Conflicts of Interest

- Patricia Walker discloses support for travel accommodations from Roche and honorarium from AstraZeneca

CN4

Patient-Reported Outcomes From the Phase 3, Randomized Study of Acalabrutinib With or Without Obinutuzumab Versus Chlorambucil Plus Obinutuzumab for Treatment-Naïve Chronic Lymphocytic Leukemia (ELEVATE-TN)

Patricia Walker[1]; Jeffrey P. Sharman[2]; Wojciech Jurczak[3]; Talha Munir[4]; Versha Banerji[5]; Steven Coutre[6]; Jennifer A. Woyach[7]; Gilles Salles[8]; William G. Wierda[9]; Priti Patel[10]; Min Hui Wang[10]; Ugochi Emeribe[11]; Emuella Flood[11]; John C. Byrd[7]; Paolo Ghia[12]

[1]Peninsula Health, and Peninsula Private Hospital, Frankston, Victoria, Australia, and Alfred Health, Melbourne, Victoria, Australia; [2]Willamette Valley Cancer Institute/US Oncology, Eugene, OR, USA; [3]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [4]St James's Institute of Oncology, Leeds, UK; [5]Max Rady Faculty of Health Sciences, College of Medicine, University of Manitoba, and Research Institute in Oncology and Hematology, and CancerCare Manitoba, Winnipeg, MB, Canada; [6]Stanford University School of Medicine, Stanford, CA, USA; [7]The Ohio State University Comprehensive Cancer Center and Division of Hematology, Columbus, OH, USA; [8]Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Service d'Hématologie Clinique, Pierre-Bénite, France; [9]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [10]AstraZeneca, South San Francisco, CA, USA; [11]AstraZeneca, Gaithersburg, MD, USA; [12]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy

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Introduction

- Acala is a potent, highly selective BTK inhibitor approved for CLL/SLL and previously treated MCL[1]
- In the ELEVATE-TN study, acala (± obin) demonstrated significant improvements in PFS vs CIT in TN CLL after a median follow-up of 28.3 months[2]
- Herein, we report PRO data from ELEVATE-TN using the same data cutoff

Acala, acalabrutinib; BTK, Bruton tyrosine kinase; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; obin, obinutuzumab; PFS, progression-free survival; PRO, patient-reported outcome; SLL, small lymphocytic lymphoma; TN, treatment-naive.

1. Calquence [package insert]. AstraZeneca Pharmaceuticals; 2019. 2. Sharman JP, et al. *Lancet*. 2020;395:1278-91.

ELEVATE-TN Study Design

- Study details and primary results have been reported[1]

TN CLL (N=535)

Age ≥65 or 18-65 years with coexisting conditions:

- CIRS-G score >6, or
- creatinine clearance 30-69 mL/min

RANDOMIZE 1:1:1

- **Acalabrutinib[a]-Obinutuzumab[b] (AO)**
- **Acalabrutinib[a] monotherapy (A)**
- **Chlorambucil[c]-Obinutuzumab[d] (CO)**

Primary endpoint

- PFS by IRC (AO vs CO)

Key secondary endpoints

- PFS by IRC (A vs CO)
- ORR
- Time to next treatment
- OS
- Safety

***Crossover** from CO to A was allowed after IRC-confirmed progression*

NCT02475681.

[a]100 mg PO BID; [b]100 mg IV on D1, 900 mg on D2, and 1000 mg on D8 and D15 of Cycle 2, then 1000 mg on D1 of Cycles 3-7; [c]0.5 mg/kg PO on D1 and D15 of each cycle for 6 cycles; [d]100 mg IV on D1, 900 mg on D2, and 1000 mg on D8 and D15 of Cycle 1, then 1000 mg on D1 of Cycles 2-6.

A, acalabrutinib; BID, twice daily; C, chlorambucil; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; CLL, chronic lymphocytic leukemia; D, day; IRC, independent review committee; IV, intravenously; O, obinutuzumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally.

1. Sharman JP, et al. *Lancet*. 2020;395:1278-91.

Methods

- PRO assessments were exploratory endpoints
  - FACIT-Fatigue GFS
    - Scores: 0–52 (lower scores = worse fatigue-related QoL)
    - Clinically meaningful improvement: score increase ≥3 points
  - EORTC QLQ-C30 GHS
    - Scores: 0–100 (lower scores = worse health status)
    - Clinically meaningful improvement: score increase ≥8 points
- Collected at screening, D1 of C1-7, then every 24 wk starting at C13 until progression

C, cycle; D, day; EORTC QLQ-C30 GHS, European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30 Global Health Status; FACIT-Fatigue GFS, Functional Assessment of Chronic Illness Therapy-Fatigue Global Fatigue Score; PRO, patient-reported outcomes; QoL, quality of life.

Methods (cont'd)

- PROs assessed in the ITT population and in patients with severe fatigue (GFS of ≤34 points) at baseline
- Analyses:
  - Changes from baseline over time in GFS and GHS (MMRM methodology)
  - Time to clinically meaningful deterioration[a] (assessed post hoc)
    - GFS[b] (score decrease of ≥3 points)
    - GHS[c] (score decrease of ≥10 points)

[a]Patients were censored at the time of disease progression, start of subsequent treatment, crossover, or death, whichever occured first, if no deterioration had occurred up to that point. [b]Patients with a baseline score of <3 were censored at their last assessment before DCO or at their death date, whichever occurred first. [c]Patients with a baseline score of <10 were censored at their last assessment before DCO or at their death date, whichever occurred first.

DCO, data cut-off, GFS, Global Fatigue Score; GHS, Global Health Status; ITT, intent-to-treat; MMRM, mixed-model repeated measures; PRO, patient-reported outcomes.

Demographics and Baseline Characteristics

Characteristic	A (n=179)	AO (n=179)	CO (n=177)
Age, median (range), years	70.0 (44-87)	70.0 (41-88)	71.0 (46-91)
≥65 years	151 (84.4)	144 (80.4)	153 (86.4)
ECOG PS score			
0-1	167 (93.3)	169 (94.4)	168 (94.9)
2	12 (6.7)	10 (5.6)	9 (5.1)
Rai stage 3 or 4			
Stage 3	50 (27.9)	48 (26.8)	40 (22.6)
Stage 4	37 (20.7)	38 (21.2)	38 (21.5)
del(17p)	19 (10.6)	21 (11.7)	17 (9.6)
GFS completion at BL	156 (87.2)	152 (84.9)	141 (79.7)
GHS completion at BL	157 (87.7)	151 (84.4)	142 (80.2)
Severe fatigue[a] at BL	56 (31.3)	53 (29.6)	42 (23.7)

Data are n (%) unless otherwise specified.
[a]FACIT-Fatigue GFS score ≤34; all patients with severe fatigue completed the GFS and GHS at baseline.
A, acalabrutinib; BL, baseline; C, chlorambucil; ECOG PS, Eastern Cooperative Oncology Group performance score; GFS, Global Fatigue Score; GHS, Global Health Status; O, obinutuzumab.

Disposition

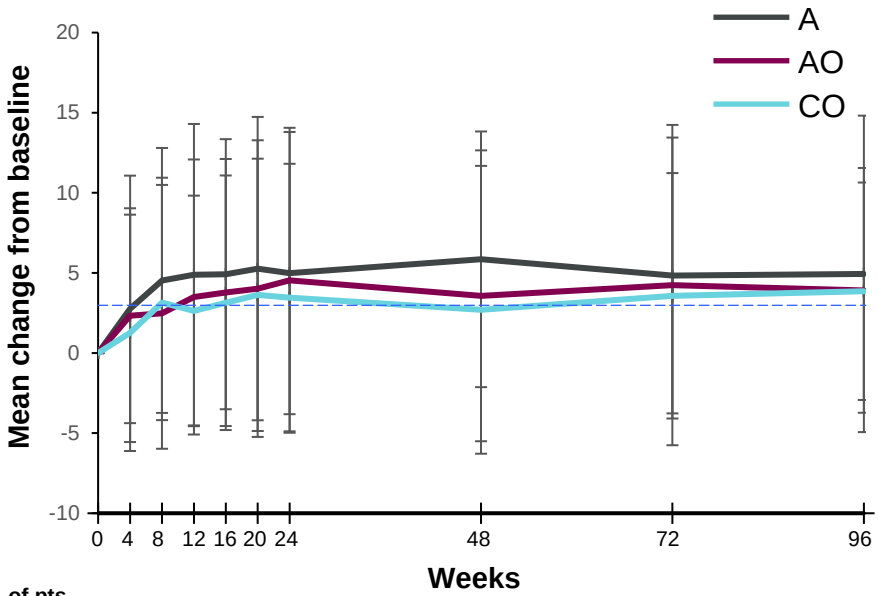
- Treatment discontinuation for any reason: A, n=36 (20.1%); AO, n=37 (20.7%); CO, n=32 (18.1%)
  - Treatment discontinuation due to PD: A, n=7 (3.9%); AO, n=6 (3.4%); CO, n=3 (1.7%)
- As of the data cutoff (Feb 8, 2019):
  - 142 (79.3%) acala patients (each arm) were continuing treatment
  - 137 (77.4%) CO patients had completed treatment; 45 (25.4%) had crossed over to A
    - GFS and GHS completion rates (CO) were low at later timepoints (week 72: 35.6% and 36.7%; week 96: 23.7% and 24.3%)

A, acalabrutinib; C, chlorambucil; GFS, Global Fatigue Score; GHS, Global Health Status; O, obinutuzumab; PD, progressive disease.

GFS and GHS Scores Improved in All Treatment Arms (ITT)

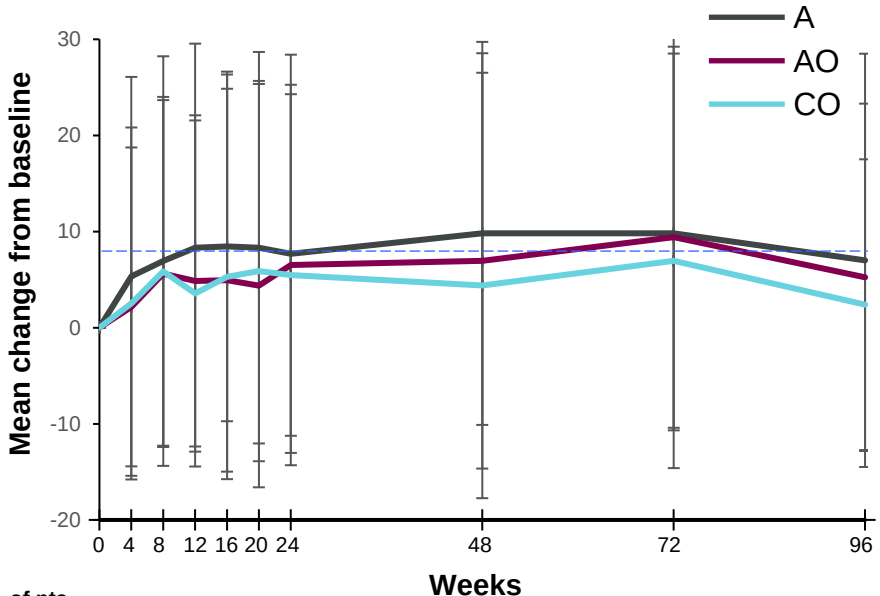
- Improvements observed by week 4 and maintained at 96 weeks in all treatment arms

GFS



No. of pts										
A	156	136	135	136	133	126	129	112	100	81
AO	152	138	133	137	132	133	132	120	107	92
CO	141	121	121	125	109	112	118	89	54	38

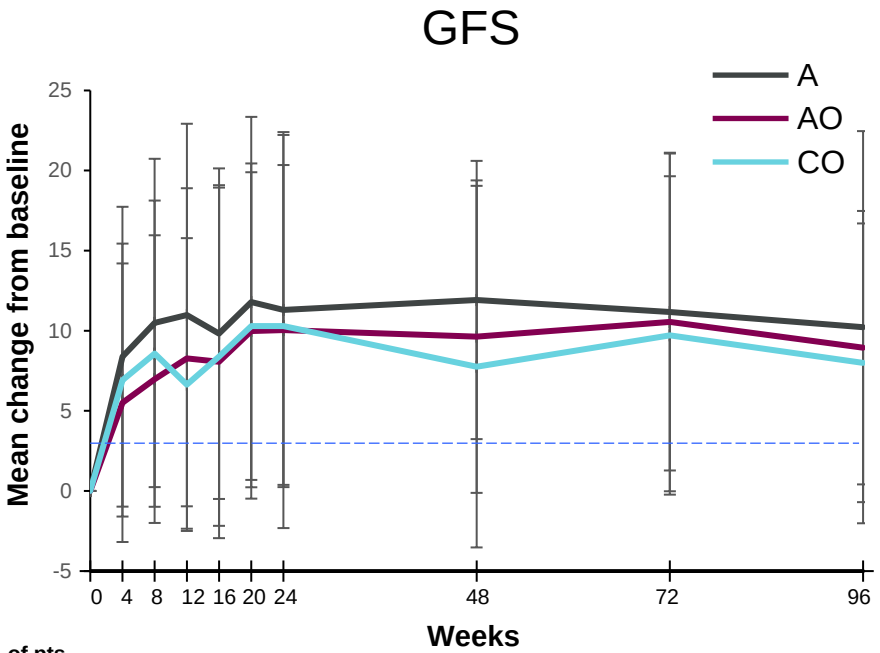
GHS



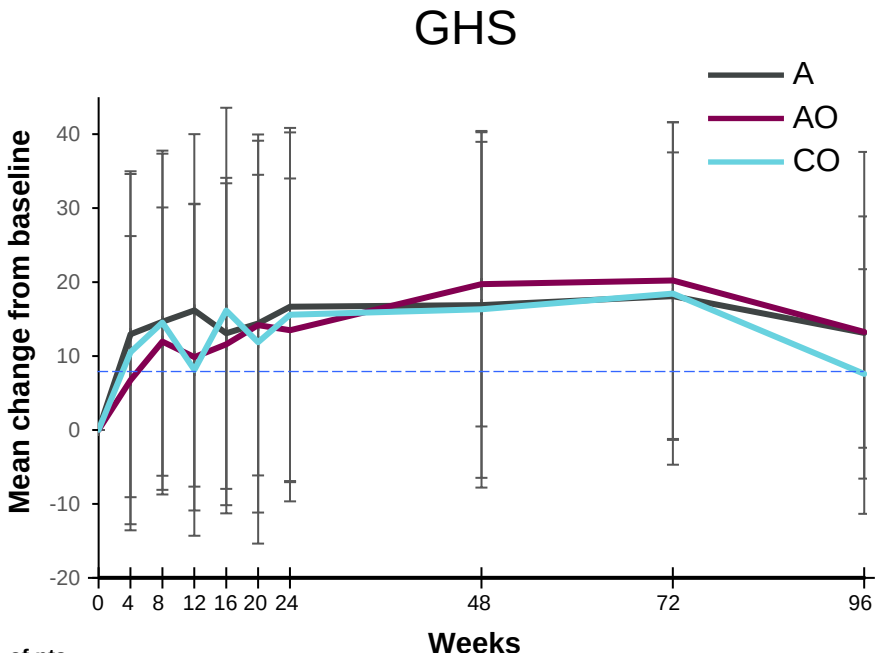
No. of pts										
A	157	137	138	137	135	127	130	112	100	82
AO	152	138	133	137	133	135	134	121	107	92
CO	142	122	122	126	110	113	120	89	55	38

Dotted lines indicate thresholds for clinically meaningful improvement.
A, acalabrutinib; C, chlorambucil; GFS, Global Fatigue Score; GHS, Global Health Status; ITT, intent-to-treat; O, obinutuzumab.

GFS and GHS Improvements Were Greater in Patients With Severe Fatigue in All Treatment Arms



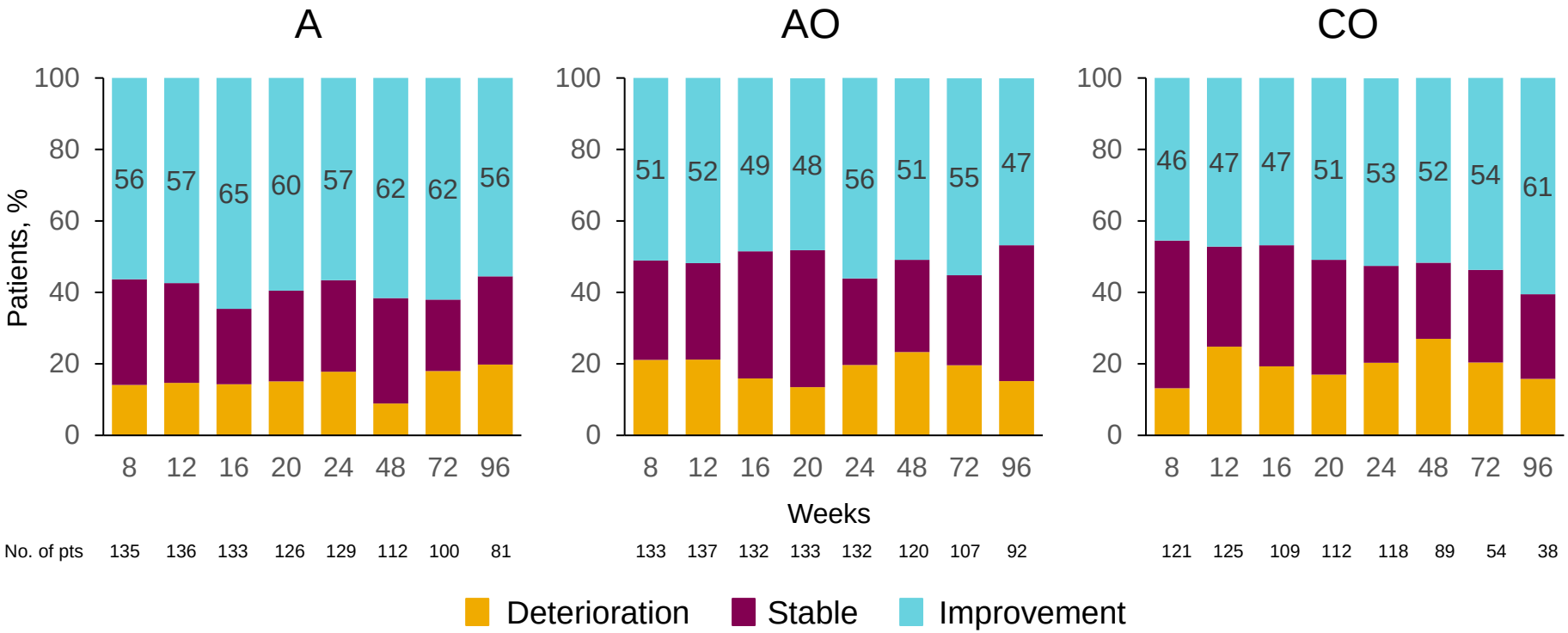
No. of pts										
A	56	47	47	49	50	44	44	38	35	33
AO	53	47	46	49	46	47	47	41	40	34
CO	42	38	35	39	32	33	31	25	14	11



No. of pts										
A	56	47	49	50	51	44	44	38	35	33
AO	53	47	46	49	46	47	47	41	40	34
CO	42	38	35	39	32	33	31	25	14	11

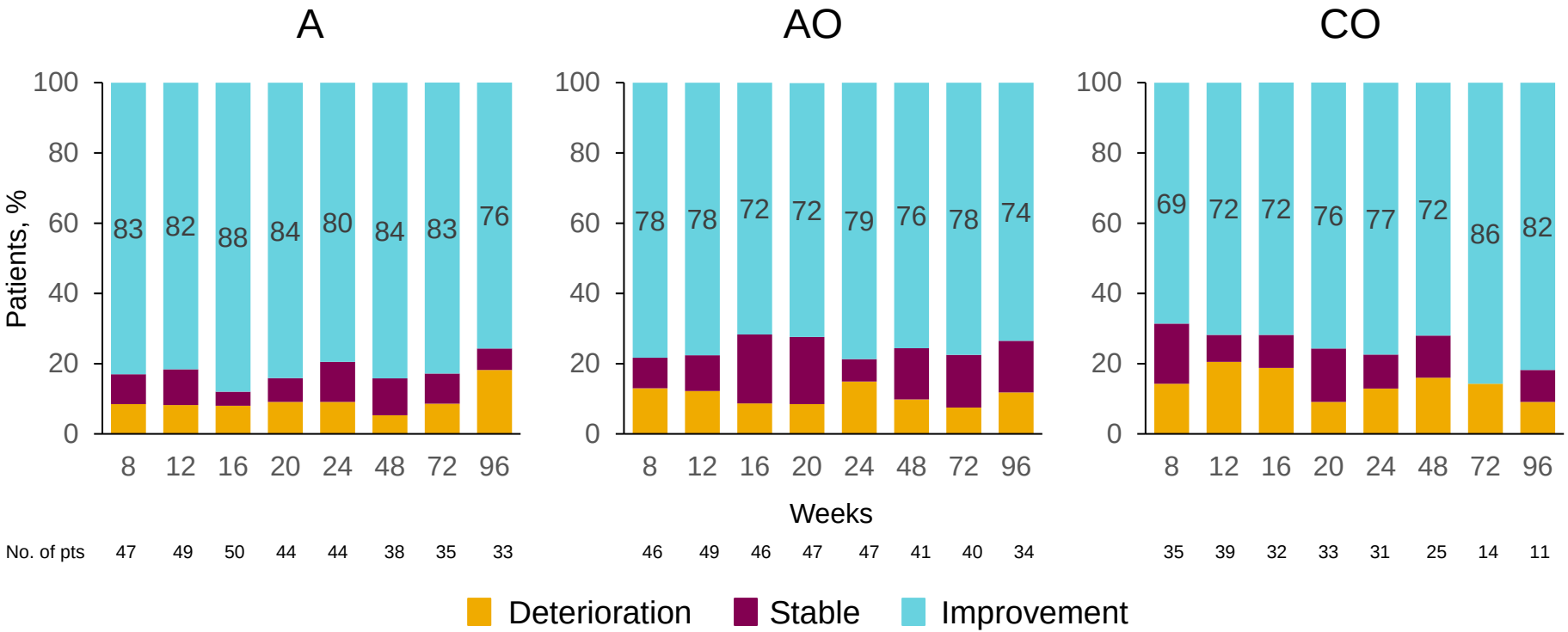
Dotted lines indicate thresholds for clinically meaningful improvement.
A, acalabrutinib; C, chlorambucil; GFS, Global Fatigue Score; GHS, Global Health Status; O, obinutuzumab.

Most Patients Had Improved or Stable GFS Over Time in All Treatment Arms (ITT)



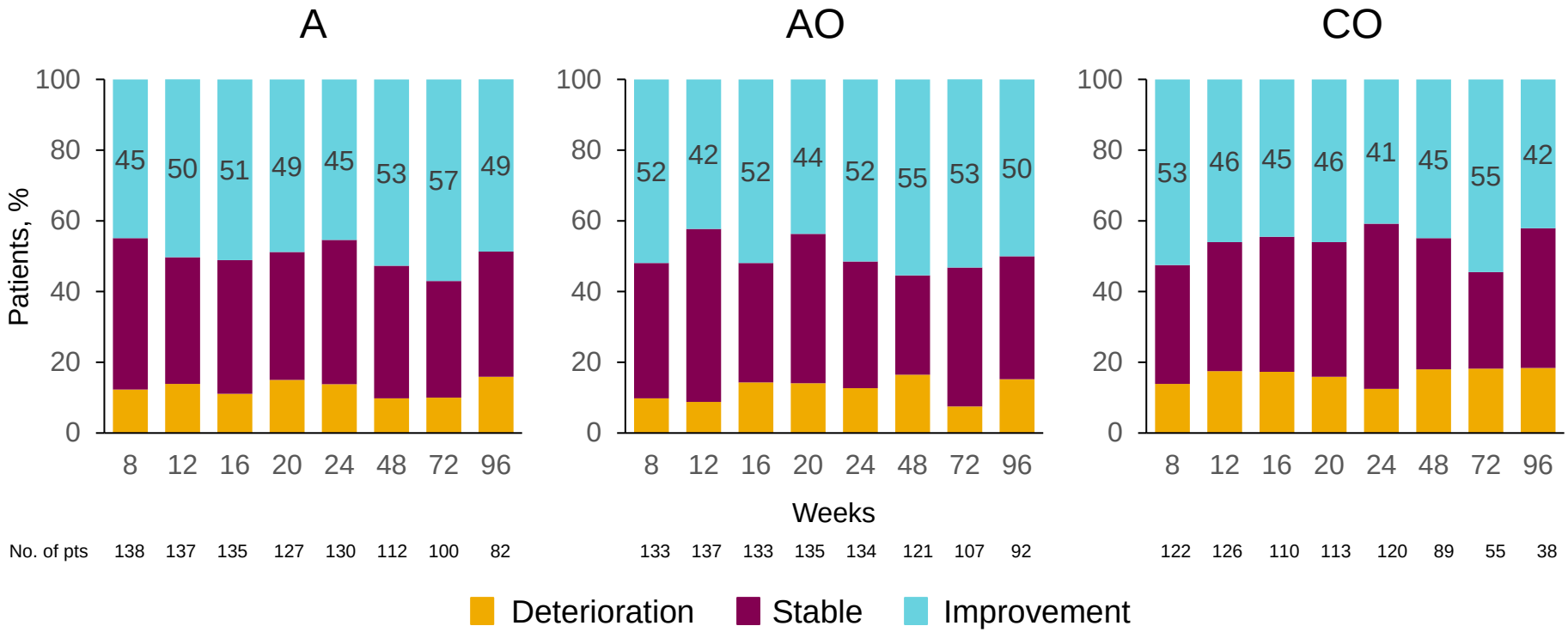
A, acalabrutinib; C, chlorambucil; GFS, Global Fatigue Score; ITT, intent-to-treat; O, obinutuzumab.

GFS Improvements Were Greater in Patients With Severe Fatigue in All Treatment Arms



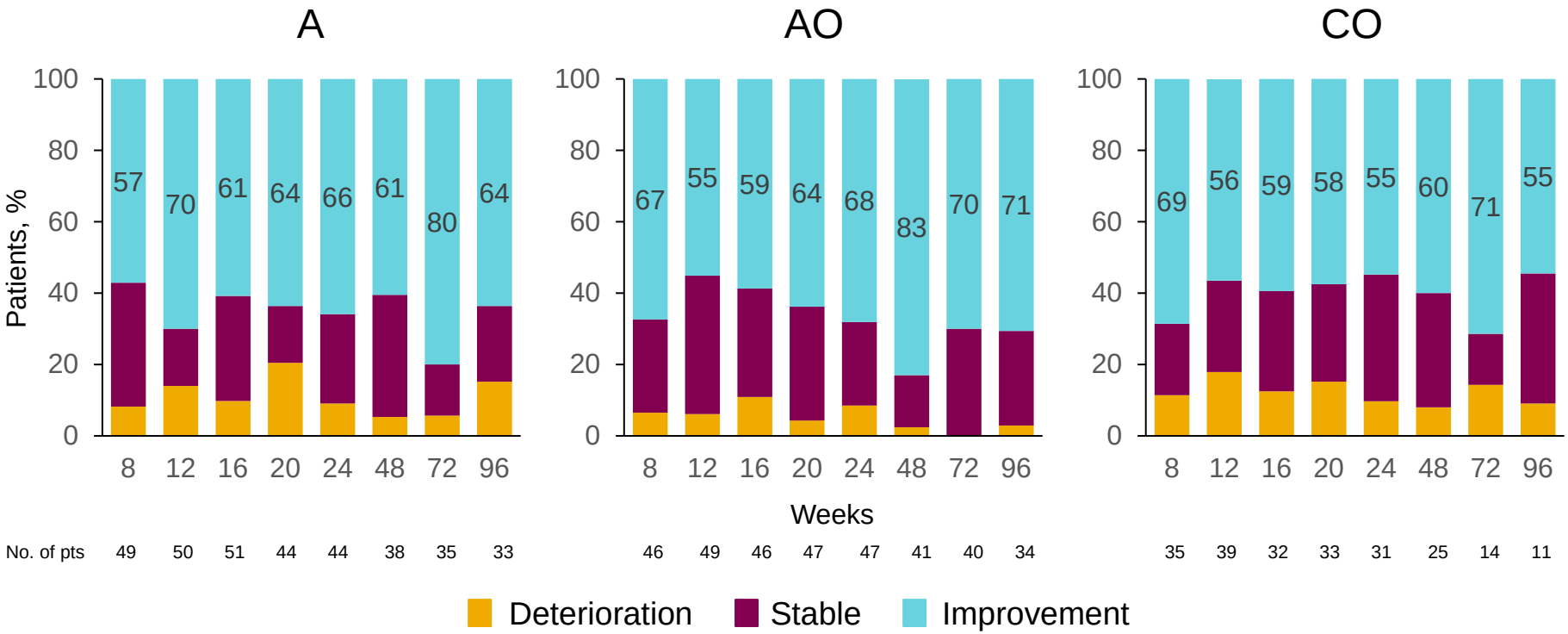
A, acalabrutinib; C, chlorambucil; GFS, Global Fatigue Score; O, obinutuzumab.

Most Patients Had Improved or Stable GHS Scores Over Time in All Treatment Arms (ITT)



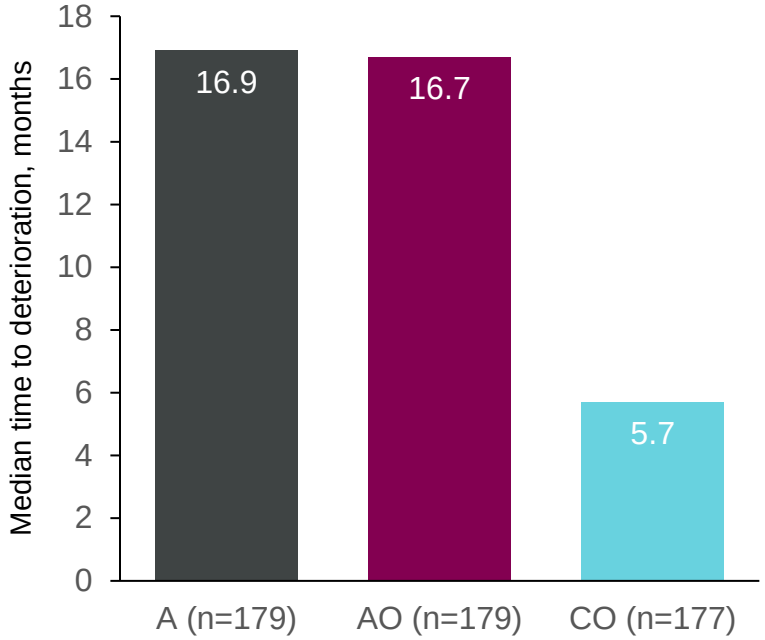
A, acalabrutinib; C, chlorambucil; GHS, Global Health Status; ITT, intent-to-treat; O, obinutuzumab.

GHS Improvements Were Greater in Patients With Severe Fatigue in All Treatment Arms



A, acalabrutinib; C, chlorambucil; GHS, Global Health Status; O, obinutuzumab.

Median Time to Deterioration in GFS Was Longer in Both Acala-containing Arms vs CO



Treatment group	No. (%) pts with events	Median time (95% CI)	HR (95% CI) vs CO	2-sided P-value
A (n=179)	63 (35.2)	16.9 (16.8, NE)	0.69 (0.48, 0.98)	**0.0376**
AO (n=179)	74 (41.3)	16.7 (5.7, NE)	0.78 (0.55, 1.10)	0.1596
CO (n=177)	68 (38.4)	5.7 (3.2, NE)	–	–

A, acalabrutinib; C, chlorambucil; CI, confidence interval; GFS, Global Fatigue Score; HR, hazard ratio; NE, not estimable; O, obinutuzumab.

Median Time to Deterioration in GHS Was Not Reached in Any Treatment Arm

Treatment group	No. (%) pts with events	Median time (95% CI)	HR (95% CI) vs CO	2-sided P-value
A (n=179)	42 (23.5)	NE (NE, NE)	0.72 (0.46, 1.10)	0.1274
AO (n=179)	56 (31.3)	NE (NE, NE)	0.89 (0.59, 1.33)	0.5605
CO (n=177)	46 (26.0)	NE (NE, NE)	–	–

A, acalabrutinib; C, chlorambucil; CI, confidence interval; GHS, Global Health Status; HR, hazard ratio; NE, not estimable; O, obinutuzumab.

Potential Limitations

- Patients and investigators were not blinded to study treatment
- Comparison of continuous vs fixed-duration therapy
- Low GFS and GHS completion rates in the CO arm at later timepoints
- PRO measures were only collected until disease progression
- Relatively short follow-up period
- Lack of analyses assessing potential correlations between PRO outcomes and AEs or efficacy outcomes

AE, adverse events; C, chlorambucil; GFS, global fatigue score; GHS, global health status; O, obinutuzumab; PRO, patient-reported outcomes.

Key Conclusions

- In the primary ELEVATE-TN report, acala (± obin) demonstrated significant improvements in PFS vs CIT in patients with TN CLL[1]
- In the PRO analysis from ELEVATE-TN, all treatments demonstrated improvements in fatigue scores over time
  - Improvements were further increased in patients with severe fatigue at baseline
- Based on time-to-deterioration data, benefits in fatigue-related QoL were more sustained in the acala-containing arms vs CIT
- Overall, the previously reported significant improvements in PFS with acala-containing treatment[1] were accompanied by clinically meaningful HRQoL benefits

CIT, chemoimmunotherapy; HRQoL, health-related quality of life; PFS, progression-free survival; PRO, patient-reported outcomes; QoL, quality of life.

1. Sharman JP, et al. *Lancet*. 2020;395:1278-91.

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Presenter contact information: Patricia Walker, trishwalker01@gmail.com