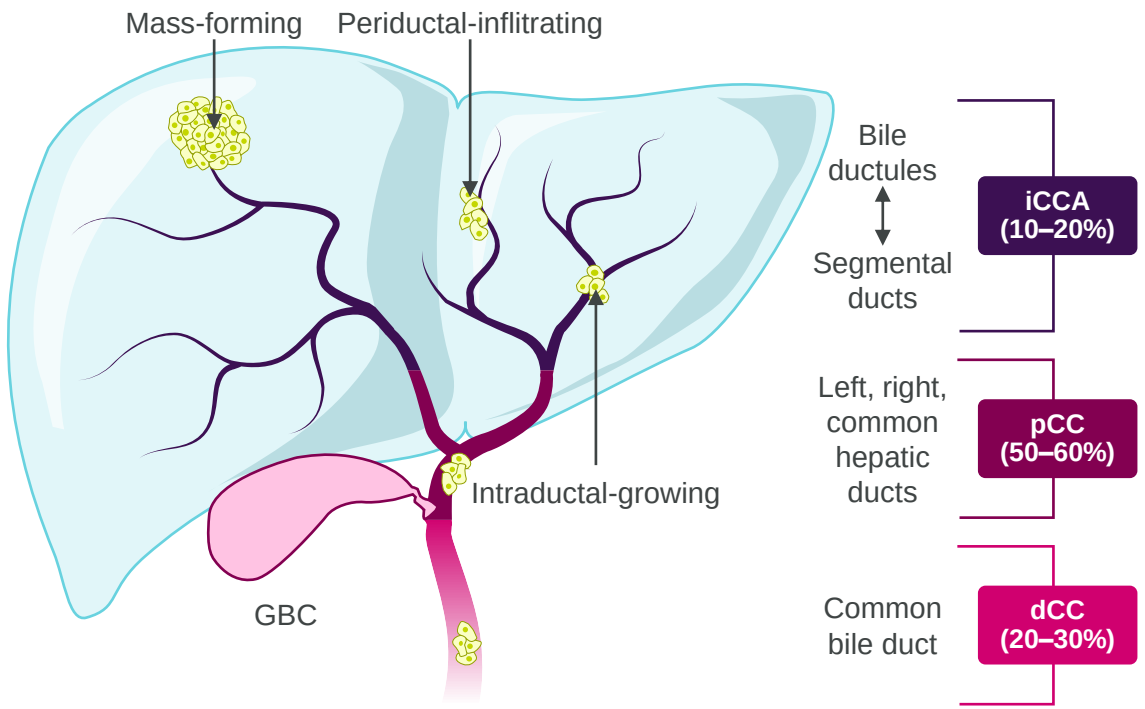
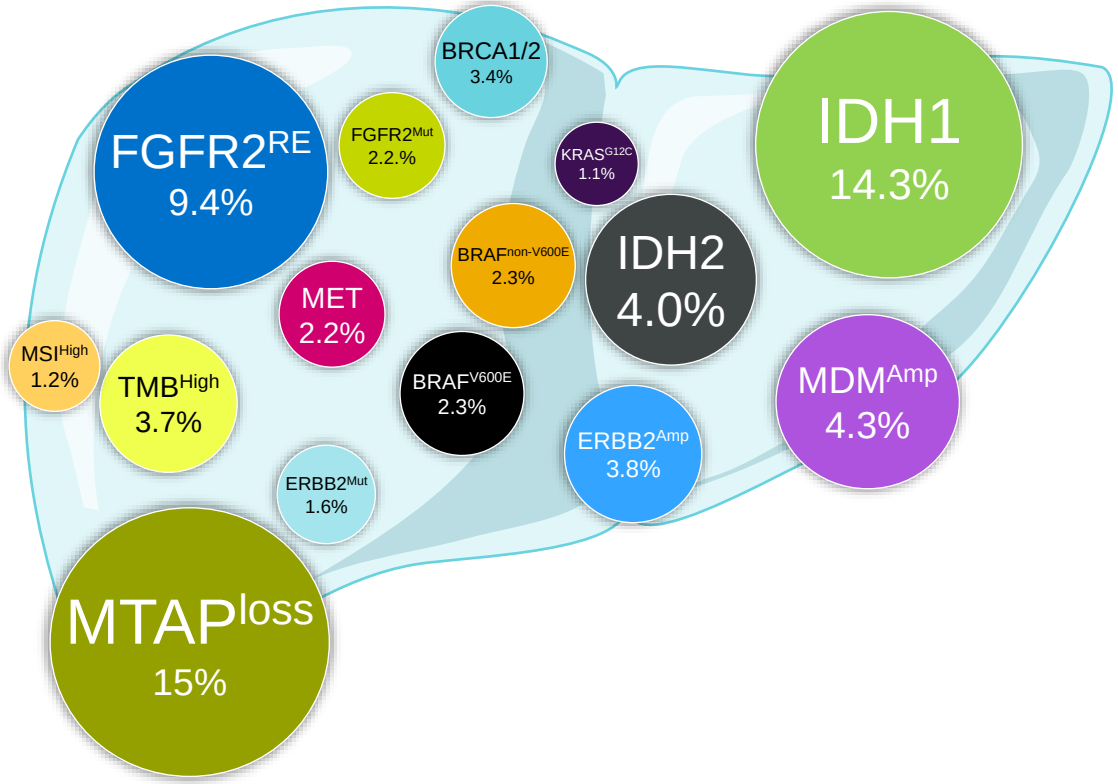
Molekulare Sequenzierung bei hepatobiliären Tumoren: Wann, wie und was tun?

BTCs: a heterogeneous disease entity

Anatomic heterogeneity



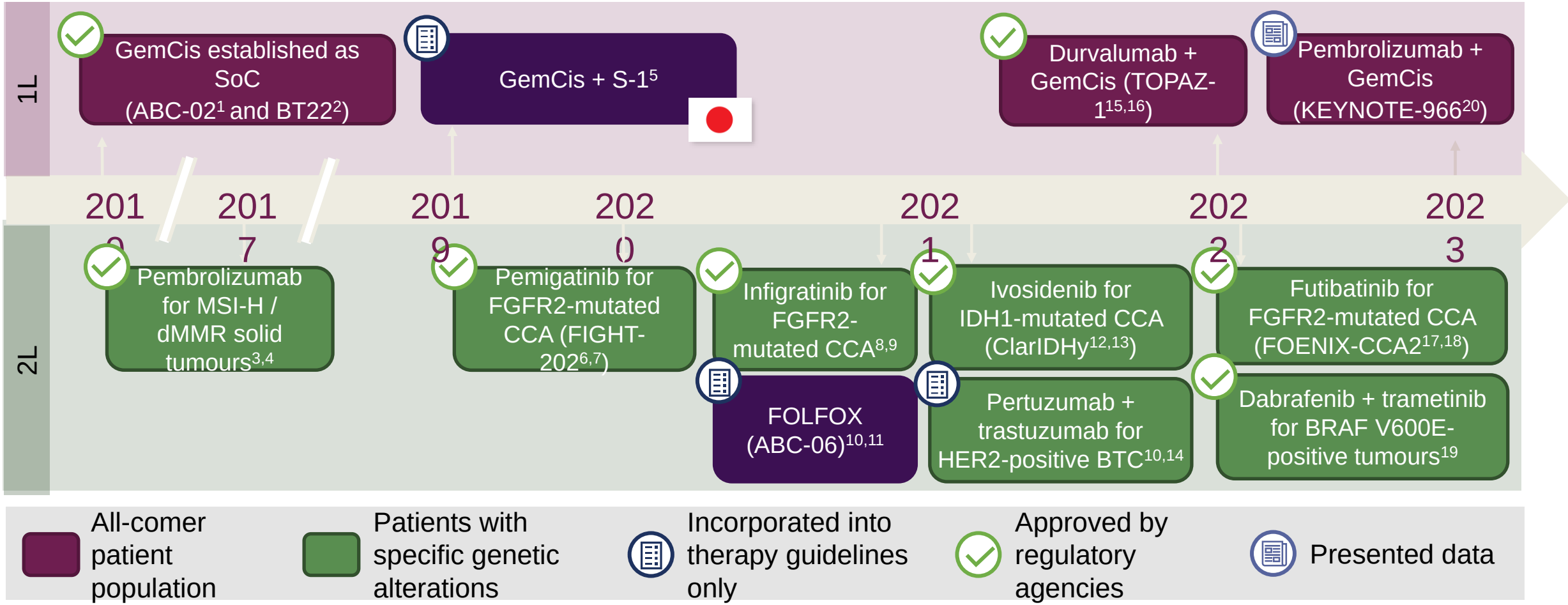
Genetic heterogeneity



Banales JM, et al. Nat Rev Gastroent Hepatol 2020

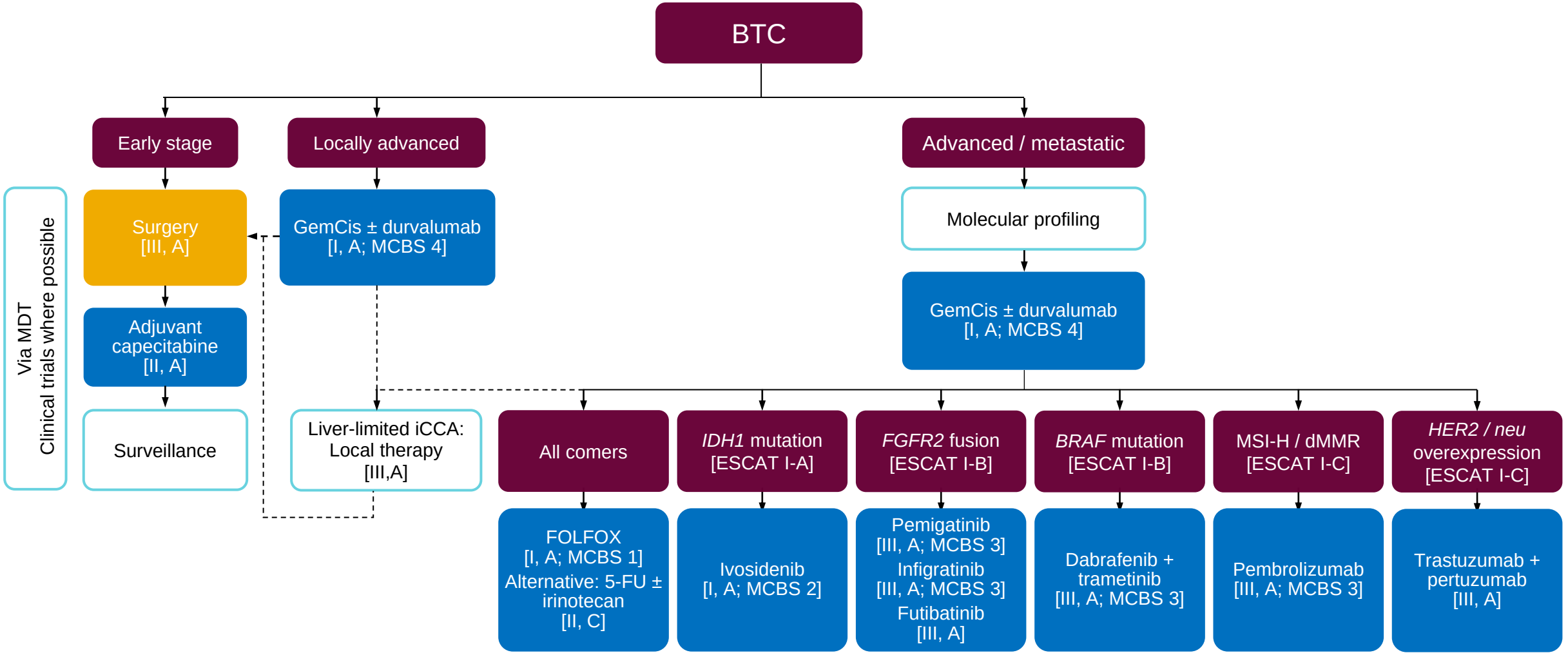
Mod from Saborowski A/Vogel A et al. J Hepatol 2023

A number of novel treatment options for advanced BTC



1. Valle J, et al. N Engl J Med 2010;362:1273–1281. 2. Okusaka T, et al. Br J Cancer 2010;103:469–474. 3. Merck 4. European Medicines Agency. 5. Nagino M, et al. J Hepatobiliary Pancreat Sci 2021;28:26–54. 6. Abou-Alfa GK, et al. Lancet Oncol 2020;21:671–684. 7. US Food and Drug Administration. 8. Javle M, et al. J Clin Oncol 2018;36:276–282. 9. US Food and Drug Administration. 10. Vogel A, et al. Ann Oncol 2023;34:127–140. 11. Lamarca A, et al. Lancet Oncol 2021;22:690–701. 12. Abou-Alfa GK, et al. Lancet Oncol 2020;21:796–807. 13. US Food and Drug Administration. https://www. 14. Javle M, et al. Lancet Oncol 2021;22:1290–1300. 15. Oh D-Y, et al. NEJM Evid 2022;1:EVIDoa2200015. 16. US Food and Drug Administration. 17. Goyal L, et al. J Clin Oncol 40(16_suppl):4009–4009. 18. US Food and Drug Administration. 19. US Food and Drug Administration. 20. Kelley RK, et al. Presented at: AACR Annual Meeting

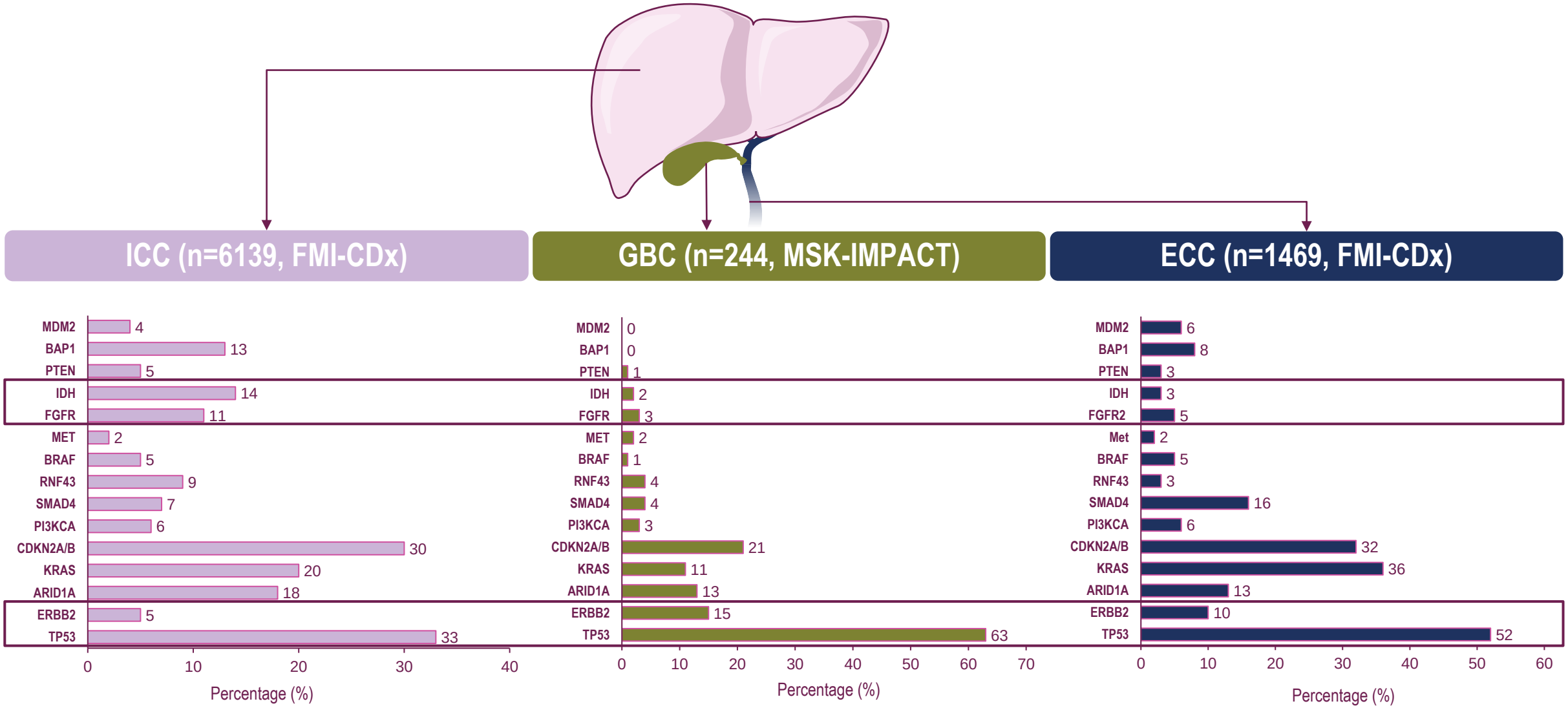
ESMO 2022 Clinical Practice Guidelines



Vogel A, et al. Ann Oncol 2023

5-FU, 5-fluorouracil; BRAF, v-Raf murine sarcoma viral oncogene homolog B; BTC, biliary tract cancer; dMMR, mismatch repair deficiency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO, European Society for Medical Oncology; FGFR2, fibroblast growth factor receptor 2; FOLFOX, folinic acid, 5-FU and oxaliplatin; GemCis, gemcitabine and cisplatin; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IDH1, isocitrate dehydrogenase 1; MCBS, Magnitude of Clinical Benefit Scale; MDT, multidisciplinary team; MSI-H, microsatellite instability-high.

BTC: a heterogeneous disease

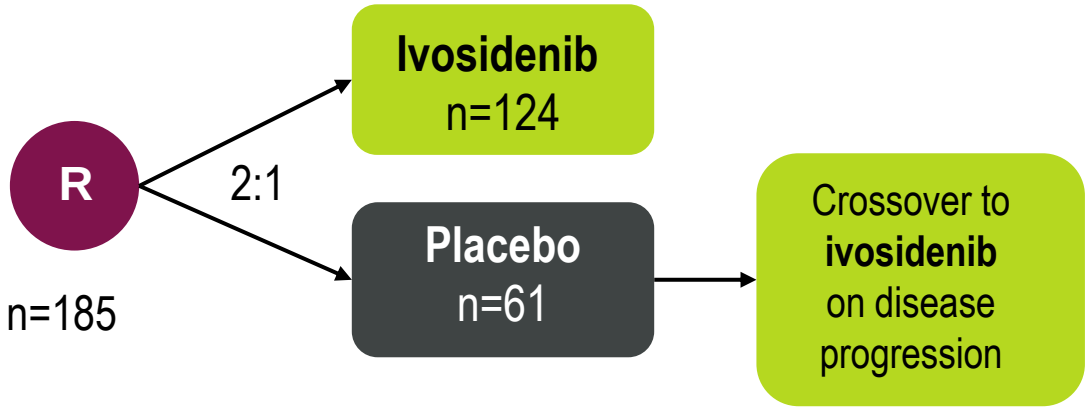


Kendre et al, J Hepatol 2022, Vogel et al. unpublished (eCCA: n=1469, FMI), Giraldo et al. Clin Can Research 2022 (GBC: n=244, MSK-IMPACT)

Targeting IDH-1 in CCA

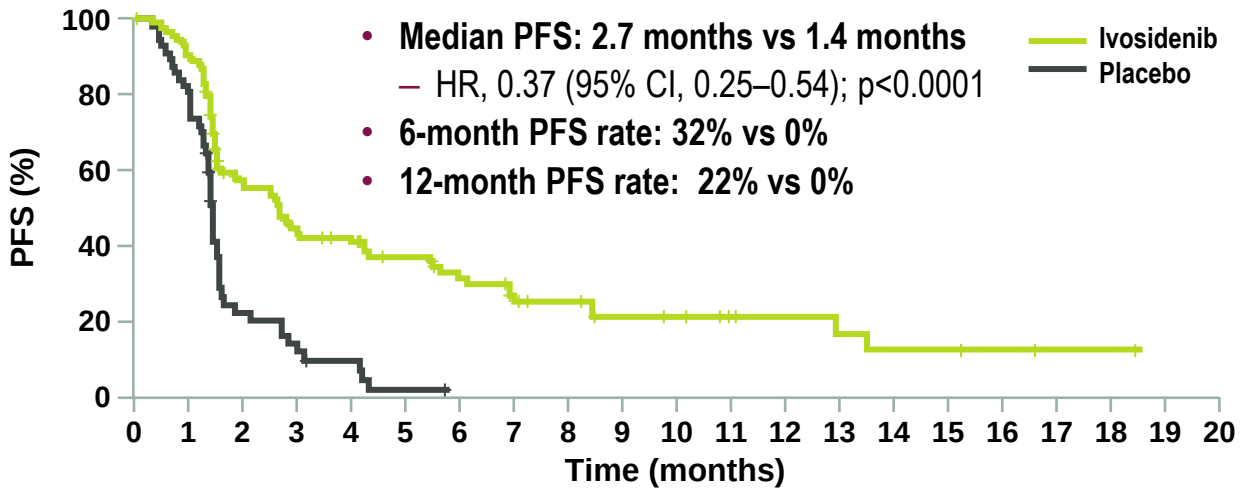
Phase 3 study, second-/third-line, placebo-controlled (ClarIDHy) [NCT02989857]

- AG-120 (ivosidenib) is a first-in-class, potent, oral inhibitor of the mutant IDH-1 enzyme



Ivosidenib is now FDA-approved for advanced or metastatic cholangiocarcinoma[2]

PFS



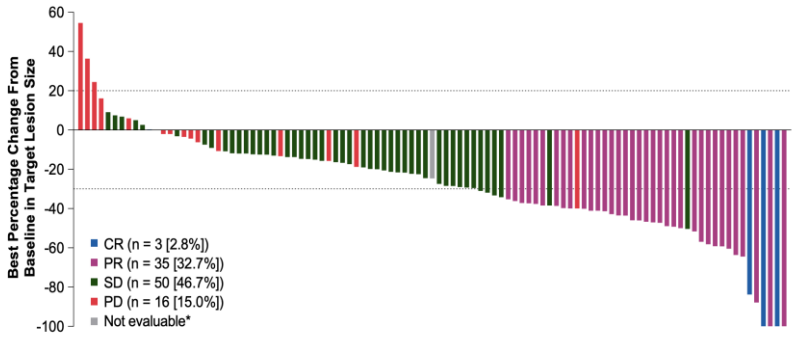
Updated OS data (May 2021)

	Ivosidenib	Placebo
Median OS (adjusted for crossover)	10.3 months	5.1 months
	HR, 0.49 (95% CI, 0.34–0.70); one-sided p<0.001	
Median OS (unadjusted for crossover)	10.3 months	7.5 months
	HR, 0.79 (95% CI, 0.56–1.12); p=0.09	

Abou-Alfa GK, et al. Lancet Oncol 2020, Zhu AX, et al. JAMA Oncol 2021

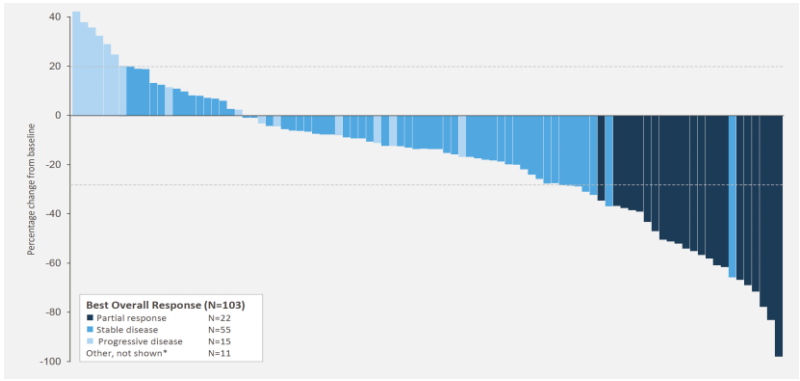
FGFR2 inhibition in biliary tract cancer

FIGHT-202
Pemigatinib



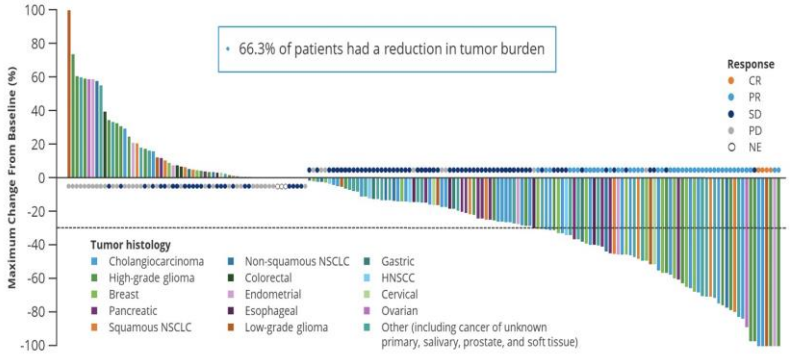
Vogel et al @ESMO 2019

FIDES-01
Derazantinib



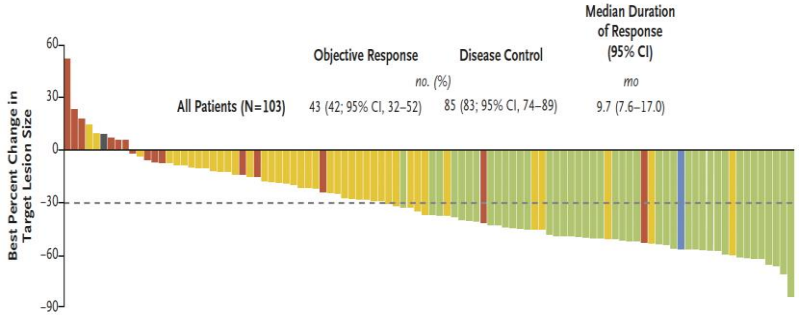
Droz ditBusset et al @ESMO 2021

RAGNAR
Erdafitinib



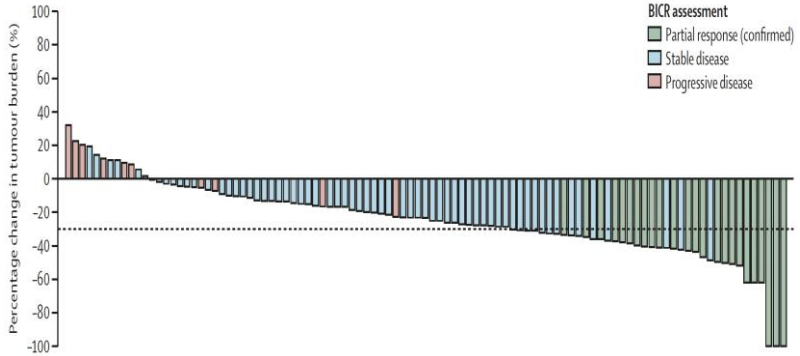
Lorio et al @ASCO 2022

FOENIX-CCA2
Futibatinib



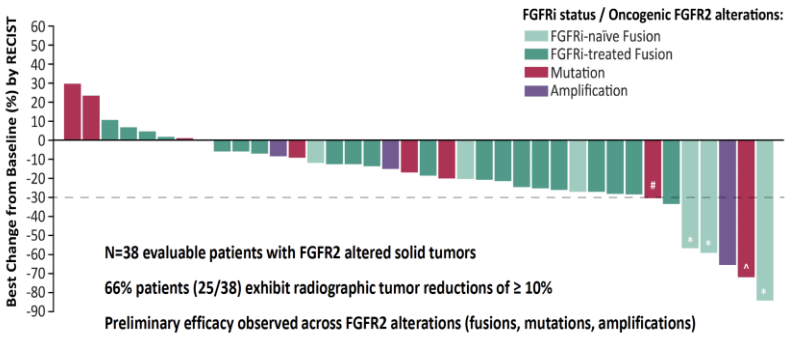
Goyal et al @NEJM 2023

Infigratinib



Javle et al. Lancet GastroHep 2021

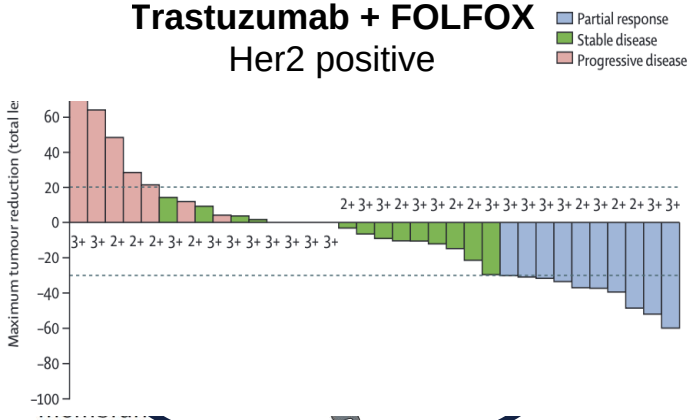
ReFocus
RLY-4008



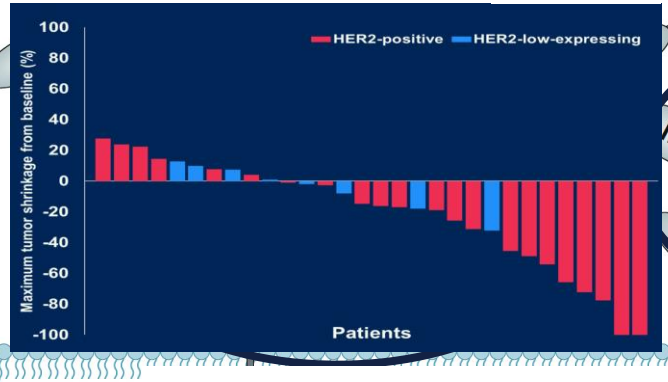
Goyal et al @AACR 2021

HER2 (ERBB2)“Old acquaintances in Oncology“ reloaded:

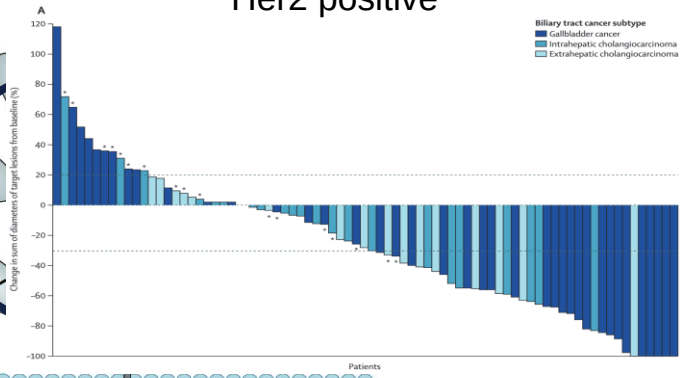
Trastuzumab + FOLFOX
Her2 positive



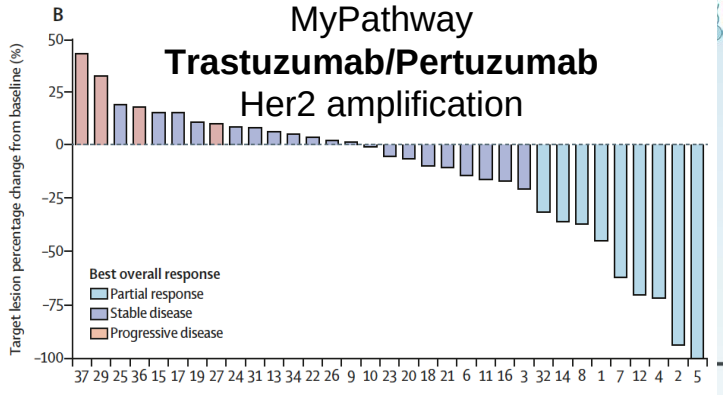
HERB
Trastuzumab-deruxteca
Her2 positive



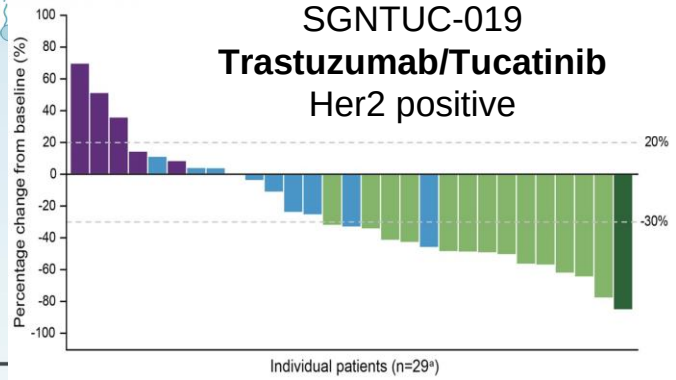
HERIZON-BTC001
Zanidatamab
Her2 positive



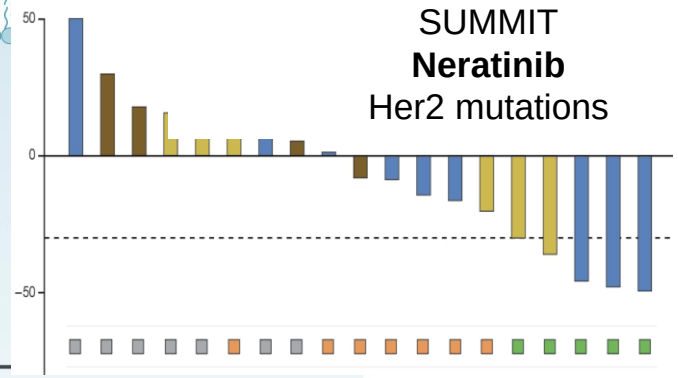
MyPathway
Trastuzumab/Pertuzumab
Her2 amplification



SGNTUC-019
Trastuzumab/Tucatinib
Her2 positive



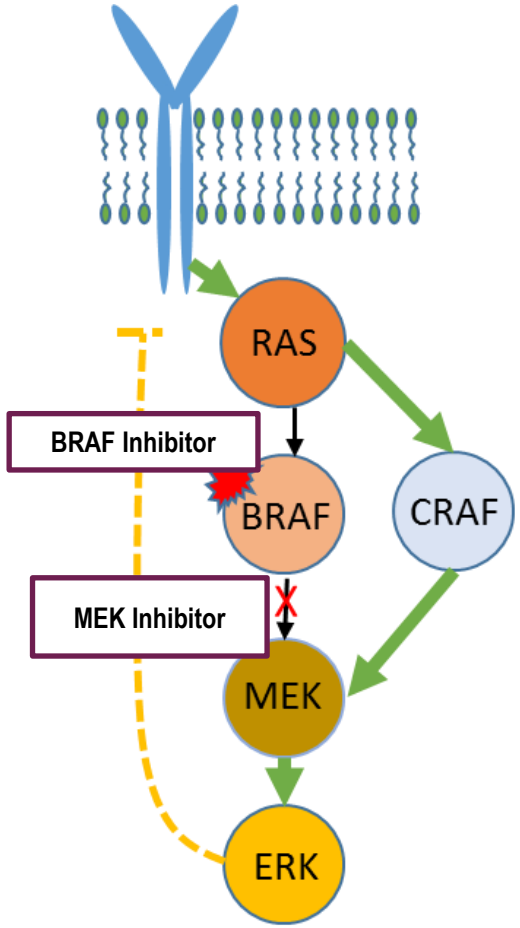
SUMMIT
Neratinib
Her2 mutations



Inhibition of PI3-kinase signalling, promoting cell-cycle arrest

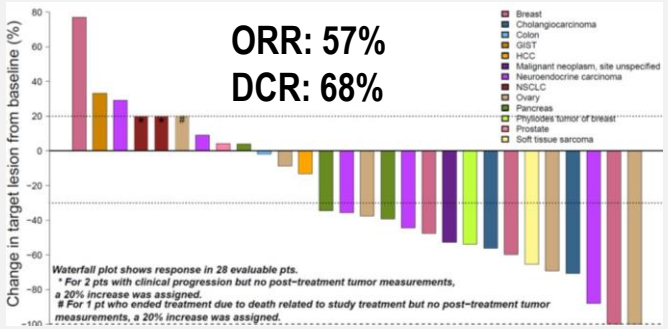
Oh DY and Bang YJU, Nat Rev Clin Oncol 2020, Javle et al, Lancet Oncology 2021, Harding et al. @ASCO 2022, Lee et al Lancet Oncology 2022, Meric-Bernstam, et al Lancet Oncology 2022, Harding, Fan et al Lancet Oncology 2023, Nakamura et al. @ASCO 2023

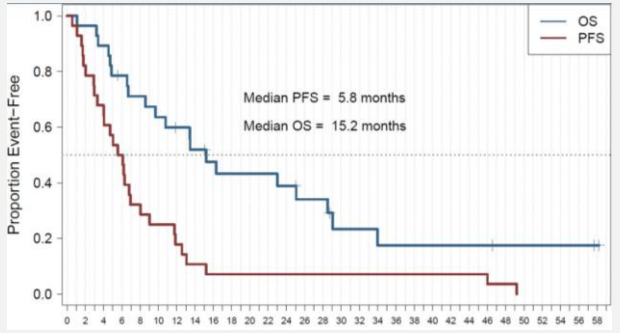
Combinatorial treatment - $BRAF^{V600E}$



TAPUR Basket Trial

Cobimetinib + Vermurafenib

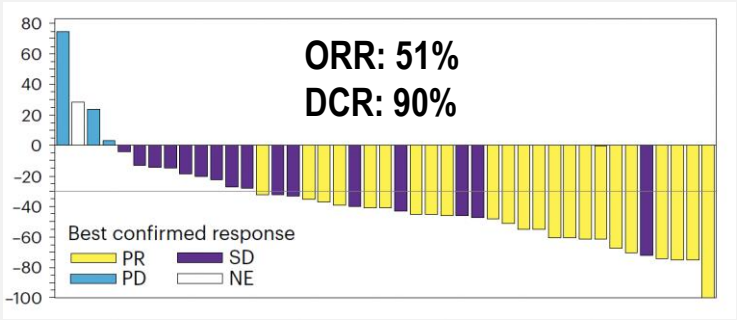


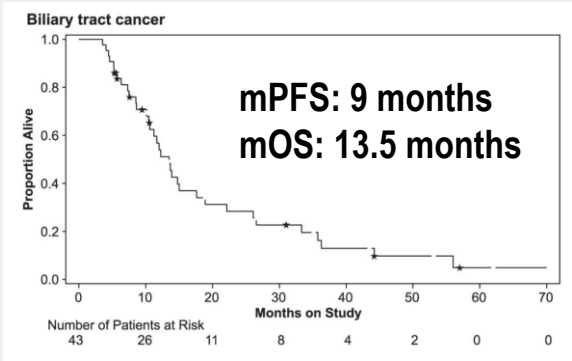


Meric-Bernstam et al ASCO 2022

ROAR Basket Trial

Dabrafenib + Trametinib

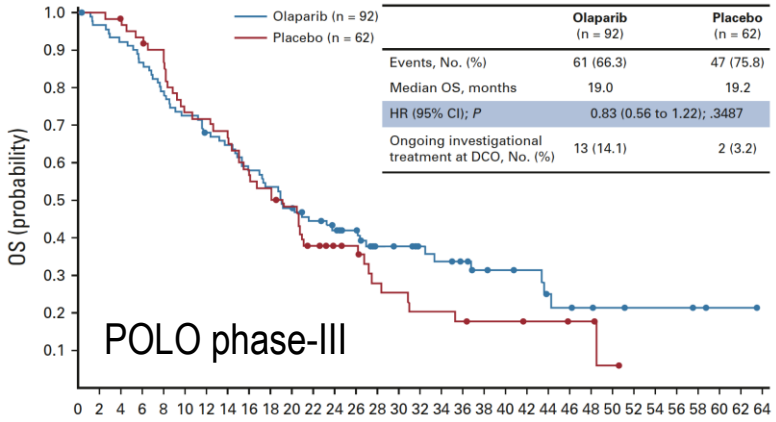




Subbiah et al Nature Medicne 2023

Targeting DNA damage repair pathway in pancreatic cancer

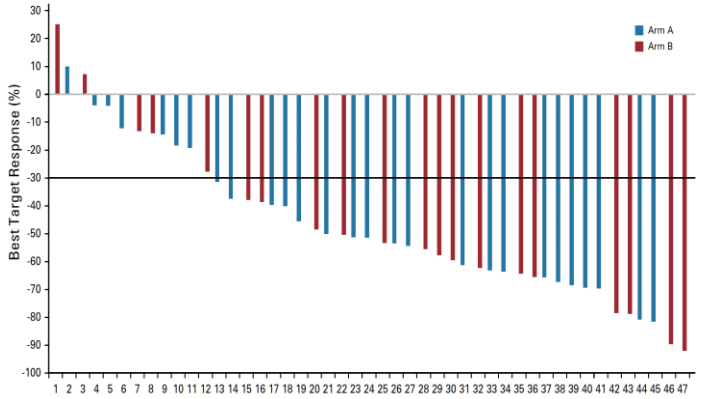
Olaparib
gBRCA1/2



	Olaparib (n = 92)	Placebo (n = 62)
Events, No. (%)	61 (66.3)	47 (75.8)
Median OS, months	19.0	19.2
HR (95% CI); *P*	0.83 (0.56 to 1.22); .3487	
Ongoing investigational treatment at DCO, No. (%)	13 (14.1)	2 (3.2)

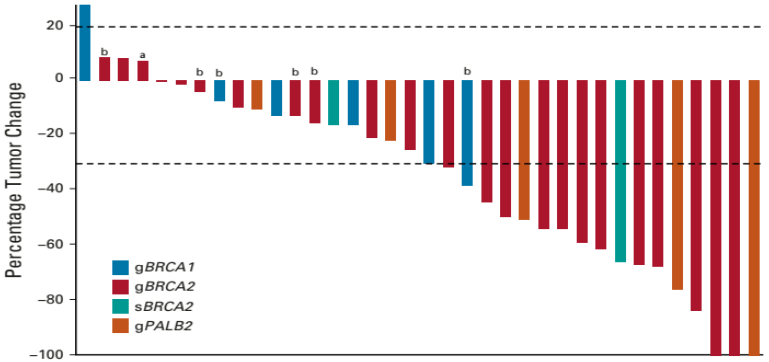
Kindler et al JCO 2021

GemCis ± Veliparib
gBRCA1/2, gPALB2



O'Reilly et al JCO 2022

Rucaparib
BRCA1/2, PALB2



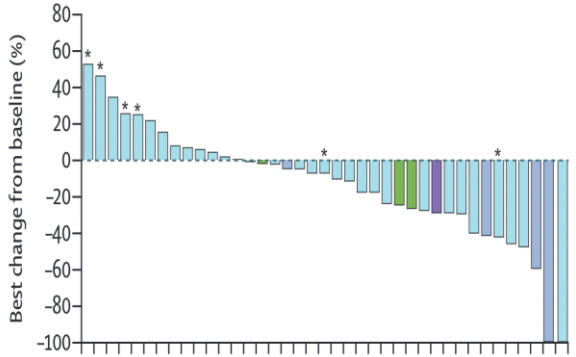
Reiss et al JCI 2021

Nivolumab/Ipilimumab
BRCA1/2, ATM, RAD51

Patient No./gender/age, y	Diagnosis	Germline variant	Best response	Duration of response, mo	PD-L1 combined positive score, %	TMB, mt/Mb	Somatic status[b]	Previous therapies
1/M/60s	PDAC	*BRCA1*	CR[c]	41.6	NA	4	Biallelic	Resection and adjuvant gemcitabine/capecitabine
2/M/70s	CCA	*BRCA1*	CR[c]	39.9	0	8	Biallelic	Gemcitabine/cisplatin
3/M/50s	PDAC	*RAD51C*	CR[c]	26.4	NA	8	Biallelic	FOLFIRINOX, olaparib, liposomal irinotecan/5-fluorouracil, and gemcitabine/nab-paclitaxel/cisplatin
4/M/70s	AMP	*BRCA2*	CR[d]	11.5	2	NA	Biallelic	Resection, adjuvant gemcitabine/cisplatin, and olaparib
5/M/40s	PDAC	*BRCA1*	PR	7.3	NA	NA	Biallelic	Gemcitabine/cisplatin/nab-paclitaxel and olaparib
10/F/50s	PDAC	*ATM*	SD	4.1	NA	NA	Monoallelic	FOLFIRINOX, gemcitabine/nab-paclitaxel, and olaparib
6/F/70s	PDAC	*BRCA1*	SD	3.5	NA	5	Biallelic	Neoadjuvant gemcitabine/cisplatin and resection
12/F/60s	PDAC	*BRCA2*	PD	2.6	NA	4	NA	Neoadjuvant FOLFIRINOX, resection, and gemcitabine/nab-paclitaxel
7/M/60s	PDAC	*BRCA2*	PD	2.3	NA	3	NA	Resection, adjuvant gemcitabine/cisplatin, FOLFIRINOX, and olaparib
9/F/50s	PDAC	*RAD51D*	PD	2.0	0	6	NA	Gemcitabine/nab-paclitaxel, FOLFIRINOX, and olaparib
8/F/60s	PDAC	*BRCA2*	PD	1.8	0	3	Monoallelic	Gemcitabine/cisplatin/nab-paclitaxel
11/M/60s	PDAC	*BRCA2*	PD	1.3	NA	3	Biallelic	FOLFIRINOX and olaparib

Terrero et al Jama Oncology 2021

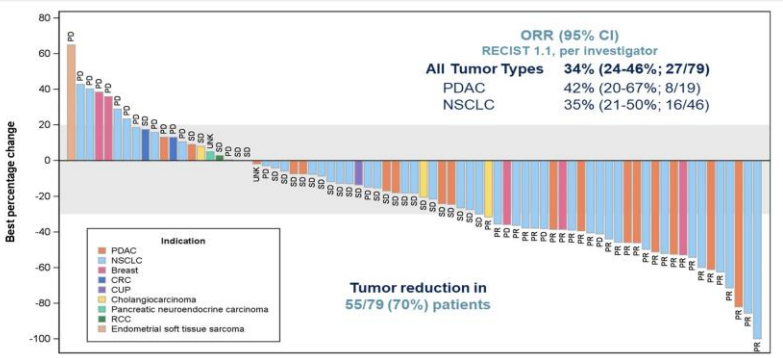
Niraparib/Ipilimumab
Platin-sensitive



Reiss et al Lancet Oncology 2022

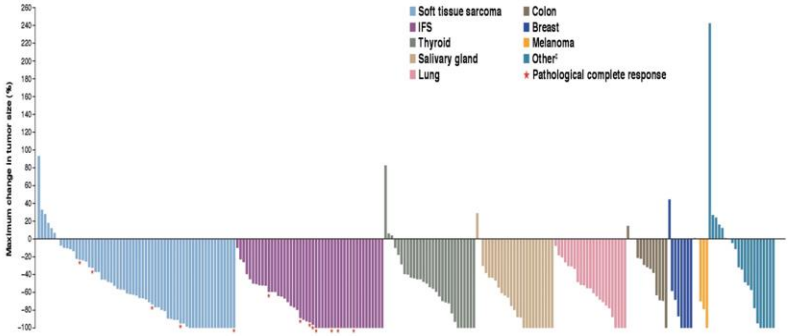
.... and rare fusions

NRG1 fusion
Zenocutumzumab



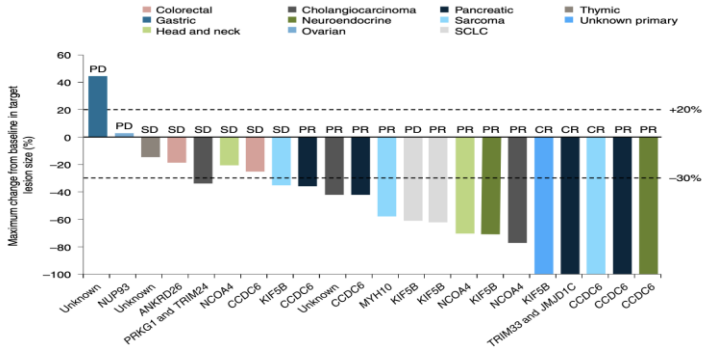
Ohba et al @ASCO 2022

NTRK fusion
Larotectinib



Drilon et al @ASCO 2022

RET fusions: ARROW
Pralsetinib

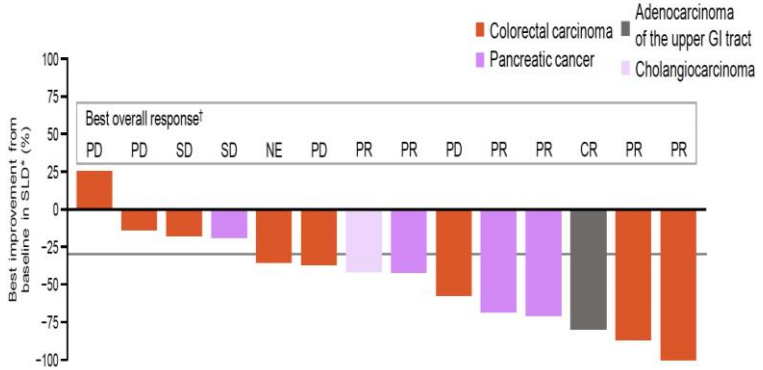


Subbiah et al. Nature Medicine 2022

NRG1 fusion: CRESTONE
Seribantumab

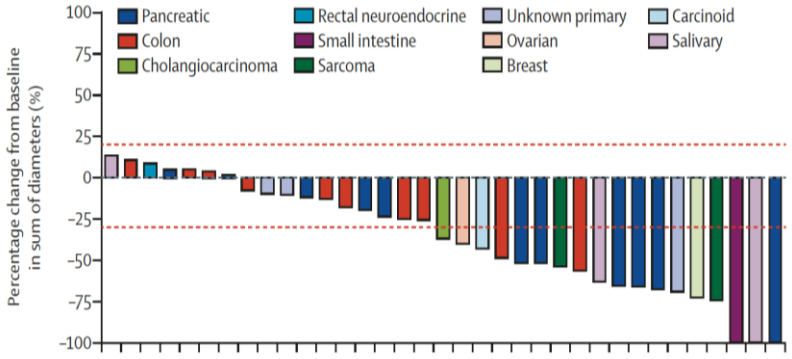
Carrizosa et al. @ASCO 2022

NTRK fusion
Entrektinib



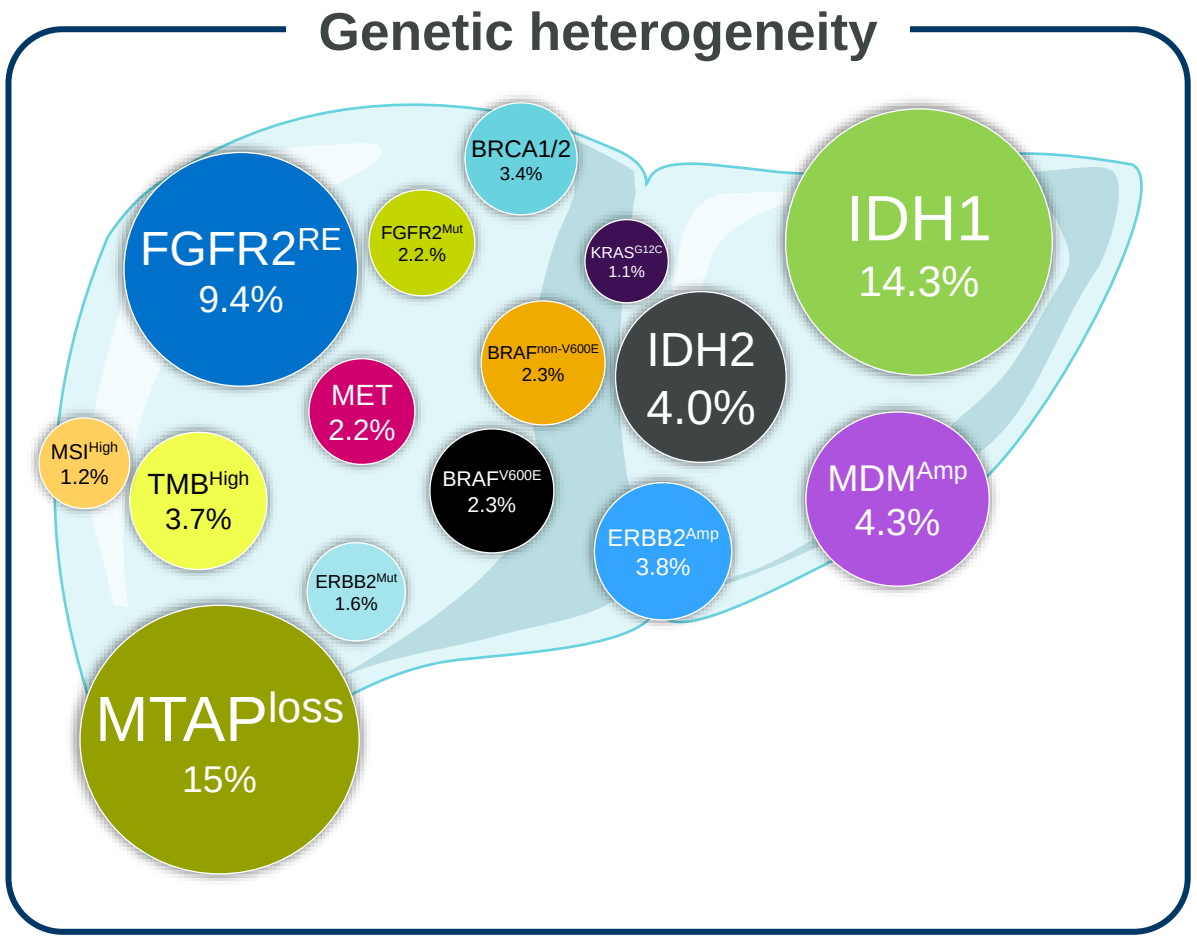
Garrido-Laguna et al. @ESMO-GI 2022

RET fusions: LIBRETTO
Selpercatinib



Subbiah et al Lancet Oncolgy 2022

BTCs: Many targeted therapies already today available



MTAP^{loss} 15% — AMG193

FGFR^{RE} 9.2% — Pemigatinib, Futibatinib, RLY-4008, Erdafininib

ERB2^{AMP} 3.8% — Trastzumab, Pertuzumab, Trastuzumab-Deruxtecan, Zanidatimab, Tucatinib, Neratinib

TMB^{high} 3.7% — Nivolumab ± Ipilimumab Pembrolizumab

BRAF^{V600E} 2.3% — Dabrafenib/Trametinib Vemurafenib/Cobimetinib

IDH1 14.3% — Ivosidenib

MDM^{AMP} 4.3% — Brigimadlin

BRCA1/2 3.8% — Olaparib, Rucaparib Nivo/Ipilimumab

BRAF^{nonV600E} 3.8% — Belvarafenib

KRAS^{G12C} 1.1% — Sotorasib Adagrasib

And more…

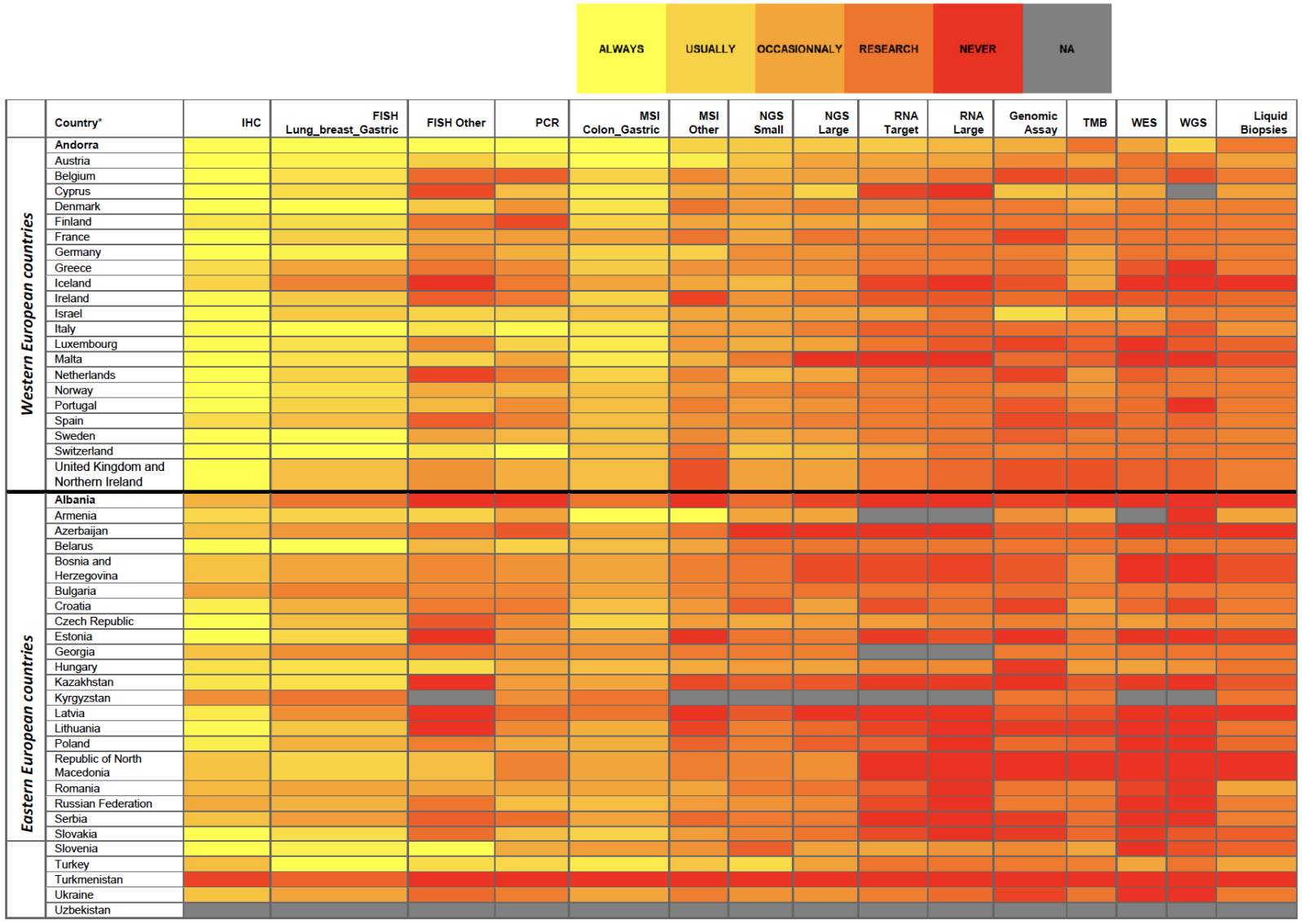
NTRK — Larotectinib Entrektinib

RET^{fusion} — Pralsetinib Selpercatinib

NRG1^{fusion} — Zenocutumzumab Seribantumab

Mod from Saborowski A/Vogel A et al. J Hepatol 2023

Availability of techniques across countries by region



Bayle et al. Annals of Oncology

Too many NGS panels: Which Panel detects which alteration???

Second Opinion @MHH: Molecular Tumorboard

FoundationOne CDx CTA

Oncomine Focus Assay

Archer FusionPlex lung v2-Panel, "anchored multiplex PCR (AMP)

STS+ Extended Panel der Fa. Sophia Genetics

VariantPlex nNGM Lung Focus v2 (Archer Dx)

Heidelberg Oncology Panel

BRCAness Custom Panel

nNGM Panel Qiagen

VariantPlex Solid Tumor

FusionPlex Solid Tumor Panel

BRAF Mutation Analysis kit

Ampliseq Cancer Hotspot for Illumina

FondationOne DX1

NGS-Basis-Panel

Colorectal Cancer Panel

Custom BRCA/HRD multimpdal Panel Qiagen

Lung multimodal Panel Qiagen

NPHD2019A
(160 Hirntumor-relevante Gene)

NEOplus v2RUO

BRCAness-IC

Oncomine Focus Assay

FusionPlex Expanded Lung

Agilent HS2-Lung

AmpliSeq for Illumina Focus

CancerHotspot v2 Panel

Molecular Health IVD Panel 600+ (Agilent)

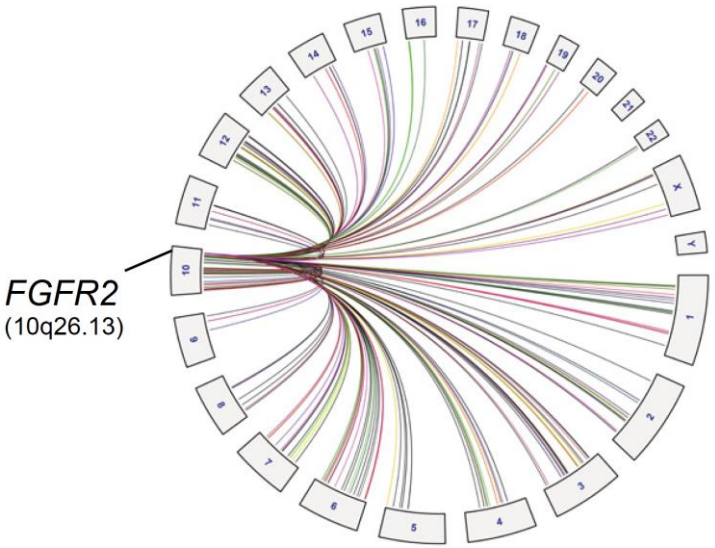
QIAseq Targeted DNA Sequencing Panel

HANDLE Classic NGS Panel

AmoyDx Handle Classic NGS Panel

Search right (!) to find–
The panel matters!

576 iCCA Patient:innen mit FGFR2 Fusion



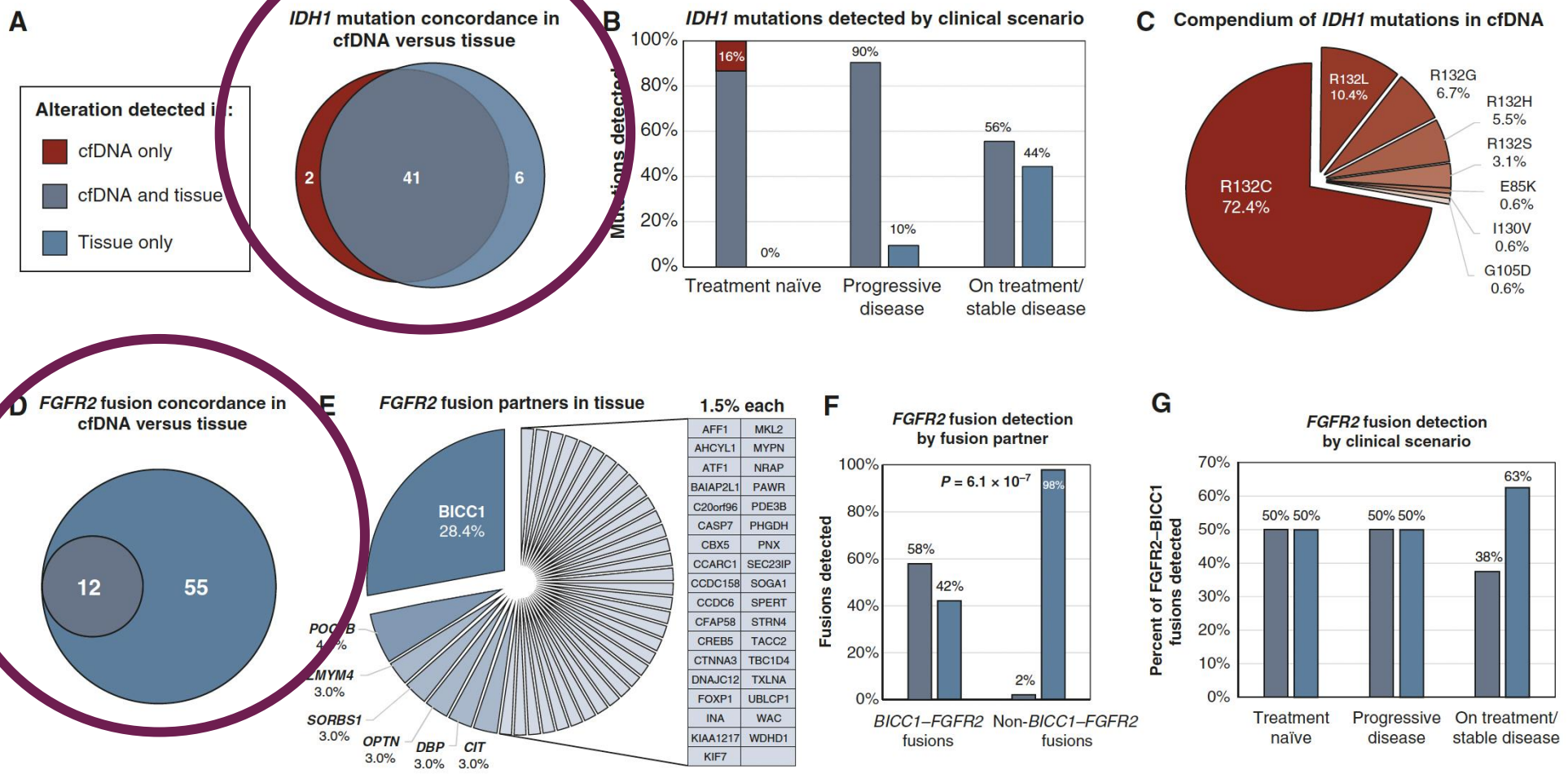
Library	Example	Nucleicacid	Input	Genetic alterations detected
Hybridcapture based	FMI1	DNA	Moderate (≥50 ng)	SNV, indels, CNA, fusions (limitedif long introns)
Hybridcapture based	Illumina2	DNA/RNA	Moderate (≥40ng)	SNV, indels, CNA (DNA) Fusions(RNA)
Amplicon based	Thermo Fisher3	DNA/RNA	Low (≥10ng)	SNV, indels, CNA (DNA) Fusions(RNA; onlyknown)
Anchored Multiplex Sequencing	Archer4	RNA	Low(≥10 ng)	SNV, indels, fusions (partner independent)

Ask your pathologist whether your Panel detects

a) FGFR2 fusions (not only mutations)
b) independent from fusion partner -> RNAseq

Search right (!) to find–
Blood vs tissue

Intra-patient concordance of of genetic alterations between cfDNA & tissue in 194 pts

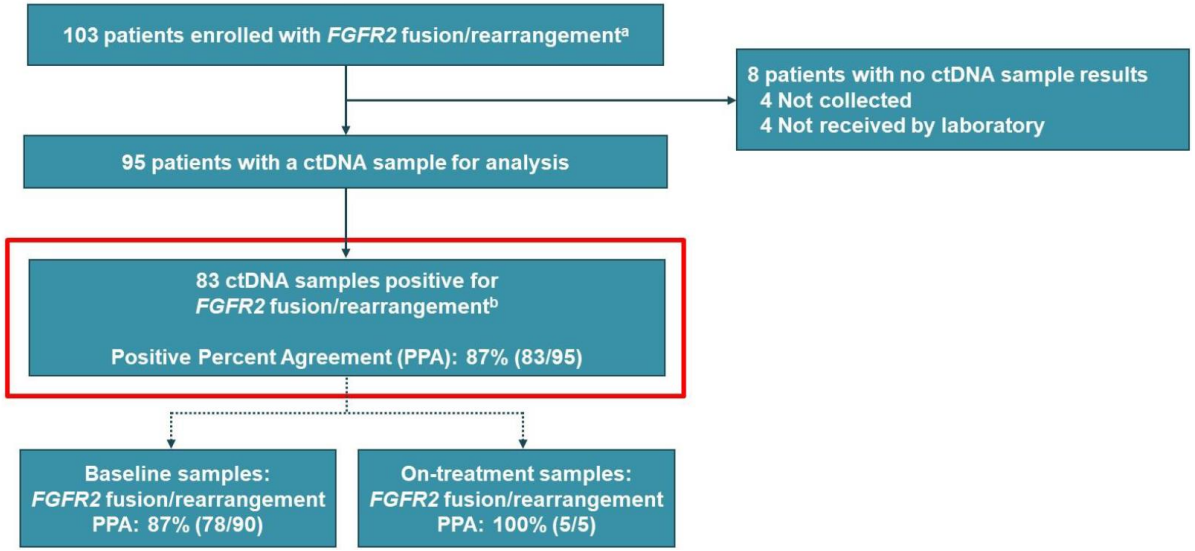


Berchuck et al. Annals of Oncology 2022

Search right (!) to find– Blood vs Tissue

	F1CDx	VHIO-iCCA panel		
	FFPE	FFPE	Plasma	
Patient ID	Rearrangements	Rearrangements	Rearrangements	FAF pre-treatment
Patient 1	*FGFR2:AHCYL1*	*FGFR2:AHCYL1*	*FGFR2:AHCYL1*	0.40%
Patient 2	*FGFR2:BICC1*	*FGFR2:BICC1*	NA	*
Patient 3	*FGFR2:BICC1*	*FGFR2:BICC1*	*FGFR2:BICC1*	6.10%
Patient 4	*FGFR2:BICC1*	*FGFR2:BICC1*	*FGFR2:BICC1*	3.10%
Patient 5	*FGFR2:RBM20*	*FGFR2:RBM20*	*FGFR2:RBM20*	16.90%**
Patient 6	*FGFR2:TACC2*	*FGFR2:TACC2*	*FGFR2:TACC2*	1.20%
Patient 7	*FGFR2:BICC1*	*FGFR2:BICC1*	*FGFR2:BICC1*	2.70%
Patient 8	*FGFR2:CUX1*	*FGFR2:CUX1*	*FGFR2:CUX1*	
Patient 9	Rearrangement	Rearrangement (*FGFR2:ROBO*)	Rearrangement (FGFR2:ROBO)	1.30%
Patient 10	Rearrangement	Rearrangement (*FGFR2:BICC1*)	NA	*
Patient 11	*FGFR2:BICC1*	*FGFR2:BICC1*	*FGFR2:BICC1*	0.50%
Patient 12	*FGFR2:CCDC147*	*FGFR2:CCDC147*	*FGFR2:CCDC147*	9.90%
Patient 13	*FGFR2:BICC1*	*FGFR2:BICC1*	*FGFR2:BICC1*	0.70%
Patient 14	*FGFR2:SORBS1*	*FGFR2:SORBS1*	*FGFR2:SORBS1*	9.60%
Patient 15	*FGFR2:BICC1*	*FGFR2:BICC1*	*FGFR2:BICC1*	1.10%
Patient 16	*FGFR2:AHCYL1*	*FGFR2:AHCYL1*	*FGFR2:AHCYL1*	0.50%
Patient 17	*FGFR2:RNF213*	*FGFR2:RNF213*	*FGFR2:RNF213*	6%
Patient 18	*FGFR2:ATF2*	*FGFR2:ATF2*	*FGFR2:ATF2*	1%

Gonzalez-Medina ASCO 22[1]
VHIO-ICCA NGS panel
16/18 patients with known fusion had same fusion detected in ctDNA



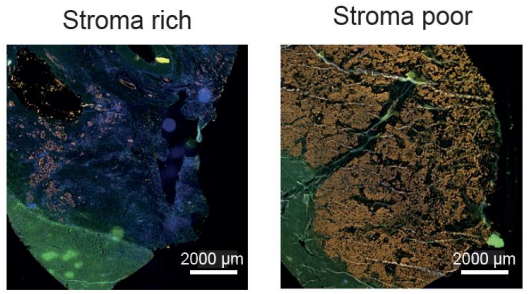
Goyal ASCO 22[2]
Illumina TSO500
83/95 patients with known fusion had same fusion detected in ctDNA

Gonzalez-Medina A, et al. Presentation at ASCO 2022

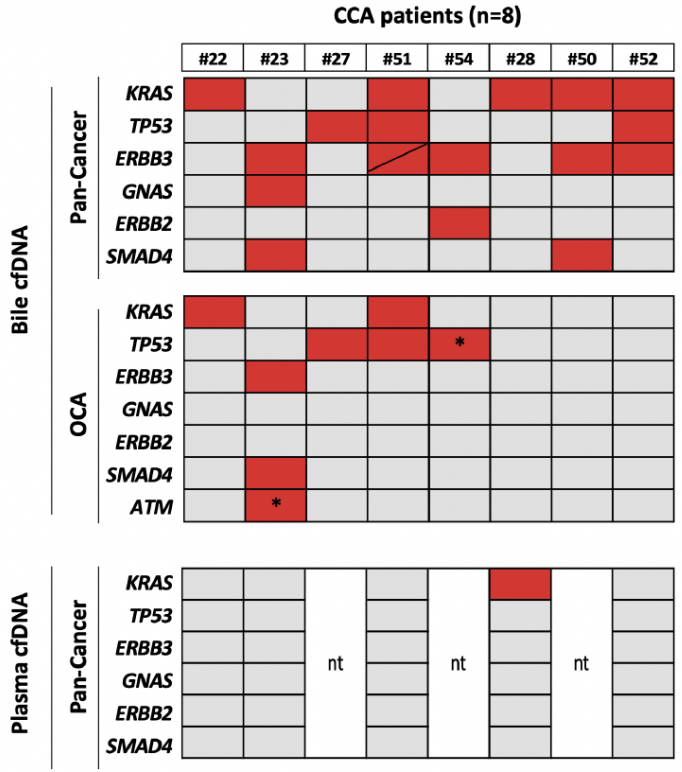
Goyal L, et al. Presentation at ASCO 2022

Search right (!) to find – The biopsy matters!

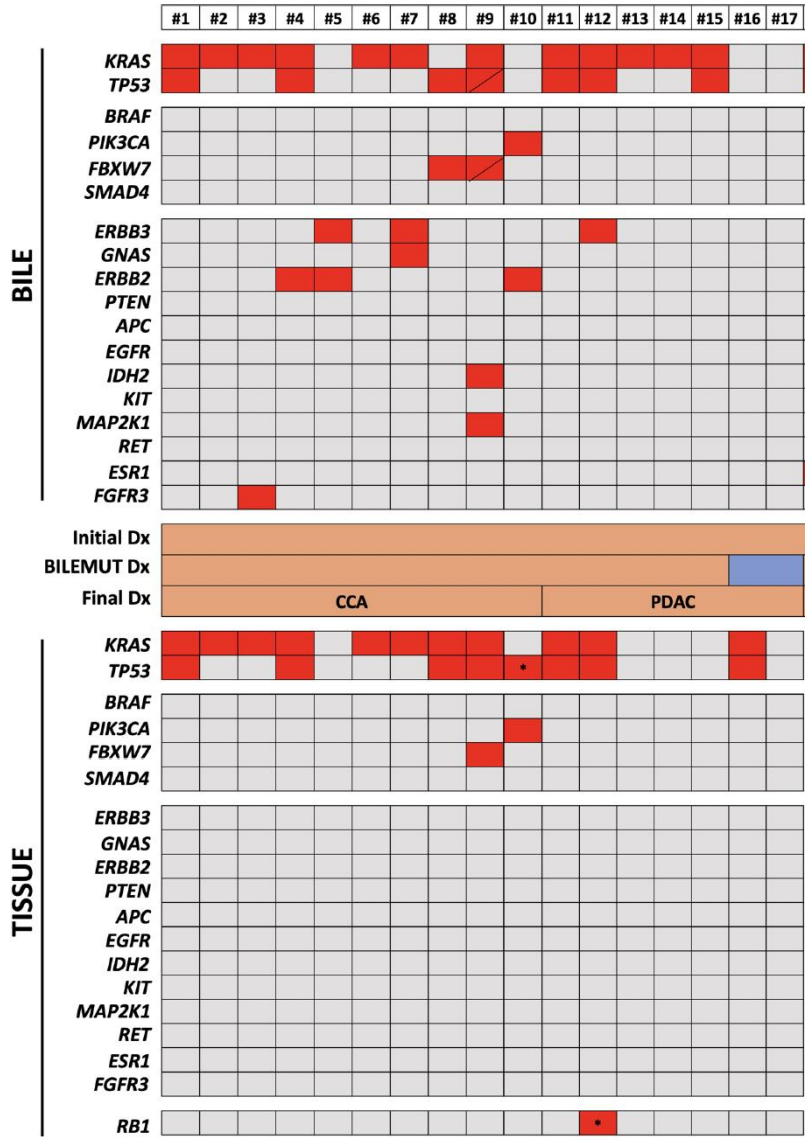
- ✓ Challenge to obtain sufficient tumor material for NGS: Core vs fine needle vs brush cytology
- ✓ Handling and preparation of FFPE samples: DNA crosslinking/fragementation
- ✓ Pre-analytic sample preparation: Micro-/macrodissection due to high stroma content, immune infiltrates
- ✓ Selecting the appropriate NGS assay: when and how?
- ✓ Source of biopsy: tissue vs blood vs bile
- ✓ Understanding and interpreting NGS results: role of molecular tumorboard



Mutational profile of bile vs plasma cell-free DNA (cfDNA)

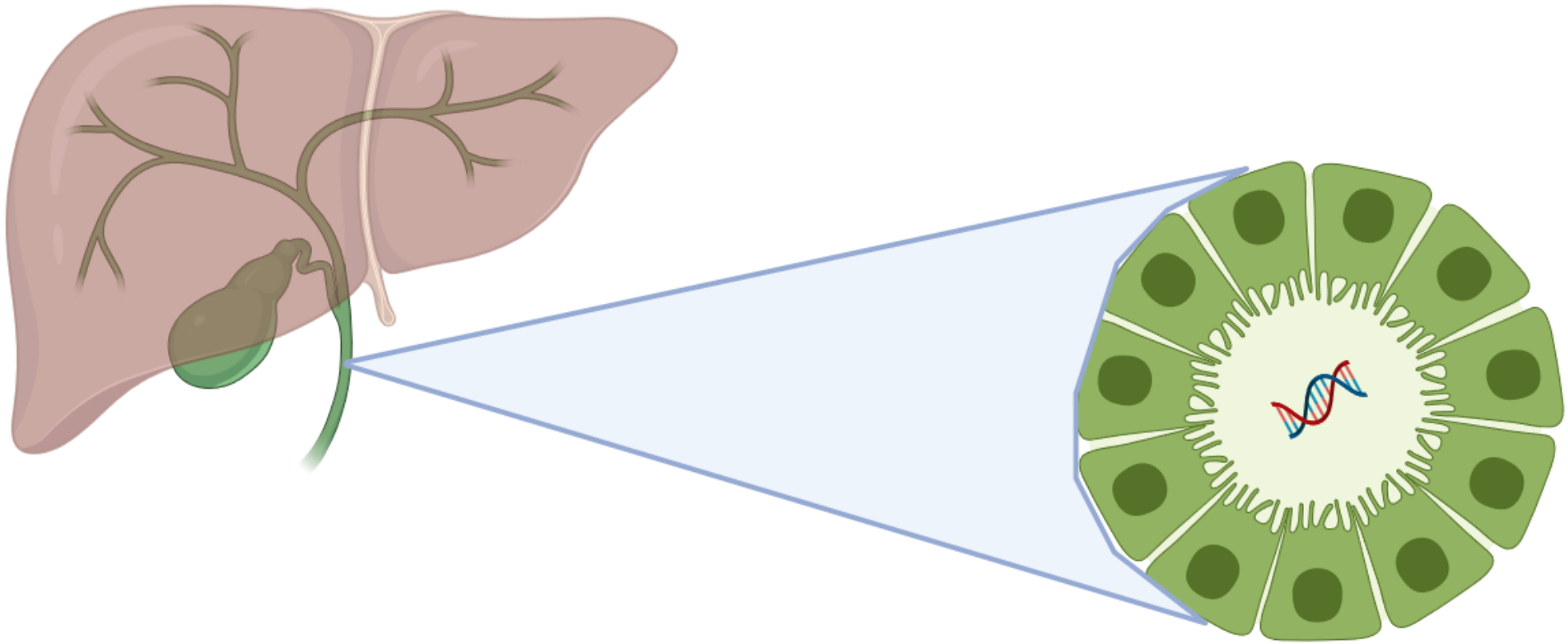


Mutational profile of bile cell-free DNA (cfDNA) and paired tissue DNA



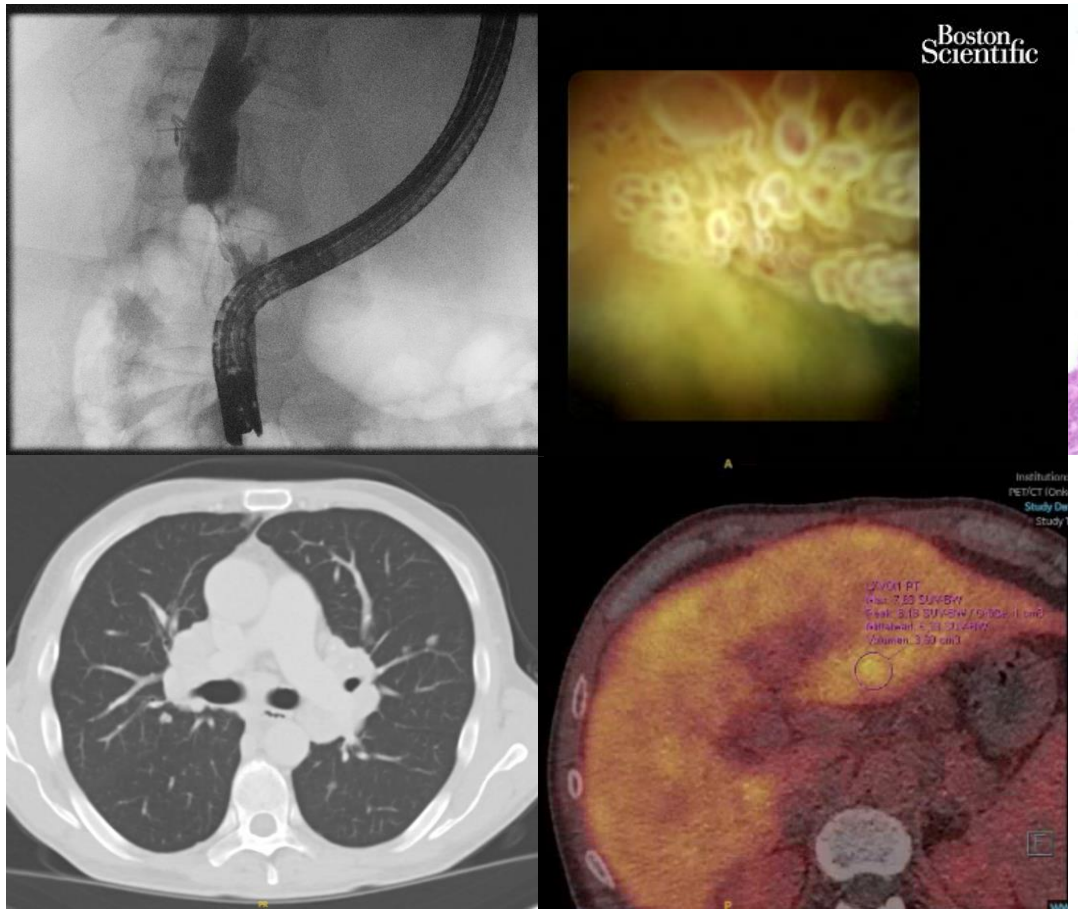
Arechederra M, et al. Gut 2022

NGS form bile



Case: Patient with PSC

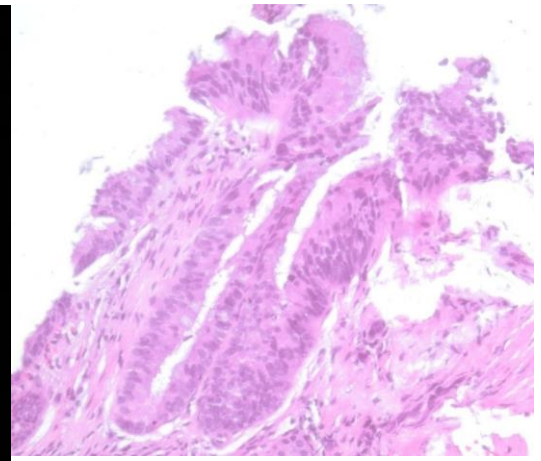
ERCP 05/2023: dominant suspicious stenosis of the common bile duct



CT 06/2023: suspected hepatic, lymphonodal, osseous and pulmonary metastasized malignancy

FAPI PET-CT 08/2023: No typical lesions in liver, in lung sarcoidosis possible;
Bronchoscopy 08/2023: epitheloid cells, no malignancy, suspicion of sarcoidosis

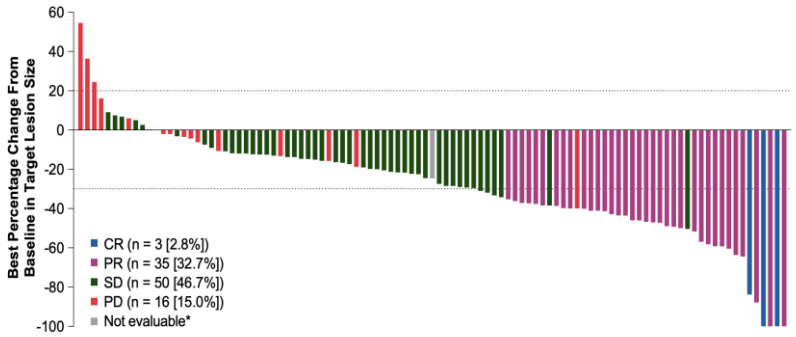
Histology 05/2023:
Metaplastic bile duct epithelium with high-grade dysplasia



Liquid biopsy bile:
KRAS p.G12D
GNAS p.Q227L
ATM p.L1238Kfs*6
NF1 p.T467I

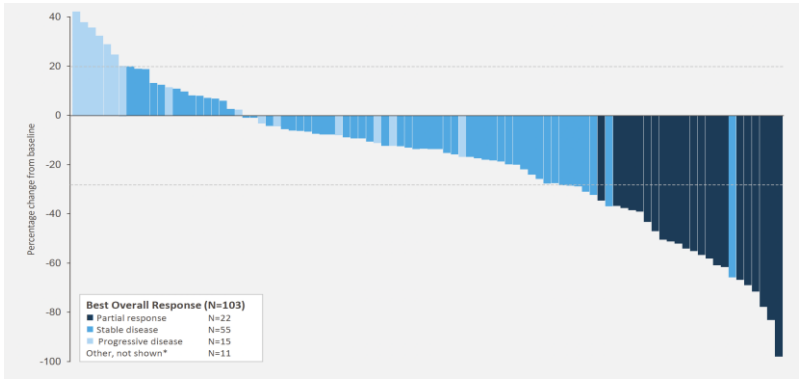
FGFR2 inhibition in biliary tract cancer

FIGHT-202
Pemigatinib



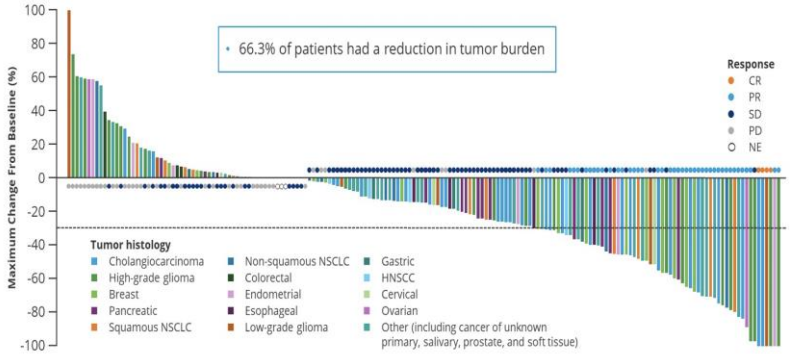
Vogel et al @ESMO 2019

FIDES-01
Derazantinib



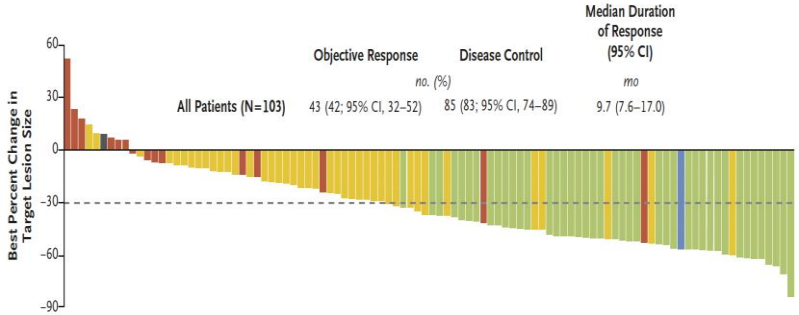
Droz ditBusset et al @ESMO 2021

RAGNAR
Erdafitinib



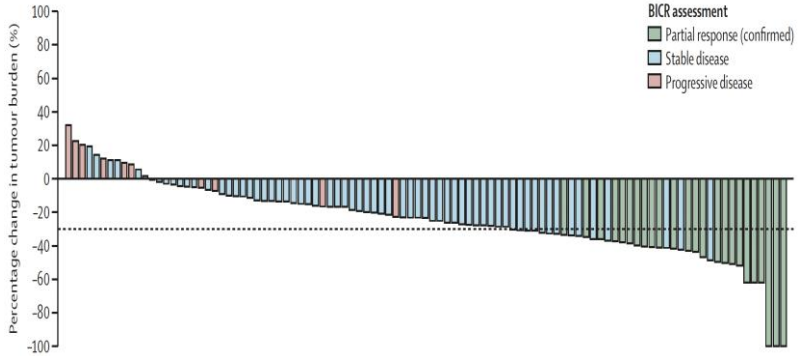
Lorio et al @ASCO 2022

FOENIX-CCA2
Futibatinib



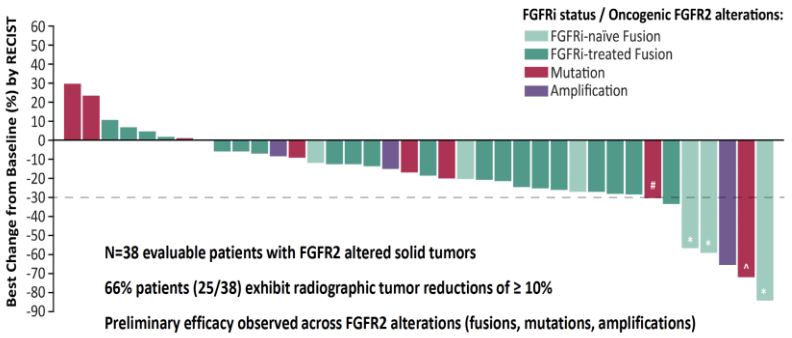
Goyal et al @NEJM 2023

Infigratinib



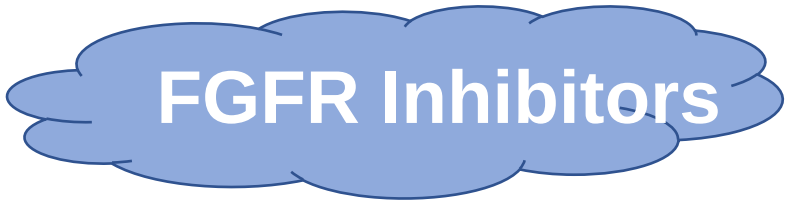
Javle et al. Lancet GastroHep 2021

ReFocus
RLY-4008



Goyal et al @AACR 2021

Too many trials for too few patients?



Futibatinib

RLY-4008

Infigratinib

Derazantinib

Pemigatinib

Gunagratinib

Participants needed: **1,000**

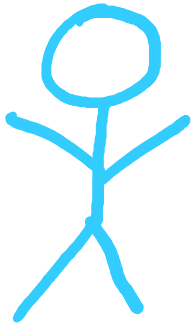
in screening: **10,000**

Incider

1:100,000

Population:

1,000,000,000



Initiated 1st line FGFR inhibitor phase 3 trials in CCA

PROOF[7]

~~withdrawn from market~~

Infig ib

Gemc ine + latin

FIGHT-302[8]

432 patients

Pemigatinib*

Gemcitabine + cisplatin

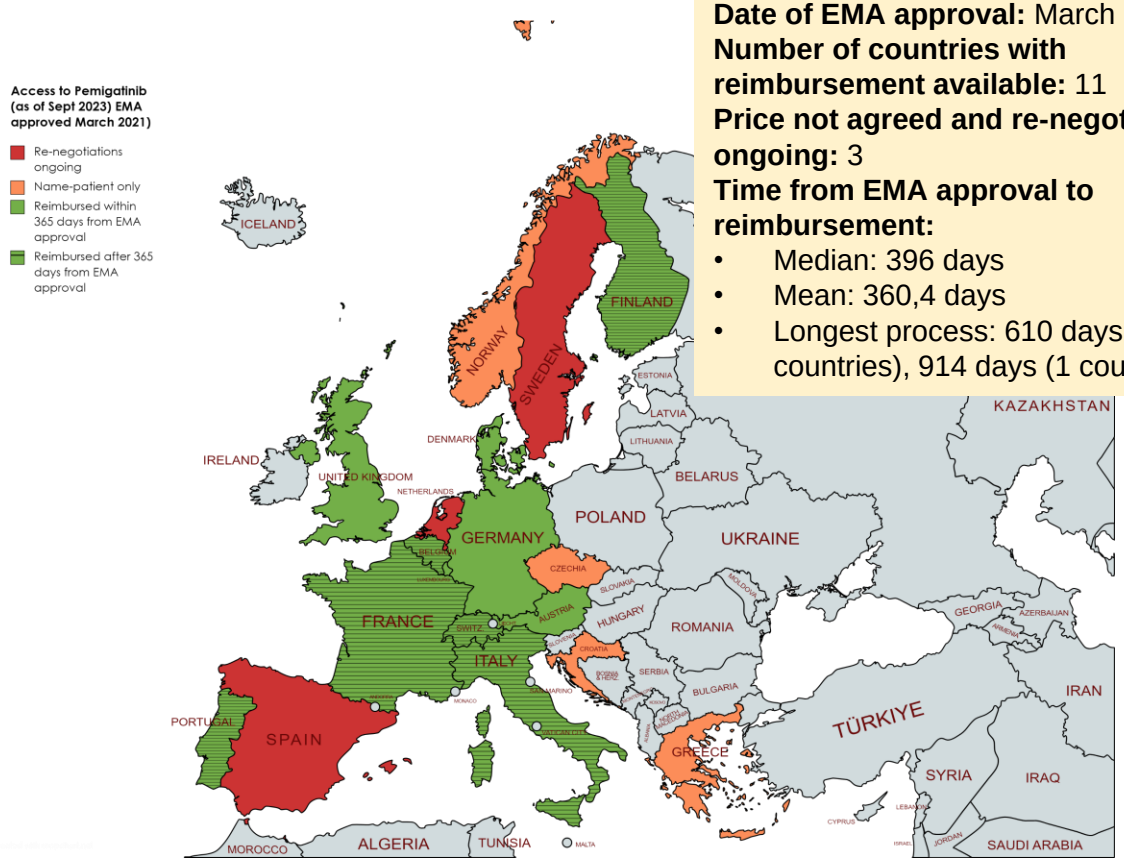
FOENIX-CCA3[9]

Futib b

Gemcit ne + latin

Access to innovative drugs in Cholangiocarcinoma

Pemigatinib as an example; data last updated Sept 2023) – Time since EMA approval 914 days



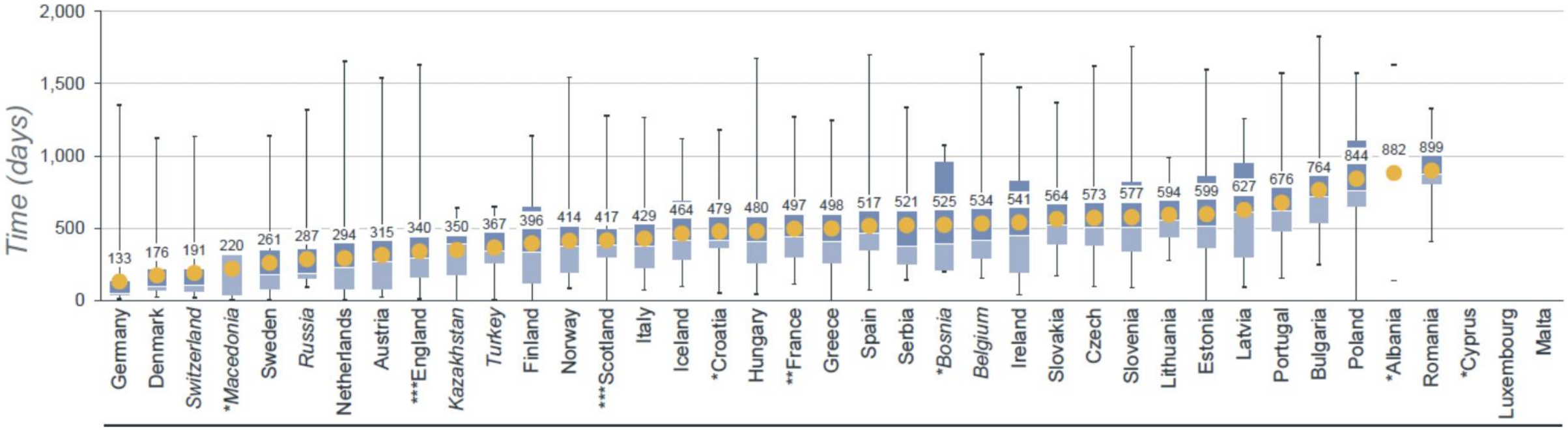
Date of EMA approval: March 2021
Number of countries with reimbursement available: 11
Price not agreed and re-negotiations ongoing: 3
Time from EMA approval to reimbursement:

- Median: 396 days
- Mean: 360,4 days
- Longest process: 610 days (2 countries), 914 days (1 country)

Futibatinib as an example; data last updated Sept 2023) – Time since EMA approval 153 days

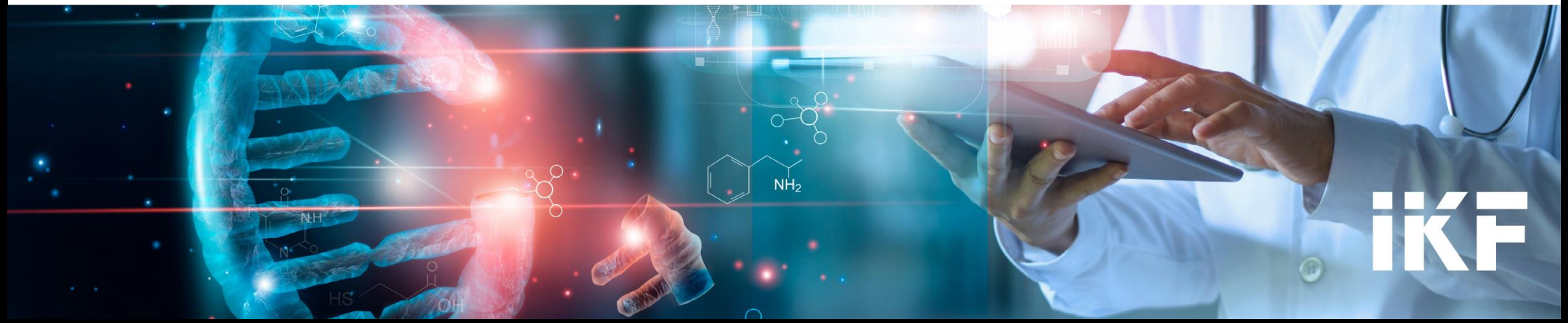
Date of EMA approval: April 2023
Number of countries with reimbursement available: 2
Price not agreed and re-negotiations ongoing: 0

Average time to reimbursement for innovative treatments across EU (2017 – 2020)

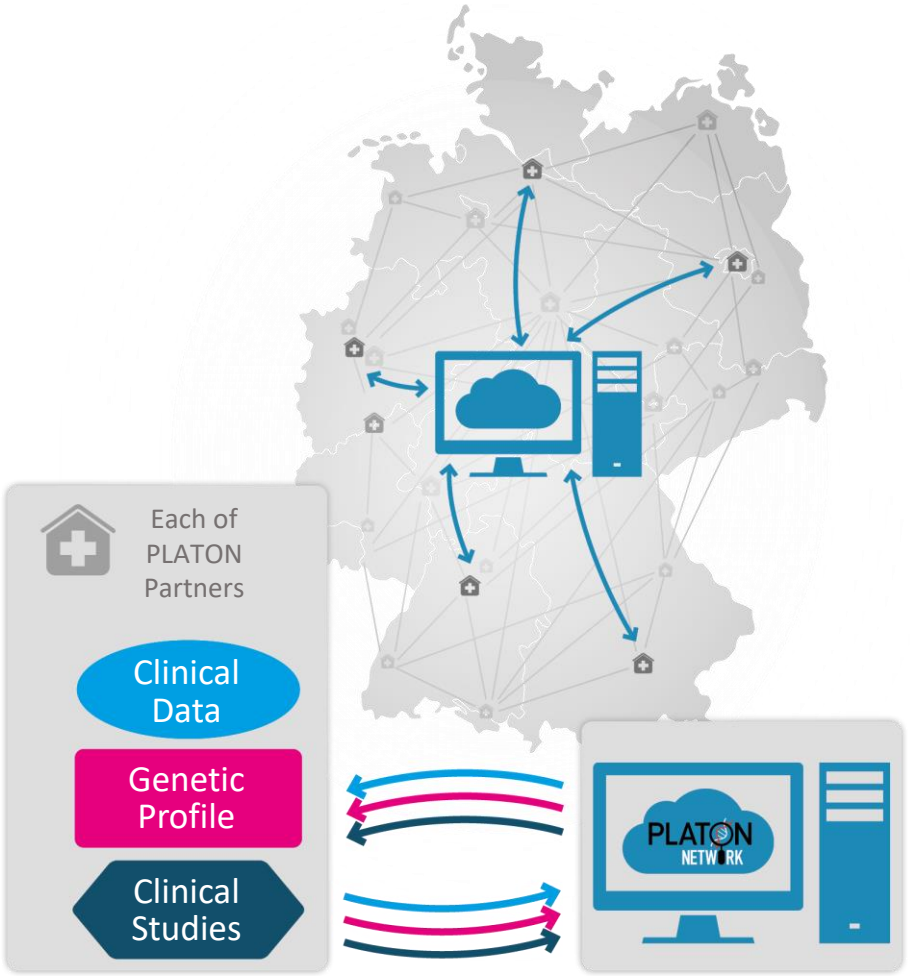


The Patients W.A.I.T. Indicator 2021

PLATON NETWORK



PLATON NETWORK – **Main Elements**



Network Design

Molecular-Pathology Discussion Board

PLATON BioDataBank

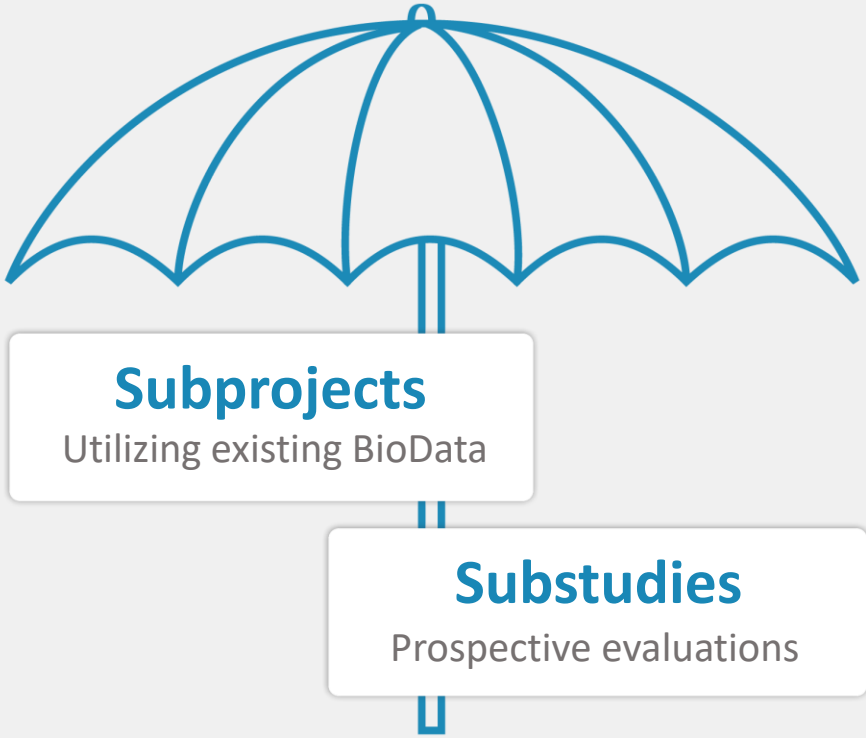
PLATON Web-App

Analyseergebnisse DNA:

Gen	Variante/Mutation	Bewertung	Frequenz	Lesetiefe an der mutierten Position
MSH6	chr2:48030669:NM_000179.3:Exon 5:c.3283C>T:p.R1095C	AMP Tier III Variante mit unklarer Relevanz, in ClinVar eingetragen: “uncertain significance“. Tendenz pathogen, passend zum MSI-H Status	52,5%	14.424
IDH1	chr2:209113113:NM_005896.4:Exon4:c.394C>T:p.R132C	AMP Tier I Hotspotmutation, potentiell sensitiv gegenüber einer Therapie mit IDH-Inhibitoren vom Typ des Ivosidenib.	34,3%	14.148
BAP1	chr3:52441213:NM_004656.4:Exon 7:c.557T>G:p.L186R	AMP Tier III Variante mit unklarer Relevanz	50,4%	2.035
FGFR2	chr10:123279561:NM_000141.5:Exon7:c.869_871del: p.W290_I291delinsF	AMP Tier I Extrazelluläre inframe Deletion, vermittelt mögliche Sensitivität gegenüber FGFR-Inhibitoren (Cleary et al. 2021 Cancer Discovery)	76,9%	15.250
ATR	chr3:142215368:NM_001184.4:Exon34:c.5739-14_5739-6delinsT	AMP Tier III Intronvariante mit unklarer Relevanz	26,4%	15.513
PTCH1	chr9:98268663:NM_000264.5:Exon 2:c.394+15_394+26del	AMP Tier III Intronvariante mit unklarer Relevanz	44,0%	21.321

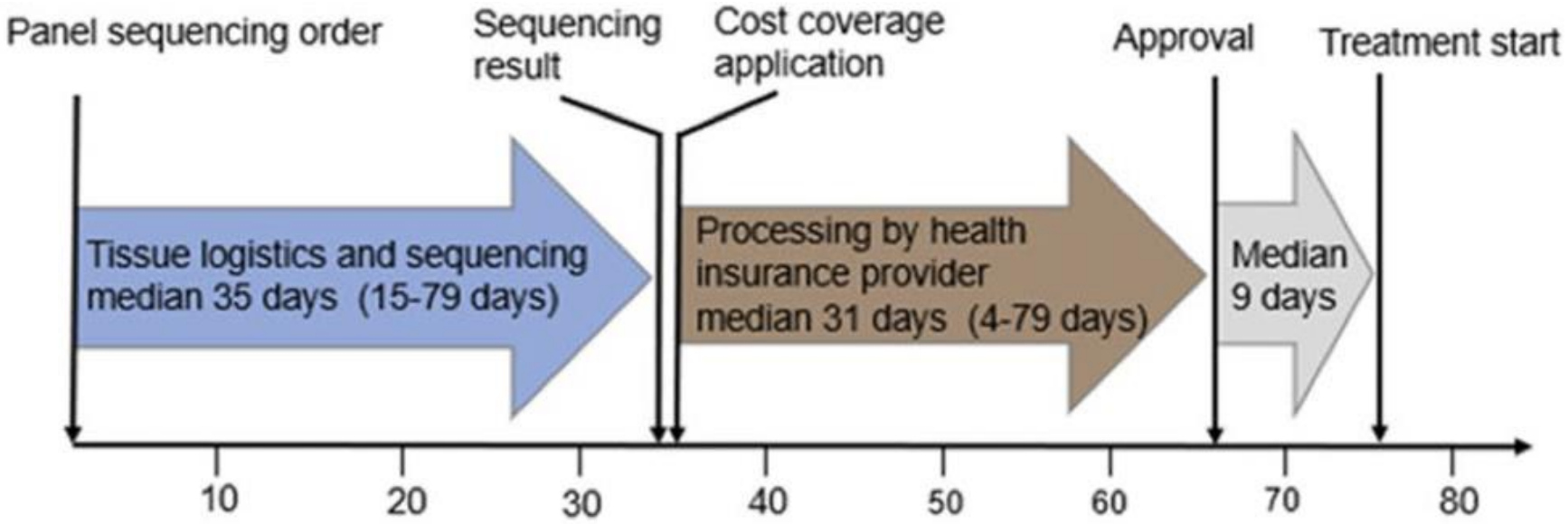
PLATON NETWORK – as an umbrella

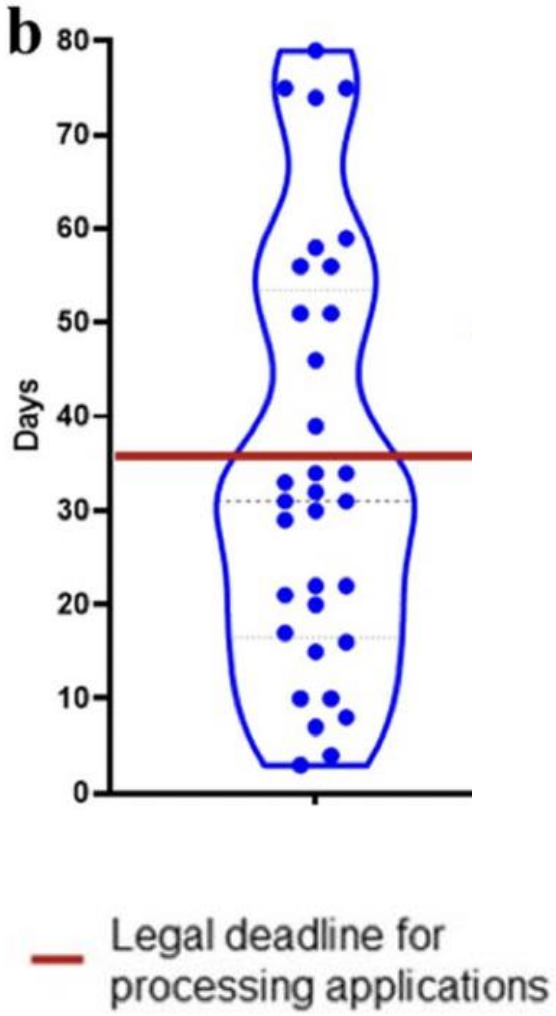
- Connects researchers and health professionals to support **precision oncology**
- Serves as a **screening platform**
- Collects **real world data** of molecularly profiled cancer patients
- Molecular-Pathology Case Discussion
- Acts as umbrella for **subprojects** and **substudies** (by PLATON PIs)
- Designs Educational series for PLATON Members



People: PLATON Members, PLATON PIs, Steering Committee, Pathology Experts

When to test? Early!!!





Median> 70 days from decision of testing to start of therapy

Welland et al, J of Cancer Res and Clin Oncol 2021

Take home messages

- Genomic alterations with potential therapeutic implications have been identified in ~40% of patients with CCA
  - IDH1 mutations: Ivosidenib; FDA & EMA approved
  - FGFR2 fusions: Pemigatinib, Futibatinib; FDA & EMA approved
  - $BRAF^{V600E}$ mutations: Trametinib/Dabrafenib; FDA approved
  - HER2, $KRAS^{G12}$, NTRK, NRG1, MDM2, RET, HDR…
- Collection of a sufficient amount of tumor tissue and use of appropriate NGS tools are essential (panel sequences must cover fusions)
- Timely diagnostic and treatment planning is essential
- We don‘t have good evidence for many alterations → molecular tumor board!
- We need to better understand primary and secondary resistance mechanisms: Detection of a druggable alteration does not guarantee long-term response
- We need new strategies/trail designs to accelerate drug development and approval: ”Classical phase-3 trials in small subgroups of rare tumors are impossible

Contact

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