# THE ECHELON-2 TRIAL: 5-YEAR RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY OF BRENTUXIMAB VEDOTIN AND CHP (A+CHP) VERSUS CHOP IN FRONTLINE TREATMENT OF PATIENTS WITH CD30-POSITIVE PERIPHERAL T-CELL LYMPHOMA

Steven Horwitz, MD[1], Owen A. O'Connor, MD[2], Barbara Pro, MD[3], Tim Illidge, MD, PhD[4], Swaminathan Iyer, MD[5], Ranjana Advani, MD[6], Nancy L. Bartlett, MD[7], Jacob Haaber Christensen[8], Franck Morschhauser, MD[9], Eva Domingo-Domenech, MD[10], Giuseppe Rossi, MD[11], Won Seog Kim MD, PhD[12], Tatyana Feldman, MD[13], Tobias Menne, MD, PhD[14], David Belada, MD, PhD[15], Árpád Illés[16], Kensei Tobinai, MD, PhD[17], Kunihiro Tsukasaki, MD, PhD[18], Su-Peng Yeh, MD[19], Andrei Shustov, MD[20], Andreas Hüttmann, MD[21], Kerry J. Savage, BSc, MD, MSc[22], Sam Yuen[23], Pier Luigi Zinzani, MD[24], Harry Miao, MD[25], Veronica Bunn, PhD[25], Keenan Fenton, MA[26], Michelle Fanale, MD[26], Markus Puhlmann, MD[26], Lorenz Trümper, MD[27]

[1]Memorial Sloan Kettering Cancer Center, New York, New York, USA; [2]E. Couric Cancer Center, University of Virginia, Charlottesville, Virginia, USA and TG Therapeutics, New York, New York, USA; [3]Division of Hematology and Oncology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [4]Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, NIHR Biomedical Research Centre, Manchester Academic Health Sciences Centre, Christie Hospital NHS Foundation Trust, Manchester, UK; [5]MD Anderson Cancer Center/University of Texas, Houston, Texas, USA; [6]Stanford Cancer Center, Blood and Marrow Transplant Program, Stanford, California, USA; [7]Washington University School of Medicine, St. Louis, Missouri, USA; [8]Odense University Hospital, Odense, Denmark; [9]CHRU de Lille, Lille cedex, Nord-Pas-de-Calais, France; [10]Institut Catala D'oncologia, L'Hospitalet de Llobregat, Barcelona, Spain; [11]Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Italy; [12]Samsung Medical Center, Seoul, Republic of Korea; [13]Hackensack University Medical Center, Hackensack, New Jersey, USA; [14]Freeman Hospital, Newcastle upon Tyne, England; [15]4th Department of Internal Medicine – Hematology, University Hospital Hradec Králové, Czech Republic and Charles University in Prague, Faculty of Medicine in Hradec Kralove, Czech Republic; [16]Debreceni Egyetem, Debrecen, Hajdu-Bihar, Hungary; [17]National Cancer Center Hospital, Tokyo, Japan; [18]Saitama Medical University International Medical Center, Saitama, Japan; [19]China Medical University Hospital, Taichung, Taiwan; [20]University of Washington Medical Center, Seattle, Washington, USA;[21]Universitatsklinikum Essen, Essen, Nordrhein-Westfalen, Germany; [22]Department of Medical Oncology and University of British Columbia, BC Cancer, Vancouver, British Columbia, Canada; [23]Calvary Mater Newcastle Hospital, Australia; [24]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [25]Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts, USA, a wholly owned subsidiary of Takeda Pharmaceuticals Limited; [26]Seagen Inc., Bothell, Washington, USA; [27]Universitätsmedizin Göttingen, Göttingen, Germany.

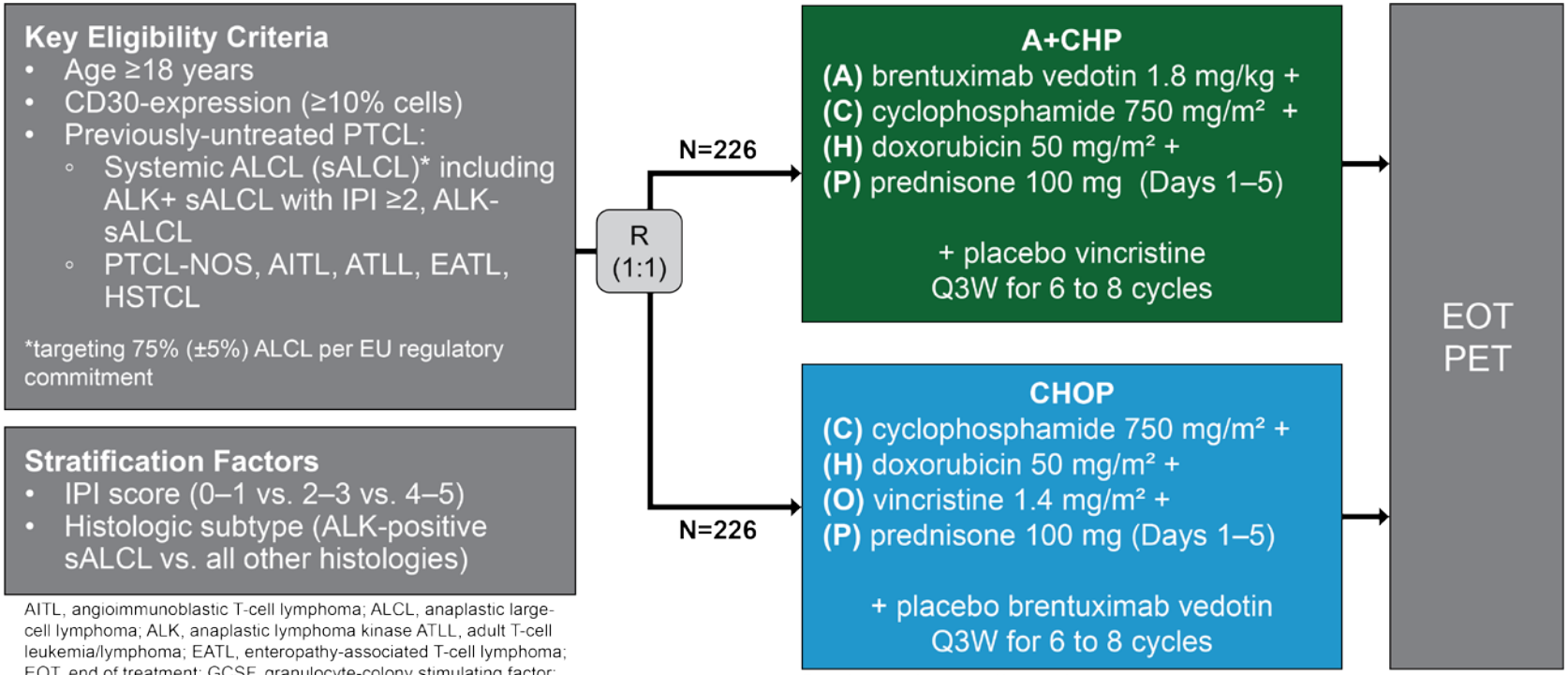
American Society of Hematology Annual Meeting; Virtual; December 5-8, Abstract No. 1150

# Background

- The phase 3 ECHELON-2 study (NCT01777152) compared brentuximab vedotin (BV) plus cyclophosphamide, doxorubicin, and prednisone (A+CHP) with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in patients (pts) with previously untreated CD30-expressing peripheral T-cell lymphoma (PTCL)
- A+CHP was superior to CHOP with a significant improvement in progression-free survival (PFS), the primary endpoint, and overall survival (OS), with a similar incidence and severity of adverse events, including peripheral neuropathy (PN), between groups (Horwitz S, et al. Lancet 2019; 393:229-40).
- At the time of the primary analysis (2018), median follow-up: PFS, 36.2 months; OS, 42.1 months
  - PFS (HR=0.71 [95% CI: 0.54, 0.93], p=0.0110)
  - OS (HR=0.66 [95% CI: 0.46, 0.95], p=0.0244)
- PFS and OS analyses for key prespecified subgroups were generally consistent with the overall study results
  - PFS in sALCL subgroup (HR=0.59 [95% CI: 0.42, 0.84], p=0.0031)
- We report the 5-year results of the ECHELON-2 study

# Study Design

- ECHELON-2 is a phase 3, randomized, double-blind, double-dummy, placebo-controlled, active-comparator, multicenter study.




AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase ATLL, adult T-cell leukemia/lymphoma; EATL, enteropathy-associated T-cell lymphoma; EOT, end of treatment; GCSF, granulocyte-colony stimulating factor; HSTCL, hepatosplenic T-cell lymphoma; IPI, international prognostic index

# Methods

- Primary endpoint: PFS assessed per blinded independent central review (BICR) in primary analysis and per investigator (INV) assessment in current analysis
- PFS per INV: time from randomization to first documentation of progressive disease, death due to any cause, or subsequent systemic chemotherapy to treat residual or progressive PTCL, whichever occurred first
- Key secondary endpoints: OS, PFS in sALCL, complete remission (CR) rate, and objective response rate (ORR)
- Subsequent therapies, including BV or BV-containing regimens, were permitted
- Response to BV retreatment (A+CHP arm) or first BV treatment (CHOP arm) by INV assessment and based on Revised Response Criteria for Malignant Lymphoma (Cheson BD, et al. J Clin Oncol 2007; 25:579-86)
- Resolution and improvement of PN monitored during extended follow-up

# Baseline Characteristics

- Baseline demographics and disease characteristics were well balanced between groups and have been previously described (Horwitz S, et al. ASH Annual Meeting, 2018).

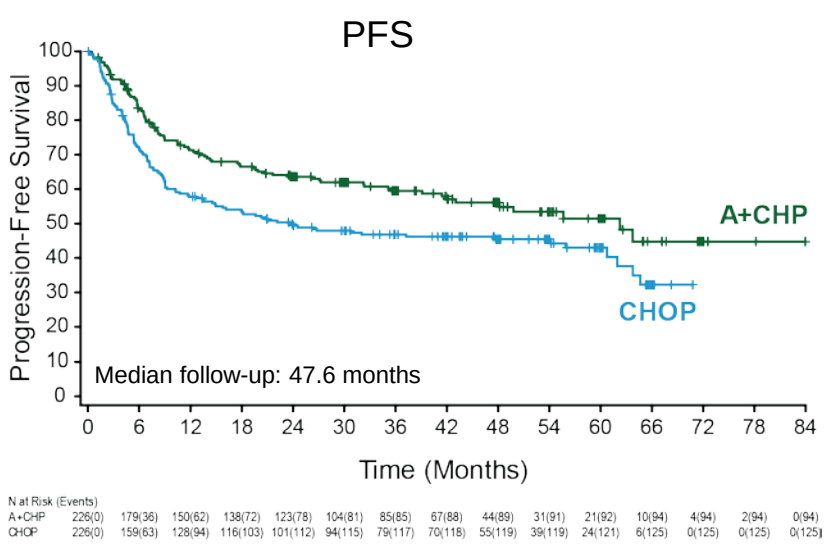
| | A+CHP N=226 | CHOP N=226 |
|---|---|---|
| Age in years, median (range) | 58 (18-92) | 58 (18-83) |
| Men, n (%) | 133 (59) | 151 (67) |
| Women, n (%) | 93 (41) | 75 (33) |
| IPI Score, n (%) | | |
| 0-1 | 53 (23) | 48 (21) |
| 2-3 | 140 (62) | 144 (64) |
| 4-5 | 33 (15) | 34 (15) |
| Stage III/IV, n (%) | 184 (81) | 180 (80) |

| | A+CHP N=226 | CHOP N=226 |
|---|---|---|
| Disease diagnosis, n (%) | | |
| sALCL | 162 (72) | 154 (68) |
| ALK+ | 49 (22) | 49 (22) |
| ALK– | 113 (50) | 105 (46) |
| PTCL-NOS | 29 (13) | 43 (19) |
| AITL | 30 (13) | 24 (11) |
| ATLL | 4 (2) | 3 (1) |
| EATL | 1 (0) | 2 (1) |

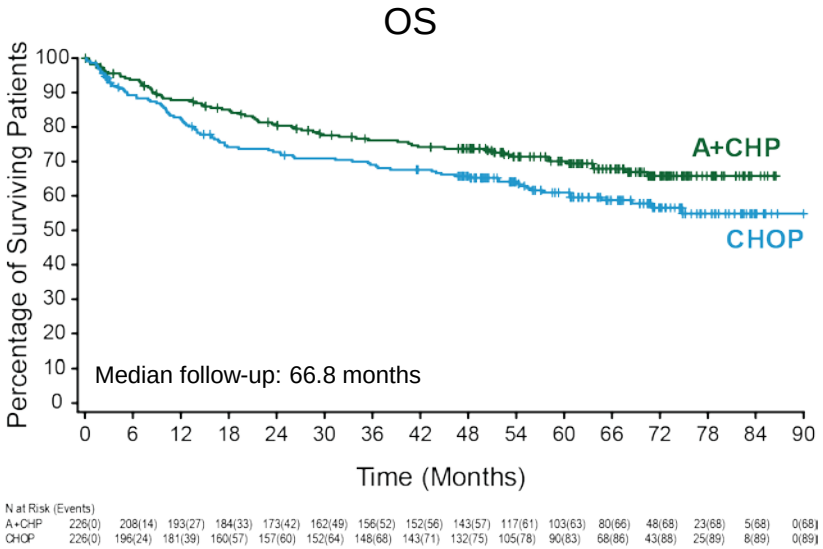
# Landmark PFS Results

| | A+CHP N=226 | CHOP N=226 |
|---|---|---|
| **3-Year results (primary analysis): PFS per BICR**<br>Median follow-up: 36.2 months<br>3-year PFS rate (95% CI)<br>HR (95% CI)<br>p-value | 57.1% (49.9, 63.7) | 44.4% (37.6, 50.9) |
| | 0.71 (0.54, 0.93)<br>p=0.0110 | |
| **5-Year results: PFS per INV assessment**<br>Median follow-up: 47.6 months<br>5-year PFS rate (95% CI)<br>HR (95% CI)<br>p-value | 51.4% (42.8, 59.4) | 43.0% (35.8, 50.0) |
| | 0.70 (0.53, 0.91)<br>p=0.0077 | |

# PFS (INV Assessment) and OS

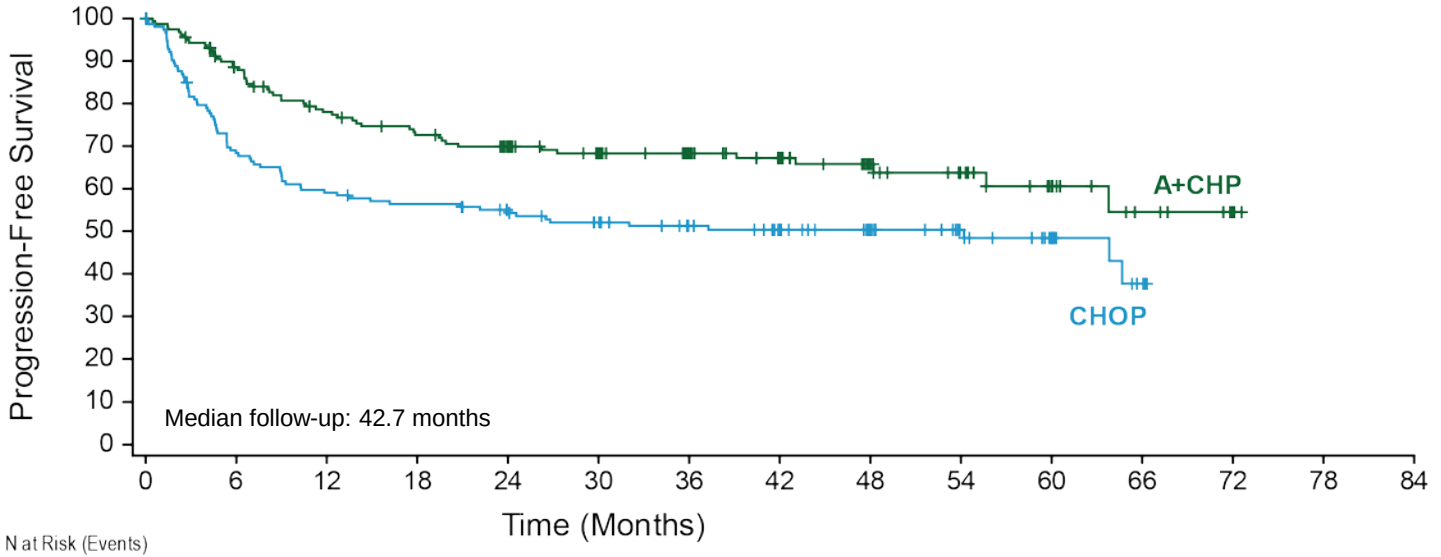



| | N | Events | Medians (Months) | HR (95% CI) | p-value* |
|---|---|---|---|---|---|
| A+CHP | 226 | 94 | 62.26 | 0.70 (0.53, 0.91) | 0.0077 |
| CHOP | 226 | 125 | 23.75 | | |




| | N | Events | Medians (Months) | HR (95% CI) | p-value* |
|---|---|---|---|---|---|
| A+CHP | 226 | 68 | – | 0.72 (0.53, 0.99) | 0.0424 |
| CHOP | 226 | 89 | – | | |

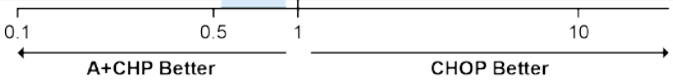
# PFS (INV Assessment) in sALCL Subset




| | N | Events | Medians (Months) | HR (95% CI) | p-value* |
|---|---|---|---|---|---|
| A+CHP | 162 | 53 | – | 0.55 (0.39, 0.79) | 0.0009 |
| CHOP | 154 | 77 | 54.18 | | |

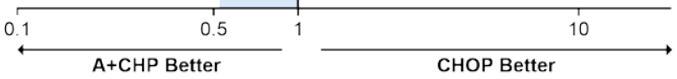
# Prespecified Subset Analyses: PFS

| ITT Subgroups | Event/N A+CHP | Event/N CHOP | Hazard Ratio (95% CI) |
|---|---|---|---|
| **PFS per Investigator** | **94/226** | **125/226** | **0.70 (0.53, 0.91)** |
| IPI Score | | | |
| **0–1** | **14/52** | **27/48** | **0.42 (0.22, 0.81)** |
| 2–3 | 59/141 | 79/145 | 0.72 (0.51, 1.01) |
| **4–5** | **21/33** | **19/33** | **1.14 (0.61, 2.15)** |
| Age | | | |
| **<65** | **51/157** | **74/156** | **0.64 (0.45, 0.92)** |
| ≥65 | 43/69 | 51/70 | 0.68 (0.45, 1.04) |
| **Sex** | | | |
| Male | 60/133 | 79/151 | 0.84 (0.60, 1.17) |
| **Female** | **34/93** | **46/75** | **0.44 (0.28, 0.69)** |
| Baseline ECOG Status | | | |
| **0** | **36/84** | **56/93** | **0.63 (0.41, 0.96)** |
| 1 | 38/90 | 50/86 | 0.61 (0.40, 0.93) |
| **2** | **20/51** | **19/47** | **0.99 (0.52, 1.88)** |
| Disease Stage | | | |
| **I** | **3/12** | **2/9** | **2.15 (0.22, 20.88)** |
| II | 12/30 | 18/37 | 0.93 (0.43, 1.99) |
| **III** | **26/57** | **36/67** | **0.63 (0.37, 1.05)** |
| IV | 53/127 | 69/113 | 0.66 (0.46, 0.95) |
| **Disease Indication** | | | |
| ALK-positive sALCL | 7/49 | 16/49 | 0.40 (0.17, 0.98) |
| **ALK-negative sALCL** | **46/113** | **61/105** | **0.58 (0.40, 0.86)** |
| ATLL | 2/4 | 2/3 | 0.69 (0.10, 4.94) |
| **AITL** | **19/30** | **12/24** | **1.41 (0.64, 3.11)** |
| EATL | 1/1 | 2/2 | not estimable |
| **PTCL-NOS** | **19/29** | **32/43** | **0.79 (0.43, 1.43)** |
| sALCL | 53/162 | 77/154 | 0.55 (0.39, 0.79) |
| **non sALCL** | **41/64** | **48/72** | **0.96 (0.63, 1.47)** |



# Prespecified Subset Analyses: OS

| ITT Subgroups | Event/N A+CHP | Event/N CHOP | Hazard Ratio (95% CI) |
|---|---|---|---|
| Overall Survival | 68/226 | 89/226 | 0.72 (0.53, 0.99) |
| IPI Score | | | |
| 0–1 | 8/52 | 13/48 | 0.58 (0.24, 1.39) |
| 2–3 | 40/141 | 59/145 | 0.61 (0.41, 0.91) |
| 4–5 | 20/33 | 17/33 | 1.23 (0.64, 2.34) |
| Age | | | |
| <65 | 37/157 | 44/156 | 0.79 (0.51, 1.23) |
| ≥65 | 31/69 | 45/70 | 0.62 (0.39, 0.98) |
| Sex | | | |
| Male | 41/133 | 59/151 | 0.73 (0.49, 1.08) |
| Female | 27/93 | 30/75 | 0.68 (0.40, 1.16) |
| Baseline ECOG Status | | | |
| 0 | 25/84 | 38/93 | 0.59 (0.35, 0.99) |
| 1 | 25/90 | 38/86 | 0.54 (0.33, 0.90) |
| 2 | 18/51 | 13/47 | 1.42 (0.69, 2.93) |
| Disease Stage | | | |
| I | 2/12 | 2/9 | 1.34 (0.12, 14.81) |
| II | 7/30 | 14/37 | 0.66 (0.26, 1.68) |
| III | 18/57 | 22/67 | 0.70 (0.37, 1.33) |
| IV | 41/127 | 51/113 | 0.73 (0.48, 1.10) |
| Disease Indication | | | |
| ALK-positive sALCL | 5/49 | 10/49 | 0.48 (0.16, 1.40) |
| ALK-negative sALCL | 34/113 | 39/105 | 0.71 (0.44, 1.12) |
| ATLL | 2/4 | 3/3 | 0.70 (0.11, 4.27) |
| AITL | 12/30 | 8/ 24 | 1.01 (0.40, 2.55 ) |
| EATL | 1/1 | 2/2 | not estimable |
| PTCL-NOS | 14/29 | 27/43 | 0.75 (0.37, 1.48) |
| sALCL | 39/162 | 49/154 | 0.66 (0.43, 1.01) |
| non sALCL | 29/64 | 40/72 | 0.76 (0.46, 1.23) |



# BV Retreatment in A+CHP Arm or First BV Treatment in CHOP Arm

| | A+CHP N=29 | CHOP N=54 |
|---|---|---|
| First BV treatment after frontline therapy, n (%) | | |
| Monotherapy | 25 (86) | 48 (89) |
| Combination therapy | 4 (14) | 6 (11) |
| Number of therapies prior to first BV treatment after frontline therapy, median (range) | 0 (0,8) | 0 (0,6) |
| Time from start of frontline treatment to first BV treatment after frontline therapy (months), median (range) | 15.0 (3, 64) | 8.2 (1, 67) |
| Received any SCT after frontline therapy, n (%) | 17 (59) | 22 (41) |
| Received autologous SCT after frontline therapy, n (%) | 16 (55) | 13 (24) |
| Duration of first BV treatment after frontline therapy (months), median (range)[a] | 2.1 (0, 18) | 2.2 (0, 11) |

a. Duration of BV retreatment or first BV treatment after frontline therapy was not calculated for 12 pts (2 pts in A+CHP arm and 10 pts in CHOP arm). For 2 of these pts, treatment was ongoing, and for the remaining 10 patients, the end date of treatment was missing.

# Response to BV Retreatment (A+CHP Arm) or First BV Treatment (CHOP Arm) After Frontline Therapy

**BV Retreatment Regimen in A+CHP Arm**

| | Overall N=29 | sALCL N=19 | PTCL-NOS N=5 | AITL N=5 |
|---|---|---|---|---|
| **Response rate, n (%)** | **17 (59)** | **12 (63)** | **3 (60)** | **2 (40)** |
| CR | 11 (38) | 8 (42) | 2 (40) | 1 (20) |
| PR | 6 (21) | 4 (21) | 1 (20) | 1 (20) |

**BV First Treatment Regimen in CHOP Arm**

| | Overall N=54 | sALCL N=39 | PTCL-NOS N=10 | AITL N=4 | Other (N=1) |
|---|---|---|---|---|---|
| **Response rate, n (%)** | **27 (50)** | **23 (59)** | **3 (30)** | **1 (25)** | **0** |
| CR | 16 (30) | 12 (31) | 3 (30) | 1 (25) | 0 |
| PR | 11 (20) | 11 (28) | 0 | 0 | 0 |

# Treatment-Emergent Peripheral Neuropathy

| | A+CHP N=223 | CHOP N=226 |
|---|---|---|
| Treatment-emergent PN, n | 117 | 124 |
| Resolution or improvement of all PN events | 84 (72) | 97 (78) |
| Resolution[a] | 71 (85) | 82 (85) |
| Improvement[b] | 13 (15) | 15 (15) |
| Pts with ongoing PN at last visit | 47 (40) | 42 (34) |
| Grade 1 | 33 (70) | 30 (71) |
| Grade 2 | 13 (28) | 11 (26) |
| Grade 3 | 1 (2) | 1 (2) |

a. Resolution was defined as resolved/recovered with or without sequelae; or return to baseline or lower severity as of the latest assessment for pre-existing events.

b. Improvement was defined as decrease by at least 1 grade from the worst grade with no higher grade thereafter. Pts with improvement in any event at last follow up were those with at least one improved event and the date of improvement was before last follow up date. Subjects with all events resolved were excluded.

# Summary and Conclusions

- At 5 years, frontline treatment with A+CHP continues to provide clinically meaningful improvement in PFS and OS versus CHOP

  **ITT Analysis Set**
  - PFS: HR 0.70 (95% CI: 0.53, 0.91); 30% reduction in the risk of a progression event
  - OS: HR 0.72 (95% CI: 0.53, 0.99); 28% reduction in the risk of death

  **sALCL Subset**
  - PFS: HR 0.55 (95% CI: 0.39, 0.79); 45% reduction in the risk of a progression event
  - OS: HR 0.66 (95% CI: 0.43, 1.01); 34% reduction in the risk of death

- After frontline therapy, the response to BV retreatment was 59% for A+CHP arm, and the response to first BV treatment was 50% for CHOP arm
- A+CHP continues to have a manageable safety profile with extended follow-up
  - A+CHP 72% versus CHOP 78% had resolution or improvement of PN events
  - For ongoing PN events, A+CHP 98% versus CHOP 98% were Grade 1 or 2

# Funding


- Study funded by Seagen Inc. and Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.
- This research was funded in part through the National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748.