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TUCATINIB AND TRASTUZUMAB FOR PREVIOUSLY TREATED HER2-POSITIVE METASTATIC BILIARY TRACT CANCER (SGNTUC-019): A PHASE 2 BASKET STUDY

Yoshiaki Nakamura, MD, PhD,[1] Nobumasa Mizuno, MD, PhD,[2] Yu Sunakawa, MD, PhD,[3] Erika Hamilton, MD,[4] Hidetoshi Hayashi, MD, PhD,[5] Seung Tae Kim, MD,[6] Keun-Wook Lee, MD, PhD,[7] Bradley J. Monk, MD,[8] Danny Nguyen, MD,[9] Alicia Okines, MBChB, MD (Res),[10] David O'Malley, MD,[11] Paula R. Pohlmann, MD,[12] Martin Reck, MD, PhD,[13] Evan Y. Yu, MD,[14] Roman Groisberg, MD,[15] Jorge Ramos, DO,[16] Sherry Tan, PhD,[16] Thomas E. Stinchcombe, MD,[17] Tanios Bekaii-Saab, MD.[18]

[1]National Cancer Center Hospital East, Kashiwa, Japan; [2]Aichi Cancer Center Hospital, Nagoya, Japan; [3]St. Marianna University Hospital, Kawasaki, Japan; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [5]Kindai University Hospital, Osakasayama, Japan; [6]Samsung Medical Center, Seoul, South Korea; [7]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; [8]Honor Health, Phoenix, AZ, USA; [9]City of Hope National Medical Center, Duarte, CA, USA; [10]The Royal Marsden Hospital and Institute of Cancer Research, London, UK; [11]The Ohio State University & James Comprehensive Cancer Center, Columbus, OH, USA; [12]MD Anderson Cancer Center, Houston, USA; [13]Lungen Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [14]Fred Hutchinson Cancer Center/ University of Washington, Seattle, WA, USA; [15]Merck, & Co Inc., Rahway, NJ, USA; [16]Seagen, Inc., Bothell, WA, USA; [17]Duke Cancer Institute, Durham, NC, USA; [18]Mayo Clinic Scottsdale, AZ, USA.

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Background

- Biliary tract cancer (BTC) is an aggressive malignancy, with the majority of patients having advanced disease at diagnosis[1,2]
- Current 1L therapy for metastatic BTC (mBTC) is gemcitabine plus cisplatin with or without durvalumab[3]
- 2L treatment options (eg, FOLFOX, S-1) have modest clinical benefit, with ORRs of 5% and 7.5% and median OS of 6.2 months and 6.8 months, respectively[4,5]
- HER2 is emerging as an important actionable target in HER2+ mBTC[6-10]
- HER2 overexpression or amplification (HER2+) is observed in up to 20% of BTC[11-13]
- Tucatinib is an oral TKI highly selective for HER2[14] currently approved to treat HER2+ MBC and mCRC[15]

1L: first-line; **2L:** second-line; **BTC:** biliary tract cancer; **MBC:** metastatic breast cancer; **mBTC:** metastatic biliary tract cancer; **mCRC:** metastatic colorectal cancer; **ORR:** objective response rate; **OS:** overall survival

1. Valle JW. Ann Oncol. 2010: vii345-8. **2.** Jarnagin WR. Ann Surg. 2001: 507-19. **3.** Oh D-Y. NEJM Evid. 2022: 1. **4.** Lamarca A. Lancet Oncol. 2021: 690-701. **5.** Suzuki E. Cancer Chemother Phamacol. 2013: 1141-6. **6.** Javle M. Lancet Oncol. 2021: 1290-300. **7.** Meric-Bernstam F. Lancet Oncol. 2022: 1558-70. **8.** Ohba A. ASCO 2022: Abstract 4006. **9.** Lee CK. Lancet Gastroenterol Hepatol. 2023: 56-65. **10.** Harding JJ. Nat Commun. 2023: 630. **11.** Galdy S. Metastasis Rev. 2017: 141-57. **12.** Valle JW. Cancer Discov. 2017: 943-62. **13.** Nam A-R. Oncotarget. 2016: 58007-21. **14.** Kulukian A. Mol Cancer Ther. 2020: 976-87. **15.** TUKYSA. Prescribing information. Seagen Inc., Jan 2023. Accessed Apr 10, 2023.

Study Design

- SGNTUC-019 (NCT04579380) is an open-label phase 2 basket study evaluating antitumor activity and safety of tucatinib and trastuzumab[a] in patients with HER2-altered solid tumors

Key eligibility criteria

- HER2 overexpression, amplification, or mutation per IHC/ISH or NGS testing determined locally
- Unresectable locally advanced or metastatic cancer
- Baseline measurable disease
- Previously treated with ≥1 prior systemic treatment for locally advanced or metastatic disease
- No prior HER2-directed therapy[b]

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- Cohort 1: Cervical (overexpression or amplification)
- Cohort 2: Uterine (overexpression or amplification)
- **Cohort 3: Biliary Tract (overexpression or amplification)[c]**
- Cohort 4: Urothelial (overexpression or amplification)
- Cohort 5: Nonsquamous NSCLC (overexpression or amplification)
- Cohort 6: Other solid tumors (overexpression or amplification)
- Cohort 7: Nonsquamous NSCLC (mutation)
- Cohort 8: Breast (mutation)
- Cohort 9: Other solid tumors (mutation)

Outcomes

Primary endpoint:
Confirmed ORR per RECIST 1.1 by investigator

Secondary endpoints:
Safety, DCR, DOR, PFS, and OS

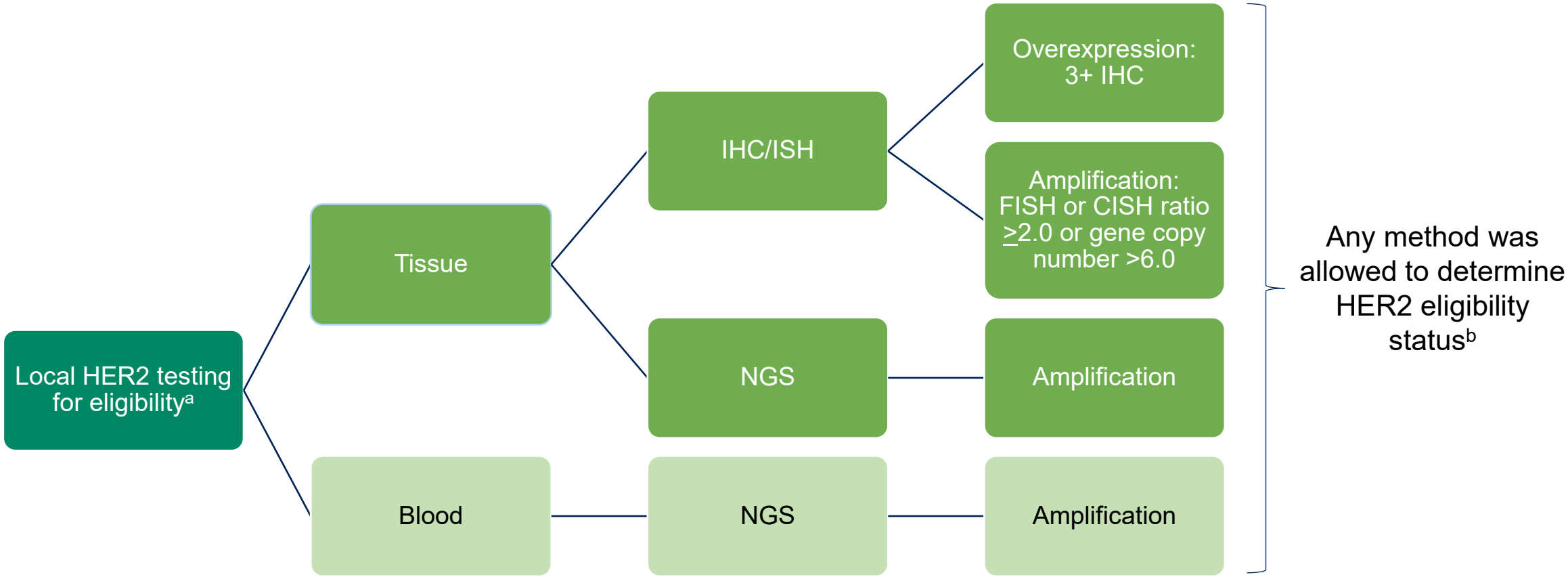
BID: twice daily; **C1D1:** Day 1 of Cycle 1; **DCR:** disease control rate; **DOR:** duration of response; **IHC:** immunohistochemistry; **ISH:** in situ hybridization; **IV:** intravenous; **NGS:** next-generation sequencing; **NSCLC:** non-small cell lung cancer; **ORR:** objective response rate; **OS:** overall survival; **PFS:** progression-free survival; **PO:** orally; **Q3W:** every 3 weeks; **RECIST:** Response Evaluation Criteria in Solid Tumors

[a]Tucatinib dose: 300 mg PO BID; trastuzumab dose: 6 mg/kg IV Q3W (loading dose of 8 mg/kg C1D1); each treatment cycle is 21 days.

[b]Except for patients with uterine serous carcinoma or HER2-mutated gastroesophageal cancer without HER2-overexpression or amplification.

[c]The cohort aimed to enroll up to 30 patients, a number calculated per the 90% exact CI given a range of expected confirmed ORR of 10% to 30%.

HER2 Testing for Eligibility for BTC Cohort



BTC: biliary tract cancer; **CISH:** chromogenic in situ hybridization; **CLIA:** Clinical Laboratory Improvement Amendments; **FISH:** fluorescence in situ hybridization; **IHC:** immunohistochemistry; **ISH:** in situ hybridization; **ISO:** International Organization for Standardization; **NGS:** next-generation sequencing

[a]Processed locally in a CLIA- or ISO-accredited laboratory before enrollment in the study.

[b]Patients deemed positive by any method were considered eligible.

Patient Disposition for BTC Cohort

Disposition, n (%)		Total (N=30)
Patients enrolled		30 (100)
Patients who received ≥1 dose of tucatinib or trastuzumab		30 (100)
Patients on study		11 (36.7)
Patients on treatment		3 (10.0)
Patients off treatment		8 (26.7)
Reason for treatment discontinuation	Progressive disease	25 (83.3)
	Adverse event	1 (3.3)
	Patient decision	1 (3.3)

Data cutoff: Jan 30, 2023[a]
Median study follow-up: 10.8 months (range, 1.5-17.1)

BTC: biliary tract cancer
[a]Patients were enrolled from June 2021 to May 2022.

Demographics and Baseline Characteristics

Characteristics		Total (N=30)
Median age, years (range)		68.5 (33 to 79)
Male, n (%)		15 (50.0)
Race, n (%)	Asian	23 (76.7)
	Others	7 (23.3)
ECOG PS score, n (%)	0	17 (56.7)
	1	13 (43.3)
Tumor location, n (%)	Cholangiocarcinoma extrahepatic	8 (26.7)
	Cholangiocarcinoma intrahepatic	7 (23.3)
	Gallbladder	15 (50.0)
Stage at initial diagnosis, n (%)	I to III	12 (40.0)
	IV	18 (60.0)
Previous lines of systemic therapy in any setting, median (range)		2.0 (1 to 4)

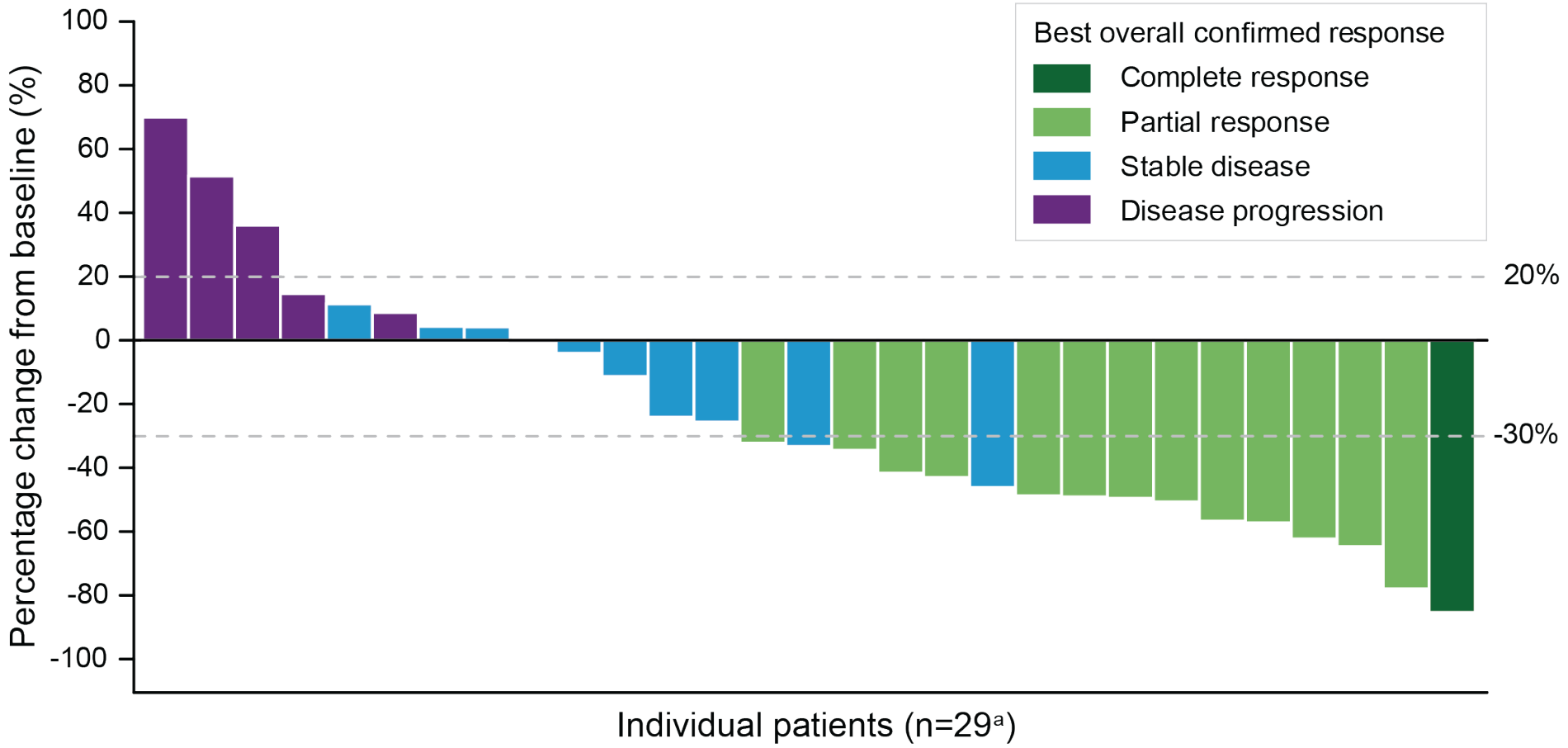
Data cutoff: Jan 30, 2023.
ECOG PS: Eastern Cooperative Oncology Group Performance Status

Response to Treatment

		Total (N=30)
Best overall response, n (%)	CR	1 (3.3)
	PR	13 (43.3)
	SD	9 (30.0)
	PD	6 (20.0)
	Not available	1 (3.3)[a]
cORR, % (90% CI)		**46.7 (30.8-63.0)**
Median DOR, months (90% CI)		6.0 (5.5-6.9)
DCR, n (%)		23 (76.7)

Data cutoff: Jan 30, 2023.
[a]The patient had no postbaseline response assessment.
cORR: confirmed objective response rate; **CR:** complete response; **DCR:** disease control rate; **DOR:** duration of response; **PD:** progressive disease; **PR:** partial response; **SD:** stable disease

Maximum Change in Tumor Size

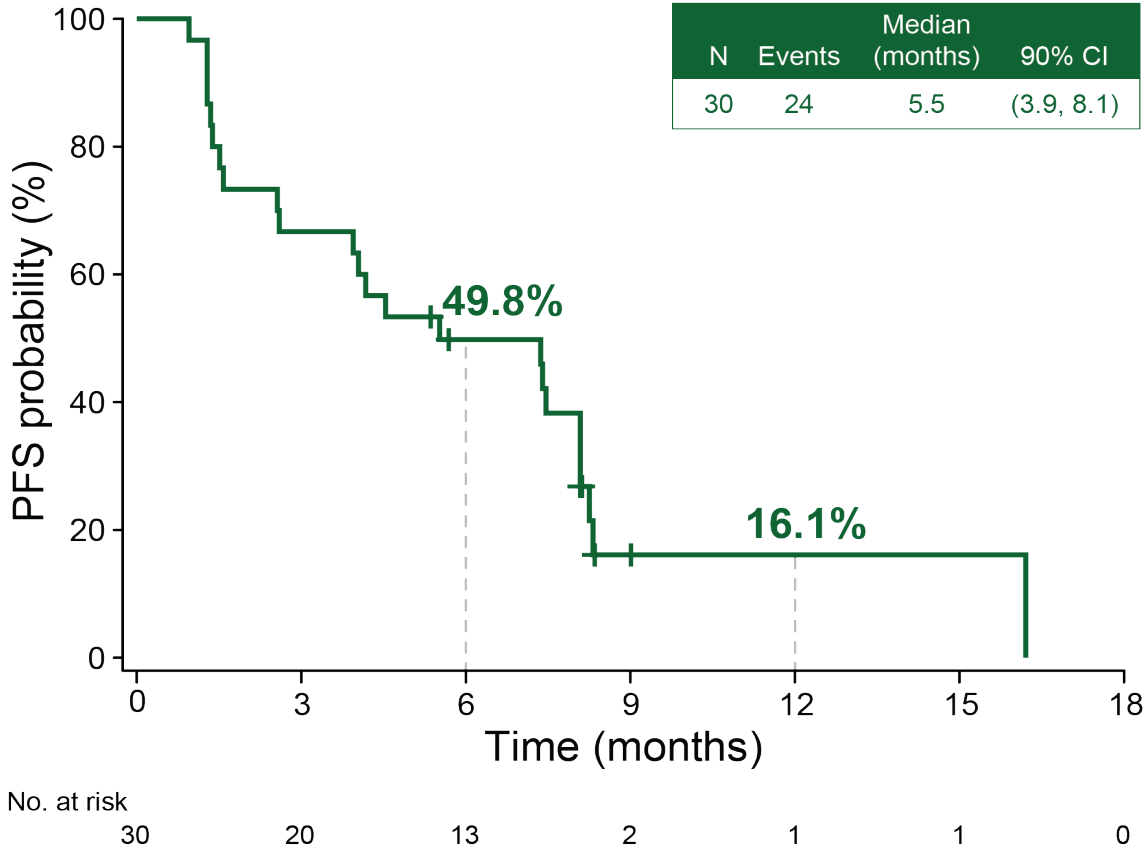


Twenty-one patients (70.0%[b]) had a reduction in tumor size
Median time to first response was 2.1 months (range, 1.2-4.3)

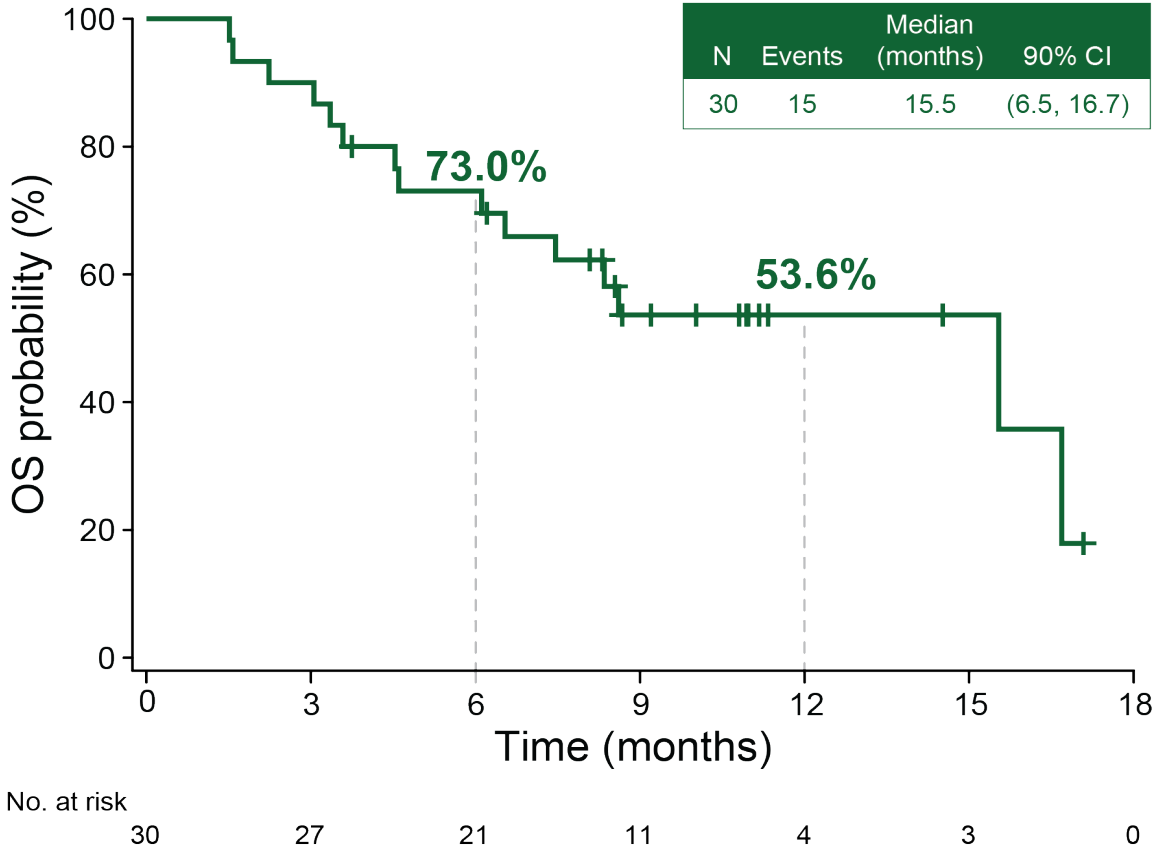
Data cutoff: Jan 30, 2023.
[a]Excludes 1 patient with no postbaseline response assessment.
[b]Percentage was calculated with 30 as the denominator.

Progression-Free Survival and Overall Survival

Progression-Free Survival



Overall Survival



Data cutoff: Jan 30, 2023.
PFS: progression-free survival; **OS:** overall survival

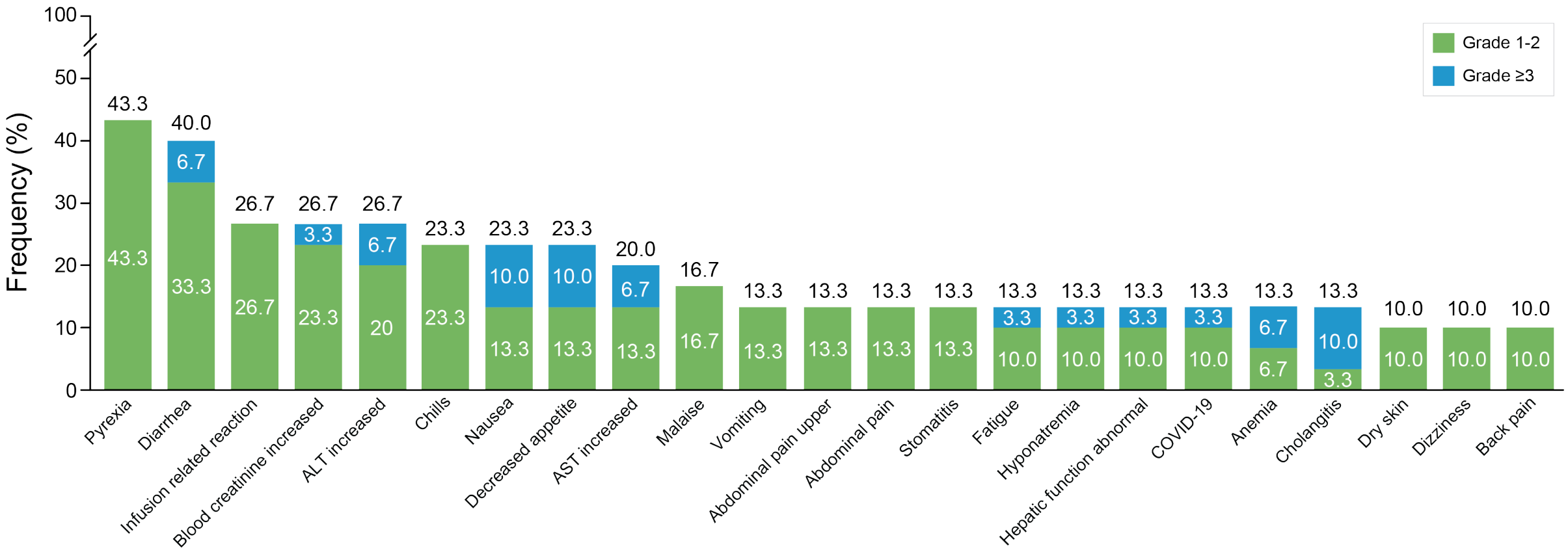
Safety Summary

TEAEs, n (%)	Total (N=30)
Any TEAE	30 (100)
Grade ≥3 TEAE	18 (60.0)
Any serious TEAE	13 (43.3)
TEAEs leading to discontinuation of any study treatment	3 (10.0)[a]
Tucatinib	3 (10.0)[b]
Trastuzumab	1 (3.3)[c]
TEAEs leading to death	0

Most grade ≥3 and serious TEAEs were not related to tucatinib
Seven patients (23.3%) had tucatinib-related grade ≥3 AEs, and 3 patients (10.0%) had tucatinib-related serious AEs

Data cutoff: Jan 30, 2023.
AEs: adverse events; **TEAEs:** treatment-emergent adverse events
[a]One patient discontinued both tucatinib and trastuzumab due to interstitial lung disease.
[b]Cholangitis, interstitial lung disease, or liver disorder.
[c]Interstitial lung disease.

Most Common TEAEs (≥10%)[a]



Most common grade ≥3 TEAEs were nausea, decreased appetite, and cholangitis (each in 3 patients [10.0%])

Data cutoff: Jan 30, 2023.
ALT: alanine aminotransaminase; **AST:** aspartate aminotransferase; **TEAEs:** treatment-emergent adverse events
[a]Percentages may not add up to total due to rounding.

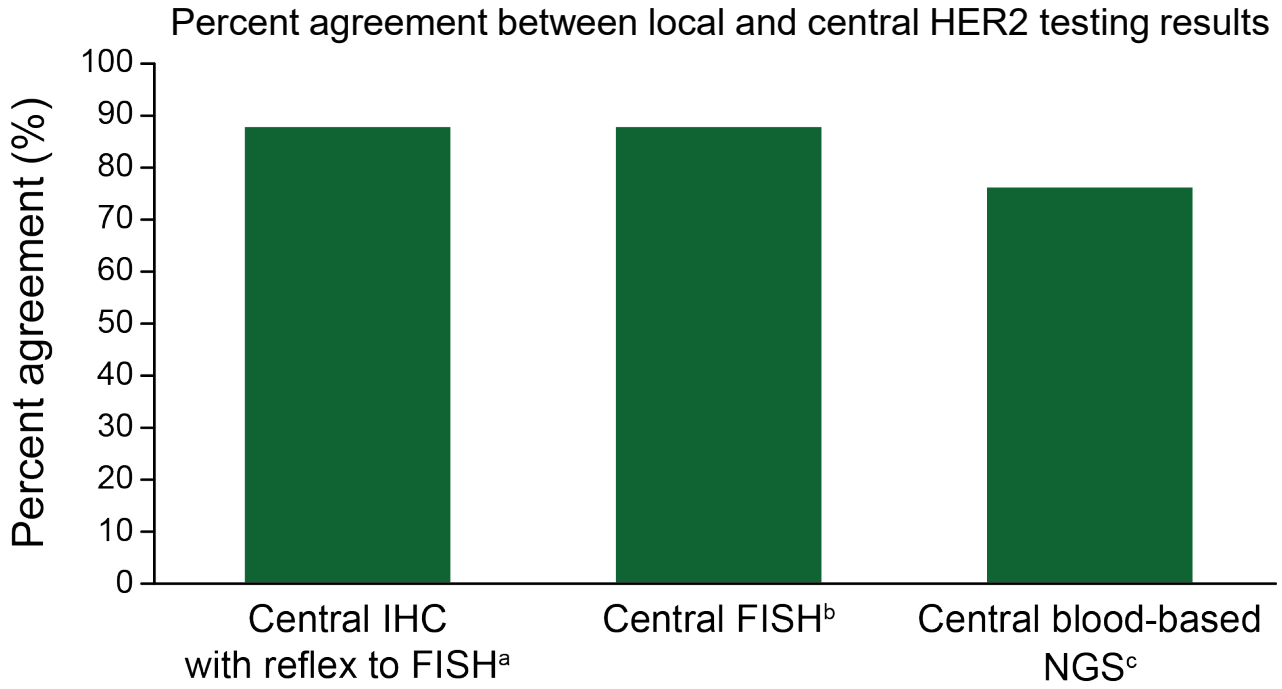
HER2 Testing Exploratory Analyses

Exploratory biomarker analyses:

1. Percent agreement between local and central HER2 testing
2. Clinical response for different testing methods

Central HER2 testing methods:

IHC, FISH, and blood-based NGS



n/N	21/24	21/24	22/29
%	87.5	87.5	75.9
90% CI	70.8-96.5	70.8-96.5	59.4-88.1

Data cutoff: Jan 30, 2023.

ASCO-CAP: American Society of Clinical Oncology-College of American Pathologists; **FISH:** fluorescence in situ hybridization; **IHC:** immunohistochemistry; **ISH:** in situ hybridization; **NGS:** next-generation sequencing

[a]IHC and FISH results were evaluated by using the ASCO-CAP gastric scoring criteria (Bartley AN. J Clin Oncol. 2017: 446-64). HER2 overexpression defined as IHC 3+ or IHC 2+ and ISH+, and no overexpression defined as IHC 0, IHC 1+, or IHC 2+ and ISH–.

[b]FISH results were evaluated by using HER2 IQFISH pharmDx assay (Agilent).

[c]Blood-based NGS results were evaluated by using Guardant 360®.

ORRs for Different Central HER2 Testing Methods

	Centrally HER2+		Centrally HER2–	
	Responder/Total	ORR (90% CI)	Responder/Total	ORR (90% CI)
IHC/FISH[a]	12/21	57.1% (37.2-75.5)	0/3	0% (0-63.2)
FISH[b]	12/21	57.1% (37.2-75.5)	0/3	0% (0-63.2)
Blood-based NGS[c]	14/22	63.6% (43.9-80.4)	0/7	0% (0-34.8)

Regardless of testing method, all central HER2– patients were nonresponders

Data cutoff: Jan 30, 2023.
FISH: fluorescence in situ hybridization; **IHC:** immunohistochemistry; **NGS:** next-generation sequencing; **ORRs:** objective response rates
[a]IHC and FISH results were evaluated by using the ASCO-CAP gastric scoring criteria (Bartley AN. J Clin Oncol. 2017: 446-64). HER2 overexpression defined as IHC 3+ or IHC 2+ and ISH+, and no overexpression defined as IHC 0, IHC 1+, or IHC 2+ and ISH–.
[b]FISH results were evaluated by using HER2 IQFISH pharmDx assay (Agilent).
[c]Blood-based NGS results were evaluated by using Guardant 360®.

Authors' Conclusions

- The combination of tucatinib and trastuzumab had clinically meaningful antitumor activity in patients with previously treated HER2+ mBTC
  - Confirmed ORR of 46.7% with DCR of 76.7% and median DOR of 6.0 months
  - Median PFS of 5.5 months and median OS of 15.5 months
- Tucatinib plus trastuzumab was well tolerated
  - Low rate of study treatment discontinuation (3.3%) and no deaths due to AEs
- Multiple HER2 testing modalities can be used to identify patients who may be eligible for tucatinib and trastuzumab treatment
- Results further validate HER2 as an actionable biomarker in BTC

AEs: adverse events; **BTC:** biliary tract cancer; **DCR:** disease control rate; **DOR:** duration of response; **mBTC:** metastatic biliary tract cancer; **ORR:** objective response rate; **OS:** overall survival; **PFS:** progression-free survival