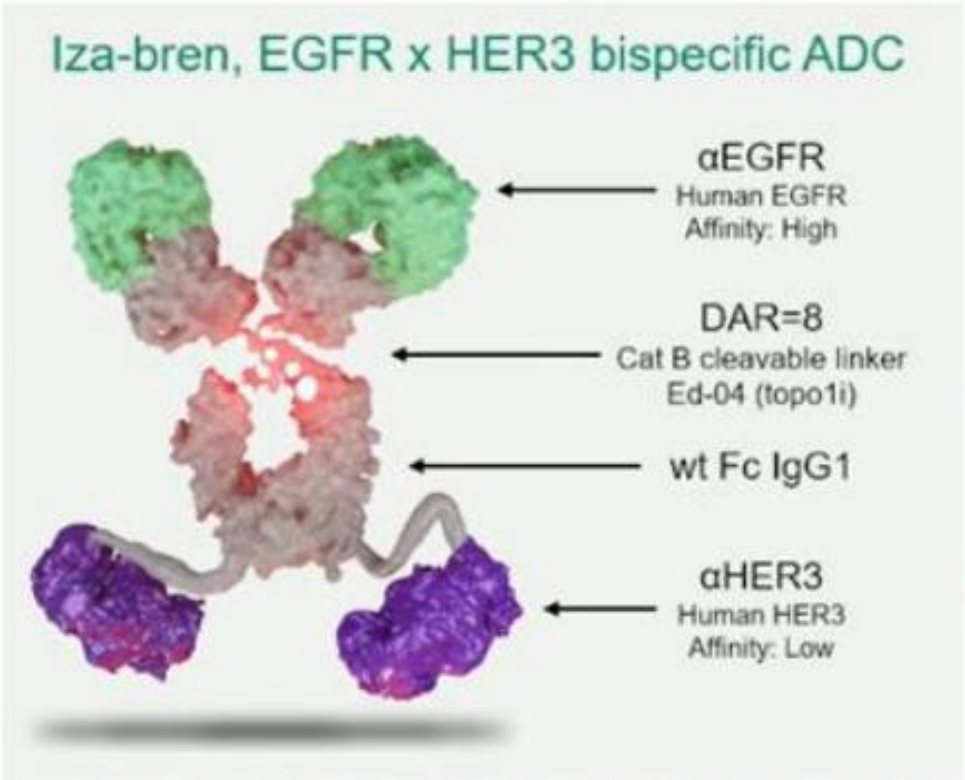
PANKU-Esophagus01

A Multicenter, Randomized, Open-Label, Phase III Study Evaluating Izalontamab Brengitecan (Iza-bren) versus Chemotherapy in Patients with Recurrent or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

PANKU-Esophagus01 Key Takeaways

- The study met both dual primary endpoints of PFS and OS at pre-specified interim analysis.
- The EGFR x HER3 bispecific ADC iza-bren demonstrated statistically significant and clinically meaningful improvements in PFS and OS compared with chemotherapy in patients with recurrent or metastatic ESCC who had progressed after first-line platinum-based chemotherapy plus a PD-1/PD-L1 inhibitor.
- The safety profile was manageable and consistent with previous studies, with no new safety signals observed.
- The results support iza-bren as a possible new second-line standard of care for ESCC in China.

Background



- Chemotherapy plus a PD-1/PD-L1 inhibitor is the standard first-line treatment for advanced ESCC. However, most patients inevitably develop resistance to first-line therapy, and second-line chemotherapy shows an ORR of less than 10% and a median OS of less than 6 months, highlighting an urgent need for novel therapeutics[1-3].
- Iza-bren is a potentially first-in-class ADC consisting of an EGFR-HER3 bispecific antibody conjugated to a potent topoisomerase I inhibitor (topo1i) Ed-04 via a cleavable linker.
- Iza-bren has shown promising clinical activity in previously treated ESCC patients in phase I study[4].

Here, we present the interim results from PANKU-Esophagus01, a randomized phase III study conducted in China, evaluating the efficacy and safety of iza-bren versus chemotherapy as second-line treatment for advanced ESCC (NCT06304974).

PANKU-Esophagus01 Study Design

A multicenter, randomized, open-label, phase III study conducted at 80 study centers across China.

Key eligibility criteria

- Histologically or cytologically confirmed recurrent/metastatic ESCC
- Measurable lesion per RECIST v1.1
- Progressed after first-line treatment with a PD-1/PD-L1 inhibitor plus platinum-based chemotherapy
- ECOG PS 0-1

Treatment until
Disease progression per RECIST v1.1 or intolerable toxicity

R 1:1
N=488

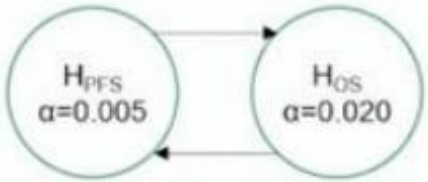
Iza-bren
2.5 mg/kg D1D8 Q3W

Chemotherapy
- Irinotecan, D1D8 Q3W
- Paclitaxel, Q3W
- Docetaxel, Q3W

Stratified by
- Baseline ECOG PS (0 vs 1)
- Definitive treatment (surgery or radiotherapy for the primary tumor, yes vs no)

Dual primary endpoints

PFS (BICR) & OS



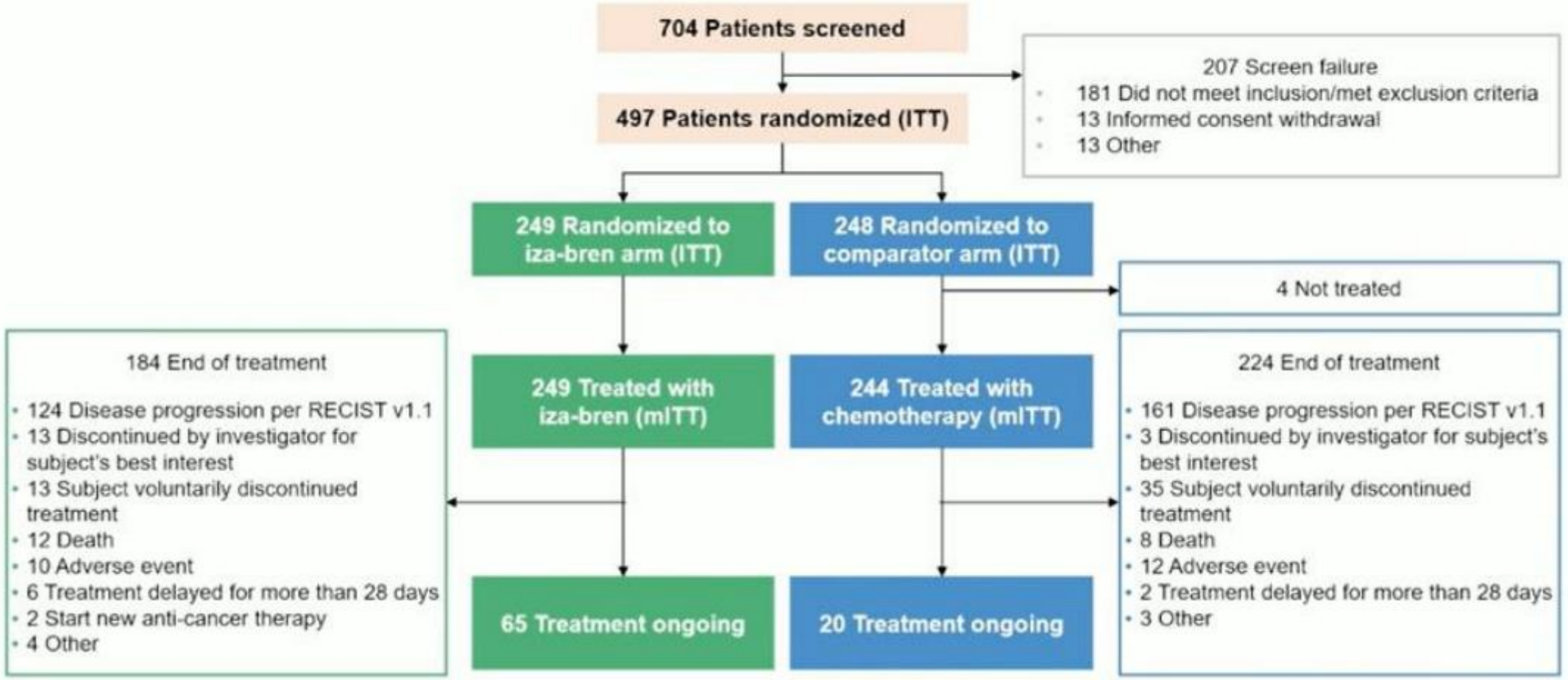
Secondary endpoints

ORR (BICR)
PFS (INV)
DCR, DoR, Safety, PK, Immunogenicity

Note: The planned enrollment was 488 subjects. Iza-bren was dosed with 10% compensation per protocol; irinotecan 125 mg/m^2 on days 1 and 8 Q3W; paclitaxel 175 mg/m^2 on day 1 Q3W; docetaxel 75 mg/m^2 on day 1 Q3W.

ECOG PS, Eastern Cooperative Oncology Group performance status; **Q3W**, every 3 weeks; **BICR**, blinded independent central review; **INV**, investigator assessed; **PFS**, progression-free survival; **OS**, overall survival; **ORR**, objective response rate; **PK**, pharmacokinetics; **DCR**, disease control rate; **DoR**, duration of response.

Patient Disposition



Data cut off: October 17, 2025

Baseline Characteristics

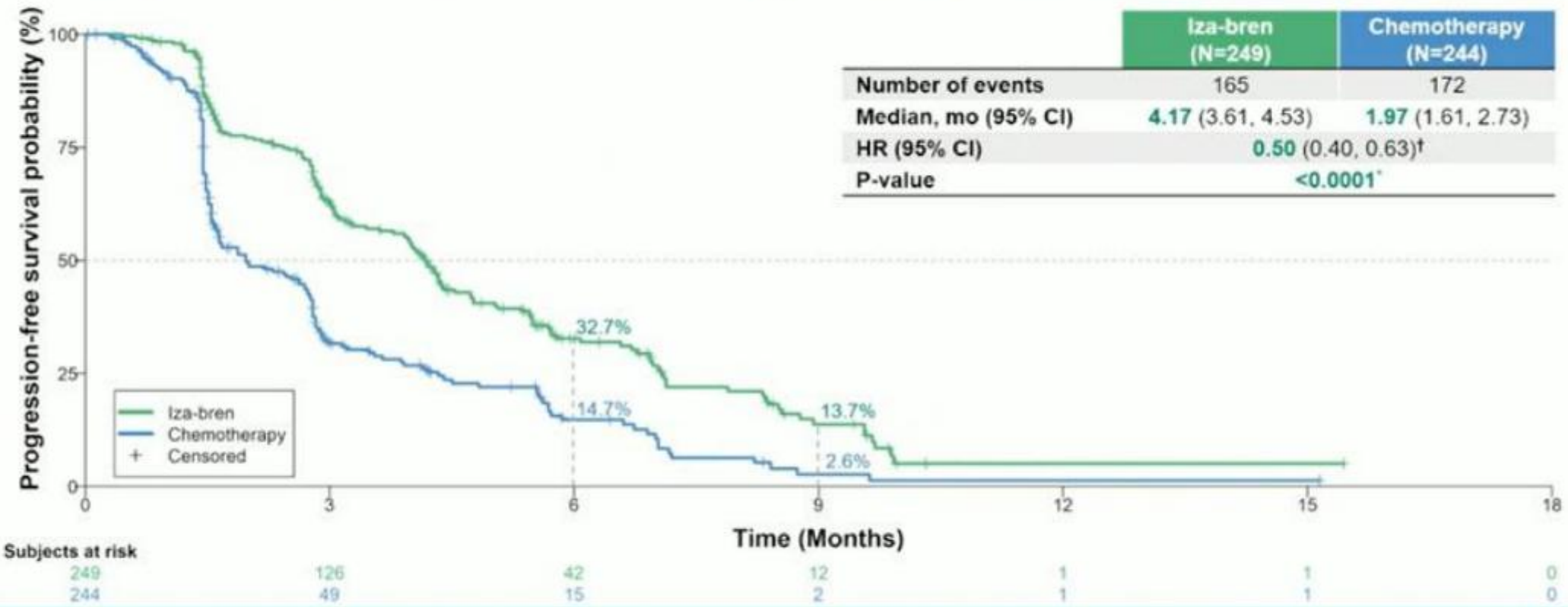
Characteristics	Iza-bren (N=249)	Chemotherapy (N=244)
Median (range) age, years	61.0 (34.0, 76.0)	60.5 (41.0, 76.0)
Age group (years), n (%)		
< 65	170 (68.3)	173 (70.9)
≥ 65	79 (31.7)	71 (29.1)
Male, n (%)	220 (88.4)	224 (91.8)
ECOG PS, n (%)		
0	41 (16.5)	39 (16.0)
1	208 (83.5)	205 (84.0)
Smoking status, n (%)		
Never/missing	97 (39.0)	87 (35.7)
Former/current	152 (61.0)	157 (64.3)
Prior anti-cancer therapy, n (%)		
PD-1/PD-L1 inhibitor	249 (100)	244 (100)
PBC	249 (100)	244 (100)

Characteristics	Iza-bren (N=249)	Chemotherapy (N=244)
Definitive surgery or radiotherapy, n (%)		
Yes	139 (55.8)	132 (54.1)
No	110 (44.2)	112 (45.9)
Metastatic site at baseline, n (%)		
Liver	62 (24.9)	74 (30.3)
Bone	30 (12.0)	32 (13.1)
Lung	58 (23.3)	70 (28.7)
Overall stage at baseline, n (%)		
Stage III	11 (4.4)	5 (2.0)
Stage IV	236 (94.8)	237 (97.1)
Missing	2 (0.8)	2 (0.8)
Disease status, n (%)		
Locally Recurrent	19 (7.6)	14 (5.7)
Distant Metastasis	230 (92.4)	230 (94.3)

Baseline characteristics were balanced between the two groups.

PBC, platinum-based chemotherapy.
Analysis set: mITT population, defined as all randomized patients who received at least one dose of study drug.

PFS (BICR): Dual Primary Endpoint



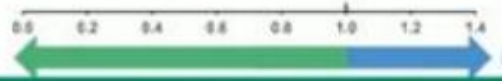
	Iza-bren (N=249)	Chemotherapy (N=244)
Number of events	165	172
Median, mo (95% CI)	4.17 (3.61, 4.53)	1.97 (1.61, 2.73)
HR (95% CI)	0.50 (0.40, 0.63)†	
P-value	<0.0001*	

Iza-bren showed statistically significant and clinically meaningful improvement in PFS vs chemotherapy (median Δ 2.20 mo).

PFS (BICR) was evaluated in the mITT population. The median duration of follow-up for PFS was 5.8 months.
Similar results were observed for PFS (BICR) in the ITT population, with 165 events in the iza-bren arm and 173 events in the chemotherapy arm. The hazard ratio (95% CI) was 0.50 (0.40, 0.63).
†Based on a stratified Cox regression model. *One-sided, based on a stratified log-rank test.

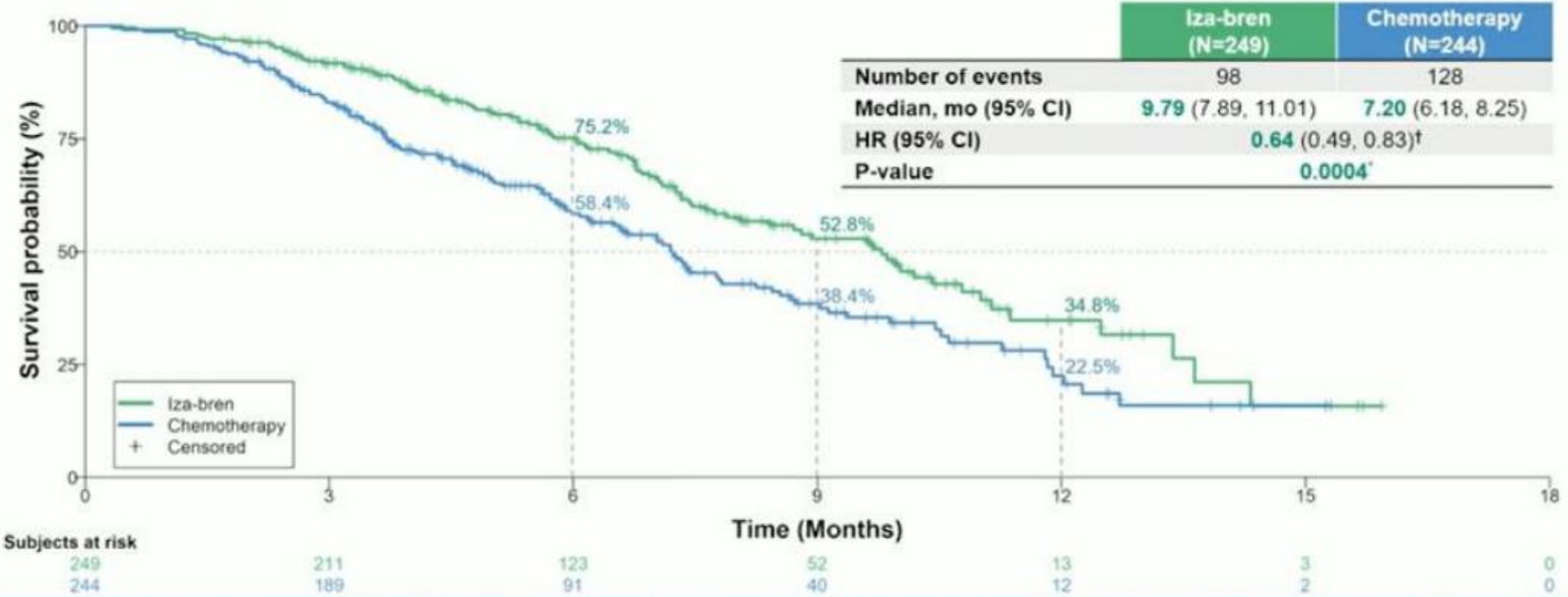
Subgroup Analysis of PFS (BICR)

Category	Subgroup	Iza-bren		Chemotherapy		Hazard ratio (95% CI)
		Events/n	mPFS (mo)	Events/n	mPFS (mo)	
All subjects		165/249	4.17	172/244	1.97	0.50 (0.40, 0.62)
Age	<65	108/170	4.34	124/173	1.64	0.43 (0.33, 0.56)
	≥65	57/79	3.98	48/71	2.79	0.71 (0.48, 1.04)
ECOG-PS score	0	22/40	6.70	26/39	2.79	0.30 (0.16, 0.55)
	1	143/209	4.01	146/205	1.87	0.55 (0.43, 0.69)
Baseline QLQ-C30 score	≤Median score	102/150	3.78	96/127	1.61	0.46 (0.34, 0.61)
	>Median score	63/99	4.40	76/115	2.73	0.52 (0.37, 0.72)
Smoking status	Never/missing	64/97	4.27	57/87	2.73	0.59 (0.41, 0.85)
	Former/current	101/152	4.07	115/157	1.87	0.45 (0.34, 0.59)
Disease staging	Local recurrent	10/19	4.37	8/14	2.63	0.20 (0.06, 0.65)
	Distant metastasis	155/230	4.17	164/230	1.97	0.52 (0.41, 0.65)
Number of organ metastases	≤1	74/120	4.37	65/103	2.73	0.49 (0.35, 0.69)
	≥2	91/129	3.91	107/141	1.61	0.51 (0.38, 0.68)
Definitive treatment	Yes	89/139	4.27	92/133	1.97	0.52 (0.39, 0.70)
	No	76/110	4.04	80/111	1.97	0.48 (0.34, 0.66)



Consistent PFS benefit was seen across the various subgroups.

OS: Dual Primary Endpoint



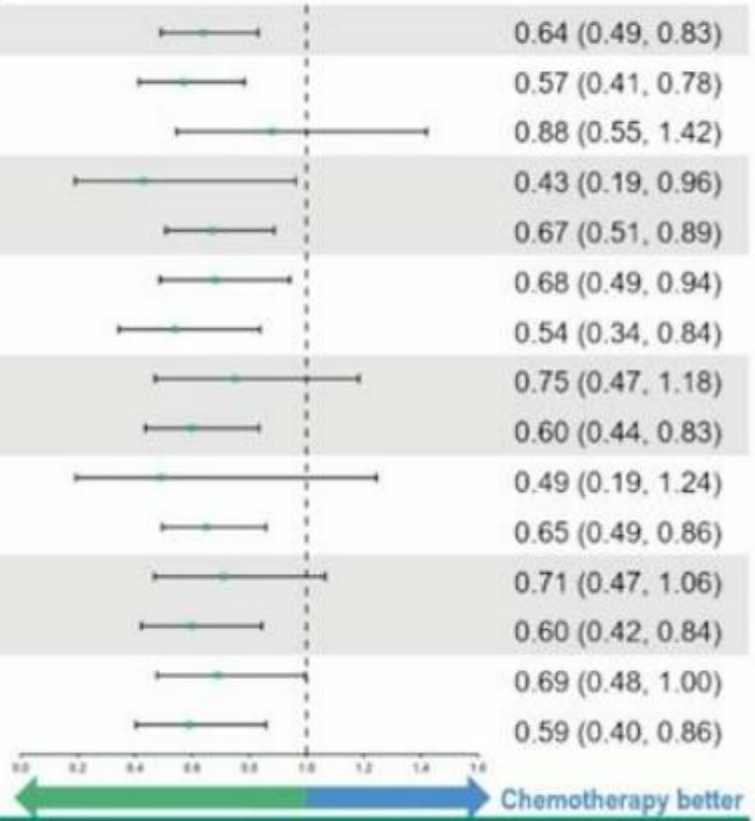
	Iza-bren (N=249)	Chemotherapy (N=244)
Number of events	98	128
Median, mo (95% CI)	9.79 (7.89, 11.01)	7.20 (6.18, 8.25)
HR (95% CI)	0.64 (0.49, 0.83)†	
P-value	0.0004*	

Iza-bren showed statistically significant and clinically meaningful improvement in OS vs chemotherapy (median Δ 2.59 mo).

OS was evaluated in the mITT population. The median duration of follow-up for OS was 7.8 months. At the analysis, the information fraction was 71.7%. A P-value of 0.00602 was required for interim analysis superiority.
Similar results were observed for OS in the ITT population, with 98 events in the iza-bren arm and 130 events in the chemotherapy arm. The hazard ratio (95% CI) was 0.63 (0.48, 0.82).
†Based on a stratified Cox regression model. *One-sided, based on a stratified log-rank test.

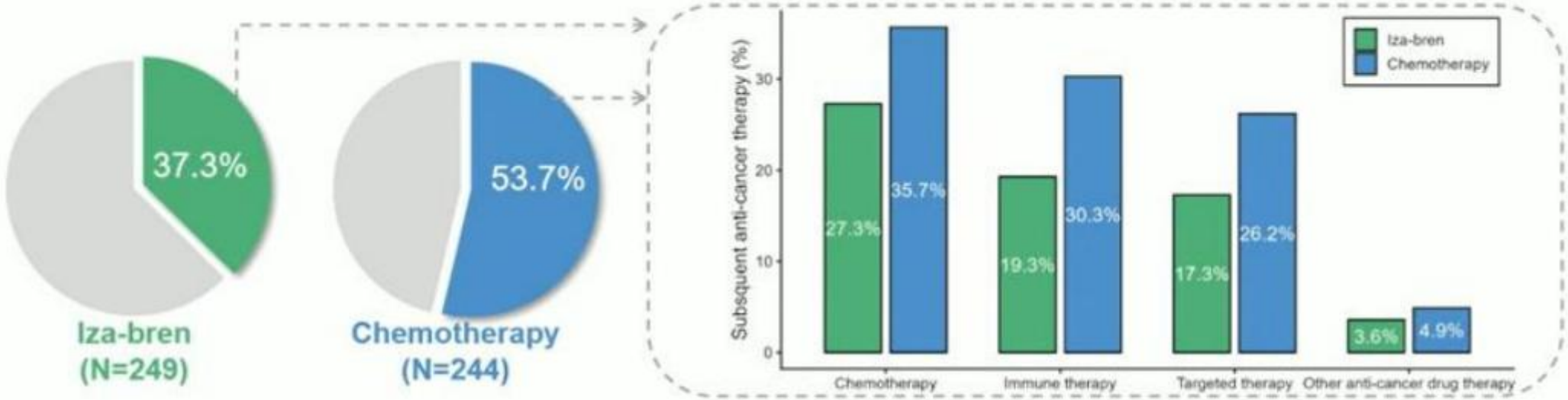
Subgroup Analysis of OS

Category	Subgroup	Iza-bren		Chemotherapy		Hazard ratio (95% CI)
		Events/n	mOS (mo)	Events/n	mOS (mo)	
All subjects		98/249	9.79	128/244	7.20	0.64 (0.49, 0.83)
Age	<65	62/170	9.69	96/173	7.23	0.57 (0.41, 0.78)
	≥65	36/79	9.96	32/71	7.20	0.88 (0.55, 1.42)
ECOG-PS score	0	10/40	13.63	17/39	11.27	0.43 (0.19, 0.96)
	1	88/209	8.80	111/205	7.10	0.67 (0.51, 0.89)
Baseline QLQ-C30 score	≤Median score	67/150	8.94	75/127	6.60	0.68 (0.49, 0.94)
	>Median score	31/99	11.01	52/115	7.82	0.54 (0.34, 0.84)
Smoking status	Never/missing	36/97	9.95	37/87	11.27	0.75 (0.47, 1.18)
	Former/current	62/152	9.63	91/157	6.60	0.60 (0.44, 0.83)
Disease staging	Local recurrent	9/19	7.03	10/14	6.67	0.49 (0.19, 1.24)
	Distant metastasis	89/230	9.79	118/230	7.23	0.65 (0.49, 0.86)
Number of organ metastases	≤1	44/120	10.02	48/103	7.39	0.71 (0.47, 1.06)
	≥2	54/129	9.69	80/141	7.03	0.60 (0.42, 0.84)
Definitive treatment	Yes	52/139	10.02	63/133	7.75	0.69 (0.48, 1.00)
	No	46/110	8.94	65/111	7.03	0.59 (0.40, 0.86)



Consistent OS benefit was seen across the various subgroups.

Most Common Subsequent Anti-cancer Therapy



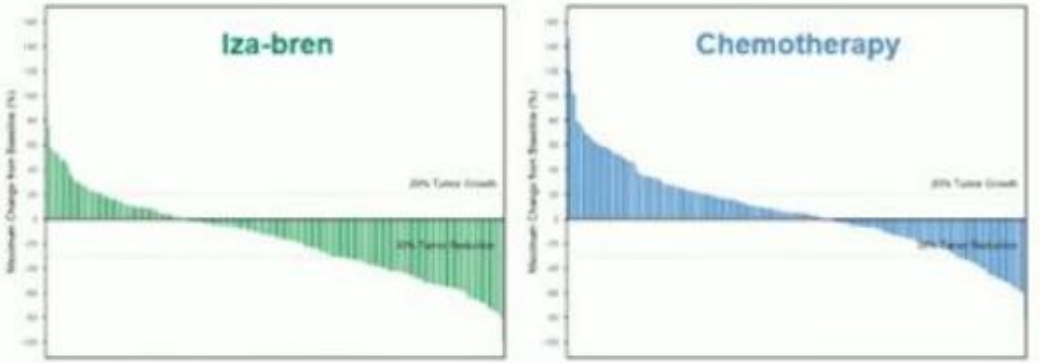
- More patients in the chemotherapy arm (53.7%) received at least one subsequent anti-cancer therapy than the iza-bren arm (37.3%).
- In the iza-bren arm and the chemotherapy arm, the most common subsequent chemotherapies were pyrimidine analogues (20.1% vs. 23.4%), platinum compounds (13.3% vs. 16.8%), taxanes (10.0% vs. 12.7%), and topo1i (6.0% vs. 5.3%), respectively.
- In the iza-bren arm and the chemotherapy arm, the most common subsequent immune therapies were PD-1/PD-L1 inhibitors (16.1% vs. 26.6%).

Note: Data for the new anti-cancer drug therapy were presented.

ORR (BICR): Secondary Endpoint

	Iza-bren (N=249)	Chemotherapy (N=244)
ORR, % (95% CI)	**35.3** (29.4, 41.6)	**13.1** (9.1, 18.0)
Confirmed ORR, % (95% CI)	**27.7** (22.2, 33.7)	**9.4** (6.1, 13.8)
Odds ratio (95% CI)	**3.6** (2.2, 6.1)	
DCR, % (95% CI)	74.3 (68.4, 79.6)	45.5 (39.1, 52.0)
Median DoR, mo (95% CI)	5.7 (4.1, 6.9)	5.6 (4.2, 6.8)
Median TTR, mo (range)	1.5 (0.7, 9.9)	1.5 (1.3, 4.8)

CR, complete response; **PR**, partial response; **uPR**, PR pending confirmation
ORR (BICR) was evaluated based on mITT population.
ORs were calculated using the stratified Mantel-Haenszel method.
In the iza-bren arm, 65.9% of patients (164/249) had tumor shrinkage and the median (range) shrinkage (%) was -31.5 (-100.0, -0.7); in the chemotherapy arm, 38.5% of patients (94/244) had tumor shrinkage and the median (range) shrinkage (%) was -20.5 (-80.5, -0.2).



ORR (BICR) was approximately three-fold higher in iza-bren arm compared with chemotherapy arm.

Safety Summary

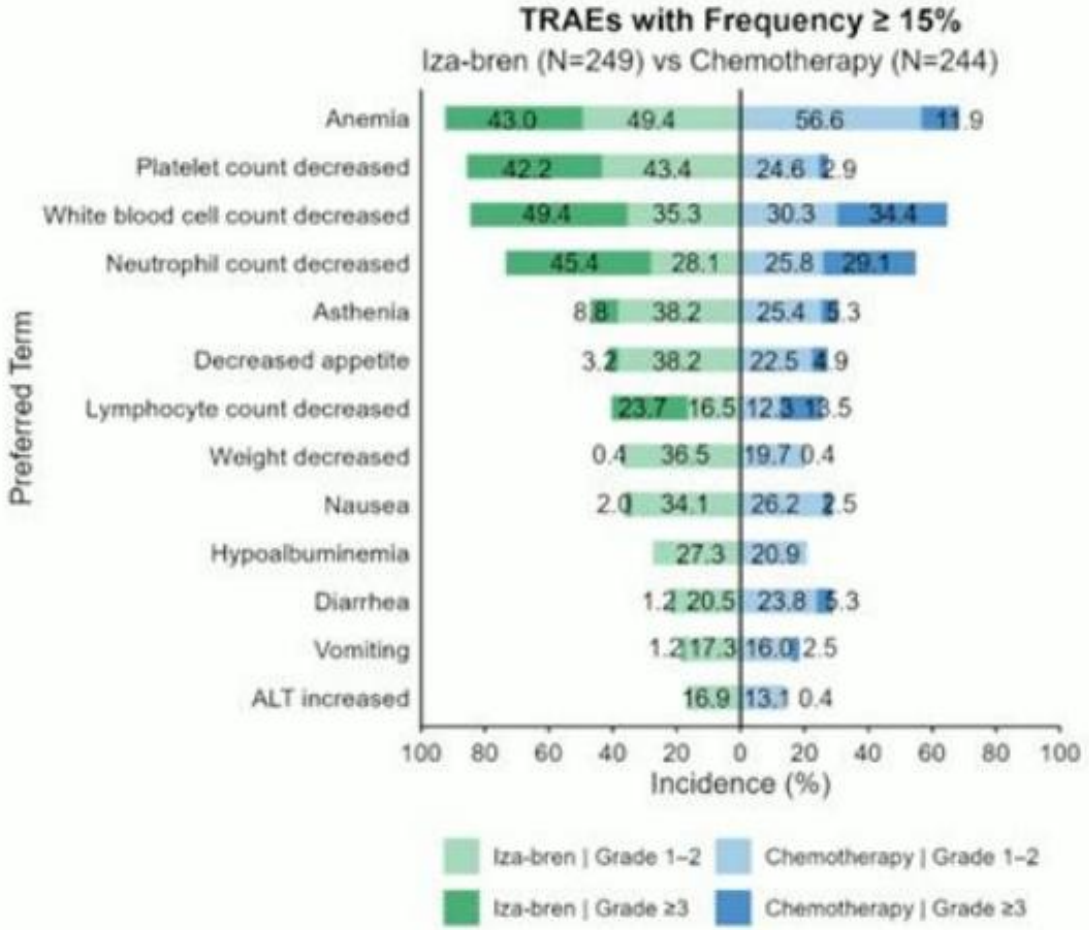
Characteristics	Iza-bren (N=249)	Chemotherapy (N=244)
TRAEs, n (%)	249 (100)	237 (97.1)
≥Grade 3 TRAEs, n (%)	212 (85.1)	147 (60.2)
Treatment-related SAEs, n (%)	112 (45.0)	74 (30.3)
TRAEs leading to death, n (%)	3 (1.2)	4 (1.6)
TRAEs leading to treatment discontinuation, n (%)	5 (2.0)	8 (3.3)
TRAEs leading to dose reduction, n (%)	141 (56.6)	70 (28.7)
TRAEs leading to dose interruption, n (%)	151 (60.6)	91 (37.3)

- Median (range) duration of treatment, mo:
  - Iza-bren: 3.5 (0.3, 16.1)
  - Chemotherapy: 1.6 (0.1, 15.9)
- Median (range) number of treatment cycles:
  - Iza-bren: 4 (1, 23)
  - Chemotherapy: 2 (1, 23)

- Iza-bren had a manageable safety profile. The rate of treatment discontinuation due to TRAEs was low (2.0%) vs chemotherapy (3.3%).
- TRAEs leading to death occurred in 3 patients (1.2%) receiving iza-bren and in 4 patients (1.6%) receiving chemotherapy.

TRAE, treatment related adverse events.
Safety data based on the safety analysis set. GCSF was not mandatory in this study.
TRAEs leading to death occurred in 3 patients (1.2%) receiving iza-bren: septic shock (1), pneumonia (1), interstitial lung disease (1, with pulmonary interstitial changes at baseline).
TRAEs leading to death occurred in 4 patients (1.6%) receiving chemotherapy: sepsis (1), death (3).

TRAEs in ≥15% of Patients



- TRAEs were managed through standard supportive measures including dose delay and dose reductions, which allowed majority of patients to continue iza-bren treatment with low discontinuation rate.
- Grade ≥3 anemia resolved in a median of 10.0 days in the iza-bren arm and 9.5 days in the chemotherapy arm.
- Grade ≥3 neutropenia and thrombocytopenia generally resolved within 4 days in the iza-bren arm.
- Non-hematologic AEs were mostly low grade; asthenia was the most common in both groups (47.0% with iza-bren and 30.7% with chemotherapy), followed by decreased appetite (41.4% and 27.5%, respectively).
- The rates of all grade and grade 3 or higher ILD were low in the iza-bren arm (1.6% / 0.8%) and chemotherapy arm (0.4% / 0%).

Conclusions

- The study has met both dual primary endpoints of PFS and OS at the pre-specified interim analysis.
- Iza-bren has demonstrated statistically significant and clinically meaningful improvements in PFS and OS compared with chemotherapy in patients with recurrent or metastatic ESCC who had progressed after first-line platinum-based chemotherapy plus a PD-1/PD-L1 inhibitor.
  - The median PFS was 4.17 months with iza-bren and 1.97 months with chemotherapy (HR=0.50, P<0.0001).
  - The median OS was 9.79 months with iza-bren and 7.20 months with chemotherapy (HR=0.64, P=0.0004).
- The safety profile was manageable.
  - Through dose delay, dose reduction, and supportive care, most patients were able to continue iza-bren treatment and only 5 (2.0%) patients discontinued treatment due to TRAEs.
  - Most common TRAEs were hematologic. ILD rate was low.
- The results support iza-bren as a possible new standard of care in China for the treatment of ESCC in second-line after progression on platinum-based chemotherapy plus a PD-1/PD-L1 inhibitor.