS; summarized in Table 1)
 - ORRs were lowest for the R study at 38%, ranged from 42% to 59% for PI3K studies, and were highest in the CAR-T study at 85%
 - The mDOR was lowest for PI3K and EZH2 studies and highest for R and CAR-T studies
 - mPFS was available for PI3K and EZH2 studies with EZH2 having higher mPFS
 - mOS was available for PI3K, EZH2, and CAR-T studies with the majority showing that OS was not reached
- Safety outcomes
 - Safety profiles varied by drug class. Commonly reported safety outcome categories across publications included hematological and nonhematological adverse events and treatment-emergent adverse events (TEAEs)
- Where available, the incidence of Grade ≥3 TEAEs by drug class and study are shown in Figure 2
- PROs
 - PRO data was reported in one study and the overall HRQoL reported to be stable or improved in patients treated with idelalisib (PI3K) monotherapy

Figure 1. Number of publications including interventions of interest by drug class

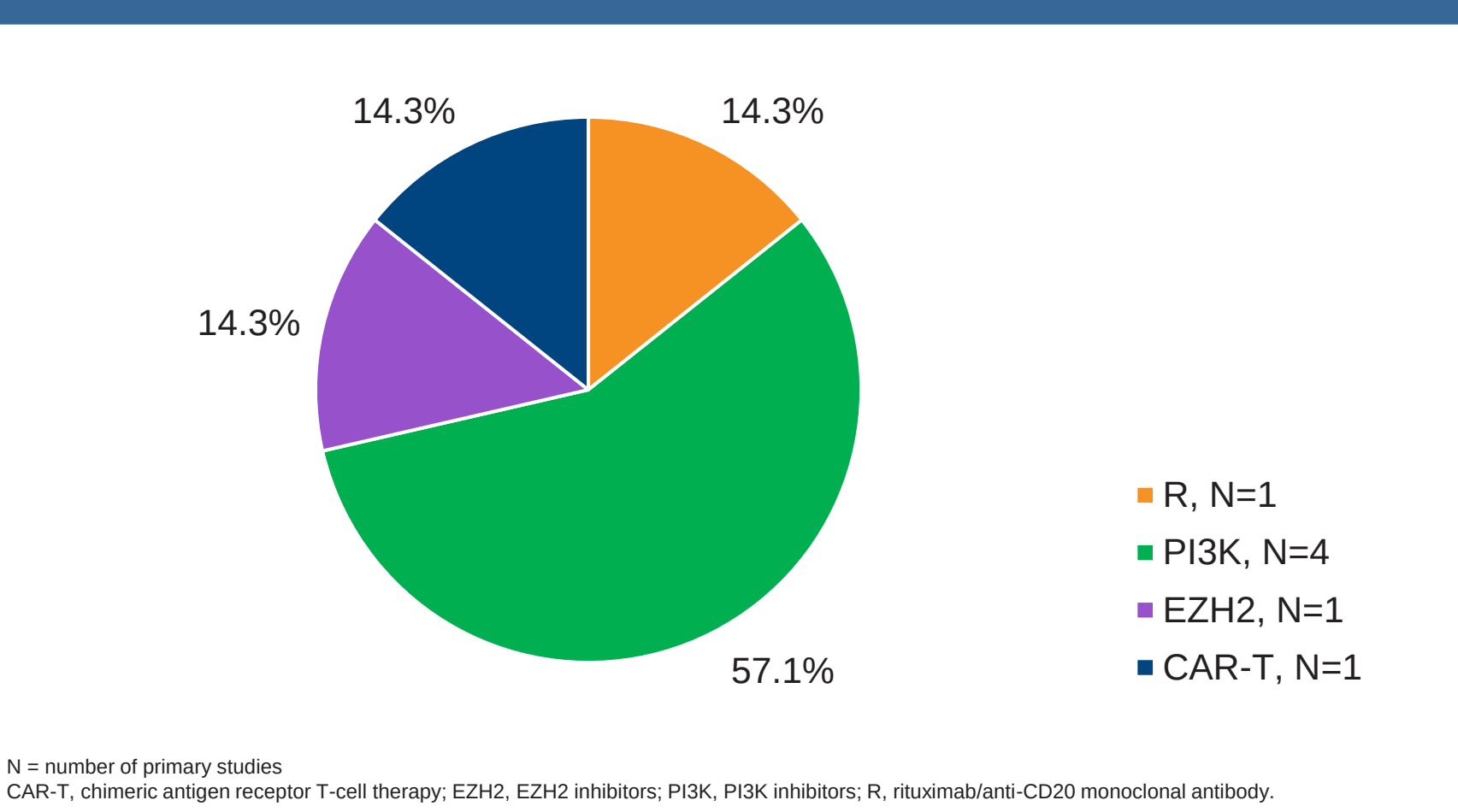


Figure 2. ORR and CR rates by drug class and trial

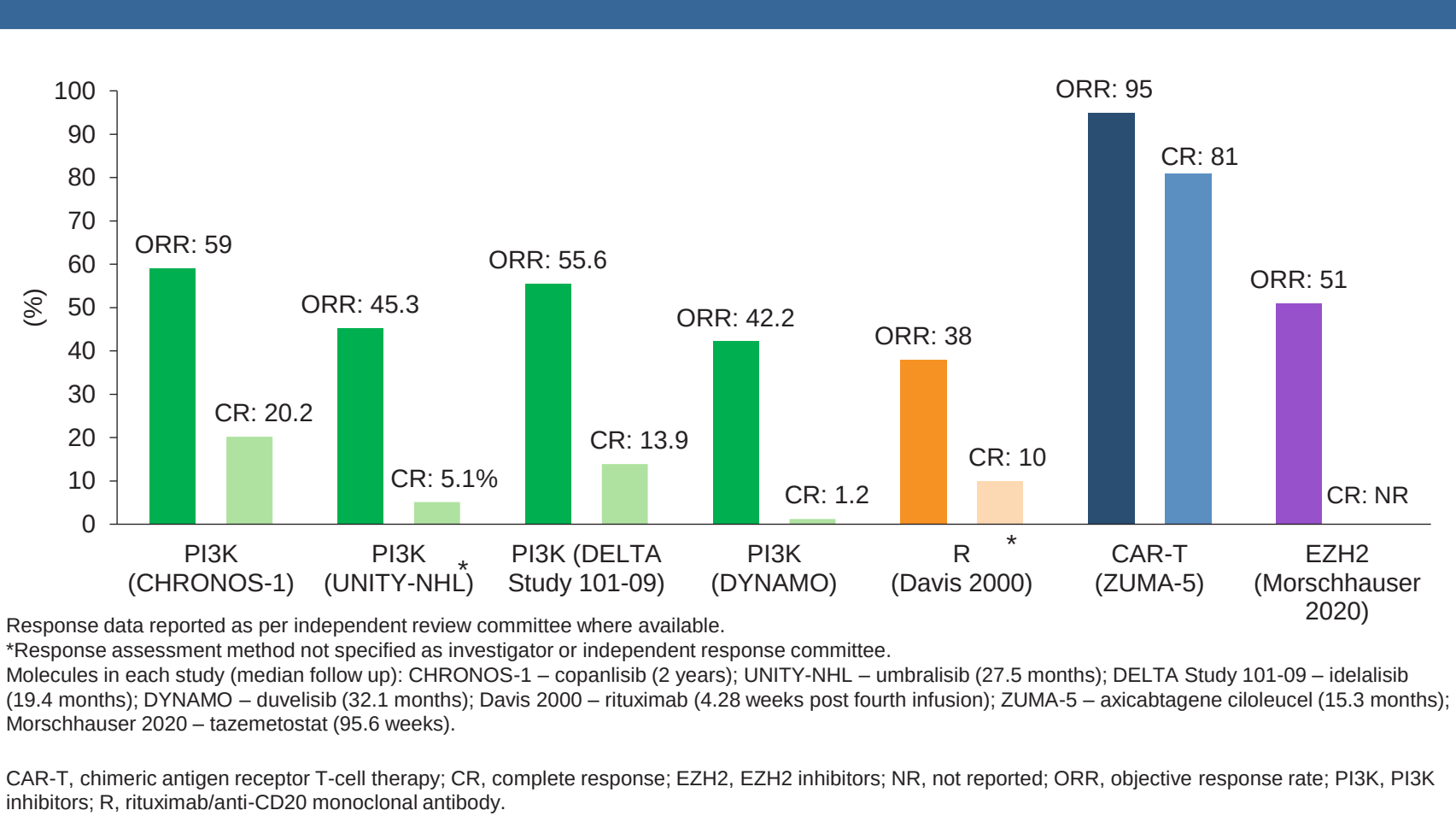


Figure 3. Incidence of Grade ≥3 TEAEs by drug class and trial

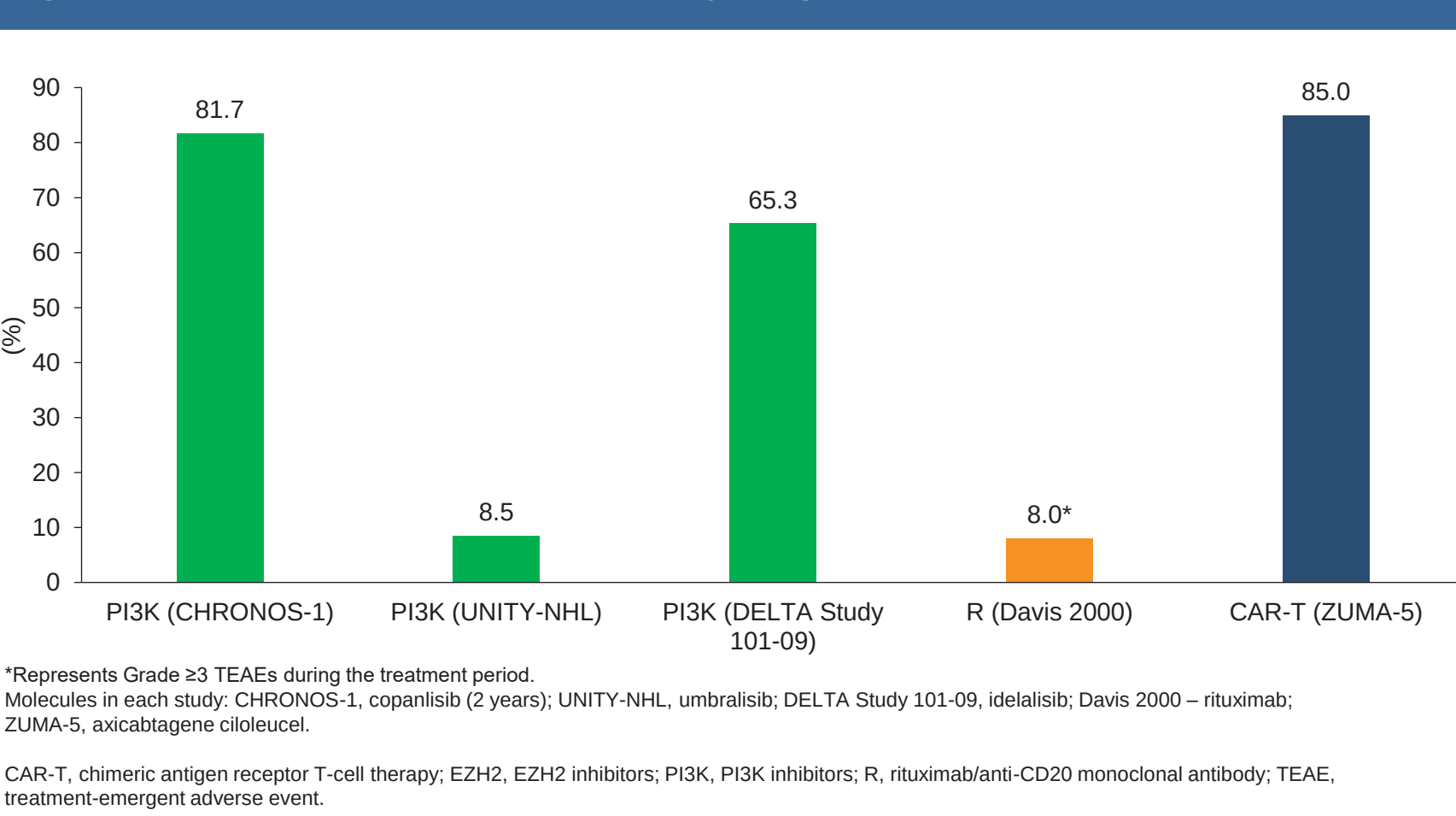


Table 1. Summary of trials reporting clinical outcomes of 3L+ treatments for R/R FL

Treatment; Drug class	Trial Name (Author & Year)	Study design details; N allocated	Median FU; cut-off date	Median no. of prior lines of therapy	Efficacy results			Safety results
					Median DoR (weeks) (95% CI)	Median PFS (months) (95% CI) Rate by month/year	Median OS (months) (95% CI) Rate by year	
Copanlisib (PI3K)	CHRONOS-1 (Dreyling 2017) ^{7,8}	Ph 2 single arm, OL, MC, international; N=104	2 yrs; Safety FU: 24 wks (range 1–104) Feb 2018	3 (range 2–8)	53.01 (33.02–96.90)	11.2 (8.1–17.6) 2 yr rate: 33%	38.3 (28.5–not estimable); 2 yr rate: 67%	98.1% (81.7%) Hyperglycemia: 40.4%; hypertension: 23.1%; neutropenia: 23%; pneumonia: 11.5% Grade 5 AE: 4.8%
Umbralisib (PI3K)	UNITY-NHL (Fowler 2021) ⁹	Ph 2 single arm, OL, MC, international; N=117	27.5 mo (range 20.9–37.1); Safety FU: 21.4 mo (range 14.6–30.8) Jan 1, 2020	3 (range 1–10); 1: 13.7% 2: 28.2% 3: 21.4% >3: 36.8%	48.23 (36.06–67.78)	10.6 (7.2–13.7); 6 mo rate: 68.3% 12 mo rate: 45.9% 18 mo rate: 31.9% 24 mo rate: 18.1%	Not reported	12.8% (8.5%); Diarrhea: 2.6%; neutropenia: 0.9%;
Rituximab (R)	Not reported (Davis 2000) ¹⁰	Single arm; ITT N=60 Assessable, N=57	After the 4 th infusion: 4.28 wks Not reported	4 (range 2–11)	70.82 [30-day FU]	Not reported	Not reported	Not reported (During study treatment: 8%; follow up: 3%) hAEs Grade 3/4: n=5 [data reported for >2% of pts]
Idelalisib (PI3K)	DELTA Study 101-09 (Salles 2017) ¹¹	Ph 2 single arm, OL, MC, international; N=72	19.4 mo Not reported	4 (range 2–12)	46.93	11 (8–14); 2 yr rate: 43%	61.2 (38.1–not estimable)*; 2 yr rate: 69.8%	98.6% (65.3%); Neutropenia: 22.2%; fever/pyrexia: 4.2%; anemia: 2.8%; [data reported for ≥10% of pts]
Axicabtagene ciloleucel (CAR-T)	ZUMA-5 (Jacobson 2020) ¹²	Ph 2 single arm, MC, USA ^a N=124	Efficacy FU: 15.3 mo (range 1.9–28.8) Safety FU: 12.8 mo (range 1.9–28.8) Nor reported	3 (range 2–9); ≥3: 70%	90.38 (85.6–Not estimable)	Not reported	Not reached (not estimable–not estimable); 1 yr rate: 93.4%	99% (85%); Neutropenia: 34%; anemia: 22% [data reported for ≥25% of pts]
Duvelisib (PI3K)	DYNAMO (Finn 2019) ^{*13,14}	Ph 2 single arm, OL, MC, international; N=83	32.1 mo (from 1 st dose until last contact date or death) Not reported	3 (range 1–10)	34.3 (17.8–54.8)	8.3 (4.2–11.0)	27.8 (20.1–not estimable)	Not reported Neutropenia: 22%; diarrhea: 16%; anemia: 13%; lipase increased: 10%; thrombocytopenia: 9%; febrile neutropenia: 9%; fatigue: 7%; vomiting: 6% [data reported for >5% Grade 3/4]
Tazemetostat (EZH2)	Not reported (Morschhauser 2020) ¹⁵	Ph 2 single arm, OL, MC, international; N=99	95.6 wks (IQR: 52.1–116); Primary analysis: Aug 9, 2019 Safety: May 24, 2019	2; 1: 3% 2: 38% 3: 21% 4: 14% 5: 23%	47.8 (30.42–39.11)	12 (8–5); EZH2mut: 13.8 (10.7–22) EZH2wt: 11.1 (3.7–14.6)	Not reached (38.2–not estimable); Not reported	99% (Not reported); Anemia: 5%; neutropenia: 4%; asthenia: 3%; UTI infection: 1%; sepsis: 2%; leukopenia: 1%; abdominal pain: 1%; fatigue: 2% TRAE any Grade: 81% Serious TRAEs: 4% TRAE Grade 3/4 Anaemia, 2%; asthenia: 1%; fatigue: 1%; leukopenia: 1%; neutropenia: 3%

^aOne conference abstract published in 2017 was included (Zinzani P, et al. *Hematological Oncology*. 2017;35(S2):69–70), although it technically did not meet the PICOS. This publication was included because the later publications did not report some of the key outcomes; ^bdata derived from Zydelig (idelalisib) Summary of product characteristics (Gilead Sciences Inc. Zydelig [idelalisib] Summary of product characteristics https://www.ema.europa.eu/en/documents/product-information/zydelig-epar-product-information_en.pdf [accessed Aug 27, 2021]).

AE, adverse event; AESI, AE of special interest; CAR-T, chimeric antigen receptor T cell therapy; CI, confidence intervals; CRS, Cytokine release syndrome; DoR, duration of response; EZH2, Enhancer of zeste homolog 2 inhibitors; FU, follow-up; hAE, hematologic adverse events; IQR, interquartile range; ITT, intention-to-treat; MC, multicenter; Mo, months; mut, mutation; OL, open label; OS, overall survival; Ph, phase; PI3K, phosphoinositide 3-kinase inhibitors; PFS, progression-free survival; R, rituximab or anti-CD20 monoclonal antibody; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UTI, urinary tract infection; wk, week; wt, wild-type; yr, year.

Conclusions

- Wide ranges of efficacy outcome results are reported in 3L+ R/R FL
- While the CAR-T drug class has reported the highest ORR at 95%, TEAEs occurred in 99% of patients, including 85% Grade ≥3
- A high unmet need still exists for additional treatment options providing a favorable benefit/risk profile for 3L+ R/R FL patients
- Limited PROs have been reported to date, and more studies characterizing R/R FL patient reported outcomes in 3L+ are warranted

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