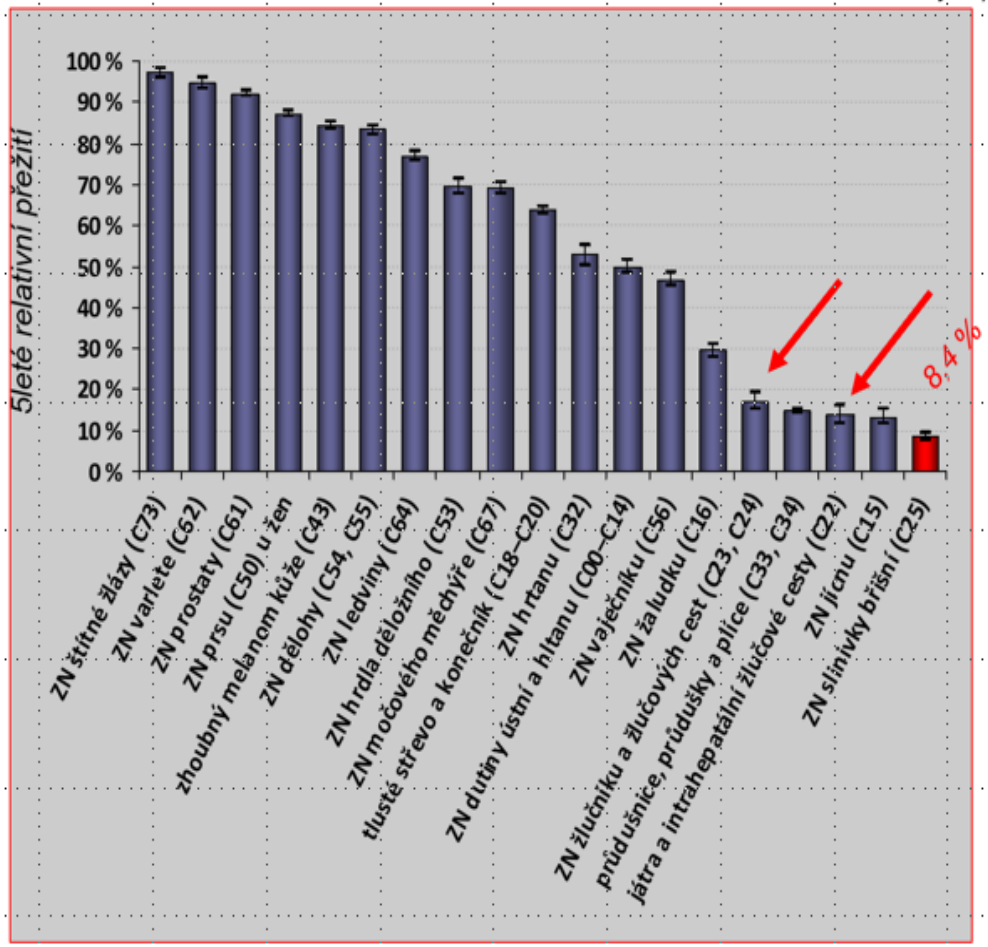
Karcinomy slinivky břišní a podjaterní krajiny

L.Petruželka

5leté relativní přežití: ZN v ČR

karcinomy žlučových cest a slinivky břišní - nejhorší 5leté přežití

Léčení pacienti, analýza periody 2010–2014



Zdroj: Národní onkologický registr, ÚZIS ČR

Zařazení radioterapie u hraničně resekabilního karcinomu pankreatu

- selekce dle biologických vlastností tumoru a celkového stavu pacienta

- důvody pro předřazení
  - chemoterapie – cytotoxický účinek systémový i lokální
  - (chemo)radioterapie / SBRT – sterilizace chirurgických okrajů, zvýšení pravděpodobnosti R0 resekce

Hraničně resekabilní karcinom pankreatu

- Je technicky resekabilní nádor s rizikem R1 a rizikem onkologického selhání při chirurgii jako úvodní modalitě

„Borderline″ resekabilní CaP vs. primárně resekabilní CaP

- Vyšší riziko okultní vzdálených metastáz nerozpoznatelných současnými zobrazovacími metodami
- Vyšší riziko R1 resekce
- Nutnost specializované komplexní chirurgie (včetně resekce a rekonstrukce cév atd.) pro vyšší riziko chirurgického „selhání“

Hraničně operabilní „borderline“ karcinomy pankreatu (BR-CaP)

- Koncept „borderline“ je víc než 15 let starý
- Bylo publikovano sedm různých definicí (BR-CaP)
- Interpretace a srovnávání klinických výsledků NAT BR-CaP je obtížné pro rozdílné a nejednotné léčebné protokoly
- Většina klinických studií obsahuje malé počty nemocných a jsou převážně retrospektivní

Barreto SG. Lancet Oncol 2016 Maurer CA, Zentralbl Chir 1999

vysoká

RESEKABILITA

nízká

- bez vzdálených metastáz
- bez arteriální či venózní infiltrace
- prorůstání do jiného orgánu (např. slezina)
- venózní postižení menší než 180° s případným dostatečným residuem k rekonstrukci
- uzavření gastroduodenální arterie s malým postižením a. hepatica bez postižení truncus coeliacus
- postižení a. mesenterica sup. menší než 180°
- postižení a. mesenterica sup. z více než 180° nebo její uzavření/trombus, nerekonstruovatelné postižení v. mesenterica sup. nebo konfluens s v. portae
- postižení v. cava inferior, aorty, truncus coeliacus nebo hepatické artérie
- metastatické postižení lymfatických uzlin mimo spádových
- vzdálené metastázy

Léčebný algoritmus hraničně resekabilního „borderline“ CaP

- Léčebný záměr je „kurativní“, ale….
  - Optimální léčebný postup nebyl dosud definován
- Základem je multimodalitní léčebný přístup
- Preferovaná léčba spočívá v 2 měsíční systémové léčbě s následným restagingem a chemoradioterapii
- „Nechirurgickou“ léčbu **nelze** zahájit bez histologické (cytologické) verifikace

Windsor JA J Gastrointest Oncol 2017

Karcinom slinivky břišní
ASCO GIT 2021

- Alliance A021501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas.
- M.Katz et al.

Alliance A021501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas.

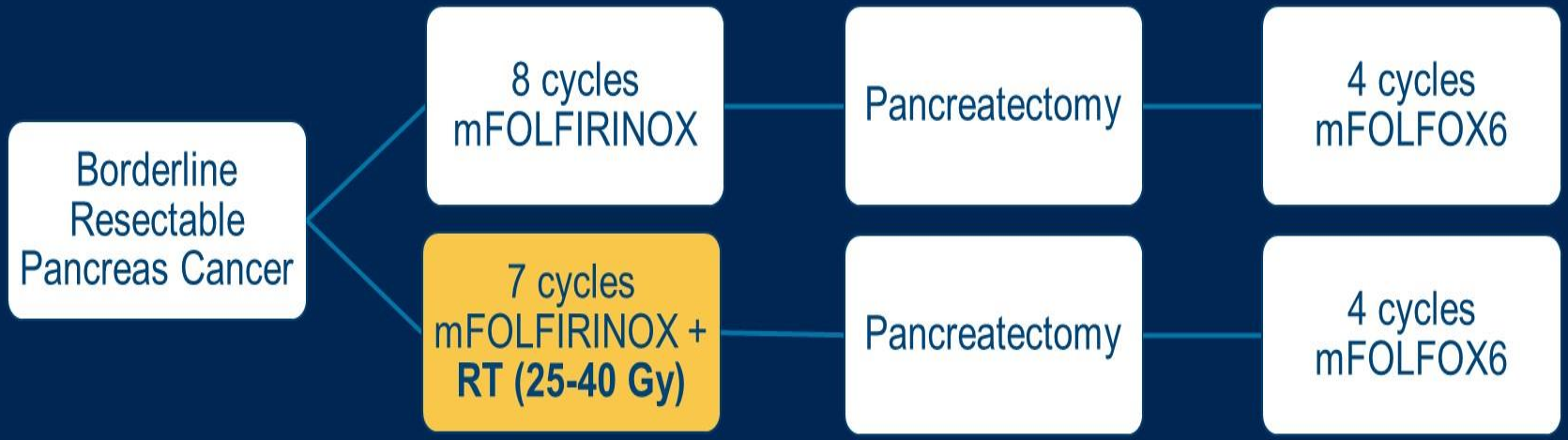
M.Katz et al.

- **Background:**Neoadjuvant therapy has been associated with a median overall survival (OS) of 18 – 23 months (mo) in patients (pts) with BR pancreatic ductal adenocarcinoma (PDAC). To establish reference regimens to which novel treatments can be compared in future studies, we evaluated neoadjuvant mFOLFIRINOX with or without RT in BR PDAC in a phase II National Clinical Trials Network (NCTN) trial.

- **Methods:**Pts with ECOG PS 0-1 and BR PDAC confirmed by central real-time radiographic review after pre-registration were randomized to either arm A: 8 cycles of neoadjuvant mFOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 over 46 hours), or arm B: 7 cycles of mFOLFIRINOX followed by stereotactic body RT (SBRT, 33-40 Gy in 5 fractions [fx]) or hypofractionated image guided RT (HIGRT, 25 Gy in 5 fx). Pts in either arm without disease progression underwent pancreatectomy, then 4 cycles of adjuvant mFOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 over 46 hours). The primary endpoint, 18-mo OS rate, of each arm was compared to a historical control of 50%. Planned interim analysis mandated closure of either arm in which $\leq$11 of first 30 accrued pts underwent R0 resection.

- **Results:**155 pts pre-registered and 126 pts were enrolled to arm A (N=70; 54 randomized, 16 following closure of arm B) or arm B (N=56; closed at interim analysis, all pts randomized prior to closure). Median age (A: 63y, B: 67y), median CA 19-9 level (A: 171 U/ml, B: 248 U/ml) and ECOG PS (A: 51% PS 0, B: 57% PS 0) of registered pts were similar between arms ($p > 0.05$). Treatment detailed in Table. The 18-mo OS rate based on Kaplan Meier estimates was 67.9% (95%CI: 54.6 – 78.0) in arm A and 47.3% (95%CI: 33.7 – 59.7) in arm B. Among pts who underwent pancreatectomy, 18-mo OS rate was 93.1% (95%CI: 84.3 – 100) and 78.9% (95%CI: 62.6 – 99.6) in arm A and B, respectively. With median follow-up of 27 and 31 mo, median OS was 31.0 (95%CI: 22.2 – NE) mo and 17.1 (95%CI: 12.8 – 24.4) mo in arm A and B, respectively.

Alliance A021501

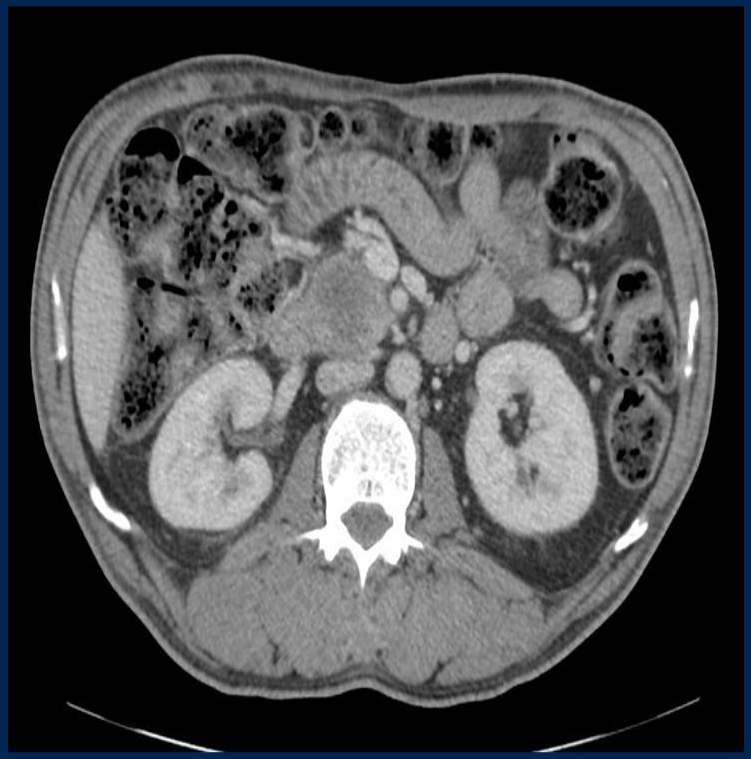


A21501 Key Findings

- Improved OS rates at 18 months in arm A (mFOLFIRINOX) vs. historical control: 66.4% (vs. 50%)
  - No difference in arm B (mFOLFIRINOX + SBRT): 47.3%
- Median OS 31 mo (arm A) and 17.1 mo (arm B)
- Resection rates: 49% (arm A), 35% (arm B)
- Similar grade 3+ adverse events rates

SBRT

- RT arm closed early– only 10/30 pts enrolled had R0 resection (33%)
  - Resection 4-10 weeks after RT
- Pathologic response
  - pCR: Arm A: 0% (n=0/32) vs. Arm B: 11% (n=2/19)
  - < 5% viable tumor cells: Arm A: 13% (4/32) vs. Arm B: 26% (n=5/19)



Evidence for Radiation

Study	Setting	N	Regimen	Outcomes
GITSG (1985)	Adjuvant	43	5-FU CRT vs. 5-FU	OS: 20 vs. 11 mo (p=0.03)
EORTC 40891 (1999)	Adjuvant	218	5-FU CRT vs. obs	OS: 17 vs. 13 mo (p=0.099)
ESPAC (2004)	Adjuvant	289	4x4 obs, CRT, chemo, chemo/CRT	OS: 16 vs. 18 mo (p=0.05) CRT vs. no CRT
RTOG 9407 (2008)	Adjuvant	451	Gem/5-FU+ XRT/Gem vs. 5-FU/5-FU + XRT/5-FU	OS: 20.8 vs. 16.9 mo (p=0.09)
RTOG 0848 (2020)	Adjuvant	322	Gem or Gem/erlotinib +/- 5-FU CRT	Pending
Jang (2018)	**NAT vs. Adj**	50	Gem + XRT NAT vs. Adjuvant	OS: 21.0 vs. 12.0 mo (p=0.028)
PREOPANC (2020)	**Neoadjuvant**	246	Gem + 15 x 2.4 Gy XRT vs. Surgery + Gem	OS: 16.0 vs. 14.3 mo (p=0.096)
A21501 (2020)	**Neoadjuvant**	126	mFOLFIRINOX & mFOLFIRINOX + RT	18 mo OS: 67.9% and 47.3% OS: 31 mo and 17.1 mo

Ongoing Studies

- Is there a role for non-SBRT radiation in the preoperative setting?
  - PREOPANC-2: 368 pts with resectable/BRPC will randomize to 8 cycles preoperative FOLFIRINOX or gemcitabine-based CRT (36 Gy) + adjuvant gemcitabine
  - PANDAS/PRODIGE44: 90 pts with BRPC will randomize to preoperative mFOLFIRINOX +/- capecitabine-based CRT (50.4 Gy) followed by surgery + adjuvant gemcitabine or 5-FU/LV

Conclusions

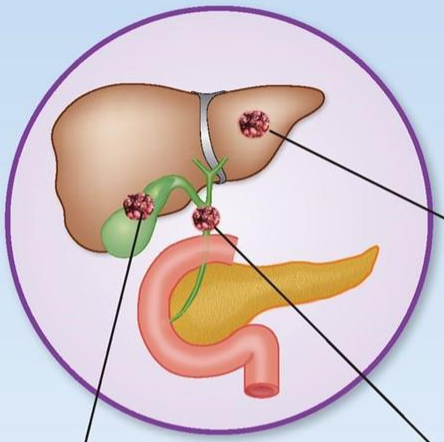
- mFOLFIRINOX is effective and tolerable in preoperative setting for BRPC.
- The addition of SBRT for management of BRPC in the preoperative setting does not appear to be justified.
- Role of XRT for specific subsets of high-risk patients with pancreatic cancer remains unknown.
- Future investigation should focus on patient-centered endpoints such as symptomatic local recurrence rates.

Neoadjuvant mFOLFIRINOX Established as Reference Standard in Borderline Resectable PDAC

- Patients with borderline resectable pancreatic ductal adenocarcinoma (PDAC) who received neoadjuvant therapy with modified FOLFIRINOX (mFOLFIRINOX) had an 18-month overall survival (OS) rate of 66.4% in a prospective phase II study conducted by the National Clinical Trials Network
- This rate exceeded the prespecified historical control of 50%, establishing mFOLFIRINOX as efficacious
- In contrast, neoadjuvant treatment with mFOLFIRINOX plus hypofractionated radiation therapy (RT) failed to exceed the 50% OS threshold at 18 months. This arm had to be closed early due to the low number of patients who proceeded to pancreatectomy.

- Karcinomy podjaterní krajiny

Biliary Cancers – A term that is SO 2010…



Biliary tract cancer

- >90% of cases are adenocarcinoma
- Level 1 evidence for adjuvant chemotherapy: capecitabine
- Palliative 1st-line chemotherapy: cisplatin/gemcitabine
- No 2nd-line palliative chemotherapy with a demonstrated survival benefit over active symptom control
- Median overall survival: ~12 months

Intrahepatic cholangiocarcinoma

- Risk factors: primary sclerosing cholangitis, cirrhosis, *Opisthorchis viverrini or Clonorchis sinensis*, obesity, diabetes, chronic hepatitis B and C, hepatolithiasis, Lynch syndrome, biliary papillomatosis, biliary duct morphologic anomalies
- Typically presents as incidental hepatic lesion(s)
- Radioembolization or radiation can be considered for liver-predominant disease

Gallbladder cancer

- Females > males
- Risk factors: gallstones, gallbladder polyps, chronic cholecystitis, *Salmonella typhi*, obesity, diabetes
- Typically presents as an incidental finding following cholecystectomy (localized stage) or with abdominal pain (advanced stage)

Extrahepatic cholangiocarcinoma

- Males > females
- Risk factors: primary sclerosing cholangitis, gallstones, Lynch syndrome, *Opisthorchis viverrini or Clonorchis sinensis,* bile duct morphologic anomalies
- Typically presents with obstructive jaundice

Why are we still lumping these together??

The definition of insanity is…

Valle, et al, Cancer Discov. 2017

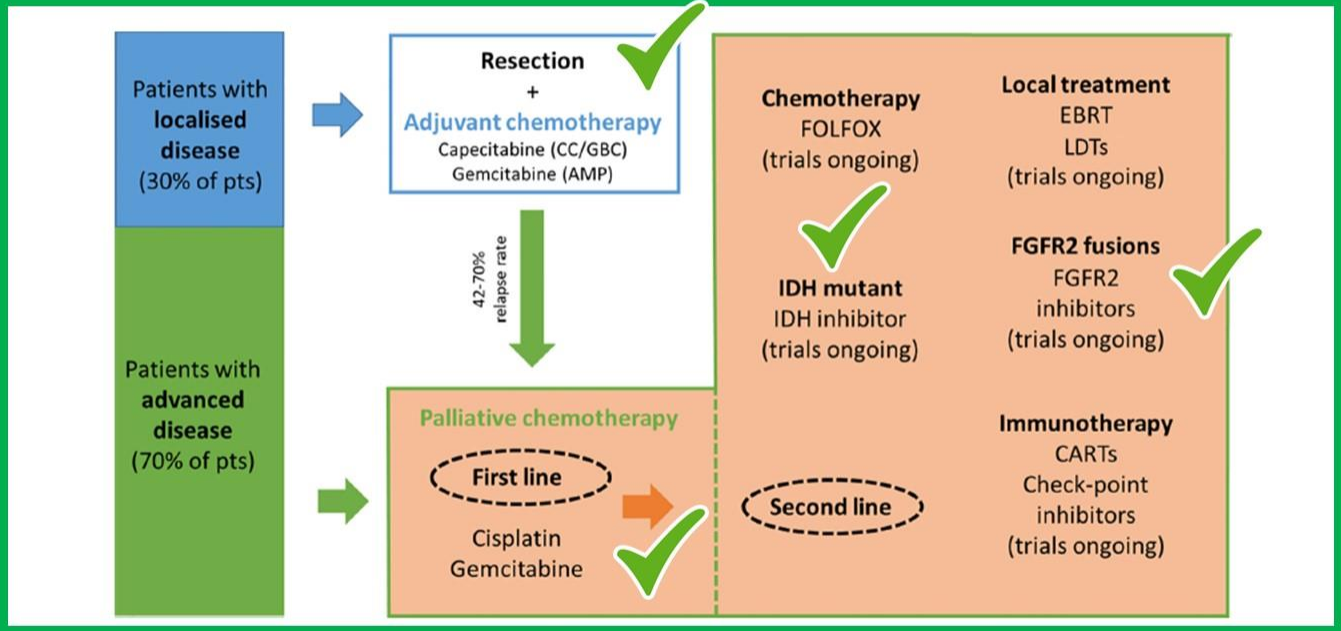
Karcinomy žlučových cest

- Medián doby přežití metastazujícího méně než 1 rok
- **Chemoterapie** (cis/gem) je základní systémová modalita současnosti

Slide modified from Angela Lamarca, MD

Meme Time: How it started...How it's going

Biliary cancers: Precision Medicine at it's finest!



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Karcinomy žlučových cest a slinivky břišní

bariery systémové léčby

bariery optimalizace léčebného algoritmu

- častá de novo rezistence
- nádorové stroma – bariéra průniku systémově podané léčby
- komplexní a nedostatečně rozpoznané nádorové mikroprostředí
- vícečetné genové mutace
- signální redundance
  - neexistující (nebo nerozpoznané) „řídící“ mutace
- vysoce „tumorigenní“ nádorové kmenové buňky zodpovědné za fenotypickou diversitu
- nerozpoznané molekulární prediktivní a prognostické biomarkery

Urgentní potřeba optimalizace genomického testování

„multiplex, pan-cancer, next-generation sequencing (NGS)“

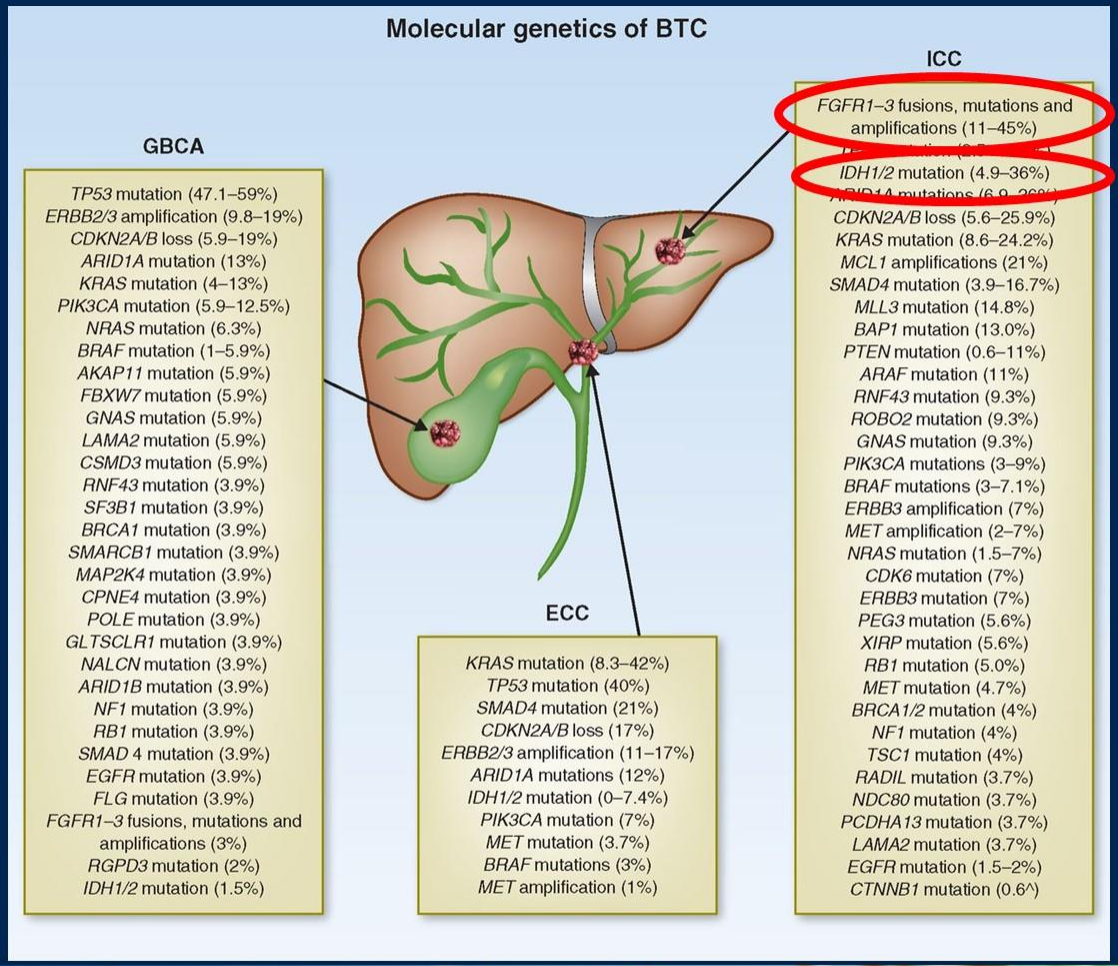
- v současnosti používaní testování typu jeden lék/jeden genový test nahradí multiplexní genomické testování nové generace
  - NGS panel (200-600 genů) umožňuje identifikovat alterace , které nezachytí menší “hotspot”panel
  - Multiplexní testování je a bude výrazně levnější než individuální testování

Subbiah V,Kurzrock R. Universal Genomic Testing Needed to Win the War Against Cancer.JAMAOncology 2016

Incidence vybraných aktivačních aberací/mutací u nádorů zažívacího traktu

Table 1. Incidence of selected actionable aberrations/mutations in upper gastrointestinal malignancy.

Gen			Ref.
HER2 amplification	Gastric Colorectal Gallbladder	22 6 13	[87–89]
FGFR fusions	Intrahepatic cholangiocarcinoma	8–14	[71,90]
IDH mutations	Intrahepatic cholangiocarcinoma	23	[69]
NTRK fusion	Colorectal Pancreatic	4 1	[91,92]
BRCA1–2 mutation	Pancreatic	1–7/1–3	[93]
MSI-H	Esophagogastric Pancreatic Cholangiocarcinoma	6 <1–1 9	[94–97]



Valle, et al, Cancer Discov. 2017

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ASCO – GI 2021

- Klinické studie
  - Ivosidenib (IDH1 mutace)
  - Infigratinib (FGFR2 fuze)

Final results from ClarIDHy, a global, phase 3, randomized, double-blind study of ivosidenib vs placebo in patients with previously treated cholangiocarcinoma and an isocitrate dehydrogenase 1 (*IDH1*) mutation

- **Andrew X Zhu**,[1,2] Teresa Macarulla,[3] Milind M Javle,[4] R Kate Kelley,[5] Sam J Lubner,[6] Jorge Adeva,[7] James M Cleary,[8] Daniel VT Catenacci,[9] Mitesh J Borad,[10] John A Bridgewater,[11] William P Harris,[12] Adrian G Murphy,[13] Do-Youn Oh,[14] Jonathan R Whisenant,[15] Bin Wu,[16] Christina X Chamberlain,[16] Liewen Jiang,[16] Camelia Gliser,[16] Shuchi S Pandya,[16] Juan W Valle,[17] Ghassan K Abou-Alfa[18,19]

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[10]Mayo Clinic Cancer Center, Phoenix, AZ, USA; [11]UCL Cancer Institute, London, UK; [12]University of Washington, Seattle, WA, USA; [13]Johns Hopkins University, Baltimore, MD, USA;
[14]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; [15]Utah Cancer Specialists, Salt Lake City, UT, USA;
[16]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [17]University of Manchester, The Christie NHS Foundation Trust, Manchester, UK; [18]Memorial Sloan-Kettering Cancer Center, New York, NY, USA;
[19]Weill Medical College at Cornell University, New York, NY, USA

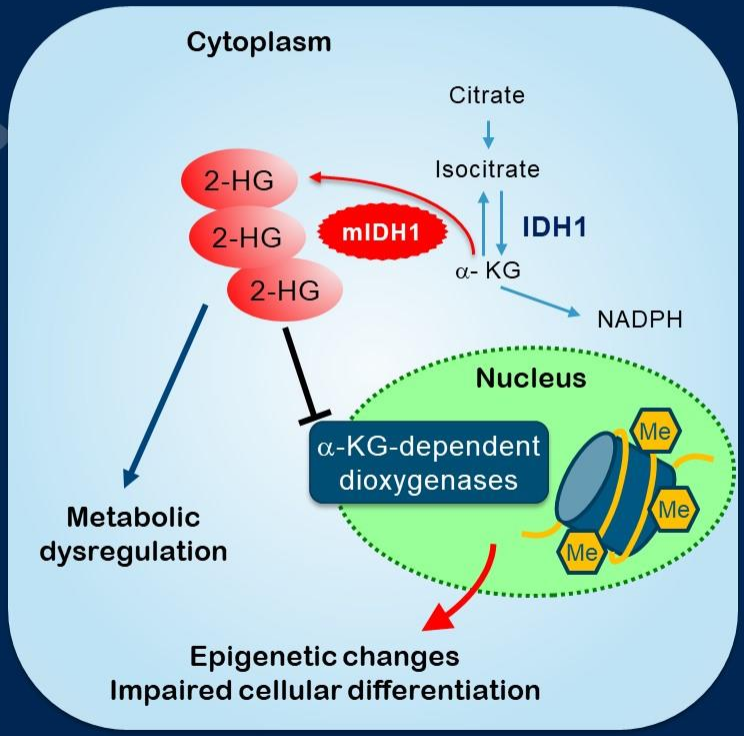
PRESENTED AT: Gastrointestinal Cancers Symposium

PRESENTED BY: Insert Name

#GI21

IDH1 mutations in advanced cholangiocarcinoma (CCA)

- CCA is a rare cancer for which there are limited effective therapies
- *IDH1* mutations occur in up to 20% of intrahepatic CCAs,[1] resulting in production of the oncometabolite D-2-hydroxyglutarate (2-HG), which promotes oncogenesis
  - *IDH1* mutations in CCA are not associated with prognosis[1]
- Ivosidenib (AG-120) is a first-in-class, oral, small-molecule inhibitor of mutant IDH1 (mIDH1)[2]
- The phase 3 ClarIDHy study aimed to demonstrate the efficacy of ivosidenib vs placebo in patients with unresectable or metastatic m*IDH1* CCA[3]



α-KG = alpha-ketoglutarate; Me = methyl groups; NADPH = nicotinamide adenine dinucleotide phosphate hydrogen

1. Boscoe AN, et al. *J Gastrointest Oncol*. 2019;10:751-765. **2.** Popovici-Muller J, et al. *ACS Med Chem Lett*. 2018;9:300-305. **3.** Abou-Alfa GK et al. *Lancet Oncol*. 2020;21:796-807.

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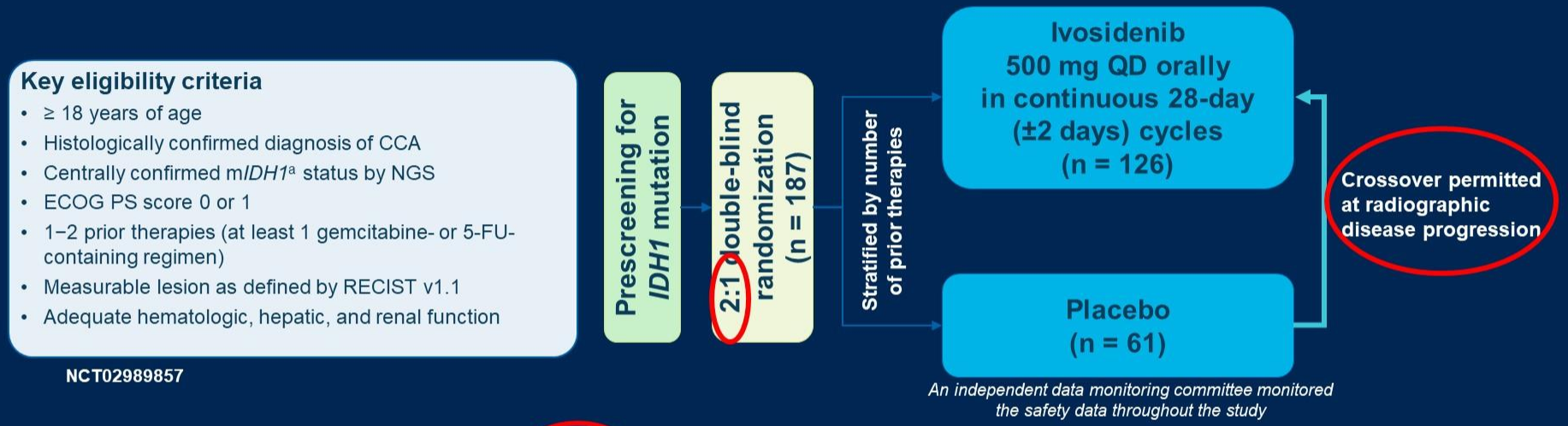
ClarIDHy: Study design and endpoints



- **Primary endpoint:** progression-free survival (PFS) by blinded independent radiology center (IRC)
- **Key secondary endpoints:** overall survival (OS); objective response rate; PFS by local review; pharmacokinetics/pharmacodynamics; health-related quality of life (HRQOL)[b]; safety and tolerability

[a]*IDH1* mutation status prospectively confirmed by NGS-based Oncomine™ Focus Assay on formalin-fixed, paraffin-embedded tumor tissue in a Clinical Laboratory Improvement Amendments-certified laboratory.
[b]Assessed using EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BIL21, and PGI questions
ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = 5-level EuroQoL-5 Dimension questionnaire; FU = fluorouracil; NGS = next-generation sequencing; PGI = Patient Global Impression; QD = once daily; QLQ-BIL21 = Cholangiocarcinoma and Gallbladder Cancer module; QLQ-C30 = Quality of Life Questionnaire Core 30; RECIST = Response Evaluation Criteria in Solid Tumors
Abou-Alfa GK et al. *Lancet Oncol.* 2020;21:796-807.

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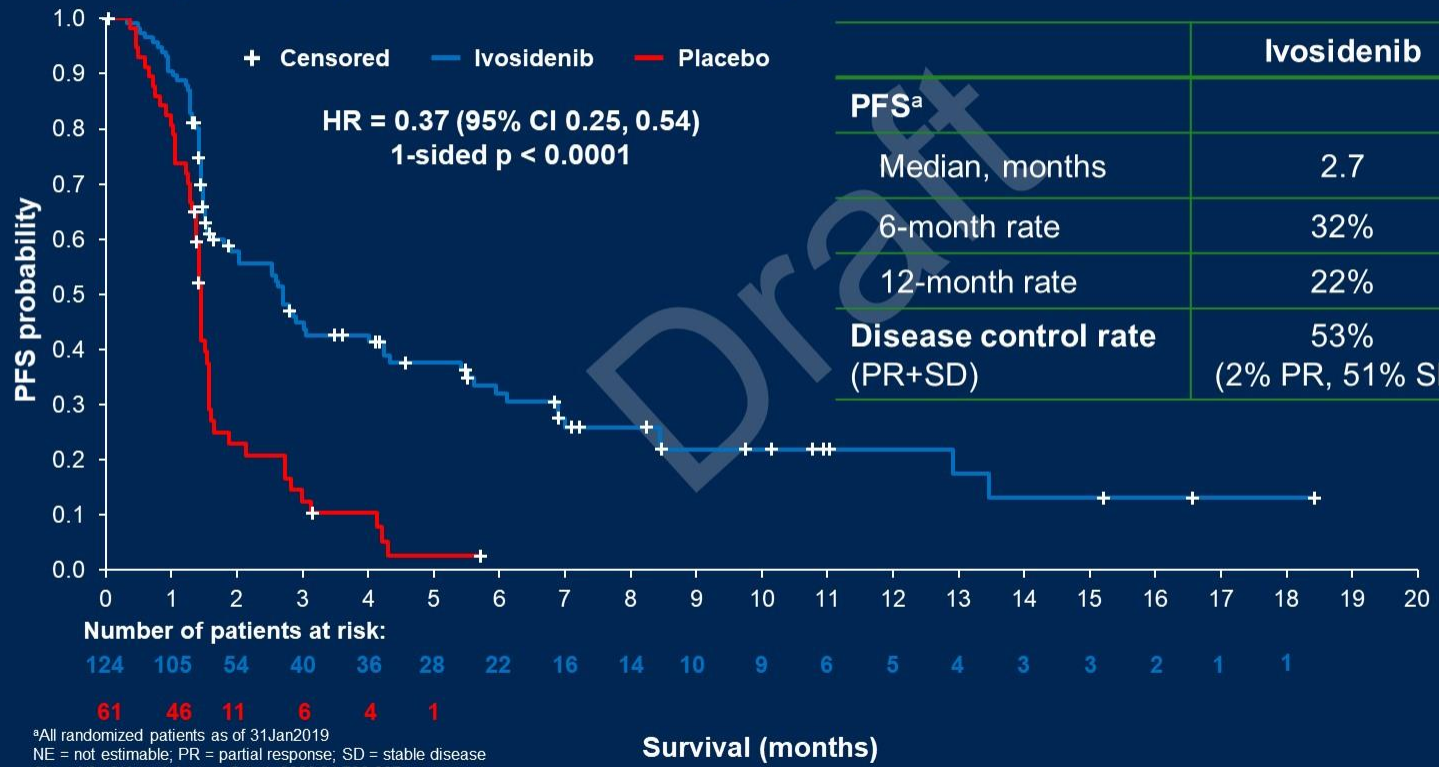
Primary endpoint of PFS by IRC was met



	Ivosidenib	Placebo
PFS[a]		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

[a]All randomized patients as of 31Jan2019
NE = not estimable; PR = partial response; SD = stable disease
Abou-Alfa GK et al. Lancet Oncol. 2020;21:796-807.

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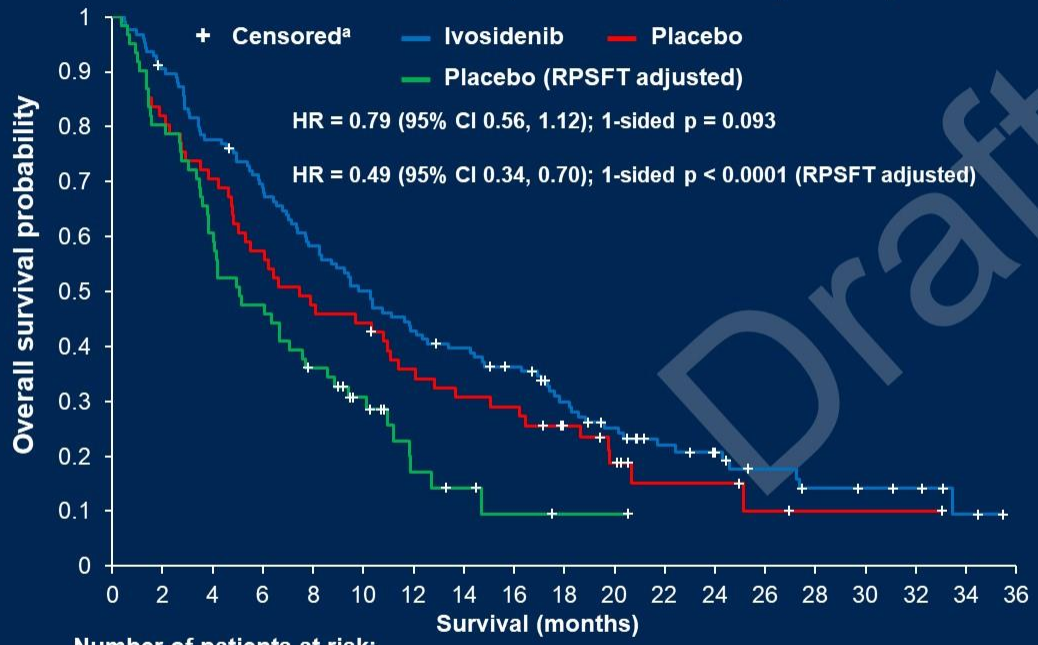
Overall survival (final analysis)



Number of patients at risk:

126	113	97	85	72	62	53	48	42	32	25	18	14	10	7	6	5	2
61	50	43	35	29	27	21	18	17	12	8	4	4	2	1	1	1	
61	49	37	29	21	14	6	4	2	1	1							

	Ivosidenib n = 126	Placebo n = 61
Number of events (%)	100 (79.4%)	50 (82.0%)
Median OS[b], months	10.3	7.5
6-month rate	69%	57%
12-month rate	43%	36%

- The rank-preserving structural failure time (RPSFT)[1,2] model was implemented as a prespecified analysis to adjust for the effect of crossover from placebo to ivosidenib
- The median OS for placebo after adjustment for crossover was **5.1 months**

[a]Patients without documentation of death at the data cutoff date were censored at the date the patient was last known to be alive or the data cutoff date, whichever was earlier
[b]All randomized patients as of 31May2020

1. Watkins C et al. *Pharm Stat*. 2013;12:348-57. **2.** Robins JM, Tsiatis AA. *Commun Stat Theory Methods*.1991;20:2609-31.

TEAEs (> 15%[a])

	Placebo (n = 59)	Ivosidenib (n = 123)	Total ivosidenib (n = 166)[b]
Any TEAE, n (%)	57 (96.6)	120 (97.6)	161 (97.0)
Most common TEAEs, n (%)			
Nausea	17 (28.8)	51 (41.5)	63 (38.0)
Diarrhea	10 (16.9)	43 (35.0)	55 (33.1)
Fatigue	10 (16.9)	38 (30.9)	48 (28.9)
Abdominal pain	9 (15.3)	30 (24.4)	37 (22.3)
Cough	5 (8.5)	31 (25.2)	36 (21.7)
Decreased appetite	11 (18.6)	30 (24.4)	36 (21.7)
Ascites	9 (15.3)	28 (22.8)	33 (19.9)
Vomiting	11 (18.6)	28 (22.8)	33 (19.9)
Anemia	3 (5.1)	22 (17.9)	30 (18.1)
Edema peripheral	6 (10.2)	17 (13.8)	25 (15.1)

- Grade ≥ 3 TEAEs: 37.3% for placebo vs 53% for total ivosidenib
  - Most common grade ≥ 3 TEAEs[c] (placebo vs total ivosidenib): ascites (6.8% vs 9.0%), anemia (0% vs 7.2%), blood bilirubin increased (1.7% vs 5.4%)
- TEAEs leading to discontinuation were more common for placebo (8.5% vs 6.6%) than total ivosidenib
- TEAEs leading to dose reductions (0% vs 3.0%) and interruptions (18.6% vs 30.1%) were less common for placebo relative to total ivosidenib

[a]> 15% cutoff used for all grade TEAEs based on total ivosidenib
[b]Total ivosidenib includes 43 patients initially assigned to placebo who had crossed over to ivosidenib upon radiographic disease progression and unblinding. All randomized patients as of 31May2020
[c]> 5% cutoff used for grade ≥ 3 TEAEs based on total ivosidenib
TEAE = treatment-emergent adverse event

Conclusions

- ClarIDHy is the first randomized phase 3 study of a targeted, oral therapeutic with a noncytotoxic mechanism of action in advanced m*IDH1* CCA
- Ivosidenib demonstrated a highly statistically significant improvement in PFS (HR = 0.37, 1-sided p < 0.0001) compared with placebo
- Ivosidenib resulted in a numeric improvement in OS despite a high rate of crossover from the placebo arm (~70%), and this improvement was further supported by the RPSFT adjustment for crossover (HR = 0.49, 1-sided p < 0.0001)
- The efficacy data coupled with a tolerable safety profile and supportive HRQOL data demonstrate the clinical benefit of ivosidenib in this aggressive disease in which there is an unmet need for new therapies

ivosidenib (IVO)

- Final results from ClarIDHy, a global, phase III, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (*IDH1*) mutation.
- AX Zhu et al

- **Conclusions:**IVO was well tolerated and resulted in a favorable OS trend vs PBO despite a high rate of crossover. These data – coupled with statistical improvement in PFS, supportive quality of life data, and favorable safety profile – demonstrate **the clinical benefit of IVO in advanced m*IDH1* CCA.**

Final results from a phase 2 study of infigratinib (BGJ398), an FGFR-selective tyrosine kinase inhibitor, in patients with previously-treated advanced cholangiocarcinoma containing *FGFR2* fusions/rearrangements

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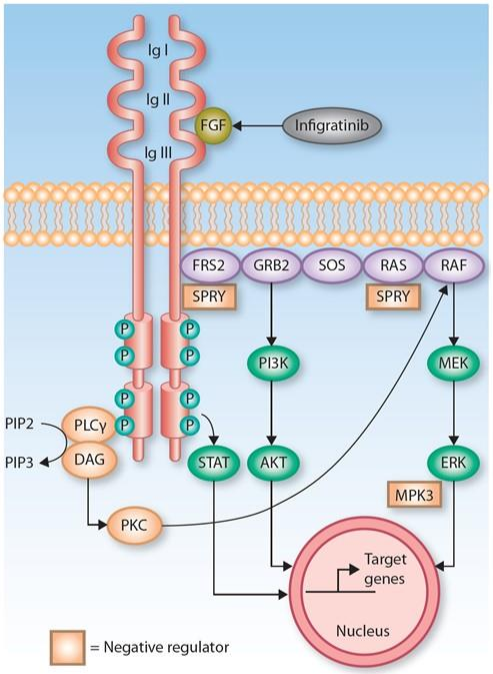
ASCO GI 2021

Background

- Cholangiocarcinomas (CCA) are rare and aggressive malignancies that are typically locally advanced or metastatic at diagnosis.[1] The 5-year relative survival for patients with distant CCA at diagnosis is 2%[2]
- Approximately 70% of patients are diagnosed with late-stage disease, for which treatment options are limited in efficacy and toxicity:[3–5]
  - First-line treatment with gemcitabine + cisplatin is the only regimen with NCCN level 1 evidence, based on findings from the ABC-02 study[6,7]
  - Second-line options include gemcitabine- or fluorouracil-based combinations.[7] The ABC-06 study demonstrated superiority of modified FOLFOX + active symptom control after gemcitabine + cisplatin, with limited benefits[8]
- The identification of molecular drivers implicated in the development of specific CCA subtypes is changing the standard of care in this disease:[9]
  - These include genomic alterations in the fibroblast growth factor receptor (FGFR), particularly *FGFR2* fusions or rearrangements, which have been shown to drive tumorigenesis in CCA as well as in other cancers[9]

1. Patel & Benipal 2019; 2. American Cancer Society, May 26 2020 (https://www.cancer.org/cancer/bile-duct-cancer/about/key-statistics.html); 3. Valle JW, et al. Ann Oncol 2016;27(suppl 5):v28–v37
4. Banales JM, et al. Nat Rev Gastroenterol Hepatol 2020;17:557–88; 5. Lamarca A, et al. J Hepatol 2020;73:170–85; 6. Valle J, et al. N Engl J Med 2010;362:1273–81; 7. NCCN Guidelines Version 5. 2020 Hepatobiliary Cancers Accessed October 20, 2020, (https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf; 8. Lamarca A, et al. J Clin Oncol 2019;37(15_suppl):4003-4003; 9. Lowery MA, et al. Clin Cancer Res 2018;24:4154–61

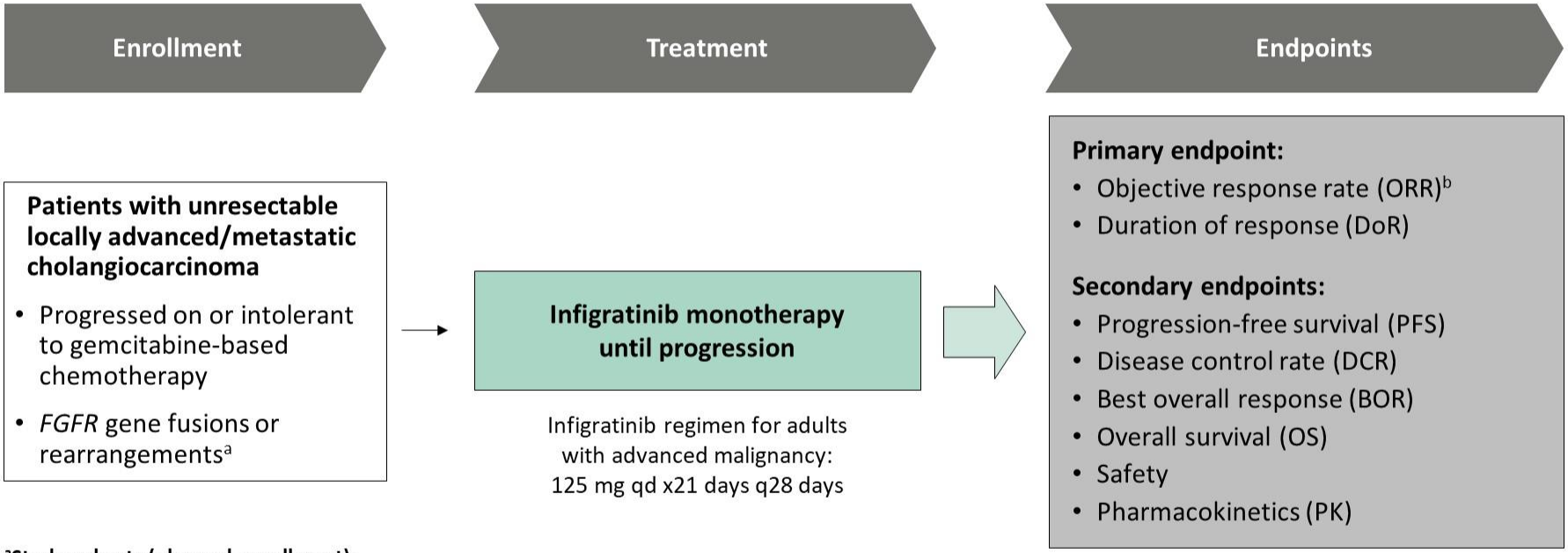
Targeting *FGFR* genomic alterations with infigratinib: an FGFR1–3 selective tyrosine kinase inhibitor



- *FGFR* fusions are found in up to ~14% of intrahepatic CCA cases and predict tumor sensitivity to FGFR inhibitors[1–4]
- Second-line chemotherapy seems to have limited efficacy in patients with CCA and *FGFR2* fusions, similar to that reported in the general CCA population:
  - A retrospective analysis of 37 patients with *FGFR2* fusions who received second-line chemotherapy showed a median PFS of only 4.6 months and an ORR of 5.4%[5]
- Infigratinib (BGJ398), an ATP-competitive FGFR1–3-selective oral tyrosine kinase inhibitor, has shown preliminary clinical activity against tumors with *FGFR* alterations[6]
- In early-phase clinical evaluation, infigratinib showed a manageable safety profile and single-agent activity[3,7]

1. Graham RP, et al. Hum Pathol 2014;45:1630–8; 2. Arai Y, et al. Hepatology 2014;59:1427–34; 3. Javle MM, et al. J Clin Oncol 2016;34(suppl 4S; abstr 335)
4. Lowery MA, et al. Clin Cancer Res 2018;24:4154–61; 5. Javle M, et al. Proc ASCO 2020 (poster #4591); 6. Guagnano V, et al. Cancer Discov 2012;2:1118–33; 7. Nogova L, et al. J Clin Oncol 2017;35:157–65

Open-label, phase 2 study design (NCT02150967)



[a]Study cohorts (planned enrollment):
Cohort 1 (n=120): patients with *FGFR2* gene fusions/rearrangements
Cohort 2 (n=20): patients with *FGFR1&3* gene fusions/rearrangements and/or *FGFR* mutations (prior selective FGFR inhibitors are not permitted in Cohorts 1&2)
Cohort 3 (n=20): patients with *FGFR2* gene fusions who have progressed following prior treatment with a selective FGFR inhibitor other than infigratinib

[b]ORR assessed by blinded independent central review (BICR, per RECIST v1.1), March 31, 2020 data cut-off

Interim analysis (n=108)

Clinical activity of infigratinib in advanced/metastatic cholangiocarcinoma

Per blinded independent central review	N=108
Objective response rate (confirmed), % (95% CI)	**23.1** (15.6–32.2)
Complete response, n (%)	1 (0.9)
Partial response, n (%)	24 (22.2)
Stable disease, n (%)	66 (61.1)
Progressive disease, n (%)	11 (10.2)
Unknown, n (%)	6 (5.6)
Best overall response (confirmed/unconfirmed), % (95% CI)	**34.3** (25.4–44.0)
Median time to response, months (range)	**3.6** (1.4–7.4)
Disease control rate, % (95% CI)	**84.3** (76.0–90.6)
Median duration of response, months (range)	**5.0** (0.9–19.1)
Median progression-free survival, months (95% CI)	**7.3** (5.6–7.6)
PFS (event free) rate at 4 month, % (95% CI)	75.2 (65.2–82.7)
Median overall survival, months (95% CI)	**12.2** (10.7–14.9)
Per investigator assessment	
Objective response rate (confirmed), % (95% CI)	**30.6** (22.1–40.2)
Median duration of response, months (range)	**6.0** (5.2–9.0)

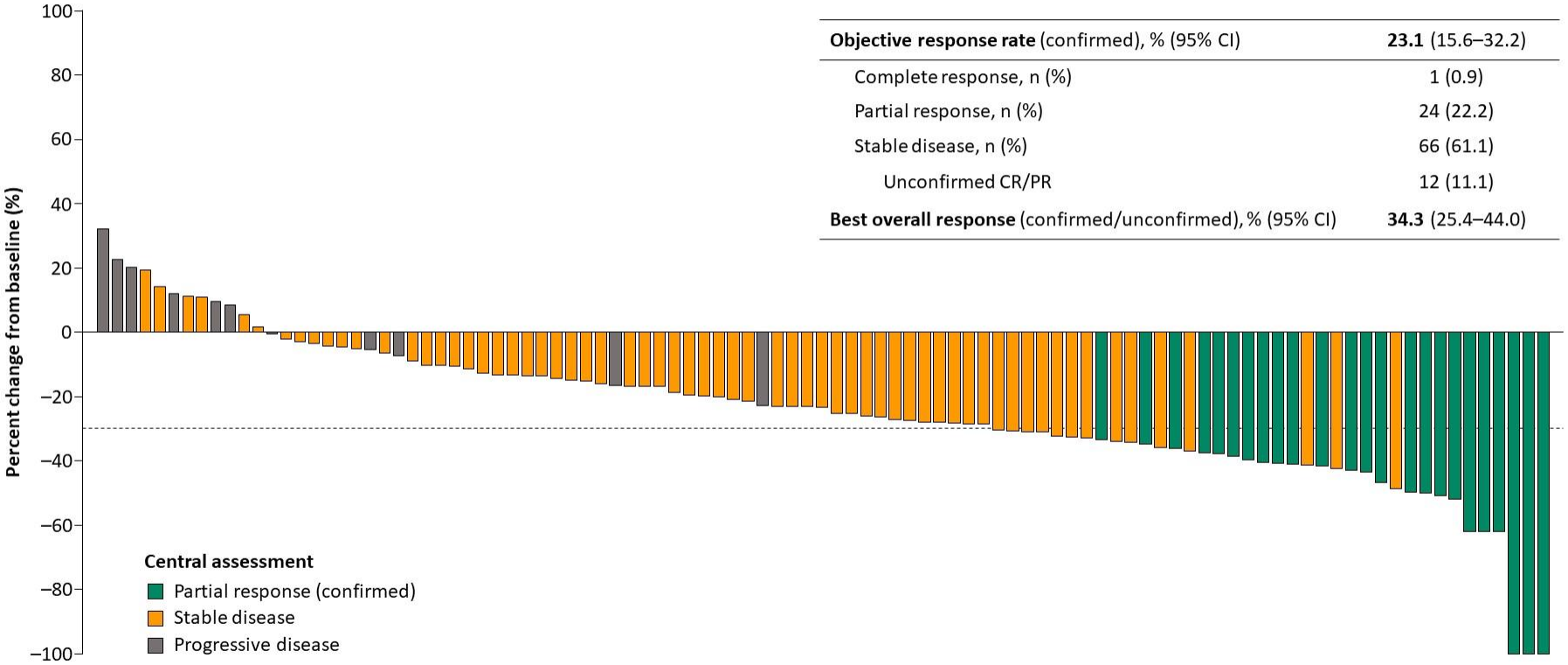
Clinical activity of infigratinib by prior lines of therapy

	Patients with ≤1 line of prior therapy (n=50)	Patients with ≥2 lines of prior therapy (n=58)
Objective response rate (confirmed), % (95% CI)	**34.0** (21.2–48.8)	**13.8** (6.1–25.4)
Complete response, n (%)	0	1 (1.7)
Partial response, n (%)	17 (34.0)	7 (12.1)
Stable disease, n (%)	27 (54.0)	39 (67.2)
Progressive disease, n (%)	4 (8.0)	7 (12.1)
Unknown, n (%)	2 (4.0)	4 (6.9)
Best overall response (confirmed/unconfirmed), % (95% CI)	**42.0** (28.2–56.8)	**27.6** (16.7–40.9)
Duration of response in confirmed responders, months (95% CI)	5.6 (3.7–9.5)	4.9 (3.7–NE)
Disease control rate, % (95% CI)	**88.0** (75.7–95.5)	**81.0** (68.6–90.1)
Median progression-free survival, months (95% CI)	**7.3** (5.6–9.3)	**7.4** (5.6–7.7)

Response evaluated by blinded independent central review

Interim analysis (n=108)

Best percentage change in target-lesion size: ORR confirmed responses by BICR

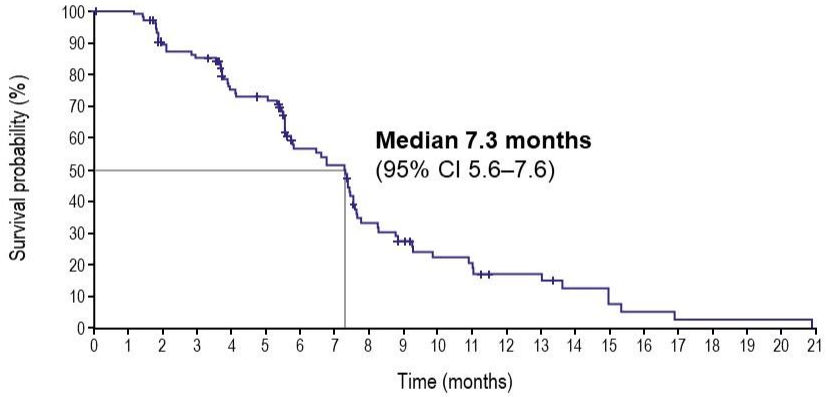


Objective response rate (confirmed), % (95% CI)	**23.1** (15.6–32.2)
Complete response, n (%)	1 (0.9)
Partial response, n (%)	24 (22.2)
Stable disease, n (%)	66 (61.1)
Unconfirmed CR/PR	12 (11.1)
Best overall response (confirmed/unconfirmed), % (95% CI)	**34.3** (25.4–44.0)

Only patients with measurable disease at baseline and with at least one post-baseline scan are shown in the waterfall plot (n=100)

Progression-free survival and overall survival

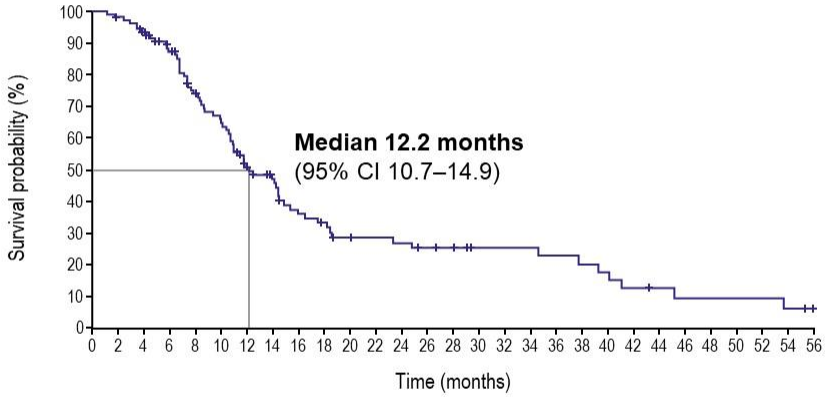
Progression-free survival



Number of subjects at risk

All subjects	108	105	87	83	66	63	42	38	23	18	13	12	8	8	5	3	2	1	1	1	1	0

Overall survival



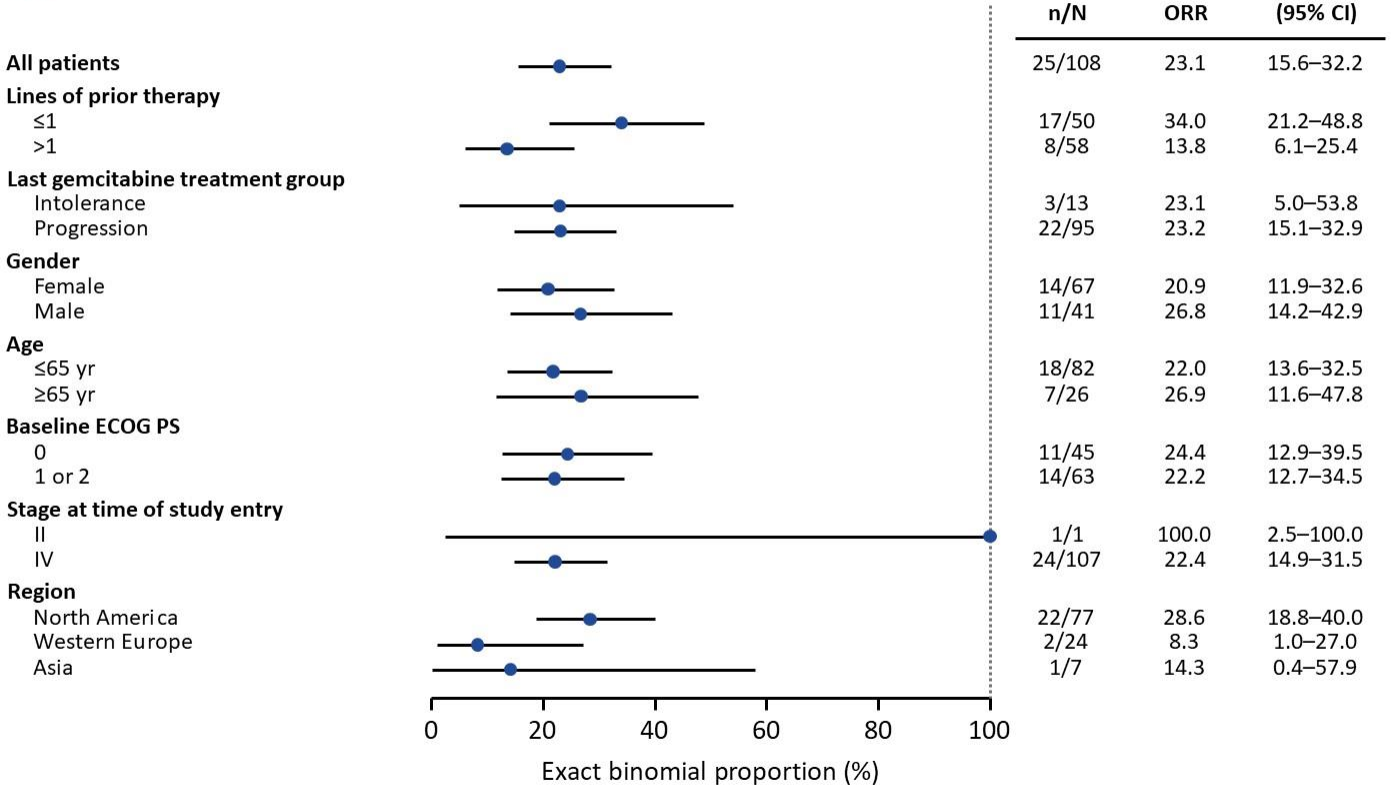
Number of subjects at risk

All subjects	108	105	96	83	66	58	41	35	26	22	18	17	16	14	13	10	10	10	9	8	7	5	4	3	3	3	3	2	0

Median follow-up time: 11.3 months (range 0.03–20.90+)

Interim analysis (n=108)

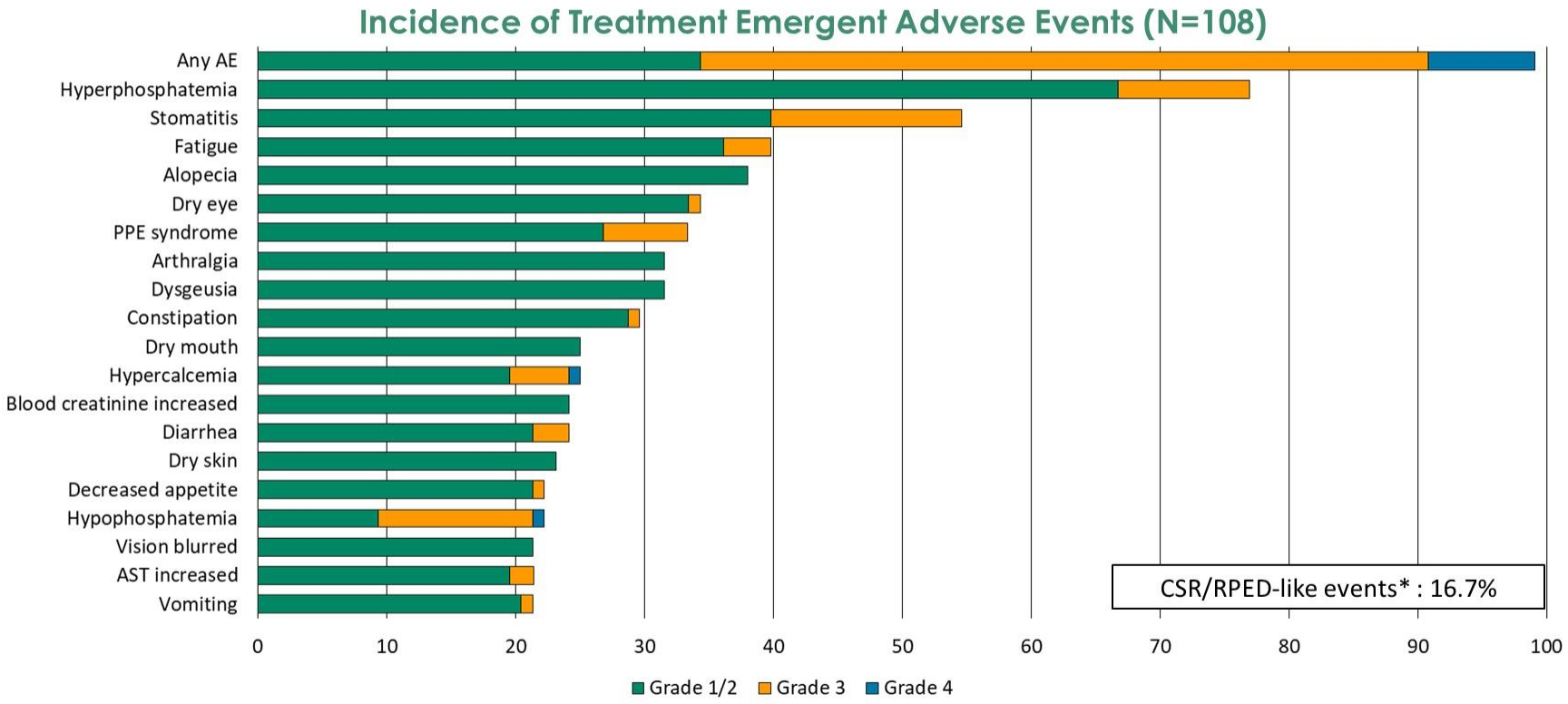
Response to infigratinib in *FGFR2* fusion-positive cholangiocarcinoma



Forest plot for ORR per BICR

Interim analysis (n=108)

Infigratinib safety profile
Most common treatment-emergent adverse events (> 20%)



*Central serous retinopathy (CSR)/retinal pigment epithelial detachment (RPED)-like events included the following terms: chorioretinopathy; subretinal fluid; serous retinal detachment; and detachment of retinal pigment epithelium, macular detachment, and retinopathy

Conclusions

- Infigratinib is an oral, FGFR1−3-selective TKI that shows meaningful clinical activity against chemotherapy-refractory CCA containing *FGFR2* fusions:
  - Confirmed ORR 23.1% (95% CI 15.6−32.2%)
  - Median DoR 5.0 months (range 0.9–19.1 months)
  - Median PFS 7.3 months (95% CI 5.6–7.6 months)
- Treatment with infigratinib was generally well tolerated in patients with advanced CCA; AEs were generally reversible and manageable and in line with previous observations in this patient population
- Infigratinib, administered as second- and later-line treatment, represents a new therapeutic option for patients with CCA and *FGFR2* fusions

Infigratinib

- Final results from a phase II study of infigratinib (BGJ398), an FGFR-selective tyrosine kinase inhibitor, in patients with previously treated advanced cholangiocarcinoma harboring an *FGFR2* gene fusion or rearrangement.
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- **Conclusions:**Infigratinib is associated with promising anticancer activity and a manageable AE profile in patients with advanced, refractory CCA with an *FGFR2* gene fusion or rearrangement. A phase III study of infigratinib versus gemcitabine/cisplatin is ongoing in the front-line setting (NCT03773302).

Conclusions

- Biliary cancers is NOT one disease anatomically or molecularly and we need to stop treating it as such (remember, the definition of insanity…)
- Cholangiocarcinoma (CCA) is the POSTER CHILD for precision medicine → biomarker testing should be done on ALL patients
- Ivosidenib hits the TARGET for IDH1 mutated CCA and MOSTLY hits the mark → mPFS significantly improved, mOS numerically improved, good QOL, clinical benefit
- Infigratinib hits the TARGET for FGFR2 fusion + CCA and MOSTLY hits the mark → comparable ORR, especially in earlier line therapy, impressive mPFS, we are learning how to manage AE's

Questions to be answered

- IVOSIDENIB
  - Will it be available to our patients?
  - What happens when other IDH1 inhibitors are available?
  - Is there a role for combinations since it is well-tolerated?

- INFIGRATINIB
  - How do we sequence all the FGFR inhibitors?
  - Can we need better understand resistance?
  - Is there a role in the front-line? PROOF study ongoing

Cesty ke zlepšení léčebných výsledků karcinomů žlučových cest a pankreatu:

- Mezioborová spolupráce
  - (funkční „tumor board“)
    - Inovace - rozšíření o „molekulárního“ experta
- Komplexní léčba
  - propojení všech léčebných modalit
- Precizní personalizovaná medicína
  - Klinické využití biomarkerů
  - Individualizace léčby