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ASTRUM-002: First-Line Serplulimab Plus Chemotherapy With or Without HLX04 in Advanced Nonsquamous Non-small Cell Lung Cancer

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Background

- The addition of a PD-(L)1 inhibitor to first-line chemotherapy has improved survival outcomes in advanced nonsquamous (nsq) NSCLC.
- While the IMpower150 trial demonstrated superior efficacy of the atezolizumab-bevacizumab-chemotherapy triplet over bevacizumab-chemotherapy, the APPLE trial revealed no survival benefit when comparing this same triplet regimen against atezolizumab-chemotherapy alone.

Current evidence on whether the addition of bevacizumab to first-line PD-1 inhibitor plus chemotherapy regimens provides synergistic efficacy compared to PD-1 inhibitor-chemotherapy combinations remains limited.

Here we report results from ASTRUM-002, a phase 3 trial sequentially evaluating serplulimab (PD-1 inhibitor) + HLX04 (bevacizumab biosimilar) + chemotherapy versus serplulimab + chemotherapy versus chemotherapy in advanced nsqNSCLC.

NSCLC, non-small-cell lung cancer; PD-(L)1, programmed death-1 or programmed death-ligand 1; PD-1, programmed death-1.

Study design

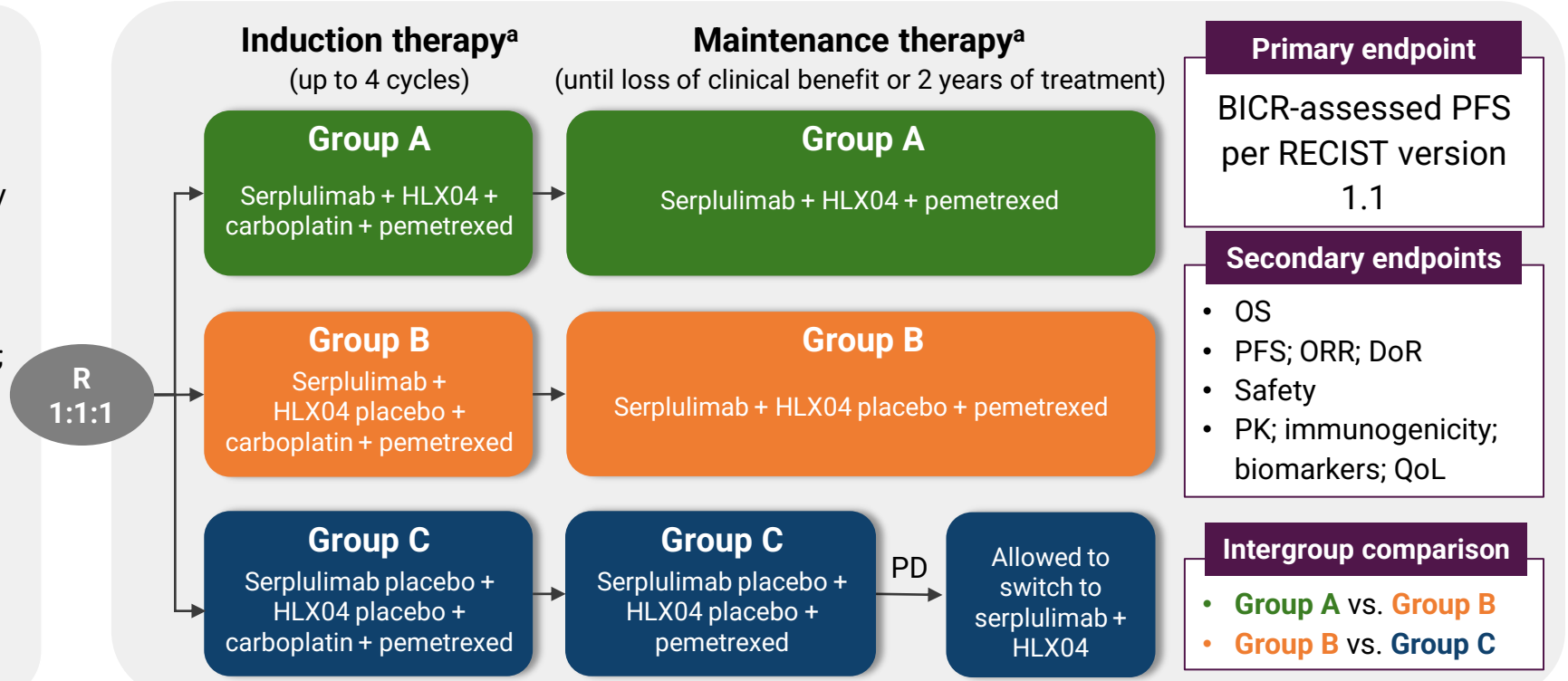
A randomized, double-blind, multicenter phase 3 study (NCT03952403)

Key inclusion criteria:

- Aged 18–75 years;
- ECOG PS of 0 or 1;
- Histologically/cytologically diagnosed with stage IIIB, IIIC, or IV nsqNSCLC that cannot be treated with surgery or radiotherapy;
- No *EGFR* sensitizing mutations or *ALK* or *ROS1* gene rearrangements;
- No prior systemic treatment for nsqNSCLC.

Stratification factors:

- PD-L1 expression level (negative vs. positive vs. not evaluable);
- Smoking history (yes vs. no);
- Brain metastasis (yes vs. no).

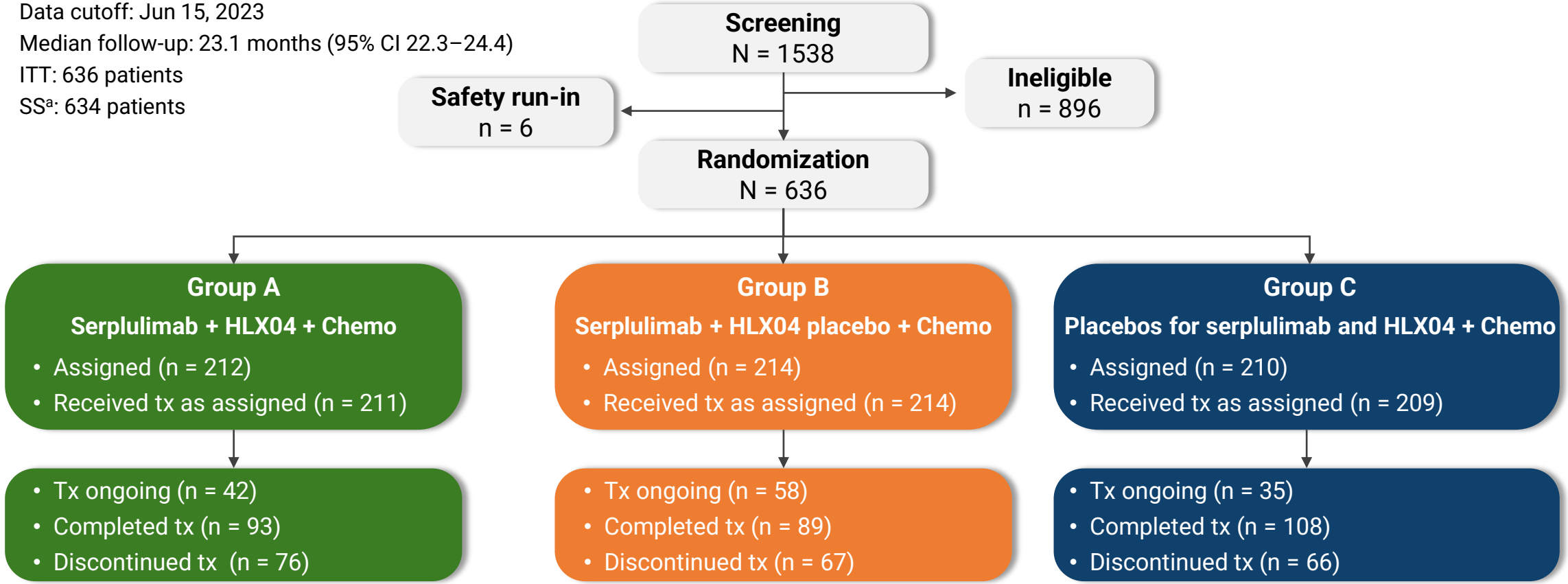


[a] Serplulimab, 4.5 mg/kg; HLX04, 15 mg/kg; carboplatin, AUC 5, up to 800 mg; pemetrexed, 500 mg/m^2. All study drugs were administered intravenously every 3 weeks.

ALK, anaplastic lymphoma kinase; AUC, area under the curve; BICR, blinded independent central review; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; PS, performance status; EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; QoL, quality of life; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; ROS1, c-ros oncogene 1; vs., versus.

Patient disposition

Between Nov 25, 2019 to Jun 15, 2022, 642 patients were enrolled
Data cutoff: Jun 15, 2023
Median follow-up: 23.1 months (95% CI 22.3–24.4)
ITT: 636 patients
SS[a]: 634 patients



[a] One patient in group A and one in group C did not receive the assigned study treatment.
Chemo, chemotherapy; CI, confidence interval; ITT, intention-to-treat; SS, safety set; tx, treatment.

Baseline demographic and disease characteristics

	Group A (n = 212)	Group B (n = 214)	Group C (n = 210)
Median age (range), years	62 (27–74)	62 (29–75)	61 (33–75)
Sex, n (%)			
Male	152 (72)	157 (73)	156 (74)
Female	60 (28)	57 (27)	54 (26)
ECOG PS, n (%)			
0	53 (25)	60 (28)	58 (28)
1	158 (75)	154 (72)	152 (72)
Missing[a]	1 (<1)	0	0
Smoking history, n (%)			
Yes	142 (67)	143 (67)	140 (67)
No	70 (33)	71 (33)	70 (33)
Histologic subtype, n (%)			
Adenocarcinoma	210 (99)	208 (97)	208 (99)
Large cell carcinoma	0	3 (1)	0
Others[c]	2 (1)	3 (1)	2 (1)

	Group A (n = 212)	Group B (n = 214)	Group C (n = 210)
Clinical stage, n (%)			
Stage IIIB/IIIC	40 (19)	30 (14)	31 (15)
Stage IV	172 (81)	184 (86)	179 (85)
Brain metastasis, n (%)			
Yes	39 (18)	41 (19)	39 (19)
No	173 (82)	173 (81)	171 (81)
PD-L1 expression by CPS, n (%)			
CPS <1	43 (20)	44 (21)	43 (20)
CPS ≥1	166 (78)	166 (78)	164 (78)
Indeterminable	3 (1)	4 (2)	3 (1)
PD-L1 expression by TPS[b], n (%)			
TPS <1%	94 (44)	84 (39)	68 (32)
1% ≤ TPS <50%	58 (27)	64 (30)	73 (35)
TPS ≥50%	55 (26)	62 (29)	62 (30)

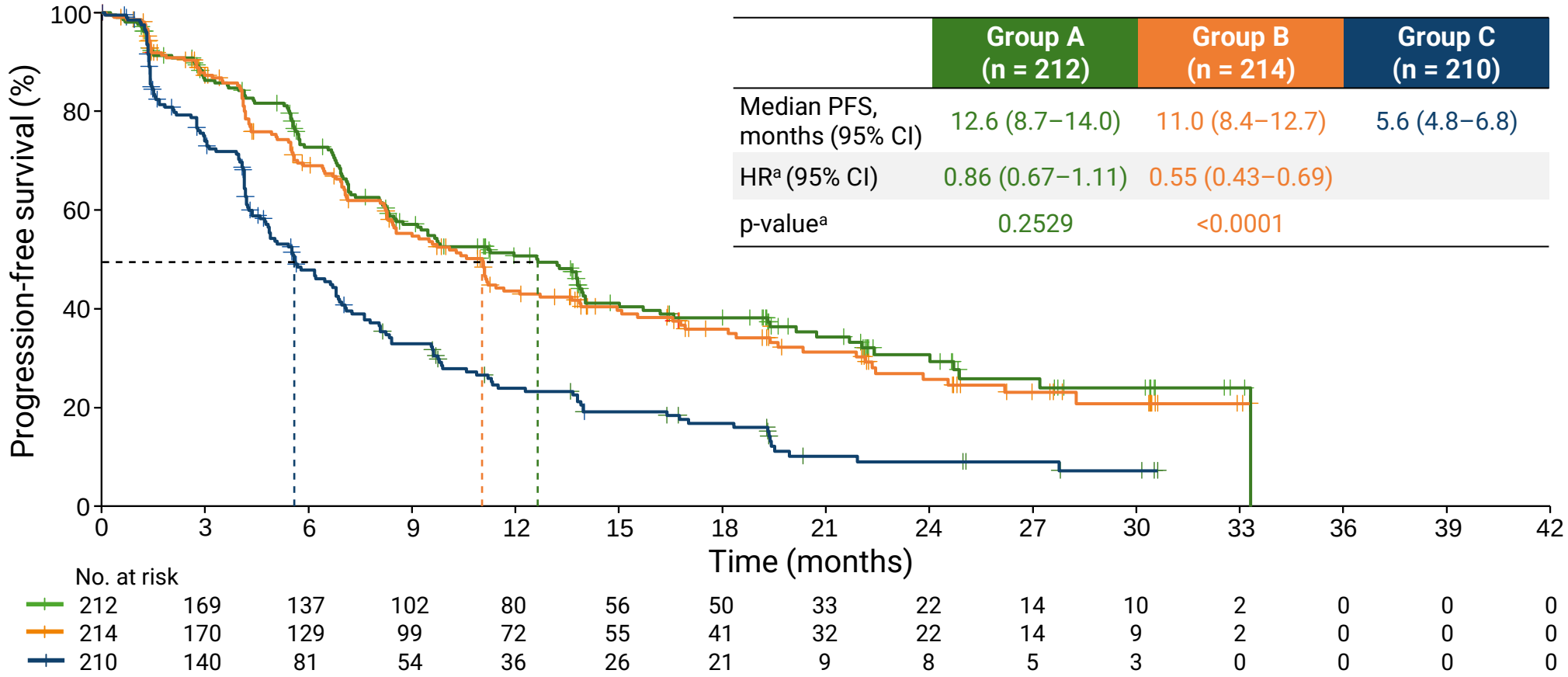
[a] One patient in group A had an ECOG PS score of "not available" recorded during the screening period. [b] Assessed among the evaluable patients during the screening period. [c] Two patients in group C had a mucinous adenocarcinoma, one patient each in group A and B had a lympho-epithelioma-like carcinoma, one patient each in group A and B had a sarcomatoid carcinoma, and one patient in group B had a spindle cell neoplasm.

CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

Primary endpoint: BICR-assessed PFS

Improved PFS upon adding serplulimab to chemotherapy

	Group A (n = 212)	Group B (n = 214)	Group C (n = 210)
Median PFS, months (95% CI)	12.6 (8.7–14.0)	11.0 (8.4–12.7)	5.6 (4.8–6.8)
HR[a] (95% CI)	0.86 (0.67–1.11)	0.55 (0.43–0.69)	
p-value[a]	0.2529	<0.0001	

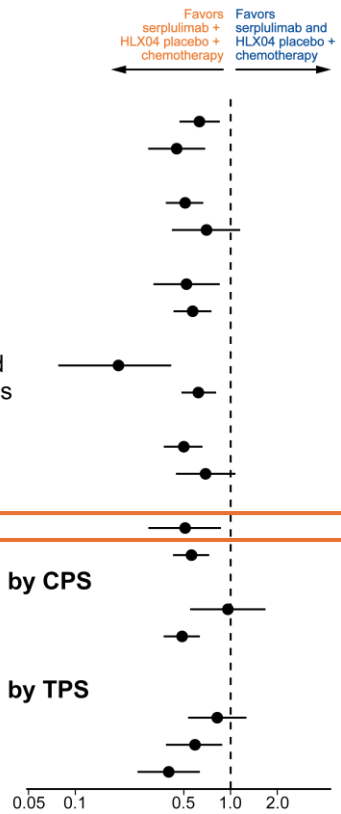


[a] Group B was statistically compared to Group C, while Group A was compared to Group B.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; No., number; PFS, progression-free survival.

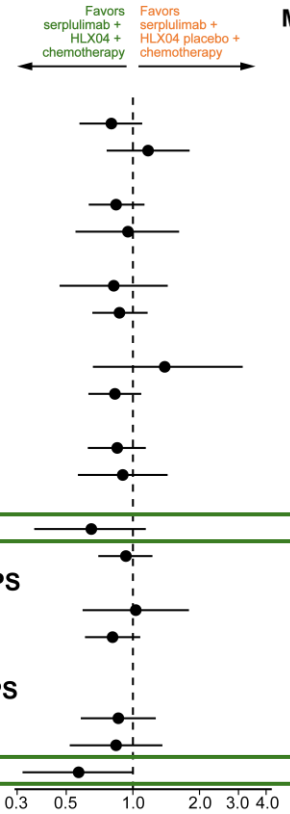
Subgroup analysis of BICR-assessed PFS

Group B versus Group C



Subgroup	Median PFS (months) Group B (n = 214)	Group C (n = 210)	HR (95% CI)	p-value
Age				
<65 years	8.5	5.6	0.63 (0.47–0.85)	0.0024
≥65 years	12.7	5.8	0.45 (0.30–0.69)	0.0001
Sex				
Male	9.0	4.9	0.51 (0.38–0.67)	<0.0001
Female	11.1	8.3	0.70 (0.42–1.15)	0.1543
ECOG PS				
0	12.7	6.2	0.52 (0.32–0.85)	0.0082
1	9.6	5.6	0.57 (0.43–0.75)	<0.0001
Clinical stage				
Locally advanced	20.3	5.6	0.19 (0.08–0.42)	<0.0001
Distant metastasis	10.3	5.6	0.62 (0.48–0.81)	0.0003
Smoking history				
Yes	10.4	4.9	0.50 (0.37–0.66)	<0.0001
No	11.1	8.1	0.69 (0.45–1.07)	0.0973
Brain metastasis				
Yes	8.1	4.1	0.51 (0.30–0.87)	0.0115
No	11.2	6.2	0.56 (0.43–0.73)	<0.0001
PD-L1 expression by CPS				
CPS <1	11.4	7.0	0.96 (0.55–1.68)	0.8773
CPS ≥1	10.4	5.6	0.49 (0.37–0.63)	<0.0001
Indeterminable	NA	NA	NA	NA
PD-L1 expression by TPS				
TPS <1%	8.5	6.2	0.82 (0.53–1.26)	0.3649
1%≤ TPS <50%	10.3	6.8	0.59 (0.38–0.88)	0.0105
TPS ≥50%	12.1	4.4	0.40 (0.25–0.63)	<0.0001

Group A versus Group B

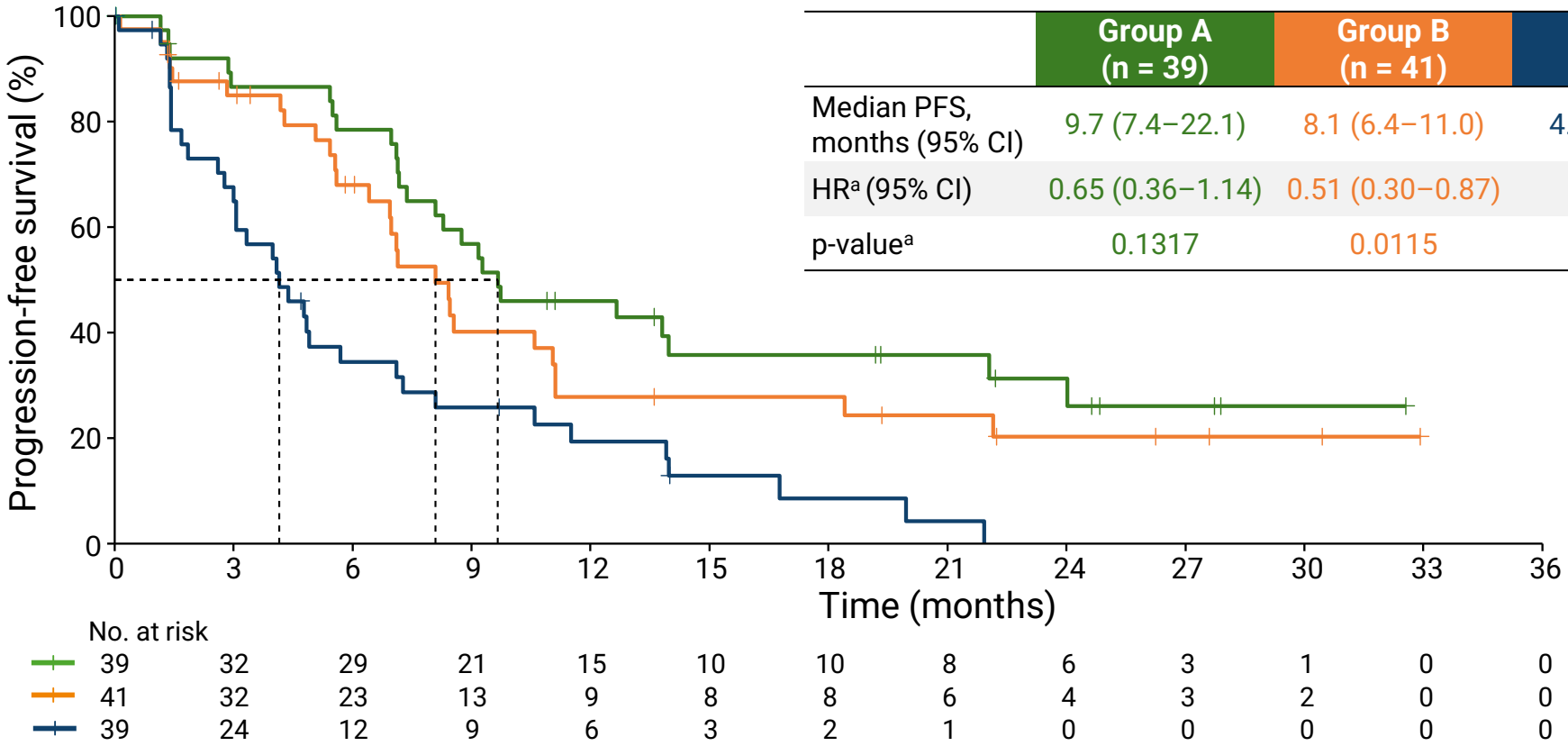


Subgroup	Median PFS (months) Group A (n = 212)	Group B (n = 214)	HR (95% CI)	p-value
Age				
<65 years	9.7	8.5	0.80 (0.58–1.10)	0.1690
≥65 years	13.9	12.7	1.17 (0.76–1.80)	0.4712
Sex				
Male	13.2	9.0	0.84 (0.63–1.13)	0.2514
Female	9.8	11.1	0.95 (0.55–1.61)	0.8490
ECOG PS				
0	14.0	12.7	0.82 (0.47–1.43)	0.4954
1	12.0	9.6	0.87 (0.66–1.16)	0.3587
Clinical stage				
Locally advanced	16.6	20.3	1.39 (0.66–3.12)	0.3959
Distant metastasis	11.3	10.3	0.83 (0.63–1.09)	0.1813
Smoking history				
Yes	13.3	10.4	0.85 (0.63–1.14)	0.2778
No	12.0	11.1	0.90 (0.57–1.43)	0.6681
Brain metastasis				
Yes	9.7	8.1	0.65 (0.36–1.14)	0.1317
No	13.3	11.2	0.93 (0.70–1.22)	0.5914
PD-L1 expression by CPS				
CPS <1	8.3	11.4	1.03 (0.59–1.79)	0.9075
CPS ≥1	13.8	10.4	0.81 (0.61–1.08)	0.1517
Indeterminable	NA	NA	NA	NA
PD-L1 expression by TPS				
TPS <1%	8.3	8.5	0.86 (0.58–1.27)	0.4408
1%≤ TPS <50%	11.3	10.3	0.84 (0.52–1.36)	0.4887
TPS ≥50%	27.2	12.1	0.57 (0.32–0.99)	0.0470

BICR, blinded independent central review; CI, confidence interval; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NA, not available; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

Patients with brain metastasis

Improved PFS upon adding serplulimab to chemotherapy



	Group A (n = 39)	Group B (n = 41)	Group C (n = 39)
Median PFS, months (95% CI)	9.7 (7.4–22.1)	8.1 (6.4–11.0)	4.1 (3.0–5.7)
HR[a] (95% CI)	0.65 (0.36–1.14)	0.51 (0.30–0.87)	
p-value[a]	0.1317	0.0115	

[a] Group B was statistically compared to Group C, while Group A was compared to Group B.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; No., number; PFS, progression-free survival.

Secondary efficacy endpoints

Endpoint (according to BICR assessments)	Group A (n = 212)	Group B (n = 214)	Group C (n = 210)
Confirmed tumor response			
CR, n (%)	2 (1)	2 (1)	2 (1)
PR, n (%)	114 (54)	111 (52)	56 (27)
SD, n (%)	68 (32)	72 (34)	94 (45)
PD, n (%)	13 (6)	19 (9)	38 (18)
NE, n (%)	15 (7)	10 (5)	20 (10)
Confirmed ORR[a], % (95% CI)	55 (48–62)	53 (46–60)	28 (22–34)
Odds ratio[a] (95% CI)	1.07 (0.73–1.58)	2.84 (1.90–4.23)	
p-value[a]	0.7139	<0.0001	
Median DoR[a], months (95% CI)	18.3 (11.2–29.1)	15.4 (11.0–21.2)	9.7 (5.5–13.9)
HR[a] (95% CI)	0.87 (0.60–1.27)	0.57 (0.37–0.88)	
p-value[a]	0.4823	0.0096	

As of data cutoff date, the study was still blinded to obtain overall survival results, which will be presented in subsequent reports.

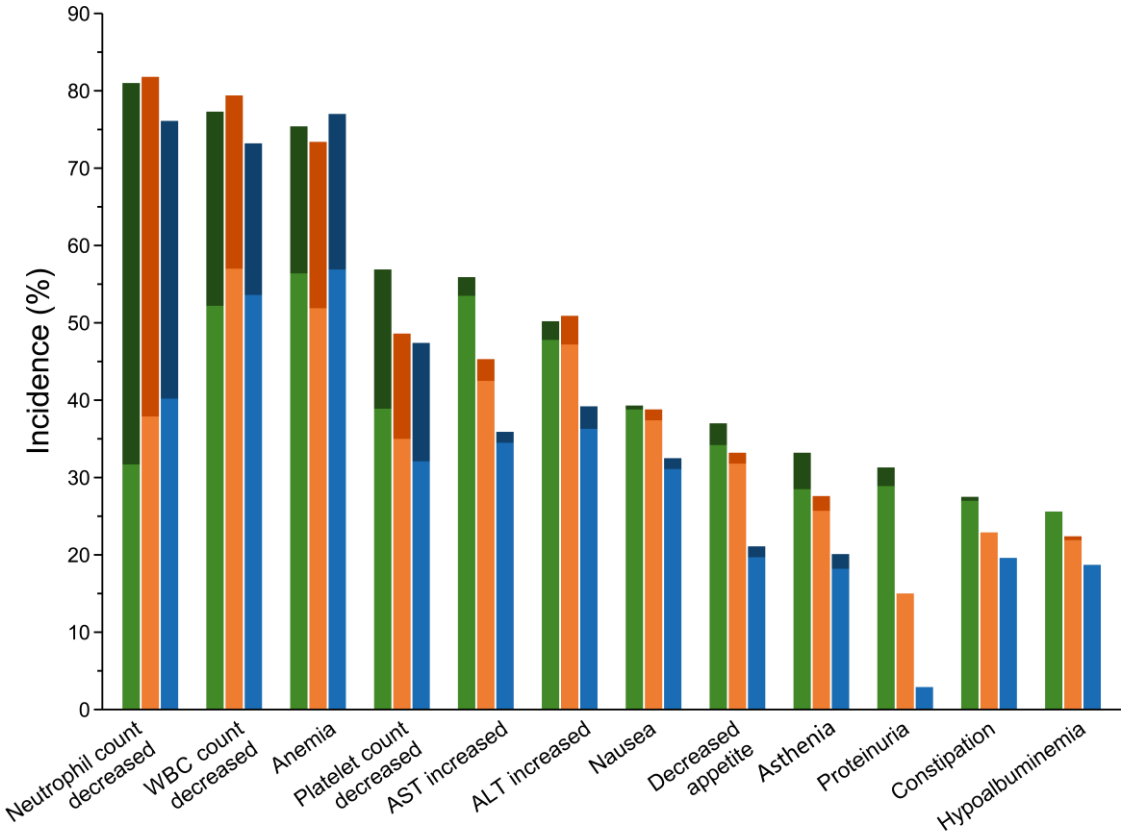
[a] Group B was statistically compared to Group C, while Group A was compared to Group B.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Safety

Adverse event, n (%)	Group A (n = 211)	Group B (n = 214)	Group C[a] (n = 209)
Any TEAE	210 (100)	212 (99)	208 (100)
≥Grade 3	164 (78)	153 (71)	142 (68)
Serious	106 (50)	96 (45)	85 (41)
Leading to tx discontinuation	45 (21)	37 (17)	25 (12)
Leading to death	32 (15)	18 (8)	28 (13)
Immune-related	67 (32)	65 (30)	26 (12)
Infusion-related reactions	3 (1)	0	1 (<1)
Any TRAE, n (%)	208 (99)	212 (99)	206 (99)
Related to serplulimab/placebo	195 (92)	192 (90)	163 (78)
Related to HLX04/placebo	198 (94)	180 (84)	159 (76)
≥Grade 3	149 (71)	142 (66)	119 (57)
Related to serplulimab/placebo	97 (46)	87 (41)	63 (30)
Related to HLX04/placebo	100 (47)	75 (35)	64 (31)
Serious	82 (39)	79 (37)	51 (24)
Leading to tx discontinuation	42 (20)	33 (15)	15 (7)
Leading to death	10 (5)	5 (2)	7 (3)

Most common TRAEs[a,b]



[a] Adverse events that occurred after switching to serplulimab plus HLX04 were excluded. [b] Occurring in ≥25% of patients in any group.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; tx, treatment; WBC, white blood cell.

Conclusions

- The addition of serplulimab to chemotherapy significantly improved PFS and other efficacy endpoints in treatment-naïve patients with locally advanced or metastatic nsqNSCLC. Consistent PFS benefit were observed across most subgroups, including those with brain metastases.
- While the addition of bevacizumab to serplulimab plus chemotherapy did not demonstrate statistically significant efficacy improvements overall, prolonged PFS trends were observed in patients with brain metastases, and markedly improved PFS was seen in those with PD-L1 TPS ≥50%.
- Both investigated treatment regimens had manageable safety profiles.

Combination therapy of serplulimab and chemotherapy is a promising first-line treatment option for patients with locally advanced or metastatic nsqNSCLC. Adding bevacizumab to this combination did not confer additional clinical benefit.

NSCLC, non-small-cell lung cancer; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

Acknowledgments

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Thank You

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