Healthcare utilization in the AETHERA trial: Phase 3 study of brentuximab vedotin in patients at increased risk of residual Hodgkin lymphoma post-ASCT

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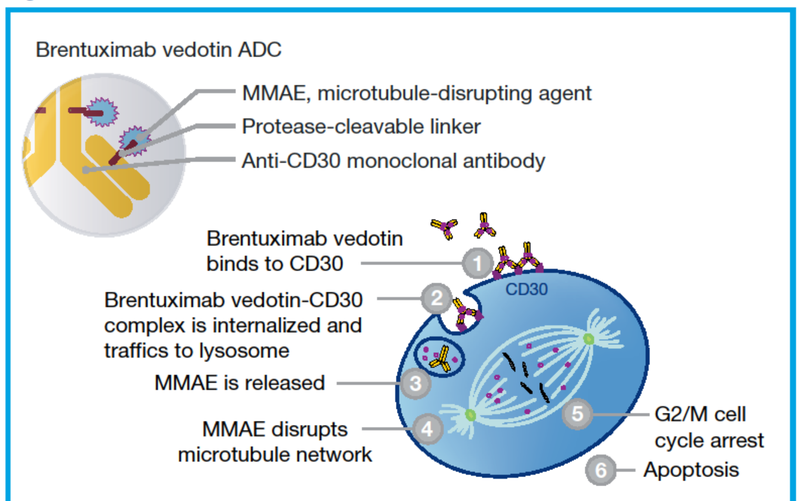
INTRODUCTION

- Brentuximab vedotin (ADCETRIS®), an anti-CD30 antibody-drug conjugate (ADC), comprises 3 components (Figure 1):
  1. A CD30-targeted monoclonal antibody (cAC10)[1,2]
  2. The microtubule-disrupting agent monomethyl auristatin E (MMAE)[2,3]
  3. A protease-cleavable linker that covalently attaches MMAE to cAC10.[2–4]

Figure 1. Mechanism of action of brentuximab vedotin



- CD30 is expressed on specific tumor cells such as Reed-Sternberg cells of Hodgkin lymphoma (HL),[1,2] but has limited expression in healthy tissue and on resting leukocytes[5,6] making it a rational target for antibody-based therapies.
  - CD30 is variably expressed in some other T-cell lymphoproliferative disorders.[5–7]
- In the USA, brentuximab vedotin received accelerated approval by the Food and Drug Administration for:
  - The treatment of patients with HL after failure of autologous stem cell transplant (ASCT) or after failure of ≥2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates
  - The treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of ≥1 prior multi-agent chemotherapy regimen.
- In Europe, brentuximab vedotin has received conditional approval from the European Medicines Agency for:
  - The treatment of adult patients with relapsed/refractory (R/R) CD30-positive HL following ASCT or following failure of ≥2 prior therapies where ASCT or multi-agent chemotherapy is not a treatment option
  - The treatment of adult patients with R/R sALCL.
- In patients with R/R HL, ASCT cures approximately 50% of patients, although the majority of patients with unfavorable risk factors progress after transplantation.[8–10]
- AETHERA is a Phase 3, randomized, placebo-controlled trial to assess whether consolidative treatment with brentuximab vedotin can prevent progression in patients with HL at risk of relapse post-ASCT:[11–13]
  - Early consolidation with brentuximab vedotin post-ASCT improved progression-free survival (PFS) per independent review compared with placebo (median PFS 43 vs 24 months; hazard ratio [HR]=0.57, P=0.001)
    - PFS benefit was sustained, with 2-year PFS rates per investigator of 65% and 45% on the brentuximab vedotin and placebo arms, respectively (HR=0.55)
  - A summary of the safety data from the AETHERA trial is shown in Table 1.

Table 1. Summary of safety data from the AETHERA trial[a]

	Brentuximab vedotin plus BSC (n=167)	Placebo plus BSC (n=160)	Total (N=327)
Most common grade ≥3 treatment-emergent AEs, n (%)			
Neutropenia	49 (29)	16 (10)	65 (20)
Peripheral sensory neuropathy	17 (10)	2 (1)	19 (6)
Peripheral motor neuropathy	10 (6)	1 (1)	11 (3)
Thrombocytopenia	7 (4)	5 (3)	12 (4)
Anemia	6 (4)	3 (2)	9 (3)
Most common serious AEs, n (%)			
Pneumonia	7 (4)	4 (3)	11 (3)
Pyrexia	6 (4)	2 (1)	8 (2)
Vomiting	5 (3)	1 (1)	6 (2)
Nausea	4 (2)	1 (1)	5 (2)
Treatment discontinuation due to AEs, n (%)[b]	54 (33)	10 (6)	64 (19)
On-study deaths, n (%)	28 (17)	25 (16)	53 (16)
Most common reasons for death, n (%)			
Disease-related	18 (11)	17 (11)	35 (11)
Acute respiratory distress syndrome	2 (1)	0	2 (1)

[a]Data presented is based upon the safety analysis set. Two patients allocated to the placebo group received a dose of brentuximab vedotin.
[b]Percentages are based upon the intention-to-treat analysis set which consisted of 165 patients who received brentuximab vedotin and 164 patients who received placebo.
AE, adverse event; BSC, best supportive care.

- Brentuximab vedotin consolidation therapy post-ASCT did not have a sustained impact on quality of life. Quality of life declined marginally in both treatment arms over time; however, the change in EQ-5D scores during treatment did not exceed the accepted minimally important difference threshold.
- Patients with HL at risk of relapse or progression post-ASCT often report a high disease and treatment burden requiring healthcare intervention.[14]
  - Healthcare resource utilization (HRU) is an important endpoint when assessing the impact of new healthcare intervention on healthcare resource.

OBJECTIVE

- To evaluate HRU during use of brentuximab vedotin and placebo in patients with HL at risk of relapse or progression post-ASCT in the AETHERA trial.

METHODS

- HL patients aged ≥18 years at risk of relapse or progression post-ASCT (indicated by the presence of at least 1 of the following) were eligible for inclusion:
  - History of refractory HL
  - Relapse or progression of HL <12 months after front-line therapy
  - Extranodal involvement at the time of pre-ASCT relapse.
- Patients were randomized 1:1 to receive brentuximab vedotin 1.8 mg/kg or placebo administered as a single IV infusion on day 1 of a 21-day cycle, for up to 16 cycles or until disease progression.
- HRU including the total number of hospitalizations, outpatient visits, and missed days of work/other activity for patients/caregivers, from the date of informed consent until 24 months after the first study treatment, were summarized by treatment group in the intent-to-treat (ITT) population.

RESULTS

- A total of 329 patients (median age 32 years [range 18–76]; 53% male) were randomized to receive brentuximab vedotin plus best supportive care (BSC) (n=165) or placebo plus BSC (n=164) at 78 sites in the USA and Europe.
- The total follow-up time was 303.83 versus 306.09 patient-years for the brentuximab vedotin and placebo arms, respectively.
- A summary of hospitalization events in the ITT population is shown in Table 2. There were 68 (41%) versus 61 (37%) patients with ≥1 hospitalization on the brentuximab vedotin versus placebo arms, respectively, with a total of 176 versus 198 hospitalizations. The hospitalization rate per patient-year was 0.58 (95% confidence interval [CI]: 0.49, 0.67) versus 0.65 (95% CI: 0.56, 0.74).

Table 2. Summary of hospitalization events in the ITT population

	Brentuximab vedotin plus BSC (n=165)	Placebo plus BSC (n=164)	Total (N=329)
Patients with ≥1 hospitalization event, n (%)	68 (41)	61 (37)	129 (39)
Hospitalization events[a]			
Median	2	2	2
Total	176	198	374
Hospitalization rate per patient-year (95% CI)	0.58 (0.49, 0.67)	0.65 (0.56, 0.74)	0.61 (0.55, 0.68)
Median duration of stay per patient (days)	16	26	20
Reasons for hospitalization, n (%)[b]			
AE	51 (29)	29 (15)	80 (21)
Disease-related signs and symptoms	64 (36)	79 (40)	143 (38)
Pre-planned surgery	6 (3)	0	6 (2)
Other	55 (31)	92 (46)	147 (39)
Visit type, n (%)[b]			
Acute care unit	57 (32)	72 (36)	129 (34)
Palliative care unit	9 (5)	15 (8)	24 (6)
Hospice	1 (<1)	12 (6)	13 (3)
Intensive care unit	6 (3)	6 (3)	12 (3)
Other	107 (61)	106 (54)	213 (57)

[a]Hospitalizations that overlap are counted as a single hospitalization.
[b]Percentages are based upon the number of hospitalization events; a patient may have >1 reason/visit type for a given hospitalization event.
AE, adverse event; BSC, best supportive care; CI, confidence interval.

- A summary of outpatient visits in the ITT population is shown in Table 3. There were 119 (72%) versus 133 (81%) patients with ≥1 outpatient visit on the brentuximab vedotin versus placebo arms, respectively, with a total of 2687 versus 3803 visits. The outpatient visit rate per patient-year was 8.84 (95% CI: 8.51, 9.18) versus 12.43 (95% CI: 12.03, 12.82).

Table 3. Summary of outpatient visits in the ITT population

	Brentuximab vedotin plus BSC (n=165)	Placebo plus BSC (n=164)	Total (N=329)
Patients with ≥1 outpatient visit, n (%)	119 (72)	133 (81)	252 (77)
Outpatient visits			
Median	7	15	11.5
Total[a]	2687	3803	6490
Outpatient visit rate per patient-year (95% CI)	8.84 (8.51, 9.18)	12.43 (12.03, 12.82)	10.64 (10.38, 10.90)
Reasons for outpatient visit, n (%)[b]			
AE	595 (22)	531 (14)	1126 (17)
Disease-related signs and symptoms	970 (36)	1594 (42)	2564 (40)
Pre-planned surgery	12 (<1)	16 (<1)	28 (<1)
Other	1110 (41)	1662 (44)	2772 (43)
Visit type, n (%)[b]			
Emergency room	30 (1)	28 (<1)	58 (<1)
Study physician or study site	789 (29)	1387 (36)	2176 (34)
Other physician or clinic	591 (22)	712 (19)	1303 (20)
Laboratory department	669 (25)	932 (25)	1601 (25)
Other	608 (23)	744 (20)	1352 (21)

[a]Total number of outpatient visits excludes scheduled study visits.
[b]Percentages are based upon the number of outpatient visits; a patient may have >1 reason/visit type for a given outpatient visit.
AE, adverse event; BSC, best supportive care; CI, confidence interval.

- A summary of missed days of work or other activity reported by patients in the ITT population and caregivers is shown in Table 4.
  - There were 85 (52%) versus 94 (57%) patients with ≥1 missed day of work/other activity on the brentuximab vedotin versus placebo arms, respectively, with a median of 15 versus 26 missed days.
  - A total of 7 (4%) versus 24 (15%) caregivers had ≥1 missed day of work/other activity, with a median of 7 versus 16 missed days.

Table 4. Summary of missed days of work or other activity among patients (ITT population) and caregivers

	Brentuximab vedotin plus BSC (n=165)	Placebo plus BSC (n=164)	Total (N=329)
Patients			
Patients with ≥1 missed day of work/other activity, n (%)	85 (52)	94 (57)	179 (54)
Missed days of work/other activity			
Median	15	26	16
Total	1648	3147	4795
Caregivers			
Caregivers with ≥1 missed day of work/other activity, n (%)	7 (4)	24 (15)	31 (9)
Missed days of work/other activity			
Median	7	16	11
Total	48	436	484

BSC, best supportive care.

CONCLUSIONS

- These preliminary results suggest a trend toward lower HRU with brentuximab vedotin compared with placebo in patients with HL at increased risk of relapse or progression post-ASCT, as indicated by hospitalizations and outpatient visits, plus working days/other activity missed by patients and caregivers.
- These data provide further support for a benefit with brentuximab vedotin in the consolidation setting. The findings suggest the need for further investigation of the economic impact of early consolidation post-ASCT with brentuximab vedotin in HL.

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