Yescarta® (axicabtagene ciloleucel) Outcomes by Age in ZUMA-1

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Summary

Relevant Prescribing Information[1]

In the ZUMA-1 study, the median age of the study population was 58 years (range: 23 to 76 years).

Of the 422 patients with NHL who received YESCARTA in clinical trials, 127 patients (30%) were 65 years of age and older. No clinically important differences in safety or effectiveness were observed between patients aged 65 years and older, and younger patients.

Outcomes in ZUMA-1 by Age[2]

A post hoc subgroup analysis of ZUMA-1 assessed the safety and efficacy of Yescarta autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy in patients with refractory large B-cell lymphoma (LBCL) who were over or under 65 years of age.[2]

- Baseline characteristics were similar for patients ≥65 years (n=27) and <65 years (n=81). Exceptions included a numerically greater proportion of patients ≥65 years with an International Prognostic Index (IPI) score 3-4 and a greater proportion of patients <65 with prior autologous stem cell transplantation (ASCT)
- With a median follow-up of 27.1 months, investigator-assessed objective response rates (ORRs) were comparable by age, at 92% in patients ≥65 years and 81% in patients <65 years. The complete response (CR) rate was 75% for patients ≥65 years, numerically greater than 53% for patients <65 years. Responses were ongoing at data cutoff in 42% of patients ≥65 years and 38% of patients <65 years. The 2-year overall survival (OS) rates were similar by age, at 54% for patients ≥65 years and 49% for patients <65 years
- Rates of grade ≥3 adverse events (AEs) with Yescarta were similar in patients ≥65 years and <65 years. The incidence of grade ≥3 cytokine release syndrome (CRS) was observed in 7% of patients ≥65 years and 12% of patients <65 years. Grade ≥3 neurologic events were observed in 44% of patients ≥65 years and 28% of patients <65 years. Neutropenias were the most common Grade ≥3 cytopenia present on or after Day 93, occurring in 15% of patients ≥65 years and 10% of patients <65 years
- Anti-CD19 CAR T-cell expansion was similar in patients ≥65 years and <65 years

Relevant Prescribing Information[1]

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Outcomes by Age

ZUMA-1 Study

Background

ZUMA-1 (NCT02348216) was a phase 1/2 multicenter, single-arm, open-label study which evaluated the safety and efficacy of Yescarta in patients with chemorefractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), or transformed follicular lymphoma (tFL).[2,3] This study enrolled 111 patients from 22 institutions in the US and Israel.[2] Manufacturing was successful for 110 patients and 101 of these patients were eventually treated (DLBCL, n=77; PMBCL/tFL, n=24).[2] The primary endpoint for Phase 1 was the incidence of dose-limiting toxicities.[3] The primary endpoint for Phase 2 was objective response rate (ORR) per investigator assessment. Secondary endpoints included overall response (OR) as assessed by independent review committee, duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, and biomarker assessments.[3]

A post hoc subgroup analysis of the 2-year follow up of ZUMA-1 assessed the efficacy and safety of Yescarta in patients ≥65 vs those <65 years of age.[4]

Methods

A total of 108 patients from 22 medical centers received Yescarta: 7 in Phase 1 and 101 in Phase 2.[2,3]

- Bridging chemotherapy was not allowed per study protocol[2]
- At data cutoff, August 11, 2018, the median follow-up was 27.1 months from Yescarta infusion[4]
- Safety assessments included all treated patients enrolled in Phases 1 and 2 (≥65 years, n=27; <65 years, n=81).[4]
- Efficacy assessments included treated patients in Phase 2 only (≥65 years, n=24; <65 years, n=77).[4]

Patient Characteristics

Baseline characteristics were largely similar between patients ≥65 years of age and patients <65 years of age, with notable exceptions of a numerically greater proportion of patients ≥65 years with an International Prognostic Index (IPI) score 3-4, attributable to age (>60 years) being a component of the score, and a greater proportion of patients <65 with prior autologous stem cell transplantation (ASCT), as patients ≥65 years were less likely to be considered for ASCT (Table 1).[2]

Table 1. Baseline Patient Characteristics by Age Group in ZUMA-1 Phase 1/2 Patients[2]

Characteristic	≥65 years (n=27)	<65 years (n=81)
Median age (range), years	69 (65-76)	55 (23-64)
Male, n (%)	22 (81)	51 (63)
ECOG performance status 1, n (%)	16 (59)	46 (57)
IPI score 3-4, n (%)	19 (70)	29 (36)
Disease stage III/IV, n (%)	22 (81)	68 (84)
≥3 Prior lines, n (%)	18 (67)	58 (72)
Median tumor burden by SPD (range), mm^2	3790 (600-16764)	3574 (171-23297)
Disease histology, n (%)		
DLBCL	20 (74)	64 (79)
TFL	7 (26)	9 (11)
PMBCL	0	8 (10)
Prior ASCT, n (%)	5 (19)	24 (30)
Refractory subgroup before enrollment, n (%)		
Primary refractory	1 (4)	2 (2)
Refractory to second-line or later therapy	21 (78)	59 (73)
Relapse after ASCT	5 (19)	20 (25)

ASCT=autologous stem cell transplantation; DLBCL=diffuse large B-cell lymphoma; ECOG=Eastern Cooperative Oncology Group; IPI=International Prognostic Index; PMBCL=primary mediastinal B-cell lymphoma; SPD=sum of the products of diameters; TFL=transformed follicular lymphoma.

Efficacy

In Phase 2 of ZUMA-1 (N=101), investigator-assessed ORRs were similar by age: 92% for patients ≥65 and 81% for patients <65 years of age.[4]

A numerically greater proportion of patients ≥65 years than those aged <65 years had a CR as the best response (75% vs 53%, respectively) and ongoing response at data cutoff (42% vs 38%, respectively).[4]

The 2-year OS rate was similar for both age groups, at 54% for patients ≥65 years and 49% for patients <65 years (Table 2).[4]

Table 2. Efficacy Outcomes by Age Group in ZUMA-1 Phase 2 Patients[4]

Efficacy Outcomes	≥65 years (n=24)	<65 years (n=77)
ORR, n (%)	22 (92)	62 (81)
CR	18 (75)	41 (53)
PR	4 (17)	21 (27)
Ongoing response,[a] n (%)	10 (42)	29 (38)
24-month OS rate, %	54	49

[a] Patients in response as of the data cutoff on August 11, 2018.
Abbreviations: CR=complete response; ORR=objective response rate; OS=overall survival; PR=partial response.

With a median follow up of 27.1 months, the median DOR was 12.0 months for patients ≥65 years and 8.1 months for patients <65 years (Figure 1A).[4]

The median PFS was 13.2 months for patients ≥65 years and 5.6 months for patients <65 years (Figure 1B).[4]

Figure 1. DOR (A) and PFS (B) by Age Group in ZUMA-1 Phase 2 Patients[4]

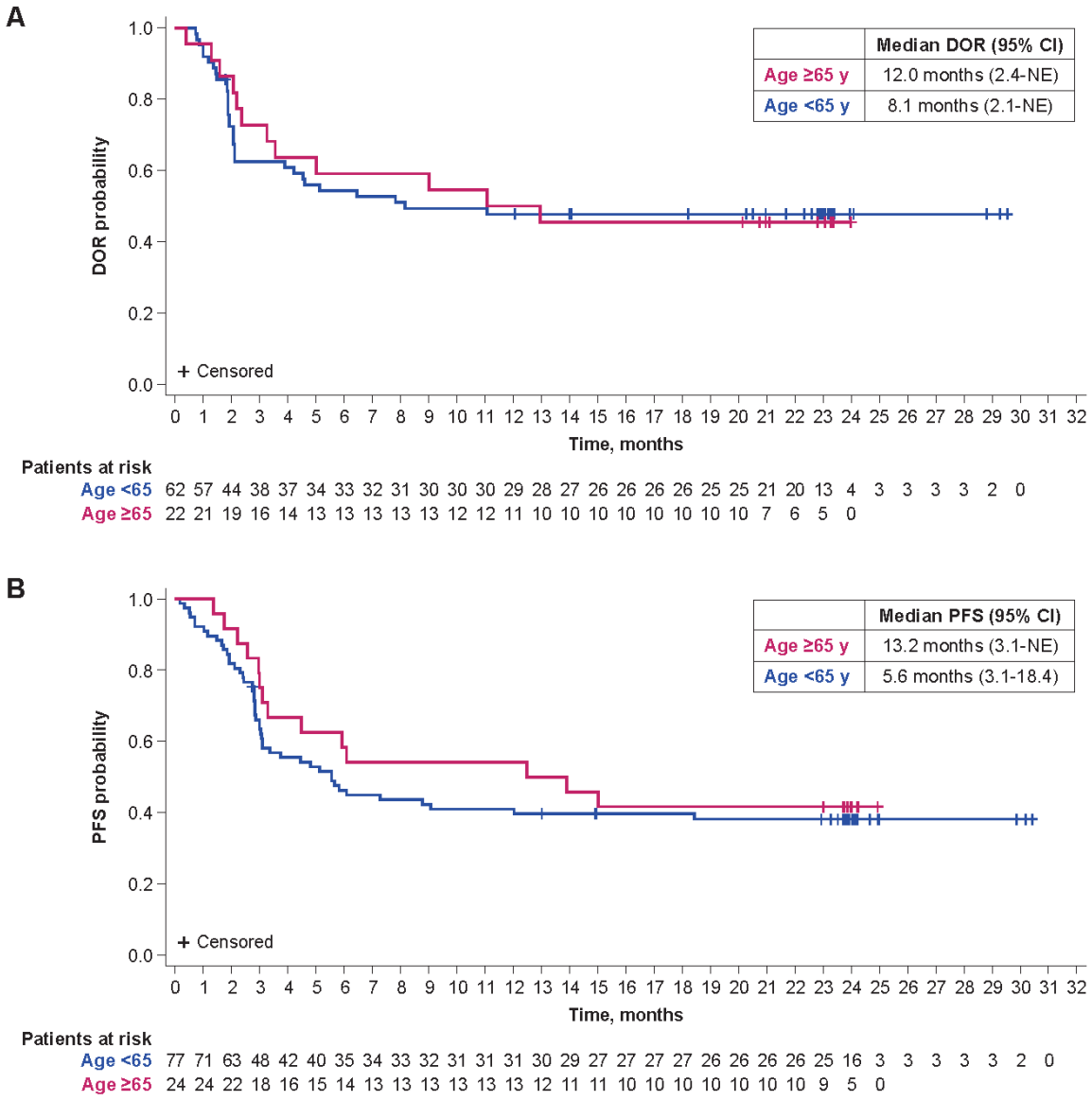


Figure adapted with permission.
DOR=duration of response; NE=not estimable; PFS=progression-free survival.

Safety

In ZUMA-1, the rates of the most common Grade ≥3 AEs with Yescarta were largely similar in patients ≥65 and <65 years of age. (Table 3).[4]

Table 3. Safety Outcomes by Age Group in ZUMA-1 Phase 1/2 Patients[4]

Grade ≥3 AEs n (%)	≥65 years (n=27)	<65 years (n=81)
Any grade ≥3 AE[a]	27 (100)	79 (98)
Neutropenia[b]	20 (74)	66 (81)
Anemia	13 (48)	36 (44)
Thrombocytopenia[c]	12 (44)	31 (38)
Decreased white blood cell count	9 (33)	22 (27)
Encephalopathy	8 (30)	17 (21)
Lymphocyte count decreased	8 (30)	14 (17)
Grade ≥3 infection	5 (19)	25 (31)
Grade ≥3 CRS[d]		
Any Grade ≥3 CRS	2 (7)	10 (12)
Pyrexia	3 (12)	9 (12)
Hypotension	2 (8)	8 (11)
Hypoxia	3 (12)	6 (7)
Grade ≥3 neurologic events[d]		
Any Grade ≥3 neurologic events	12 (44)	23 (28)
Encephalopathy	8 (30)	17 (21)
Confusional state	2 (7)	8 (10)
Aphasia	0	8 (10)
Agitation	3 (11)	2 (2)
Delirium	3 (11)	0

[a] Most common Grade ≥3 AEs that occurred in ≥25% of either age group.
[b] Neutropenia included the terms neutropenia, febrile neutropenia, and neutrophil count decreased.
[c] Thrombocytopenia included the terms thrombocytopenia and platelet count decreased.
[d] Symptoms shown include those that occurred in ≥10% of patients in either age group. CRS was graded according to Lee et al.[5] Severity of symptoms of CRS and neurologic events was graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.
AE=adverse event; CRS=cytokine release syndrome.

The most common grade ≥3 cytopenias present on or after day 93 (prolonged cytopenias) were neutropenias, occurring in 15% of patients ≥65 years and 10% of patients <65 years.[4]

Rates of Grade ≥3 cytokine release syndrome (CRS) were 7% for patients ≥65 and 12% for those <65 years of age.[4]

Grade ≥3 neurologic events were observed in 44% of patients ≥65 and 28% of those >65 years of age. Numerically higher rates of some neurologic event–associated symptoms were observed in patients ≥65 than in those <65 years of age, including Grade ≥3 delirium and encephalopathy.[4]

In ZUMA-1, 26% of patients ≥65 years and 32% of patients <65 years received intravenous immunoglobulin (IVIG) therapy, at the discretion of the investigator.[4]

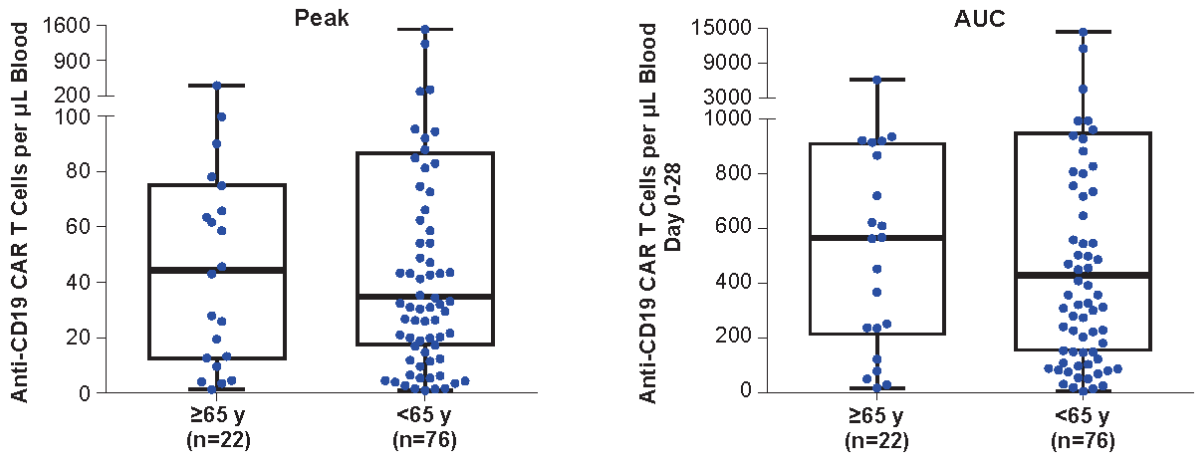
Grade 5 AEs were observed in 4 patients, representing 4% of each age groups.[4]

CAR T-Cell Expansion

In ZUMA-1, anti-CD19 CAR T-cell expansion *in vivo* was similar in patients ≥65 and <65 years of age (Figure 2).[4]

- The median peak expansion was 43.0 CAR T cells/µL blood in patients ≥65 and 35.3 CAR T cells/µL blood in patients <65 years of age (*P*=0.769).
- The median area under the curve from days 0 to 28 was 562.0 CAR T cells/µL blood in patients ≥65 and 448.4 CAR T cells/µL blood in patients <65 years of age (*P*=0.983).

Figure 2. Peak CAR T-cell Expansion by Age Group in ZUMA-1 Phase 2 patients[4]



Peak levels (left) and AUC (days 0-28; right) of anti-CD19 CAR T-cells/µL blood in patients ≥65 and >65 years of age. Phase 2 patients (n=101) are shown. CAR T-cell levels were not available for 3 patients.
AUC=area under the curve; CAR=chimeric antigen receptor.

References

1. YESCARTA® (axicabtagene ciloleucel) [US Prescribing Information]. Santa Monica, CA: Kite Pharma, Inc. 2024
2. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma.New Engl J Med. 2017;377(26):2531-2544.
3. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019 Jan;20(1):31-42.
4. Neelapu SS, Jacobson CA, Oluwole OO, et al. Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2020;135(23):2106-2109. DOI: 10.1182/blood.2019004162
5. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014; 124(2): 188-95. DOI: 10.1182/blood-2014-05-552729

Abbreviations

AE=adverse event
ASCT=autologous stem cell transplantation
AUC=area under the curve
CAR=chimeric antigen receptor
CR=complete response
CRS=cytokine release syndrome
DLBCL=diffuse large B-cell lymphoma
DOR=duration of survival
ECOG=Eastern Cooperative Oncology Group
IPI=International Prognostic Index
IV=intravenous
LBCL=large B-cell lymphoma
NE=not estimable
NR=not reached
ORR=objective response rate
OS=overall survival
PFS=progression-free survival
PMBCL=primary mediastinal B-cell lymphoma
PR=partial response
SPD=sum of the products of diameters
TFL=transformed follicular lymphoma

Product Label

For the full indication, important safety information, and Boxed Warning(s), please refer to the YESCARTA® (axicabtagene ciloleucel) US Prescribing Information available at: https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf.

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