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# 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

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# DECLARATION OF INTERESTS

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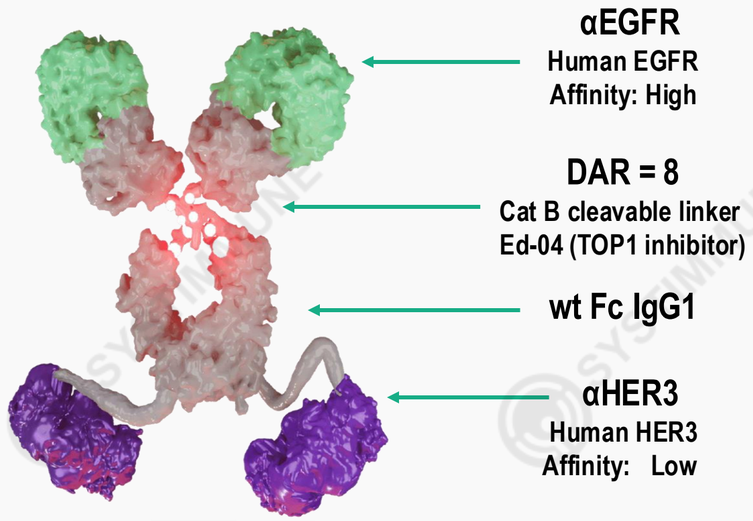
I do not have any financial relationship to disclose.

# Background

## Iza-bren, EGFR×HER3 bispecific ADC




- Nasopharyngeal carcinoma (NPC) accounts for about 129100 newly diagnosed cancer cases and 73000 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 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 results of interim analysis from a randomized phase III clinical trial comparing the efficacy and safety of iza-bren with chemotherapy in patients with heavily pretreated R/M NPC (BL-B01D1-303, NCT06118333).

**Wt**, wild type; **Cat B**, cathepsin B; **TOPI**, Topoisomerase I

1. Chen YP et al., Lancet 2019; 394(10192): 64-80; 2. Mai HQ et al., JAMA 2023; 330(20): 1961-70; 3. Yang Y et al., Lancet Oncol 2021; 22(8): 1162-74; 4. Yang Y et al., Cancer Cell 2023; 41(6): 1061-72.e4; 5. Chua DT et al., Oral Oncol 2003; 39(4): 361-6; 6. Zhang L et al., Cancer Chemother Pharmacol 2008; 61(1): 33-8; 7. Ngeow J et al., Ann Oncol 2011; 22(3): 718-22; 8. Ma Y et al., Lancet Oncol 2024; 25(7): 901-11; 8. Ma Y et al., Lancet Oncol 2024; 25(7): 901-11

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# Study Design

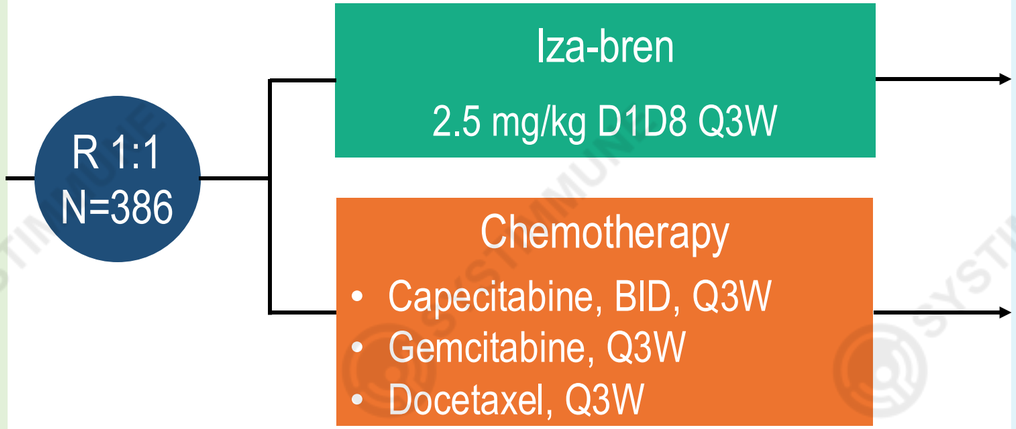
## A multicenter, randomized, open-label, phase III study conducted at 55 study centers across China

### 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.

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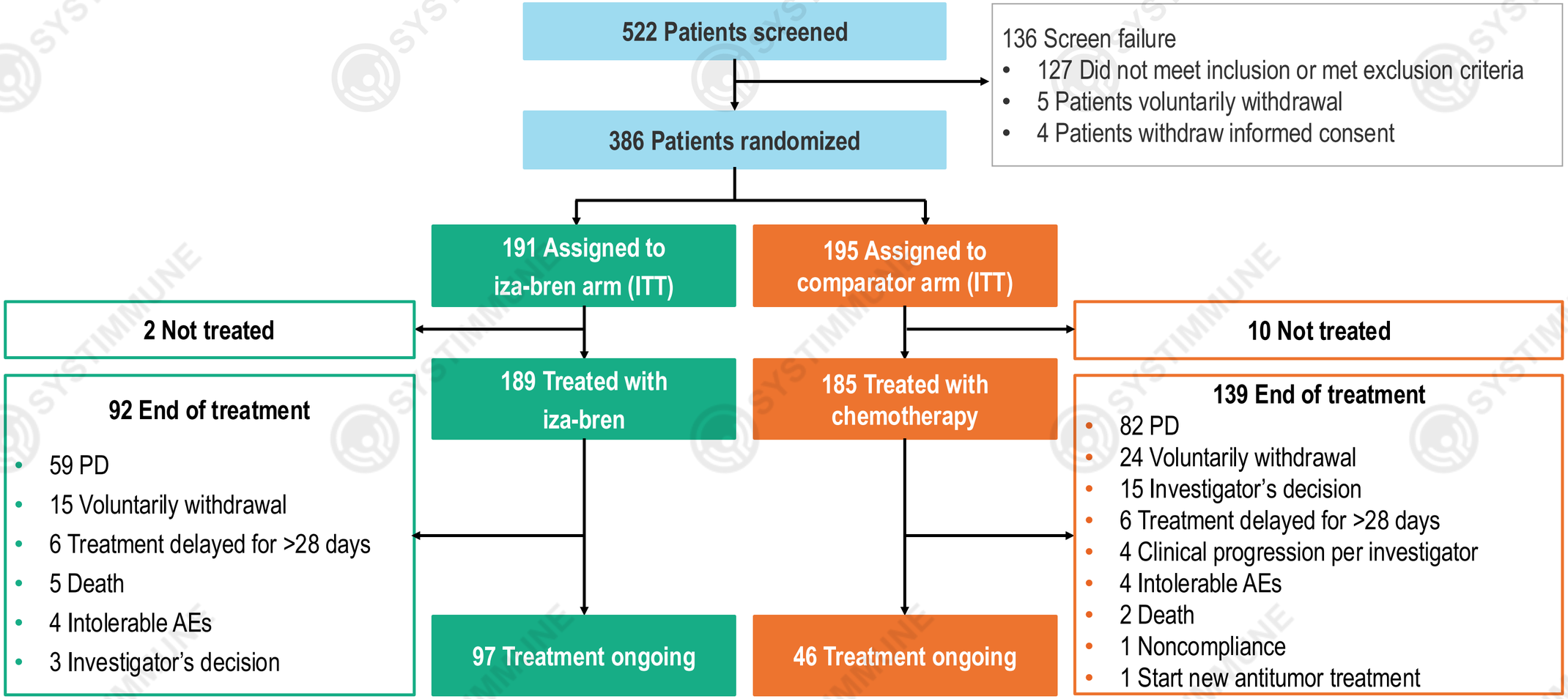
# Patient Disposition




***Data cut off: March 30, 2025***

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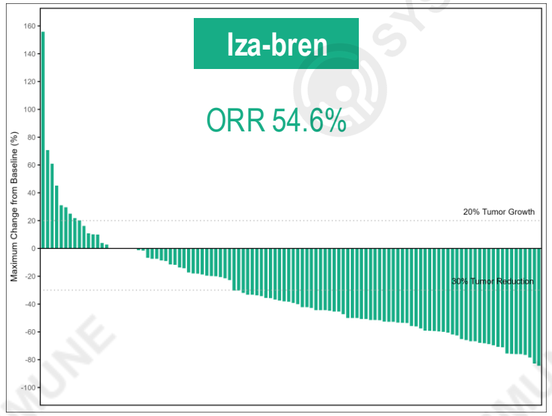
# Baseline Characteristics (ITT Population)

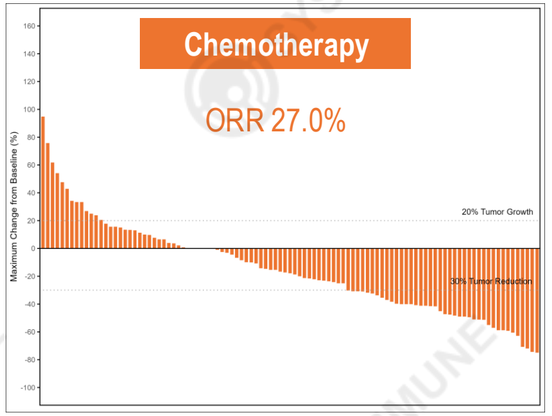
| Characteristics | Iza-bren (N=191) | Chemotherapy (N=195) |
|---|---|---|
| **Median (range) age, years** | 50.0 (27.0, 72.0) | 49.0 (19.0, 70.0) |
| **Age group (years), n (%)** | | |
| <50 | 95 (49.7) | 100 (51.3) |
| ≥50 | 96 (50.3) | 95 (48.7) |
| **Male, n (%)** | 163 (85.3) | 158 (81.0) |
| **ECOG 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) |

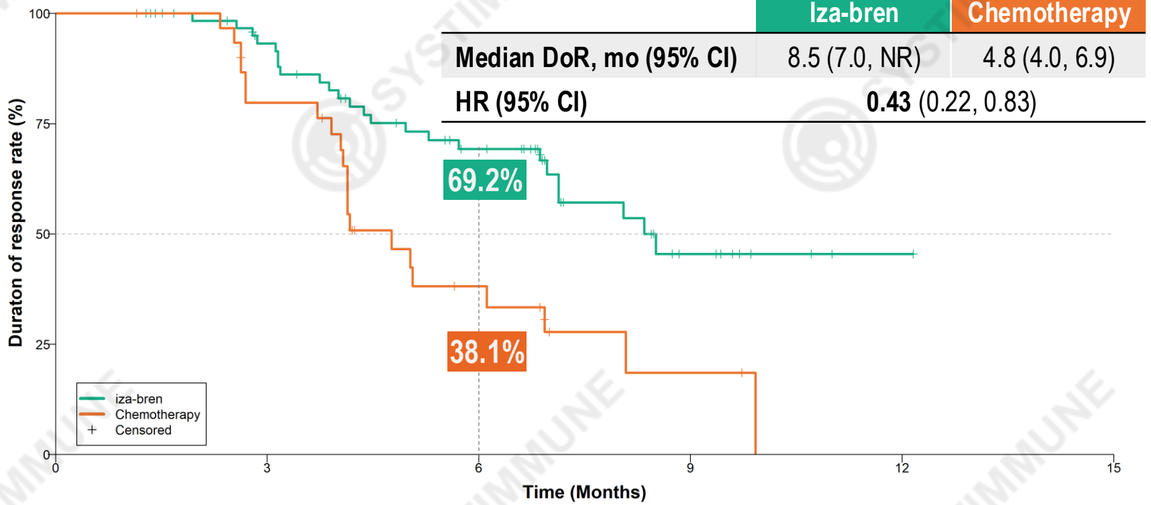
| Characteristics | Iza-bren (N=191) | Chemotherapy (N=195) |
|---|---|---|
| **Prior chemotherapy lines, n (%)** | | |
| 1 | 0 | 1 (0.5) |
| 2 | 124 (64.9) | 121 (62.1) |
| ≥3 | 67 (35.1) | 73 (37.4) |
| **Prior PBC lines, n (%)** | | |
| 0 | 1 (0.5) | 0 |
| 1 | 75 (39.3) | 84 (43.1) |
| 2 | 92 (48.2) | 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.

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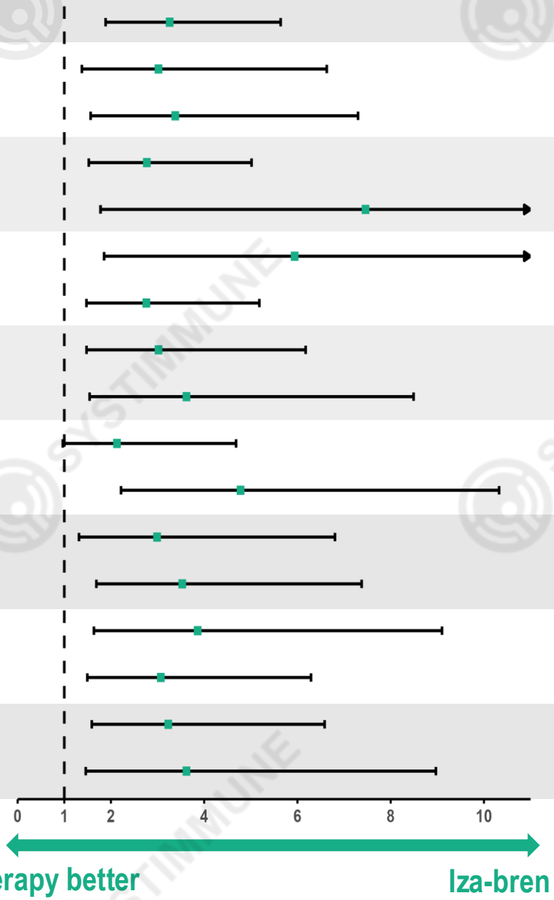
# Subgroup Analysis of ORR by BICR

| 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 same ORR benefit from iza-bren.

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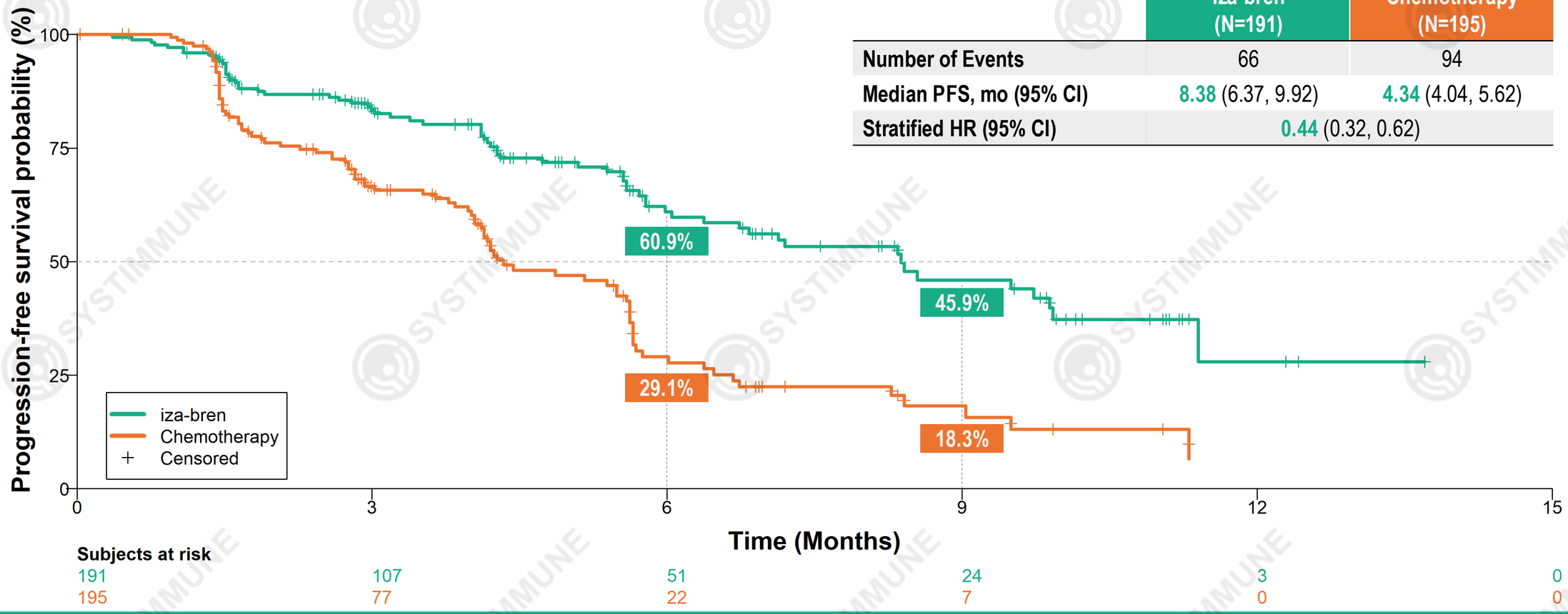
# BICR-Assessed PFS (Key Secondary Endpoint)

| | 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.

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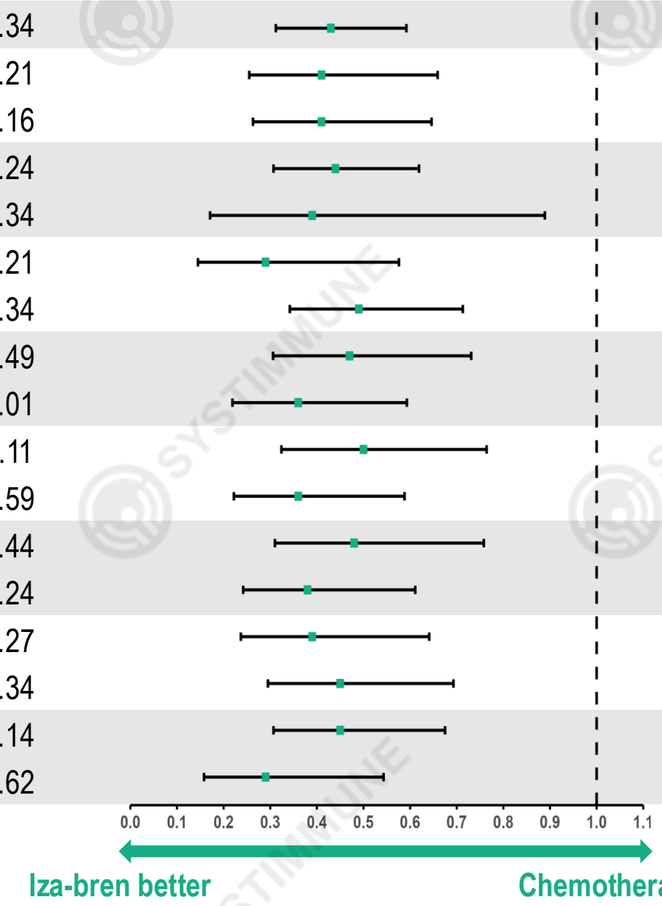
# Subgroup Analysis of PFS by BICR

| 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) |




Significant PFS benefit was also seen across the various subgroups.

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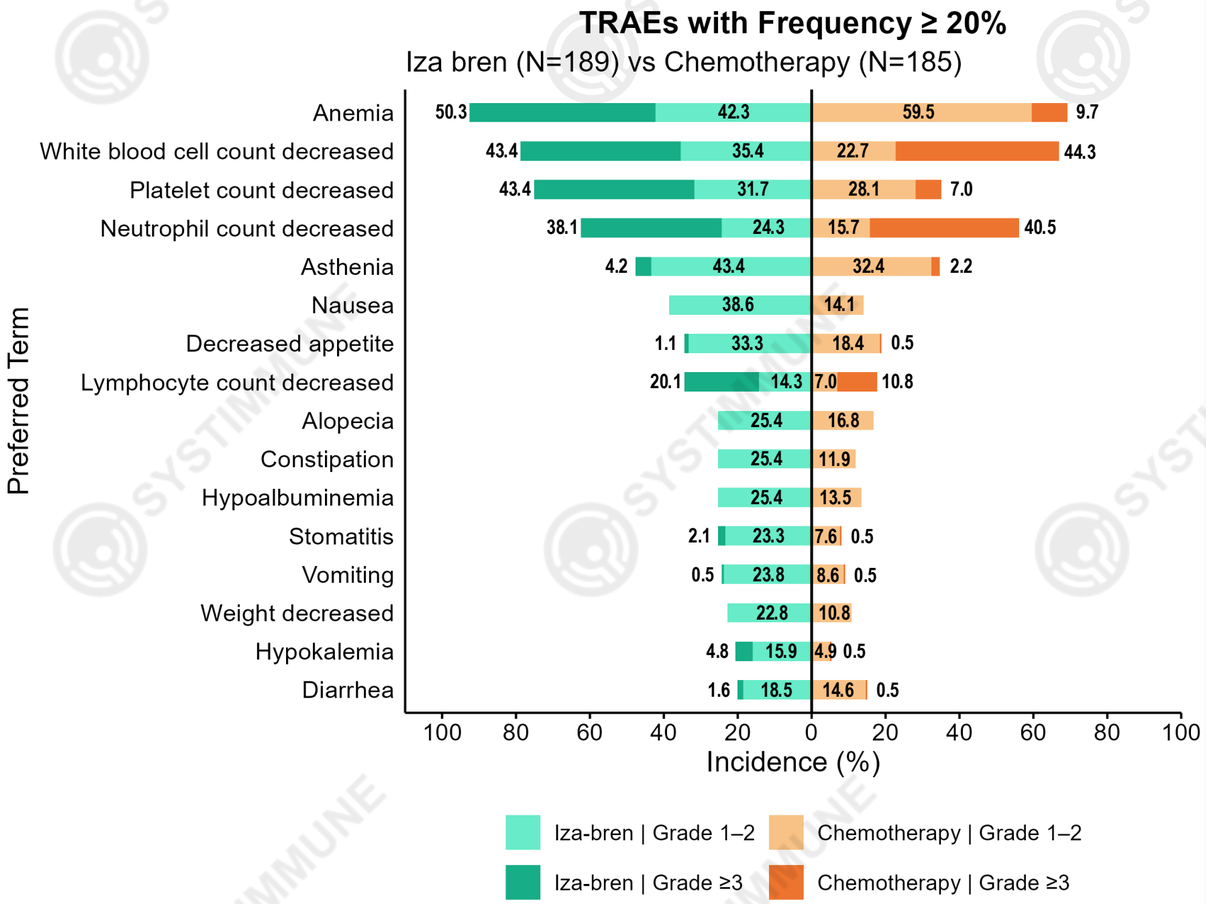
# Safety Summary (Safety Analysis Set)

| | 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).

**TRAE**, treatment related adverse events

# TRAEs in >20% of Patients in Either Group (Safety Set)




- The most frequent Grade ≥3 TRAEs in the iza-bren arm were mainly hematologic and were effectively managed using 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 reported in 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 in the iza-bren arm experienced Grade 2 ILD versus two (1.1%) Grade 3 in the chemotherapy arm.
- No new safety signals were identified.

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# Conclusions

- Iza-bren demonstrated a statistically significant and clinically meaningful improvement in ORR by BICR compared with 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 (95% CI), 0.43 (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 (95% CI), 0.44 (0.32, 0.62).
  - Subgroup analyses of PFS by BICR consistently favored iza-bren vs 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.
- OS data are not presented at this time as they are not yet mature.

**Iza-bren may represent a new standard of care for heavily pretreated patients with R/M NPC.**

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# Publication

THE LANCET

## 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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