Final analysis results from the NIFTY trial, a phase IIb, randomized, open-label study of liposomal irinotecan plus fluorouracil and leucovorin in patients with previously treated metastatic biliary tract cancer

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Background

- There are clinical unmet needs of second-line treatment options for patients with advanced biliary tract cancer (BTC) who progressed to first-line gemcitabine plus cisplatin (GemCis).
- The NIFTY trial showed improvement of survival outcomes with liposomal irinotecan (nal-IRI) plus fluorouracil and leucovorin (5-FU/LV) compared to 5-FU/LV alone for patients with previously treated advanced BTC in terms of progression-free survival (PFS) assessed by blinded-independent central review (BICR).[1]
- Nal-IRI plus 5-FU/LV is recommended (Category 2B) as subsequent-line therapy for patients with advanced BTC in the NCCN Clinical Practice Guidelines in Oncology.[2]
- There is a need for additional BICR and analysis as there was concern about the large discrepancy rates (30%) between BICR and investigator review in the previous analysis.

➢ **Purpose of the study**

1) **Long term efficacy with extended follow-up (1.3 years)**
2) **Re-performed BICR**
3) **Post-hoc exploratory analysis of prognostic factors**

Methods

➢ **Design: Multicenter, randomized, open-label, phase 2b trial**

Key eligibility criteria

1) Histologically or cytologically confirmed BTC
2) At least one or more metastasis
3) Radiologic progression on prior first-line GemCis
4) At least one measurable lesion per RECIST version 1.1
5) ECOG performance status 0-1
6) Adequate organ function

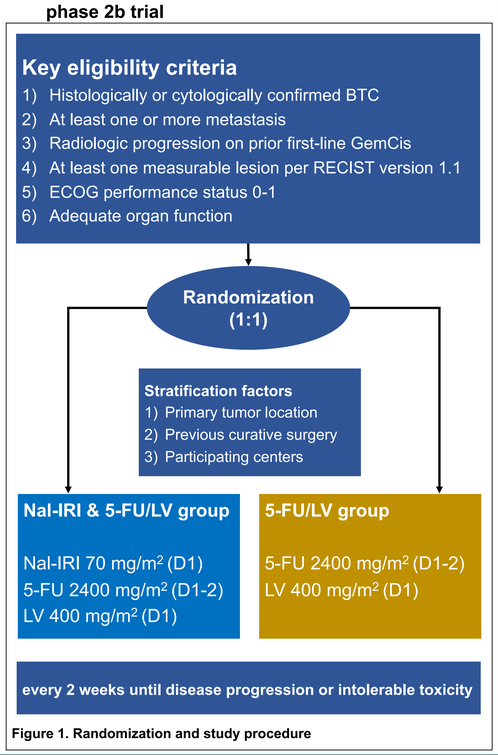

Figure 1. Randomization and study procedure

➢ **Assessment**

- Assessment of radiologic response by RECIST version 1.1 every 6 weeks fixed schedule
- Re-performed BICR with three newly invited independent radiologists along with external monitoring

➢ **Outcomes**

- Primary endpoint

-PFS assessed by BICR (RECIST version 1.1)
*PFS defined as from randomization to disease progression or death of any cause

- Secondary endpoints

-PFS assessed by investigators (RECIST version 1.1)
-Overall survival (OS) defined as from randomization to any cause of death
-Objective response rate (ORR) defined as CR or PR as best response by RECIST version 1.1

Results

➢ **Participants**

- A total of 193 patients assessed for eligibility, 178 patients were randomized for the study as of December 31, 2021 (data cut-off).
- Total 174 patients were included in the full analysis set population (88 patients in nal-IRI plus 5-FU/LV group vs. 86 patients in 5-FU/LV group) (Figure 1).
- Median age was 64 years (IQR, 38-84), 75 patients (43%) were female, 74 patients (43%) had intrahepatic cholangiocarcinoma, 47 patients (27%) had extrahepatic cholangiocarcinoma, and 53 patients (30%) had gallbladder cancer

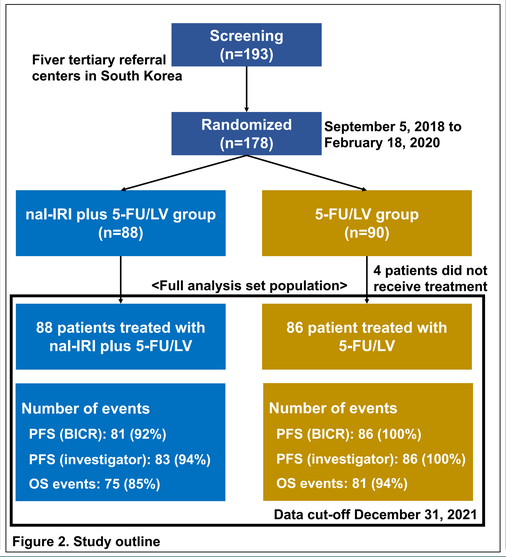

Figure 2. Study outline

Table 1. Baseline clinical characteristics

Characteristics	Patients, No. (%) Nal-IRI plus 5-FU/LV (n=88)	5-FU/LV (n=86)
Sex		
Female	37 (42)	38 (44)
Male	51 (58)	48 (56)
Median age, years (IQR)	63 (38-84)	65 (37-80)
Primary tumor location		
Intrahepatic	35 (40)	39 (45)
Extrahepatic	22 (25)	25 (29)
Gallbladder	31 (35)	22 (26)
Previous surgery with curative intent	26 (30)	29 (34)
Median duration of first-line gemcitabine plus cisplatin		
< 6 months	57 (65)	55 (64)
≥ 6 months	31 (35)	31 (36)
Median serum CA 19-9		
< 172 U/mL	48 (55)	39 (45)
≥ 172 U/mL	40 (45)	47 (55)
Site of metastasis		
Liver	59 (67)	64 (74)
Lung	22 (25)	16 (19)
Lymph node	57 (65)	48 (56)
Peritoneum	25 (28)	20 (23)
Bone	5 (6)	9 (10
ECOG performance status		
0	23 (26)	15 (17)
1	65 (74)	71 (83)

Nal-IRI, liposomal irinotecan; 5-FU/LV, fluorouracil and leucovorin; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group

➢ **Efficacy outcomes**

Table 2. Efficacy outcomes in the full analysis set population

	Nal-IRI plus 5-FU/LV group (n=88)	5-FU/LV group (n=86)	*P*	HR (95% CI)[a]
BICR				
Median PFS (95% CI)	4.2 months (2.8-5.3)	1.7 months (1.4-2.6)	0.004[b]	0.61 (0.44-0.86)
6-months PFS rate (95% CI)	31.8% (21.7-41.8)	15.1% (7.5-22.7)		
ORR	12.5%	3.5%	0.04[c]	
Investigator review				
Median PFS (months, 95% CI)	3.9 months (2.7-5.2)	1.6 months (1.3-2.2)	< 0.001[b]	0.51 (0.36-0.71)
6-months PFS rate (95% CI)	30.0% (20.2-39.8)	11.6% (4.9-18.4)		
ORR	19.3%	2.3%	< 0.001[c]	
OS				
Median OS (95% CI)	8.6 months (5.4-10.5)	5.3 months (4.7-7.2)	0.02[b]	0.68 (0.48-0.95)
6-months OS rate (95% CI)	60.7% (50.3-71.2)	44.7% (34.2-55.3)		

CI, confidence interval; nal-IRI, liposomal irinotecan; 5-FU, fluorouracil; LV, leucovorin; HR, hazards ratio; BICR, blinded independent central review; PFS, progression-free survival; ORR, objective response rate; OS, overall survival
[a] Using stratified Cox regression of HR of the liposomal irinotecan plus fluorouracil and leucovorin over the fluorouracil and leucovorin
[b] *P*-value by stratified log-rank tests, stratified by the randomization stratification factors
[c] *P*-value by Cochran-Mantel-Haenszel test stratified by the randomization stratification factors

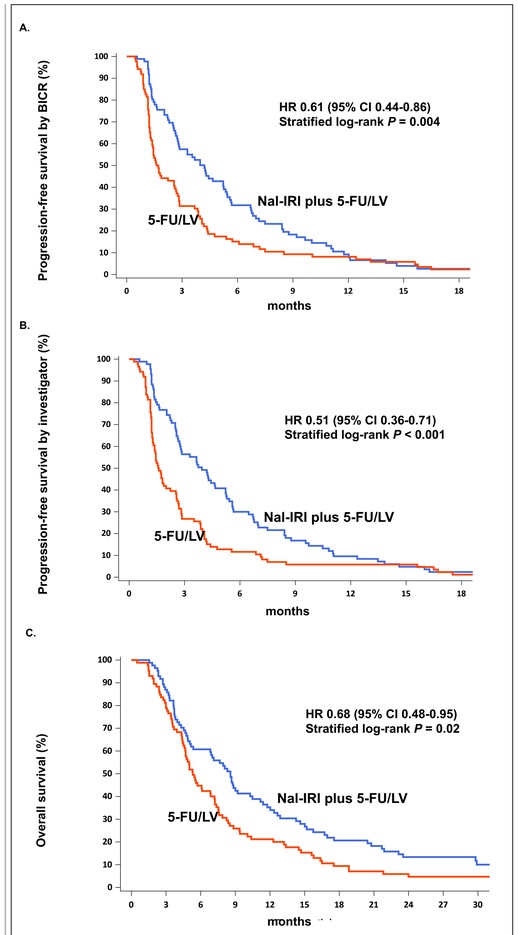

Figure 3. Kaplan-Meier estimates and comparison of survival outcomes according to the study treatments (nal-IRI plus 5-FU/LV vs. 5–FU/LV) A. Progression-free survival by BICR-assessment. B. Progression-free survival by investigator assessment. C. Overall survival

- Median follow-up duration 6.1 months (IRQ, 3.5-12.6)
- Median PFS by BICR assessment and investigator assessment, and OS were significantly longer in the nal-IRI plus 5-FU/LV group compared to the 5-FU/LV group.
- ORR assessed by both BICR and investigator were significantly higher in the nal-IRI plus 5-FU/LV group compared to the 5-FU/LV group.
- Discordance rate between BICR and investigator assessed tumor progression date was 17.8%.

➢ **Post-hoc prognostic factors analysis**

- Higher baseline CA 19-9 and CRP level were independently associated with both poor PFS and OS.
- Male and peritoneal metastasis were independently associated with poor prognosis in terms of OS.
- Nal-IRI plus 5-FU/LV independently associated with better PFS and OS after adjustment with prognostic factors

Table 3. Multivariable analysis using Cox proportional hazards regression modeling according to the study group and potential prognostic variables in terms of progression-free survival assessed by the BICR and overall survival

	Progression-free survival HR (95% CI)	*P*	Overall survival HR (95% CI)	*P*
Study treatment				
Nal-IRI plus 5-FU/LV	1(Ref)		1(Ref)	
5-FU/LV	1.62 (1.17-2.23)	0.004	1.42 (1.01-1.99)	0.04
Age (per 1-unit increase)	0.99 (0.97-1.01)	0.24	1.02 (0.99-1.04)	0.16
Sex				
Female	1(Ref)		1(Ref)	
Male	0.99 (0.70-1.41)	0.97	1.53 (1.07-2.19)	0.02
ECOG PS				
0	1(Ref)		1(Ref)	
1	0.83 (0.56-1.23)	0.36	1.11 (0.74-1.68)	0.61
Primary tumor site				
Intrahepatic	1(Ref)		1(Ref)	
Extrahepatic	0.78 (0.50-1.20)	0.25	0.87 (0.56-1.34)	0.52
Gallbladder	0.75 (0.50-1.13)	0.18	0.82 (0.54-1.24)	0.34
Prior surgery				
Yes	1(Ref)		1(Ref)	
No	0.86 (0.58-1.26)	0.43	0.73 (0.49-1.09)	0.12
Duration of prior Gem/Cis (months) (per 1-unit increase)	0.98 (0.95-1.02)	0.29	0.98 (0.94-1.01)	0.21
Metastatic site: Liver				
No	1(Ref)		1(Ref)	
Yes	1.22 (0.83-1.78)	0.31	1.40 (0.93-2.11)	0.10
Metastatic site: Lung				
No	1(Ref)		1(Ref)	
Yes	0.79 (0.52-1.20)	0.27	0.80 (0.51-1.26)	0.33
Metastatic site: Bone				
No	1(Ref)		1(Ref)	
Yes	1.58 (0.83-2.99)	0.16	1.81 (0.92-3.58)	0.09
Metastatic site: Peritoneum				
No	1(Ref)		1(Ref)	
Yes	1.22 (0.82-1.82)	0.33	1.59 (1.05-2.42)	0.03
Baseline CA 19-9 level (per 1,000-unit increase)	1.01 (1.00-1.02)	0.005	1.02 (1.01-1.03)	<0.001
Baseline CRP (per 1-unit increase)	1.11 (1.04-1.18)	0.001	1.22 (1.14-1.31)	<0.001
Baseline albumin (per 1-unit increase)	1.09 (0.77-1.56)	0.62	0.83 (0.57-1.21)	0.34

Nal-IRI, liposomal irinotecan; 5-FU/LV, fluorouracil and leucovorin; ECOG, Eastern Cooperative Oncology Group; Gem/Cis, gemcitabine plus cisplatin; CRP, C-reactive protein; HR, hazards ratio; CI, confidence interval; PS, performance status

Conclusion

- **Survival benefit of nal-IRI plus 5-FU/LV compared to 5-FU/LV was maintained with an extended follow-up in patients with advanced BTC who progressed to first-line GemCis.**
- **Nal-IRI plus 5-FU/LV could be a second-line treatment option for patients with previously treated advanced biliary tract cancer.**
- **ClinicalTrials.gov identifier: NCT03524508**

References

1. Yoo C, Kim KP, Jeong JH, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. *Lancet Oncol.* 2021;22(11):1560-1572. doi:10.1016/s1470-2045(21)00486-1

2. National Comprehensive Cancer Network. Hepatobiliary Cancer version 1.2022.

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