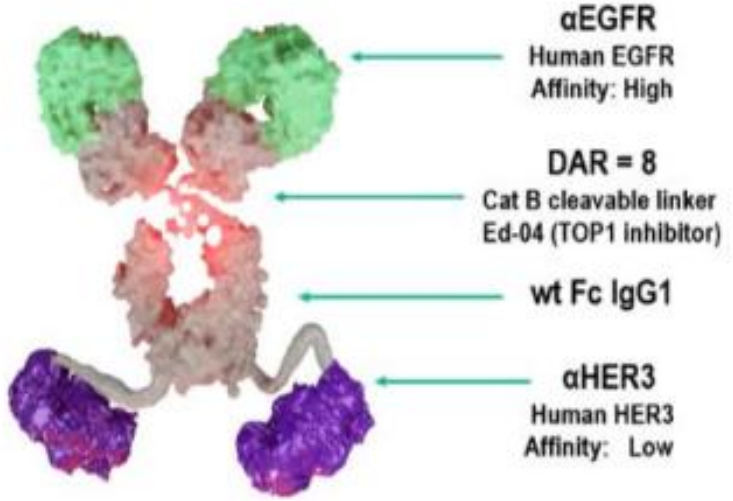
Izalontamab Brengitecan, An EGFR*HER3 Bispecific Antibody-drug Conjugate, versus Chemotherapy in Heavily Pretreated Recurrent/Metastatic Nasopharyngeal Carcinoma: A Multicenter, Randomized, Open-label, Phase III Study

Background

Iza-bren, EGFR×HER3 bispecific ADC



- Nasopharyngeal carcinoma (NPC) accounts for about 129,100 newly diagnosed cancer cases and 73,000 deaths annually worldwide. It predominantly distributed in Southeast Asia, the Middle East, and North Africa[1].
- About 20-30% of patients have recurrent or distant metastasis. The first-line therapy for recurrent/metastatic (R/M) NPC is immunochemotherapy, but the treatment options are limited for later-line[2-4]. Conventional chemotherapy typically yields low response rates and short durations of benefit[5-7]. There is an unmet medical need in later-line therapy.
- Izalontamab brengitecan (iza-bren, BL-B01D1) is a first-in-class bispecific ADC targeting both EGFR and HER3, conjugated to a novel topoisomerase I inhibitor payload (Ed-04), with a drug-to-antibody ratio of 8.
- A prior phase I study demonstrated encouraging antitumor activity of iza-bren in patients with heavily pretreated R/M NPC, with an observed ORR of 59.5%[8].

Here we report the first interim analysis from a randomized phase III clinical trial comparing the efficacy and safety of iza-bren vs chemotherapy in patients with heavily pretreated R/M NPC (BL-B01D1-303, NCT06118333).

Study Design

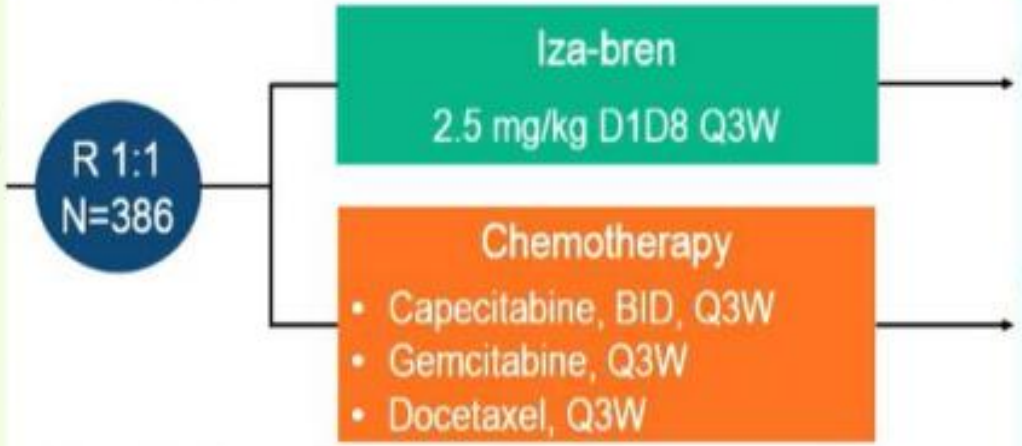
A multicenter, randomized, open-label, phase III study conducted at 55 study centers across China

Key eligibility criteria

- Histologically or cytologically confirmed R/M NPC
- Measurable lesion per RECIST v1.1
- Progressed after at least two lines of systemic chemotherapy including at least one PBC and PD(L)-1 inhibitors
- ECOG PS 0-1

Treatment until

Disease progression per RECIST v1.1 or intolerable toxicity



Stratified by

- Baseline ECOG PS (0 vs 1)
- Liver metastases (Yes vs No)
- Previous lines of PBC (1 line vs ≥ 2 lines)

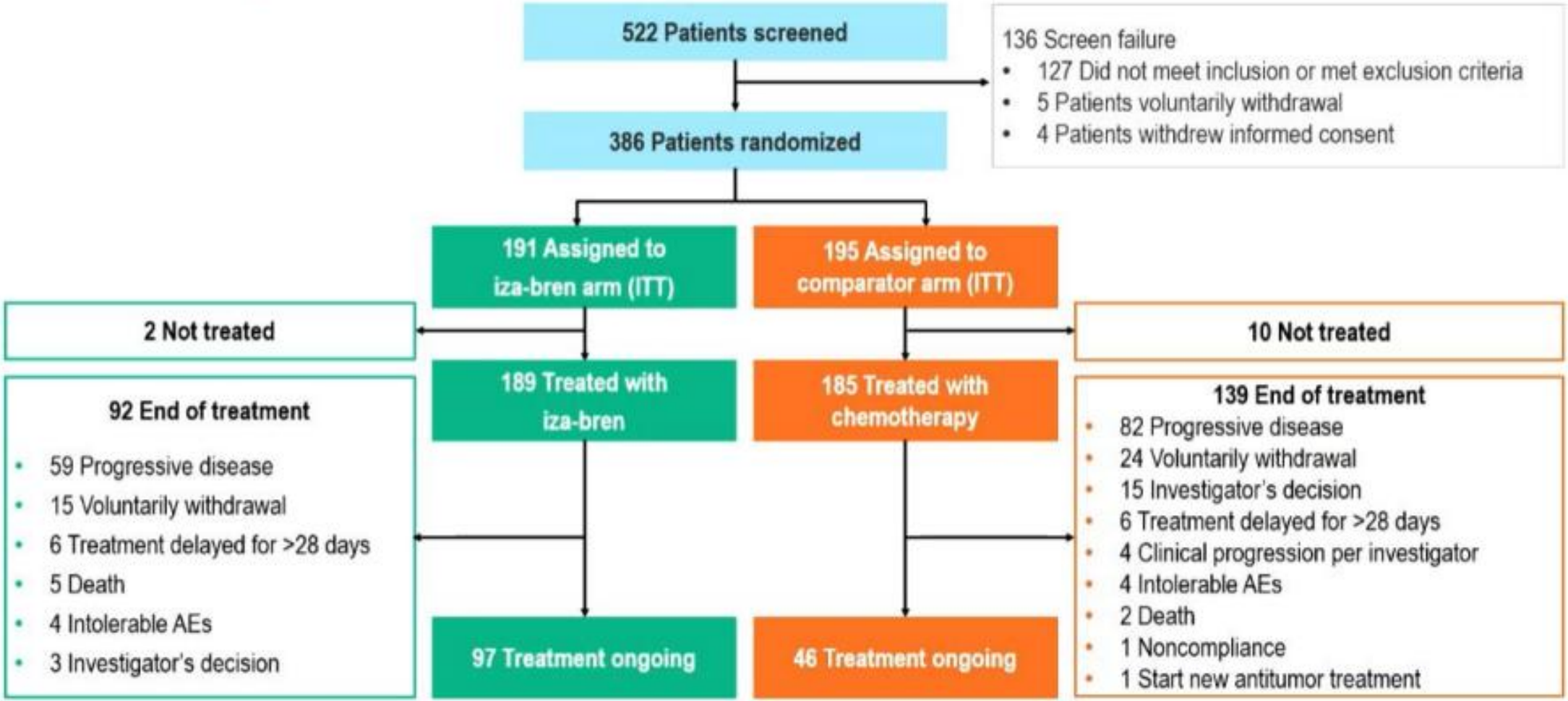
Study endpoints

- **Dual primary endpoints:**
  ORR (by BICR)
  OS
- **Secondary endpoints:**
  PFS (by BICR, key secondary)
  PFS (by INV), ORR (by INV)
  DoR, DCR, Safety, PK, Immunogenicity

Note: Iza-bren dose is compensated per protocol; capecitabine 1000 mg/m^2, BID from days 1 to 14 Q3W; gemcitabine 1000 mg/m^2 on days 1 and 8 Q3W; docetaxel 75 mg/m^2 Q3W.

PBC, platinum-based chemotherapy; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **Q3W**, every 3 weeks; **D**, day; **BICR**, blinded independent central review; **INV**, investigator assessed; **ORR**, objective response rate (confirmed); **DoR**, duration of response; **DCR**, disease control rate; **OS**, overall survival; **PFS**, progression-free survival.

Patient Disposition



Data cut off: March 30, 2025

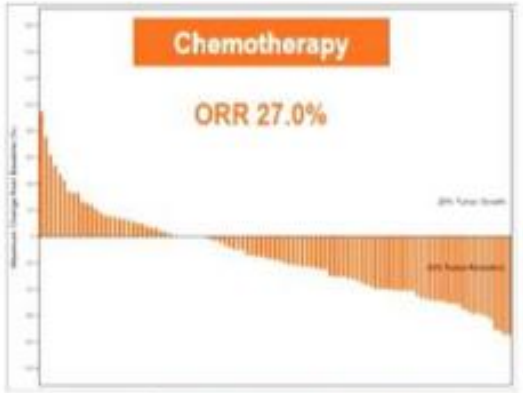
Baseline Characteristics (ITT Population)

Characteristics	Iza-bren (N=191)	Chemotherapy (N=195)
Median (range) age, years	50.0 (27.0, 72.0)	49.0 (19.0, 70.0)
Age group (years), n (%)		
<50	95 (49.7)	100 (51.3)
≥50	96 (50.3)	95 (48.7)
Male, n (%)	163 (85.3)	158 (81.0)
ECOG PS, n (%)		
0	46 (24.1)	47 (24.1)
1	145 (75.9)	148 (75.9)
Prior treatment lines, n (%)		
2	108 (56.5)	103 (52.8)
≥3	83 (43.4)	92 (47.1)

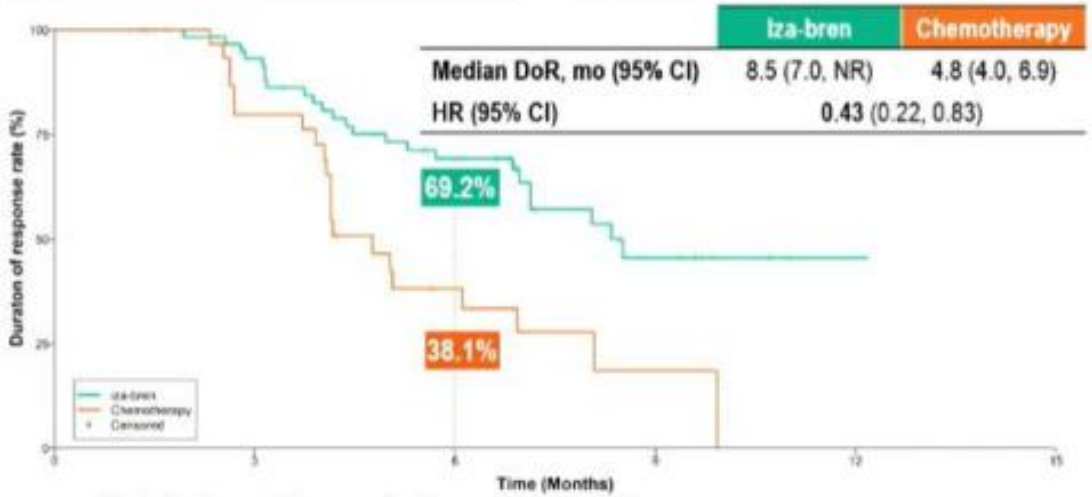
Characteristics	Iza-bren (N=191)	Chemotherapy (N=195)
Prior chemotherapy lines, n (%)		
1	0	1 (0.5)
2	124 (64.9)	121 (62.1)
≥3	67 (35.1)	73 (37.4)
Prior PBC lines, n (%)		
0	1 (0.5)	0
1	75 (39.3)	84 (43.1)
2	92 (48.2)	94 (48.2)
≥3	23 (12.0)	17 (8.7)
Prior radiotherapy, n (%)	171 (89.5)	172 (88.2)
Liver metastases, n (%)	91 (47.6)	95 (48.7)
Bone metastases, n (%)	94 (49.2)	91 (46.7)
Lung metastases, n (%)	89 (46.6)	73 (37.4)

BICR-Assessed ORR (Primary Endpoint)

	Iza-bren (N=119)	Chemotherapy (N=115)
Best overall response, n (%)		
CR	1 (0.8)	0
PR	64 (53.8)	31 (27.0)
SD	33 (27.7)	49 (42.6)
PD	12 (10.1)	23 (20.0)
NE	9 (7.6)	12 (10.4)
ORR, % (95% CI)	54.6 (45.2, 63.8)	27.0 (19.1, 36.0)
Difference, % (95% CI)	27.9 (15.5, 39.4)	
Odds ratio (95% CI)	3.3 (1.9, 5.8)	
P-value	<0.0001	
DCR, % (95% CI)	82.4 (74.3, 88.7)	69.6 (60.3, 77.8)
Median DoR (mo), 95% CI	8.5 (7.0, NR)	4.8 (4.0, 6.9)



	Iza-bren	Chemotherapy
Median DoR, mo (95% CI)	8.5 (7.0, NR)	4.8 (4.0, 6.9)
HR (95% CI)	0.43 (0.22, 0.83)	



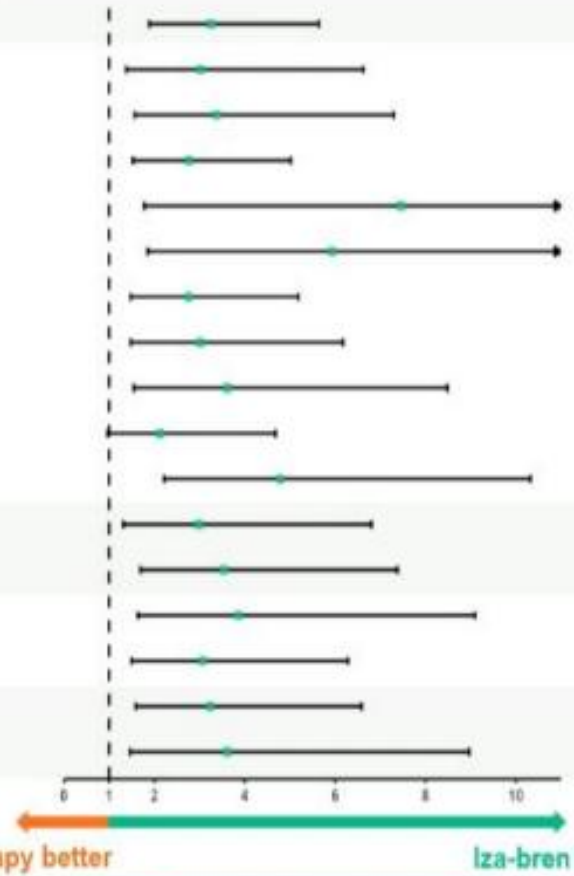
1. Per protocol, the interim analysis (the final analysis of ORR) is triggered by the first 234 randomized patients with at least 6 months of follow-up. The primary endpoint ORR was evaluated based on the first randomized 234 patients as defined in the protocol.
2. A stratified Cochran-Mantel-Haenszel test was used to compare ORRs between the two arms.
3. In the iza-bren arm, 74.8% of patients (89/119) had tumor shrinkage and the median (range) shrinkage (%) was -45.5 (-84.4, -1.3), in the chemotherapy arm, 58.3% of patients (67/115) had tumor shrinkage and the median (range) shrinkage (%) was -33.6 (-75.0, -1.0).

ORR, objective response rate (confirmed); **DCR**, disease control rate; **DoR**, duration of response; **CR**, complete response; **PR**, partial response; **SD**, stable disease; **PD**, progressive disease; **NE**, not evaluable

BICR-assessed ORR was significantly higher in iza-bren versus chemotherapy.

Subgroup Analysis of ORR by BICR

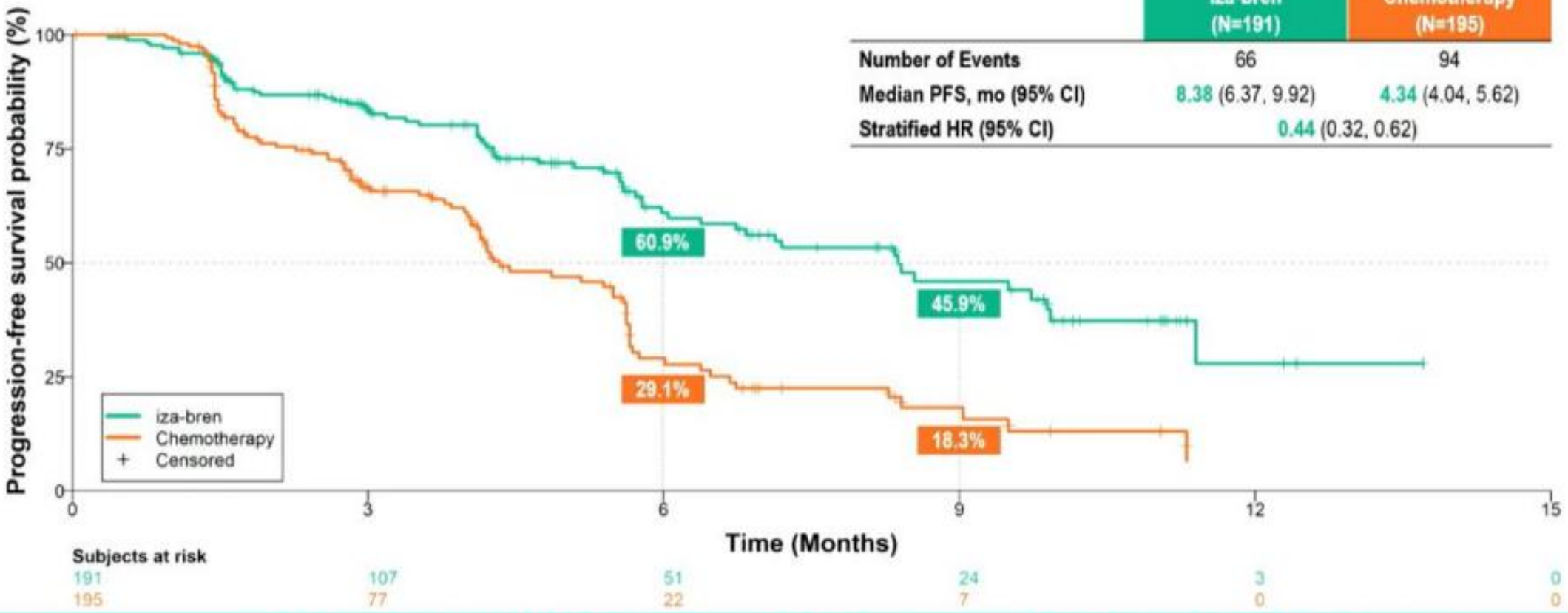
Category	Subgroup	Iza-bren		Chemotherapy		Odds ratio (95% CI)
		Responders/n	ORR (%)	Responders/n	ORR (%)	
All Subjects		65/119	54.6	31/115	27.0	3.3 (1.9-5.6)
Age	< 50	27/55	49.1	15/62	24.2	3.0 (1.4-6.6)
	≥ 50	38/64	59.4	16/53	30.2	3.4 (1.6-7.3)
Sex	Male	54/101	53.5	27/92	29.3	2.8 (1.5-5.0)
	Female	11/18	61.1	4/23	17.4	7.5 (1.8-31.4)
ECOG PS	0	20/28	71.4	8/27	29.6	5.9 (1.9-19.0)
	1	45/91	49.5	23/88	26.1	2.8 (1.5-5.2)
Number of metastatic organs	< 3	39/72	54.2	18/64	28.1	3.0 (1.5-6.2)
	≥ 3	26/47	55.3	13/51	25.5	3.6 (1.5-8.5)
Liver metastases	Presence	26/55	47.3	16/54	29.6	2.1 (1.0-4.7)
	Absence	39/64	60.9	15/61	24.6	4.8 (2.2-10.3)
Number of prior treatment lines	2 lines	30/57	52.6	13/48	27.1	3.0 (1.3-6.8)
	≥ 3 lines	35/62	56.5	18/67	26.9	3.5 (1.7-7.4)
Number of prior PBC lines	1 prior line	27/45	60.0	14/50	28.0	3.9 (1.6-9.1)
	≥ 2 prior lines	38/73	52.1	17/65	26.2	3.1 (1.5-6.3)
Baseline BLQ - C30 scale score	≤ Median score	45/85	52.9	16/62	25.8	3.2 (1.6-6.6)
	> Median score	20/34	58.8	15/53	28.3	3.6 (1.5-9.0)



All subgroups have the consistent ORR benefit from iza-bren.

BICR-Assessed PFS (Key Secondary Endpoint)

	Iza-bren (N=191)	Chemotherapy (N=195)
Number of Events	66	94
Median PFS, mo (95% CI)	8.38 (6.37, 9.92)	4.34 (4.04, 5.62)
Stratified HR (95% CI)	0.44 (0.32, 0.62)	

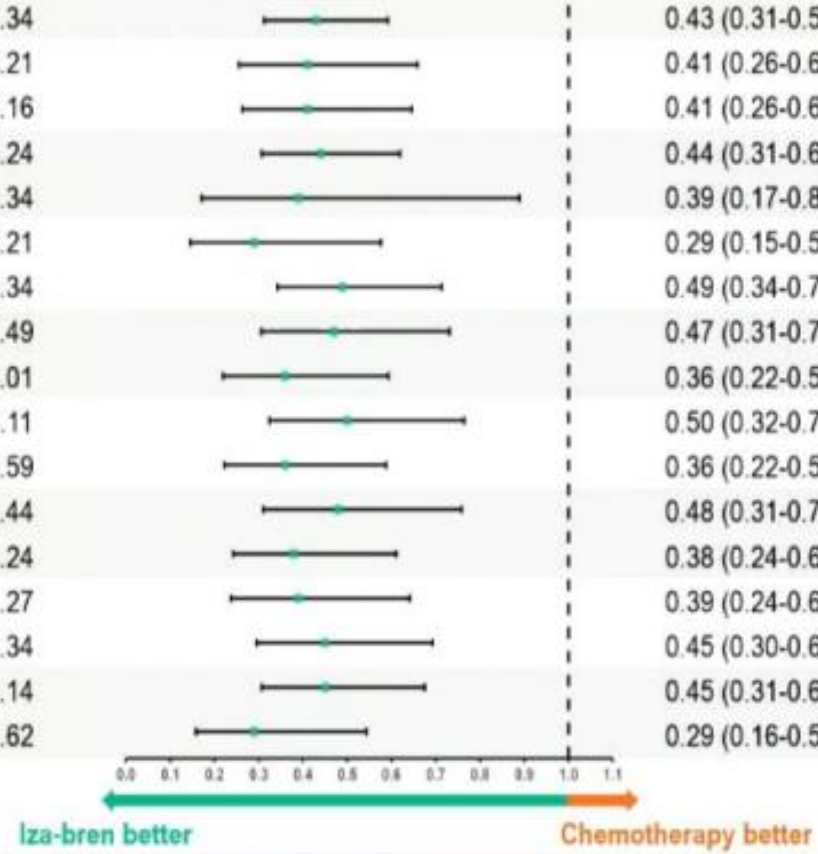


Iza-bren demonstrated clinically meaningful improvement in PFS vs chemotherapy.

BICR-assessed PFS was evaluated based on ITT population.

Subgroup Analysis of PFS by BICR

Category	Subgroup	Iza-bren		Chemotherapy		Hazard Ratio (95% CI)
		Events/n	mPFS (mo)	Events/n	mPFS (mo)	
All Subjects		66/191	8.38	94/195	4.34	0.43 (0.31-0.59)
Age	< 50	28/95	9.72	47/100	4.21	0.41 (0.26-0.66)
	≥ 50	38/96	7.20	47/95	5.16	0.41 (0.26-0.65)
Sex	Male	57/163	8.41	78/158	4.24	0.44 (0.31-0.62)
	Female	9/28	8.38	16/37	4.34	0.39 (0.17-0.89)
ECOG PS	0	12/45	9.49	27/46	4.21	0.29 (0.15-0.58)
	1	54/146	6.74	67/149	4.34	0.49 (0.34-0.71)
Number of metastatic organs	< 3	37/123	9.72	48/117	5.49	0.47 (0.31-0.73)
	≥ 3	29/68	7.13	46/78	4.01	0.36 (0.22-0.59)
Liver metastases	Presence	38/91	6.83	50/95	4.11	0.50 (0.32-0.76)
	Absence	28/100	9.89	44/100	5.59	0.36 (0.22-0.59)
Number of prior treatment lines	2 lines	36/108	8.38	45/103	4.44	0.48 (0.31-0.76)
	≥ 3 lines	30/83	9.49	49/92	4.24	0.38 (0.24-0.61)
Number of prior PBC lines	1 prior line	28/75	6.83	42/84	4.27	0.39 (0.24-0.64)
	≥ 2 prior lines	38/115	9.89	52/111	4.34	0.45 (0.30-0.69)
Baseline BLQ - C30 scale score	≤ Median score	51/128	6.74	53/106	4.14	0.45 (0.31-0.68)
	> Median score	15/63	11.40	41/87	5.62	0.29 (0.16-0.54)



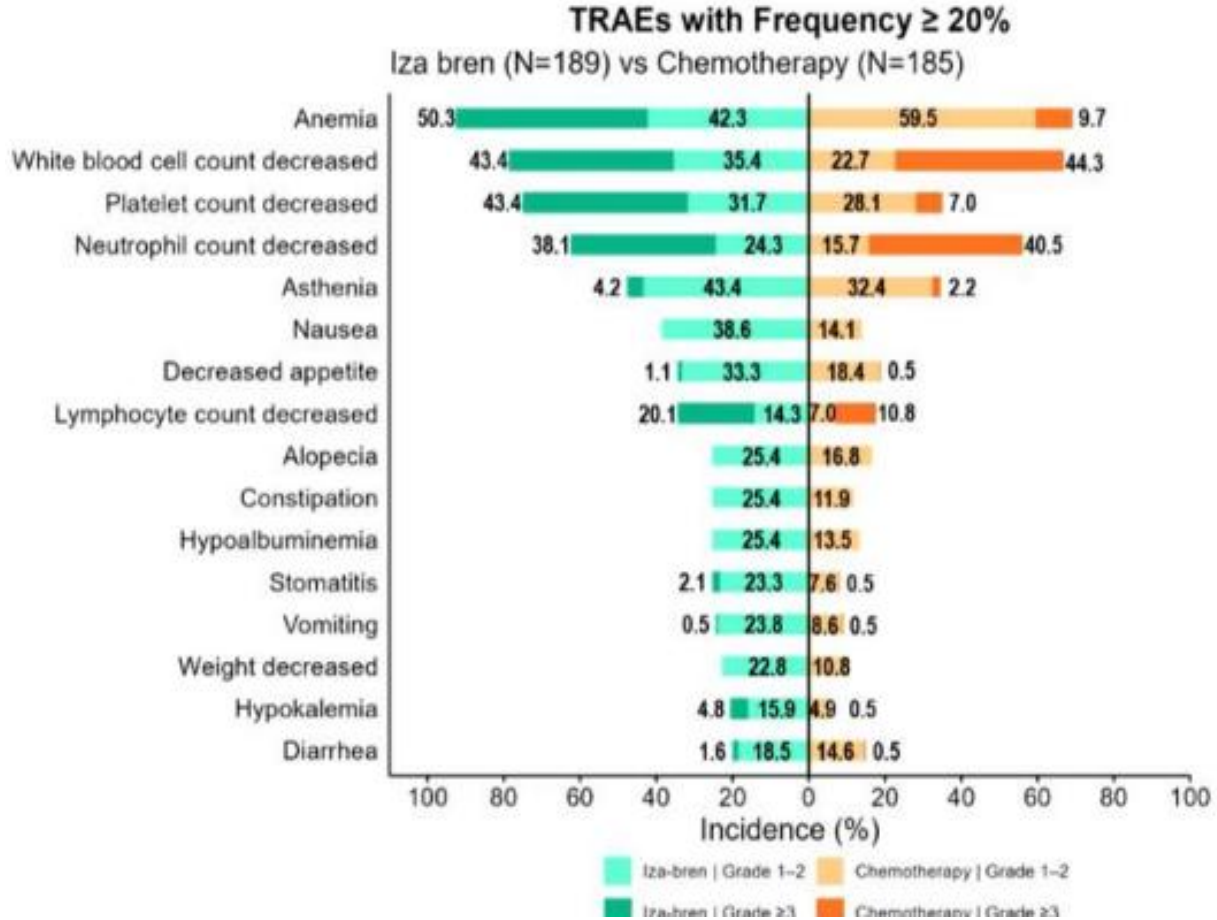
Clinically meaningful PFS benefit was seen across the various subgroups.

Safety Summary

	Iza-bren (N=189)	Chemotherapy (N=185)
TRAEs, n (%)	189 (100)	176 (95.1)
≥Grade 3 TRAEs, n (%)	151 (79.9)	114 (61.6)
Treatment-related SAEs, n (%)	82 (43.4)	50 (27.0)
TRAEs leading to death, n (%)	4 (2.1)	0
TRAEs leading to treatment discontinuation, n (%)	5 (2.6)	6 (3.2)
TRAEs leading to dose reduction, n (%)	79 (41.8)	45 (24.3)
TRAEs leading to dose interruption, n (%)	116 (61.4)	34 (18.4)

- Iza-bren had a manageable safety profile. The rate of treatment discontinuation due to TRAEs was low (2.6%) vs chemotherapy (3.2%).
- TRAEs leading to death occurred in 4 patients (2.1%) receiving iza-bren: febrile neutropenia (2), platelet count decreased (1), and death of unknown cause (1).

TRAEs in >20% of Patients



- The most frequent Grade ≥3 TRAEs in the iza-bren arm were mainly hematologic and effectively managed by standard supportive care.
- In the iza-bren arm:
  - The incidence of neutropenia was comparable to chemotherapy, while anemia and thrombocytopenia occurred at higher rates.
  - Dose reductions due to neutropenia and thrombocytopenia occurred in 14.3% and 21.2% of patients, respectively; discontinuations were 0.5% and 1.6%.
  - Median resolution times for Grade ≥3 neutropenia and thrombocytopenia were 4 and 5 days, respectively.
- The majority of non-hematologic TRAEs were Grade 1 or 2.
- Two (1.1%) patients experienced Grade 2 ILD in the iza-bren arm versus two (1.1%) Grade 3 in the chemotherapy arm.
- No new safety signals were identified.

Conclusions

- Iza-bren demonstrated a statistically significant and clinically meaningful improvement in ORR by BICR compared to chemotherapy in heavily pretreated patients with R/M NPC.
  - ORR, 54.6% vs 27.0%; odds ratio, 3.33; P<0.0001.
  - DoR, 8.5 mo vs 4.8 mo; HR 0.43 (95% CI, 0.22, 0.83).
- Iza-bren showed a clinically meaningful improvement in PFS by BICR.
  - Median PFS, 8.38 mo vs 4.34 mo; HR 0.44 (95% CI, 0.32, 0.62).
  - Subgroup analyses of PFS by BICR consistently favored iza-bren over chemotherapy.
- Iza-bren had manageable safety profile, and no new safety signals were identified.
  - Most common TRAEs were hematologic toxicities.
  - Low incidence of TRAEs leading to treatment discontinuation.
  - No increased incidence of ILD compared to chemotherapy.
- OS data are not presented at this time as they are not yet mature.

Iza-bren represents a potential new standard of care for heavily pretreated patients with R/M NPC.

Publication

Izalontamab brengitecan, an EGFR and HER3 bispecific antibody–drug conjugate, versus chemotherapy in heavily pretreated recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 study in China

Yunpeng Yang, Huaqiang Zhou*, Linquan Tang*, Sufang Qiu*, Yaqian Han*, Dongmei Ji*, Xiaozhong Chen, Feng Lei, Song Qu, Bin Deng, Lusi Chen, Jianli Huang, Ye Guo, Zhigang Liu, Dongping Chen, Jingao Li, Xiaolei Shu, Yan Qin, Zhichao Fu, Bihui Li, Peng Zhang, Shaoqing Chen, Jinsheng Hong, Yan Wei, Xintian Qin, Shenhong Qu, Kunyu Yang, Daren Lin, Junxian Wang, Lei Yang, Sa Xiao, Hai Zhu, Yi Zhu, Li Zhang, on behalf of the BL-B01D1–303 Investigators†*

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