# Pancreatic and Hepatobiliary Cancer: Emerging Strategies

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# Outline

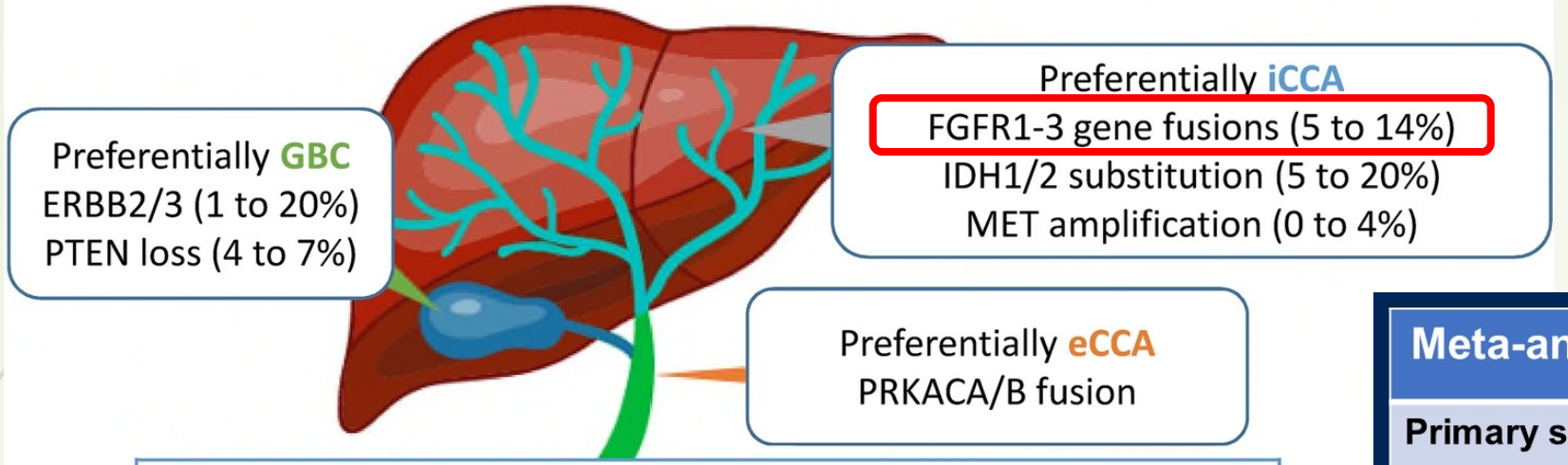
1) Biliary

2) HCC

3) PDAC

# Biliary

## Targetable mutations in BTC




| All BTC subtypes | | | |
|---|---|---|---|
| **Alteration frequency (%)** | **iCCA** | **eCCA** | **GBC** |
| ***KRAS*** | 9 to 35% | 12 to 47% | 11 to 19% |
| ***CDKN2A/B*** | 1 to 18% | 0 to 17% | 0 to 19% |
| ***PI3K/mTOR*** | 4 to 16% | 4 to 25% | 7 to 14% |
| ***TP53*** | 3 to 32% | 18 to 45% | 43 to 46% |
| ***BRAF*** | 4 to 22% | 3% | 0 to 33% |
| **MGMT methylation** | 38% | 26% | 62% |
| **dMMR/MSI-H** | 1 to 10% | 1 to 13% | 1 to 36% |
| ***NTRK* gene fusions** | 0 to 3.6% (all subtypes) | | |

Front Genet. 2018 Aug 15;9:309.

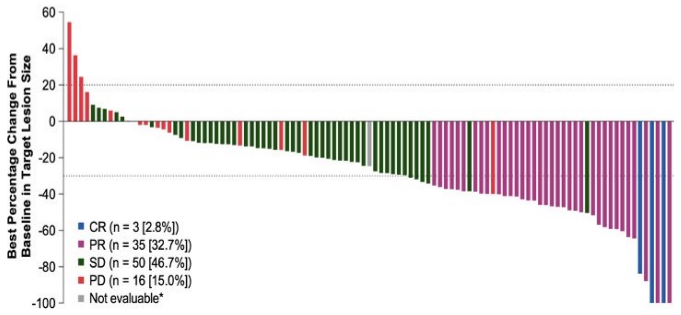
| Meta-analysis (n=27 studies) | |
|---|---|
| **Primary site** | **HER2 expression (moderate/high)** |
| IHCC | 4.8% |
| EH-BTC | 19.9% |
| EHCC | 17.4% |
| Gallbladder | 19.1% |
| Ampullary | 27.9% |

Galdy et al, *Cancer Metastasis Rev* 2017;36:141-57.

Biliary

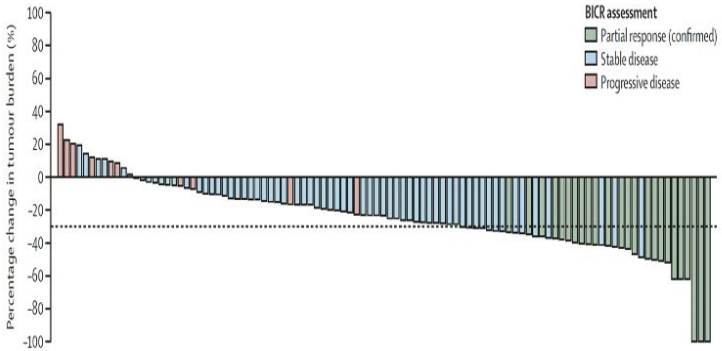
# FGFR inhibition in biliary tract cancer: FGFR2 fusion

**FIGHT-202**
**Pemigatinib**



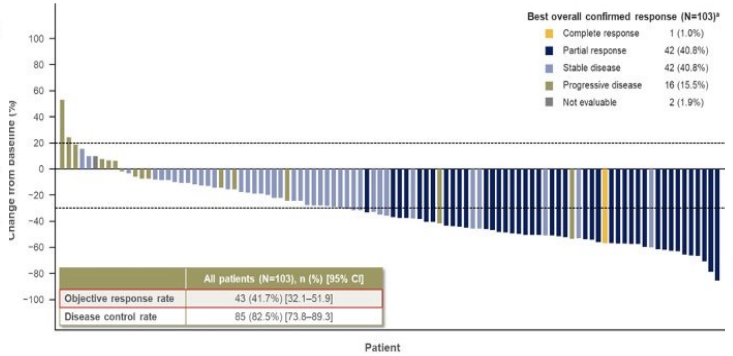

Vogel et al @ESMO 2019

**Infigratinib**




Javle et al. Lancet GastroHep 2021

**FOENIX-CCA2**
**Futibatinib**




Goyal et al @ASCO 2022

## FGFR Inhibitors for Previously Treated CCA

| FGFR Inhibitor | Binding Features | Trial (Phase 2, Single-Arm) | Approval | |
|---|---|---|---|---|
| **Pemigatinib** | Reversible FGFR1-3 inhibitor | FIGHT-202 (NCT02924376) | FDA (April, 2020) EMA (March, 2021) | Adults with locally advanced or metastatic CCA with an FGFR2 fusion or rearrangement, that have progressed after at least one prior line of systemic therapy |
| **Infigratinib** | Reversible FGFR1-3 inhibitor | NCT02150967 | FDA (May, 2021) EMA (Withdrawn) | |
| **Futibatinib (TAS-120)** | Irreversible FGFR1-4 inhibitor | FOENIX-CCA2 (NCT02052778) | FDA (September, 2022) EMA (CHMP positive opinion: April 28, 2023) | |

# Biliary

## Co-mutations

**Table S8. Outcomes in Patients With or Without Co-occurring Genetic Alterations.***

| Molecular Status | n | ORR, % (95% CI) | Median PFS, mo (95% CI) |
|---|---|---|---|
| All patients | 93 | 43.0 (32.8–53.7) | 8.9 (6.6–13.1) |
| *BAPI* | | | |
| Unaltered | 53 | 49.1 (35.1–63.2) | 8.0 (4.9–13.8) |
| Altered | 40 | 35.0 (20.6–51.7) | 9.0 (5.1–13.3) |
| *CDKN2A* | | | |
| Unaltered | 73 | 43.8 (32.2–55.9) | 9.7 (6.9–13.8) |
| Altered | 20 | 40.0 (19.1–63.9) | 4.9 (3.4–13.3) |
| *CDKN2B* | | | |
| Unaltered | 77 | 42.9 (31.6–54.6) | 11.0 (7.2–15.1) |
| Altered | 16 | 43.8 (19.8–70.1) | 4.8 (3.4–4.9) |
| *TP53* | | | |
| Unaltered | 80 | 43.8 (32.7–55.3) | 9.0 (6.6–13.3) |
| Altered | 13 | 38.5 (13.9–68.4) | 7.0 (1.4–13.8) |
| *ARID1A* | | | |
| Unaltered | 81 | 42.0 (31.1–53.5) | 9.0 (6.2–13.1) |
| Altered | 12 | 50.0 (21.1–78.9) | 8.8 (4.9–18.2) |
| *MLL2* | | | |
| Unaltered | 82 | 40.2 (29.6–51.7) | 8.9 (6.2–13.1) |
| Altered | 11 | 63.6 (30.8–89.1) | 9.0 (2.7–NE) |
| *PIK3C2B* | | | |
| Unaltered | 82 | 40.2 (29.6–51.7) | 8.9 (6.0–13.1) |
| Altered | 11 | 63.6 (30.8–89.1) | 9.0 (4.7–15.2) |

*Analyses included only patients with available Foundation Medicine reports (n=93). Table shows genetic co-alterations detected in ≥11 patients.

CI denotes confidence interval, ORR objective response rate, PFS progression-free survival, and NE not evaluable.

## Acquired Resistance

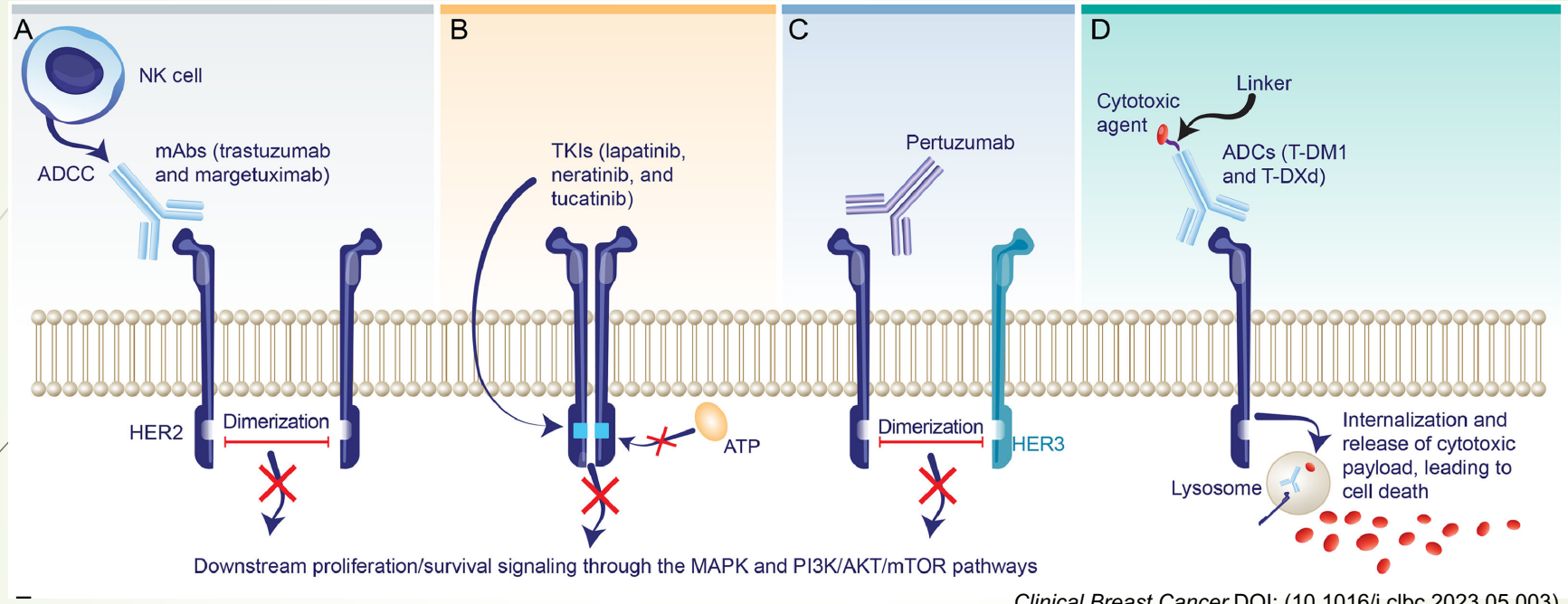
| *FGFR2* Mutation | Kinase Domain Region | Factor Change in $IC_{50}$ vs. Wild-Type *FGFR2* | | | |
|---|---|---|---|---|---|
| | | Futibatinib | Pemigatinib | Infigratinib | Erdafitinib |
| Wild-type | — | 1 | 1 | 1 | 1 |
| N550D | Regulatory triad | 2 | 102 | 81 | 10 |
| N550K | Regulatory triad | 8 | 164 | 68 | 13 |
| V563L | — | 3 | 5 | 14 | 1 |
| V565I | Gatekeeper | 4 | 42 | >236 | 1 |
| V565L | Gatekeeper | 44 | 335 | >236 | 23 |
| E566A | Regulatory triad | 3 | 8 | 12 | 1 |
| E566G | Regulatory triad | 2 | 6 | 10 | 1 |
| K642I | Regulatory triad | 2 | 20 | 15 | 22 |
| K642R | Regulatory triad | 2 | 7 | 16 | 1 |
| K660M | Activation loop | 5 | 23 | 63 | 19 |

L Goyal et al. N Engl J Med 2023;388:228-239.

Combination strategies ?

Biliary

# HER2 targeting in Biliary Tumors




*Clinical Breast Cancer* DOI: (10.1016/j.clbc.2023.05.003)

| HER2-directed rx | Eligibility | Sample size | ORR | Median PFS (mos) |
|---|---|---|---|---|
| Pertuzumab + trastuzumab[1] | HER2 overexpression (IHC 3+) or amplification by ISH or NGS | N = 39 | 23% | 4.0 |
| Neratinib[2] | **HER2 mutation** | N = 25 | 16% | 2.8 |
| Trastuzumab deruxtecan[3] | HER2 IHC 3+ or IHC 2+/amplification by ISH | N = 22 | 36.4% | 5.1 |
| | HER2 low | N=8 | 12.5% | 3.5 |

1. Javle et al, Lancet Oncol 2021. 2. Harding et al, Nat Commun 2023. 3. Ohba et al, J Clin Oncol 2022 (abstract).

Biliary

# Tucatinib and Trastuzumab for Previously Treated HER2-Positive Metastatic Biliary Tract Cancer (SGNTUC-019): A Phase 2 Basket Study

**Cohort 3: Biliary Tract (overexpression or amplification)[c]**

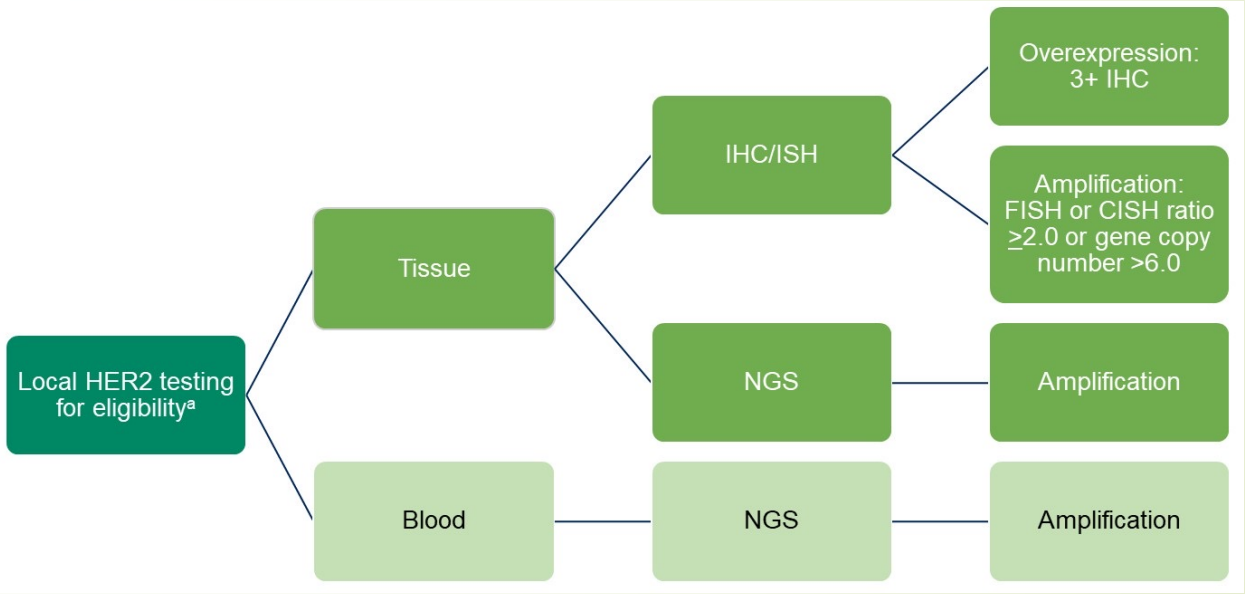
**Key eligibility criteria**

- 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]

**Outcomes**

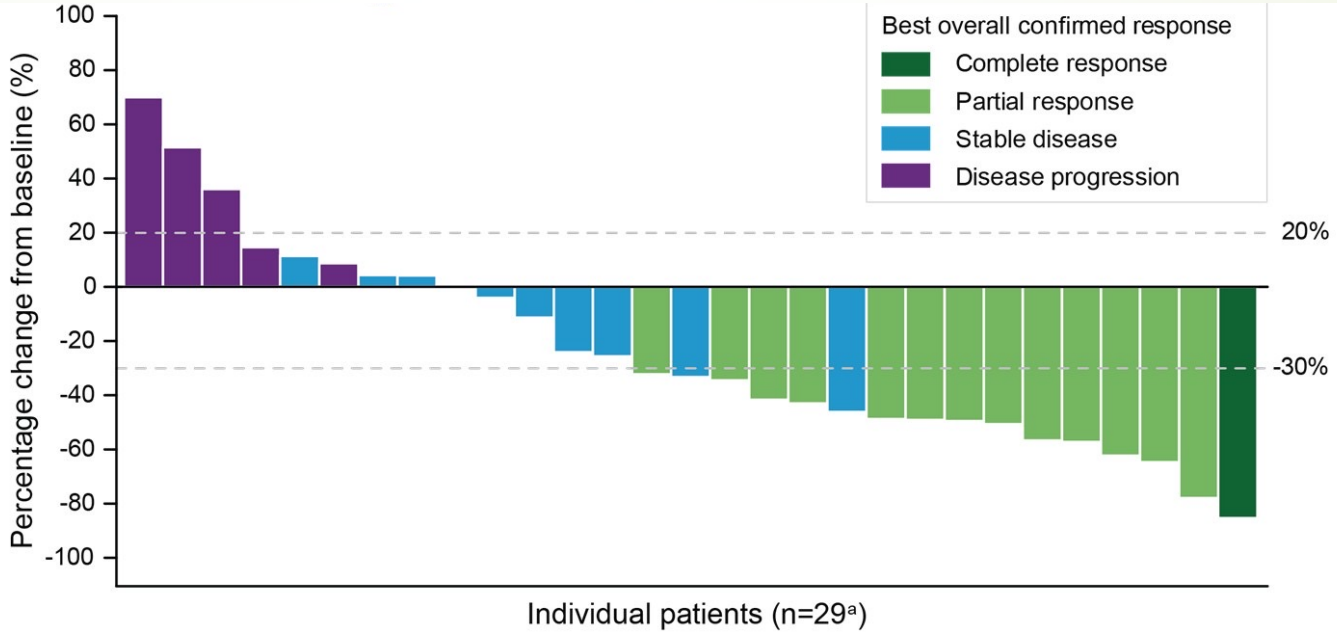
Primary endpoint:
Confirmed ORR per RECIST 1.1 by investigator

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



# Biliary

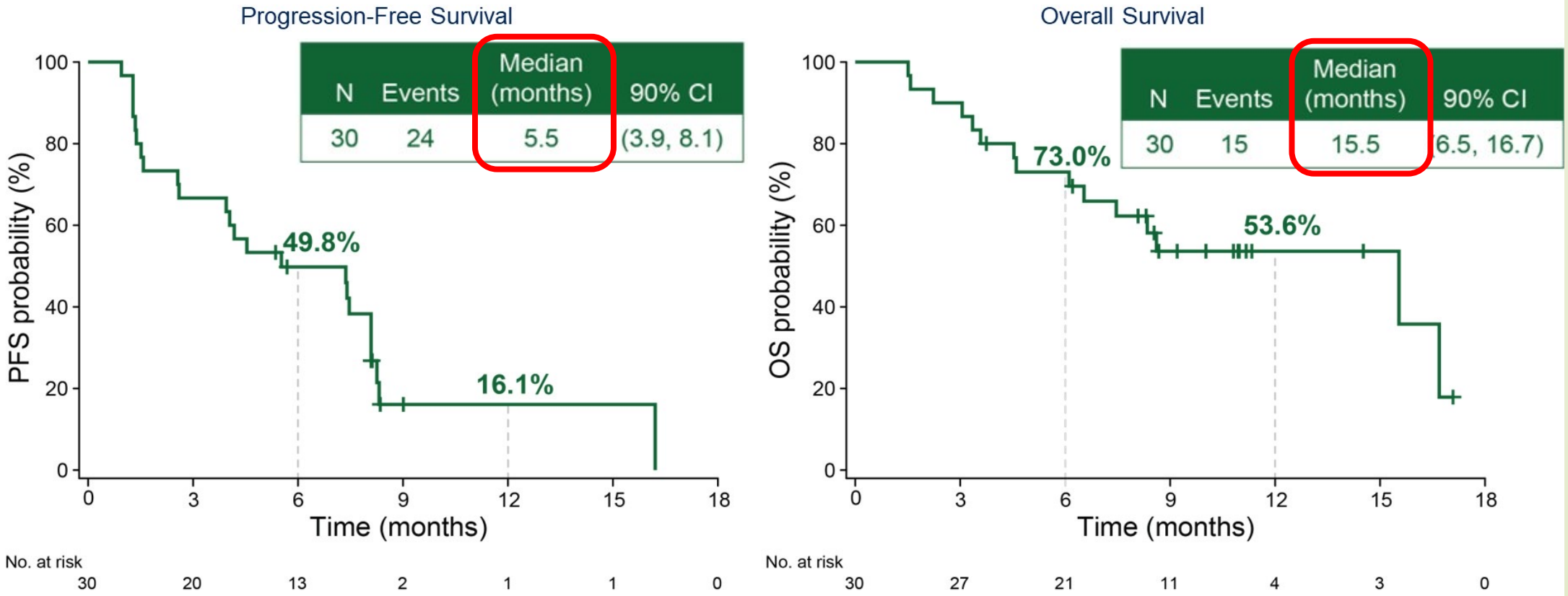
| | | Total (N=30) |
|---|---|---|
| Best overall response, n (%) | CR | 1 (3.3) |
| | PR | 13 (43.3) |
| | SD | 9 (30.0) |
| | PD | 6 (20.0) |
| | Not available | 1 (3.3)[a] |
| **cORR, % (90% CI)** | | **46.7 (30.8-63.0)** |
| Median DOR, months (90% CI) | | 6.0 (5.5-6.9) |
| DCR, n (%) | | 23 (76.7)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




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)

# Biliary

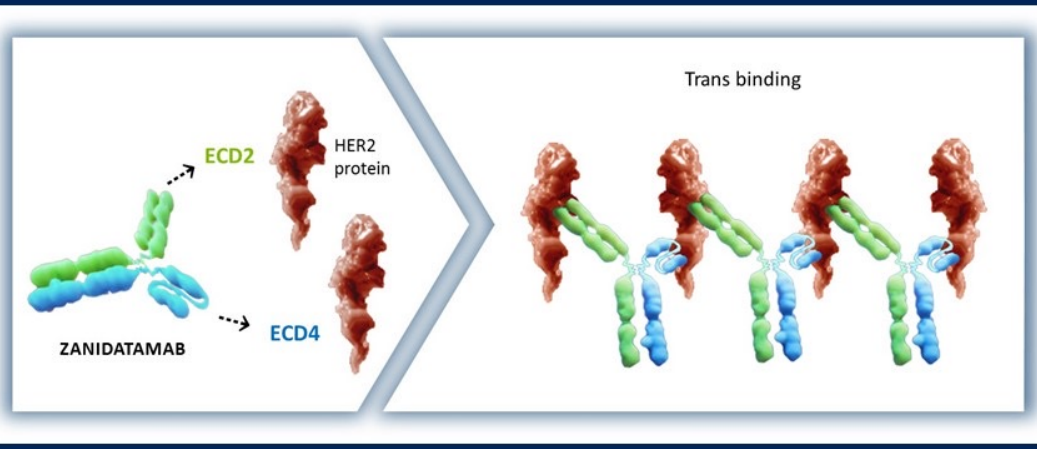
## Progression-Free Survival and Overall Survival




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

Biliary

# Results from the Pivotal Phase 2b HERIZON-BTC-01 Study: Zanidatamab in Previously-treated HER2-amplified Biliary Tract Cancer (BTC)




ECD = extracellular domain

## Key Eligibility Criteria

- Locally advanced or metastatic BTC[1]
- Tissue required to confirm HER2 status by central lab
- Progressed after treatment with a gemcitabine-containing regimen
- No prior HER2-targeted therapies
- ECOG PS of 0 or 1

**Patients with HER2-amplified BTC**

**Cohort 1 (HER2-positive):**
- IHC 2+ or 3+

**Cohort 2:**
- IHC 0 or 1+

28 Day Cycles

Day 1 — Day 15

**Zanidatamab 20 mg/kg IV* (Q2W)**

Every 8 weeks: CT/MRI per RECIST v1.1

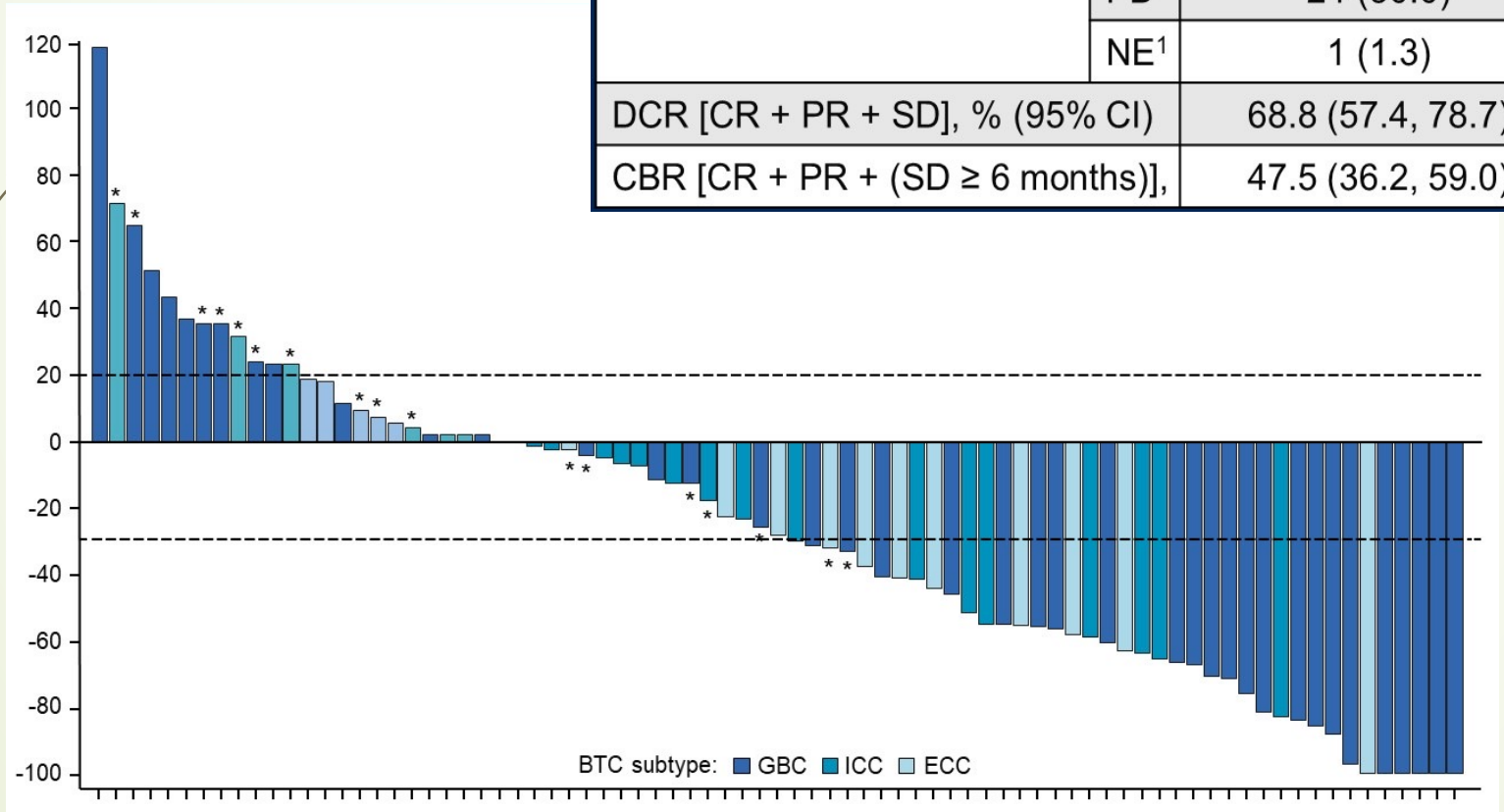
**Primary Endpoint:**
(Assessed in Cohort 1)
- cORR per ICR

**Select Secondary Endpoints:**
- DOR
- DCR
- PFS
- OS
- Frequency & severity of AEs
- Frequency of SAEs & deaths

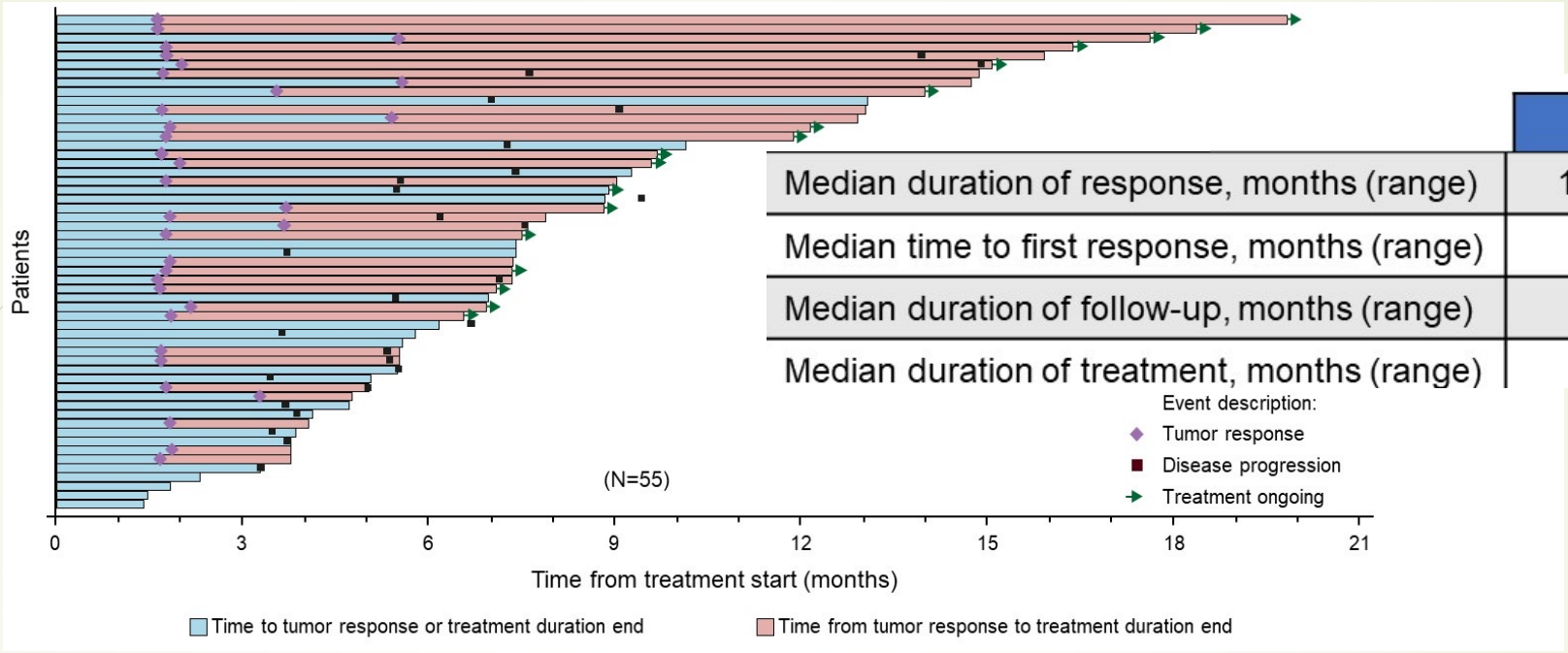
*With mandatory premedication for IRR prophylaxis

# Biliary

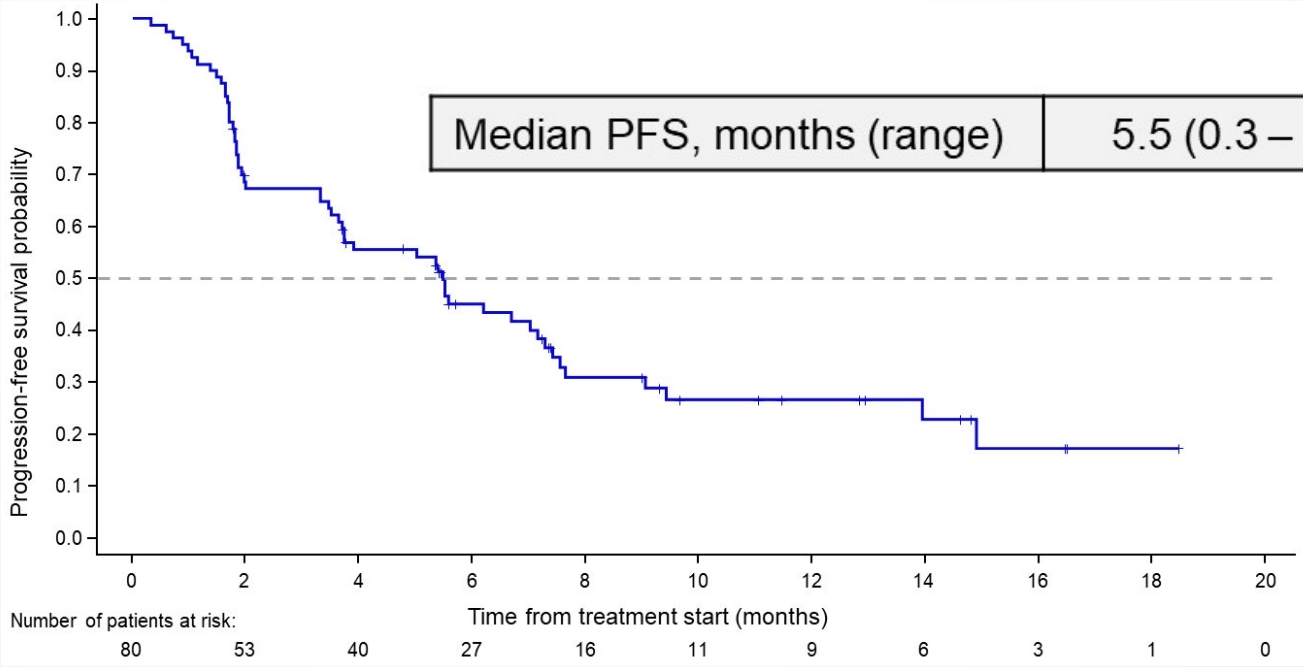
| | | By ICR Assessment (N = 80) | By Investigator Assessment (N = 80) |
|---|---|---|---|
| cORR, % (95% CI) | | 41.3 (30.4, 52.8) | 41.3 (30.4, 52.8) |
| Confirmed BOR, n (%) | CR | 1 (1.3) | 4 (5.0) |
| | PR | 32 (40.0) | 29 (36.3) |
| | SD | 22 (27.5) | 21 (26.3) |
| | PD | 24 (30.0) | 25 (31.3) |
| | NE[1] | 1 (1.3) | 1 (1.3) |
| DCR [CR + PR + SD], % (95% CI) | | 68.8 (57.4, 78.7) | 67.5 (56.1, 77.6) |
| CBR [CR + PR + (SD ≥ 6 months)], | | 47.5 (36.2, 59.0) | 47.5 (36.2, 59.0) |



# Biliary




| | N=80 |
|---|---|
| Median duration of response, months (range) | 12.9 (1.5, 16.9+) |
| Median time to first response, months (range) | 1.8 (1.6, 5.5) |
| Median duration of follow-up, months (range) | 12.4 (7, 24) |
| Median duration of treatment, months (range) | 5.6 (0.5, 19.8+) |




| | |
|---|---|
| Median PFS, months (range) | 5.5 (0.3 – 18.5) |

Biliary

# Discussion

## Conclusions

- HER2-directed therapies appear to have highly effective potential
- HER2 testing should be done for all advanced biliary cancers

| HER2-directed rx | Eligibility | Sample size | ORR | Median PFS (mos) |
|---|---|---|---|---|
| Pertuzumab + trastuzumab[1] | HER2 overexpression (IHC 3+) or amplification by ISH or NGS | N = 39 | 23% | 4.0 |
| Neratinib[2] | **HER2 mutation** | N = 25 | 16% | 2.8 |
| Trastuzumab deruxtecan[3] | HER2 IHC 3+ or IHC 2+/amplification by ISH | N = 22 | 36.4% | 5.1 |
| | HER2 low | N=8 | 12.5% | 3.5 |
| **Tucatinib + trastuzumab** | **HER2 overexpression (IHC 3+) or amplification by ISH OR NGS** | **N = 29** | **46.7%** | **5.5** |
| **Zanidatamab** | **HER2 overexpression (IHC 2-3+) and amplification by ISH** | **N = 80** | **41.3%** | **5.5** |

## Questions

- Definition of HER2 "positivity"
- HER2 mutations
- Sequencing/Resistance

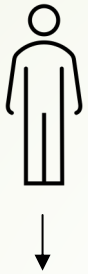
# Outline

1) Biliary

2) HCC

3) PDAC

# HCC



sorafenib

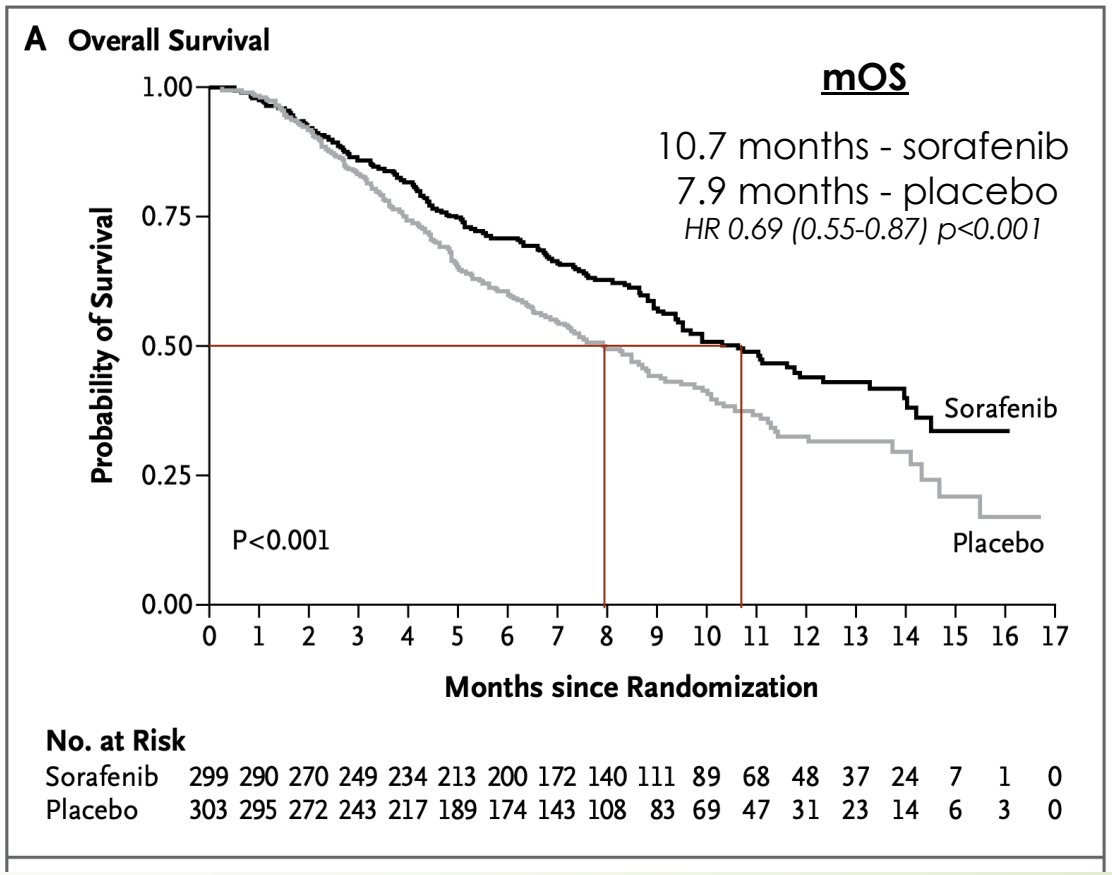
sorafenib

**2007**

The NEW ENGLAND JOURNAL of MEDICINE

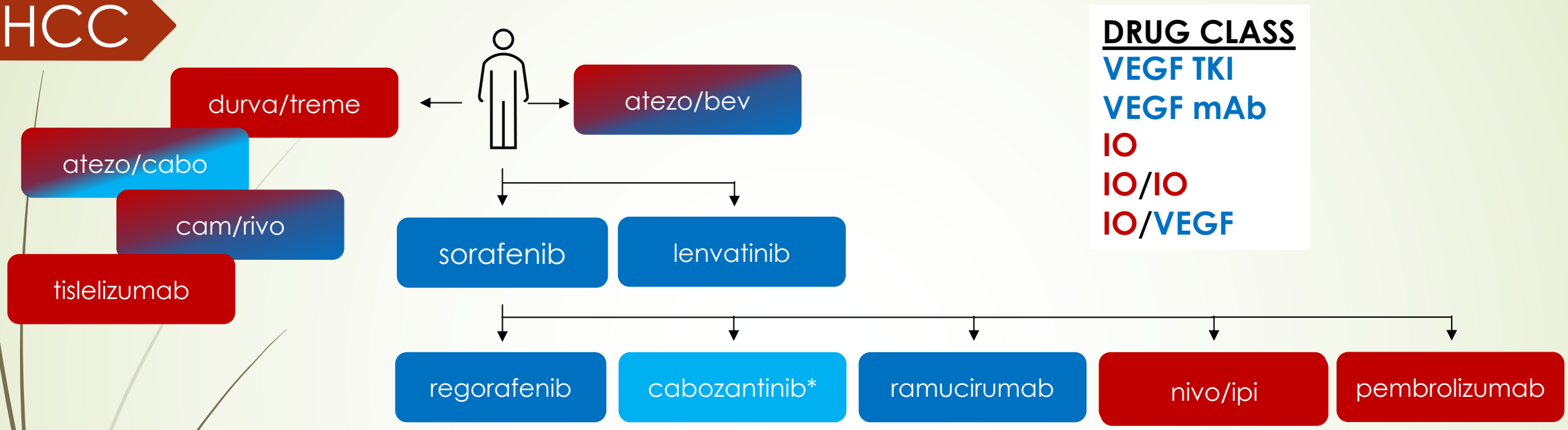
ORIGINAL ARTICLE

## Sorafenib in Advanced Hepatocellular Carcinoma

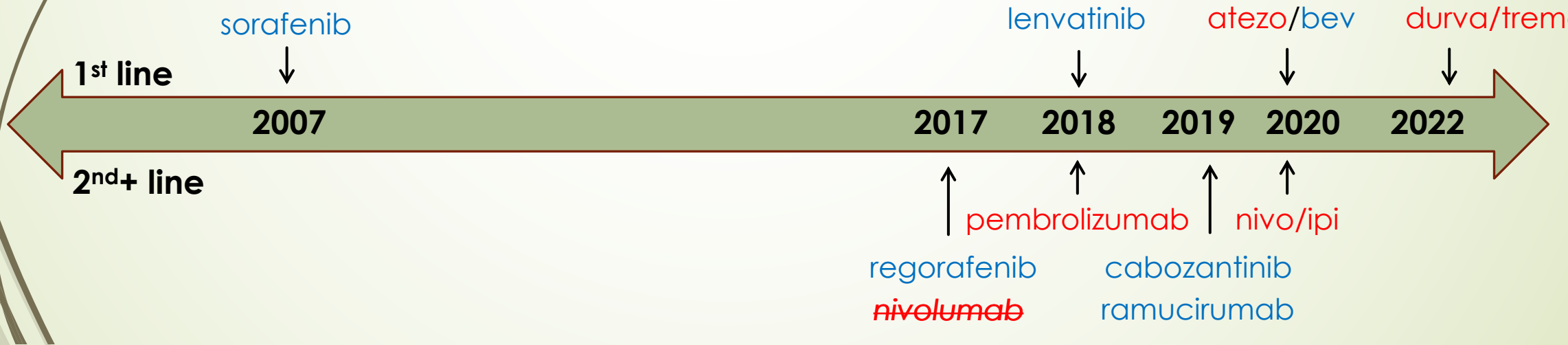



N Engl J Med 2008;359:378-90.

# HCC




**DRUG CLASS**
VEGF TKI
VEGF mAb
IO
IO/IO
IO/VEGF



HCC

# REFLECT: Lenvatinib vs Sorafenib

- Multicenter, randomized, open-label phase III trial noninferiority study

Patients with unresectable HCC with no prior systemic therapy; BCLC stage B/C **Child-Pugh A**; ECOG PS ≤1 (N = 954)

→ **Lenvatinib**
**8mg (wt<60kg) or 12mg (wt≥60kg) QD**
(n = 478)

→ **Sorafenib** 400 mg BD
(n = 476)

- Primary endpoints: OS

HCC

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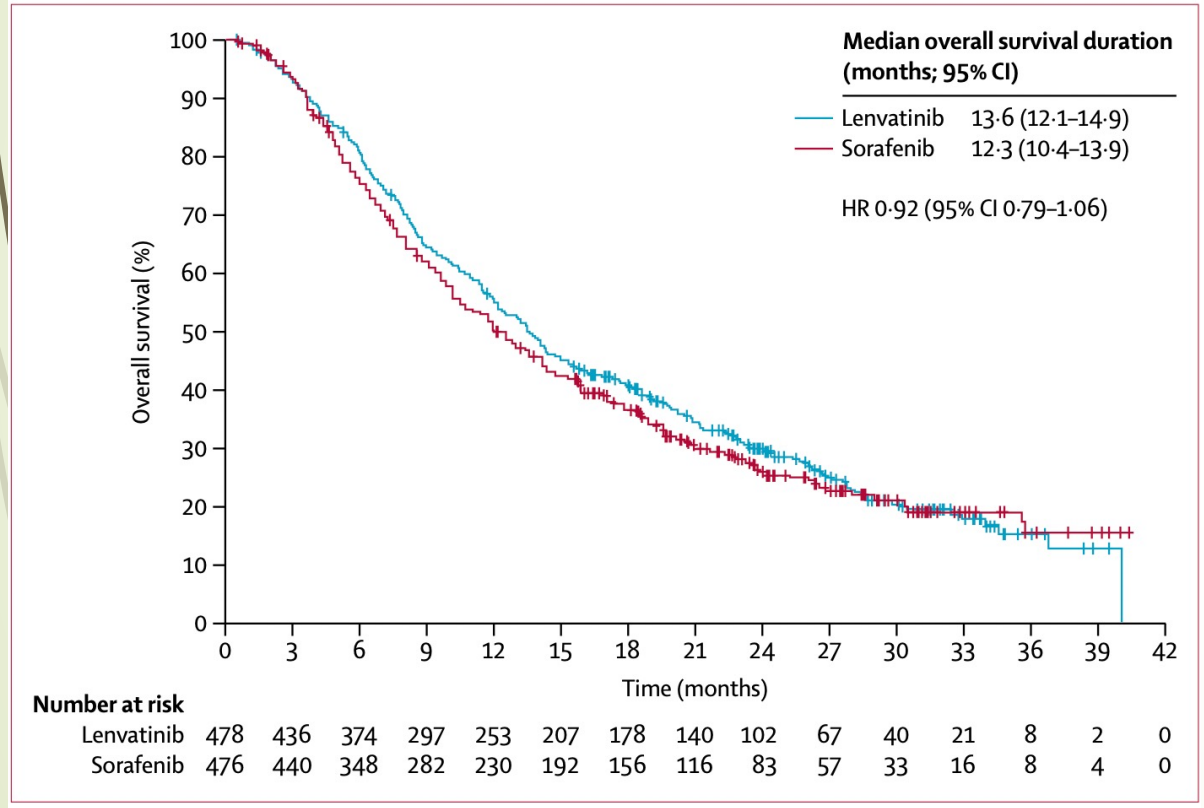
- Primary endpoints: OS

HCC

# REFLECT: Lenvatinib vs Sorafenib




| Masked independent imaging review according to mRECIST | | |
|---|---|---|
| Progression-free survival (months) | 7·3 (5·6–7·5) | 3·6 (3·6–3·7) |
| Time to progression (months) | 7·4 (7·2–9·1) | 3·7 (3·6–3·9) |
| Objective response (%, 95% CI) | 194 (40·6%, 36·2–45·0) | 59 (12·4%, 9·4–15·4) |
| Complete response | 10 (2%) | 4 (1%) |
| Partial response | 184 (38%) | 55 (12%) |
| Stable disease | 159 (33%) | 219 (46%) |
| Durable stable disease lasting ≥23 weeks | 84 (18%) | 90 (19%) |
| Progressive disease | 79 (17%) | 152 (32%) |
| Unknown or not evaluable | 46 (10%) | 46 (10%) |
| Disease control rate (%, 95% CI) | 353 (73·8%, 69·9–77·8) | 278 (58·4%, 54·0–62·8) |

HCC

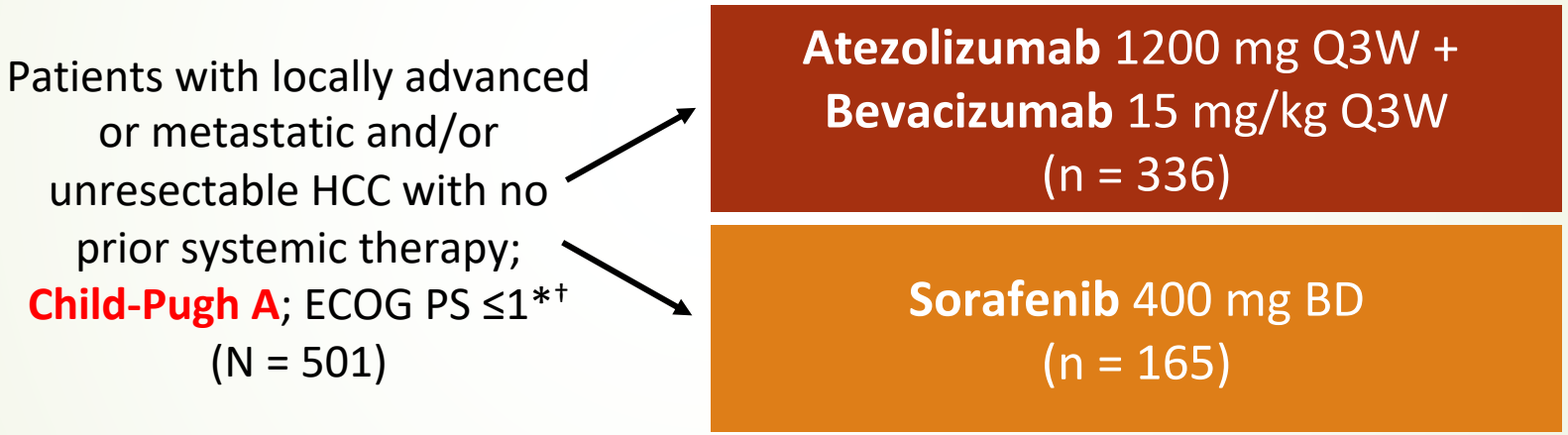
# REFLECT: Lenvatinib vs Sorafenib

| AE, % | Lenvatinib (n = 476) | | Sorafenib (n = 475) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Total | 99 | 75 | 99 | 67 |
| **Palmar-plantar erythrodysaesthesia** | **27** | **3** | **52** | **11** |
| **Hypertension** | **42** | **23** | **30** | **14** |
| Diarrhea | 39 | 4 | 46 | 4 |
| Decreased appetite | 34 | 5 | 27 | 1 |
| Decreased weight | 31 | 8 | 22 | 3 |
| Fatigue | 30 | 4 | 25 | 4 |

HCC

# IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib

- Multicenter, randomized, open-label phase III trial




- Coprimary endpoints: OS and PFS

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# IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib

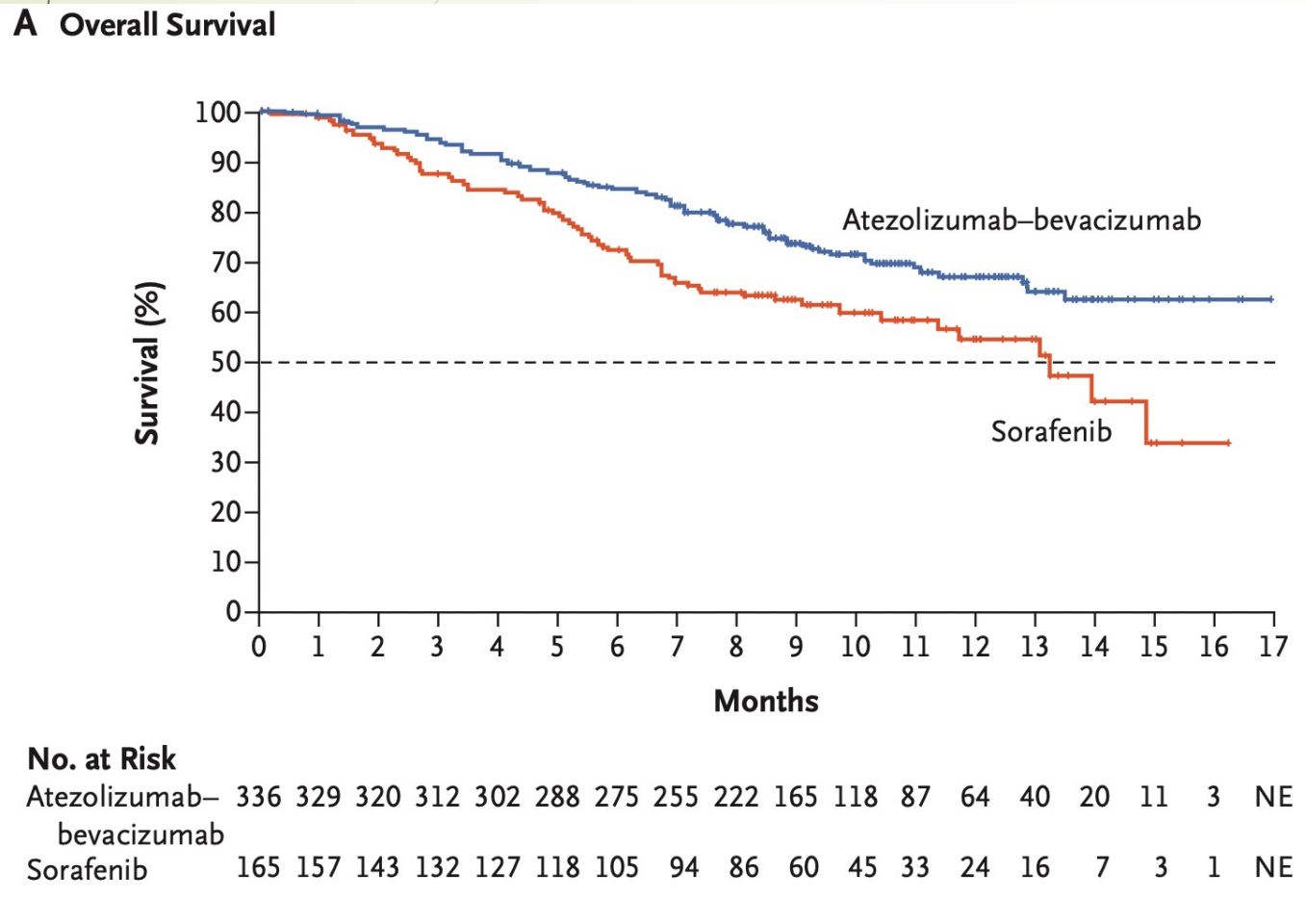
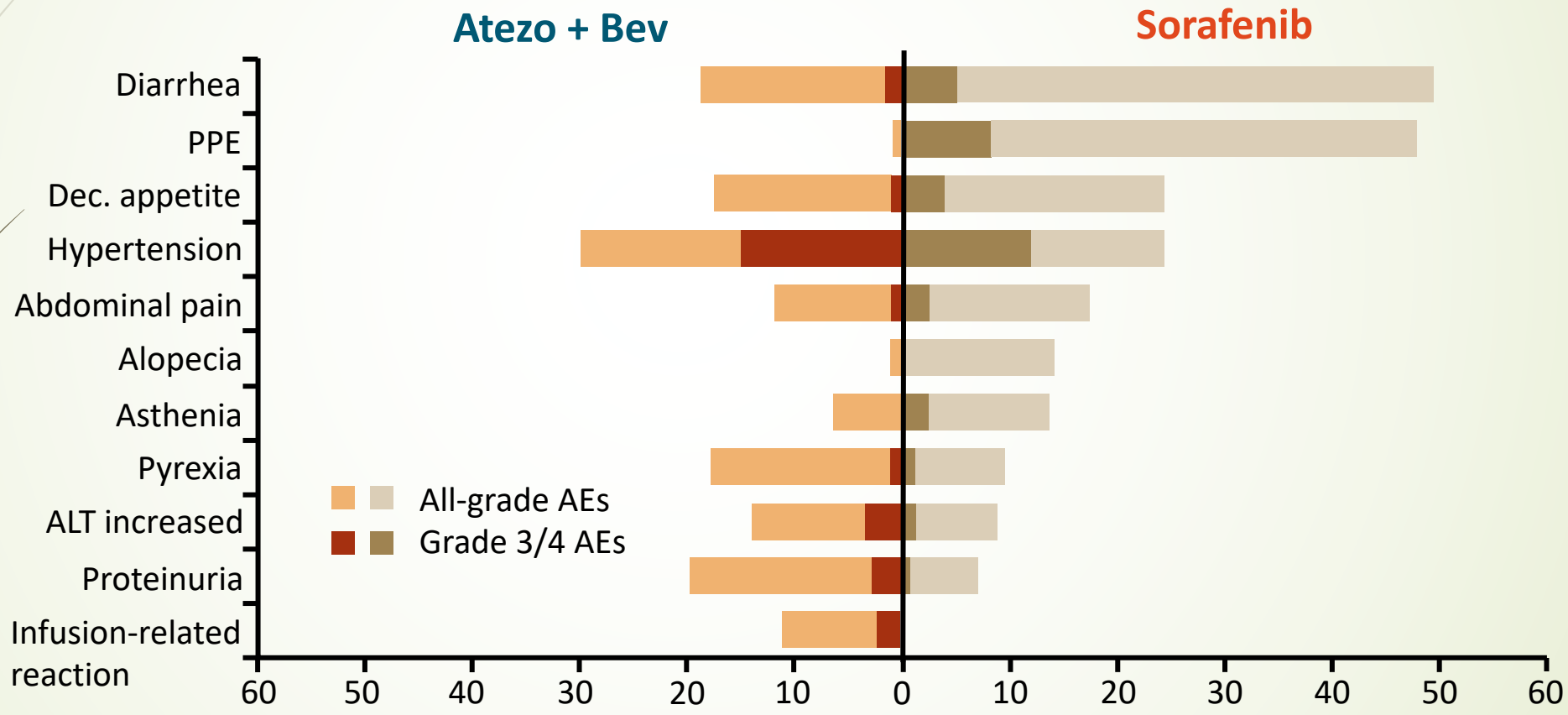



**Table 2. Secondary Efficacy Outcomes.***

| Variable | HCC-Specific mRECIST | |
|---|---|---|
| | Atezolizumab–Bevacizumab (N=325) | Sorafenib (N=158) |
| Confirmed objective response — no. (% [95% CI])‡ | 108 (33.2 [28.1–38.6]) | 21 (13.3 [8.4–19.6]) |
| Complete response — no. (%) | 33 (10.2) | 3 (1.9) |
| Partial response — no. (%) | 75 (23.1) | 18 (11.4) |
| Stable disease — no. (%) | 127 (39.1) | 66 (41.8) |
| Disease control rate — no. (%)§ | 235 (72.3) | 87 (55.1) |
| Progressive disease — no. (%) | 66 (20.3) | 40 (25.3) |
| Could not be evaluated — no. (%) | 10 (3.1) | 14 (8.9) |
| Data missing — no. (%) | 14 (4.3) | 17 (10.8) |
| Ongoing objective response at data cutoff — no./total no. (%) | 84/108 (77.8) | 13/21 (61.9) |

HCC

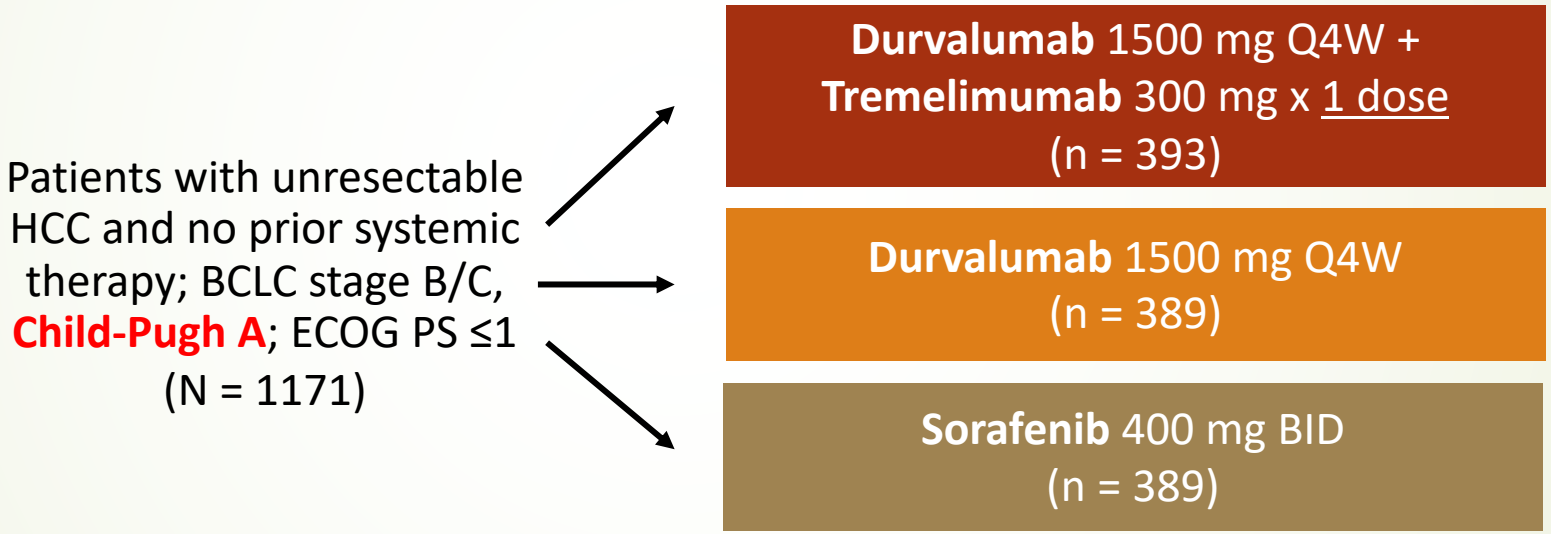
# IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib



HCC

# HIMALAYA: Durvalumab + Tremelimumab vs Sorafenib

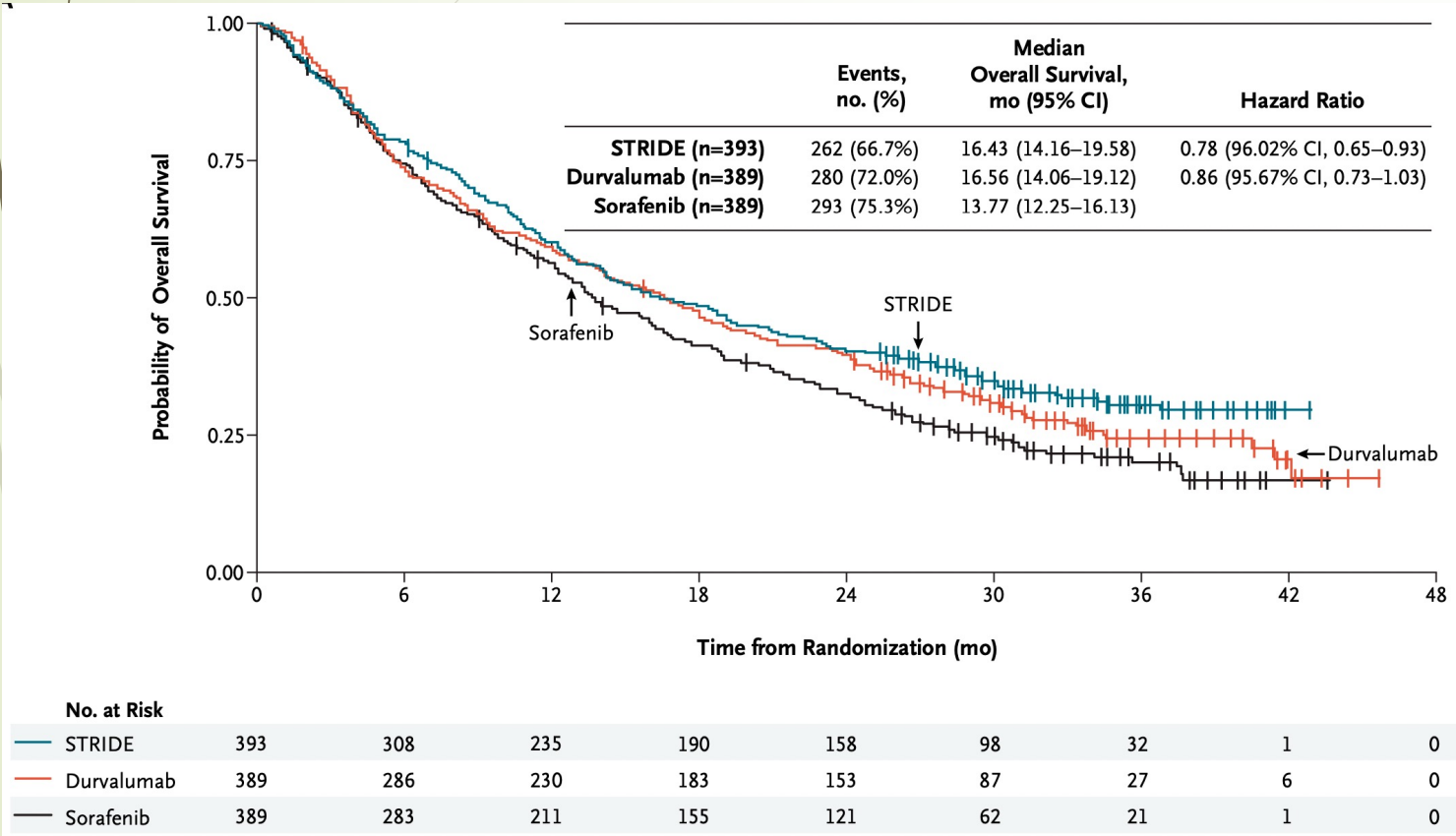
- Multicenter, randomized, open-label phase III trial




- Primary endpoint: OS (durvalumab + tremelimumab vs sorafenib)

HCC

# HIMALAYA: Durvalumab + Tremelimumab vs Sorafenib




| Parameter | STRIDE (n=393) | Durvalumab (n=389) | Sorafenib (n=389) |
|---|---|---|---|
| Response — no. (%) | | | |
| Objective† | 79 (20.1) | 66 (17.0) | 20 (5.1) |
| Complete | 12 (3.1) | 6 (1.5) | 0 |
| Partial | 67 (17.0) | 60 (15.4) | 20 (5.1) |
| Stable disease — no. (%) | 157 (39.9) | 147 (37.8) | 216 (55.5) |
| Disease control rate — % | 236 (60.1) | 213 (54.8) | 236 (60.7) |
| Duration of response — mo‡ | | | |
| Median | 22.34 | 16.82 | 18.43 |
| IQR | 8.54–NR | 7.43–NR | 6.51–25.99 |
| Time to response — mo | | | |
| Median | 2.17 | 2.09 | 3.78 |
| 95% CI | (1.84–3.98) | (1.87–3.98) | (1.89–8.44) |

HCC

# HIMALAYA: Durvalumab + Tremelimumab vs Sorafenib

| Treatment-emergent AEs | STRIDE (n=388) | | Durvalumab (n=388) | | Sorafenib (n=374) | |
|---|---|---|---|---|---|---|
| Event | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| Diarrhea | 103 (26.5) | 17 (4.4) | 58 (14.9) | 6 (1.5) | 167 (44.7) | 16 (4.3) |
| Constipation | 36 (9.3) | 0 | 42 (10.8) | 0 | 35 (9.4) | 0 |
| Abdominal pain | 46 (11.9) | 5 (1.3) | 37 (9.5) | 4 (1.0) | 63 (16.8) | 12 (3.2) |
| Nausea | 47 (12.1) | 0 | 37 (9.5) | 0 | 53 (14.2) | 0 |
| Pruritus | 89 (22.9) | 0 | 56 (14.4) | 0 | 24 (6.4) | 1 (0.3) |
| Rash | 87 (22.4) | 6 (1.5) | 40 (10.3) | 1 (0.3) | 51 (13.6) | 4 (1.1) |
| Alopecia | 2 (0.5) | 0 | 5 (1.3) | 0 | 53 (14.2) | 0 |
| Palmar-plantar erythrodysesthesia syndrome | 3 (0.8) | 0 | 1 (0.3) | 0 | 174 (46.5) | 34 (9.1) |
| Aspartate aminotransferase increased | 48 (12.4) | 20 (5.2) | 56 (14.4) | 26 (6.7) | 24 (6.4) | 12 (3.2) |
| Alanine aminotransferase increased | 36 (9.3) | 10 (2.6) | 44 (11.3) | 12 (3.1) | 20 (5.3) | 7 (1.9) |

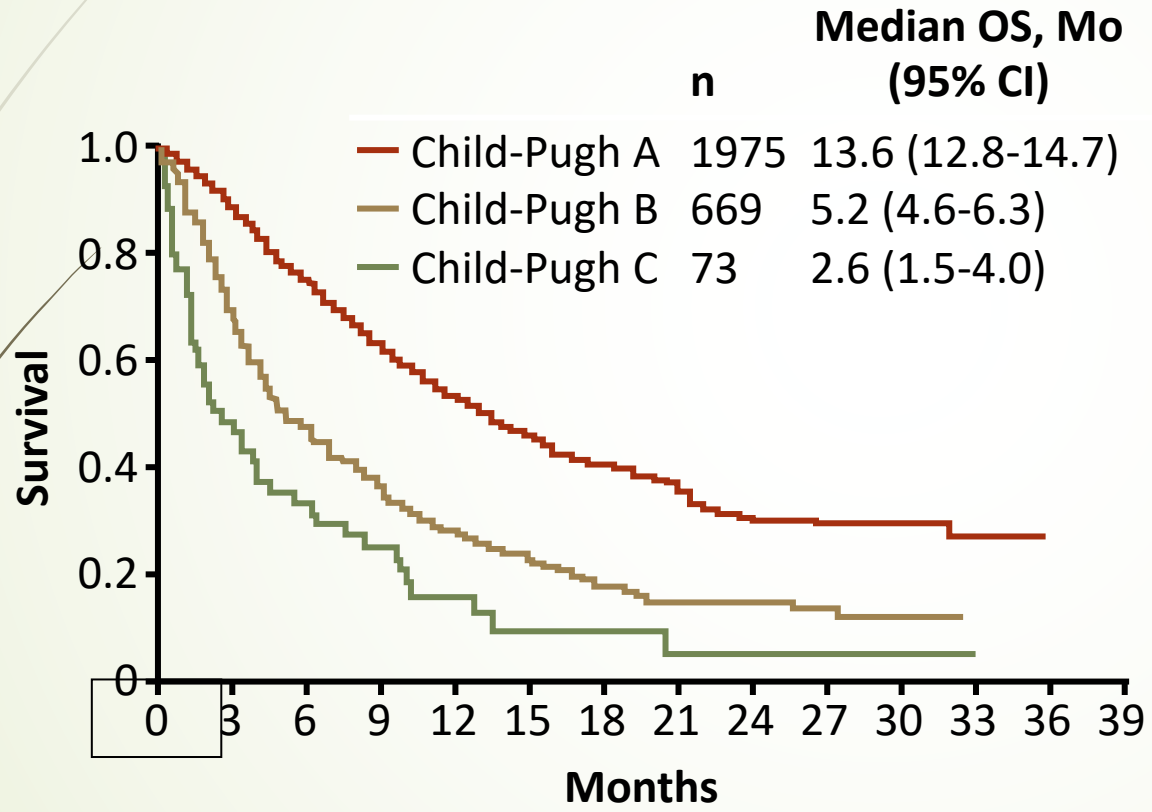
HCC

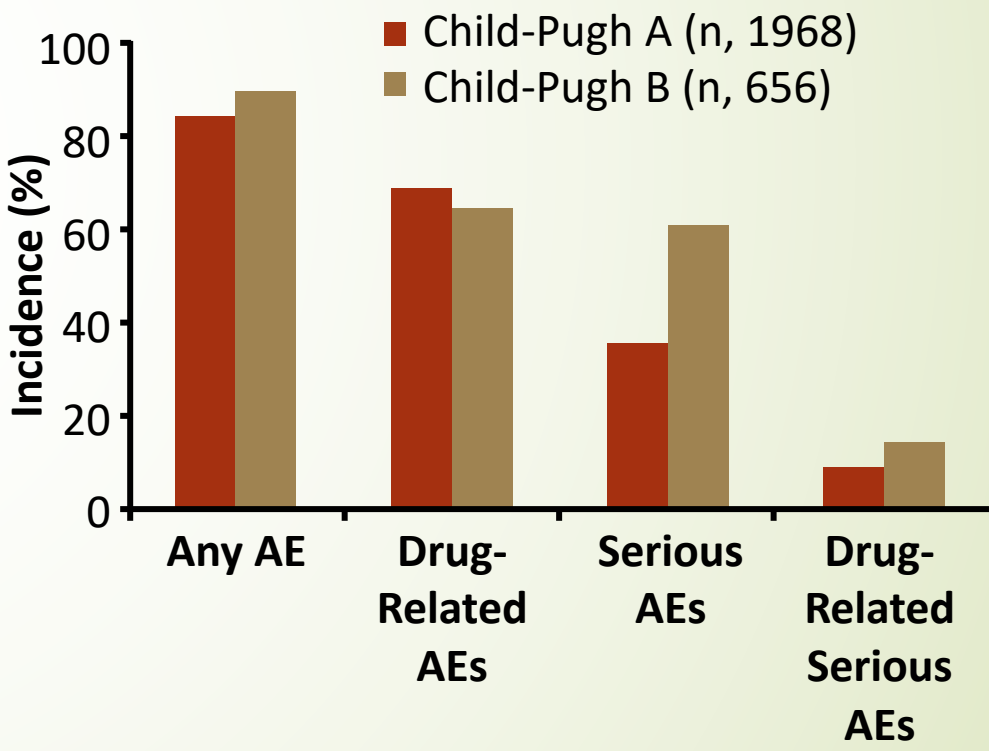
# Ongoing challenges in HCC

- Optimal sequencing of treatment options
- Applicability to general population – CP-A only
- Application in earlier stage disease
- Clinical trial design/execution in this environment

HCC

# GIDEON: Observational Study of Sorafenib Child-Pugh A/B/C



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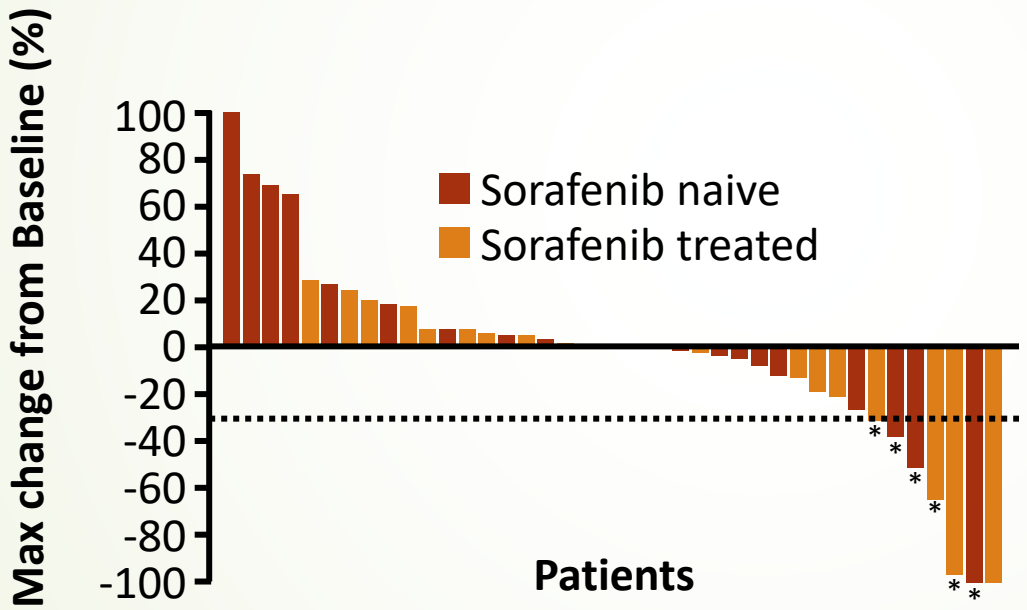
# CheckMate 040: Nivolumab for Patients With Child-Pugh B Cirrhosis




- rates of discontinuation due to TRAEs not higher than Child-Pugh A cohort
- Hepatic TRAEs similar between Child-Pugh B vs A
- ORR: 10.2%
- median OS: overall 7.6 months

- Child-Pugh B7/B8 cohort (n = 49)

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THERAPEUTIC ADVANCES in
*Medical Oncology*

*Original Research*

# Lenvatinib in patients with unresectable hepatocellular carcinoma who progressed to Child-Pugh B liver function

*Ther Adv Med Oncol*

2022, Vol. 14: 1–11

DOI: 10.1177/
17588359221116608

HCC

**Table 1.** Baseline and disease characteristics.

| Category | Lenvatinib | | Sorafenib | |
|---|---|---|---|---|
| | CP-B subgroup[a], *n* = 60 | CP-A subgroup[b], *n* = 413 | CP-B subgroup[a], *n* = 47 | CP-A subgroup[b], *n* = 427 |
| Factor of carcinogenesis, *n* (%) | | | | |
| Hepatitis B | 29 (48.3) | 219 (53.0) | 20 (42.6) | 206 (48.2) |
| Hepatitis C | 15 (25.0) | 75 (18.2) | 12 (25.5) | 114 (26.7) |
| Alcohol | 7 (11.7) | 28 (6.8) | 3 (6.4) | 18 (4.2) |
| Other | 6 (10.0) | 32 (7.7) | 3 (6.4) | 29 (6.8) |
| Macroscopic portal vein invasion, extrahepatic spread, or both, *n* (%) | | | | |
| Yes | 45 (75.0) | 280 (67.8) | 38 (80.9) | 297 (69.6) |
| No | 15 (25.0) | 133 (32.2) | 9 (19.1) | 130 (30.4) |
| Underlying cirrhosis[c], *n* (%) | | | | |
| Yes | 54 (90.0) | 298 (72.2) | 39 (83.0) | 324 (75.9) |
| No | 6 (10.0) | 115 (27.8) | 8 (17.0) | 103 (24.1) |
| BCLC stage, *n* (%) | | | | |
| B | 14 (23.3) | 89 (21.5) | 2 (4.3) | 90 (21.1) |
| C | 46 (76.7) | 324 (78.5) | 45 (95.7) | 337 (78.9) |
| CP score, *n* (%) | | | | |
| 5 | 21 (35.0) | 345 (83.5) | 21 (44.7) | 335 (78.5) |
| 6 | 36 (60.0) | 68 (16.5) | 21 (44.7) | 92 (21.5) |

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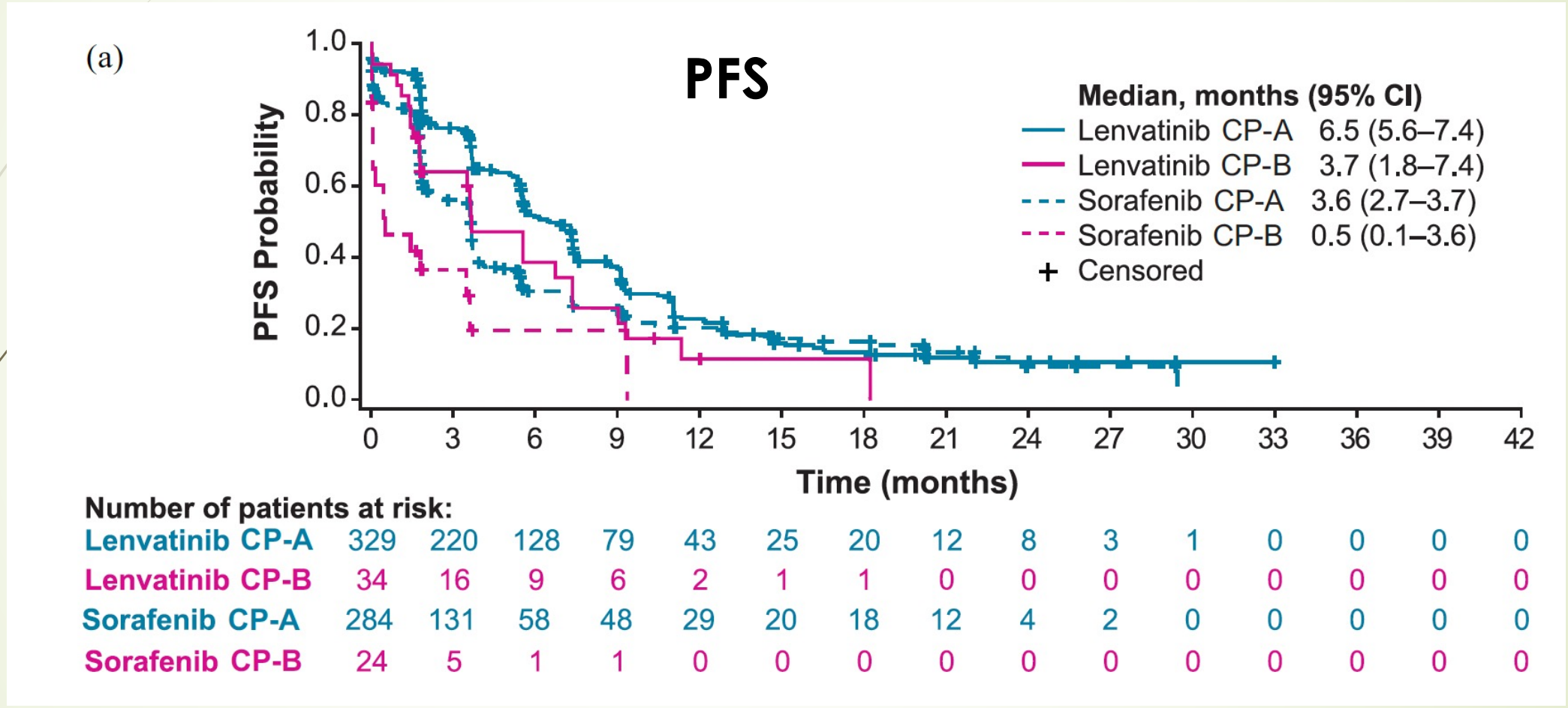
# Efficacy



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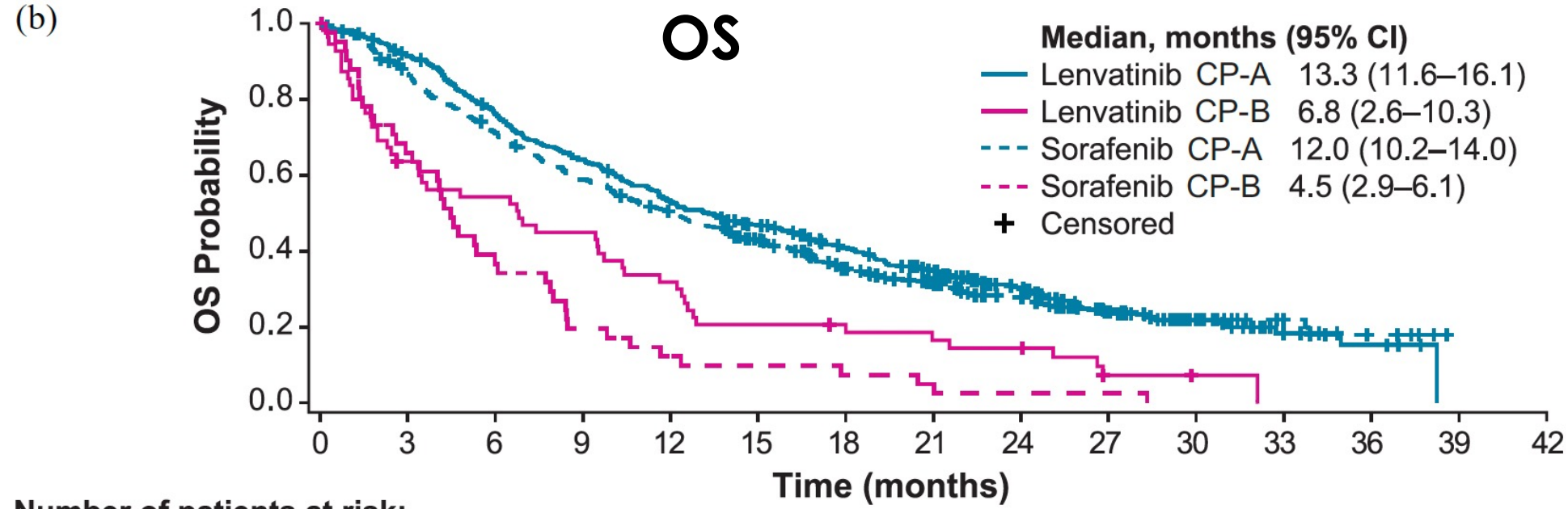
# Efficacy




**Number of patients at risk:**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lenvatinib CP-A | 401 | 360 | 298 | 251 | 207 | 176 | 142 | 111 | 75 | 43 | 27 | 10 | 5 | 0 | 0 |
| Lenvatinib CP-B | 55 | 34 | 29 | 24 | 17 | 11 | 10 | 8 | 7 | 2 | 1 | 0 | 0 | 0 | 0 |
| Sorafenib CP-A | 416 | 355 | 290 | 239 | 201 | 165 | 124 | 98 | 70 | 40 | 18 | 11 | 5 | 0 | 0 |
| Sorafenib CP-B | 43 | 27 | 15 | 8 | 5 | 4 | 3 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |

HCC

# Safety

**Table 3.** Safety outcomes summary[a], adjusted by treatment duration.

| Parameter | Lenvatinib | | Sorafenib | |
|---|---|---|---|---|
| | **CP-B subgroup, *n* = 60, TTD: 26.0 years** | **CP-A subgroup, *n* = 413, TTD: 297.9 years** | **CP-B subgroup, *n* = 47, TTD: 12.4 years** | **CP-A subgroup, *n* = 427, TTD: 226.6 years** |
| Mean daily dose intensity, mg/day (SD) | 8.4 (3.07) | 9.5 (6.01) | 653.2 (165.75) | 664.8 (174.23) |
| Median duration of treatment, months (range) | 3.2 (0.3–31.5) | 6.9 (0–35.0) | 1.9 (0.2–22.4) | 3.7 (0.1–38.7) |
| Any treatment-related AE episodes, adjusted by patient-years[a], *n* (AE rate[b]) | 478 (18.36) | 3060 (10.27) | 248 (19.93) | 2617 (11.55) |
| Grade ⩾3 episodes | 95 (3.65) | 419 (1.41) | 42 (3.38) | 388 (1.71) |
| Any serious TEAE episodes, adjusted by patient-years, *n* (AE rate[b]) | 108 (4.15) | 293 (0.98) | 45 (3.62) | 185 (0.82) |
| Treatment-related AEs leading to study drug, *n*[c] (AE rate[b]): | | | | |
| Withdrawal | 15 (0.58) | 35 (0.12) | 5 (0.40) | 37 (0.16) |
| Dose reduction | 46 (1.77) | 227 (0.76) | 20 (1.61) | 212 (0.94) |
| Interruption | 59 (2.27) | 275 (0.92) | 18 (1.45) | 235 (1.04) |
| Dose reduction or interruption | 89 (3.42) | 421 (1.41) | 33 (2.65) | 389 (1.72) |

[a]AEs were graded using Common Terminology Criteria for Adverse Events version 4.0.
[b]Number of AE episodes per patient-year.
[c]Patients may be counted in >1 sub-category.
AE, adverse event; CP, Child-Pugh; SD, standard deviation; TEAE, treatment-emergent adverse event; TTD, total treatment duration.

# Outline

1) Biliary

2) HCC

3) PDAC

PDAC



# NAPOLI 3: NALIRIFOX versus nab-paclitaxel + gemcitabine in treatment-naive patients with mPDAC: additional results from the phase 3 NAPOLI 3 trial

**N = 770**

**Key inclusion criteria**

- Aged ≥ 18 years
- Confirmed PDAC not previously treated in the metastatic setting
- Metastatic disease diagnosed ≤ 6 weeks prior to screening
- ≥ 1 metastatic lesions measurable by CT/MRI according to RECIST v1.1
- ECOG PS of 0 or 1

**R**1:1

**Stratification**

- ECOG PS 0/1
- Region
- Liver metastases

**NALIRIFOX**

**Liposomal irinotecan** 50 mg/m$^2$[a]
+ **5-FU** 2400 mg/m$^2$
+ **LV** 400 mg/m$^2$
+ **oxaliplatin** 60 mg/m$^2$
Days 1 and 15 of a 28-day cycle[b]

**Gem+NabP**

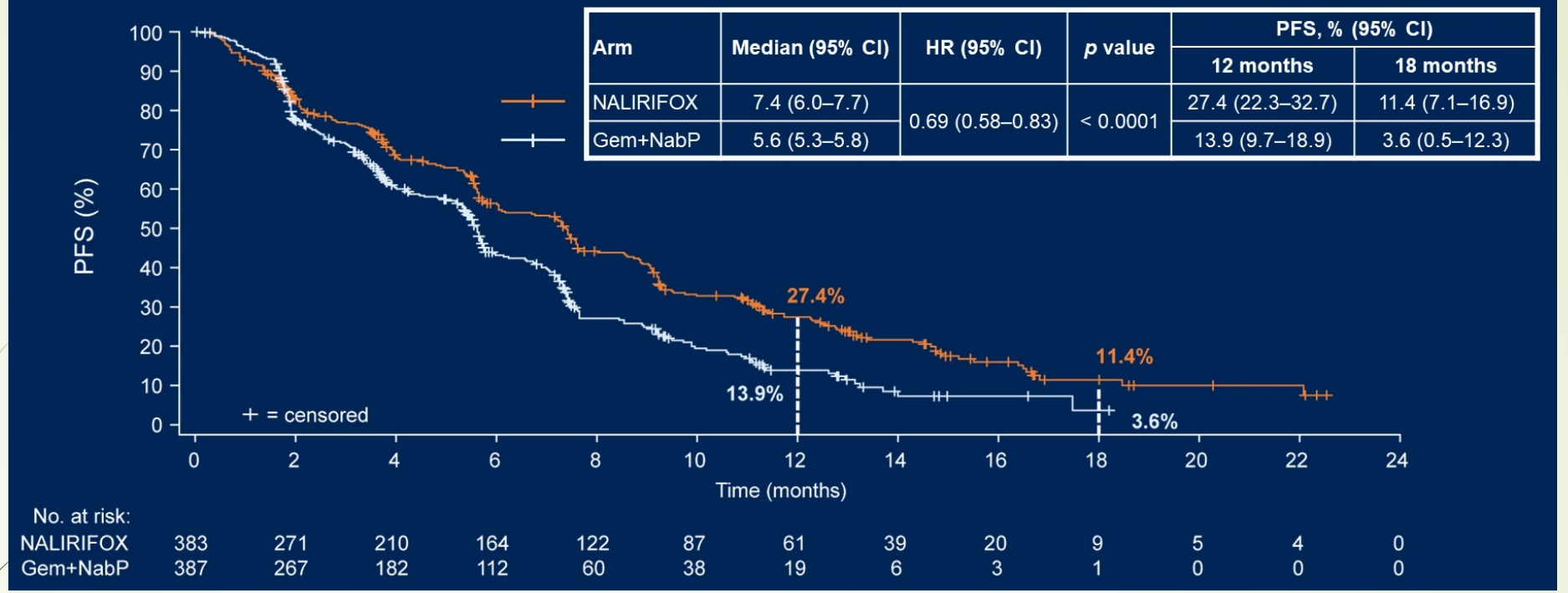
**Gem** 1000 mg/m$^2$
+ **NabP** 125 mg/m$^2$
Days 1, 8, and 15 of a 28-day cycle

- Tumor assessment every 8 weeks per RECIST v1.1[c]
- Treatment until disease progression, unacceptable toxicity or study withdrawal
- AEs recorded and coded using MedDRA (v24.0); severity graded by NCI-CTCAE (v5.0)
- Follow-up every 8 weeks until death or study end[d]

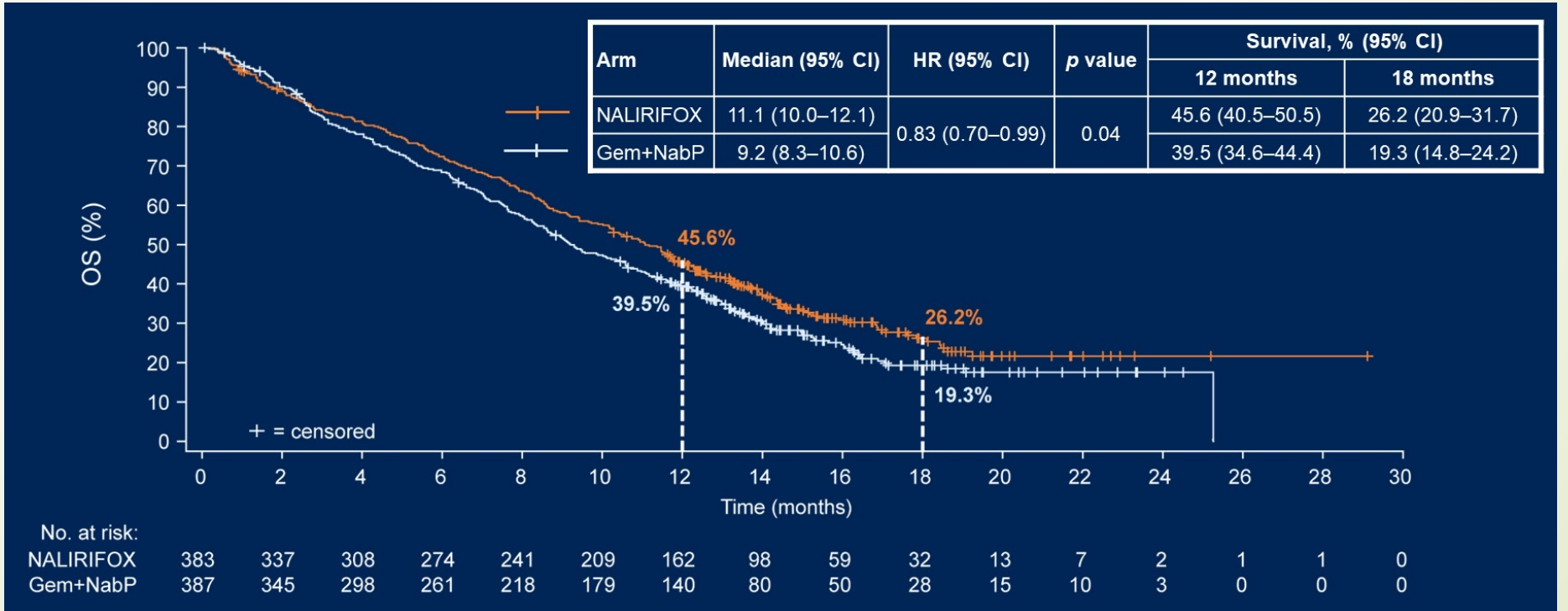
- Primary endpoint: OS
- Secondary endpoints: PFS and ORR per investigator using RECIST v1.1, safety
- Exploratory endpoints: HRQOL, biomarker assessments

# PDAC

| Arm | Median (95% CI) | HR (95% CI) | *p* value | PFS, % (95% CI) | |
|---|---|---|---|---|---|
| | | | | 12 months | 18 months |
| NALIRIFOX | 7.4 (6.0–7.7) | 0.69 (0.58–0.83) | < 0.0001 | 27.4 (22.3–32.7) | 11.4 (7.1–16.9) |
| Gem+NabP | 5.6 (5.3–5.8) | | | 13.9 (9.7–18.9) | 3.6 (0.5–12.3) |




| Arm | Median (95% CI) | HR (95% CI) | *p* value | Survival, % (95% CI) | |
|---|---|---|---|---|---|
| | | | | 12 months | 18 months |
| NALIRIFOX | 11.1 (10.0–12.1) | 0.83 (0.70–0.99) | 0.04 | 45.6 (40.5–50.5) | 26.2 (20.9–31.7) |
| Gem+NabP | 9.2 (8.3–10.6) | | | 39.5 (34.6–44.4) | 19.3 (14.8–24.2) |



PDAC

# NAPOLI 3: Tumor response[a]

| | NALIRIFOX (n = 383) | Gem+NabP (n = 387) |
|---|---|---|
| Objective response rate (95% CI), % | 41.8 (36.8–46.9) | 36.2 (31.4–41.2) |
| Best overall response, % | | |
| Complete response | 0.3 | 0.3 |
| Partial response | 41.5 | 35.9 |
| Stable disease | 25.8 | 26.1 |
| Progressive disease | 9.9 | 14.5 |
| Not evaluable[b] | 22.5 | 23.3 |
| Disease control rate,[c] % | 67.6 | 62.3 |
| Duration of response, median (95% CI), months | 7.3 (5.8–7.6) | 5.0 (3.8–5.6) |

PDAC

# Discussion

## Conclusions

- 1st head-to-head comparison of 5FU-triplet vs gem-doublet
- NALIRIFOX yields higher mOS, mPFS, 12m/18m OS+PFS
- New option for 1L

## Questions

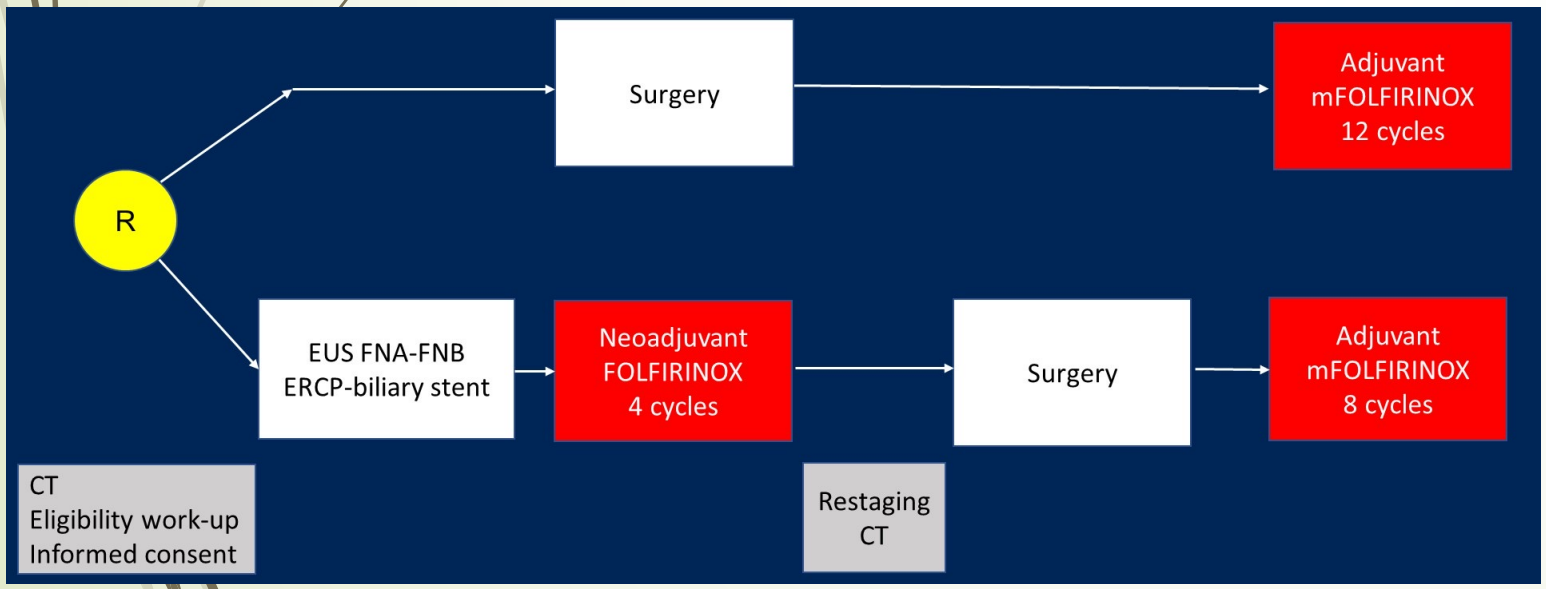
- Is NALIRIFOX better than FOLFIRINOX ?
- Cost-effectiveness
- What should be the control/reference regimen for future studies

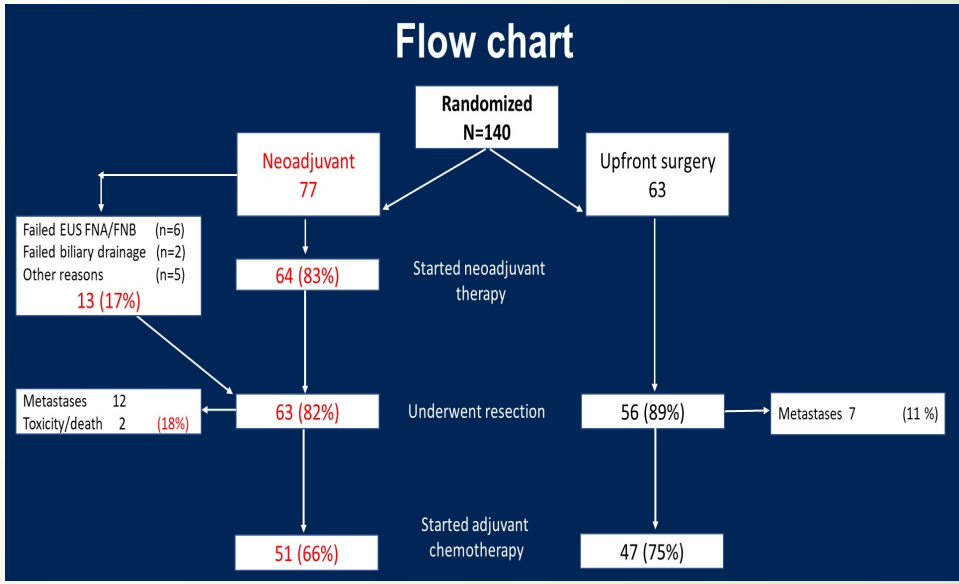
PDAC

# Short-course neoadjuvant FOLFIRINOX versus upfront surgery for resectable pancreatic head cancer - A multicenter randomized phase-2 trial (NORPACT-1)

Radiologically (CT) resectable pancreatic head cancer (NCCN criteria)

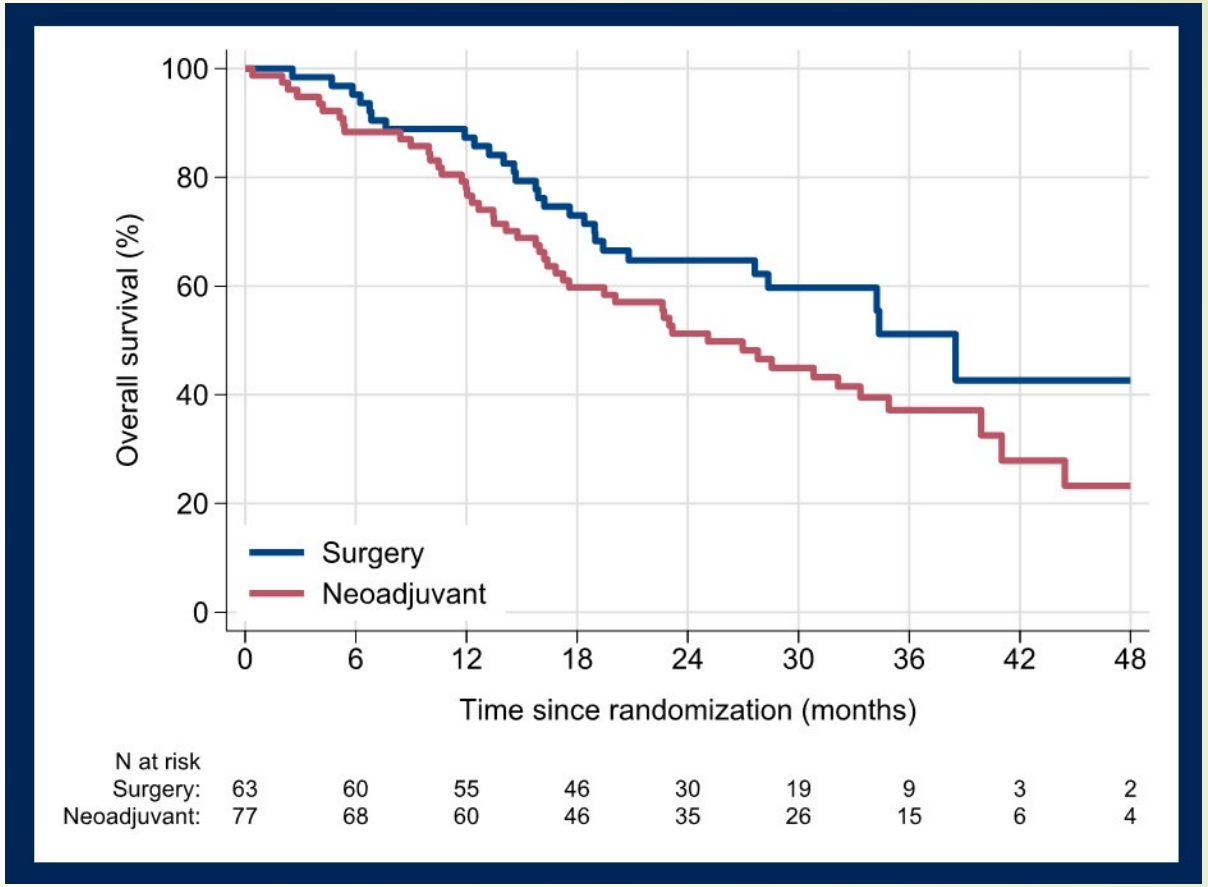
- no arterial involvement (celiac, hepatic, superior mesenteric)
- < 180º interface with portal/superior mesenteric vein, no contour irregularity
- no distant metastases



# PDAC

**Median overall survival**
25.1 months (neoadjuvant)
38.5 months (upfront surgery)
HR 1.52 (95% CI, 0.94-2.46), p=0.096




| | Neoadjuvant group (n=63) | Upfront surgery (n=56) | p-value |
|---|---|---|---|
| Intention-to-treat | | | |
| R0 | 56% | 39% | 0.076 |
| N0 | 29% | 14% | 0.060 |

PDAC

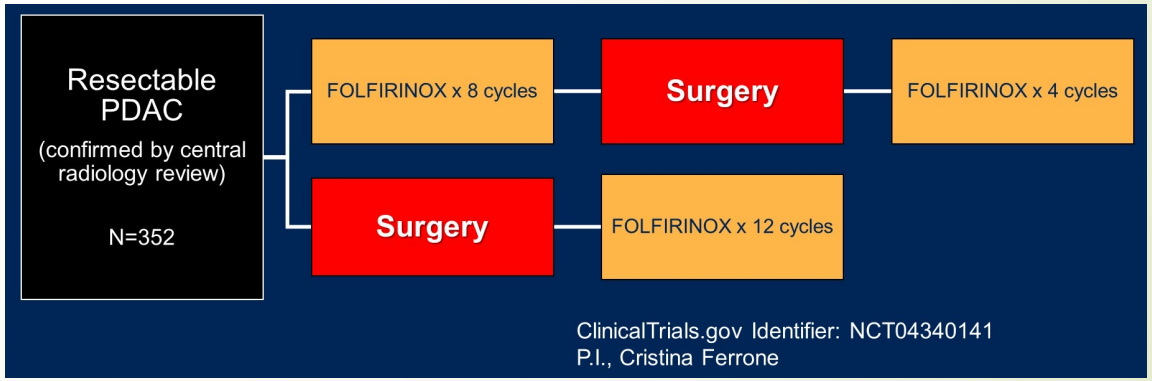
# Discussion

## Conclusions

- No improvement in OS with neoadjuvant approach
- Does not provide evidence of benefit to neoadjuvant approach in resectable disease

## Questions

- Disconnect between path (RO rate) and outcome
- Adjuvant – switch?
- Alliance A021806



Questions?

Thank you!