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Beyond Chemotherapy: New Treatments for Advanced Liver and Bile Duct Cancers

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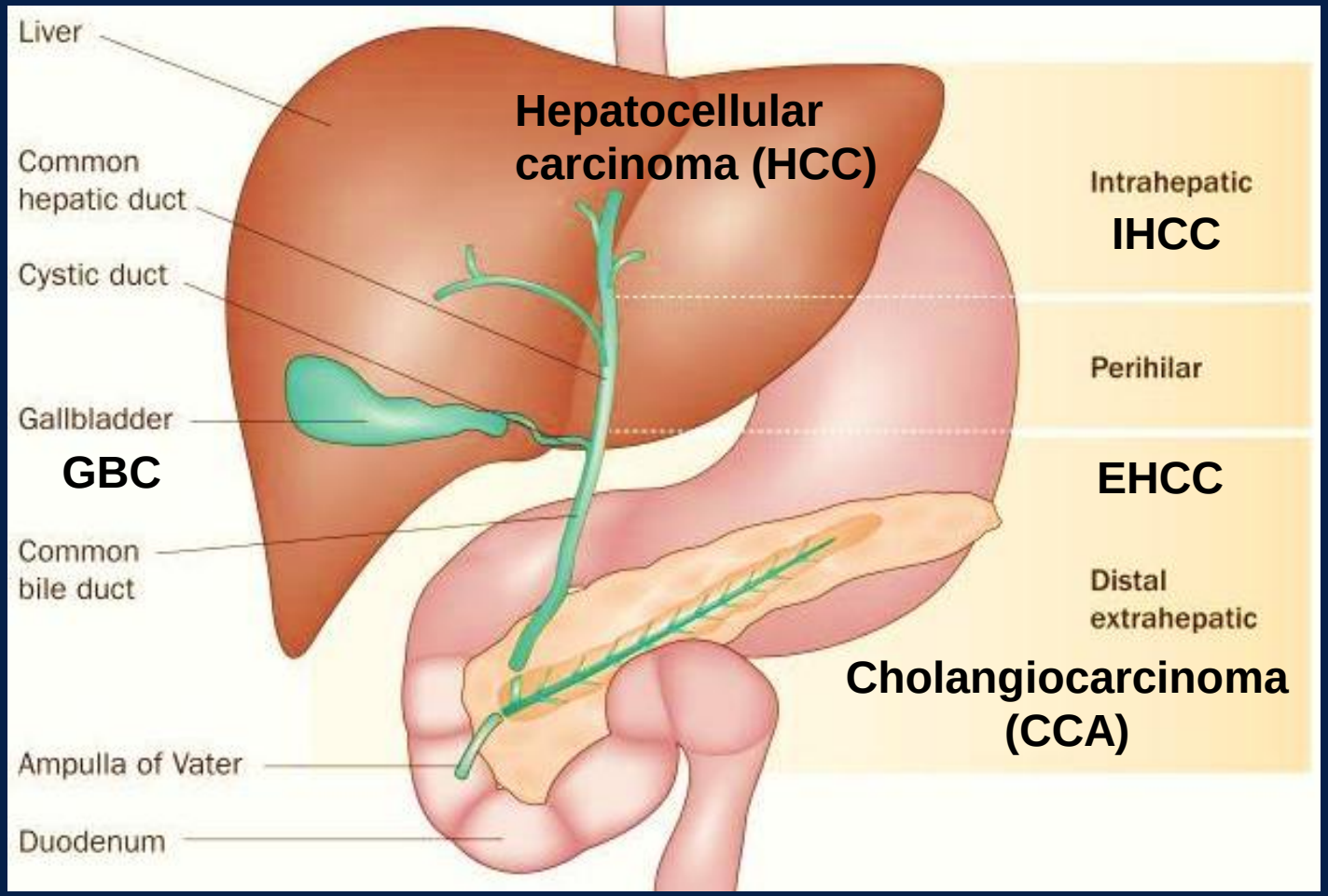
Disclosures

- Research funding from: Novartis, Agios, Eli Lilly, BMS, Merck, Medimmune/AZ, Exelixis, Sanofi, and Regeneron Inc. for conduct of clinical trials and/or translational/biomarker research

Objectives

1. Review current treatment options and outcomes in advanced liver and biliary cancers
2. Introduce new targets and treatments in liver and biliary cancers
   - Molecularly-targeted therapies
   - Immunotherapy
3. Looking ahead: How to combine old with new?

Anatomic Classification of Hepatobiliary Cancers



Blechacz et al Nat Rev Gastroenterol Hepatol 8(9) 2011

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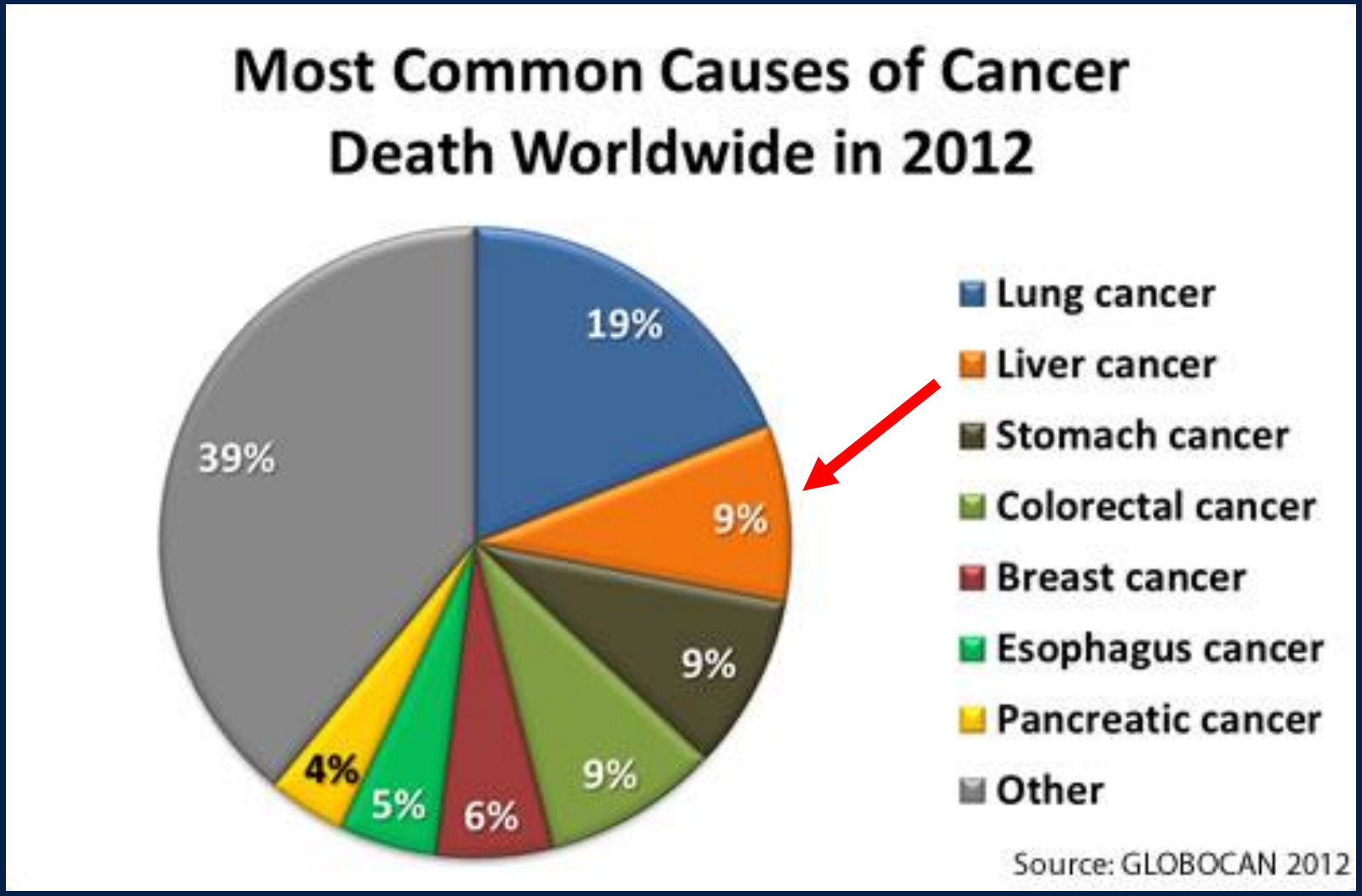

Mortality HCC+IHCC: 745,500 deaths worldwide in 2012

GLOBOCAN 2012

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Objectives

1. Review current treatment options and outcomes in advanced liver and bile duct cancers

Treatment of Advanced HCC in 2016: A Review

- Before 2007: No chemotherapy had achieved survival benefit
- 2008, 2009: SHARP and Asia-Pacific trials showed survival benefit from TKI sorafenib (SOR) in Western and Asian populations[1,2]
  - Median survival 10.7 vs. 7.9 mos. (SHARP)
  - Median survival 6.5 vs, 4.2 mos. (Asia-Pacific)
- 2009-2016 ~9 negative, multinational randomized phase 3 trials (sunitinib, linifanib, brivanib 1st, brivanib 2nd, SOR+erlotinib, SOR+doxorubicin, ramucirumab, everolimus, SOR adjuvant) all conducted in unselected HCC populations
- In 2016: SOR remains only FDA-labeled treatment; still no 2nd line or adjuvant agents

NCCN Guidelines

Options:[bb]
- Sorafenib (Child-Pugh Class A [category 1] or B)[aa,ee,ff]
- Clinical trial
- Best supportive care

www.NCCN.org

1. Llovet et al NEJM 2008; 2. Cheng et al Lancet 2009

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Treatment of Advanced Biliary Cancers in 2016: A Review

- Before 2010: No established 1st-line chemotherapy
- In 2010: ABC-02 trial[1] established gemcitabine plus cisplatin (GEMCIS) as standard of care
  - Median survival 11.7 months, PFS 8 mos. 1st line
- In 2016: Still no established 2nd line therapy
  - Median PFS in 2nd line ~3 mos., RR ~12%[2-4]

NCCN Guidelines

Options:[e]

- Gemcitabine/cisplatin combination therapy[f] (category 1)
- Clinical trial[g]
- Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen[f]
- Locoregional therapy (category 2B)
- Best supportive care

www.NCCN.org

1. Valle et al NEJM 362(14) 2010; 2. Brieau et al Cancer 121(18) 2015;
3. Lowery et al GI ASCO 2016; 4. Rogers et al J Gastroint Oncol 5(6) 2014

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What are the unique challenges in this family of cancers?

- Complex anatomy
- Competing comorbidity of organ dysfunction
  - E.g. cirrhosis, biliary obstruction, viral hepatitis
- Inherent chemoresistance?
  - MDR genes, efflux mechanisms, etc.
- Heterogeneous tumor and microenvironment biology
  - “One-size-fits-all”/unselected clinical trial designs are inadequate in highly heterogeneous populations
  - Therapeutic targets not well understood

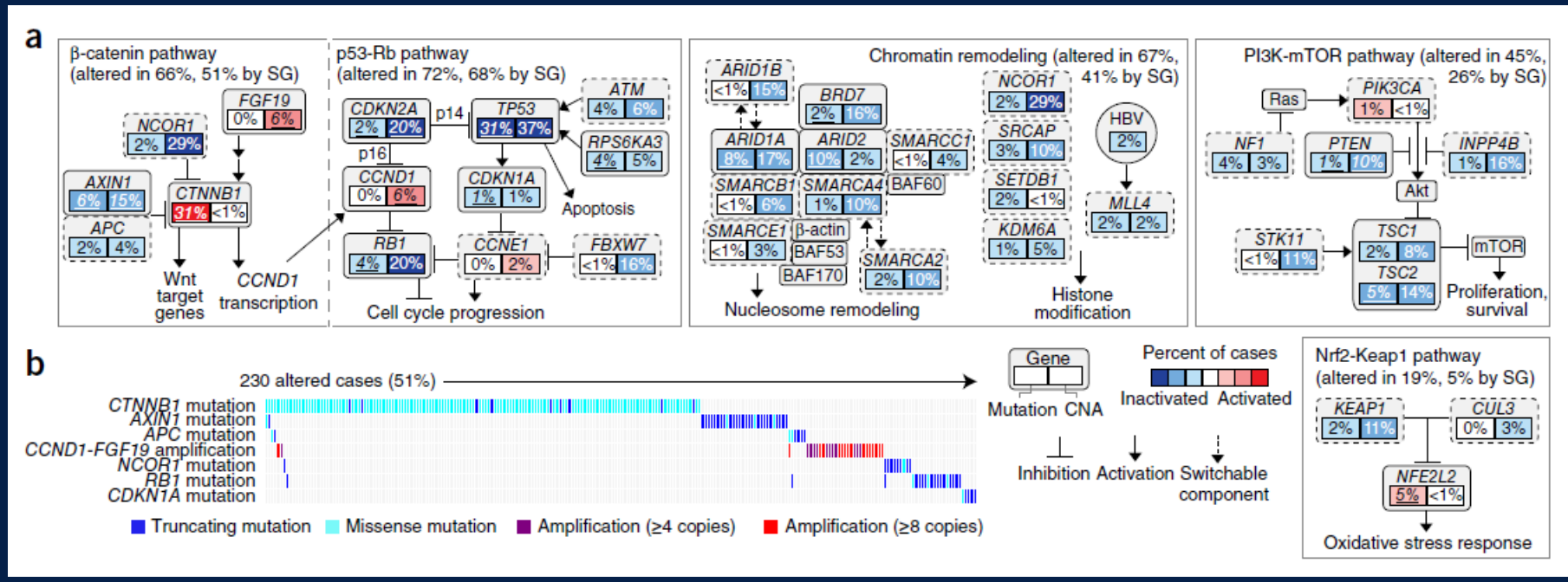
Impact of Tumor Location on Genetics of Biliary Cancers

Tumor Genomic Aberrations	IHCC	EHCC	GBC
ERBB2 Amplification **(HER2)**	4%	11%	**16%**
BRAF Substitutions	5%	3%	1%
KRAS Substitutions	22%	**42%**	11%
PI3KCA Substitution	5%	7%	14%
FGFR1-3 Fusions and Amplifications	**11%**	0	3%
CDKN2A/B Loss	27%	17%	19%
IDH1/2 Substitutions	**20%**	0	0
ARID1A Alterations	18%	12%	13%
MET Amplification	2%	0	1%

N=554: IHCC n=412, EHCC n=57, GBC n=85

Javle et al Cancer epub Sep 13, 2016

Oncogenic Networks in HCC



- N=503 HCC cases (including TCGA and ICGC)
- WES ± WGS, CNA, oncovirome analyses
- Identified multiple biologically distinct subgroups within HCC

Totoki et al Nat Gen 46(12) 2014

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What are the clinical implications?

- There are subgroups defined by high frequency somatic mutations, pathway aberrations, and/or microenvironment within HCC and biliary cancers
- Some may be prognostic
- Some of these mutations (esp. in biliary cancers) may be driver oncogenes amenable to targeted therapies
- Signals of response can be difficult to detect in subpopulations

Need to define biologic subpopulations in hepatobiliary cancer clinical research …and in future treatment decisions?

Objectives

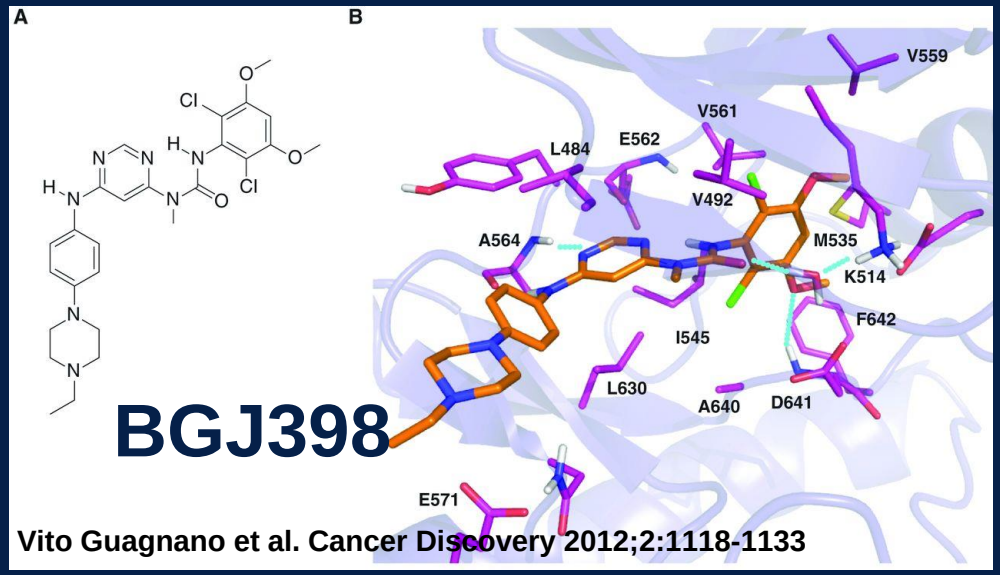
2. Introduce new targets and treatments in liver and biliary cancers
   - Molecularly targeted therapies
   - Immunotherapy

High Frequency Molecular Targets in Liver and Biliary Cancers

Target	Est. Incidence by Location	Targeted Agents	Mechanism
FGFR2 fusions	~20% IHCC	BGJ398, ARQ 087, others	FGFR inhibition
IDH1/2 mutations	~20% IHCC	AG-120, AG-221, AG-881, IDH305, others	Restore differentiation
HER2	~15% gall bladder	Trastuzumab, TDM-1, others	HER2 inhibition, cytotoxicity
c-MET expression	~50% HCC	tivantinib	TKI, cytotoxicity?
Immune activation	Unknown: PD-L1+: 20-40%? MSI-H: <10%?	Pembrolizumab, nivolumab, others	T-cell activation

FGFR2 Inhibitors in IHCC: Approaching the Clinic?

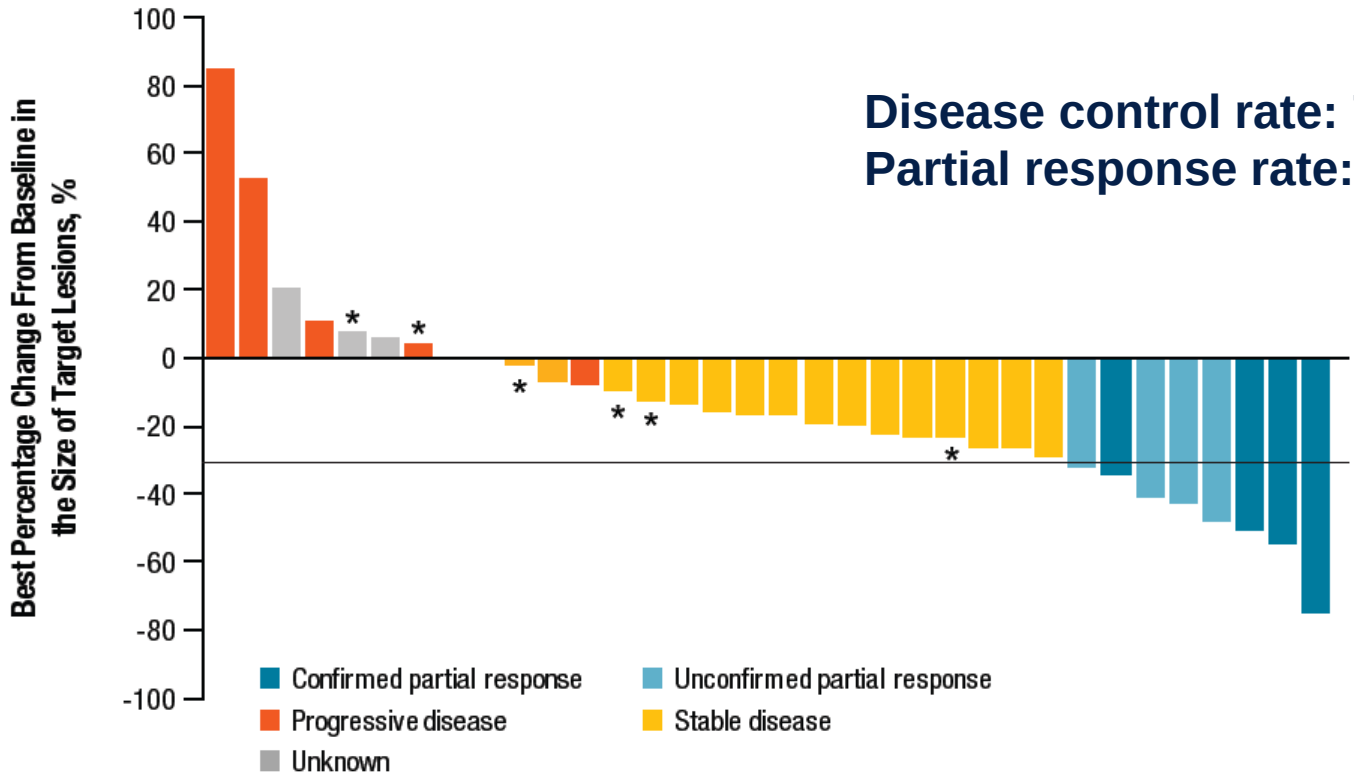
- Activating FGFR2 fusions: ~20% IHCC
- Multiple agents in trials:
  - BGJ398 (Novartis)
  - ARQ 087 (ArQule)
  - INCB054828 (Incyte)
  - Others



Vito Guagnano et al. Cancer Discovery 2012;2:1118-1133

Results: BGJ398 in FGFR2-Mutated IHCC

Figure 3. Best Percentage Change From Baseline in the Size of Target Lesions With BGJ398 Treatment (n = 34)[a,b]



[a] Two patients were not included in the analysis (best percentage change could not be calculated because the scan modality changed [n = 1], patient had no postbaseline scan due to treatment discontinuation [n = 1]).

[b] Patients marked with an asterisk had *FGFR2* mutations (n = 2) or amplification (n = 3), or *FGFR3* amplification (n = 1). All other patients had *FGFR2* fusions (n = 28).

Javle et al GI ASCO 2016

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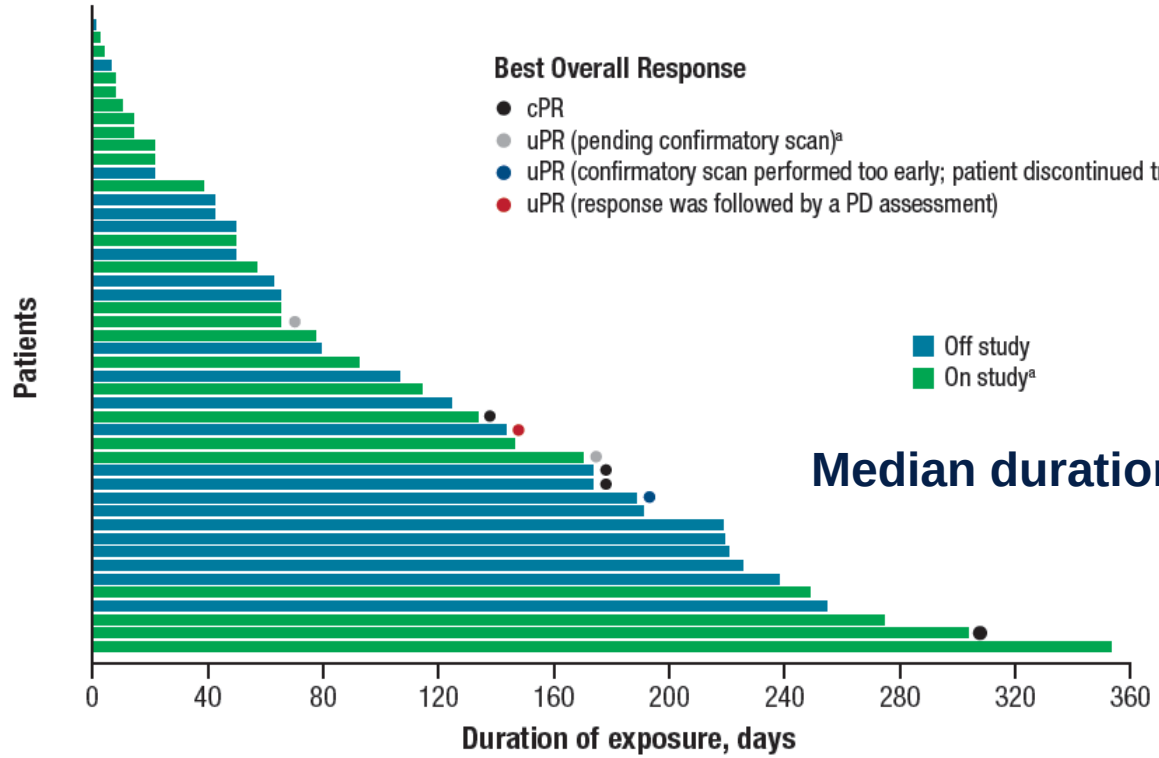
Results: BGJ398 in FGFR2-Mutated IHCC

Figure 2. Prolonged Duration of Exposure to BGJ398 (N = 47)[a]



cPR, confirmed partial response; **uPR**, unconfirmed partial response.

[a] Data cutoff, November 4, 2015.

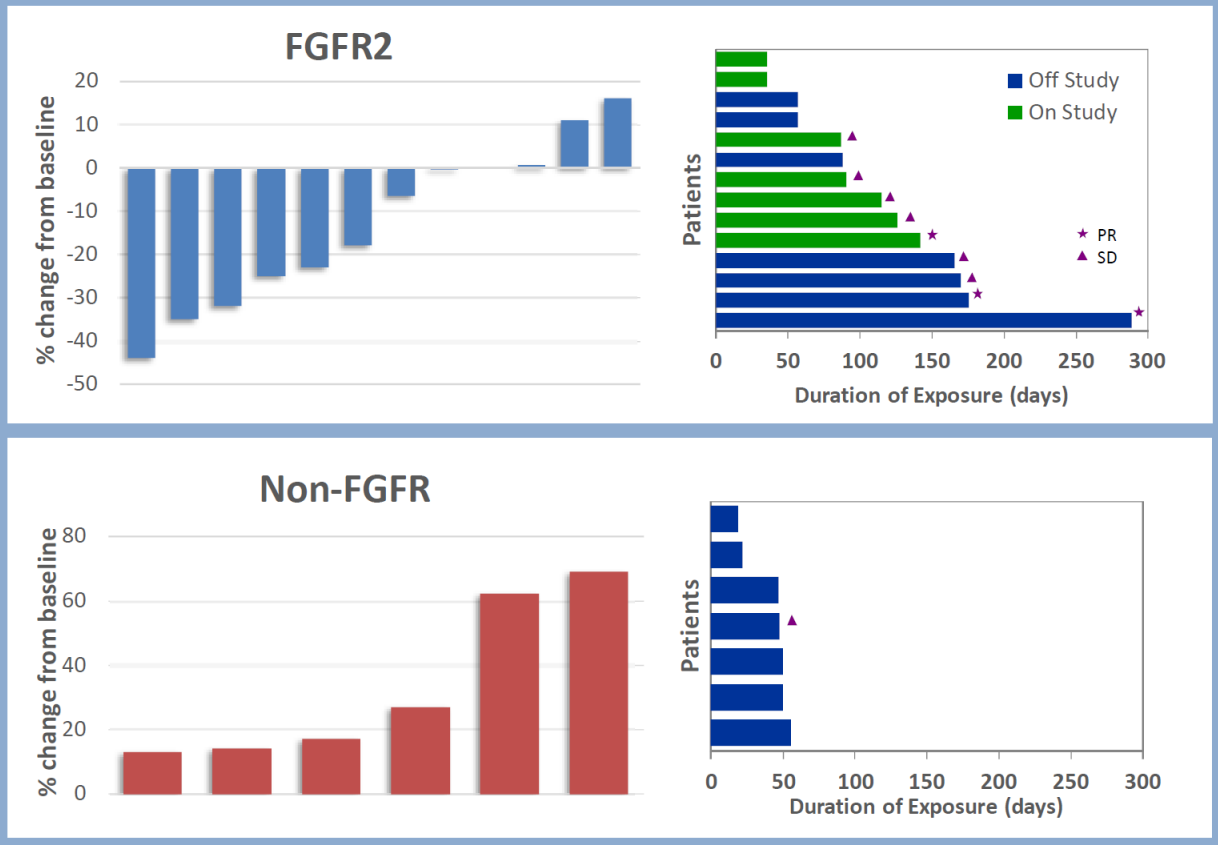
Javle et al GI ASCO 2016

Results: ARQ 087 in IHCC

- N=21 IHCC
  - n=12 with FGFR2 fusion
  - n=9 wild type
- Disease control rate:
  - 75% for fusion+
  - 0 for wild type

Figure 1. Best % Change from Baseline in Size of Target Lesions and Duration of Exposure

Tumor control (complete or partial response or stable disease) was achieved in one of seven iCCA pts in whom FGFR2 fusions were not identified and in nine of twelve pts with iCCA with FGFR2 fusions.



Mazzaferro V. et al ESMO World GI Abstract #340 2016

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Retrospective Analysis: FGFR2 Inhibitor Therapy Correlated with OS

- Pooled analysis of 412 IHCC patients across 3 centers including UCSF
  - n=54 with FGFR mutations
    - 20 received FGFR targeted therapy

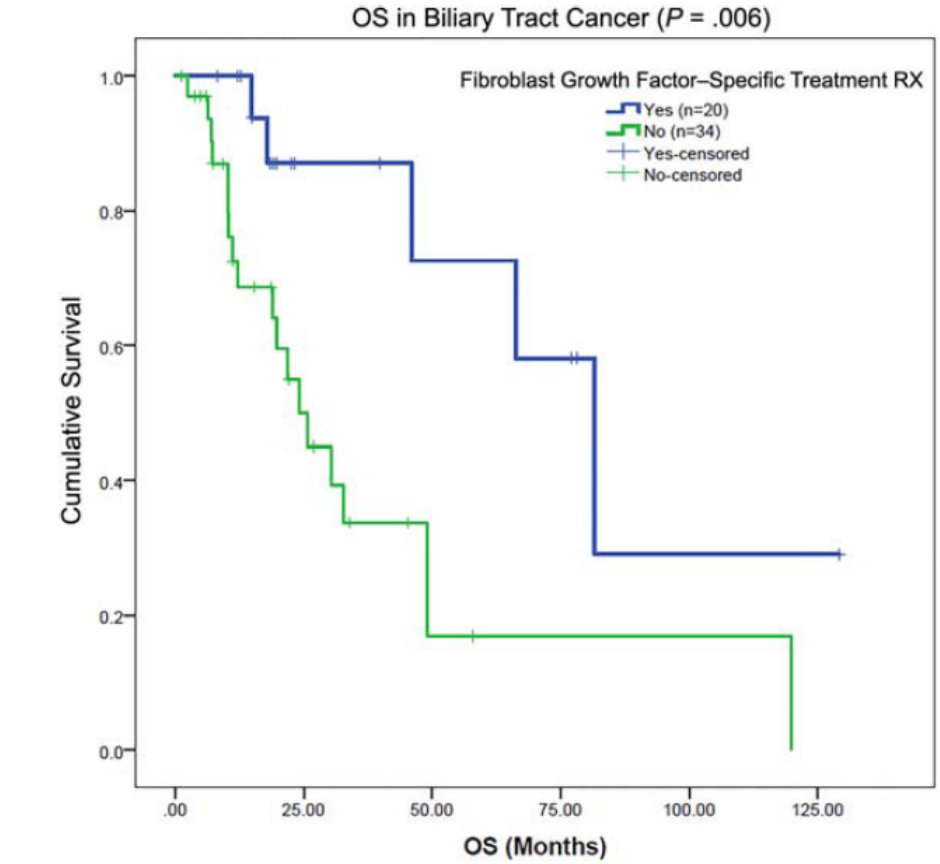

Figure 6. Kaplan-Meier curves of overall survival (OS) for 54 patients with a fibroblast growth factor receptor pathway genetic aberration with (n = 20) and without (n = 34) fibroblast growth factor receptor–specific treatment.

Javle et al Cancer epub Sep 13, 2016

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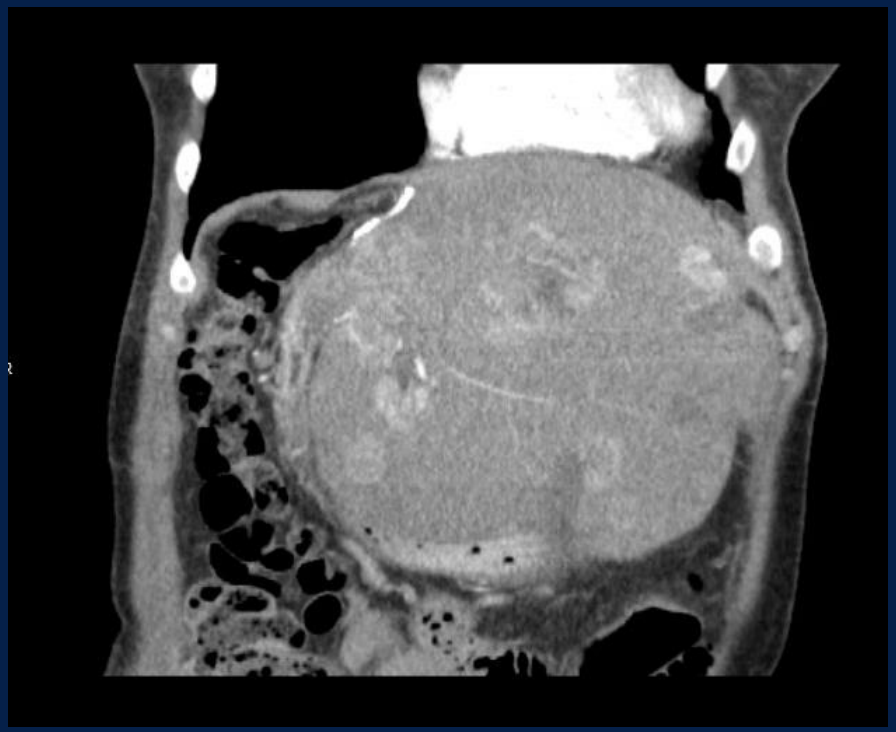
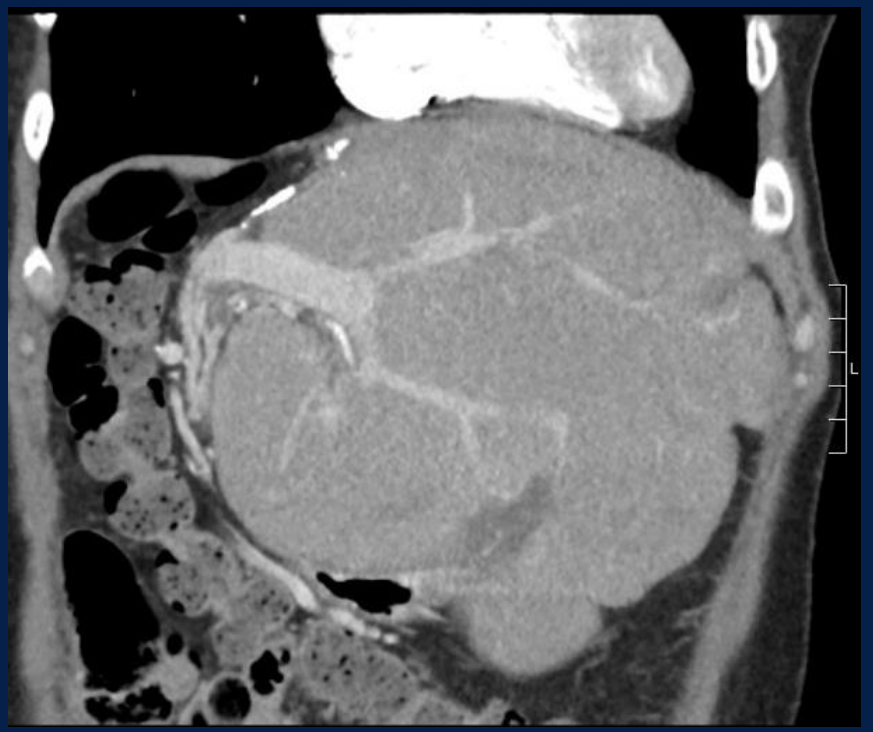
Case: UCSF FGFR2+ IHCC Patient Treated with FGFR Inhibition



- 1/2016: Multifocal IHCC lesions

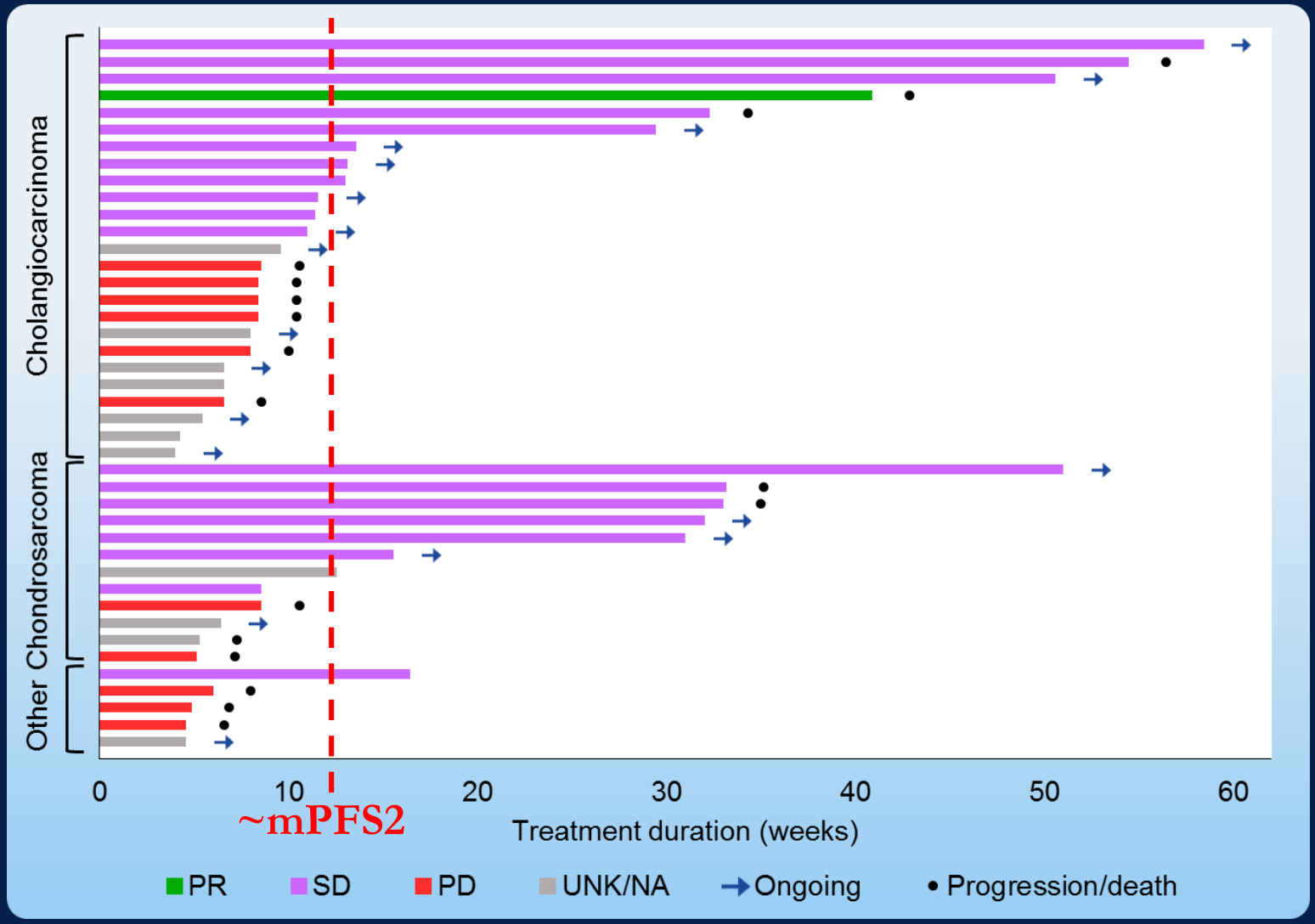


- 8/2016: Sustained partial response, 57% reduction in multifocal liver tumors

IDH 1/2 Inhibitors for IHCC

- Activating IDH1 or 2 mutations: ~20% of IHCC, lead to dedifferentiation and uncontrolled proliferation
- IDH1/2 inhibitors being tested in cholangiocarcinoma cohorts:
  - AG-120, AG-221, AG-881 (IDH1 and IDH2 inhibitors, Agios)
  - BAY1436032 (IDH1 inhibitor, Bayer)
  - Others

Duration on AG-120 Treatment: IHCC



Burris et al AACR/NCI/EORTC 2015

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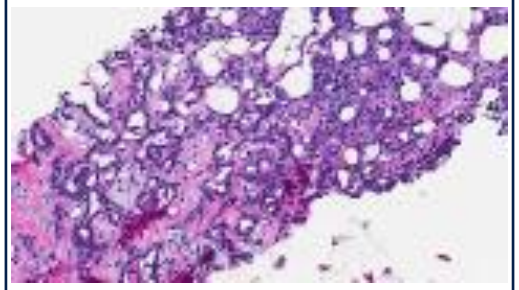
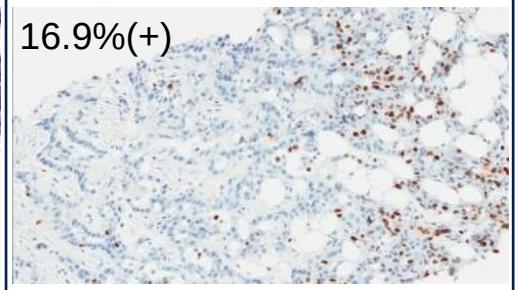
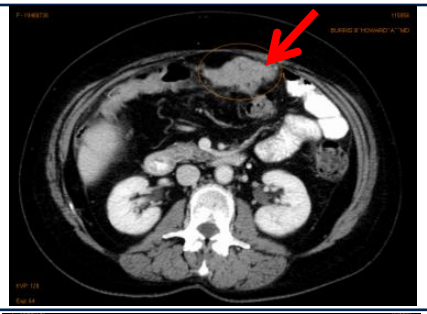
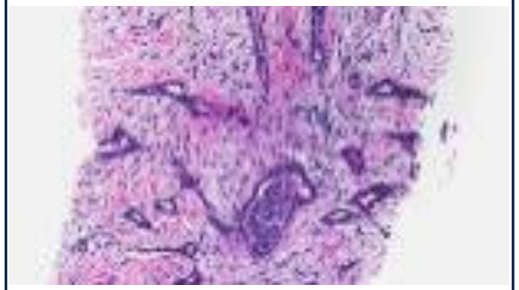
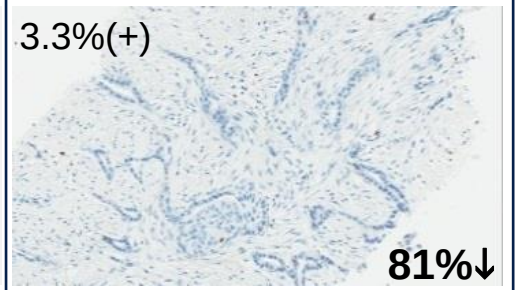
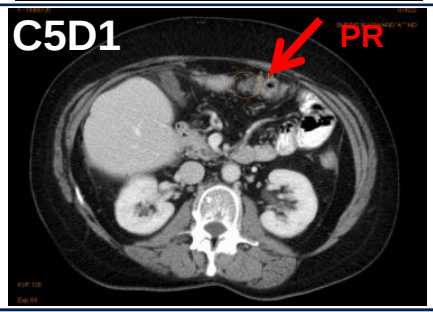
Case: IDH-1 Mutant IHCC with Partial Response to AG-120

- A 65 year old female with IHCC, progressed on 3 prior lines of treatment
- 98.7% reduction in tumor 2-HG level at C3D1
- 81% reduction in Ki-67 staining

	H&E	Ki-67	MRI
Screening			
C3D1			

Burris et al AACR/NCI/EORTC 2015

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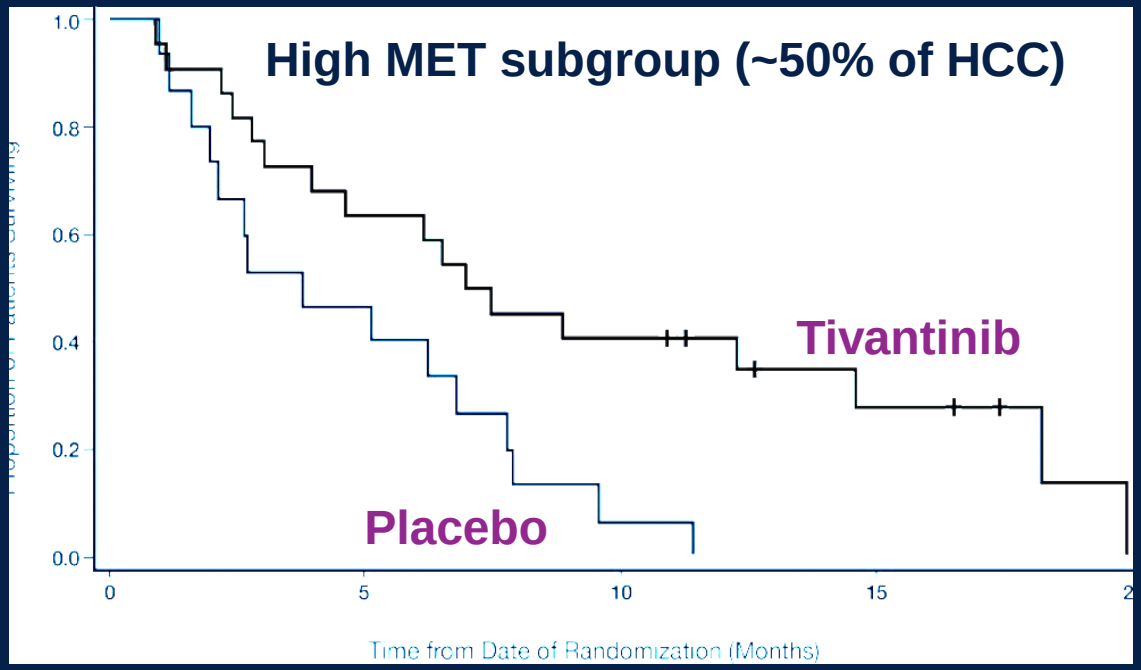
c-MET Inhibition with Tivantinib (ARQ-197) in HCC with High MET Expression: Phase II Trial Results



	Median OS	Patients	Events
Tivantinib:	7.2 mo.	22	17
Placebo:	3.8 mo.	15	15

HR: 0.38, Log Rank: *p*=0.01

Santoro et al, Lancet 14(1), 2013

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METIV-HCC Trial: Tivantinib (ARQ-197) vs. Placebo for MET-High HCC

METIV-HCC (ARQ 197-A-U303)*

Phase 3 clinical trial in the Americas, Australia, Europe, New Zealand

Eligibility and IHC criteria comparable to the ARQ 197-215 phase 2 RCT (except METIV-HCC selected MET-High patients only). Accrual completed in December 2015

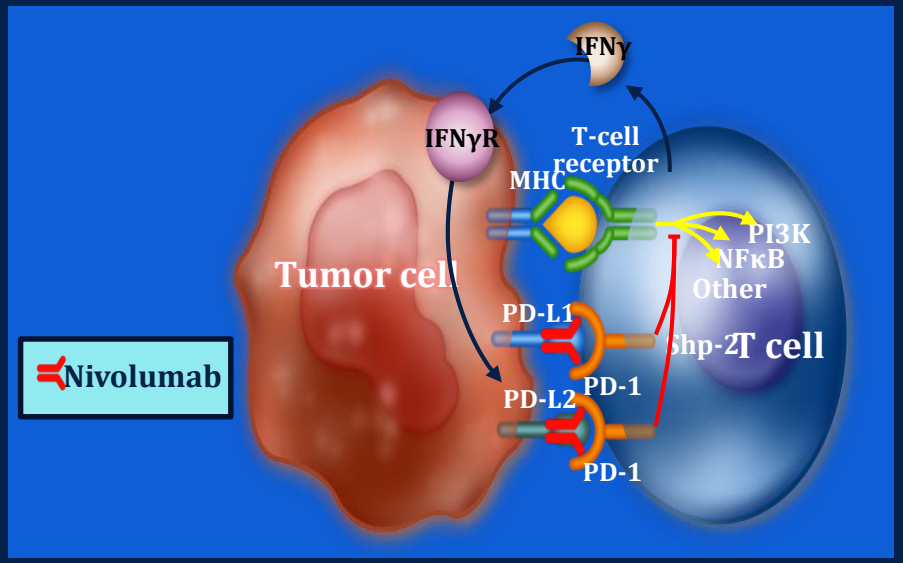
Rimassa et al GI ASCO 2016

Objectives

2. Introduce new targets and treatments in liver and biliary cancers
   - Molecularly targeted therapies
   - Immunotherapy

Immune Checkpoint Inhibitors

- "Checkpoint inhibitors" boost anti-tumor immune response
  - PD-1/PD-:L1 inhibitors
  - CTLA-4 inhibitors
- PD-1/-L1 inhibitors now approved by FDA for many cancers: melanoma, lung, kidney, bladder, head and neck, Hodgkin's
  - Pembrolizumab, nivolumab, atezolizumab; others pending



- **Promising early results in HCC and biliary cancers have led to rapid development of multiple ongoing registration trials**

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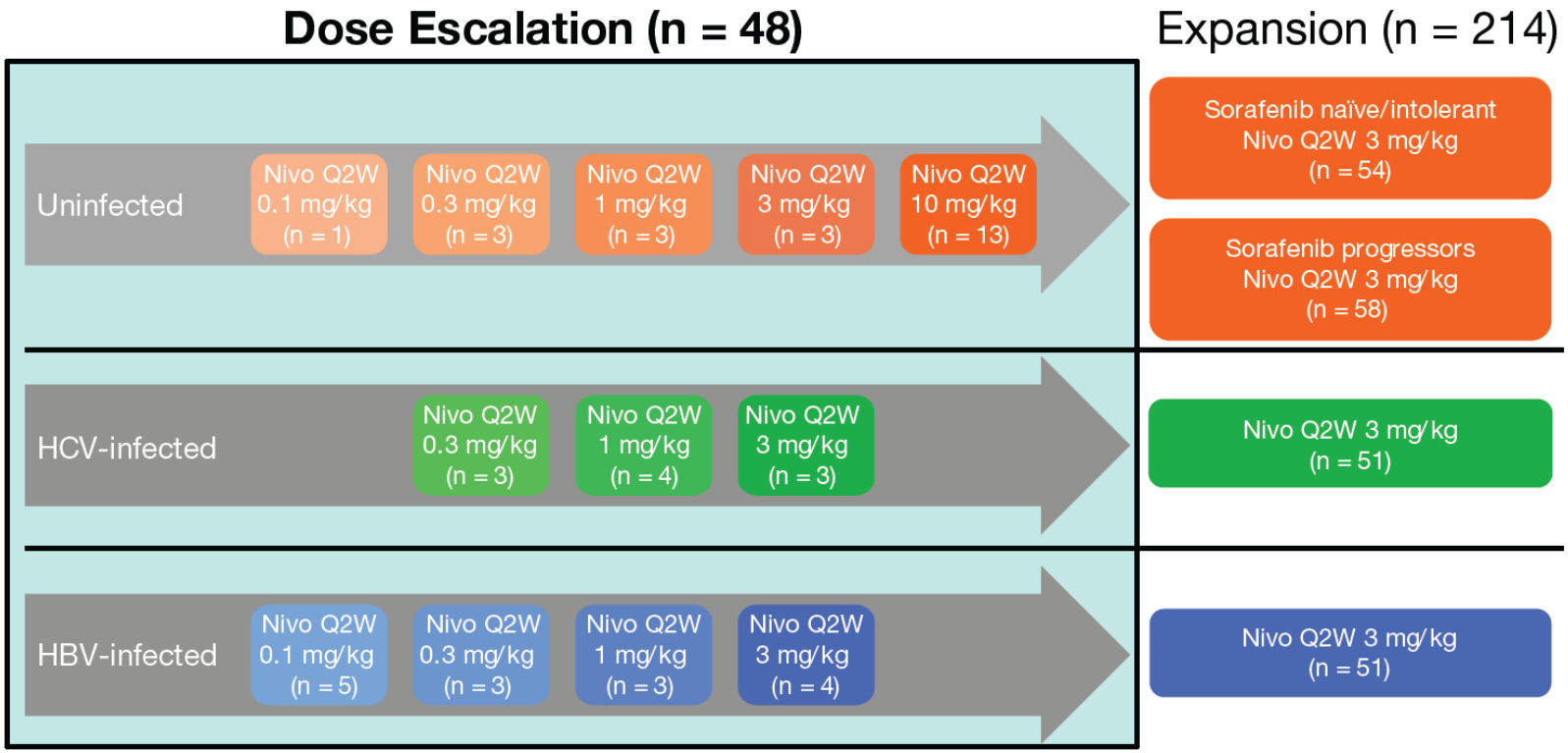
CheckMate 040: Phase 1/2 Trial of PD-1 Inhibitor Nivolumab in Advanced HCC

Figure 1. Study design



El-Khoueiry et al ASCO 2016 Abstract 4012;
Sangro et al ILCA 2016 Abstract O-019

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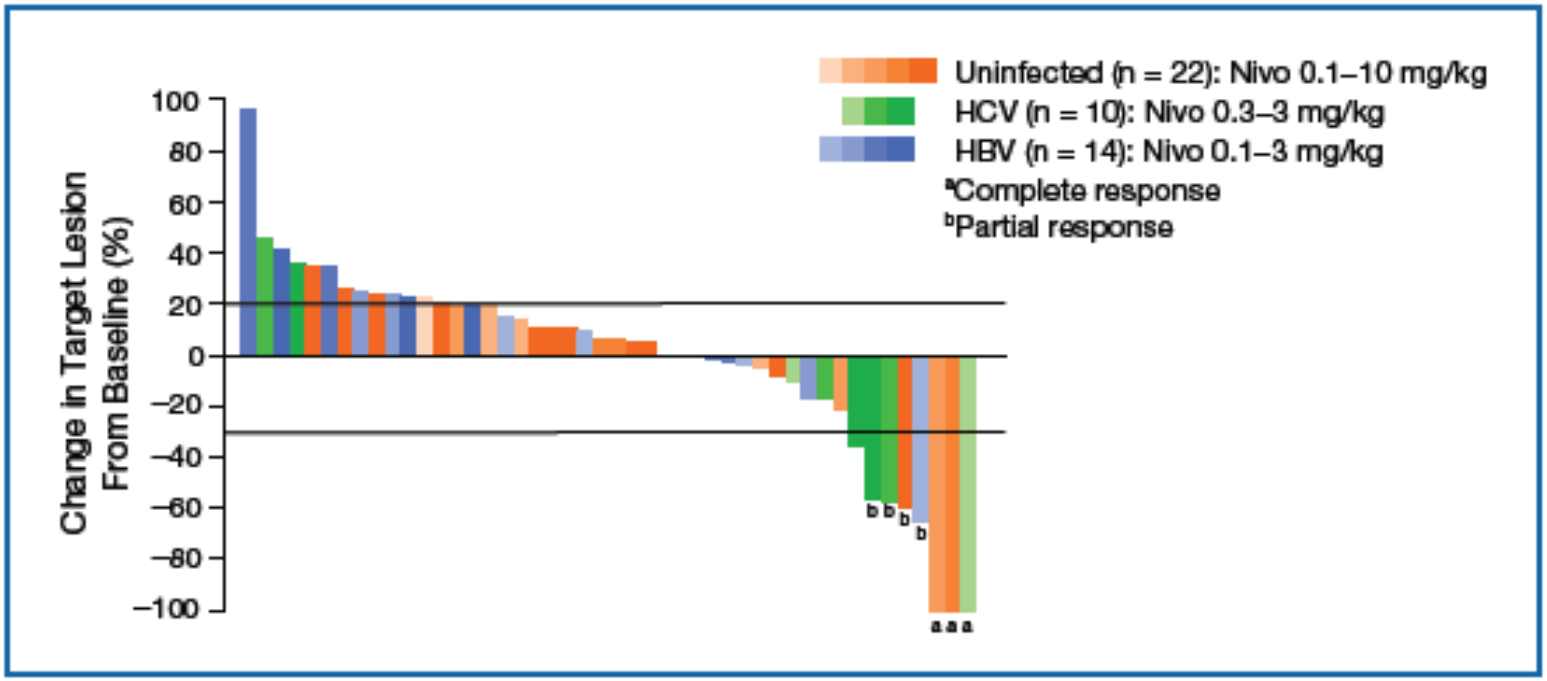
CheckMate 040: Safety and Efficacy Nivolumab in Advanced HCC (N=48)

Figure 2. Maximal change in target lesions from baseline



Nivo = nivolumab

- Response rate: 17%, including 3 complete responses
- Median duration of response: 17 months

El-Khoueiry et al ASCO 2016 Abstract 4012

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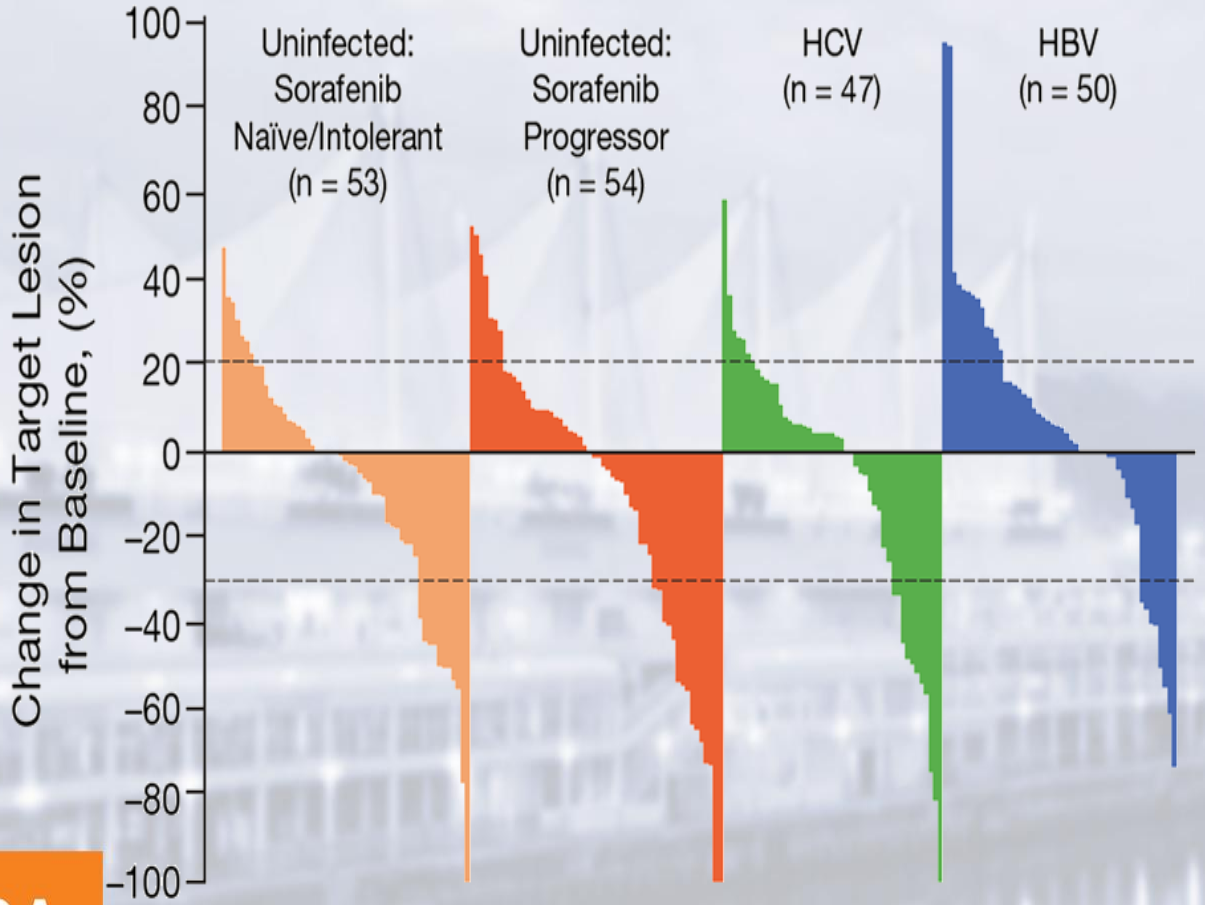
CheckMate 040 Expansion Cohorts: Maximal Change in Target Lesions From Baseline

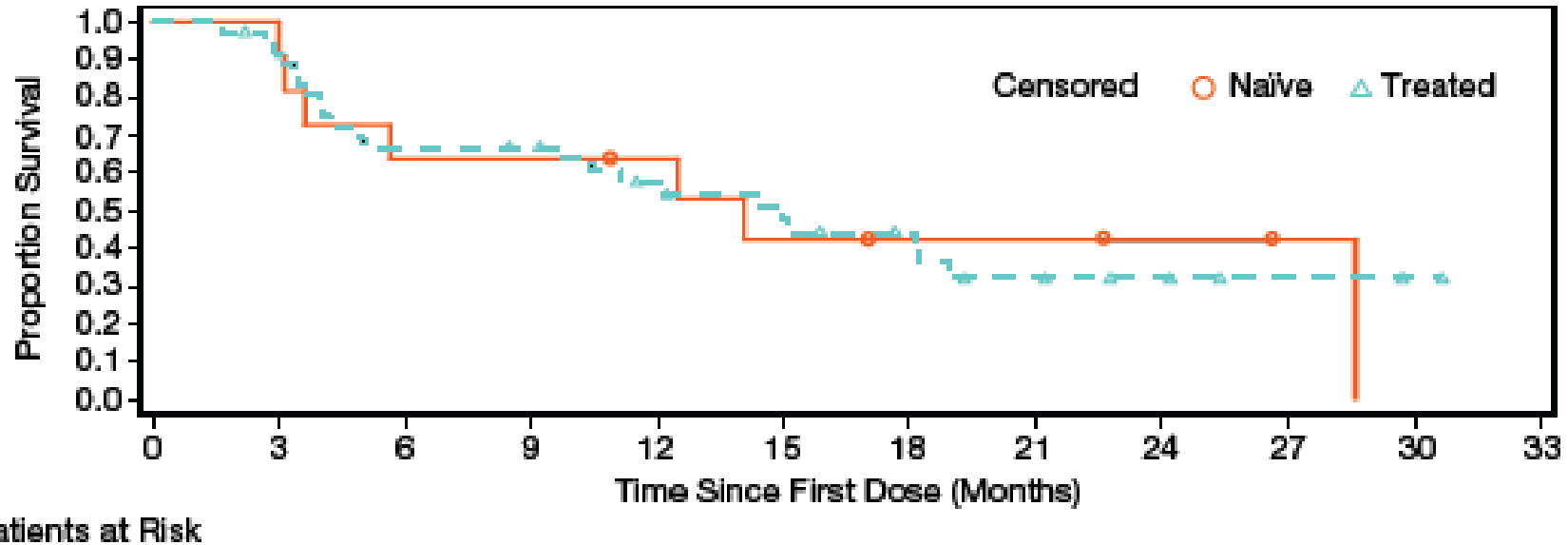


Response rate: 16%
Median duration of response: NR

Of 214 patients, five were not evaluable (two in the uninfected sorafenib progressor cohort and three in the HCV cohort), and data for percent maximal change in target lesion from baseline were missing for a further five (one in the uninfected sorafenib naïve/intolerant cohort, two in the uninfected sorafenib progressor cohort, one in the HCV cohort, and one in the HBV cohort)

CheckMate 040: Survival Outcomes (N=48)

Figure 5. OS by prior sorafenib



Patients at Risk

Naïve	11	10	7	7	6	4	3	3	2	1	0	0
Treated	37	33	24	23	18	14	11	7	5	3	2	0

Group	Died/Treated	Median (95% CI)
Sorafenib-naïve	7/11	14.1 (3.2, 28.6)
Sorafenib-treated	22/37	15.0 (5.0, 18.9)

El-Khoueiry et al ASCO 2016 Abstract 4012

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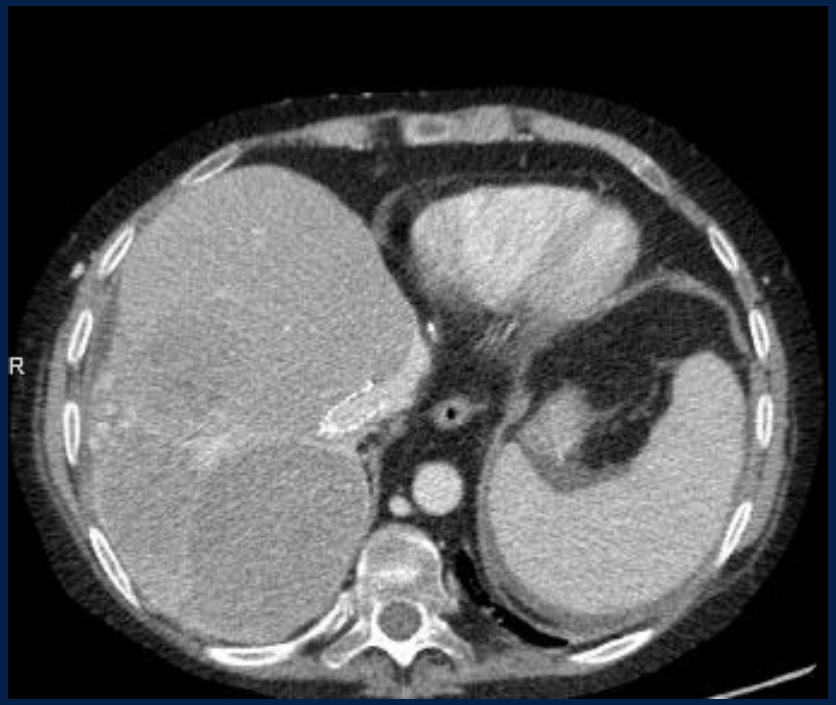
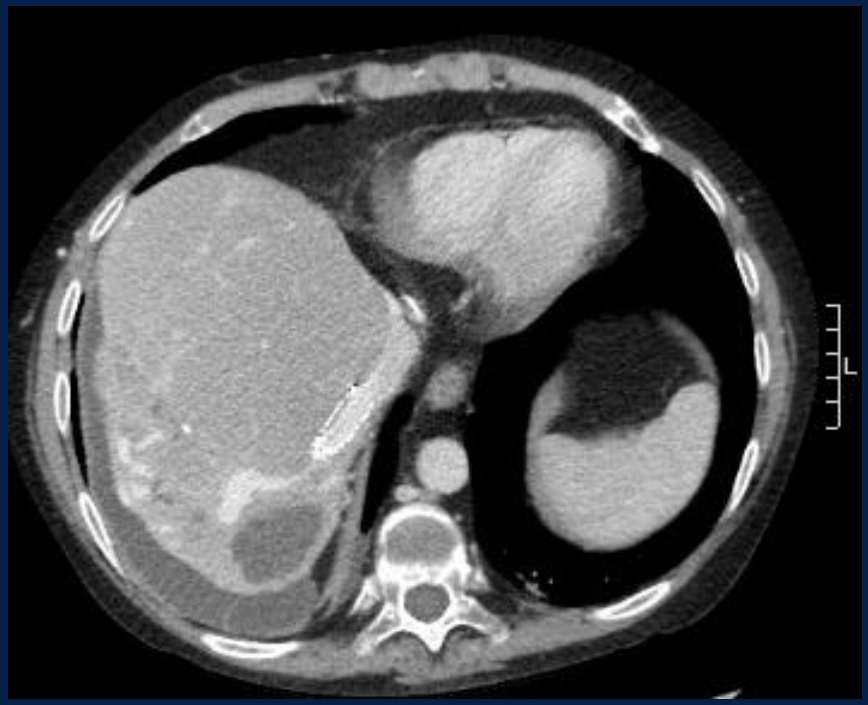
Case: PD-1 Inhibition by Nivolumab in UCSF Patient with Nonviral HCC

- 28yo male with nonviral HCC with lung, bone, and scalp/dermal metastases, progressed after surgery, TACE, Y90, and 6 prior lines of systemic therapy



12/2015: AFP 46,051, bilirubin 3.8



8/2016: AFP 766, bilirubin 1.1

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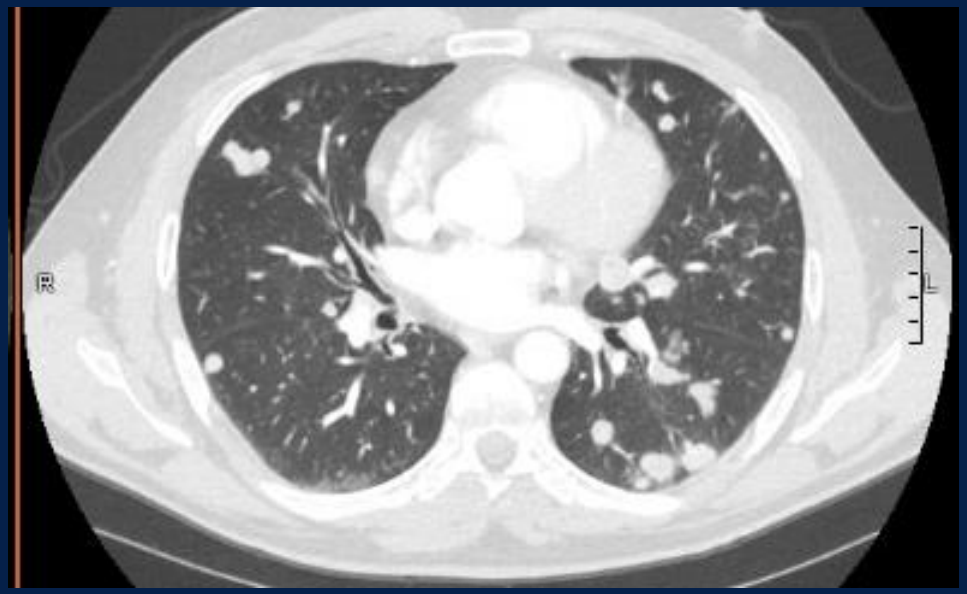
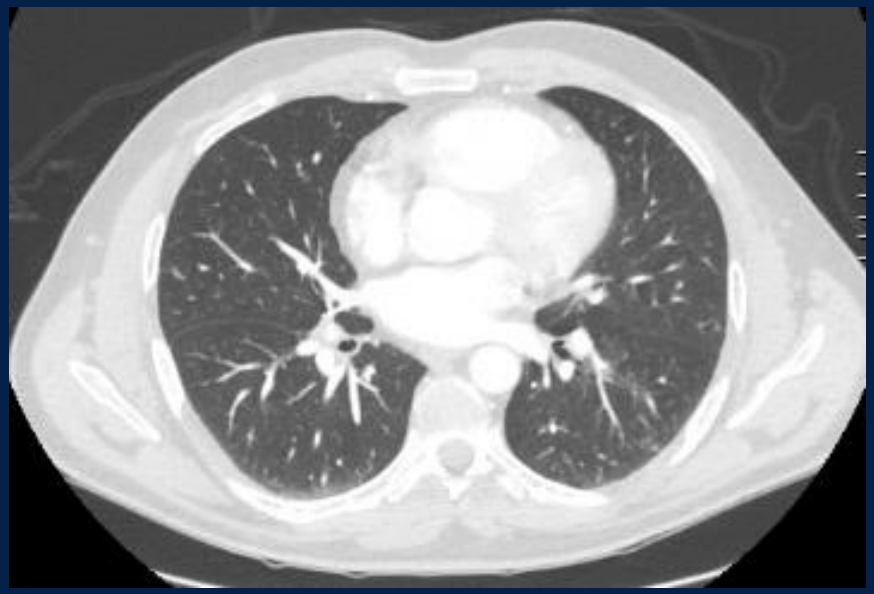
Case: Combined PD-L1 plus CTLA-4 Inhibition in UCSF Patient with Nonviral HCC



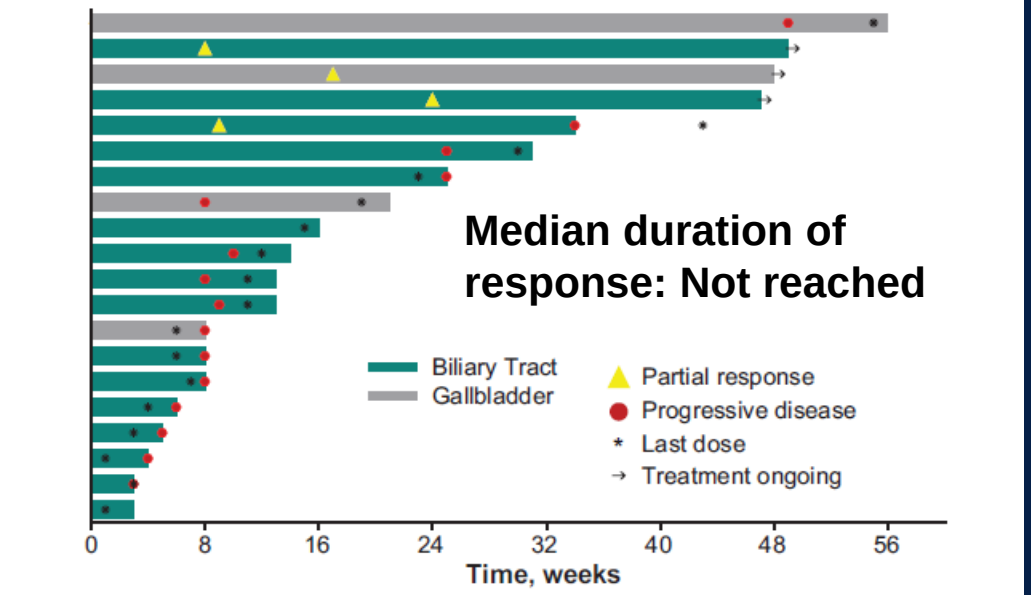


- 6/2016: AFP 8264
- 9/2016: AFP 46

Pembrolizumab (MK-3475, anti-PD-1) in Cholangiocarcinoma: KEYNOTE-028

- Screened 87 patients:
  - 41% tumor PD-L1+
  - Enrolled 24
    - CCA 83%
    - Gall bladder 17%
- Outcomes:
  - Partial response 17%
  - Stable disease 17%
  - Treatment-related grade 3 AE: 17%

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).



Bang et al ESMO 2015, Abstract 525

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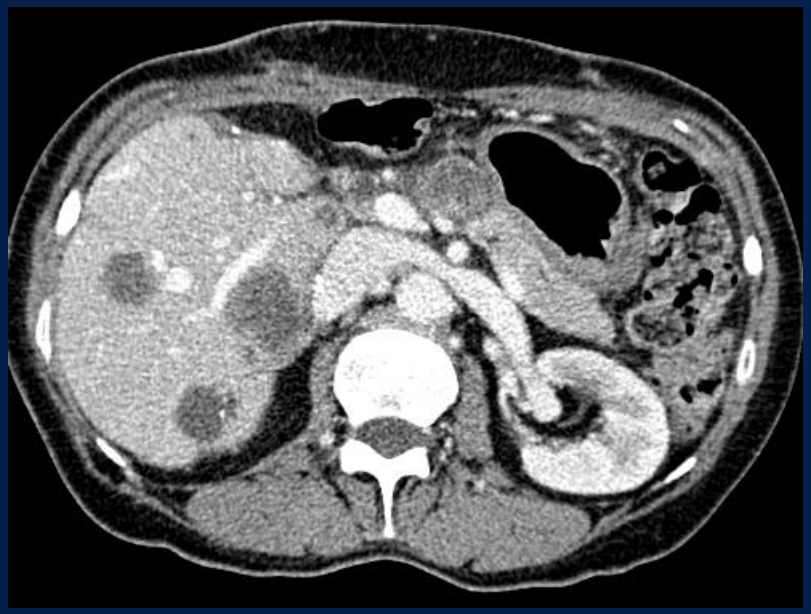
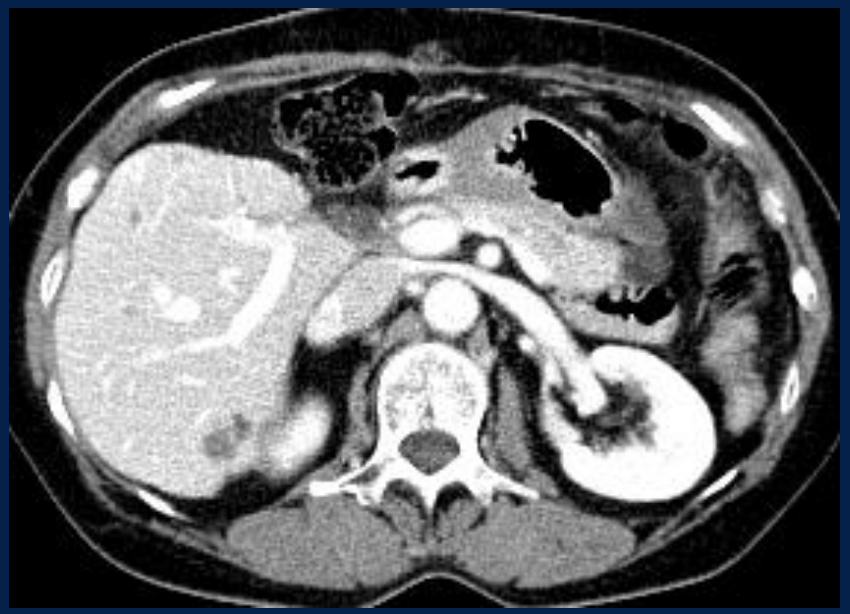
Case: Complete Response to PD-1 Inhibition in UCSF Patient with IHCC

- 66yo female with CCA with liver, bone, lymph node, dermal, and cardiac metastases after surgery, progressed on 1st line GEMCIS chemotherapy





- Treated with 2nd line therapy on clinical trial of PD-1 inhibitor mAb
- Dramatic, durable response ("super-responder"); completed 2 years on treatment, no toxicity; now off treatment without recurrence since 6/2016

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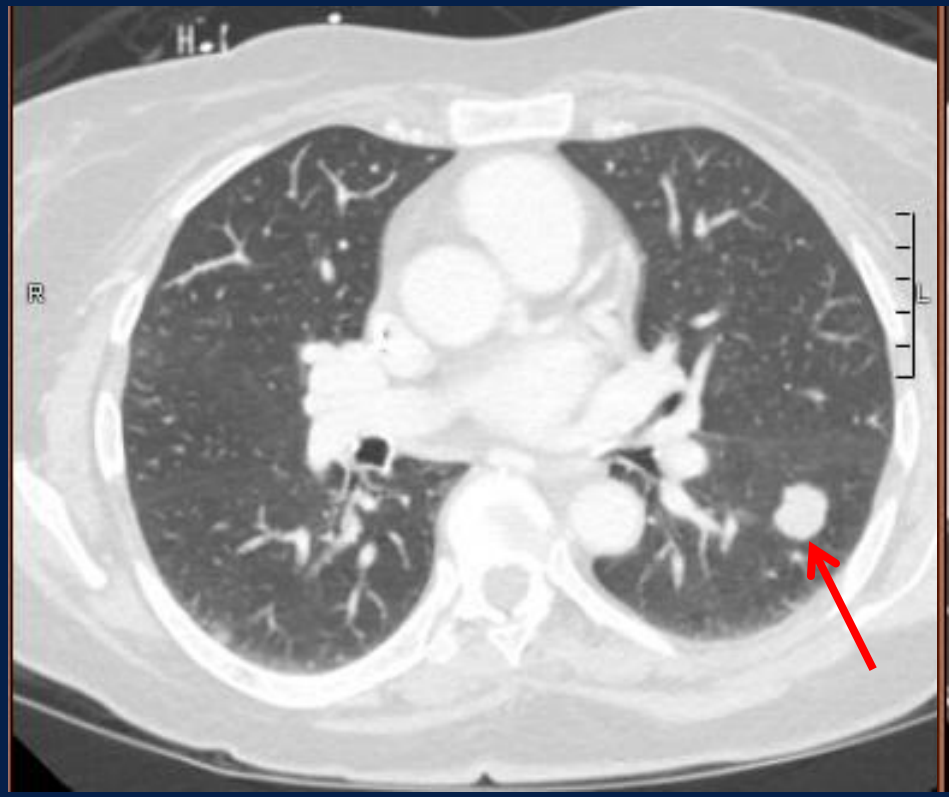
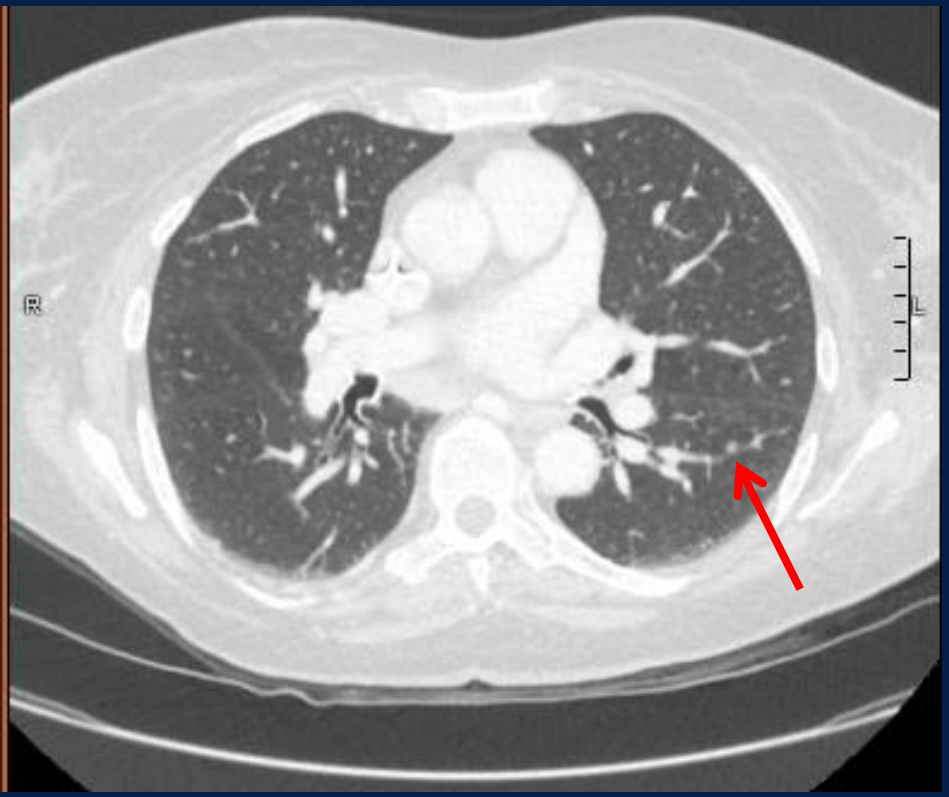
Case: PD-1 Inhibition plus GM-CSF in UCSF Patient with Mixed HCC-Cholangiocarcinoma



- 6/2016



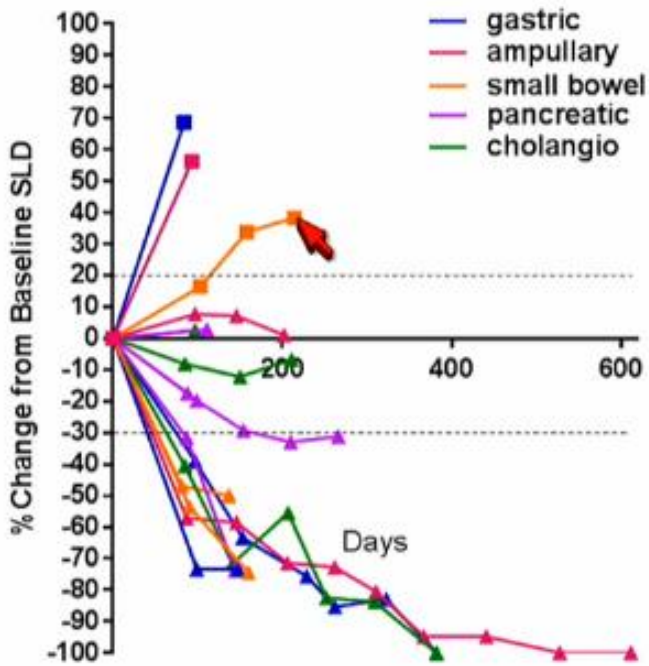
- 8/2016

Immunotherapy: Ongoing Studies of Biomarkers, Combinations

- Biomarkers:
  - Microsatellite instability (MSI-high)/deficient mismatch repair (e.g. Lynch/HNPCC or sporadic cases of tumor MSI)
  - Tumor PD-L1 expression level, mutational burden, specific gene signatures?
- Combination strategies for PD-1/-L1 inhibitors:
  - CTLA-4 inhibitors, other immunotherapy agents
  - Chemotherapy?
  - Local therapies such as radiation, arterial therapies, ablation?

High Response Rates to PD-1/PD-L1 Inhibition in Mismatch-Repair Deficient Tumors

Durability of Disease Control



Response rate: 47%; 7 of 8 responders still ongoing at reporting

2016 Gastrointestinal Cancers Symposium

Le et al Gastrointestinal Cancers Symposium 2016, Abstract 195

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Immunotherapy: Immune-Related Adverse Events

- Immune-mediated adverse events can range from mild to severe (rare, generally <5% grade ≥3 each) including:
  - Endocrinopathies (thyroid, diabetes, pituitary, etc.)
  - Colitis including bleeding and perforations
  - Hepatitis, liver failure
  - Pneumonitis, respiratory failure
  - Myocarditis, pericardial effusions
  - Encephalitis, neuropathy, myasthenic syndrome
  - Nephritis including renal failure
  - Dermatitis, rashes
  - Allograft rejection **(cannot be used before/after transplant)**

Objectives

3. Looking ahead: How to integrate the old with the new?

Advanced HCC: Integrating Old and New

- Sorafenib remains current/only standard of care
- Multiple ongoing pivotal trials reporting soon:
  - 1st line sorafenib versus PD-1 inhibitor nivolumab trial ongoing (CheckMate 459, NCT02576509)
  - 2nd line: regorafenib, cabozantinib after sorafenib failure
  - MET-high: tivantinib phase 3 trial due to report late 2016
- Combination immunotherapy trials including PD-1/-L1 plus CTLA-4 inhibition suggest promise to improve response rates over PD-1/-L1 alone
- Role for immunotherapy in earlier stage disease and/or in combination with liver-directed therapies?
  - Immune-related toxicity is a significant concern in early-stage disease
  - Not thought safe before/after transplant

Advanced Biliary Cancers: Integrating Old and New

- GEMCIS remains current/only standard of care
- Emerging data support obtaining tumor sequencing for advanced biliary cancers:
  - Our practice is to obtain sequencing at diagnosis/during 1st line therapy
    - If positive for FGFR2, IDH1/2, BRAF, HER2, NTRK, ROS1, or other actionable mutation: Refer to targeted therapy trials
      - FGFR2-targeted therapy may be approved by FDA for FGFR2+ in future?
    - If known MSI-high/mismatch-repair deficient advanced biliary cancer: Refer for immunotherapy trials
      - Anti-PD-1 immunotherapy may be FDA-approved MSI-high/mismatch repair deficient advanced cancers in future?

Summary: Take-Home Points

- We recommend obtaining next-generation sequencing of advanced biliary cancer patients at diagnosis or during 1st line therapy; refer for clinical trials if targetable aberration such as FGFR2, IDH1/2, BRAF, HER2, NTRK, ROS1, ALK1, MSI-high
- Immunotherapy studies show subset with extraordinary responses in both HCC and biliary cancers
  - Lynch syndrome/MSI have ~50% response rate or higher
  - Toxicity issues: Cannot use before/after transplant; caution in earlier stages of disease
  - Many studies are underway to identify predictive biomarkers and combinations/strategies to augment response

These are promising times in hepatobiliary cancer treatment!

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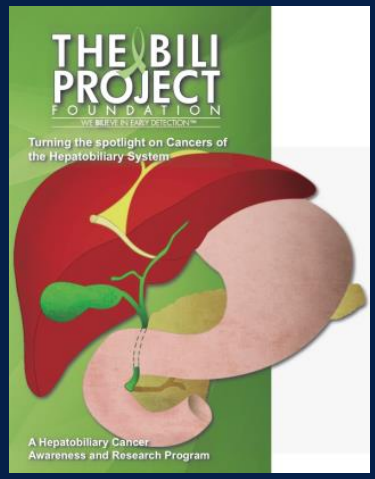
- The Bili Project Foundation, Inc.
- Cholangiocarcinoma Foundation
- Our patients and their families



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