Biliary Cancers
Targeted therapy

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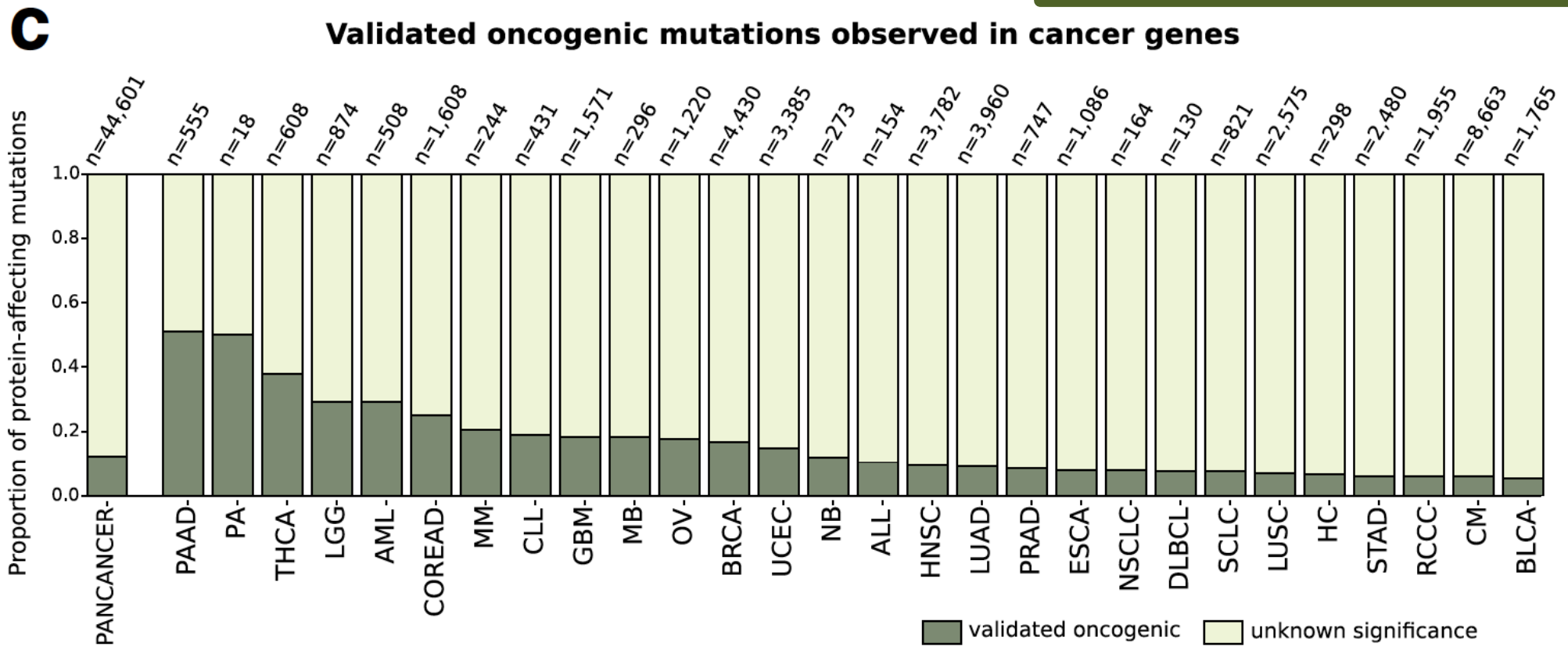
Tamborero *et al. Genome Medicine* (2018) 10:25
https://doi.org/10.1186/s13073-018-0531-8

Genome Medicine

DATABASE Open Access

Cancer Genome Interpreter annotates the biological and clinical relevance of tumor alterations

12% of ~ 7000 tumors of 28 cancer types were validated clinically or experimentally as clinically or potentially clinically relevant variants.



ESCAT

ESMO Scale for Clinical Actionability of Molecular Targets

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

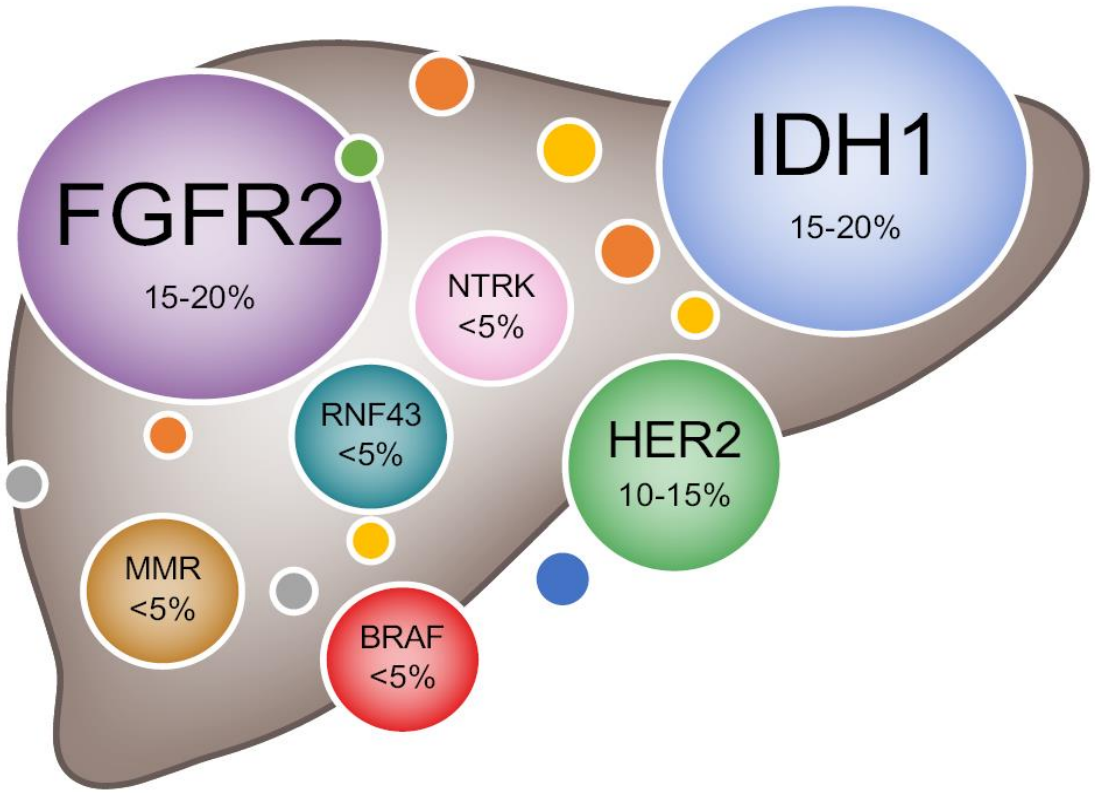


Fig. 4. Current overview of "Precision Medicine" in biliary

Targeted Approaches for BTC

Target	~Frequency in CC	Drug	Benefit	Status
MSI-H/dMMR	3%	Pembrolizumab	ORR 40%[1]	Tumor agnostic approval
TMB >10 mut/Mb	2.4%	Pembrolizumab	ORR 29%[1]	Tumor agnostic approval
NTRK fusion	1%	Larotrectinib	ORR 75%[2]	Tumor agnostic approval
FGFR2 fusion	14% (intrahepatic)	Pemigatinib or infigratinib	ORR 37% (pemigatinib)[3]; 23% (infigratinib)[4]	Cholangiocarcinoma approval
IDH1 mutation	10%-20% (intrahepatic)	Ivosidenib	PFS HR: 0.37[5]	Cholangiocarcinoma approval
BRAF V600E	4%	Dabrafenib/trametinib	ORR 41% (ROAR)[6]	Open-label basket study
HER2	9% of BTC*†	Pertuzumab/trastuzumab	ORR 23% (MyPathway)[7]	Open-label basket study
RET	1%	Pralsetinib	Responses[8]	2/2 PR in basket trial
BRCA1/2, DDR	20%*	PARP inhibitor	Responses reported	Case reports
ROS1	1%	Crizotinib	Response reported	Case reports

Most common in *extrahepatic or †GB.

1. Pembrolizumab PI. 2. Lenvatinib PI. 3. Pemigatinib PI. 4. Infigratinib PI. 5. Ivosidenib PI. 6. Subbiah. Lancet Oncol. 2020;21:1234.
7. Javle. Lancet Oncol. 2021;22:1290. 8. Subbiah. ASCO 2020. Abstr 109. Thornblade. Cancers (Basel). 2021;13:4062.

Targeted Approaches for BTC – ESCAT tier 1

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Somatic *IDH1* and *IDH2* Gene Mutations in Malignancy

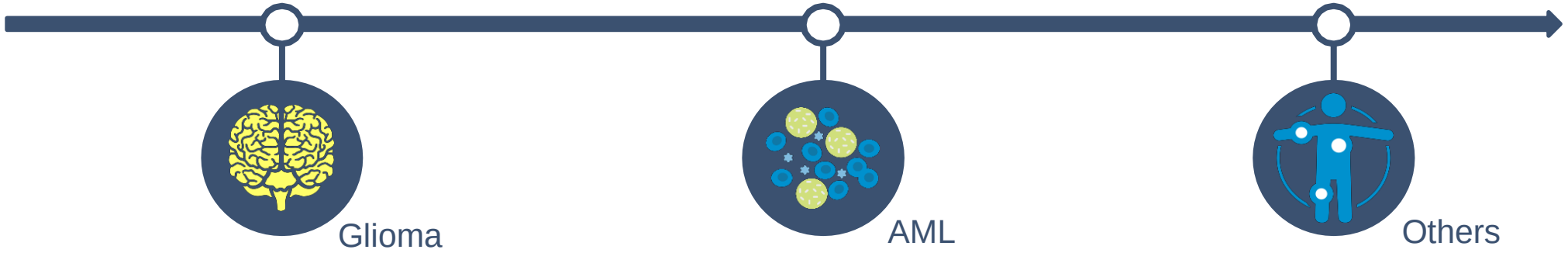
Genome-wide mutation analysis first identified somatic mutation hot-spots in *IDH1* and *IDH2* genes in glioma[2,3]

- Grade 2/3 astrocytomas and oligodendrogliomas
- Secondary glioblastomas

IDH1 and *IDH2* gene mutations discovered in AML[4–6]

Additional hematologic and solid tumors harboring *IDH1* and *IDH2*[a] gene mutations continue to be *identified*[7]

First described in CCA in 2012



[a]Cancer-associated mutations in *IDH3* have not been observed.[8,9] AML, acute myeloid leukemia; IDH, isocitrate dehydrogenase.

1. Hanahan D, Weinberg RA. *Cell*. 2011;144(5):646–674. 2. Yan H, et al. *N Engl J Med.* 2009;360(8):765–773. 3. Parsons DW, et al. *Science.* 2008;321(5897):807–812. 4. Mardis ER, et al. *N Engl J Med.* 2009;361(11):1058–1066. 5. Paschka P, et al. *J Clin Oncol.* 2010;28(22):3636–3643.

6. Marcucci G, et al. *J Clin Oncol.* 2010;28(14):2348–2355. 7. Losman JA, et al. *Genes Dev.* 2013;27(8):836–852. 8. Krell D, et al. *PLoS One.* 2011;6(5):e19868. 9. Reitman ZJ, Yan H. *J Natl Cancer Inst.* 2010;102(13):932–941.

Isocitrate dehydrogenase IDH

- Essential metabolic enzyme for cellular respiration - Krebs cycle.
- IDH1 > IDH2 and both mutually exclusive.
- More in iCCA.
- More described in fluke negative CCA could explain why IDH more frequent in non-Asian centers than in Asian-centers (16.5% vs 8.8%). Also negative correlation was also shown for viral hepatitis infection (2% vs 20%).
- The overproduction of 2HG both in tissue and blood has also been described in CCA

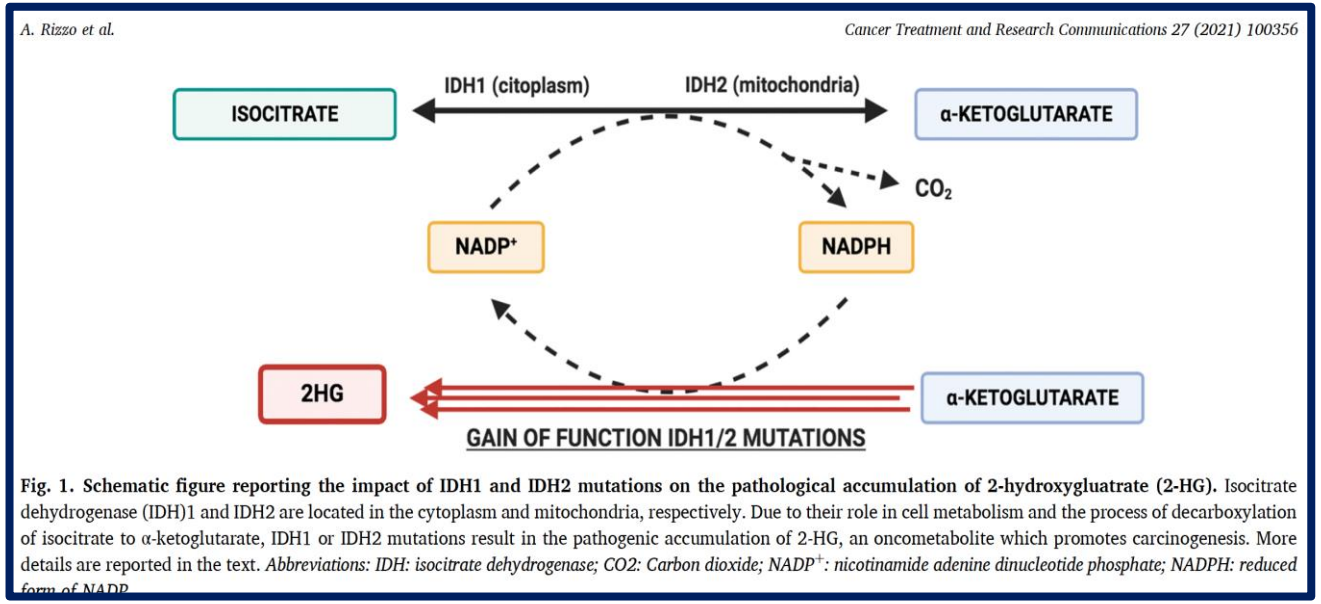
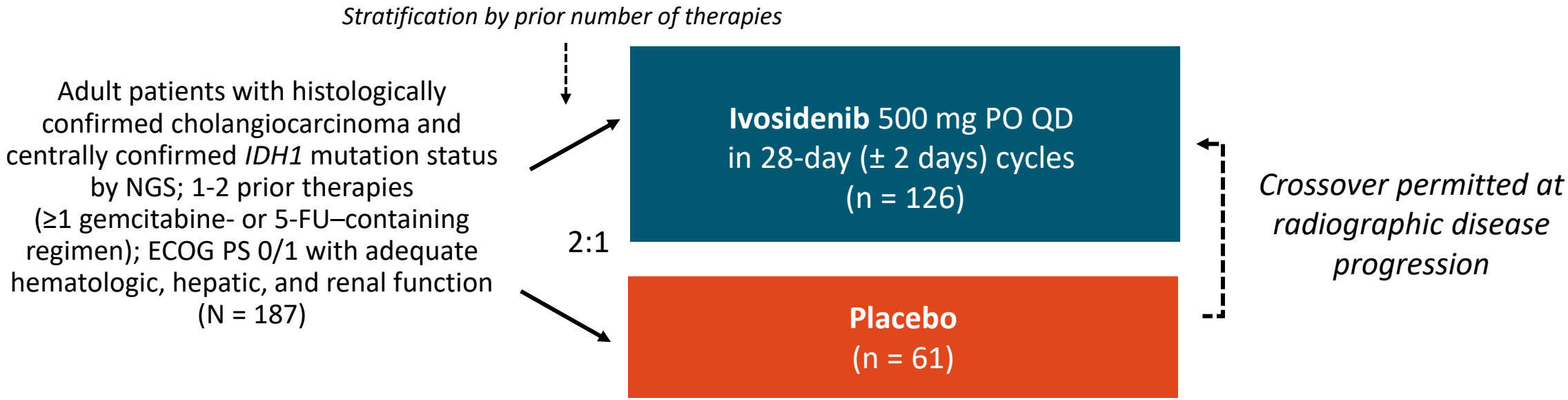


Fig. 1. Schematic figure reporting the impact of IDH1 and IDH2 mutations on the pathological accumulation of 2-hydroxygluatrate (2-HG). Isocitrate dehydrogenase (IDH)1 and IDH2 are located in the cytoplasm and mitochondria, respectively. Due to their role in cell metabolism and the process of decarboxylation of isocitrate to α-ketoglutarate, IDH1 or IDH2 mutations result in the pathogenic accumulation of 2-HG, an oncometabolite which promotes carcinogenesis. More details are reported in the text. *Abbreviations: IDH: isocitrate dehydrogenase; CO2: Carbon dioxide; $NADP^+$: nicotinamide adenine dinucleotide phosphate; NADPH: reduced form of NADP.*

	Chromosome	Ubication	Typical mutation	Targeted drug (approved)	Frequency mutated in CCA
IDH1	2q34	Cytosol Microsomes	R132	Ivosidenib (AG-120)	14%
IDH2	15q26.1	Mitochondria	R172 R140	Enasidenib (AG-221)	4%

ClarIDHy: Ivosidenib vs Placebo in Previously Treated Cholangiocarcinoma With *IDH1* Mutation

- An international, double-blind, randomized phase III trial

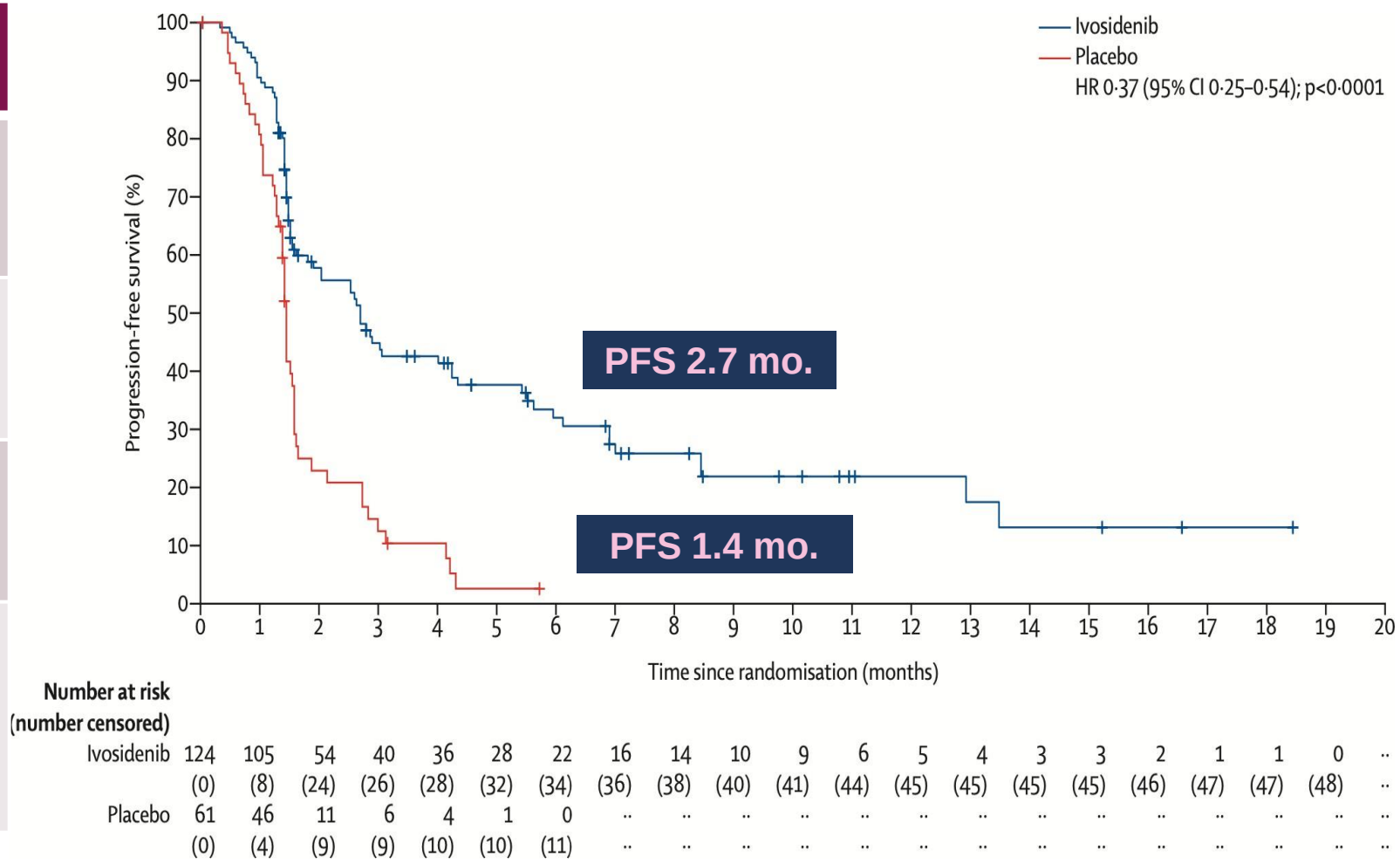


- **Primary endpoint:** PFS by blinded IRC
- **Key secondary endpoints:** PFS by local review, OS, ORR, safety, QoL, PK/PD

Abou-Alfa. Lancet Oncol. 2020;21:796. Zhu. JAMA Oncol. 2021;e213836.

ClarIDHy: Phase III Trial of Ivosidenib in 2L and 3L Intrahepatic Cholangiocarcinoma

	Ivosidenib	Placebo
mPFS, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
DCR (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)



Abou Alfa et al, *Lancet Oncol* 2020

ClarIDHy: TEAEs in >15% of Patients

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

Most Common Grade ≥3 TEAEs, %	Total Ivosidenib* (n = 166)	Placebo (n = 59)
Any	53.0	37.3
Ascites	9.0	6.8
Anemia	7.2	0
Bilirubin increase	5.4	1.7

- TEAEs leading to discontinuation more common for placebo vs total ivosidenib (8.5% vs 6.6%)
- TEAEs leading to dose reductions (3.0% vs 0%) and interruptions (30.1% vs 18.6%) were more common for total ivosidenib vs placebo

*Includes 43 patients who crossed over from placebo arm to receive ivosidenib upon PD.

Abou-Alfa. Lancet Oncol. 2020;21:796. Zhu. ASCO GI 2021. Abstr 266.

Ivosidenib (FDA approved for IDH1 mutant cholangiocarcinoma on 25Aug2021)

INDICATION

- Adult patients with a susceptible IDH1 mutation as detected by an FDAapproved test with locally advanced or metastatic cholangiocarcinoma who have been previously treated

WARNING

- QTc interval prolongation
- Guillain-Barré síndrome

Dosing

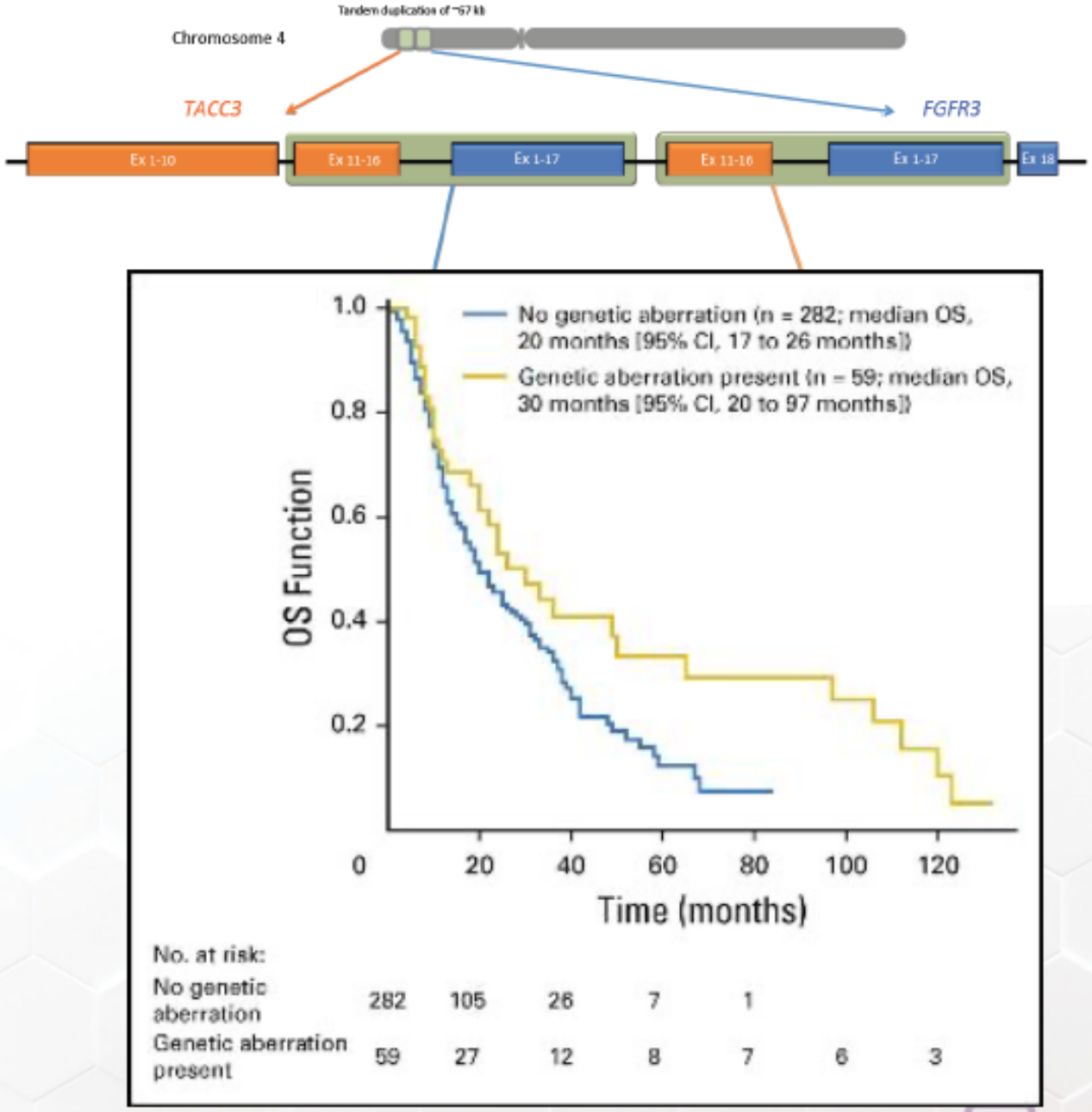
- 500 mg orally once daily with or without food until disease progression or unacceptable toxicity; avoid a high-fat meal

Adverse Events (incidence ≥15%)

- Fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, rash

FGFR2 Fusion

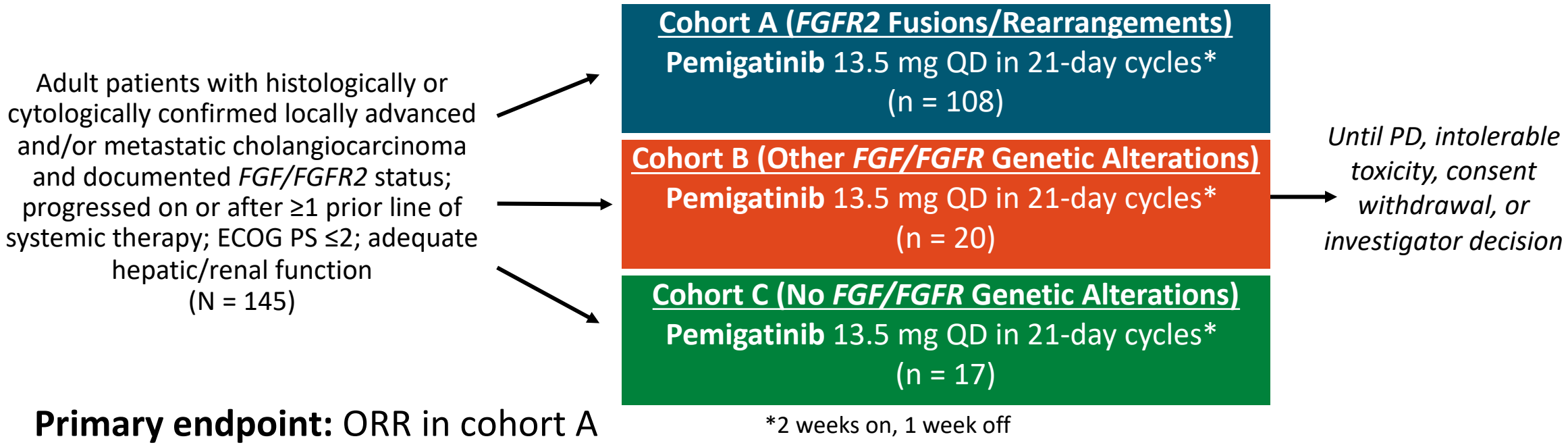
- Seen in approximately 10-15% iCCA
- Tested in multiple trials
- Prognostic



Jain A, et al. *JCO Precis Oncol.* 2018;2:1-12.

FIGHT-202: Pemigatinib in Previously Treated Cholangiocarcinoma With *FGFR2* Fusions

- A multicenter, open-label, multicohort, single-arm phase II trial



- **Primary endpoint:** ORR in cohort A
- **Key secondary endpoints:** ORR in cohorts B, A + B, and C; DoR; DCR; safety; PFS; OS in all cohorts

Abou-Alfa. Lancet Oncol. 2020;21:671. Abou-Alfa. ASCO 2021. Abstr 4086.

Pemigatinib in Previously Treated Cholangiocarcinoma (FIGHT-202): Updated Safety and Efficacy Results

TEAE in ≥25%, n (%)	N = 147	
	All Grades	Grade 3/4
Hyperphosphatemia	86 (58.5)	0
Alopecia	73 (49.7)	0
Diarrhea	69 (46.9)	5 (3.4)
Fatigue	64 (43.5)	8 (5.4)
Nausea	61 (41.5)	3 (2.0)
Dysgeusia	60 (40.8)	0
Stomatitis	55 (37.4)	9 (6.1)
Constipation	54 (36.7)	1 (0.7)
Decreased appetite	50 (34.0)	3 (2.0)
Dry mouth	50 (34.0)	0
Vomiting	43 (29.3)	2 (1.4)
Dry eye	41 (27.9)	1 (0.7)
Arthralgia	38 (25.9)	9 (6.1)

Efficacy Outcome, Cohort A	N = 108
ORR, % (95% CI)	37.0 (27.9-46.9)
▪ CR, n (%)	4 (3.7)
▪ PR, n (%)	36 (33.3)
▪ SD, n (%)	49 (45.4)
▪ PD, n (%)	16 (14.8)
▪ NE, n (%)	3 (2.8)
DCR, % (95% CI)	82.4 (73.9-89.1)
Median DoR, mo (95% CI)	8.1 (5.7-13.1)
Median PFS, mo (95% CI)	7.0 (6.1-10.5)
Median OS, mo (95% CI)	17.5 (14.4-23.0)

- **Other observed toxicities**
  - Nail changes (discoloration, breakage, separation from nail bed)
  - Ocular disorder (including serious retinal detachment)
  - Hand–foot syndrome (late toxicity)
  - GI toxicities

Abou-Alfa. ASCO 2021. Abstr 4086.

Slide credit: clinicaloptions.com

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April 2020:
FDA Approval of pemigatinib for patients with FGFR2 fusion positive advanced cholangiocarcinoma

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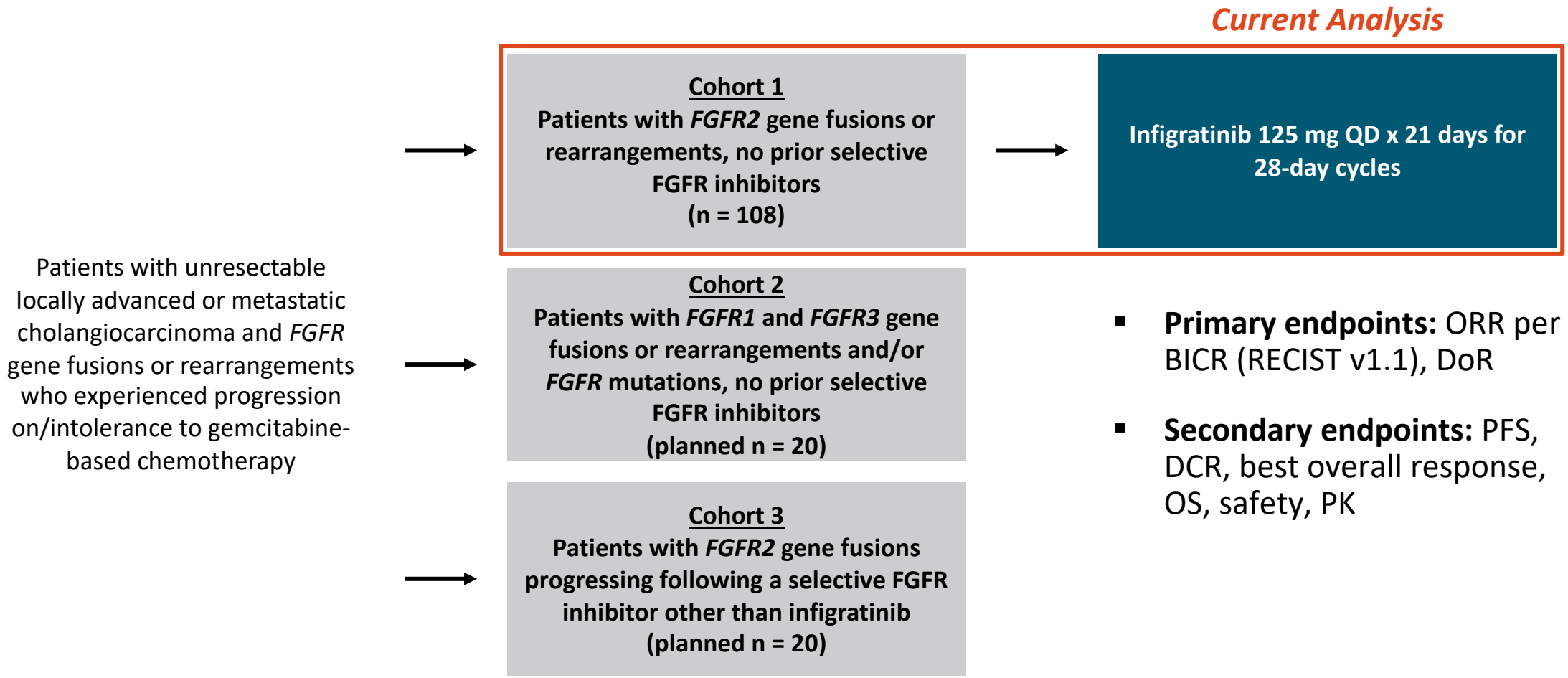
- Ocular disorder (including serious retinal detachment)
- Hand–foot syndrome (late toxicity)
- GI toxicities

Abou-Alfa. ASCO 2021. Abstr 4086.

Slide credit: clinicaloptions.com

Infigratinib for Advanced Cholangiocarcinoma With *FGFR2* Fusion/Rearrangement

- Open-label, single-arm phase II trial



- **Primary endpoints:** ORR per BICR (RECIST v1.1), DoR
- **Secondary endpoints:** PFS, DCR, best overall response, OS, safety, PK

Javle. Lancet Gastroenterol Hepatol. 2021;6:803. Javle. ASCO GI 2021. Abstr 265.

Slide credit: clinicaloptions.com

Infigratinib in Advanced Cholangiocarcinoma With *FGFR2* Fusion/Rearrangement: Efficacy

Efficacy Outcome	Infigratinib (n = 108)
Confirmed ORR, % ▪ CR, n (%) ▪ PR, n (%) ▪ SD, n (%) ▪ PD, n (%)	23.1* 1 (1) 24 (22) 66 (61) 11 (10)
Median TTR, mo (range)	3.6 (1.8-3.8)
DCR, % (95% CI)	84.3 (76.0-90.6)
Median DoR, mo (range)	5.0 (3.7-9.3)
Median PFS, mo (range)	7.3 (5.6-7.6)
Median OS, mo	12.2 (10.7-14.9)

*ORR higher with ≤1 vs ≥2 prior lines (34.0% vs 13.8%).

Javle. Lancet Gastroenterol Hepatol. 2021;6:803. Javle. ASCO GI 2021. Abstr 265.

Infigratinib in Advanced Cholangiocarcinoma With *FGFR2* Fusion/Rearrangement: Efficacy

Efficacy Outcome	Infigratinib (n = 108)
Confirmed ORR, %	23.1*
▪ CR, n (%)	
▪ PR, n (%)	
▪ SD, n (%)	
▪ PD, n (%	
Median TTR	.8)
DCR, % (95%	90.6)
Median DoR	.3)
Median PFS	.6)
Median OS, mo	12.2 (10.7-14.9)

May 2021:
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Javle. Lancet Gastroenterol Hepatol. 2021;6:803. Javle. ASCO GI 2021. Abstr 265.

FGFR inhibitors in *FGFR2* fusion-positive cholangiocarcinoma

	Infigratinib (N = 108)	Pemigatinib (N = 107; Cohort A)	Futibatinib; TAS 120 (N = 45)[a]	Deranzantinib (N = 29)	Erdafitinib (N = 7)
Patient demographics					
Prior treatment lines, % 1 2 3+	 46 30 24	 51 32 17	 29 29 42	 52 35 13	 36 36 27
Stage IV at enrollment, %	99	66	Not reported	62	Not reported
Outcomes					
ORR, %	23 2L: 34 3L+: 18	35.5	25.0	20.7	57.1
DCR, %	84	82	78.6	82.8	100
mPFS, mo	7.3	6.9	Not reported	5.7	5.6[b]
mOS, mo	12.2	21.1	Not reported	Not reached	Not reported

[a]*FGFR* alteration. [b]Includes four nonfusion patients.

1. Javle M, et al. Presented at GIASCO 2021; 2. Hollebecque A, et al. *Ann Oncol* 2018;29(suppl 8):viii205–viii270; 3. Saleh M, et al. *Mol Cancer Ther* 2018;17(1 suppl): Abstract A098; 4. Mazzaferro V, et al. *J Clin Oncol* 2017;35(15 suppl):4017; 5. Mazzaferro V, et al. *Br J Cancer* 2019;120:165–171; 6. Goyal L, et al. *Ann Oncol* 2017;28(suppl 3): Abstract O-020; 7. Kuboki Y, et al. *Ann Oncol* 2017;28(suppl 5):mdx367.006. 8. Meric-Bernstam F, et al. Presented at ESMO 2018 Congress. Abstract O-001; 9. Chen Y-Y, et al. *Ann Oncol* 2018;29:mdy282.008

Adverse events associated with FGFR inhibition

AEs nonspecific for FGFR signaling pathway inhibition

- Fatigue, anorexia, pyrexia
- Gastrointestinal disorders
- Arthralgia
- Liver toxicity
- AEs related to VEGFR inhibition
  - Hypertension
  - Proteinuria
  - Thrombotic microangiopathy
  - Hypothyroidism

AEs specific for FGFR signaling pathway inhibition

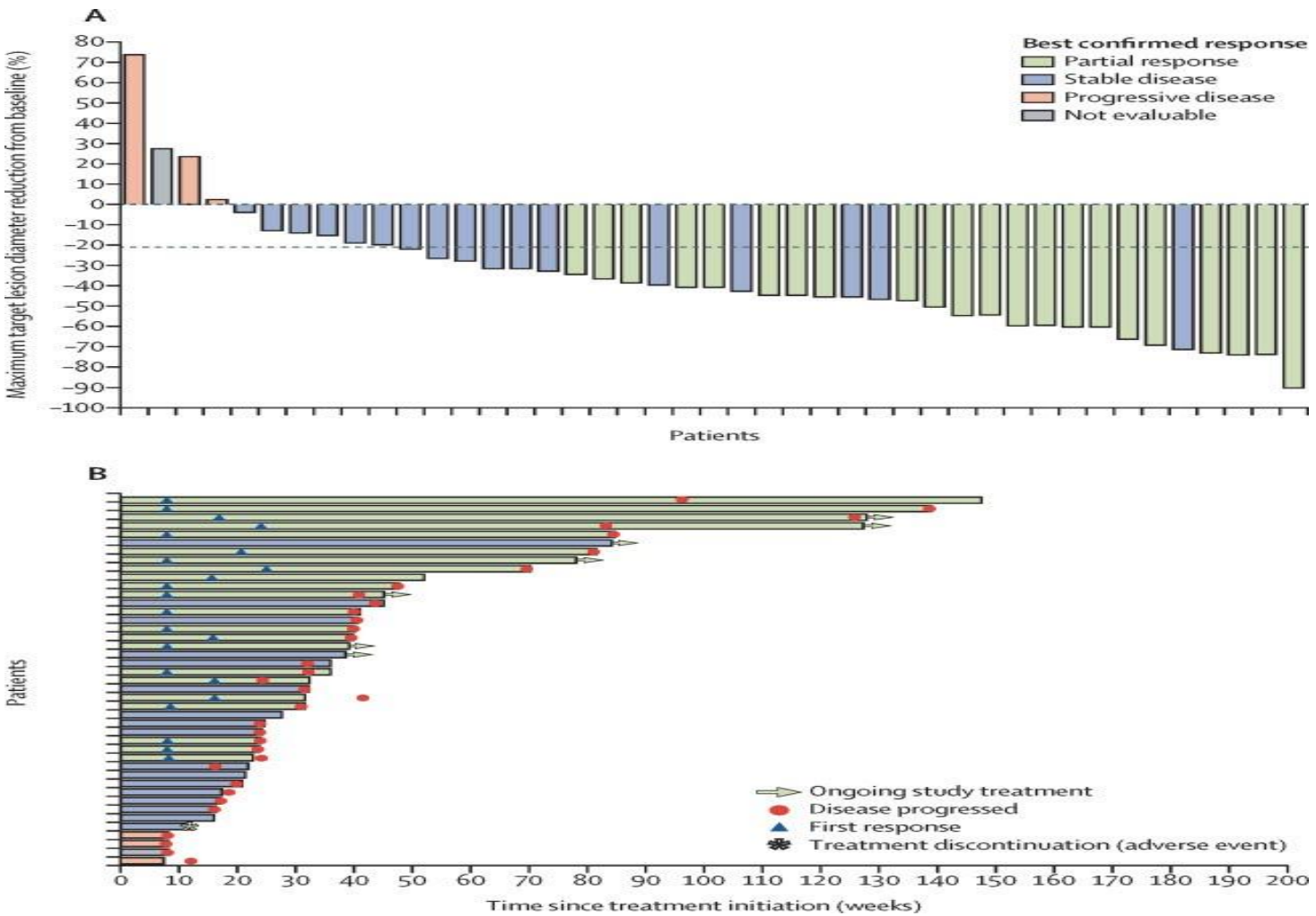
- Hyperphosphatemia
- Nail changes with onycholysis
- Alopecia, hair modification
- Mucosal dryness, dysgeusia, mucositis
- Dry eye, conjunctivitis, keratitis
- Asymptomatic retinal pigment epithelial detachment
- Osteoarticular pains, myalgias, muscle cramps

Touat M, et al. *Clin Cancer Res* 2015;21:2684–2694

BRAF V600E mutated cholangiocarcinoma (ROAR study): 43 patients

Efficacy of Dabrafenib + Trametinib

ORR: 47%

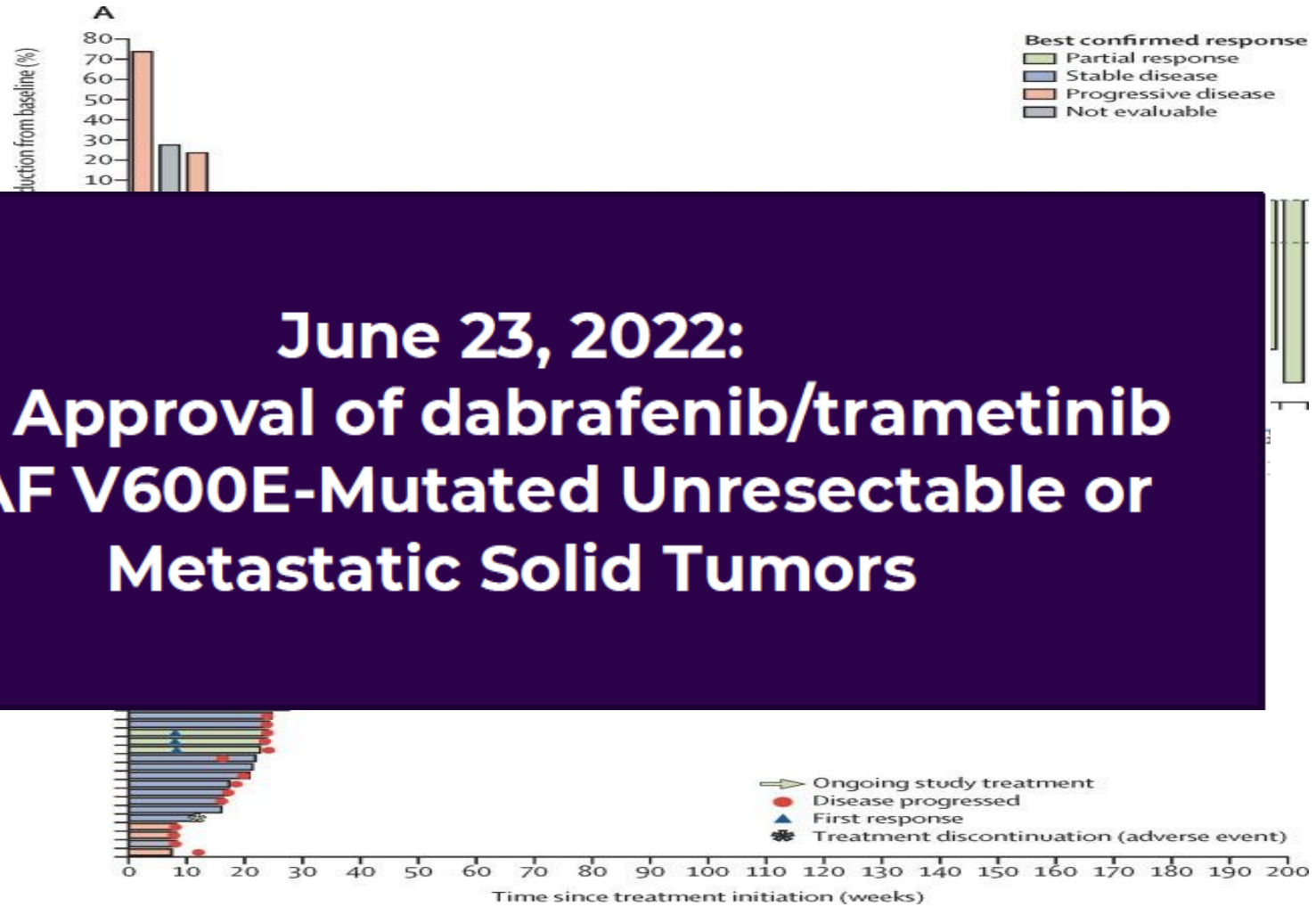


Subbiah V, et al. *Lancet Oncol* 2020;21:1234–1243

BRAF V600E mutated cholangiocarcinoma (ROAR study): 43 patients

Efficacy of Dabrafenib + T

ORR: 47



June 23, 2022:
FDA Approval of dabrafenib/trametinib BRAF V600E-Mutated Unresectable or Metastatic Solid Tumors

Subbiah V, et al. *Lancet Oncol* 2020;21:1234–1243

Conclusion

- Genomic profiling has shifted the paradigm in the management of cancer in the last few years and BTC are not an exception.
- Magnitude of benefit is not very impressive and apparently the C-kit targeted imatinib module in GIST could not be repeated.
- Primary and secondary resistance are substantial and predictive markers.
- Liquid biopsy (ctDNA) needs to be quickly validated and be commercially available to overcome the pressing needs in the routine practice.
- Dilemma is still ongoing in the second line setting: chemotherapy vs. targeted therapy.