Memorial Sloan Kettering
Cancer Center

Current and Future Management of Advanced Biliary Tract Cancers

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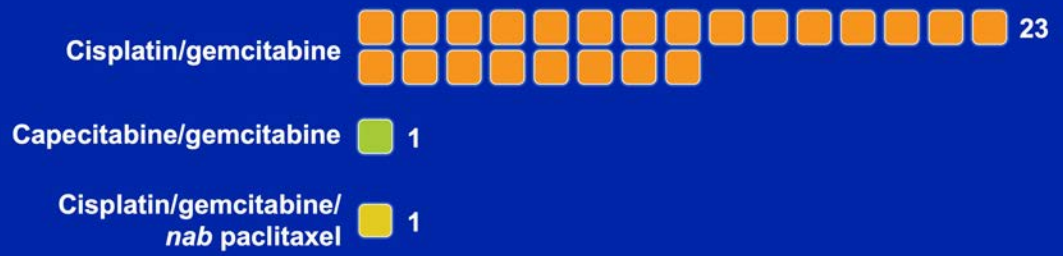
Memorial Sloan Kettering Cancer Center

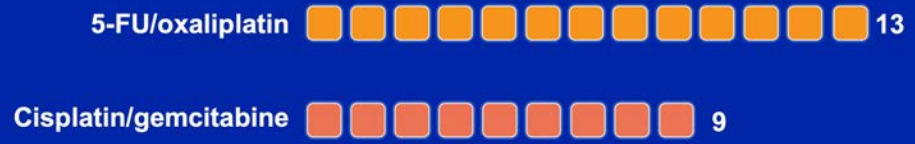
Research To Practice
Hepatobiliary Cancers
San Francisco, January 24, 2020

Is cholangiocarcinoma the new nonsquamous cell lung cancer?

What would be your current preferred first-line systemic treatment for a 65-year-old patient with metastatic cholangiocarcinoma and a PS of 0?

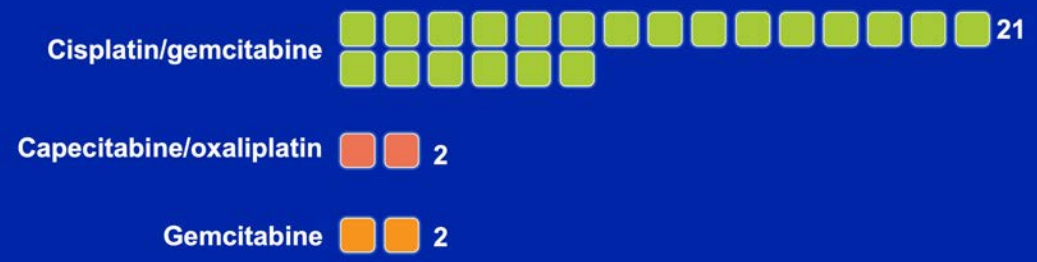


What would be your current preferred first-line systemic treatment for a 65-year-old patient with metastatic cholangiocarcinoma, persistent hyperbilirubinemia and a PS of 0?



5-FU (1), Capecitabine/oxaliplatin (1), Gemcitabine (1)

What would be your current preferred first-line systemic treatment for a 78-year-old patient with metastatic cholangiocarcinoma and a PS of 1?



Advanced Biliary Tract Cancers

- Biologic subsets, response to first-line chemotherapy
- Multiplex somatic and germline testing
- IDH somatic mutations and IDH inhibitors
- Other potentially targetable mutations/alterations (EGFR/HER2, FGFR, BRAF, NTRK)

Somatic IDH1 mutations
143 patients

Targeted treatment(s)
Ivosidenib, FGFR inhibitors, RAF inhibitors, Anti-HER2 agents, Pembrolizumab

Somatic IDH2 mutations
22 patients

Targeted treatment(s)
Enasidenib, IDH1/2 inhibitor

BRAF mutations
34 patients

Targeted treatment(s)
Encorafenib/binimetinib, Vemurafenib, Vemurafenib/cobimetinib, Dabrafenib/trametinib, Vemurafenib/irinotecan/cetuximab

FGFR alterations
154 patients

Targeted treatment(s)
Infigratinib, Pemigatinib, TAS-120, Erdafitinib, Futibatinib

NTRK gene fusions
1 patient

Targeted treatment(s)
Larotrectinib

Somatic HER2 or EGFR mutations or fusions
37 patients

Targeted treatment(s)
Trastuzumab, Trastuzumab/lapatinib, Pertuzumab

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Disclosures

- Research

ActaBiologica, Agios, Array, AstraZeneca, Bayer, BeiGene, BMS, Casi, Celgene, Exelixis, Genentech, Halozyme, Incyte, Lilly, MabVax, Novartis, Polaris, Puma, QED, Roche

- Consulting

Agios, AstraZeneca, Bayer, BeiGene, Bioline, BMS, Celgene, CytomX, Debio, Eisai, Exelixis, Flatiron, Genoscience, Incyte, Ipsen, Jansen, LAM, Lilly, Loxo, Merck, MINA, Pfizer, QED, Redhill, Sanofi, Silenseed, Sillajen, Sobi, Targovax, twoXAR, Vicus, Yiviva

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MEGA: Mutual Exclusivity of Genetic Alterations

Gene1	Gene2	Both genes altered (*n*)	Gene2 altered (*n*)	Gene1 altered (*n*)	Neither gene altered (*n*)	OR	*P* value	*q* value
IDH1	TP53	3	43	45	104	0.162	0.001	0.488
IDH1	SMAD4	0	19	48	128	0.000	0.004	1
TP53	BAP1	1	29	45	120	0.093	0.004	1
BAP1	KRAS	0	25	30	140	0.000	0.017	1
BAP1	SMAD4	0	19	30	144	0.000	0.029	1
IDH1	FGFR2	1	19	47	128	0.144	0.030	1
IDH1	KRAS	2	23	46	124	0.236	0.046	1
TP53	FGFR2	1	19	45	130	0.153	0.049	1
PBRM1	KRAS	0	25	23	147	0.000	0.049	1

Lowery, M, Abou-Alfa, GK et al. Clin Cancer Res. 2018 Sep 1;24(17):4154-4161

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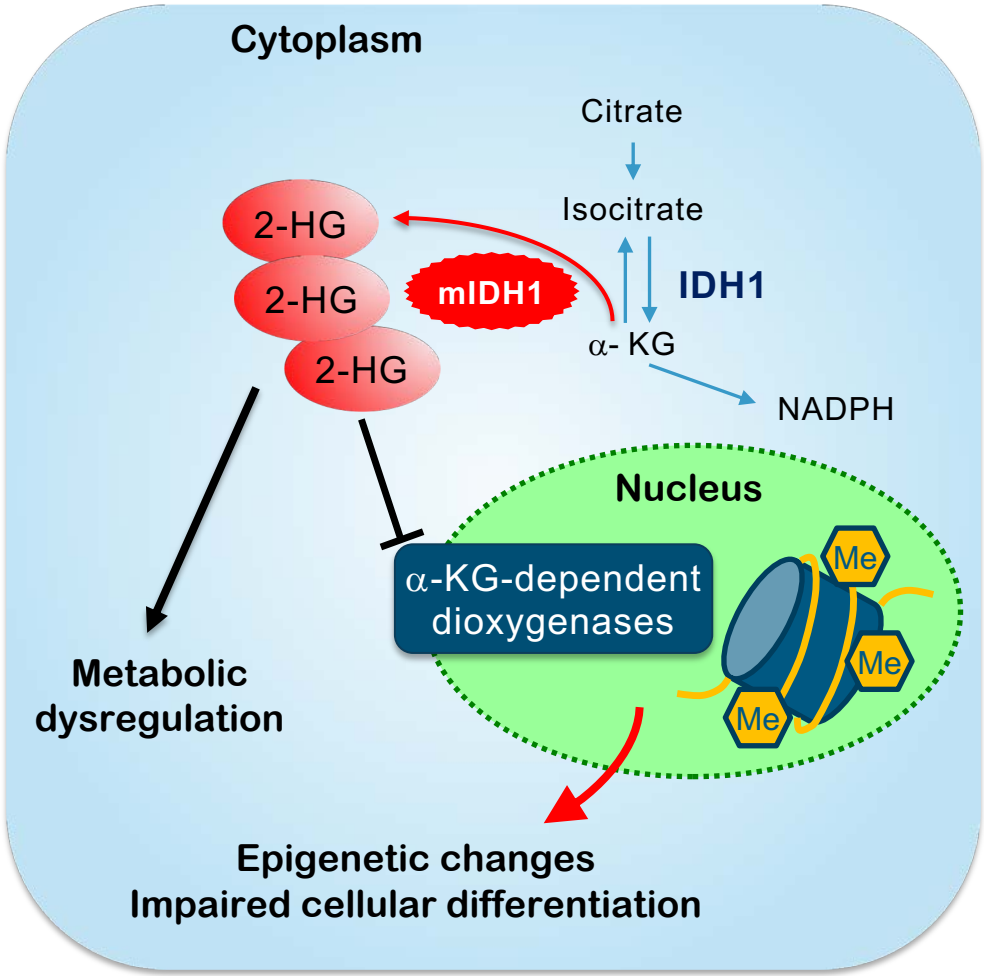
IDH1 mutations in advanced cholangiocarcinoma

- Advanced cholangiocarcinoma is an aggressive rare cancer with treatment options limited primarily to chemotherapy[1]
- IDH1 mutations occur in up to 20% of cholangiocarcinoma and do not confer a favorable prognosis[1]
- Ivosidenib (AG-120) is a first-in-class, oral, targeted, small-molecule inhibitor of the mutant IDH1 (mIDH1) protein,[2] and is FDA-approved for mIDH1 R/R AML and ND AML not eligible for intensive chemotherapy[3]
- A phase 1 study of ivosidenib included 73 previously treated mIDH1 cholangiocarcinoma patients and was associated with: median PFS, 3.8 months; 6- and 12-month PFS rates, 40.1% and 21.8%, respectively; and median OS 13.8 months[4]



2-HG=D-2-hydroxyglutarate; α-KG=alpha-ketoglutarate; AML=acute myeloid leukemia; FDA=Food and Drug Administration; Me=methyl groups; ND=newly-diagnosed; OS=overall survival; PFS=progression-free survival; R/R=relapsed/refractory.

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.** TIBSOVO highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211192s001lbl.pdf. Accessed August 5, 2019. **4.** Lowery MA, et al. *Lancet Gastroenterol Hepatol*. 2019;4:711-720.

Abou-Alfa, GK, et al. ESMO 2019

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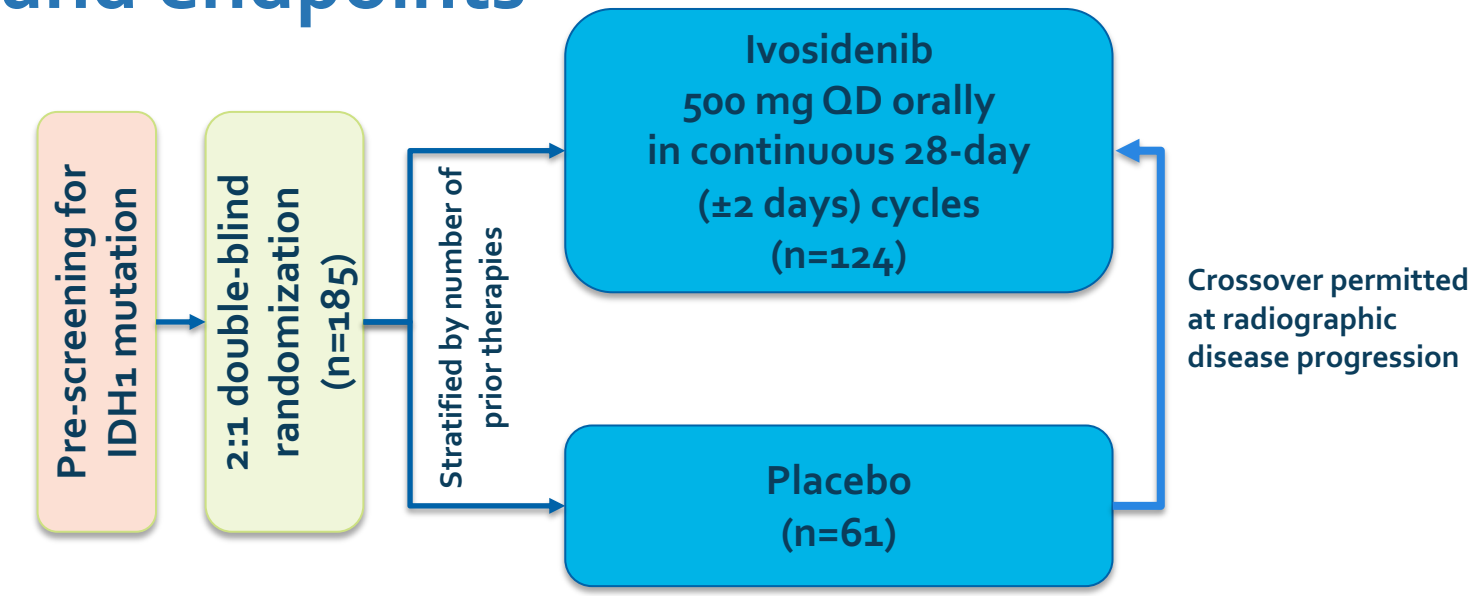
ClarIDHy: Study design and endpoints

Key eligibility criteria

- ≥18 years of age
- Histologically confirmed diagnosis of cholangiocarcinoma
- Centrally confirmed mIDH1* status by NGS
- ECOG PS score 0 or 1
- 1-2 prior therapies (at least 1 gemcitabine- or 5-FU-containing regimen)
- Measurable lesion as defined by RECIST v1.1
- Adequate hematologic, hepatic, and renal function

NCT02989857



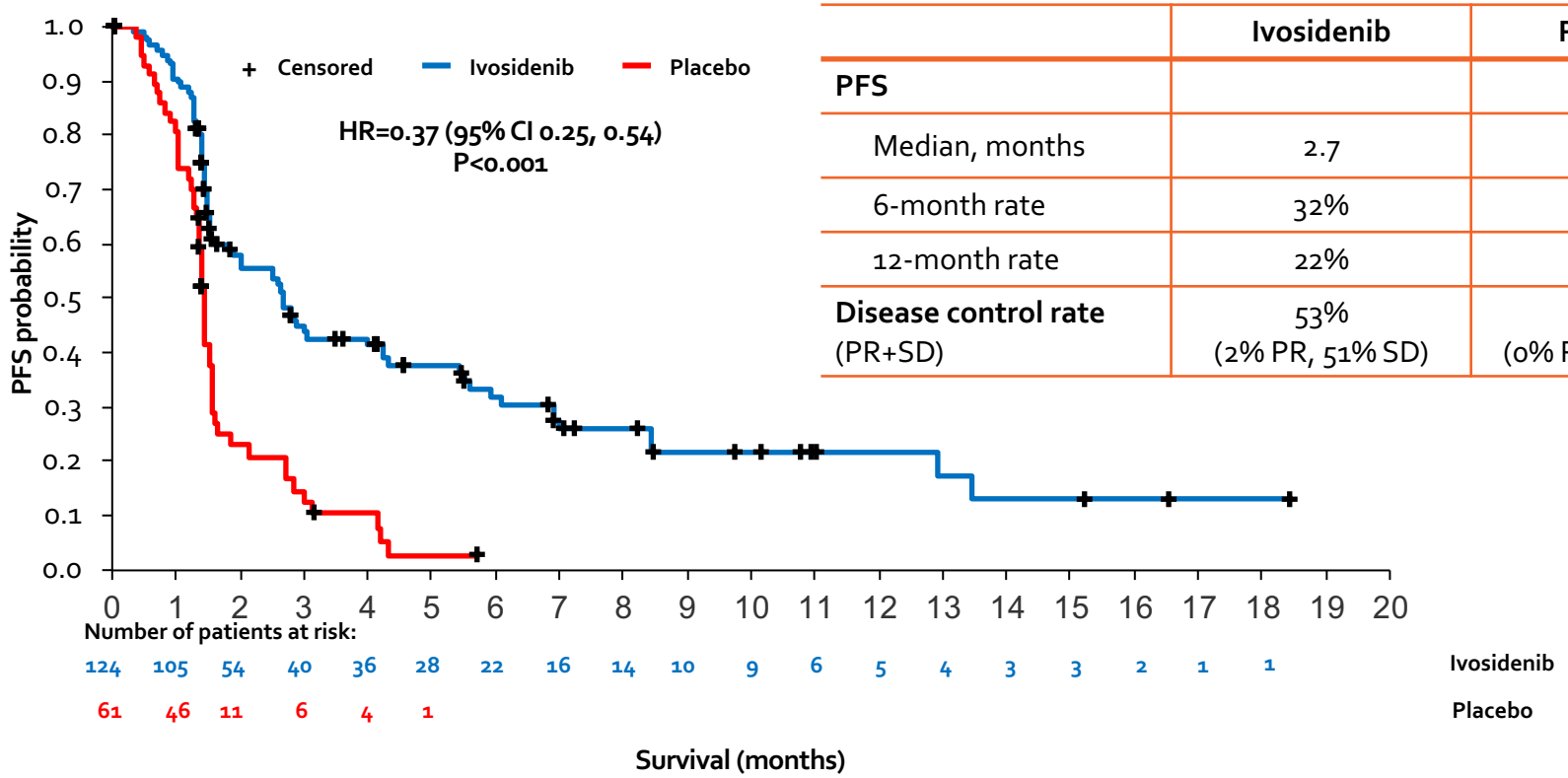
An independent data monitoring committee monitored the safety data throughout the study

- **Primary endpoint:** PFS by blinded independent radiology center (IRC)
- **Secondary endpoints included:** safety and tolerability; PFS by local review; OS; objective response rate; quality of life (QoL)†; pharmacokinetics/pharmacodynamics
- Sample size of ~186 patients based on hazard ratio (HR)=0.5, 96% power, 1-sided alpha=0.025
- 780 patients were screened for IDH1 mutations across 49 sites and 6 countries

*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.
†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. ESMO 2019

ClarIDHy: PFS by IRC



	Ivosidenib	Placebo
PFS		
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)

NE=not estimable; PR=partial response; SD=stable disease.

Abou-Alfa, GK, et al. ESMO 2019

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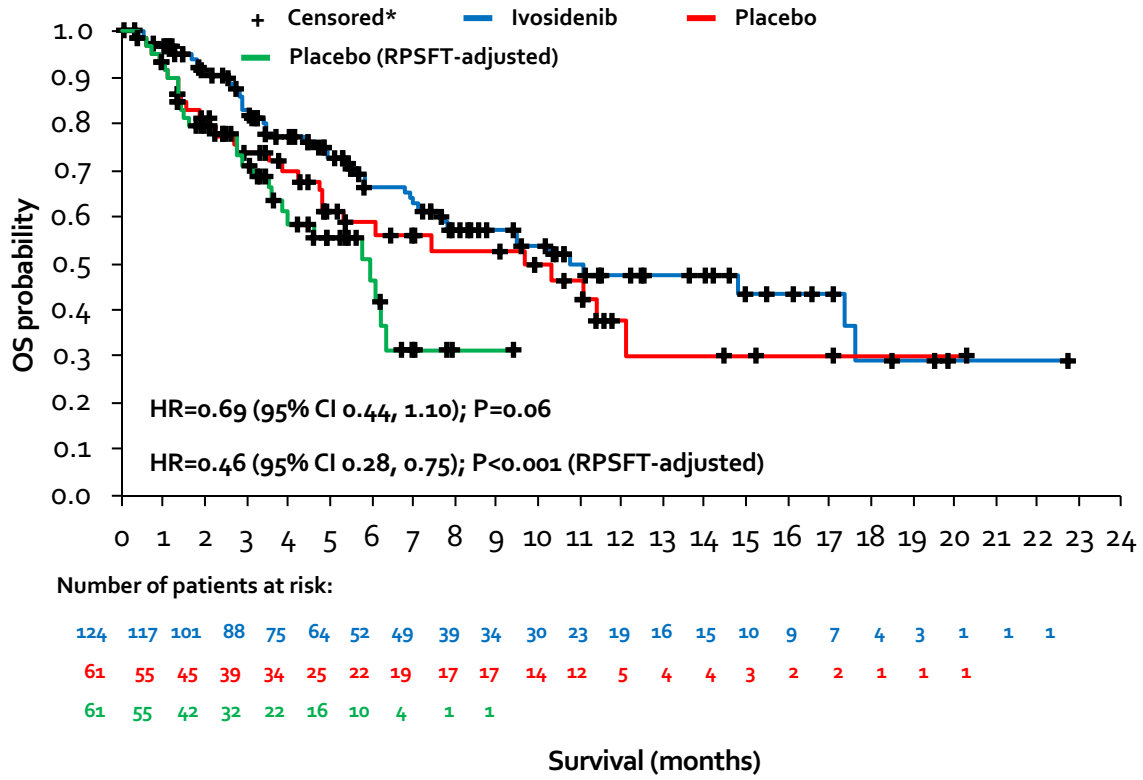
ClarIDHy: OS by intent-to-treat (ITT)

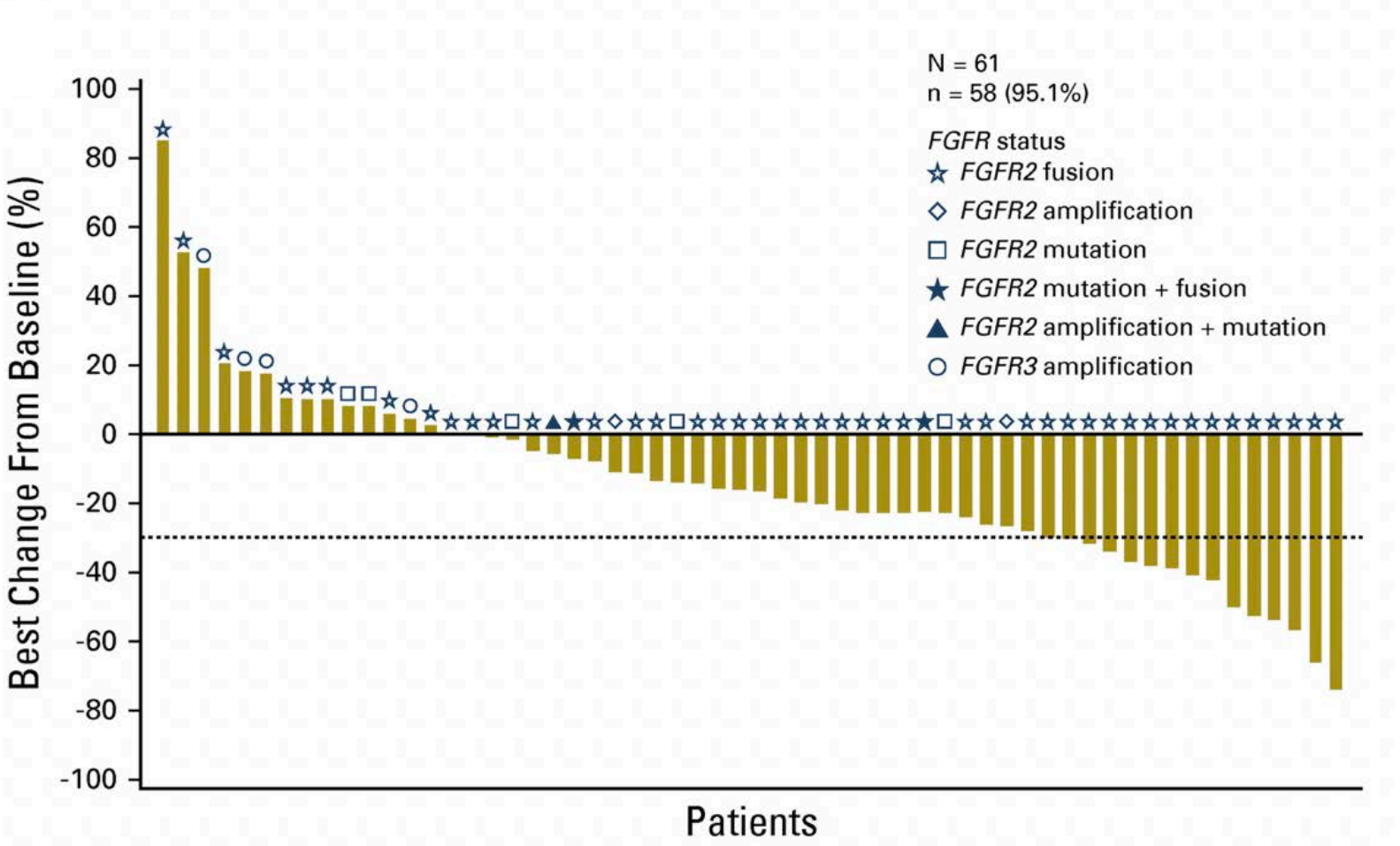


- Median OS based on 78 events was numerically longer with ivosidenib than placebo (10.8 vs. 9.7 months)
  - OS rates at 6 and 12 months for ivosidenib: 67% and 48% vs. 59% and 38% for placebo
- Rank-preserving structural failure time (RPSFT)[1,2] method used to reconstruct the survival curve for the placebo subjects as if they had never crossed over to ivosidenib
- With the RPSFT method, the median OS with placebo adjusts to 6 months

*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.

1. Watkins C, et al. *Pharm Stat*. 2013;12:348-357. **2.** Robins JM, Tsiatis AA. *Commun Stat Theory Methods*. 1991;20:2609-2631.

BGJ398 in FGFR-Altered Cholangiocarcinoma



Javle, M. et al. *Journal of Clinical Oncology* 2018;36:276-282.

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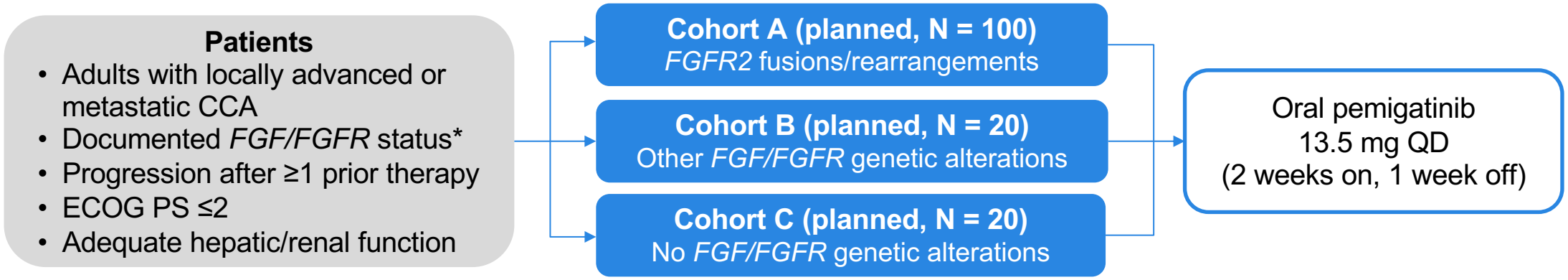
FIGHT-202 STUDY DESIGN

- **Phase 2 open-label, single-arm study evaluating the efficacy and safety of pemigatinib in patients with previously treated locally advanced or metastatic CCA (NCT02924376)**
  - **Sites opened in the United States, Europe, Middle East, and Asia**



Primary endpoint: Confirmed ORR in cohort A by independent central review
Secondary endpoints: ORR in cohorts B, A + B, and C; duration of response, disease control rate, PFS, OS, and safety in all cohorts

- Data cutoff date: March 22, 2019

* Patients prescreened for *FGF/FGFR* status, documented either centrally (FoundationOne®, Foundation Medicine), based on local assessment, or an existing Foundation Medicine report. Retrospective central confirmation of locally documented *FGF/FGFR* status was required.

Vogel, A, ESMO 2019

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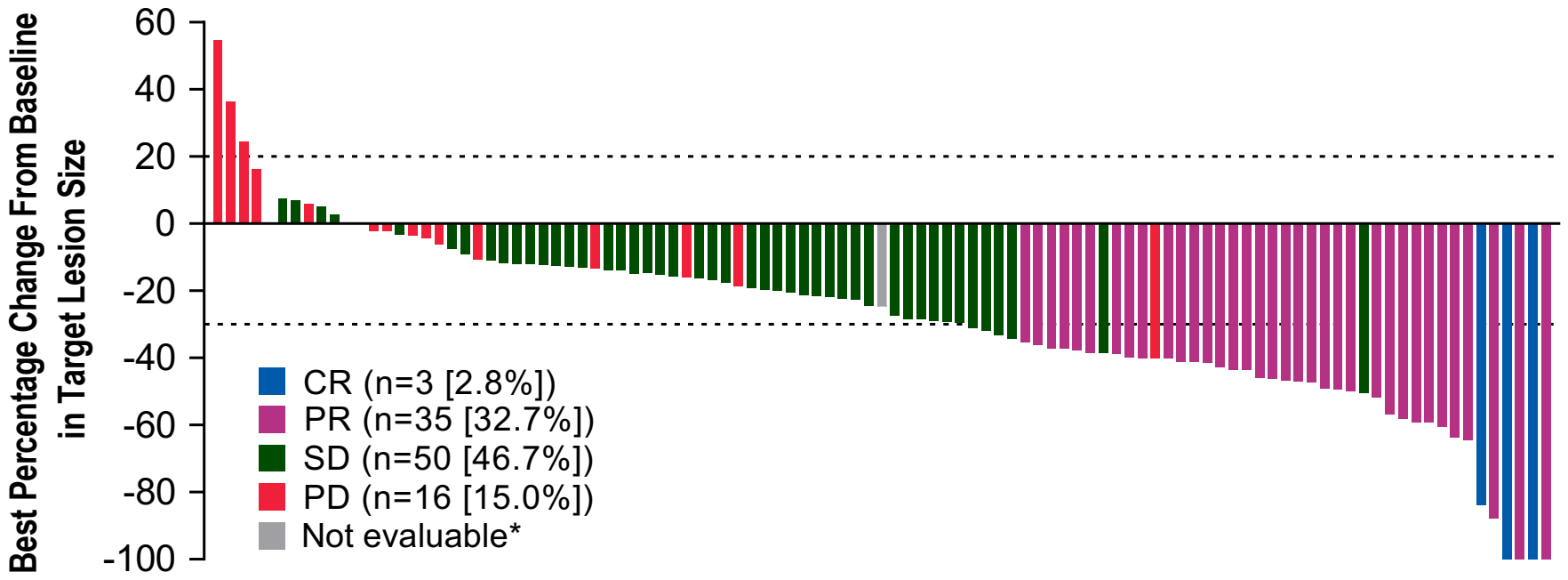
Pemigatinib in FGFR2 Altered Cholangiocarcinoma



Colored bars: confirmed responses per RECIST.
* Patient had decrease in target lesion size but was not evaluable for response per RECIST.

Vogel, A, ESMO 2019

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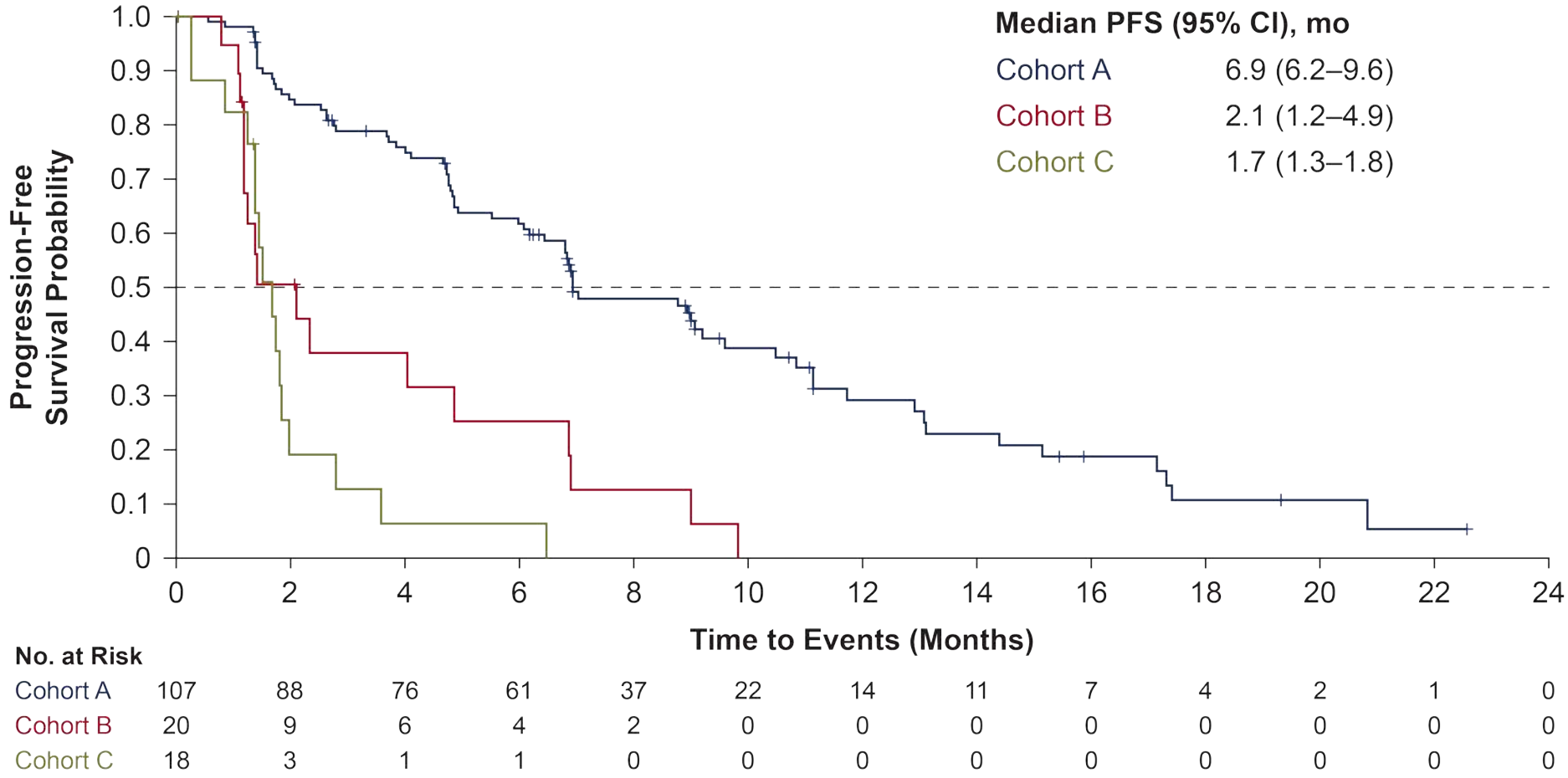
PROGRESSION-FREE SURVIVAL



The study was not designed to compare cohorts.

Vogel, A, ESMO 2019

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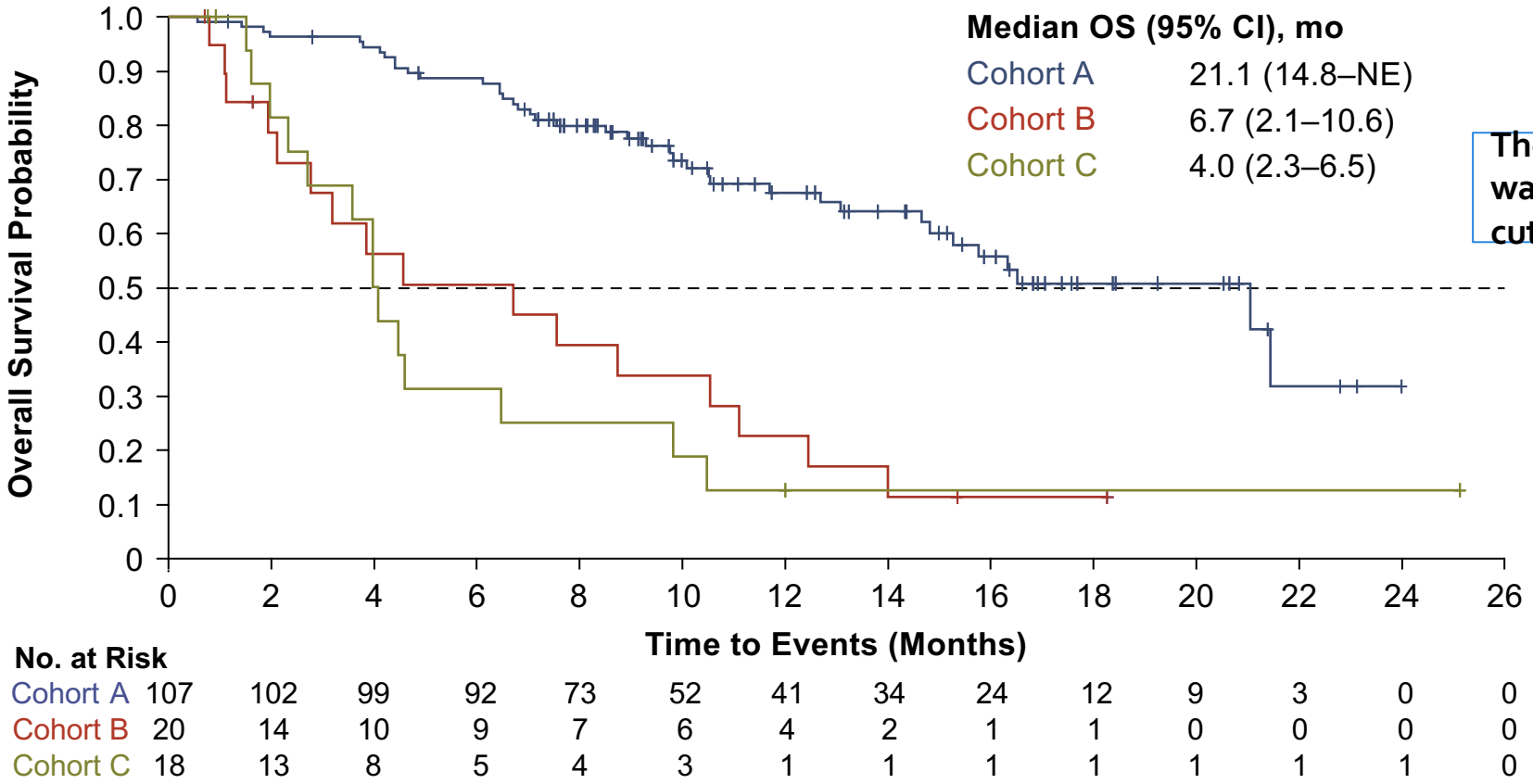
OVERALL SURVIVAL



The median OS in cohort A was not mature at the data cutoff

	Cohort A	Cohort B	Cohort C
Median (range) duration of follow-up, mo	15.4 (7.0–24.7)	19.9 (16.2–23.5)	24.2 (22.0–26.1)
Median (range) duration of treatment, mo	7.2 (0.2–24.0)	1.4 (0.2–12.9)	1.3 (0.2–4.7)

The study was not designed to compare cohorts.

Vogel, A, ESMO 2019

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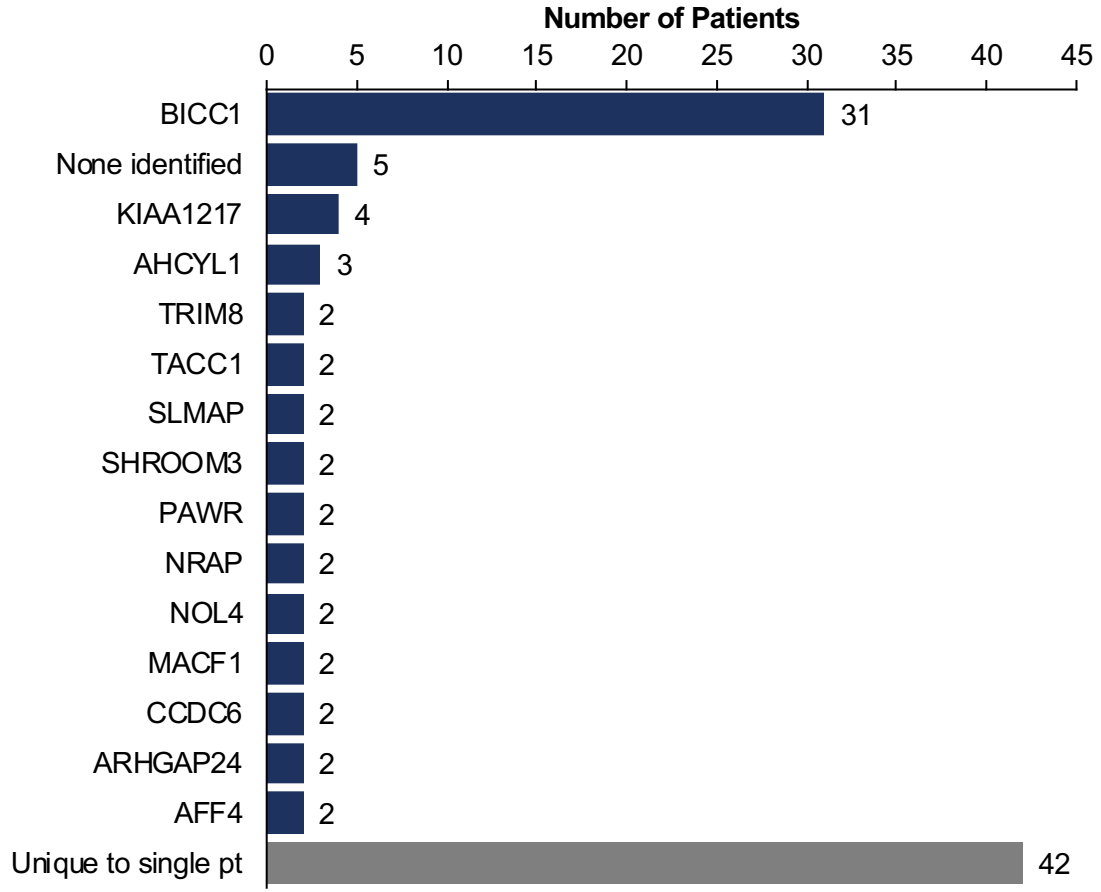
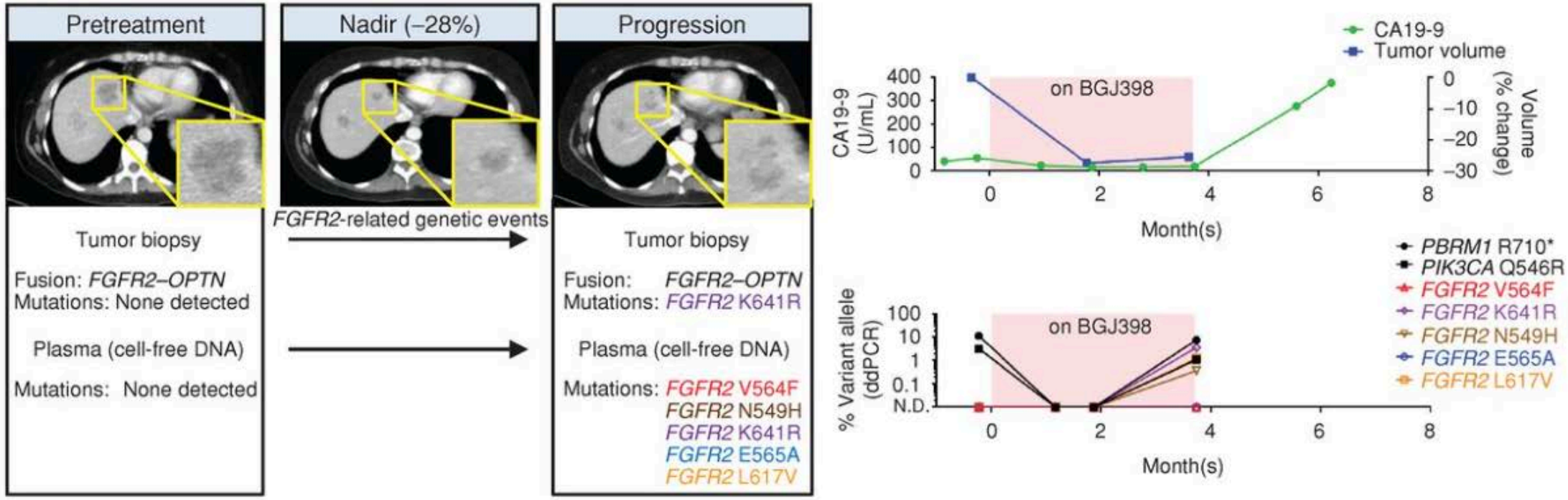
FGFR2 FUSIONS/REARRANGEMENTS (COHORT A)



- Fusions are a product of chromosomal rearrangement
  - Consistent with Foundation Medicine terminology, rearrangements are classified as fusions if the partner gene is previously described or in-frame
- Among 107 patients in cohort A:
  - 92 fusions; 15 rearrangements
  - 56 different partner genes
  - 42 partners unique to single patients
  - Most common:
    - *BICC1* (29%)
    - No partner identified (5%)

Vogel, A, ESMO 2019

Polyclonal Secondary *FGFR2* Mutations Drive Acquired Resistance to FGFR Inhibition



Goyal L, et al. Cancer Discov. 2017 Mar;7(3):252-263.

FGF Landscape

Drug	Target	Indication	Status
Infigratinib (BGJ398)	FGFR1-3 TKI	Cholangiocarcinoma	First line Phase III
Pemigatinib	FGFR1-3 TKI	Cholangiocarcinoma	First line Phase III
TAS-120	Pan-FGFR TKI	Solid tumors	Phase I
Derazantinib (ARQ 087)	Pan-FGFR TKI	Cholangiocarcinoma	Phase II
Debio 1347	Pan-FGFR TKI	Solid tumors	

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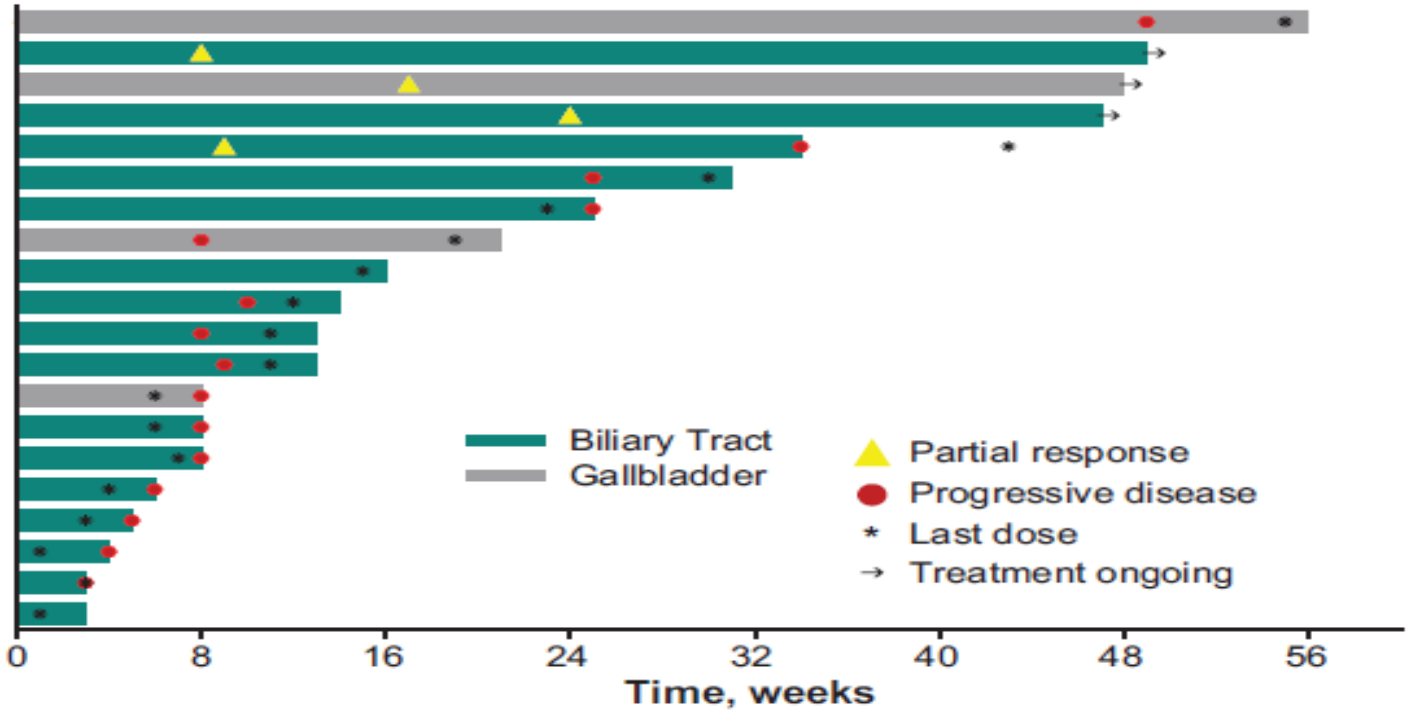
KEYNOTE-028 Phase 1b: Pembrolizumab and Bile Duct Cancers

Figure 4. Duration of exposure to pembrolizumab and summary of best overall response assessed per RECIST v1.1 by investigator review in patients who had ≥1 postbaseline tumor assessment (n = 20).



ORR = 17.4 % (95% CI, 5-39) SD = 17.4% (95% CI, 5-39) The majority of patients progress rapidly

Bang et al. ESMO 2015

Conclusions

- Advanced cholangiocarcinoma systemic therapies are evolving beyond standard chemotherapy
- Next generation sequencing helped delineate genetic alterations that are targetable
- IDH1 ivosidenib has shown an improvement in PFS and OS (when adjusting for crossover using the RPSFT method) vs. placebo
- Infigratinib showed RR of 18.8% and pemigatinib treatment resulted in 35.5% RR with durable response and a median PFS of 6.9 months
- First line efforts underway
- Checkpoint inhibitors deserve further evaluation