Gilead Sciences Israel Ltd.
4 HaHarash Street, Hod Hasharon
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דצמבר 2023

עדכון עלון לרופא ולצרכן לתכשיר:

Yescarta®

Cells dispersion for intravenous infusion

(axicabtagene ciloleucel)

רופאים ורוקחים נכבדים,

חברת גיליאד סיאנסז ישראל בע"מ מבקשת להודיעכם על עדכון עלונים לתכשיר בנדון.

ההתוויה הרשומה לתכשיר בישראל:

Yescarta is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

Yescarta is indicated for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B cell lymphoma (PMBCL), after two or more lines of systemic therapy .

Limitation of Use: Yescarta is not indicated for the treatment of patients with primary or secondary central nervous system lymphoma.

Yescarta is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

השינויים מסומנים בעלון המצורף כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק ~~בקו~~ ~~חוצה~~ נגרע ממנו. הסימונים בצהוב הינם החמרות במידע הבטיחותי.

העדכונים המשמעותיים ביותר מופיעים במכתב זה, קיימים עדכונים מינוריים נוספים.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות https://israeldrugs.health.gov.il/#!/byDrug/drugs/index.html.

כמו כן ,ניתן לקבלם מודפסים על ידי פנייה לבעל הרישום:

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התכשיר זמין בכל קופות החולים.

בברכה,

מאיה מלל

רוקחת ממונה, גיליאד סיאנסז ישראל בע"מ

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העדכונים המהותיים בעלון לרופא:

DLBCL and HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy (ZUMA-7)
The efficacy and safety of Yescarta in adult patients with r/r large B-cell lymphoma (LBCL) was demonstrated in a Phase 3 randomised, open-label, multicenter study (ZUMA-7). Enrolled patients were predominantly diagnosed with DLBCL and HGBL disease subtypes based on the 2016 WHO-classification and all patients had received first-line rituximab and anthracycline-based chemotherapy. In total, 359 patients were randomised in a 1:1 ratio to receive a single infusion of Yescarta or to receive SOCT (defined as 2 to 3 cycles of standard chemoimmunotherapy [R-ICE, R-DHAP or R-DHAX, R-ESHAP, or R-GDP] followed by high-dose therapy [HDT] and ASCT in those with disease response). Randomisation was stratified by response to first-line therapy (primary refractory, vs relapse ≤ 6 months of first-line therapy vs relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (IPI) (0 to 1 vs 2 to 3) as assessed at the time of screening. The study excluded prior HSCT, detectable cerebrospinal fluid malignant cells or brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or greater, and any history of central nervous system lymphoma. Patients with active or serious infections were excluded, however patients with simple urinary tract infection and uncomplicated bacterial pharyngitis were permitted if responding to active treatment.

Following lymphodepleting chemotherapy, Yescarta was administered as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum dose: 2×10^8 cells). The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously, both given on the 5th, 4th, and 3rd day before Yescarta. Nondisease modifying bridging therapy limited to corticosteroids, could be administered between leukapheresis and lymphodepleting chemotherapy for patients with high disease burden at screening.

In the overall study population, the median age was 59 years (range: 21 to 81 years); 66% were male, and 83% were white. Seventy-four percent of patients had primary refractory LBCL and 26% of patients had relapsed within 12 months of first-line therapy. Patients had a second-line age-adjusted IPI score of 0-1 (55%) or 2-3 (45%) and an ECOG performance status of 0 (54%) or 1 (46%). ~~The median study duration was 24.9 months.~~

Patients in the Yescarta and SOCT arms were categorized as DLBCL NOS/without further classification possible (126 patients and 120 patients, respectively); DLBCL arising from follicular lymphoma (19 patients and 27 patients, respectively); HGBL with *MYC*, *BCL2*, and/or *BCL6* (double- and triple-hit) rearrangements (31 patients and 25 patients, respectively) or HGBL NOS, (1 patient in the SOCT arm); the remaining subjects were categorized under not confirmed, missing, or other.

Of the 180 patients randomised to receive Yescarta, 178 underwent leukapheresis and 170 were treated with Yescarta. Of the patients treated, 60 (33%) received bridging corticosteroid therapy. There were no manufacturing failures. Eight patients (4%) were not treated following leukapheresis, primarily due to progressive disease, serious adverse events, or death. The median time from leukapheresis to product release was 13 days (range: 10 to 24 days), and leukapheresis to Yescarta infusion was 26 days (range: 16 to 52 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg. All 170 patients who received Yescarta were monitored at a healthcare facility for a minimum of 7 days. Of the 179 patients randomised to receive SOCT, 64 patients (36%) received HDT-ASCT ~~and 56% of patients received cellular immuno-therapy after no response to or relapse after randomisation to SOCT~~.

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The primary endpoint was event-free survival (EFS) as determined by blinded central review. Key secondary endpoints were ORR and OS. The summary of efficacy results in the overall population is shown in Table 6 and the Kaplan-Meier curves for EFS ~~is~~ and OS are shown in Figure 1 and Figure 2, respectively. The 24-month EFS was 40.5% [95% CI: 33.2, 47.7] in the Yescarta arm and 16.3% [95% CI: 11.1, 22.2] in the SOCT arm. At the time of the primary EFS analysis, t~~T~~he median progression free survival (PFS) per central assessment in the Yescarta arm was 14.7 months (95% CI: 5.4, NE) compared with 3.7 months (95% CI: 2.9, 5.3) in the SOCT arm (HR: 0.490 [95% CI: 0.368, 0.652]). The median study duration was 24.9 months at the time of the primary EFS analysis and 47.2 months at the time of the primary OS analysis. The primary analysis of OS was performed at the protocol-specified timepoint of 5 years from the first subject enrolled. A statistically significant improvement in OS in favour of Yescarta was demonstrated (see Table 6). The estimated 48-month OS rates were 54.6% in the Yescarta arm and 46.0% in the SOCT arm. Fifty-seven percent of patients received cellular immunotherapy after no response to or relapse after randomisation to SOCT.

Consistent efficacy favouring Yescarta was generally observed across selected subgroups including response to first-line therapy, second-line age-adjusted IPI score, ECOG performance status, age, double expressor lymphoma status and HGBL disease subtype (see Figure 3). ~~At a pre-specified interim analysis at the time of the primary analysis of EFS, the overall survival data were not mature.~~ Among patients with HGBL per central laboratory, Yescarta demonstrated an improvement in EFS compared to SOCT (HR: 0.285 [95% CI: 0.137, 0.594]). The ORR was 81% (95% CI: 62.5%, 92.5%) and CR rate was 68% (95% CI: 48.6%, 83.3%) in patients treated with Yescarta compared with 42% (95% CI: 23.4%, 63.1%) and 23% (95% CI: 9.0%, 43.6%) respectively in the SOCT arm. The OS HR for Yescarta versus SOCT was 0.735 [95% CI: 0.338, 1.600] for patients with HGBL per central laboratory.

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Table 6. Summary of Efficacy Results for ZUMA-7 ~~(Primary Analysis)~~

	Yescarta N = 180	Standard of Care Therapy N = 179
Event-Free Survival[a]		
Number of events (%)	108 (60)	144 (80)
Median, months [95% CI][b~~a~~]	8.3 [4.5, 15.8]	2.0 [1.6, 2.8]
Stratified hazard ratio [95% CI]	0.398 [0.308, 0.514]	
Stratified log-rank p-value[c]	<0.0001	
Objective Response Rate (%) [95% CI][a]	83 [77.1, 88.5]	50 [42.7, 57.8]
Odds ratio [95% CI]	5.31 [3.08, 8.90]	
Stratified CMH test p-value	<0.0001	
Complete Response Rate (%)	65 [57.6, 71.9]	32 [25.6, 39.8]
Partial Response Rate (%)	18 [13.0, 24.8]	18 [12.6, 24.3]
Overall Survival[d]		
Number of events (%)	82 (46)	95 (53)
Median OS, months [95% CI][b]	NR (28.6, NE)	31.1 (17.1, NE)
Stratified hazard ratio [95% CI]	0.726 (0.540, 0.977)	
Stratified log-rank p-value[c,e]	0.0335	

CI, confidence interval; CMH, Cochran-Mantel-Haenszel; NE, not estimable; NR, not reached; OS, overall survival

a. Per central assessment performed at the time of primary EFS analysis~~Kaplan-Meier method~~

b. Kaplan-Meier method

c. The p values are two-sided. Stratified log-rank test or stratified CMH adjusted for response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3)

d. Per assessment performed at the time of primary analysis of OS (five years from the first subject enrolled)

e. p-value is compared with 0.0482, the two-sided efficacy boundary (significance level) for the primary OS analysis