Intrahepatic Cholangiocarcinoma: Novel Genetic Signatures and Therapeutic Targets

Andrew X. Zhu, MD, PhD

2nd International Conference on Phase 1 and Early Phase Clinical Trials, Hong Kong

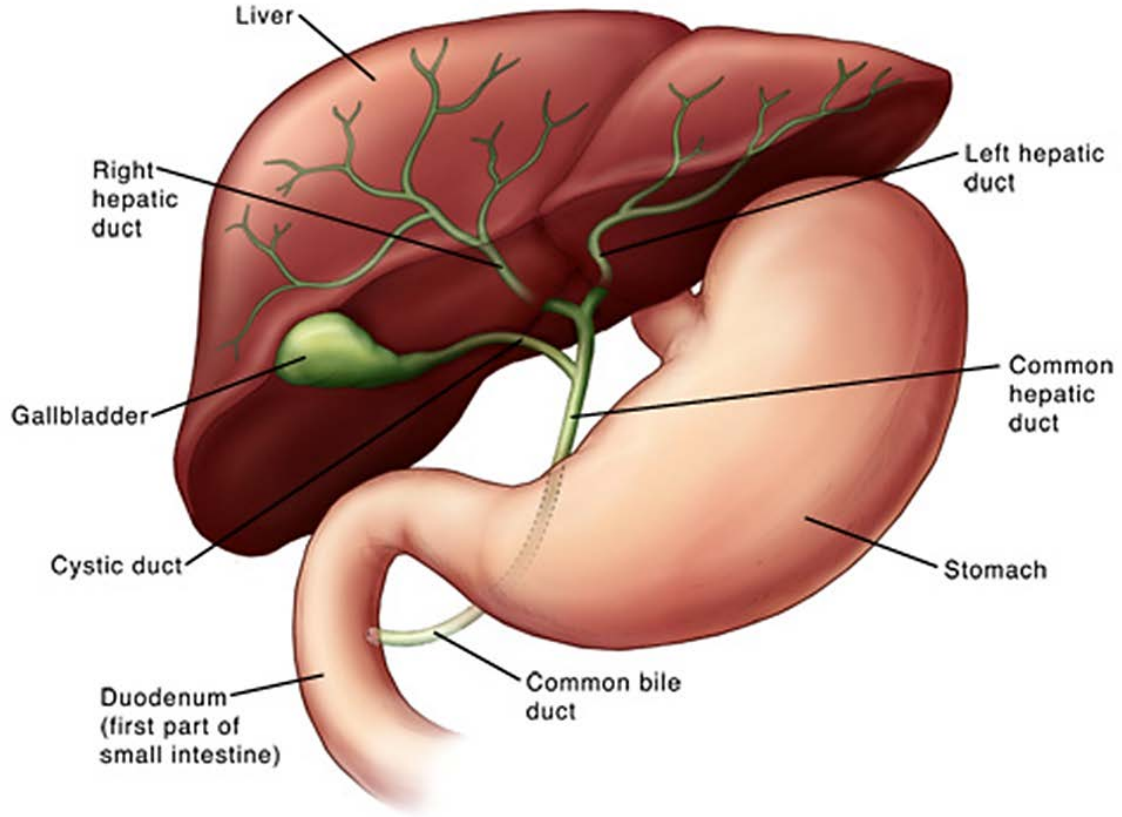
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

HARVARD MEDICAL SCHOOL

Discussion Points

- Epidemiology trends
- Diagnostic challenge
- Current standard treatment options
- New insights on the genetic landscape
- Evolving novel targets
- Future perspectives

Biliary tract cancer | Subtypes



Risk factors for Cholangiocarcinoma

General
- Age>65 yrs
- Obesity
- Diabetes

Inflammatory diseases
- Primary Sclerosing Cholangitis
- Hepatolithiasis
- Biliary tract stone disease
- Biliary-enteric anastomosis
- Liver cirrhosis

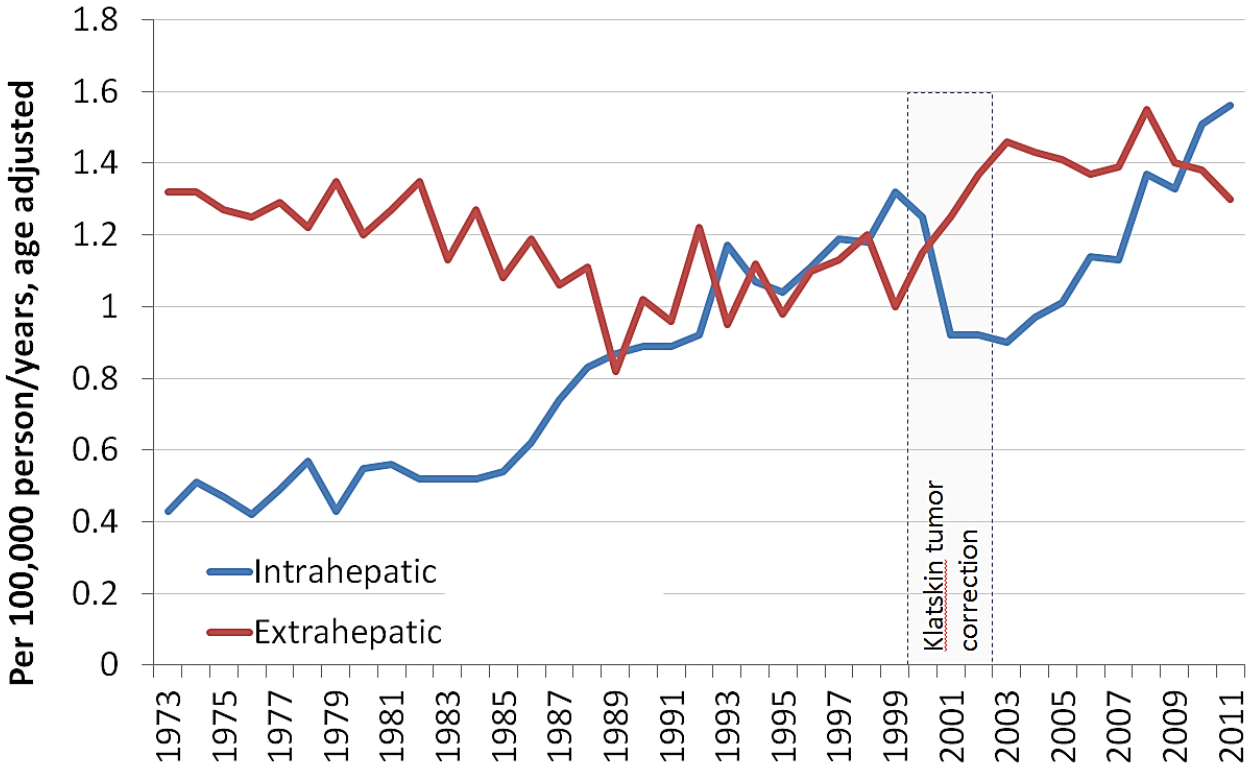
Congenital
- Choledochal cysts
- Caroli's disease
- Congenital hepatic fibrosis

Infectious diseases
- *Opisthorchis viverrini* (liver flukes)
- *Clonorchis sinensis* (liver flukes)
- Hepatitis C
- Hepatitis B
- HIV

Drugs, toxins or chemicals
- Alcohol
- Smoking
- Thorotrast (1920-1950, x300-fold)
- Dioxin
- Vinyl chloride
- Nitrosamines
- Asbestos
- Oral Contraceptive Pill
- Isoniazid

Patel *Nat Rev Gastroenterol Hepatol* 2011

Intrahepatic cholangiocarcinoma (ICC): Rising incidence



Saha, Zhu, Fuchs, Brooks, SEER 9 data, unpublished

Intrahepatic cholangiocarcinoma: Most common cause of carcinoma of unknown primary

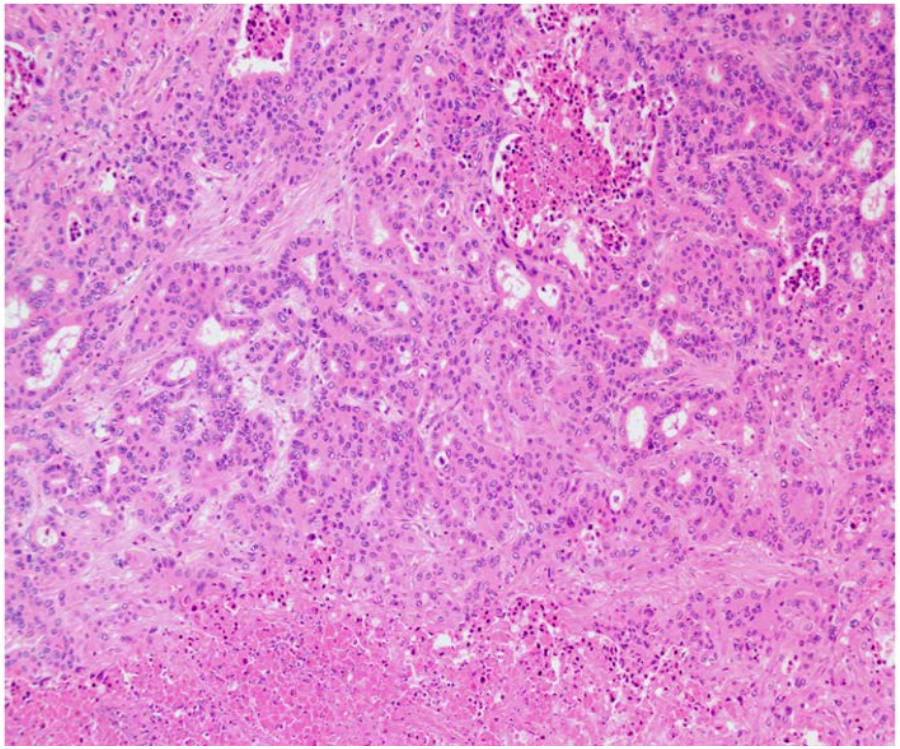
Predicted tissue of origin	Number of patients (n=253)	%
Biliary tract (gallbladder, bile ducts)	52	21
Urothelium	31	12
Colorectum	28	11

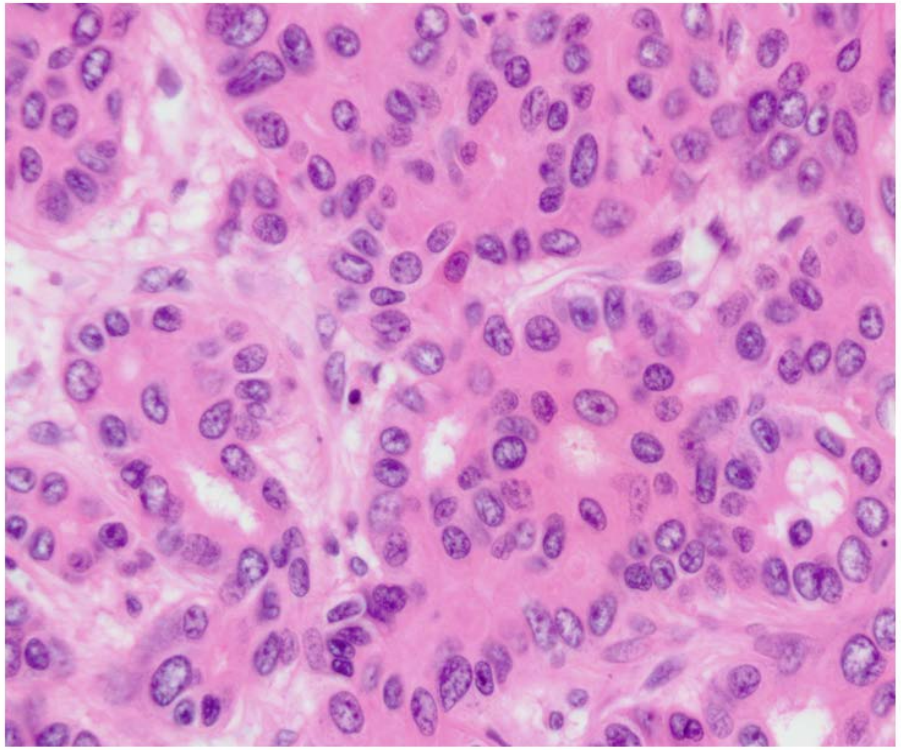
Hainsworth JCO 2013

Cholangiocarcinoma

IHC

CK7, CK19, CA19-9 positive, CEA diffusely positive in the cytoplasm, and CK20, CDX2 negative





Novel Branched DNA–Enhanced Albumin RNA In Situ Hybridization Technology

66 of 69 IHCCs (96%) were positive for albumin expression

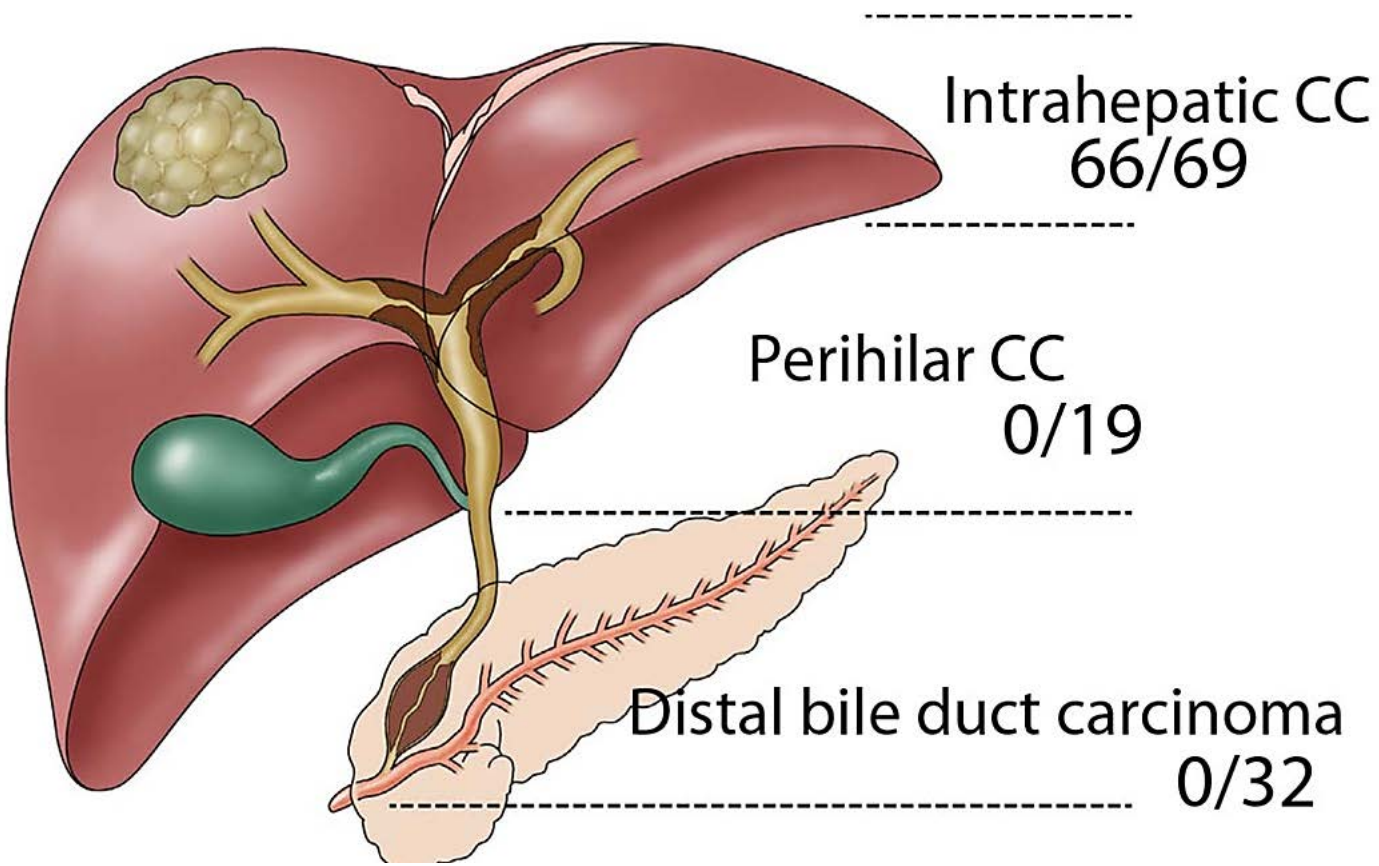
- 8 of 8 well-differentiated (100%)
- 41 of 43 moderately-differentiated (95%)
- 17 of 18 poorly-differentiated (94%)

42 of 42 HCCs (100%) were positive for albumin expression

0 of 351 non-hepatic carcinomas were positive for albumin expression

- This group included adenocarcinomas from the lung (N =22), esophagus (N =40), stomach (N =72), colon (N =40), gallbladder (N=10), pancreas (N =95), urogenital tract (N=8), ovary (N=8), and endometrium (N=8)
- Additionally, 22 carcinomas metastatic to the liver from known primary tumors of the colon, breast and lung were evaluated

Ferrone *Ann Surg Oncol* 2015

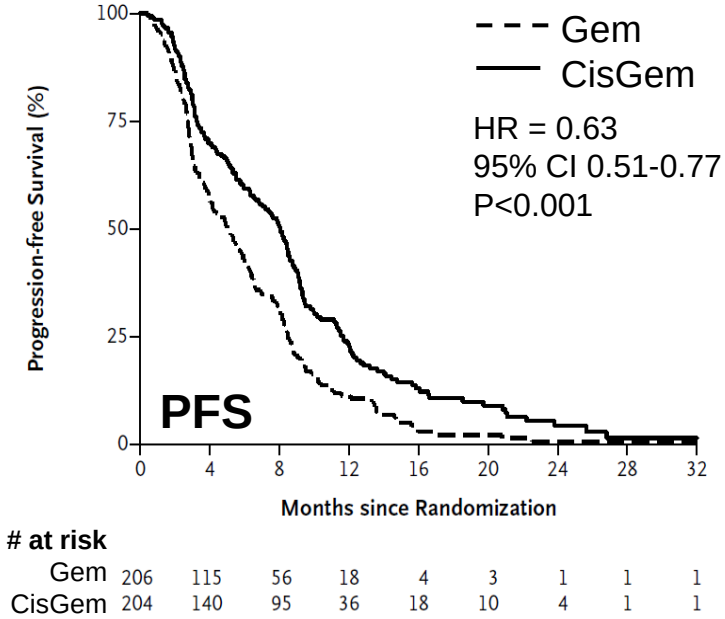


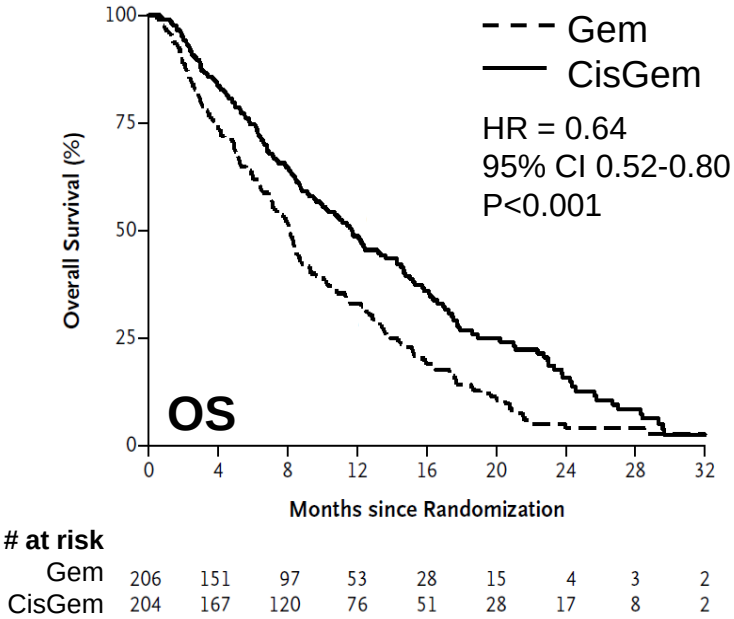
Courtesy of Dr. Vikram Deshpande

Treatment of Intrahepatic Cholangiocarcinoma

- Surgical resection: the only potentially curative regimen
- No definitive benefit for adjuvant chemo, radiation or chemoradiation therapy
- For unresectable cancer:
  - Decompression of obstructive biliary tree: important palliative regimen
  - Consideration of local-regional therapy
  - Systemic chemotherapy
  - Best supportive care

Level 1 evidence: Cisplatin + gemcitabine





		PFS (months)		**OS** (months)	
Study	**Reference**	**Gem**	**CisGem**	**Gem**	**CisGem**
ABC-02	Valle *NEJM* 2010	5.0	8.0	8.1	**11.7**
BT-22	Okusaka *BJC* 2010	3.7	5.8	7.7	**11.2**

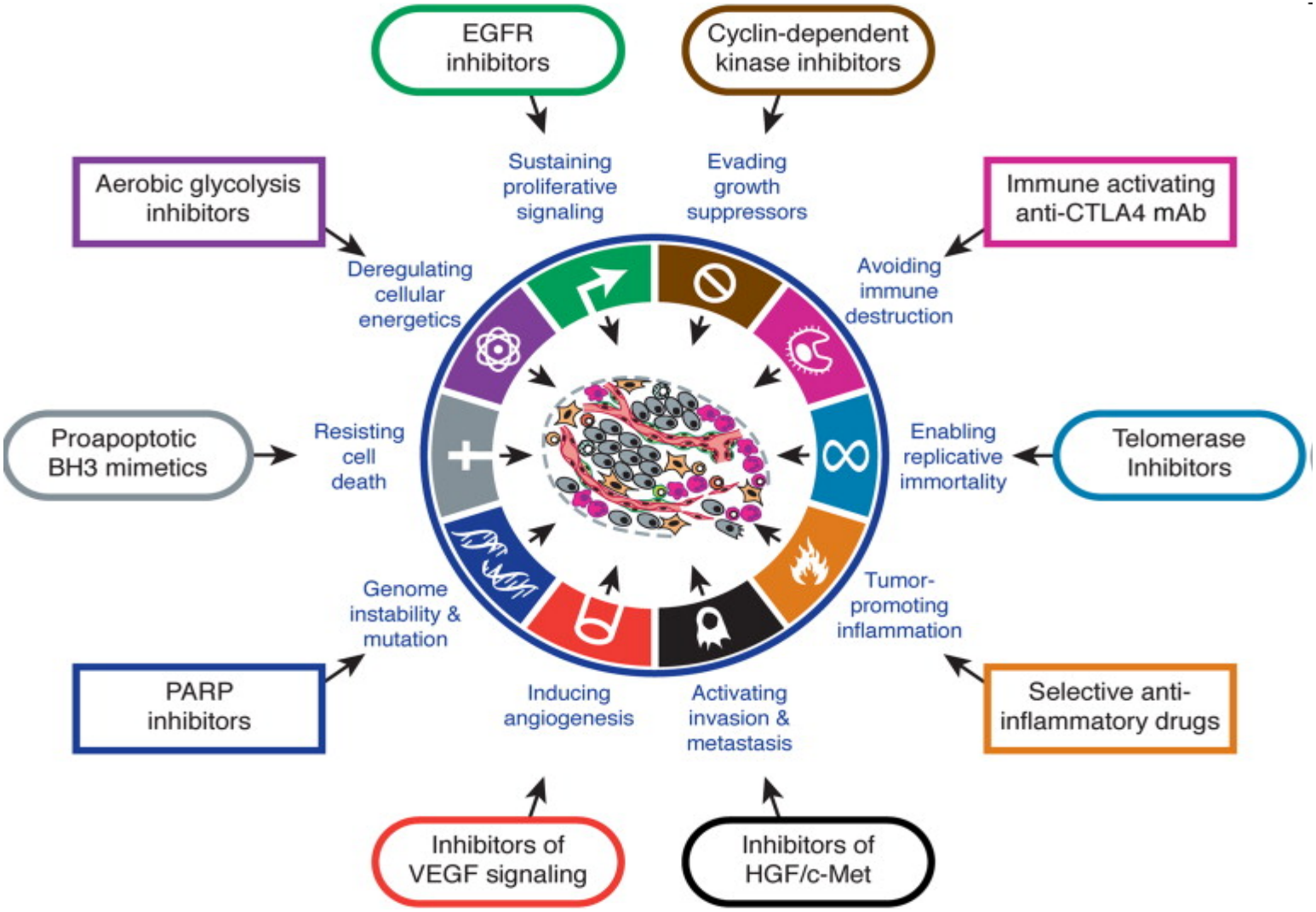
Valle et al. NEJM 2010; Okusaka et al, Br J Cancer 2010

Second Line Treatment for Advanced BTCs

- Large retrospective study from Princess Margaret Hospital: 378 received fist line chemo and 96 (25%) received 2nd chemo
- RR and SD for 2nd line chemo: 9% and 34%, respectively
- PFS and OS for 2nd line chemo: 2.8 m and 7.5 m respectively

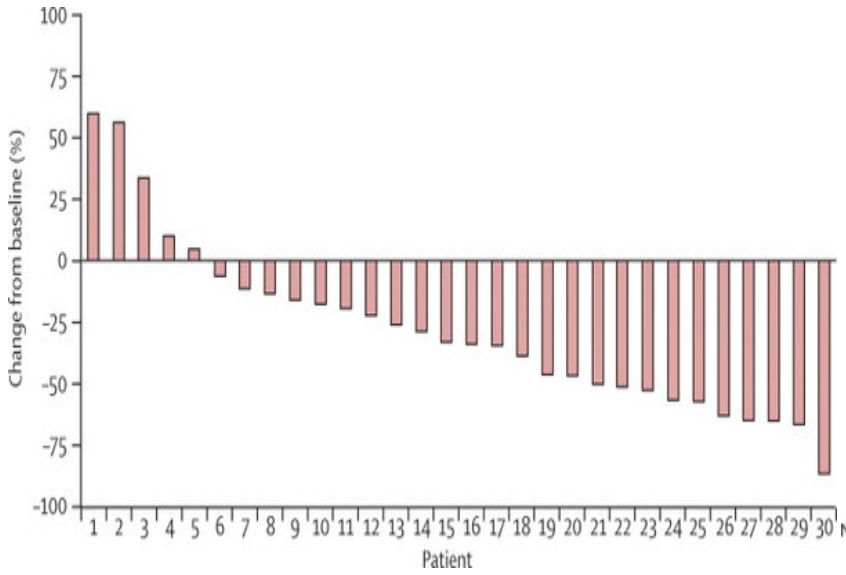
Walter T et al, Eur J Cancer 2013

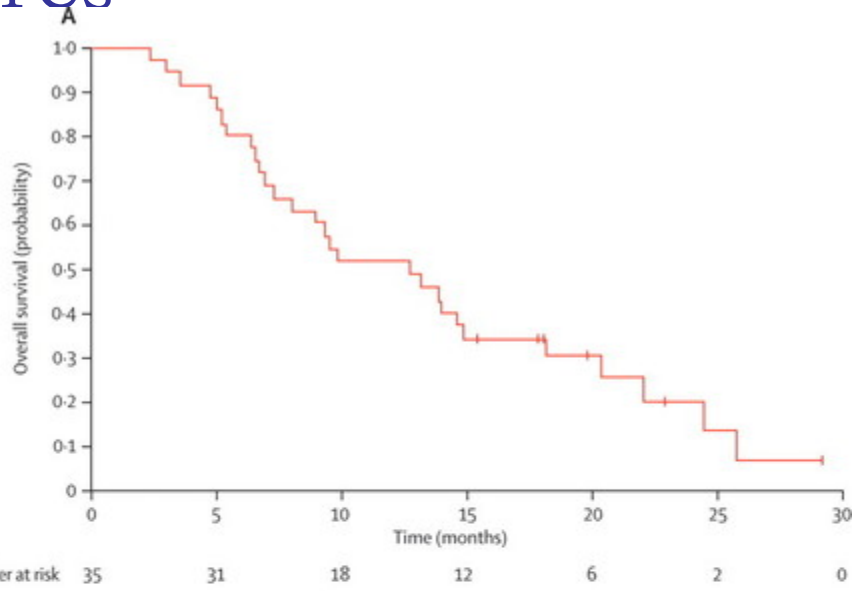
Therapeutic Targeting of the Hallmarks of Cancer



Hanahan and Weinberg, Cell,

Phase II study with GEMOX-Bevacizumab in advanced BTCs



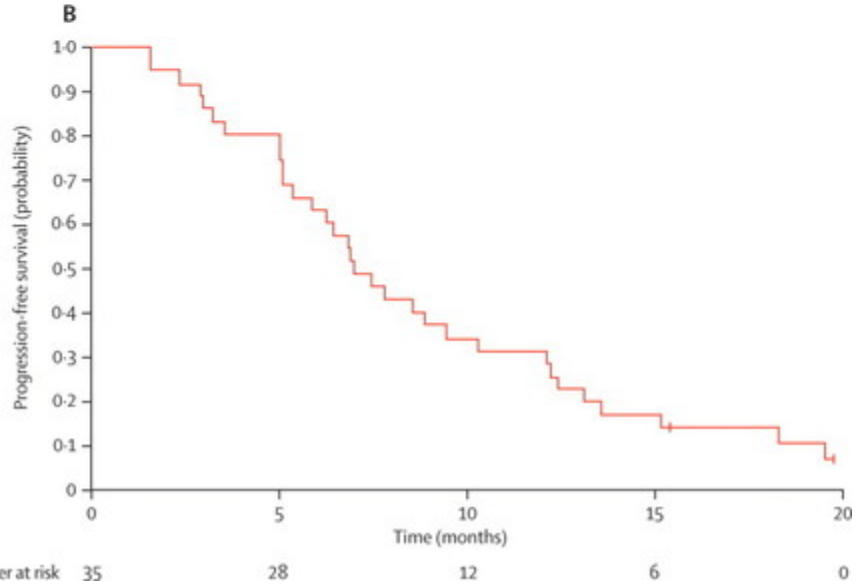


35 patients treated

RR: 40%, SD: 29%

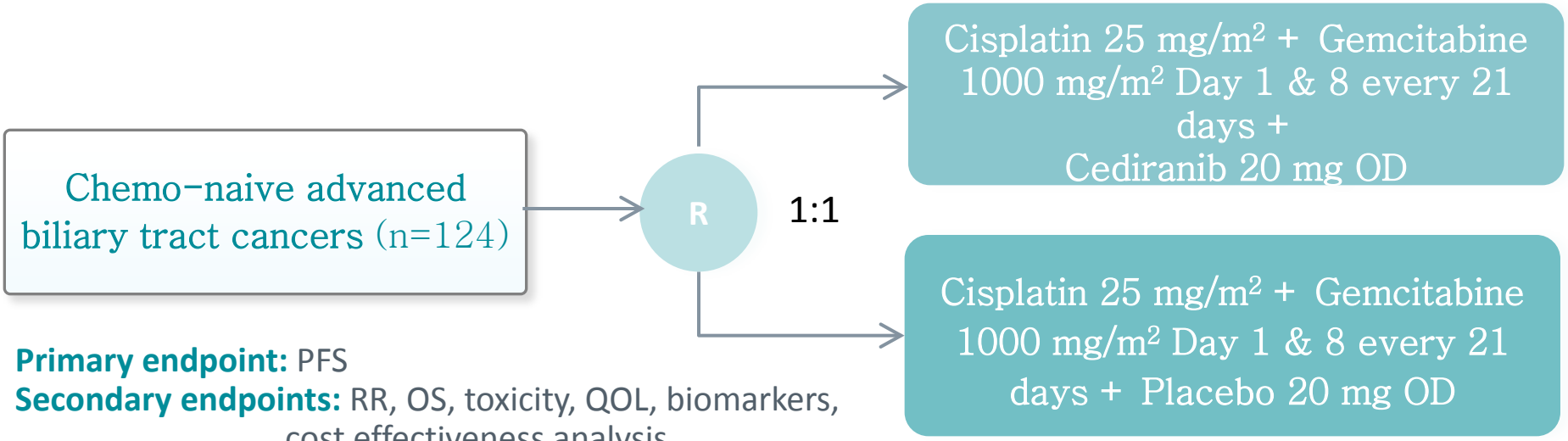
PFS: 7.0 months (95% CI, 5.3–10.3 months)

Median OS: 12.7 months (95% CI, 7.3–18.1 months)



Zhu et al, *Lancet Oncol*, 2010

ABC-03: A randomized phase II trial of cediranib or placebo in combination with cisplatin/gemcitabine (CisGem) in advanced biliary tract cancer



Primary endpoint: PFS
Secondary endpoints: RR, OS, toxicity, QOL, biomarkers, cost effectiveness analysis

Outcome	Gem/Cis + Cediranib (n=62)	Gem/Cis (n=62)	Hazard ratio (95% Ci)	p-value
PFS, mths	8	7.4	0.93 (0.65-1.35)	0.72
OS, mths	14.1	11.9	0.86 (0.58-1.27)	0.44
ORR, %	44	19		0.0036

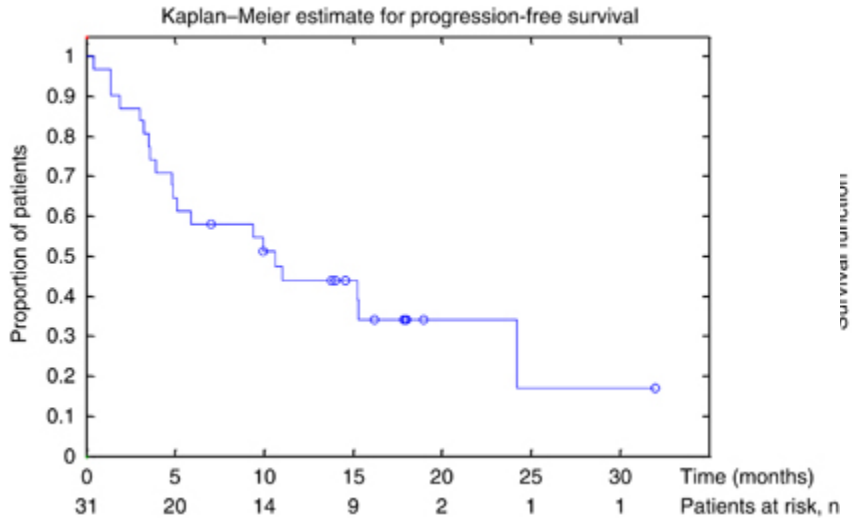
Valle, et al. Lancet Oncol, 2015

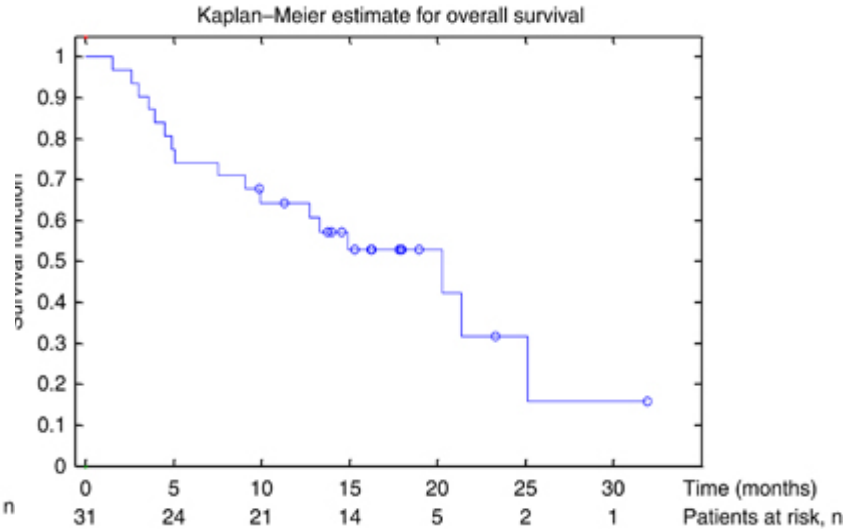
EGFR inhibition: 3 negative randomized studies

Study	Regimens	Phase	RR (%)		Median PFS (months)		Median OS (months)	
			Chemo alone	With biological	Chemo alone	With biological	Chemo alone	With biological
Malka[1]	GemOx +/- cetuximab	2	23	23	5.5	6.1	12.4	11.0
Chen[2]	GemOx +/- cetuximab	2	15	27	4	7.1	8.8	10.3
Lee[3]	GemOx +/- erlotinib	3	16	30	4.2	5.8	9.5	9.5
ABC-02[4]	*CisGem (for reference)*		*26*		*8.0*		*11.7*	

[1] Malka *Lancet Oncol* 2014, [2] Chen *J Clin Oncol* 2013, [3] Lee *Lancet Oncol* 2012, [4] Valle *NEJM* 2010

Phase II study of gemcitabine, oxaliplatin in combination with panitumumab in KRAS wild-type unresectable or metastatic biliary tract and gallbladder cancer





RR 45%, Median PFS 10.6m, Median OS 20.3m

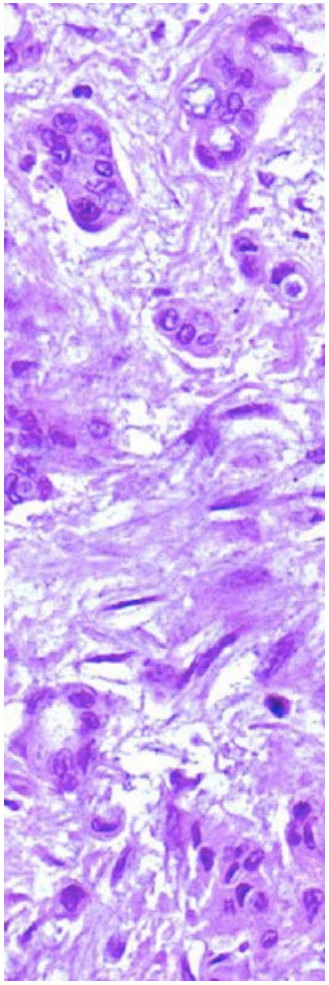
Hezel et al, *Br J Cancer*, 2011

Phase II Study of Selumetinib in Metastatic BTCs

- 28 pts treated: 39% had one prior systemic chemo
- Clinical outcome: RR 12%, SD (67%), PFS 3.7 months, OS 9.8 months
- Rash (90%) and xerostomia (54%)
- No *BRAF* V600E mutations were found
- Absence of pERK staining was associated with lack of response

Bekaii-Saab T et al, J Clin Oncol., 2011

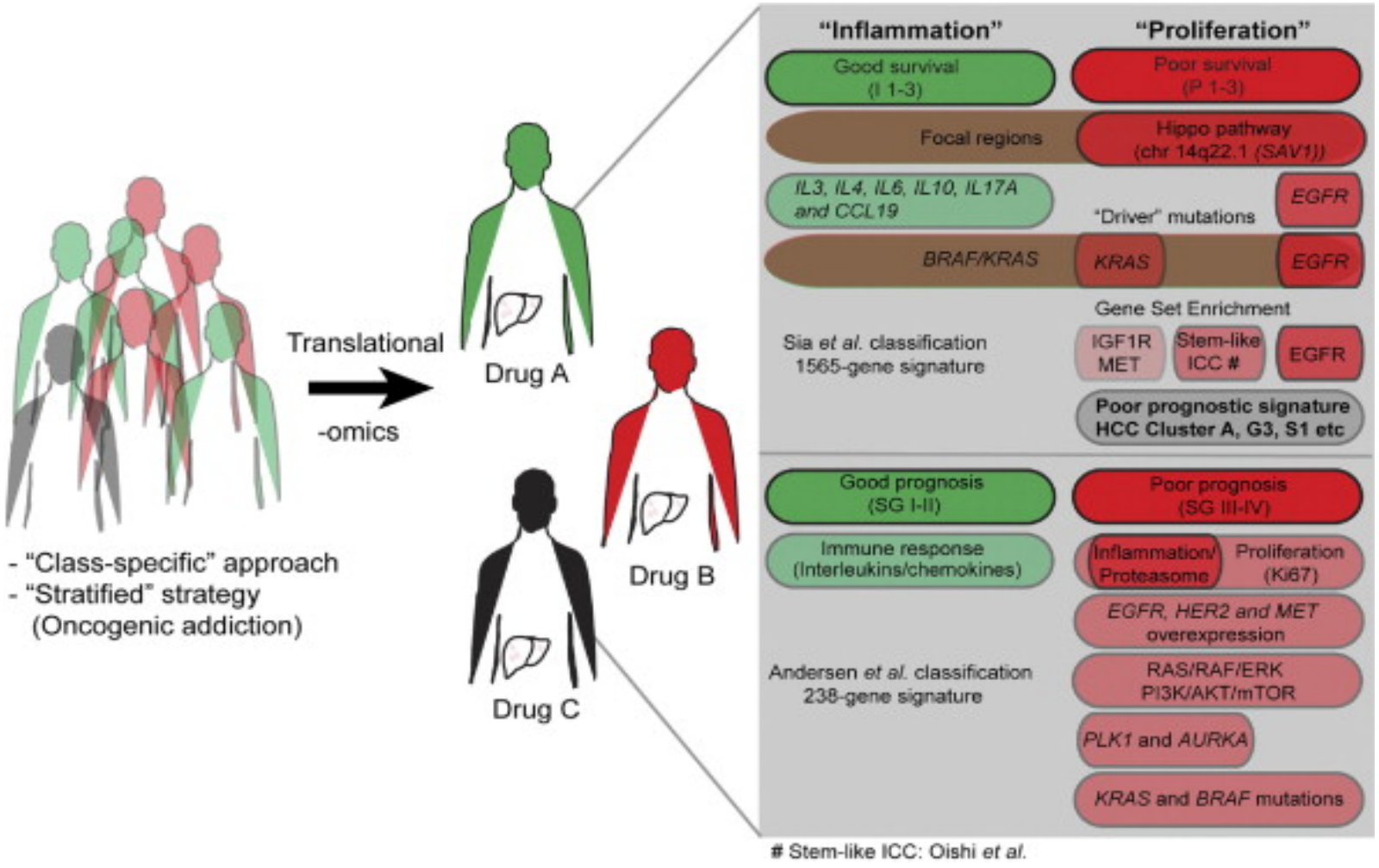
Biliary Tract Cancer: Genetics



- KRAS ~ 20-40%
- EGFR ~5-20%
- HER2NEU ~10-20% GBC
- PI3K ~5-10%
- P16/INK4A ~40%
- P53 ~50%
- SMAD4 ~30%
- LKB1
- A wide spectrum of gross chromosomal abnormalities.

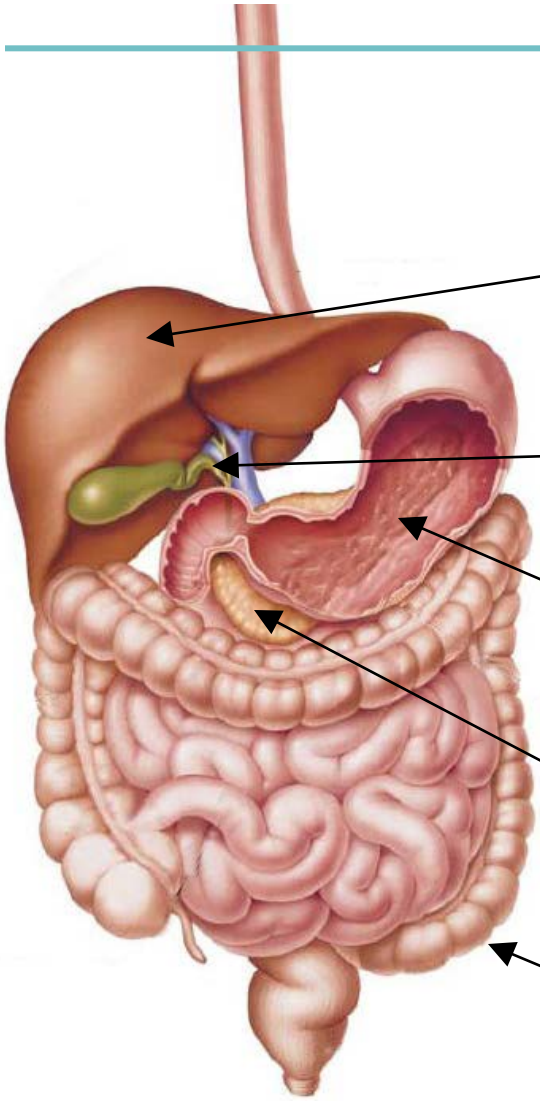
Hezel AF, Deshpande V, Zhu AX, JCO, 2010

Classification and characterization of intrahepatic cholangiocarcinoma

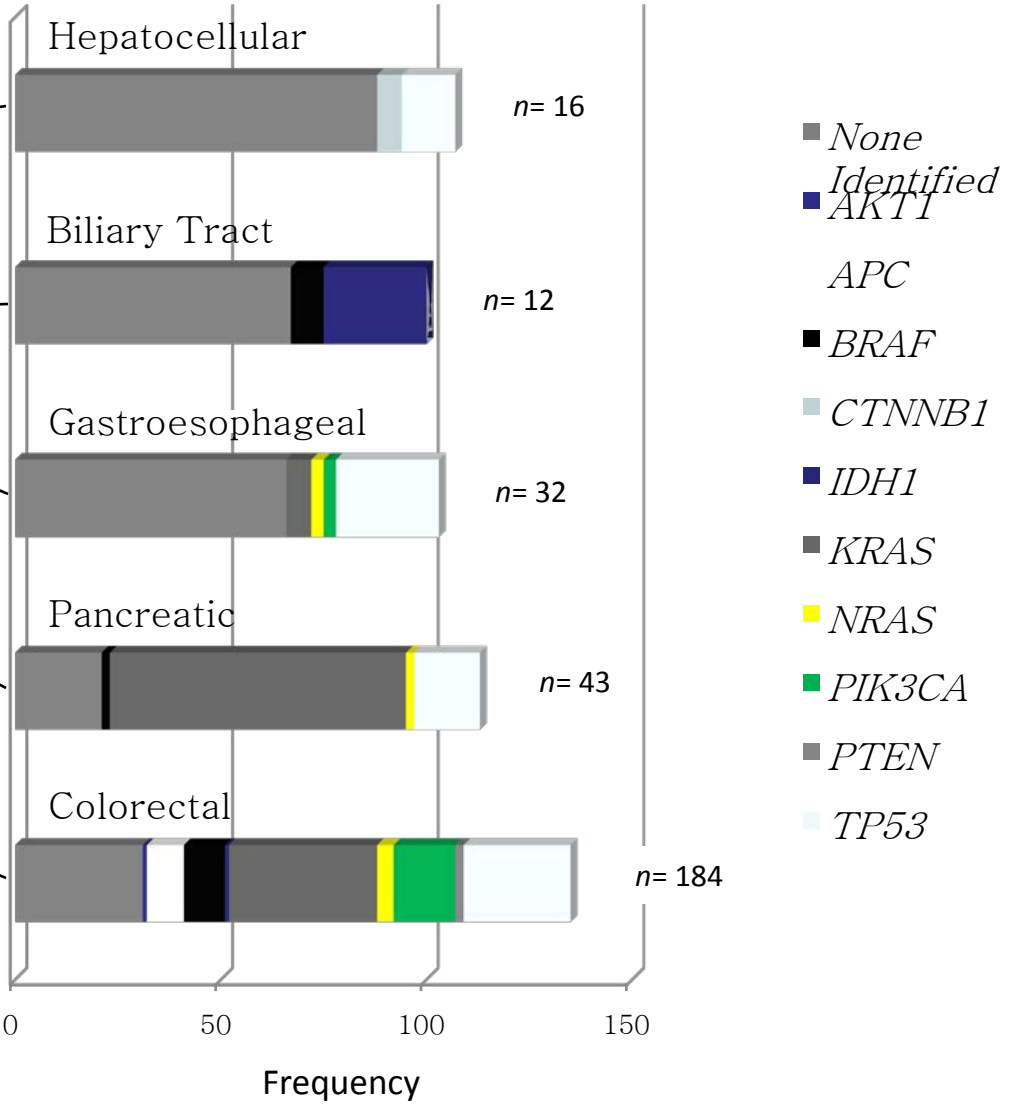


Anderson JB et al, Gastroenterology, 2012
Sia D et al, Gastroenterology, 2013

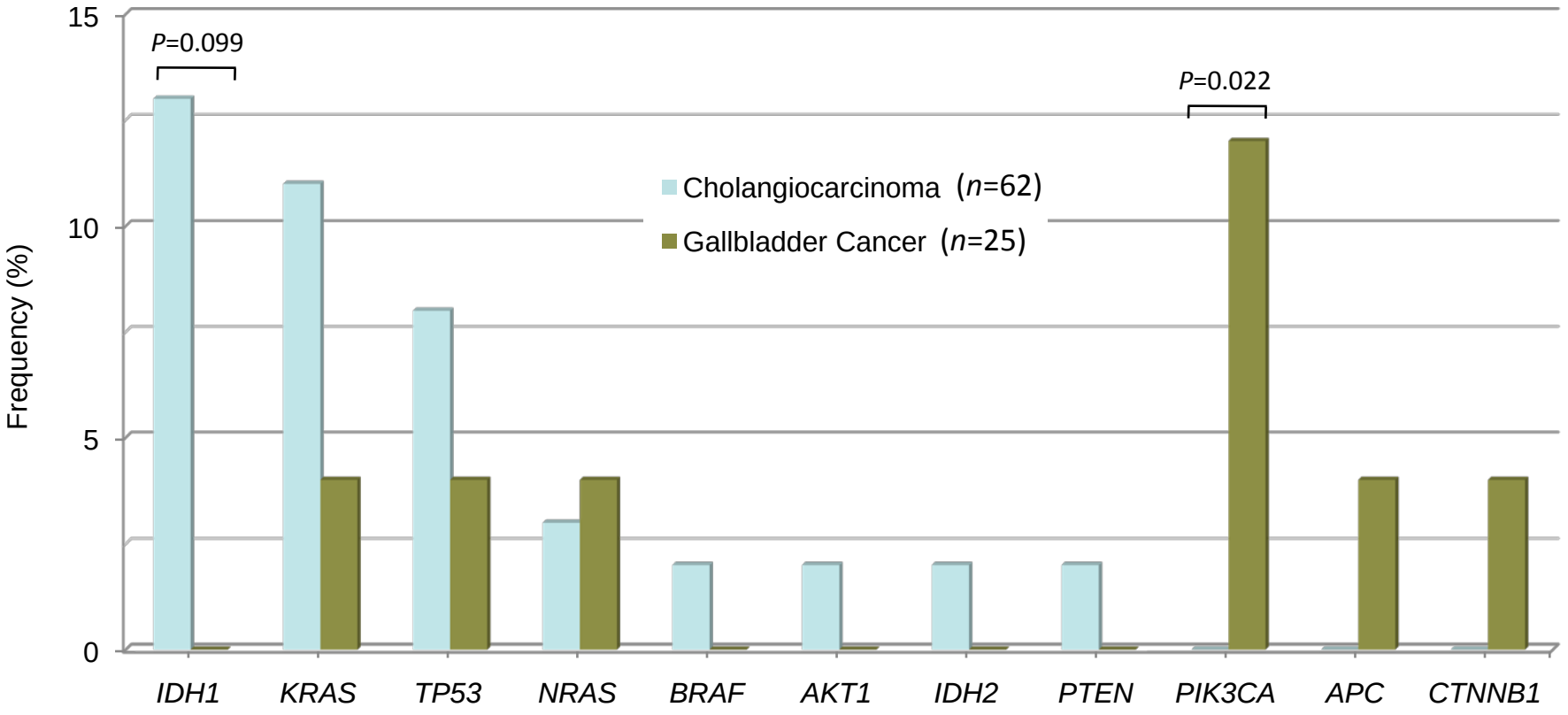
SNaPshot Mutational Profile by Gastrointestinal Organ



http://www.pfizerpro.com/resources/minisites/oncology/img/digestiveTract.jpg



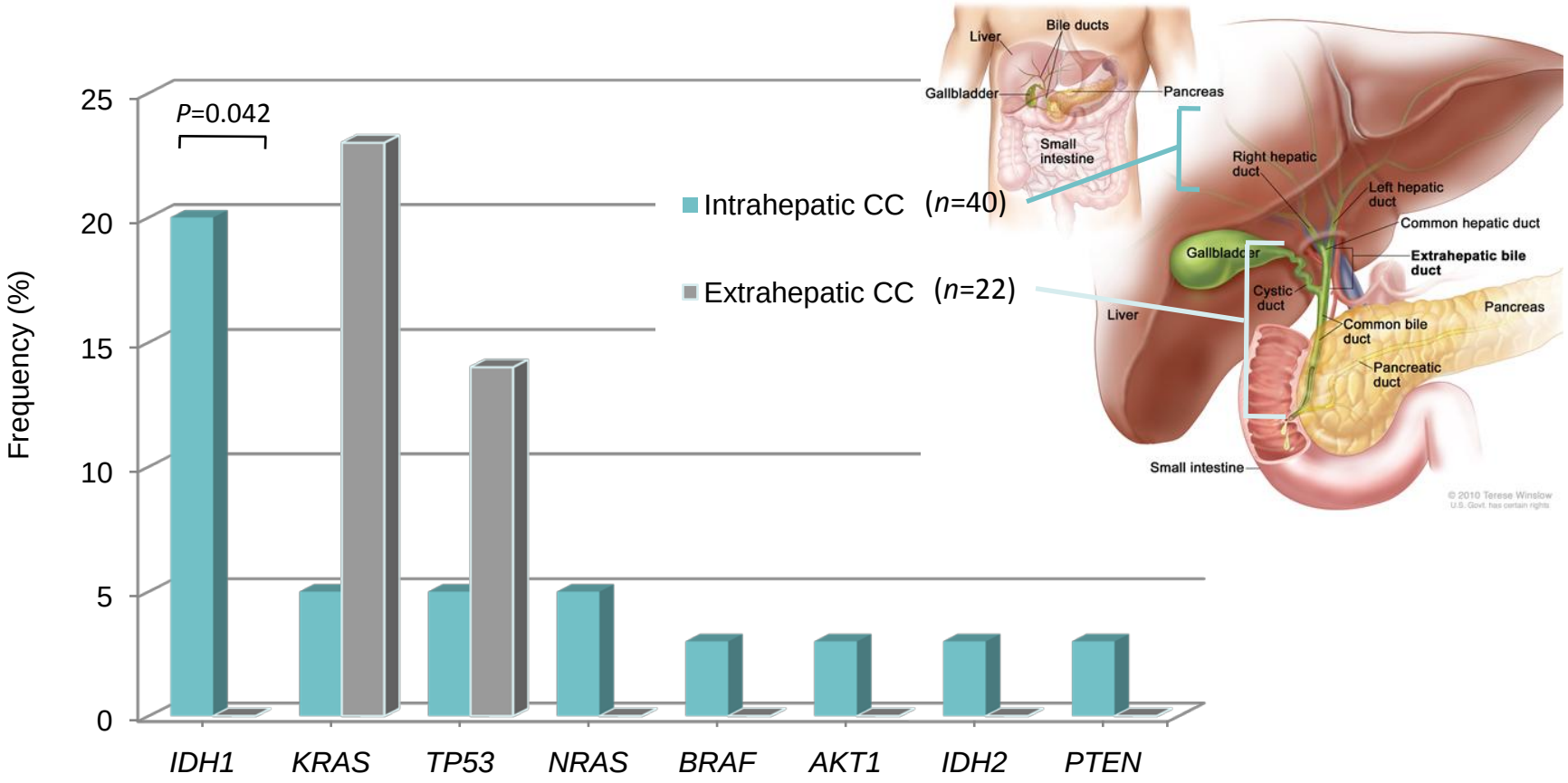
Biliary Tract Cancers Are Genetically Diverse



Borger et al, The Oncologist, 2011

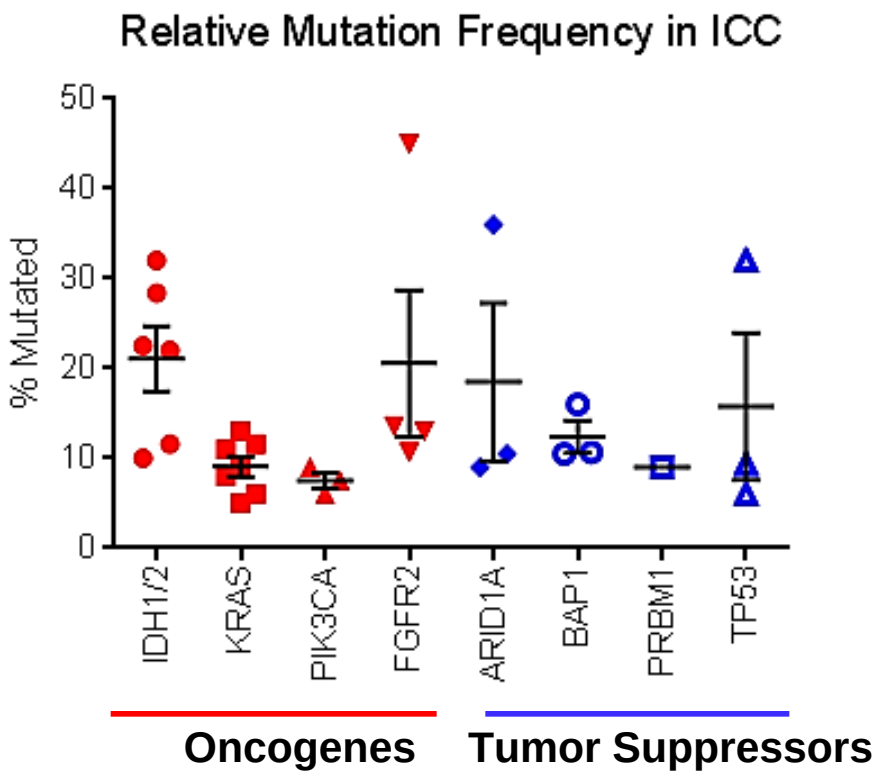
IDH1 and IDH2 Mutations Specifically in Intrahepatic Cholangiocarcinomas

http://www.cancer.gov/images/cdr/live/CDR659742-571.jpg



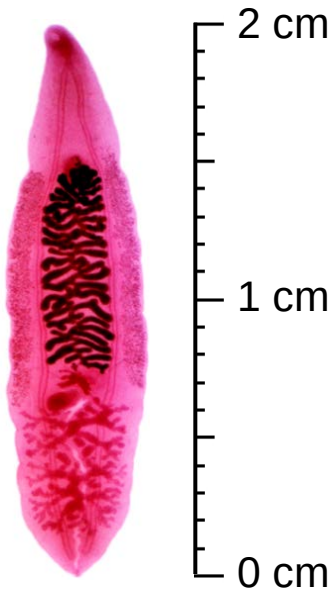
Borger et al, The Oncologist, 2011

IDH mutations found in 10-35% of ICC



Desphande *BMC Cancer* 2011
Borger *The Oncologist* 2012
Voss *Human Pathology* 2013
Sia *Gastroenterology* 2013
Ross *The Oncologist* 2014
Jiao *Nature Genetics* 2013
Chan-on *Nature Genetics* 2013
Wang *Oncogene* 2012
Riener *Genes Chromosomes Cancer* 2008
Wu *Cancer Discovery* 2013
Graham *Human Pathology* 2014
Arai *Hepatology* 2014
Sia *Nature Communications* 2015

Differential genetics of liver fluke associated vs non-liver fluke associated biliary tract cancer

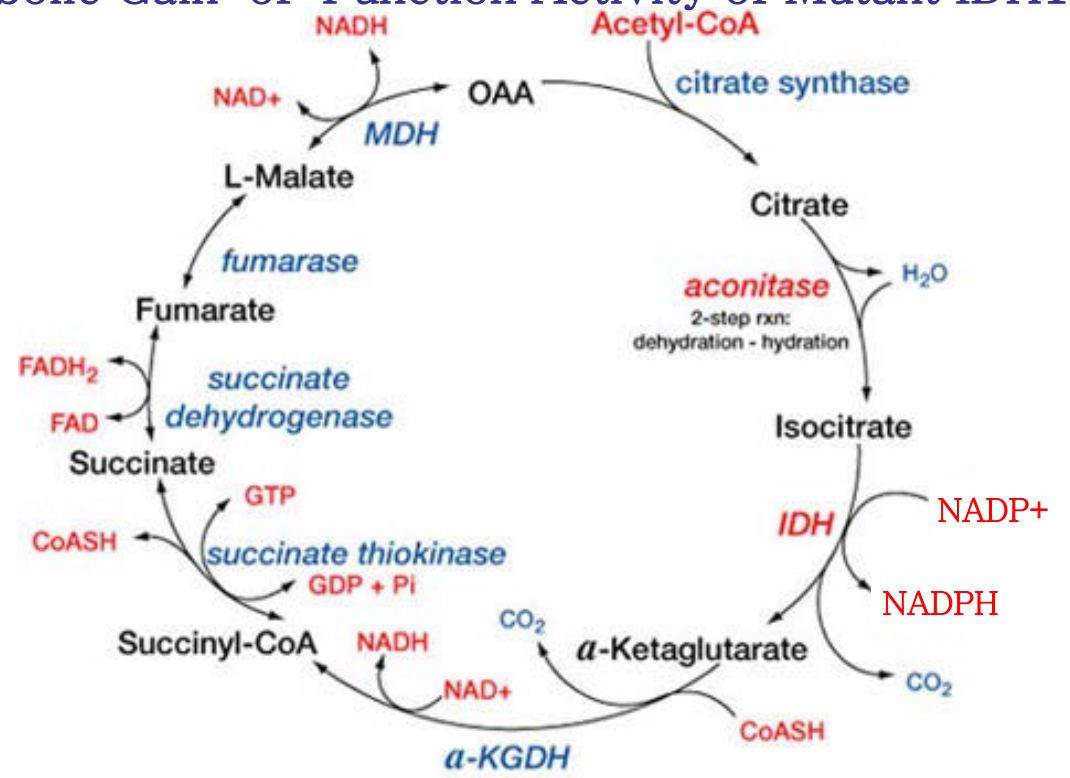


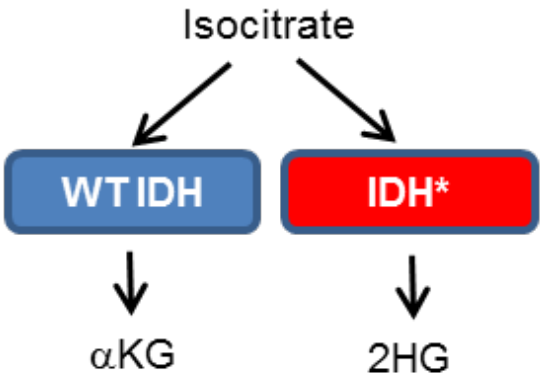
Cochineal and haematoxylin

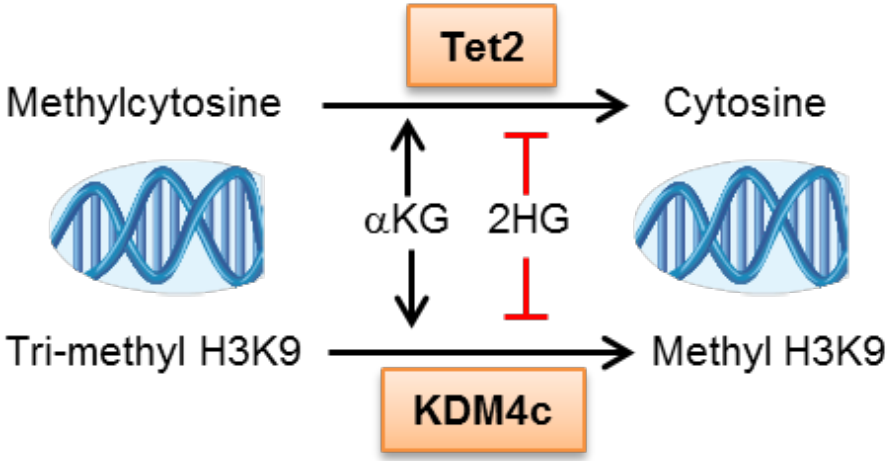
Gene	O. viverrini (%)	Non-O. viverrini (%)	FDR
TP53	39.8	9.3	1.16×10^{-5}
SMAD4	19.4	5.8	0.029
MLL3	13	3.5	0.071
GNAS	5.6	0	0.071
IDH1/2	2.8	9.3	0.107
ROBO2	5.6	2.3	0.381
RNF43	7.4	3.5	0.391
KRAS	13.9	11.6	0.673

Adapted from Chan-on *Nature Genetics* 2013

Metabolic Gain-of-Function Activity of Mutant IDH1 in Cancer

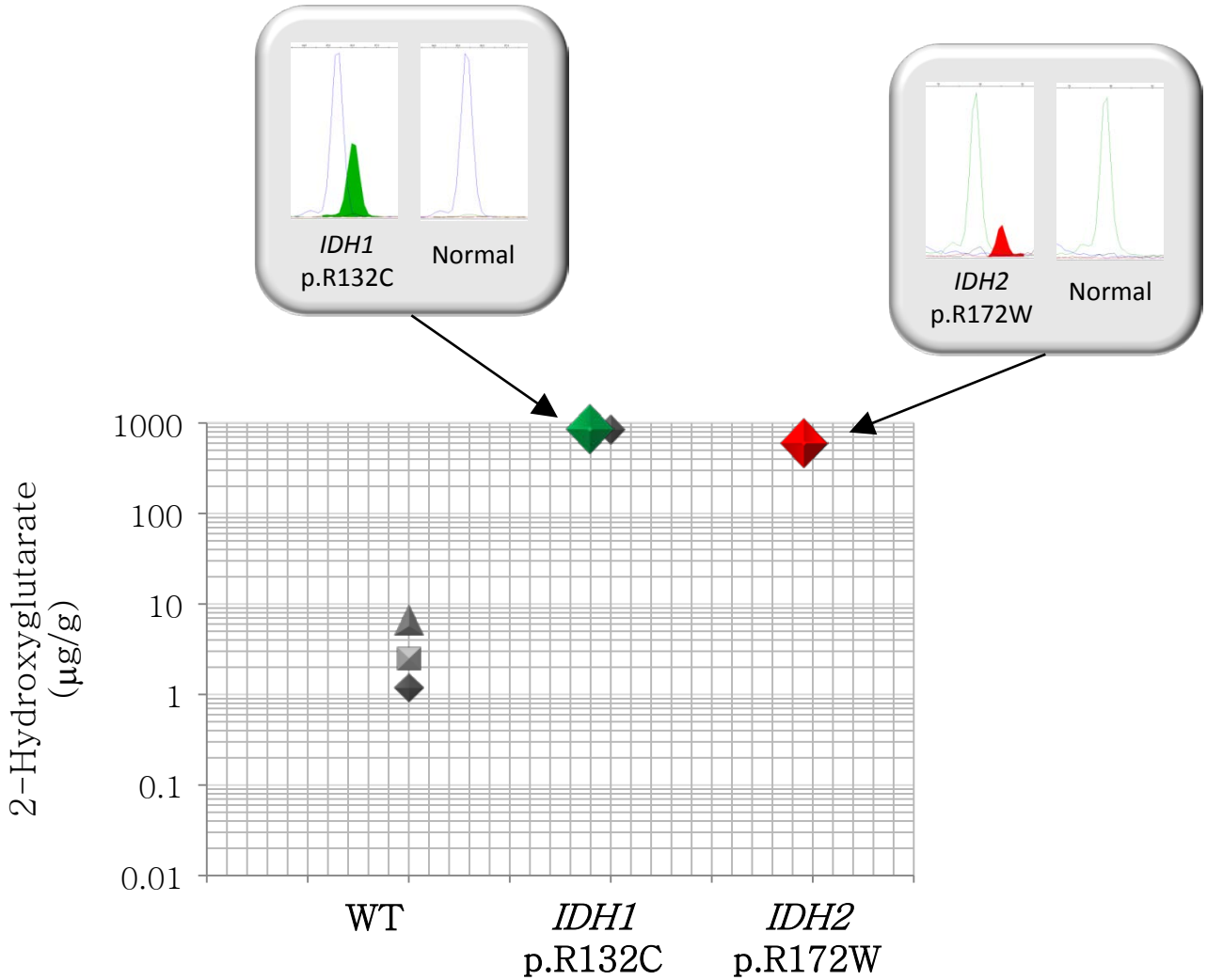






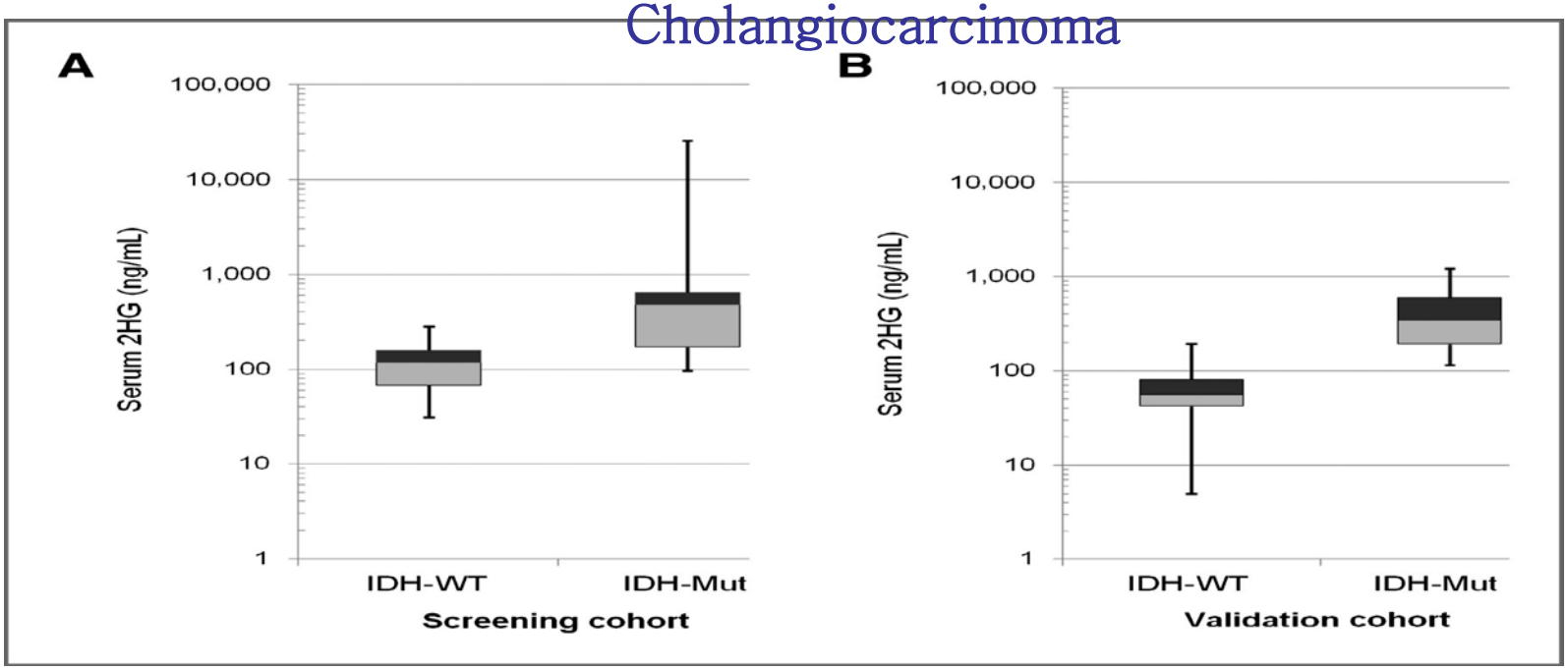
Adapted from Lu, C., Thompson, CB. Cell Metabolism,

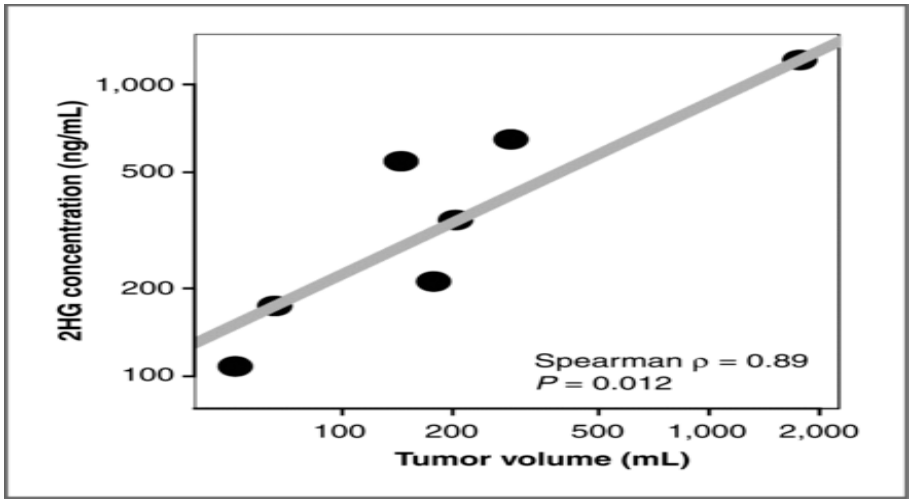
IDH1/2 Mutations in Cholangiocarcinoma Are Associated with Tumor 2HG Accumulation



Borger et al, The Oncologist, 2011

Circulating Oncometabolite 2-Hydroxyglutarate Is a Potential Surrogate Biomarker in Patients with *IDH*-Mutant Intrahepatic Cholangiocarcinoma





- Serum 2HG in the screening cohort and validation cohort were significantly elevated in patients with *IDH1/2*-mutant ($P < 0.001$);
- Levels of 2HG directly correlated with tumor burden in *IDH1/2*-mutant cases ($P < 0.05$)

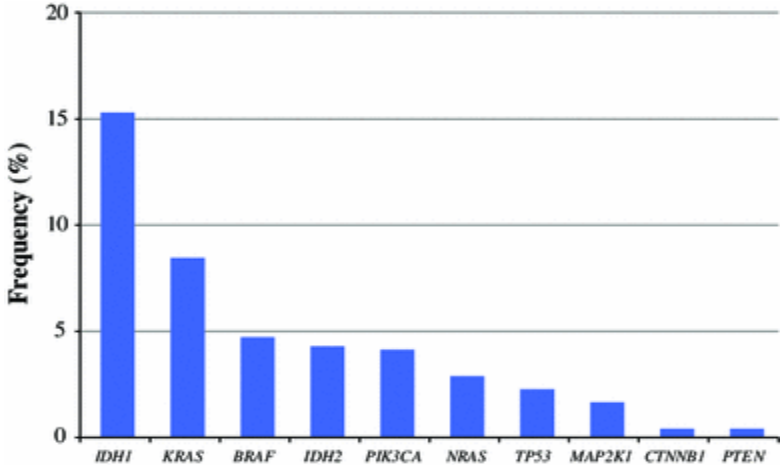
Borger et al, *Clin Cancer Res*, 2014

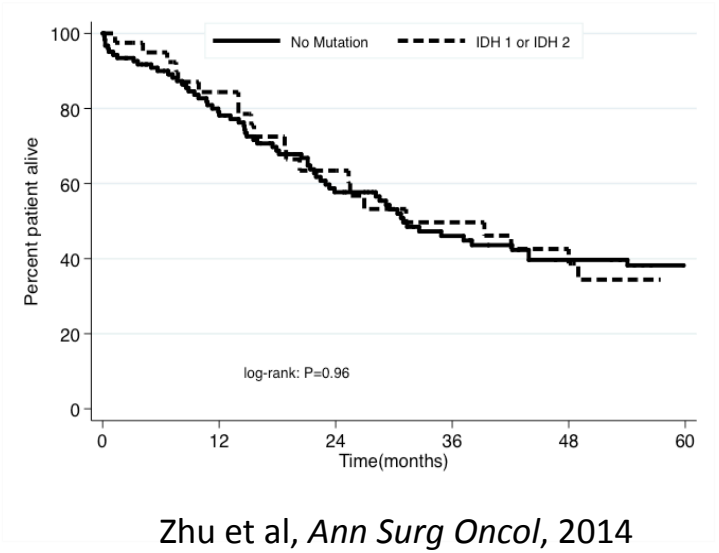
Prognostic Significance of IDH Mutations in ICC

The International ICC Collaborative Group

- Massachusetts General Hospital, Boston, MA
- Johns Hopkins School of Medicine, Baltimore, MD
- University of Virginia, Charlottesville, VA
- Fundeni Clinical Institute of Digestive Disease, Bucharest, Romania
- Medical College of Wisconsin, Milwaukee, WI
- Cliniques Universitaires Saint-Luc, Brussels, Belgium
- Queen Mary Hospital, The University of Hong Kong, China

All patients undergoing liver resection for ICC between 1973 and 2013 (n=200)





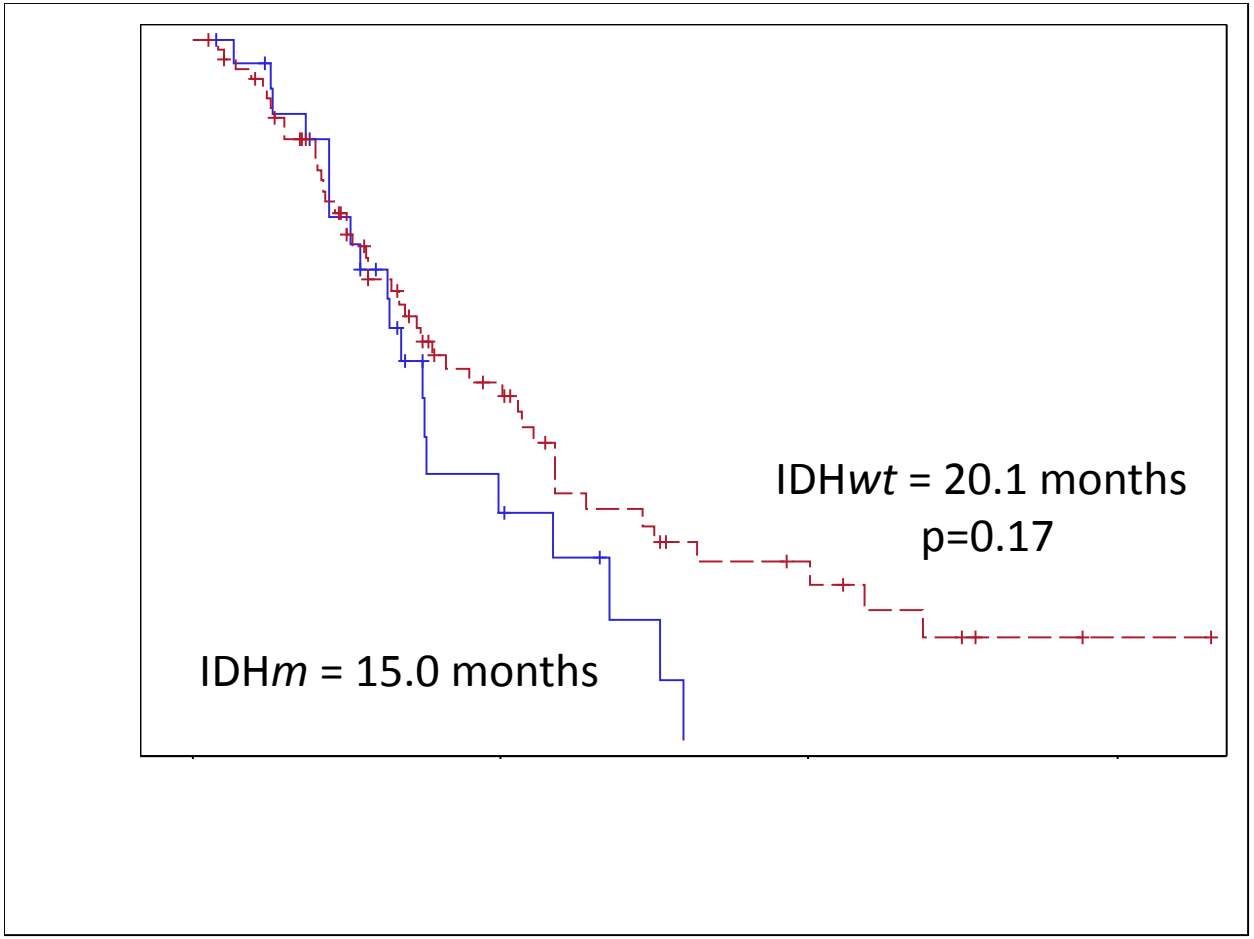
Zhu et al, *Ann Surg Oncol*, 2014

Baseline Characteristics for Patients with Advanced IDH mutant vs IDH wildtype Intrahepatic Cholangiocarcinoma

	IDH mutants (n=30)	IDH wild type (n=74)	p-value
Median age at diagnosis (range)	59 (24-77)	61 (23-83)	0.26
Male Gender [n, (%)]	12 (40%)	35 (47%)	0.50
Median Baseline CA19-9 (range)*	34.5 (1-533)	118.0 (1-94432)	0.04
Median Tumor Volume (range)*	184.0 (1.87-1074.0)	118.7 (0.8-1487.5)	0.40
Median Ratio of CA19-9 to Tumor Volume (range) *	0.51 (0.0045-4.25)	1.37 (0.0034-846.2)	0.04
Median Baseline total bilirubin (mg/dL)*	0.5 (0.3-6.3)	0.6 (0.1-22.1)	0.75
Site of Metastasis at any time [n, (%)]			
Liver	23 (76.7%)	57 (77.0%)	0.78
Lymph node	14 (46.7%)	48 (64.9%)	0.06
Lung	9 (30.0%)	31 (41.9%)	0.24
Peritoneum	7 (23.3%)	24 (32.4%)	0.32
Bone	7 (23.3%)	10 (13.5%)	0.26
Other	0 (0%)	9 (12.2%)	0.06
Histology [n, (%)]			0.28
Well differentiated	2 (6.7%)	7 (9.46%)	
Well to Moderately differentiated	0 (0%)	1 (1.35%)	
Moderately differentiated	7 (23.3%)	24 (32.4%)	
Moderately to Poorly differentiated	2 (6.7%)	9 (12.2%)	
Poorly differentiated	11 (36.7%)	13 (17.6%)	
Presentation [n, (%)]			0.76
Primary Unresectable or Metastatic	21 (70.0%)	54 (73.0%)	
Recurrent Metastatic	9 (30.0%)	20 (27.0%)	

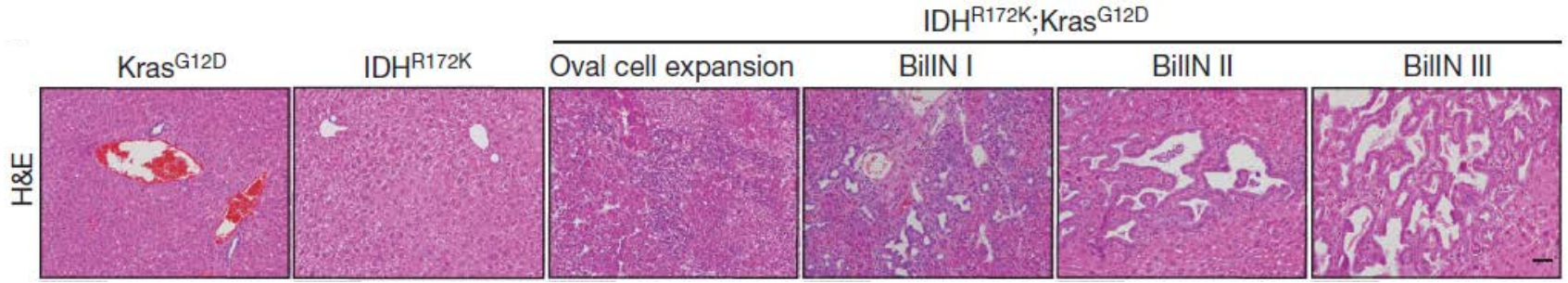
Goyal, etal, *The Oncologist*, 2015

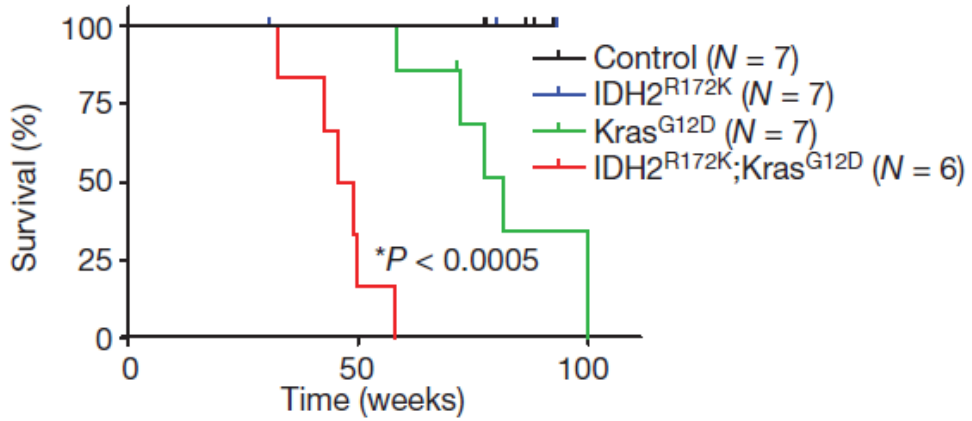
Overall survival of patients with IDH*m* versus IDH*wt* unresectable or metastatic intrahepatic cholangiocarcinoma

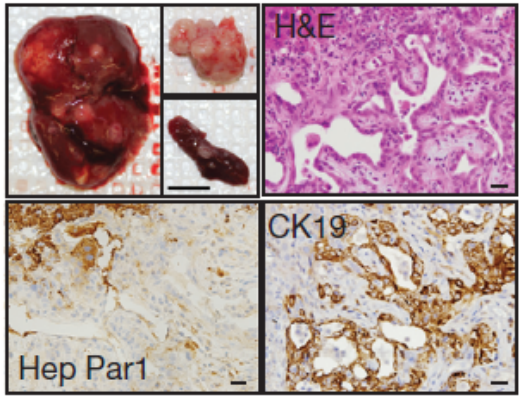


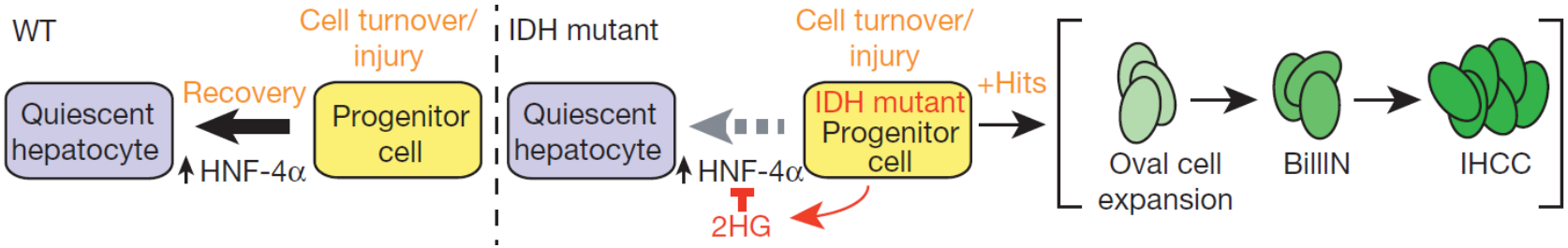
Goyal, etal, *The Oncologist*, 2015, in press

Mutant IDH cooperates with $Kras^{G12D}$ to drive ICC pathogenesis



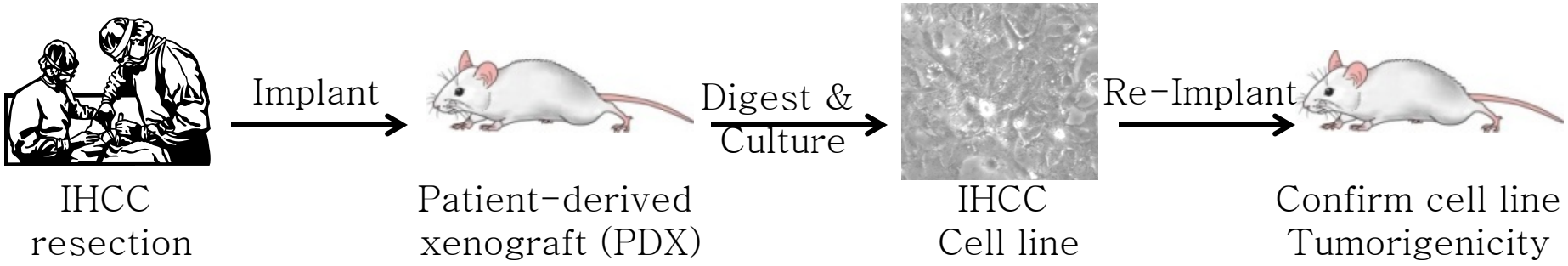


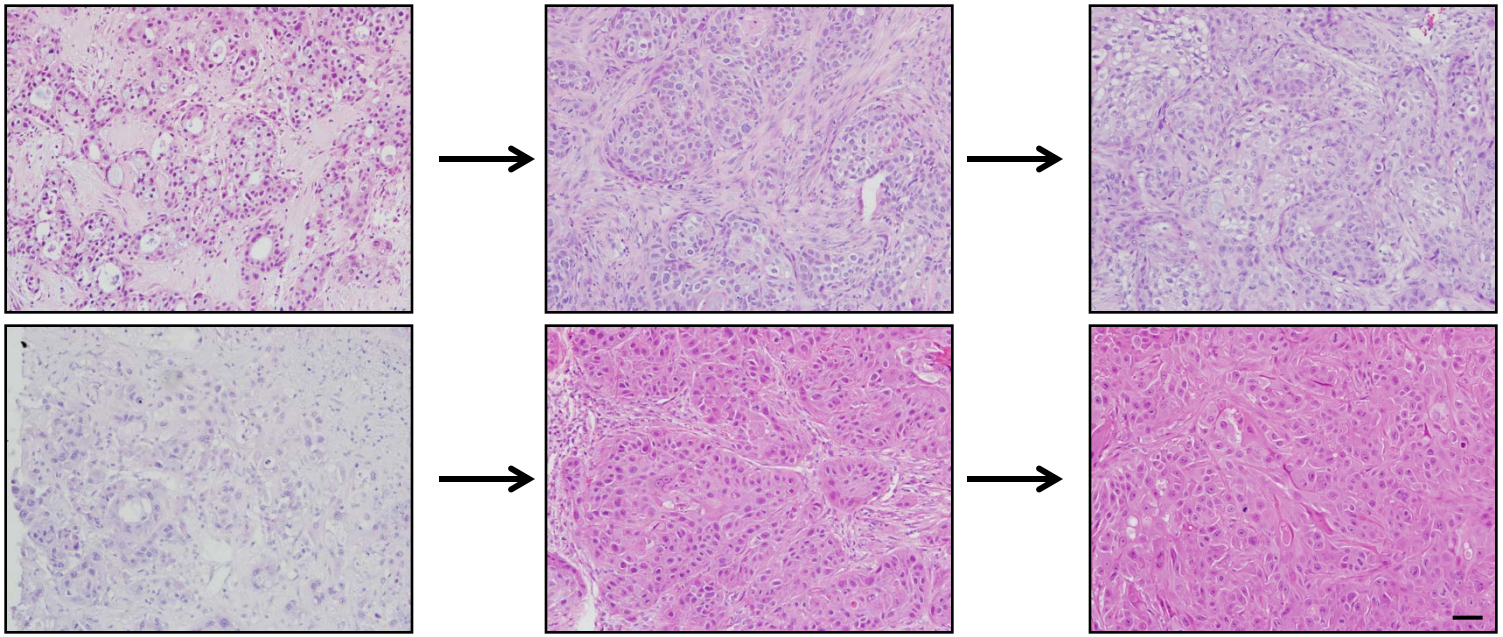




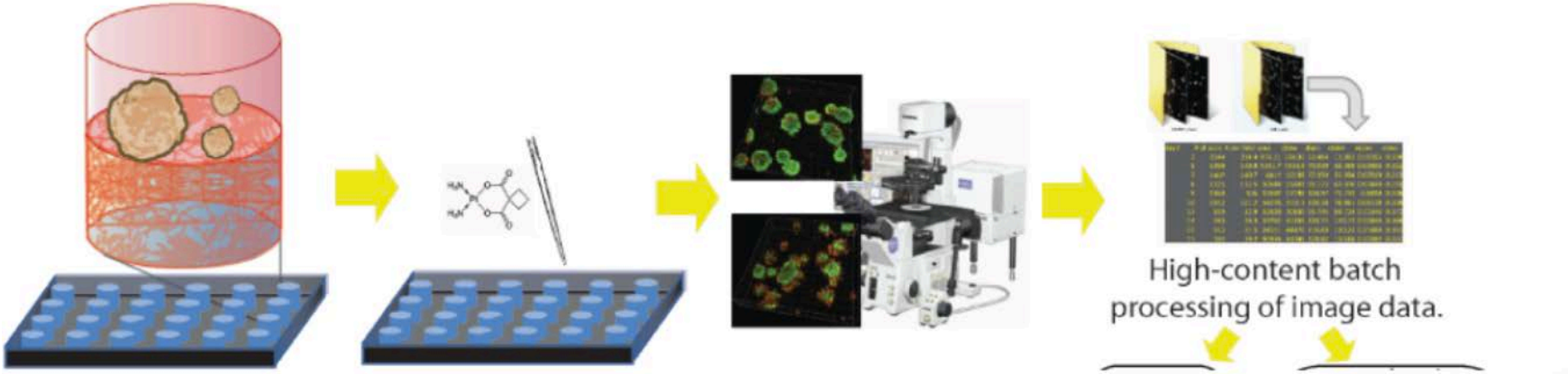
Saha, Parachoniak, et al, *Nature*, 2014

MGH IHCC cell line/PDX protocol

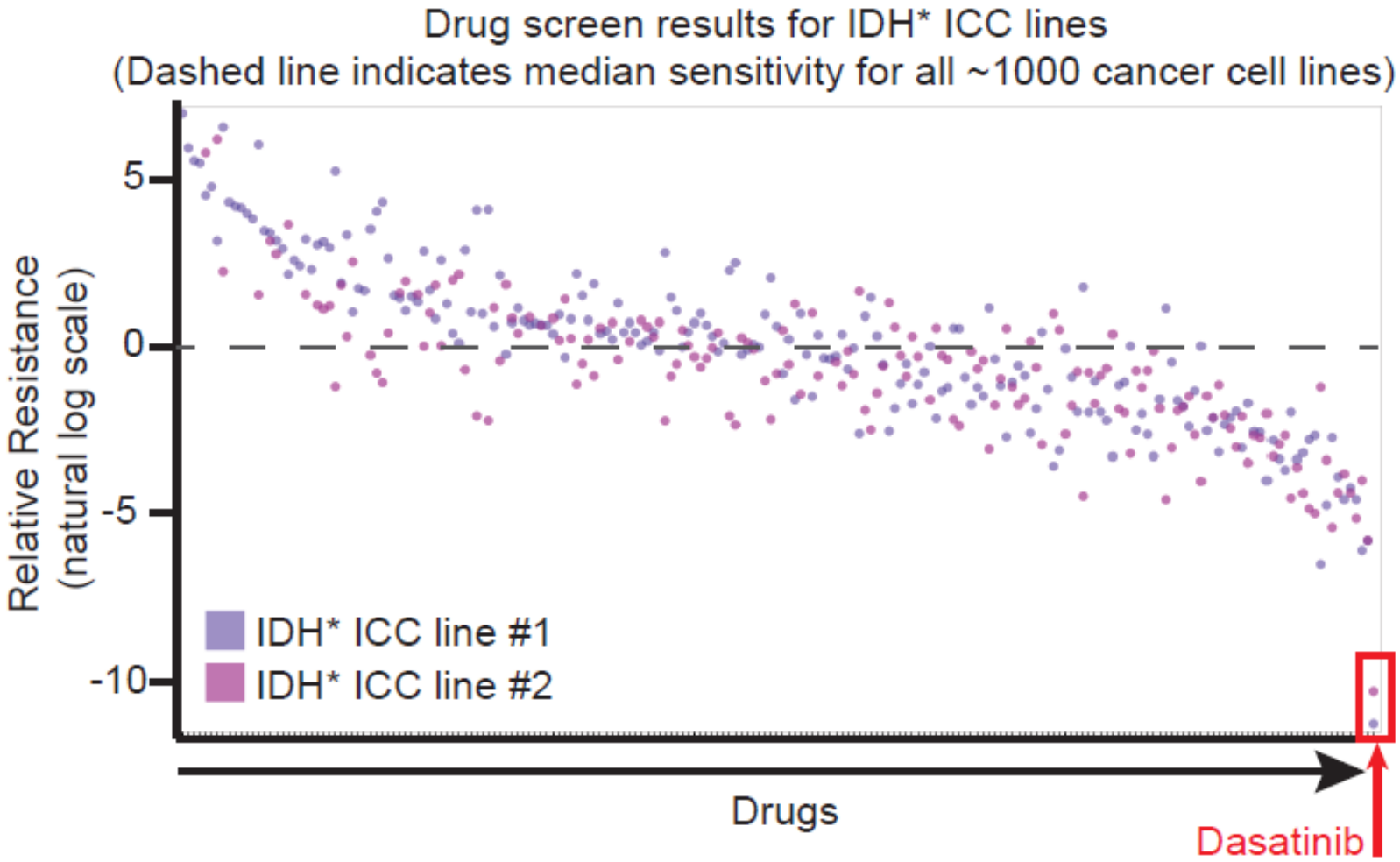




Combination drug screens in genetically-defined ICC cell lines

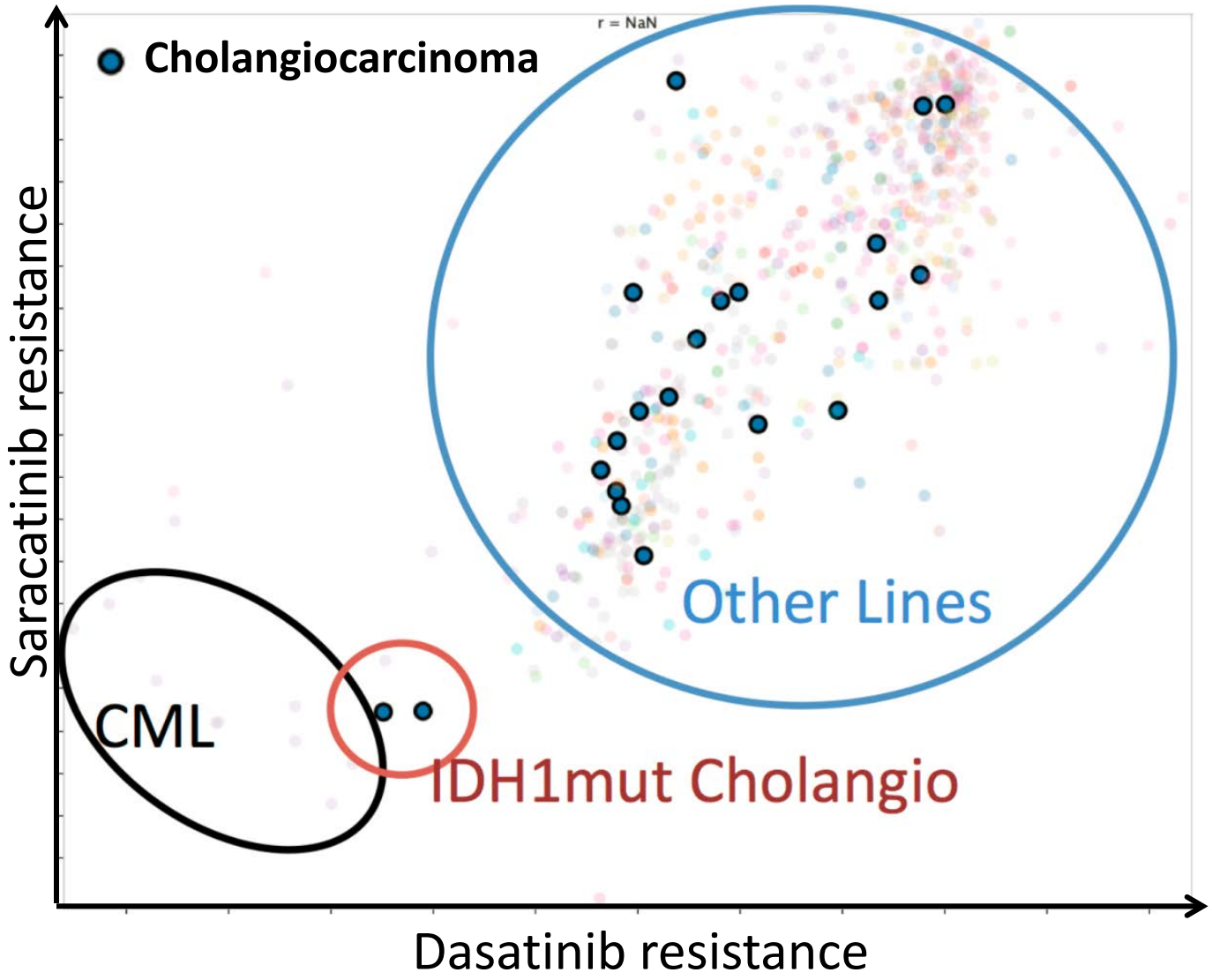


Mutant IDH ICC lines are highly sensitive to dasatinib



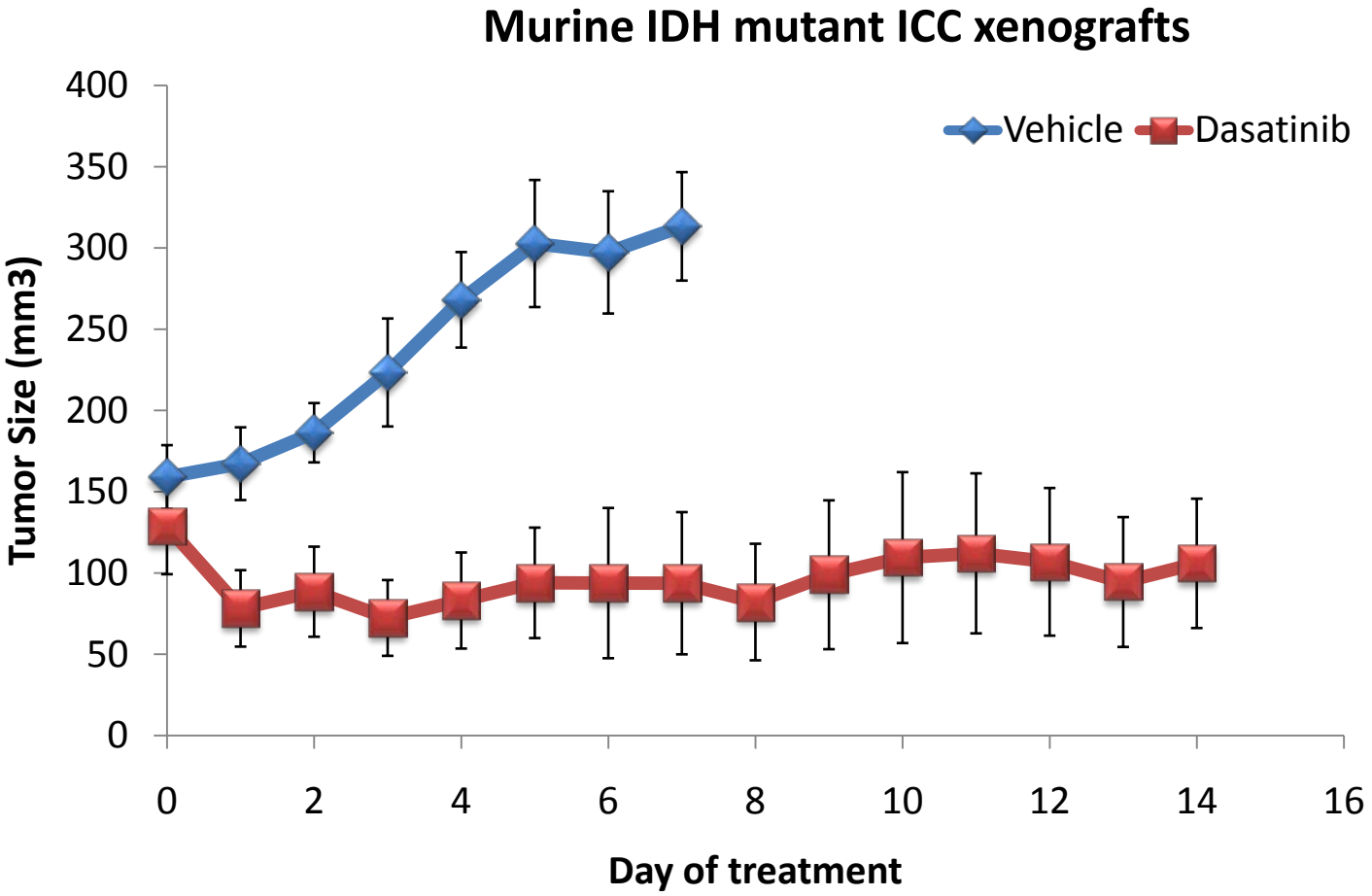
Cyril Benes

High throughput drug screen reveals extreme sensitivity of IDH mutant ICC to Src family kinase (SFK) inhibitors



Cyril Benes

Dasatinib induces sustained regression of IDH mutant ICC xenografts



Phase II trial of dasatinib in patients with isocitrate dehydrogenase (IDH)-mutant advanced intrahepatic cholangiocarcinoma

- Advanced ICC
- *IDH1* or *IDH2* mutations
- ECOG PS 0-1
- Good organ functions
- Dasatinib at 100 mg daily continuously
- Two stage design
- NCT02428855

Phase I Study of AG-120, a First-in-Class, Potent Inhibitor of the IDH1 Mutant Protein, in Patients with Advanced IDH1-Mutant Solid Tumors

Single-arm, dose escalation, 3+3 study (ClinicalTrials.gov NCT02073994)

Key objectives:

- Safety and tolerability
- Identify the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D)
- Characterize pharmacokinetics, evaluate the pharmacokinetic/pharmacodynamic (PK/PD) relationship (2-HG)
- Characterize preliminary clinical activity

Population:

- Subjects with advanced solid tumors with an IDH1 mutation

Treatment:

- Single-agent AG-120 administered continuously, oral dosing once (QD) or twice (BID) daily in 28-day cycles
- Eight dose levels explored: 100 mg BID, and 300, 400, **500,** 600, 800, 900 and 1200 mg QD

Tumor assessments:

- RECIST v1.1 criteria for solid tumors other than glioma
- RANO criteria for glioma

RECIST, response evaluation criteria in solid tumors; RANO, response assessment in neuro-oncology

Burris et al, AACR-NCI-EORTC Annual Meeting 2015

Baseline Characteristics

	Total treated N=62
Median age, years (range)	56 (23–88)
ECOG status at baseline, n (%)	
0	21 (34)
1	41 (66)
Gender (M/F)	29/33
Tumor types, n (%)	
Cholangiocarcinoma	25 (40)
Chondrosarcoma	12 (19)
Glioma	20 (32)
Grade I-II	9
Grade III-IV	11
Other*	5 (8)
Median prior lines of therapy, n (range)	3 (1–6)

*Colitis-associated, neuroendocrine, adenocarcinoma, small intestine, and ovarian cancers

Safety Summary

- No DLTs observed
- MTD was not reached
- All SAEs occurred in one patient each (N=18/62):
  - Acute kidney injury, acute respiratory failure, anemia, ataxia, brain herniation, confusional state, cystitis, urinary tract infection, headache, hyponatremia, joint effusion, esophageal varices hemorrhage, partial seizures, seizure, bacteremia, superior vena cava syndrome, vertebral fracture, urosepsis
- No treatment-related deaths*
- Median duration of AG-120 exposure = 2 months (range 0–13)
- No dose reductions, 9 (15%) subjects had dose interruptions

*2 deaths occurred > 20 days after last AG-120 dose. Neither were deemed related to treatment (anemia and respiratory failure): 1 subject discontinued due to disease progression; 1 subject discontinued due to AE.

SAE, serious adverse event

Most Frequent Adverse Events

(In ≥10% of Patients, Regardless of Relationship) N=62

- AG-120 well tolerated to date in this patient population

AE	All Grades, n (%)	Grade ≥3, n (%)
Patients experiencing ≥1 AE	55 (89)	21 (34)
Most frequent AEs:		
Nausea	16 (26)	-
Diarrhea	10 (16)	-
Vomiting	10 (16)	-
Anemia	9 (15)	3 (5)
Electrocardiogram QT prolonged	9 (15)	2 (3)
Fatigue	8 (13)	-
Headache	7 (11)	2 (3)
Peripheral edema	7 (11)	1 (2)
Abdominal pain	6 (10)	-
Ascites	6 (10)	1 (2)

*Other Grade ≥3 events in ≥2 patients: hypophosphatemia 2 (3%), hyponatraemia 2 (3%)

PK/PD Supports 500 mg PO QD Dose for Expansion

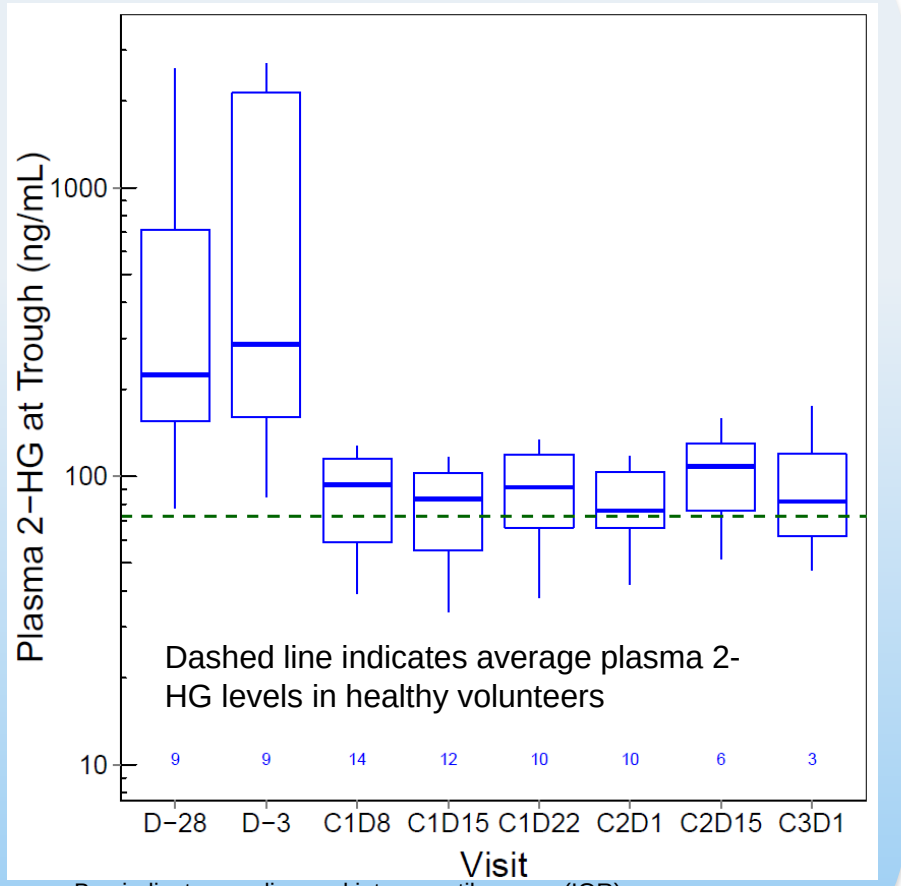
Pharmacokinetics

- High plasma AG-120 exposure, above projected efficacious level
- Long half life (71.4 ± 63.4 hr)
- Non-dose-proportional increases in plasma exposure above 500 mg QD

Pharmacodynamics

- 2-HG inhibition is observed
- Plasma 2-HG reduced to levels seen in healthy volunteers (up to 98% inhibition)

2-HG in non-glioma patients
(Dosed at 500 mg QD)



Box indicates median and inter-quartile range (IQR)
Whiskers extend to the highest/lowest value that is within 1.5*IQR
The number indicates the number of patients

Best Overall Response

(Efficacy Evaluable Subjects[1])

	Chondrosarcoma n=11	Cholangiocarcinoma n=20	Glioma n = 20	Other n=4	Total N=55
Best response, n (%)					
PR	-	1 (5)	-	-	1 (2)
SD	7 (64)	11 (55)	10 (50)	1 (25)	29 (53)
PD	2 (18)	6 (30)	10 (50)	3 (75)	21 (38)
UNK/Not Assessed	2 (18)	2 (10)	-	-	4 (7)
Clinical Benefit Rate at Month 6[2], n/N (%)	5/9 (56)	6/14 (43)	4/16 (25)	0/2	15/41 (37)

Glioma response assessments are based on RANO criteria; non-glioma are based on RECIST v1.1 criteria

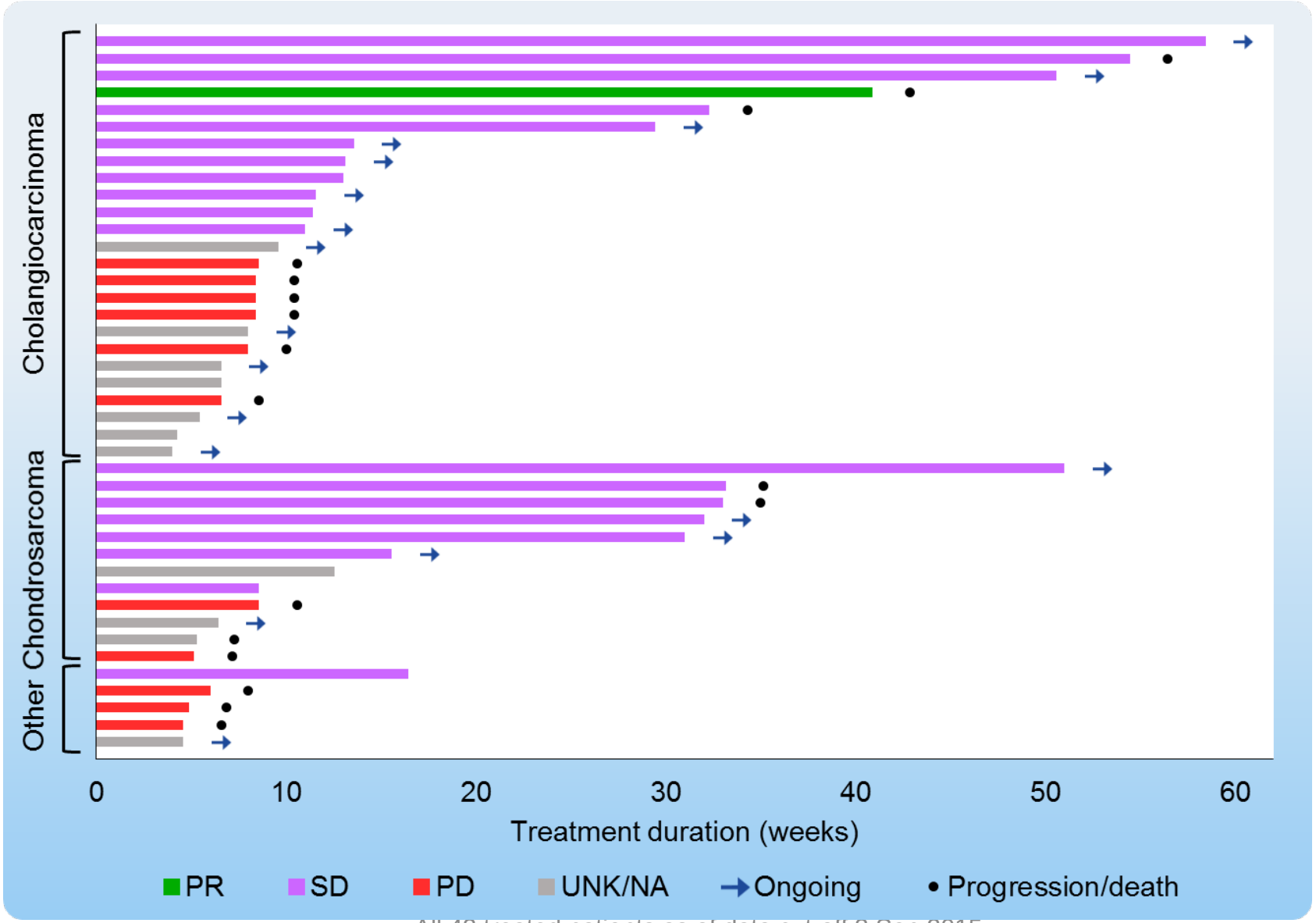
Complete responses (CR) not observed

PR, partial response; SD, stable disease; PD, progressive disease; UNK, unknown

[1]Includes subjects who had baseline and at least one post baseline tumor assessment or discontinued prematurely

[2]Defined as CR/PR/SD; among subjects whose treatment started at least 6 months prior to the data cut-off date of 3 Sep 2015

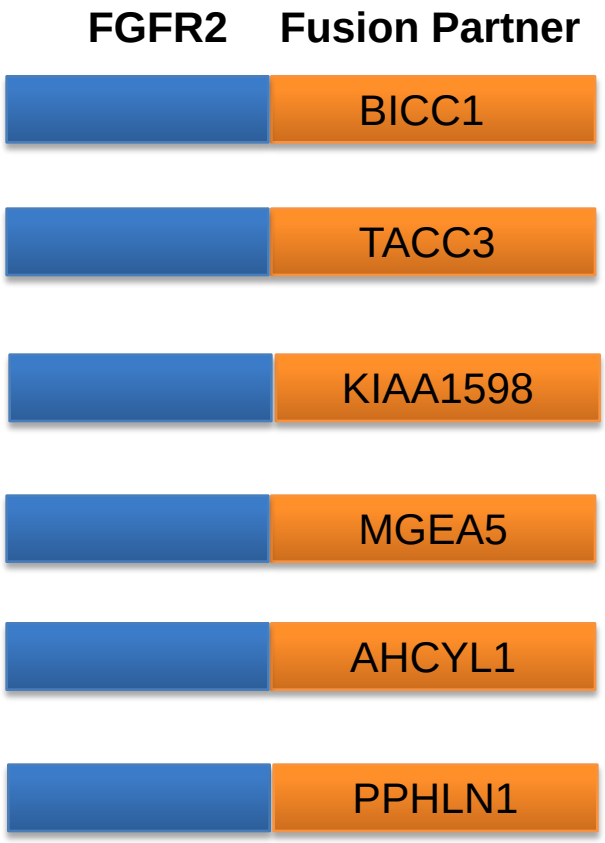
Duration on Treatment: Non-Glioma Solid Tumors



All 42 treated patients as of data cut-off 3 Sep 2015

PR, partial response; SD, stable disease; PD, progressive disease; UNK/NA, unknown/not assessed

FGFR2 translocations in Intrahepatic Cholangiocarcinoma



References

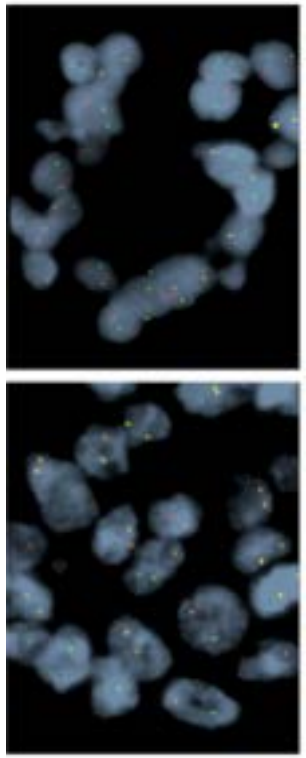
Wu *Cancer Discovery* 2013
2 reported cases of FGFR2-BICC1

Borad *PLoS Genetics* 2014
3 reported cases of FGFR2-BICC1, FGFR2-TACC3, FGFR2-MGEA5 (3/6)

Arai *Hepatology* 2013
translocations occur in 13.6% of 9/66 IHCCs reported FGFR2-AHCYL1, FGFR2-BICC1

Ross *Oncologist* 2014
FGFR2-KIAA1598, FGFR2-BICC1, FGFR2-TACC3 (3/28 samples)

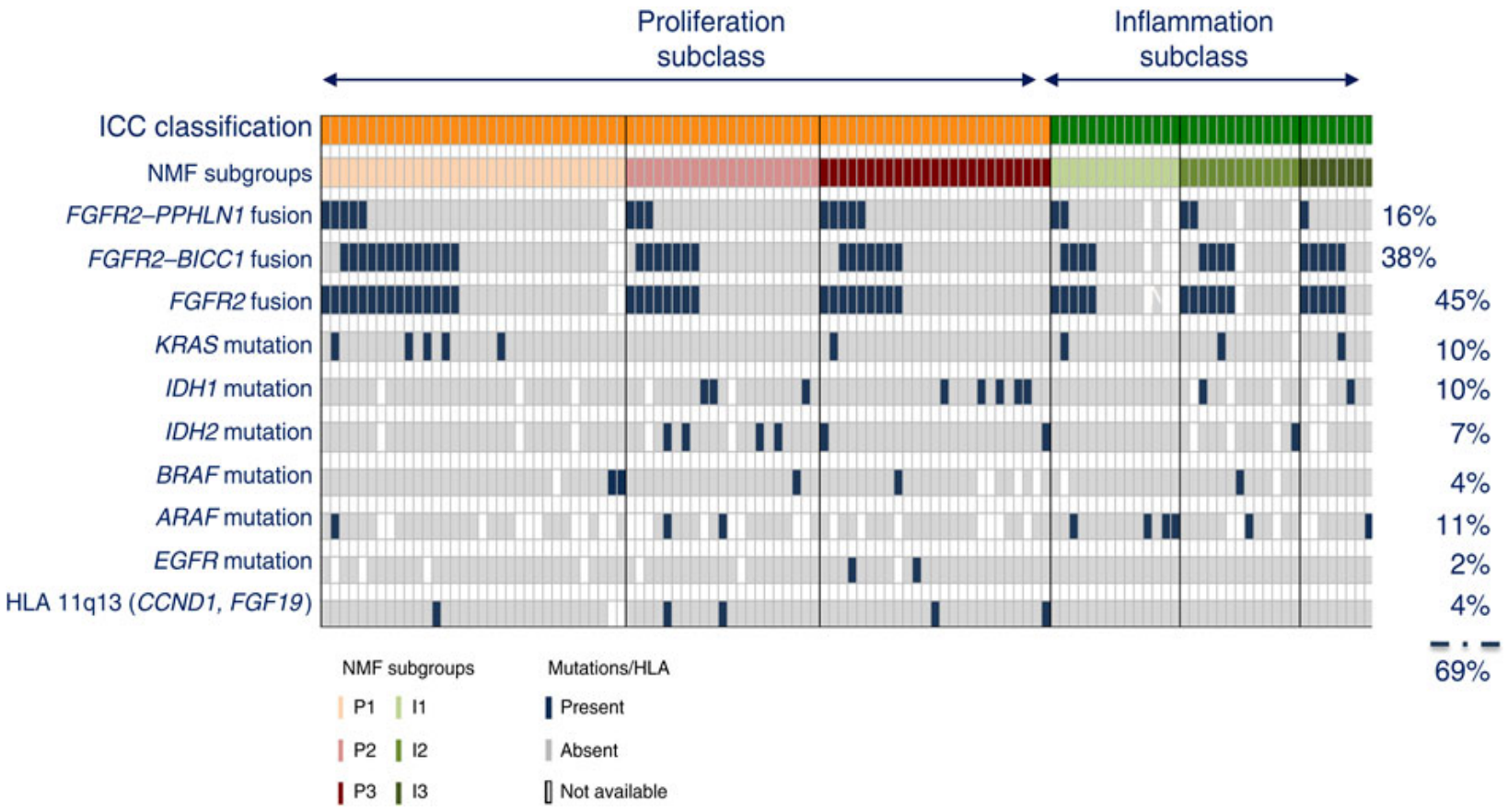
Sia *Nat C*ommun 2015
Translocations occur in ~45% of IHCCs
FGFR2-PPHLN1 (16%)



5′ FGFR2
3’ FGFR2

BGJ398, Ponatinib, TAS-120

Novel actionable FGFR2–PPHLN1 fusion and ARAF mutations in ICC



Sia *Nature Communications* 2015

Safety and Efficacy of Pembrolizumab (MK-3475) in Patients With Advanced Biliary Tract Cancer: Interim Results of KEYNOTE-028 (N=23)

Best Response	n	% (95% CI)
Complete response	0	0 (0.0–14.8)
Partial response	4	17.4 (5.0–38.8)
Stable disease	4	17.4 (5.0–38.8)
Progressive disease	12	52.2 (30.6–73.2)
No assessment[b]	3	13.0 (2.8–33.6)

[a]One patient was excluded from evaluation of best overall response because the baseline tumor scan was performed outside of the protocol-mandated period of 28 days before the first pembrolizumab dose.

[b]Patients who discontinued therapy before the first postbaseline tumor evaluation because of clinical progression (n = 2) or adverse events (n = 1).

Bang YJ et al, The European Cancer Congress 2015

Ongoing targeted trials in cholangiocarcinoma

Target	Drug	Phase	Line of treatment	NCT number
IDH1	AG-120	I	2nd & beyond	NCT02073994
	IDH305	I	2nd & beyond	NCT02381886
IDH2	AG-221	I/II	2nd & beyond	NCT02273739
FGFR2	BAY1187982	I	2nd & beyond	NCT02368951
	ARQ087	I	2nd & beyond	NCT01752920
	BAY1179470	I	Any	NCT01881217
	AZD4547	I	Any	NCT00979134
	BGJ398	II	2nd & beyond	NCT02150967
	Ponatinib Hydrochloride	II	2nd & beyond	NCT02265341
MEK	Selumetinib	II	1st/2nd	NCT00553332
	Selumetinib + Gem + Cis	I/II	Any	NCT01242605
mTOR	Everolimus	I	2nd & beyond	NCT00949949
AKT	MK2206	II	2nd	NCT01425879

Immune therapy with checkpoint inhibitors

Future perspectives and conclusions

- GemCis is the current standard systemic therapy and there is unmet need for developing more effective systemic therapies (advanced and adjuvant)
- Applying genomic technology and molecular classification critically and timely in ICC
- Genetic heterogeneity and newly identified actionable targets (IDH, FGFR) have provided the opportunity for drug development in ICC
- Innovative and efficient clinical trials through collaborations leading to practice changing new treatment for chlangiocarcinoma

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