דצמבר 2023

**רופא/ה, רוקח/ת נכבד/ה,**

# הנדון: ADCETRIS® 50mg (brentuximab vedotin)
## עדכון העלון לרופא

חברת טקדה ישראל בע"מ מבקשת לידע כי העלון לרופא של התכשיר שבנדון עודכן לאחרונה.

התוויות הרשומות לתכשיר זה:

1. **ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):**
    1) **following autologous stem cell transplant (ASCT) or**
    2) **following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.**
2. **ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).**
3. **ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.**
4. **ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.**
5. **ADCETRIS is indicated for the treatment of adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine.**
6. **ADCETRIS is indicated for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.**

מרכיב פעיל: **brentuximab vedotin 50 mg/vial**

**להלן פירוט השינויים העיקריים בעלון לרופא (טקסט שנוסף מסומן בכחול, טקסט שהושמט מסומן כטקסט אדום עם קו חוצה, טקסט המהווה החמרה מודגש בצהוב):**

## *5. PHARMACOLOGICAL PROPERTIES*

### 5.1 Pharmacodynamic properties

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*Study C25003*

….

Patients with nodular lymphocyte predominant HL (NLPHL) were excluded from the study.

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~~A pre-specified subgroup analysis of mPFS by disease stage showed that patients with Stage IV disease had a larger effect compared with the ITT population, with an unstratified hazard ratio of 0.71 (95% CI, 0.53; 0.96), compatible with a 29% reduction in the risk of modified PFS events for ADCETRIS+ AVD versus ABVD. Of the ITT population, 846 patients (64%) had Stage IV disease.~~

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25 Efal st., P.O.B 4140, Petach-Tikva 4951125
Tel:+972-3-3733140 Fax (local) : + 972-3-3733150

**Table 7: Efficacy results for previously untreated HL patients treated with 1.2 mg/kg of ADCETRIS + AVD on days 1 and 15 of a 28-day cycle (ITT ~~and Stage IV~~)**

| | Intent to Treat (ITT) Population | | | ~~Patients with Stage IV Disease~~ | | |
|---|---|---|---|---|---|---|
| | ADCETRIS + AVD n=664 | ABVD n=670 | Stratified Hazard Ratio and p-value | ~~ADCETRIS + AVD n=425~~ | ~~ABVD n=421~~ | ~~Unstratified Hazard Ratio and p-value[c]~~ |
| **Number of events (%)** | 117 (18) | 146 (22) | 0.77 (95% CI [0.60, 0.98]) p-value=0.035 | ~~77 (18)~~ | ~~102 (24)~~ | ~~0.71 (95% CI [0.53, 0.96]) p-value=0.023~~ |
| **Estimated mPFS[a] per IRF at 2 Year (%)** | 82.1 (95% CI [78.8, 85.0]) | 77.2 (95% CI [73.7, 80.4]) | | ~~82.0 (95% CI [77.8, 85.5])~~ | ~~75.3 (95% CI [70.6, 79.3])~~ | |
| **Overall Survival[b] Number of deaths (%)** | 28 (4) | 39 (6) | 0.73 (95% CI [0.45, 1.18]) p-value=0.199 | ~~14 (3)~~ | ~~26 (6)~~ | ~~0.51 (95% CI [0.27, 0.97]) p-value=0.037~~ |

[a]At the time of analysis, the median modified PFS follow-up time for both arms was 24.6 months

[b]Data from an interim OS analysis

~~[c]p-value for Stage IV disease is not adjusted for multiplicity.~~

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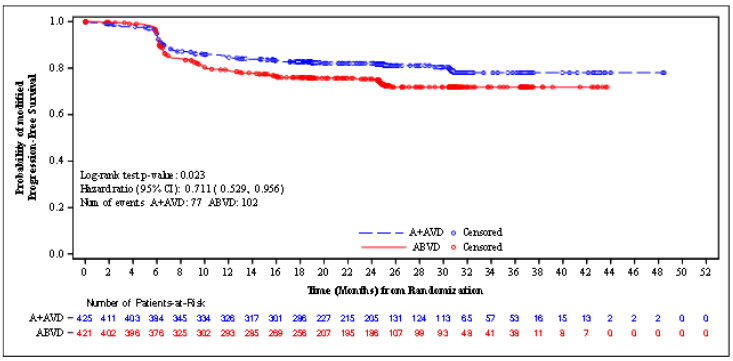
~~**Figure 2: Modified progression-free survival per IRF in patients with Stage IV disease (ADCETRIS + AVD vs. ABVD)**~~




Other secondary efficacy endpoints including CR rate and ORR at the end of randomisation regimen, CR rate at the end of first-line therapy, and the rate of PET negativity at the end of Cycle 2, duration of response (DOR), duration of complete remission (DOCR), disease-free survival (DFS) and event-free survival (EFS) all trended in favour of ADCETRIS + AVD in ~~both~~ the ITT ~~and Stage IV~~ population.

Pre-specified subgroup analyses of modified PFS per IRF ~~were performed for the ITT population including age, region, cancer stage at baseline, baseline extranodal sites, number of IPFP risk factors, baseline B symptoms, Cycle 2 PET assessment, Cycle 2 PET Deauville score, and receipt of alternative first-line medication (AFM). The analyses showed a consistent trend towards benefit for patients who received ADCETRIS + AVD compared with patients who received ABVD~~ showed no clinically meaningful difference between the two treatment arms in ~~most subgroups. The efficacy in~~ the elderly ~~patient~~ population (patients ≥ 60 years of age [n=186] [HR=1.00, 95% CI (0.58, 1.72)] and ≥ 65 years of age [n=122] [HR=1.01, 95% CI (0.53, 1.94)]) and patients ~~with no~~ without extranodal sites (n=445) (HR=1.04, 95% CI [0.67, 1.62]) ~~showed no clinically meaningful difference between the two arms~~.

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Tel:+972-3-3733140 Fax (local) : + 972-3-3733150

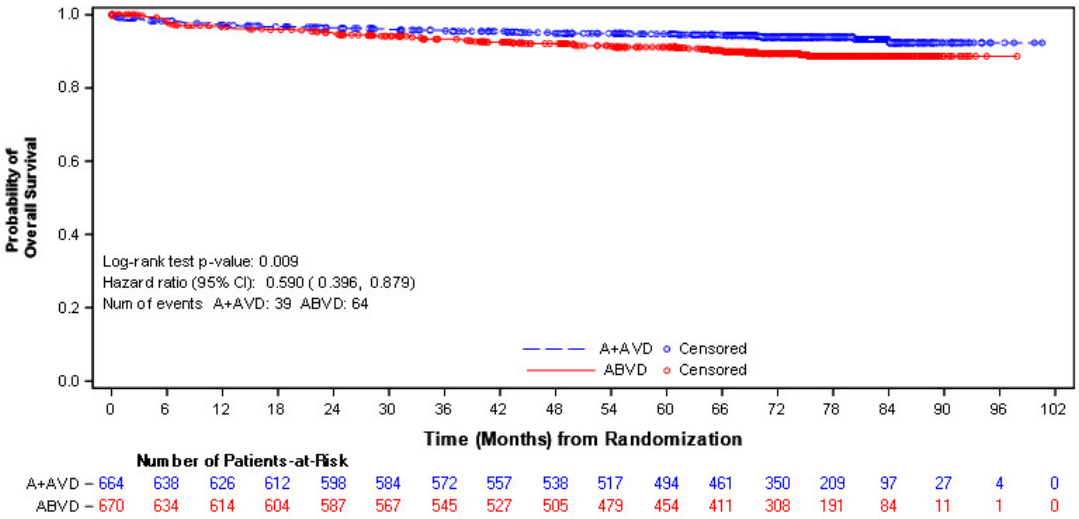
~~Post-hoc subgroup analyses of modified PFS per IRF for patients with Stage IV disease were performed including age, region, baseline extranodal sites, number of IPFP risk factors, baseline B symptoms, baseline ECOG status and gender. The analyses showed a consistent trend towards benefit for patients who received ADCETRIS + AVD compared with patients who received ABVD in most subgroups. Patients with Stage IV disease for whom extranodal disease was reported ([n=722] [HR=0.69, 95% CI (0.50, 0.94)]) showed an mPFS (per IRF) benefit. In patients with Stage IV disease for whom no extranodal disease was reported, no benefit has been shown at time of analysis ([n=85] [HR=1.49, 95% CI (0.51, 4.31)]). The significance of this finding in Stage IV HL patients with no extranodal disease is not established due to small patient numbers and low event rates (14 events). The efficacy in elderly patients with Stage IV disease in the A + AVD arm (patients ≥ 60 years of age [n=118] [HR=0.80, 95% CI (0.42, 1.53)] and ≥ 65 years of age [n=78] [HR=0.78, 95% CI (0.36, 1.67)]) showed better benefit compared with elderly patients in ITT population.~~

As of a 01 June 2021 cut-off date, approximately 5 years after enrolment of the last patient, the results in the ITT population showed a statistically significant improvement in OS in the ADCETRIS + AVD arm compared with patients treated with ABVD [HR = 0.59, 95% CI (0.396, 0.879)]~~., In the stage IV population a hazard ratio of 0.48 [95% CI (0.286, 0.799)] was observed for OS in favour of the ADCETRIS + AVD arm compared with patients treated with ABVD, see Figure 3~~ see Figure 2.

In the Stage III population, OS results indicated a 14% reduction in the risk of death in the A+AVD arm compared with patients in the ABVD arm (HR = 0.86, 95% CI [0.452, 1.648]); in the Stage IV population there was a 52% reduction in the risk of death (HR = 0.48, 95% CI [0.286, 0.799]). A subgroup analysis of OS showed no clinically meaningful difference between the two treatment arms for patients without extranodal sites (n = 445) (HR = 1.18, 95% CI [0.641, 2.187]).

Median OS was not reached for either A+AVD or ABVD patients [95%◦CI (NE, NE)].

**~~Figure 3~~Figure 2: Overall survival ~~in patients with Stage IV disease~~ (ADCETRIS + AVD vs. ABVD) (ITT, 6 years median follow up)**

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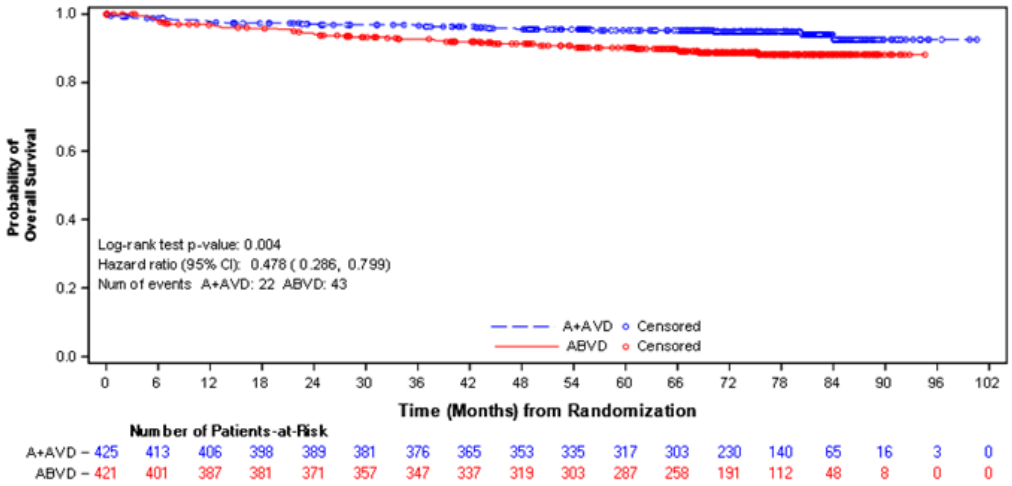


A descriptive analysis of OS was performed using data with median follow-up of over 7 years for OS. In the ITT population, a lower proportion of patients randomized to A + AVD had died (44 deaths, 7%) compared with patients randomized to ABVD (67 deaths, 10%; HR = 0.61, 95% CI [0.414, 0.892]). Similar proportions of Stage III patients randomized to A+AVD (20 deaths, 8%) and ABVD (20 deaths, 8%) had died (HR = 1.00, 95% CI [0.540, 1.866]). A lower proportion of Stage IV patients randomized to A + AVD (24 deaths, 6%) had died compared with patients randomized to ABVD (46 deaths, 11%; HR = 0.48, 95% CI [0.291, 0.784]).

In the ITT population, 33% fewer patients treated with ADCETRIS + AVD in the ITT population received subsequent salvage chemotherapy (n=66) and high-dose chemotherapy and transplant (n=36) compared with those treated with ABVD (n=99 and n=54, respectively). In the Stage IV population, 35% fewer patients treated with ADCETRIS + AVD received subsequent salvage chemotherapy (n=45) compared with those treated with ABVD (n=69) and 22% fewer patients treated with ADCETRIS + AVD received high-dose chemotherapy and transplant (n=29) compared with those treated with ABVD (n=37).

~~The European Organization for Research and Treatment of Cancer Quality of Life 30-Item Questionnaire (EORTC-QLQ-C30) showed no clinically meaningful difference between the two arms in both the ITT and Stage IV population.~~

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על ידי פניה לחברת טקדה ישראל בע"מ, רח' אפעל 25, פתח תקוה, 03-3733140

בברכה,
טקדה ישראל בע"מ

**Takeda Israel Ltd.**
25 Efal st., P.O.B 4140, Petach-Tikva 4951125
Tel:+972-3-3733140 Fax (local) : + 972-3-3733150