

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

Swaminathan Iyer¹, Lorenz Trümper², Owen A. O'Connor³, Barbara Pro⁴, Tim Illidge⁵, Ranjana Advani⁶, Jacob Haaber Christensen⁷, Franck Morschhauser⁸, Eva Domingo-Domenech⁹, Giuseppe Rossi¹⁰, Won Seog Kim¹¹, Tatyana Feldman¹², Tobias Menne¹³, David Belada¹⁴, Árpád Illés¹⁵, Kensei Tobinai¹⁶, Kunihiro Tsukasaki¹⁷, Su-Peng Yeh¹⁸, Andrei Shustov¹⁹, Andreas Hüttmann²⁰, Kerry J. Savage²¹, Sam Yuen²², Pier Luigi Zinzani²³, Harry Miao²⁴, Veronica Bunn²⁴, Keenan Fenton²⁵, Michelle Fanale²⁵, Markus Puhlmann²⁵, Steven Horwitz²⁶

¹MD Anderson Cancer Center/University of Texas, Houston, Texas, USA; ²Universitätsmedizin Göttingen, Göttingen, Germany; ³E. Couic Cancer Center, University of Virginia, Charlottesville, Virginia, USA, and TG Therapeutics, New York, New York, USA; ⁴Division of Hematology and Oncology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; ⁵Division 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; ⁶Stanford Cancer Center, Blood and Marrow Transplant Program, Stanford, California, USA; ⁷Odense University Hospital, Odense, Denmark; ⁸CHRU de Lille, Lille, Nord-Pas-de-Calais, France; ⁹Institut Català D'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain; ¹⁰Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Italy; ¹¹Samsung Medical Center, Seoul, Republic of Korea; ¹²Hackensack University Medical Center, Hackensack, New Jersey, USA; ¹³Freeman Hospital, Newcastle upon Tyne, UK; ¹⁴Department of Internal Medicine – Hematology, University Hospital Hradec Králové, Czech Republic; ¹⁵Debreceeni Egyetem, Debrecen, Hajdu-Bihar, Hungary; ¹⁶National Cancer Center Hospital, Tokyo, Japan; ¹⁷Saitama Medical University International Medical Center, Saitama, Japan; ¹⁸China Medical University Hospital, Taichung, Taiwan; ¹⁹University of Washington Medical Center, Seattle, Washington, USA; ²⁰Universitätsklinikum Essen, Essen, Germany; ²¹Department of Medical Oncology and University of British Columbia, BC Cancer, Vancouver, British Columbia, Canada; ²²Calvary Mater Newcastle Hospital, Waratah, Australia; ²³Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; ²⁴Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts, USA, a wholly owned subsidiary of Takeda Pharmaceuticals Limited; ²⁵Seagen Inc., Bothell, Washington, USA; ²⁶Memorial Sloan Kettering Cancer Center, New York, New York, USA.

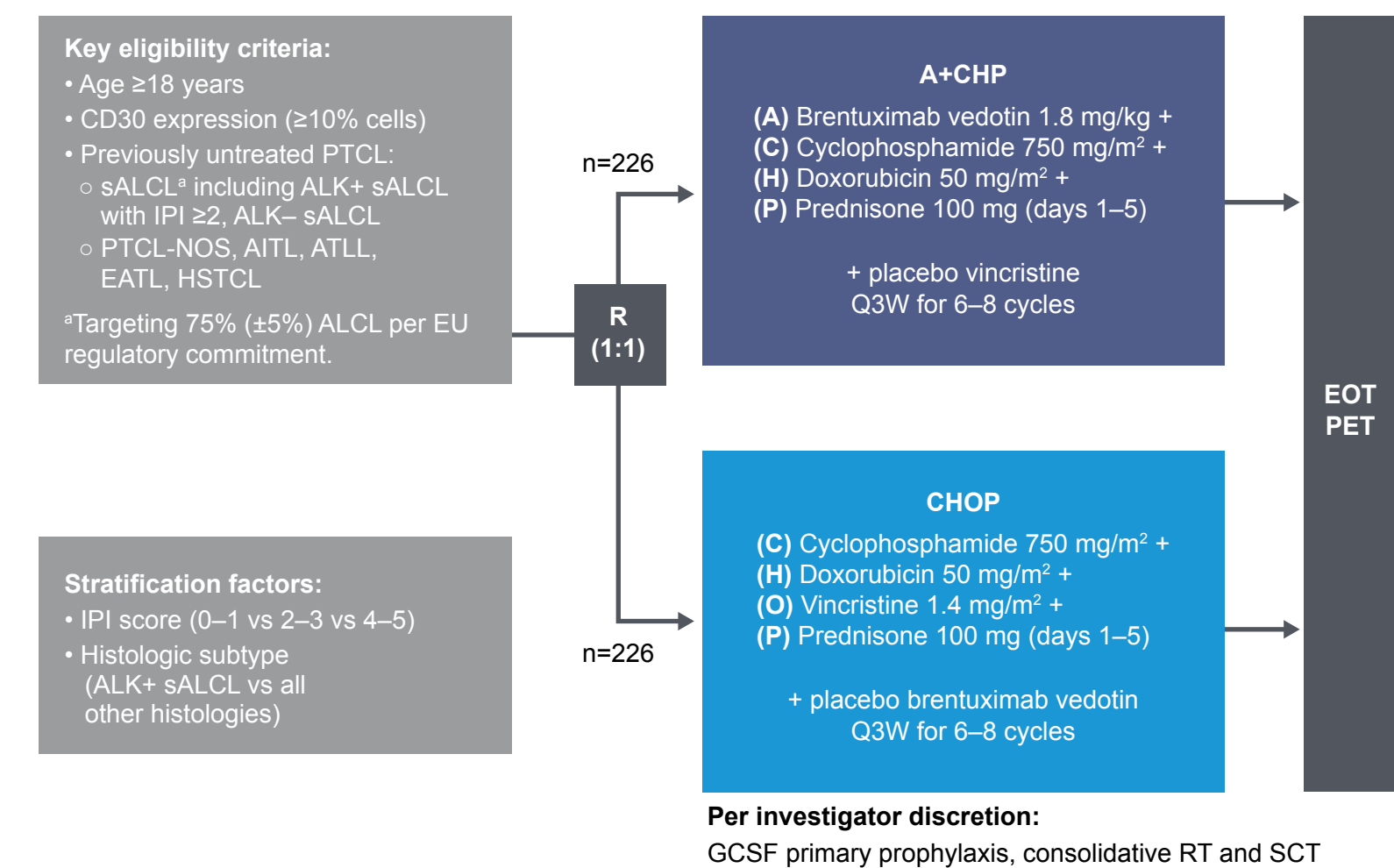
Background

- The phase 3 ECHELON-2 study (NCT01777152) compared A+CHP with CHOP in patients with previously untreated CD30-expressing PTCL.
- A+CHP was superior to CHOP, with a significant improvement in PFS, the primary endpoint, and OS, and a similar incidence and severity of adverse events, including PN, between groups.¹
- At the time of the primary analysis (2018), median follow-up was PFS: 36.2 months; OS: 42.1 months.¹
 - 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 subgroups were generally consistent with the overall study results.¹
 - PFS in sALCL subgroup (HR=0.59 [95% CI: 0.42–0.84]; P=0.0031).
- We herein report the 5-year results of the ECHELON-2 study.

Methods

- ECHELON-2 is a double-blind, double-dummy, randomized, placebo-controlled, active-comparator, multicenter, phase 3 study (Figure 1).
- Adults with untreated CD30-positive PTCL (targeting 75% ± 5% with sALCL) were randomized 1:1 to receive 6–8 cycles of A+CHP or CHOP (Figure 1). Patients were stratified by histological subtype and IPI score.
- Subsequent therapies, including brentuximab vedotin or brentuximab vedotin-containing regimens, were permitted and post-treatment consolidative stem cell transplantation or radiotherapy was permitted at the investigator's discretion.

Figure 1: ECHELON-2 study design



Results

- Baseline demographics and disease characteristics were well balanced between groups (Table 1) and have been previously described.¹

Table 1: Key patient and disease characteristics

	A+CHP n=226	CHOP n=226
Median age, years (range)	58 (18–92)	58 (18–83)
Male sex, n (%)	133 (59)	151 (67)
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)
Disease diagnosis, n (%)		
sALCL	162 (72)	154 (68)
ALK+	49 (22)	49 (22)
ALK-	113 (50)	105 (46)
PTCL-NOS	29 (13)	43 (19)
ATLL	30 (13)	24 (11)
ATLL	4 (2)	3 (1)
EATL	1 (0)	2 (1)

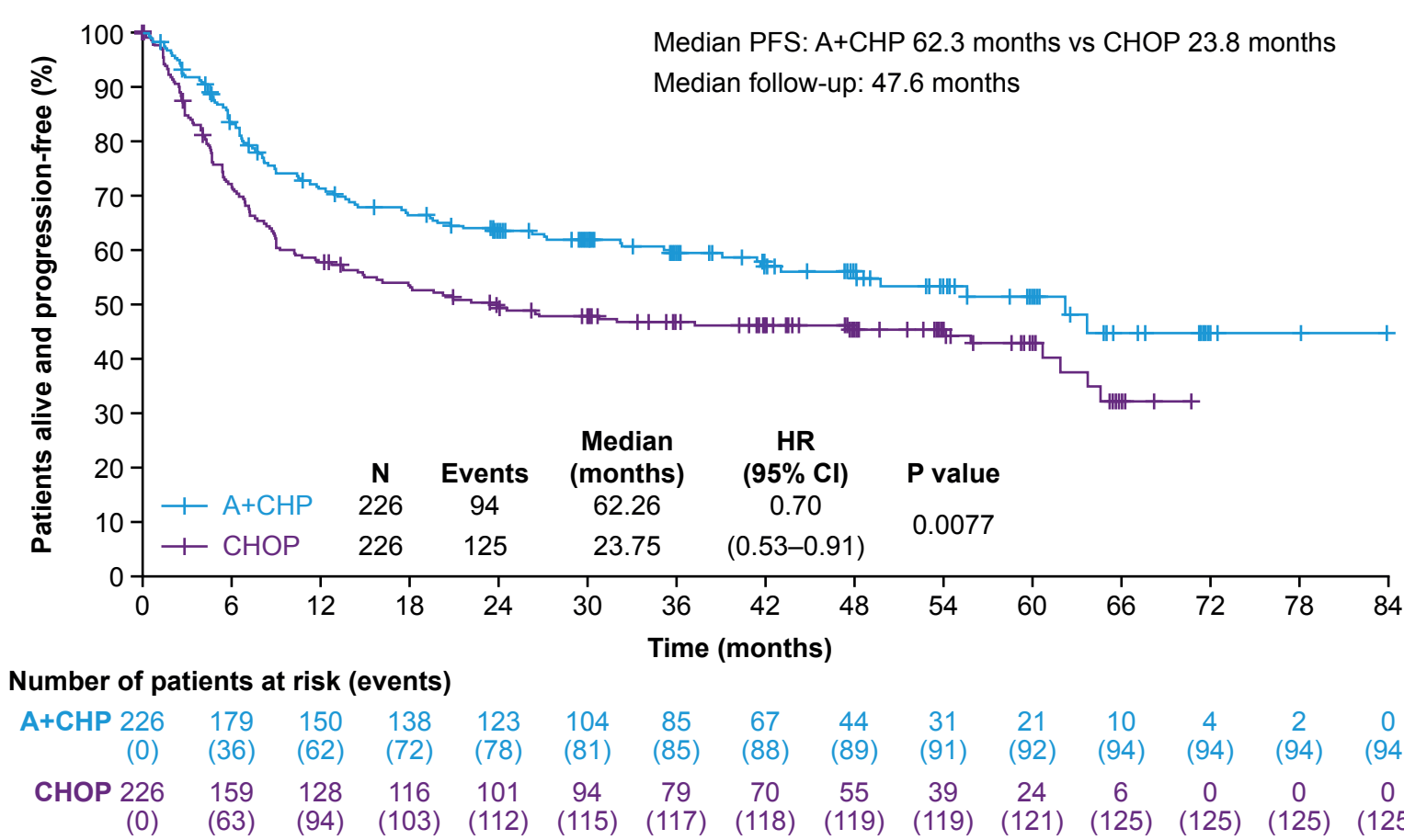
- After a median follow-up of 47.6 months, the estimated 5-year PFS was 51.4% for the A+CHP arm vs 43.0% for the CHOP arm (Table 2).

Table 2: PFS results

	A+CHP n=226	CHOP n=226
3-year results (primary analysis): PFS per BICR¹		
Median follow-up: 36.2 months		
3-year PFS rate, % (95% CI)	57.1 (49.9–63.7)	44.4 (37.6–50.9)
HR (95% CI)	0.71 (0.54–0.93)	
P value	P=0.0110	
5-year results: PFS per INV assessment		
Median follow-up: 47.6 months		
5-year PFS rate, % (95% CI)	51.4 (42.8–59.4)	43.0 (35.8–50.0)
HR (95% CI)	0.70 (0.54–0.91)	
P value	P=0.0077	

- At 5 years, the PFS per INV HR was 0.70, representing a 30% reduction in the risk of progression, death, or receipt of subsequent anticancer therapy with A+CHP vs CHOP (Table 2 and Figure 2).

Figure 2: PFS per INV at 5 years



- For the subset of patients with sALCL, median PFS was not reached for the A+CHP arm and was 54.2 months for the CHOP arm (Figure 3).
- The PFS analyses for key subgroups were consistent with overall study results and generally favored A+CHP over CHOP (Figure 4).
- The study was not powered to compare efficacy between A+CHP and CHOP in histologic subtypes.

Figure 3: PFS (INV assessment) in sALCL subset

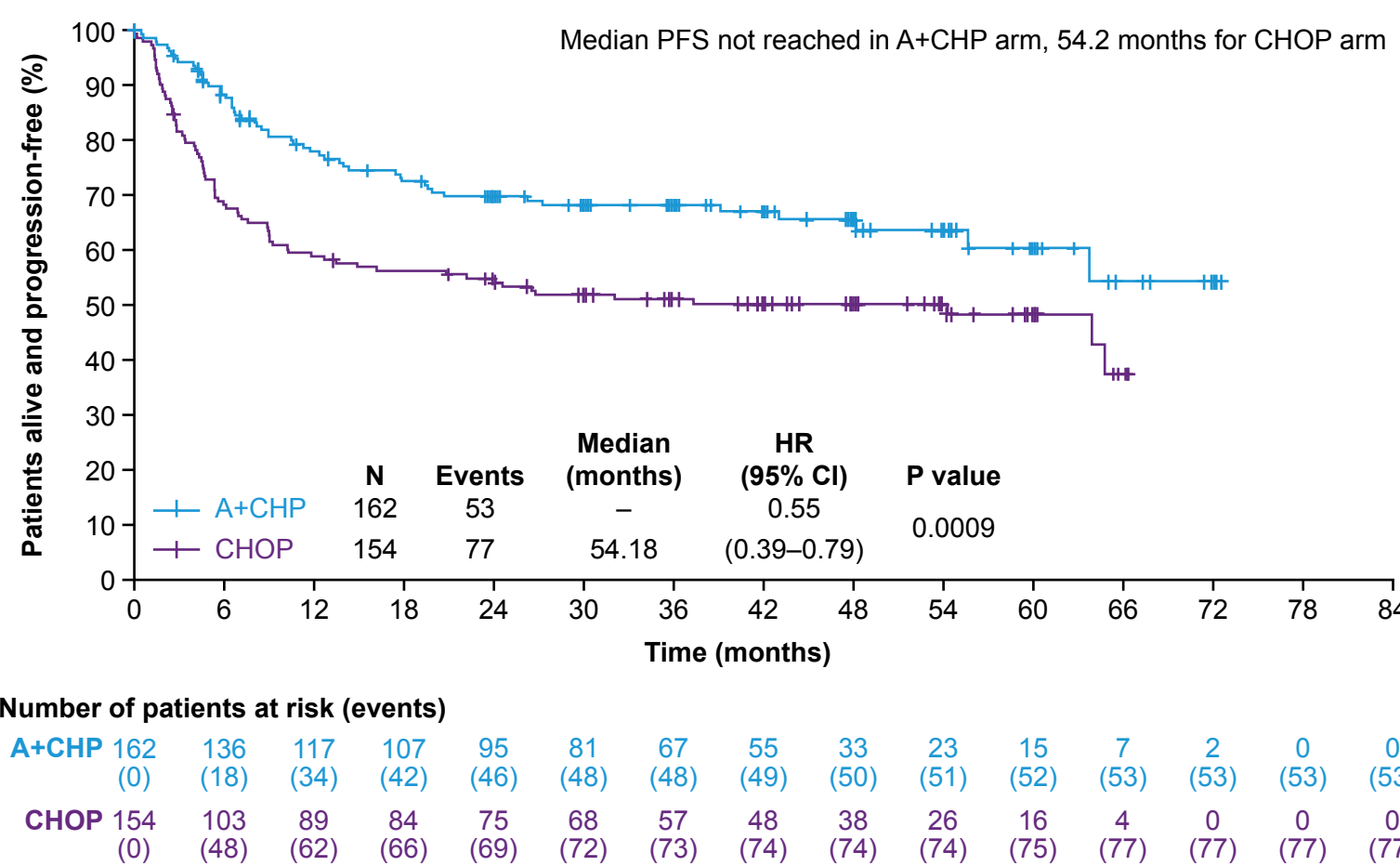
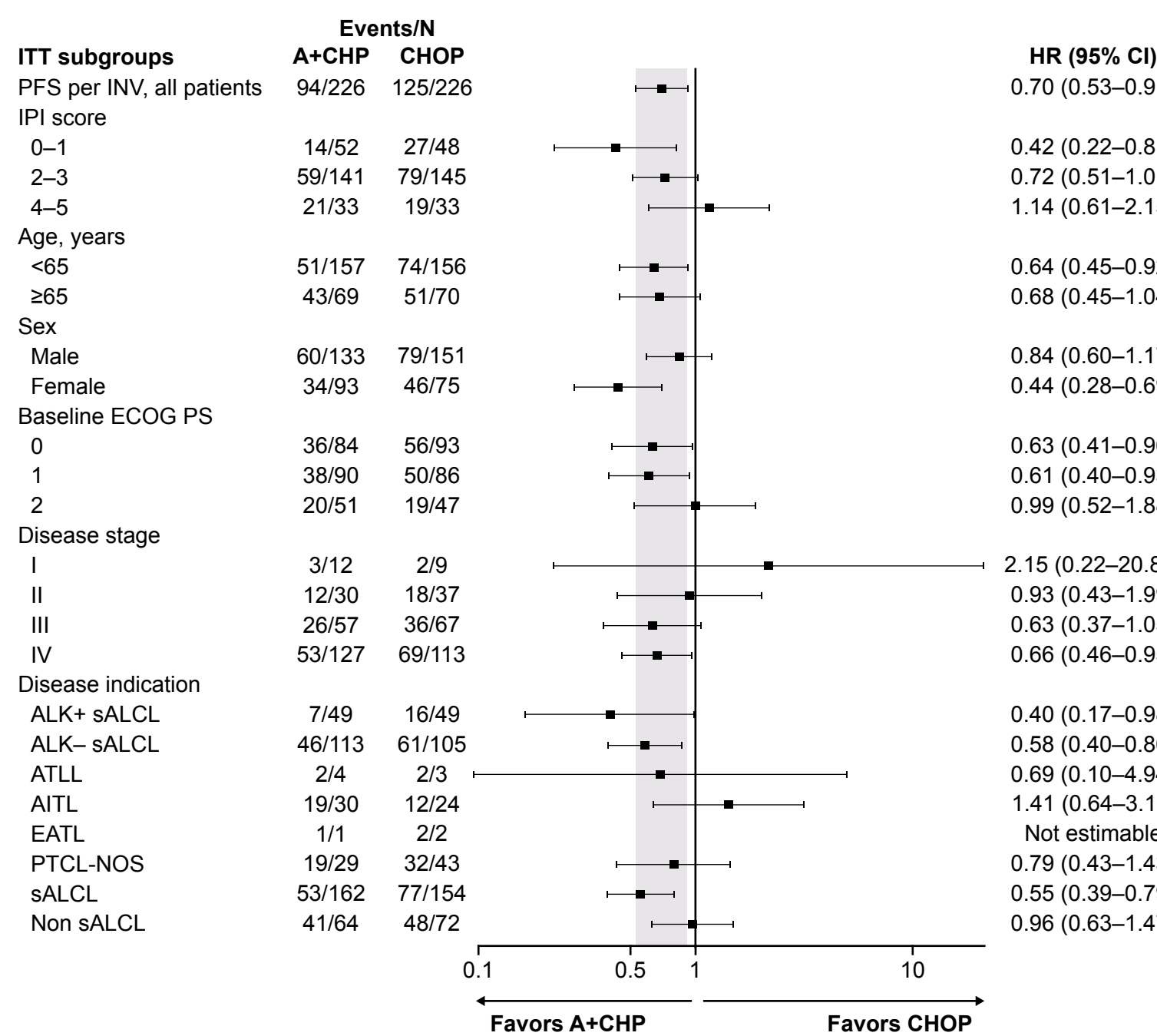


Figure 4: PFS subset analyses



- Overall, OS for the ITT population also generally favored A+CHP (Figure 5).
- This included the following patient subgroups: patients with IPI scores of ≤3, baseline ECOG scores of 0–1, Stage III and IV disease, and patients with ALK+ and ALK-sALCL (Figure 6).
- Twenty-nine patients in the A+CHP arm and 54 patients in the CHOP arm received systemic therapy with brentuximab vedotin after their initial frontline therapy (Table 3).
- In the A+CHP arm, the median time to brentuximab vedotin retreatment after frontline therapy was 15.0 months, with treatment lasting a median of 2.1 months.
- In the CHOP arm, the median time to brentuximab vedotin monotherapy or combination therapy after frontline CHOP was 8.2 months with treatment lasting a median of 2.2 months.
- Seventeen and 22 patients from the A+CHP and CHOP arms received stem cell transplants after frontline therapy; of whom, 16 and 13 received autologous transplants, respectively.
- ORR for patients retreated with brentuximab vedotin following frontline A+CHP was 59% (Table 4).
- Eleven patients had CR and 6 had PR by investigator assessment after retreatment.
- For the 19 patients with sALCL in the A+CHP arm who were retreated with brentuximab vedotin, 8 achieved CR and 4 achieved PR.
- In the CHOP arm, the ORR in patients who received subsequent brentuximab vedotin was 50%, with 16 patients achieving CR and 11 achieving PR (Table 4).

Figure 5: OS at 5 years

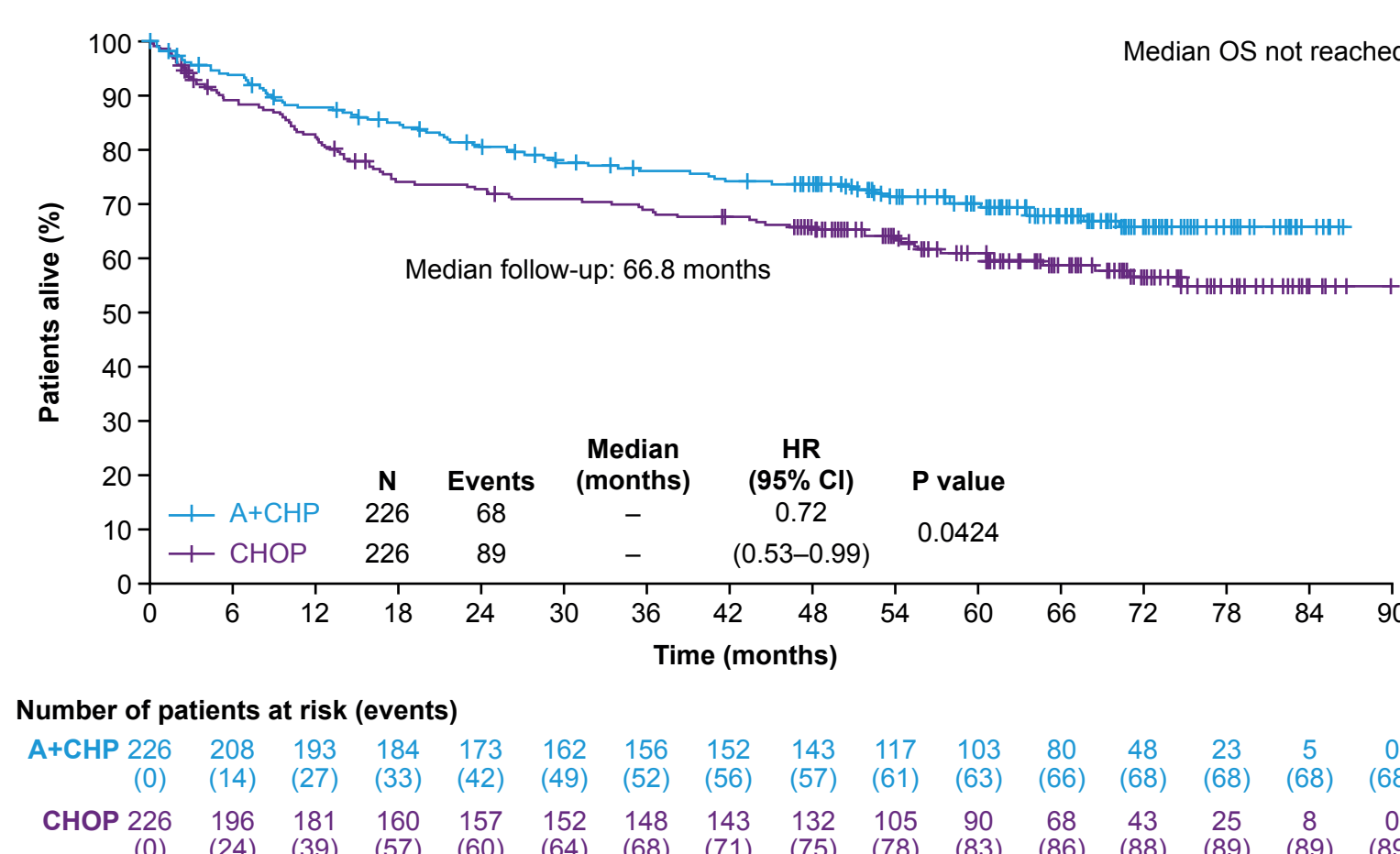


Figure 6: OS subset analyses

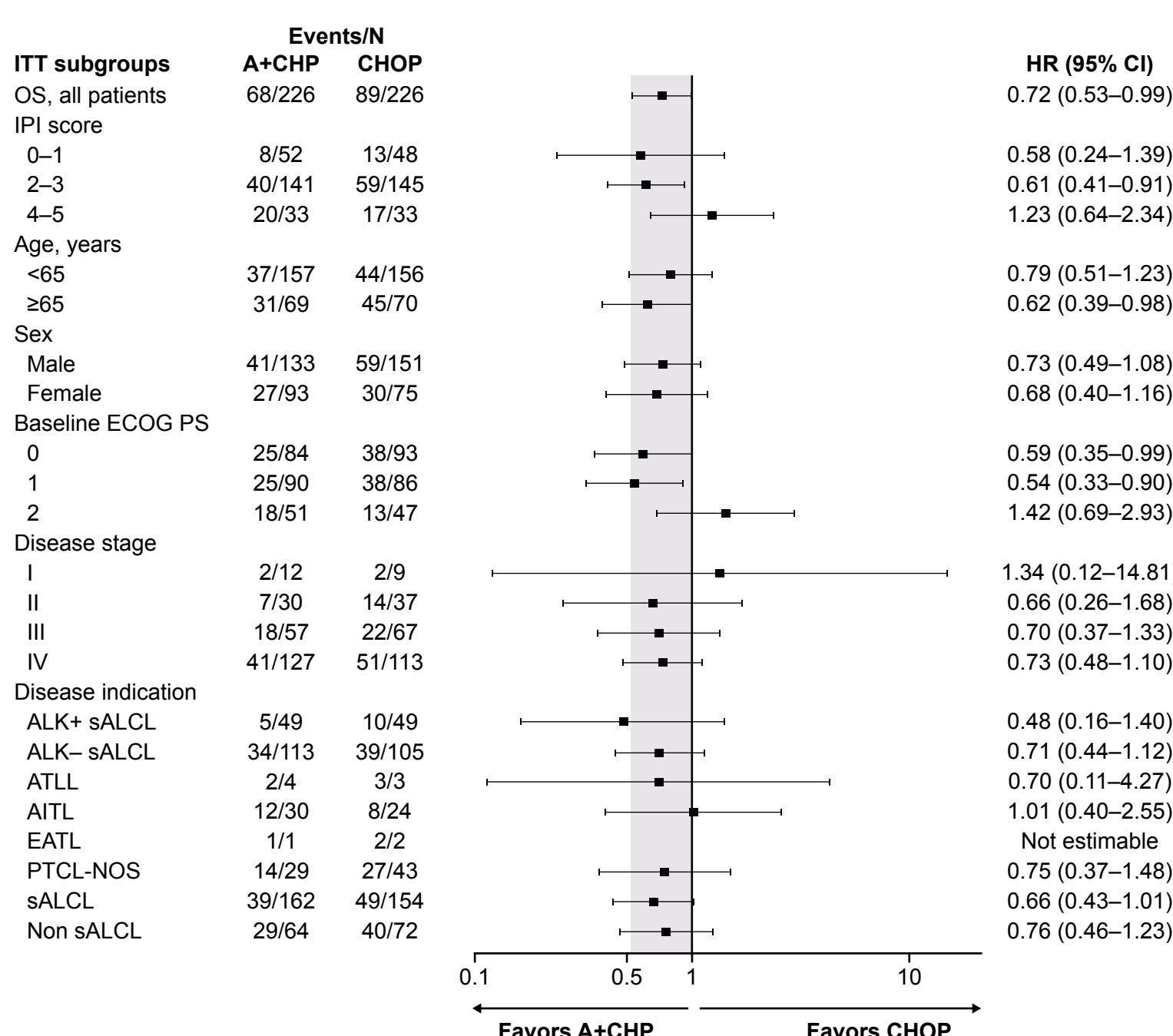


Table 3: Brentuximab vedotin retreatment in A+CHP arm or first brentuximab vedotin treatment in CHOP arm

	A+CHP n=29	CHOP n=54
First brentuximab vedotin treatment after frontline therapy, n (%)		
Monotherapy	25 (86)	48 (89)
Combination therapy	4 (14)	6 (11)
Number of therapies prior to first brentuximab vedotin treatment after frontline therapy, median (range)	0 (0–8)	0 (0–6)
Time from start of frontline treatment to first brentuximab vedotin 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 brentuximab vedotin treatment after frontline therapy (months), median (range) ^a	2.1 (0–18)	2.2 (0–11)

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

Table 4: Response to brentuximab vedotin retreatment (A+CHP arm) or first brentuximab vedotin treatment (CHOP arm) after frontline therapy

Brentuximab vedotin retreatment in A+CHP arm, n (%)	Overall n=29	sALCL n=19	PTCL NOS n=5	AITL n=5	Other n=0
ORR	17 (59)	12 (63)	3 (60)	2 (40)	NA
CR	11 (38)	8 (42)	2 (40)	1 (20)	NA
PR	6 (21)	4 (21)	1 (20)	1 (20)	NA
Brentuximab vedotin first treatment in CHOP arm, n (%)	Overall n=54	sALCL n=39	PTCL NOS n=10	AITL n=4	Other n=1
ORR	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

- PN events were reported in 117 patients in the A+CHP arm and 124 patients in the CHOP arm (Table 5).
- Of these patients, 72% in the A+CHP arm and 78% in the CHOP arm reported either complete resolution or improvement of symptoms by ≥1 grade from the worst grade reported.
- At the last visit, 40% and 34% of patients in the A+CHP and CHOP arms had ongoing PN, respectively, 98% of which were either Grade 1 or 2.

Table 5: Treatment-emergent PN

Patients	A+CHP n=223	CHOP n=226
Treatment-emergent PN, N	117	124
Resolution, ^a n/N (%)	71/117 (61)	82/124 (66)
Improvement, ^b n/N (%)	13/117 (11)	15/124 (12)
Patients with ongoing PN at last visit, N	47	42
Grade 1, n/N (%)	33/47 (70)	30/42 (71)
Grade 2, n/N (%)	13/47 (28)	11/42 (26)
Grade 3, n/N (%)	1/47 (2)	1/42 (2)

^aResolution 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.

^bImprovement was defined as decrease by at least 1 grade from the worst grade with no higher grade thereafter. Patients with improvement in any event at last follow-up were those with at least 1 improved event and the date of improvement was before last follow-up date. Patients with all events resolved were excluded.

Conclusions

- At 5 years, frontline treatment with A+CHP continues to provide clinically meaningful improvement in PFS and OS vs CHOP.
- ITT analysis set:**
 - PFS: HR, 0.70 (95% CI: 0.53–0.91); 30% reduction in the risk of progression, death, or receipt of subsequent anticancer therapy.
 - 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 progression, death, or receipt of subsequent anticancer therapy.
 - OS: HR, 0.66 (95% CI: 0.43–1.01); 34% reduction in the risk of death.
- After frontline therapy, the response to brentuximab vedotin retreatment was 59% for the A+CHP arm, and the response to first brentuximab vedotin treatment was 50% for the CHOP arm.
- PN continues to improve and resolve at 5 years' follow-up.
 - 72% vs 78% of patients (A+CHP vs CHOP) had resolution or improvement of PN events.
 - For ongoing PN events, 98% vs 98% of patients (A+CHP vs CHOP) were Grade 1 or 2.

References

1. Horwitz S, et al. (2019). Lancet 393:229-40.

Abbreviations: A+CHP: brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone; AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; ALK: anaplastic large cell lymphoma; BICR: blinded independent central review; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CI: confidence interval; CR: complete remission; EATL: enteropathy associated T-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; EOT: end of treatment; GCSF: granulocyte colony stimulating factor; HR: hazard ratio; HTCL: hepatosplenic T-cell lymphoma; INV: investigator assessment; IPI: International Prognostic Index; ITT: intention-to-treat; NOS: not otherwise specified; ORR: objective response rate; OS: overall survival; PET: positron emission tomography; PFS: progression-free survival; PN: peripheral neuropathy; PR: partial response; PTCL: peripheral T-cell lymphoma; Q3W: every 3 weeks; RT: radiotherapy; sALCL: systemic anaplastic large cell lymphoma; SCT: stem cell transplant.

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