UCSF
University of California
San Francisco

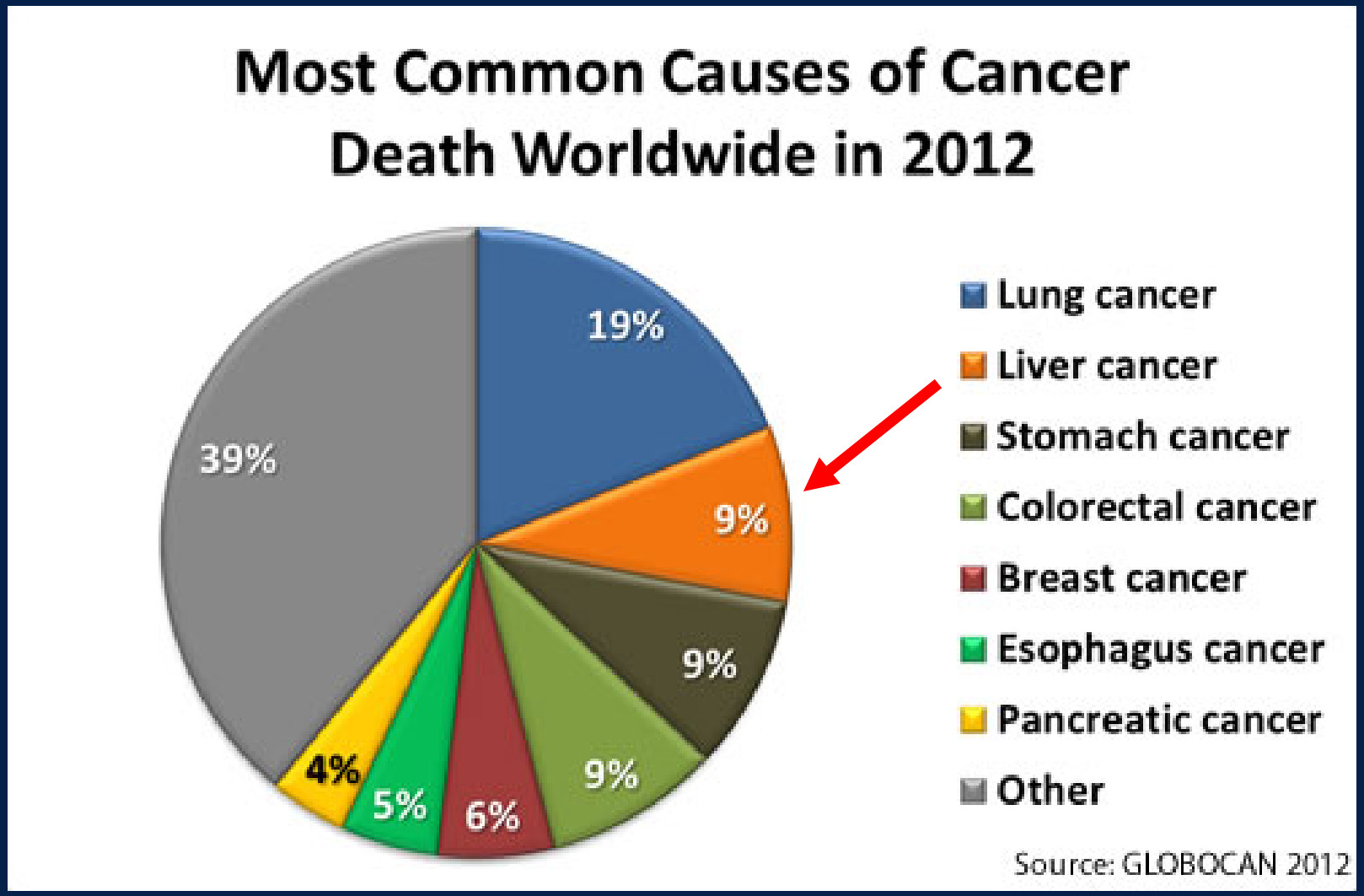
Cholangiocarcinoma: Treatment Updates

Katie Kelley, MD
Associate Professor of Clinical Medicine
Division of Hematology/Oncology
University of California, San Francisco (UCSF)

12/10/2016

Objectives

- Review incidence and prognosis of intrahepatic (IHCC) and extrahepatic (EHCC) cholangiocarcinoma (CCA)
- Review current treatments for CCA
  - Localized
  - Locally advanced/unresectable
  - Metastatic
- Introduce new targets and treatments in development

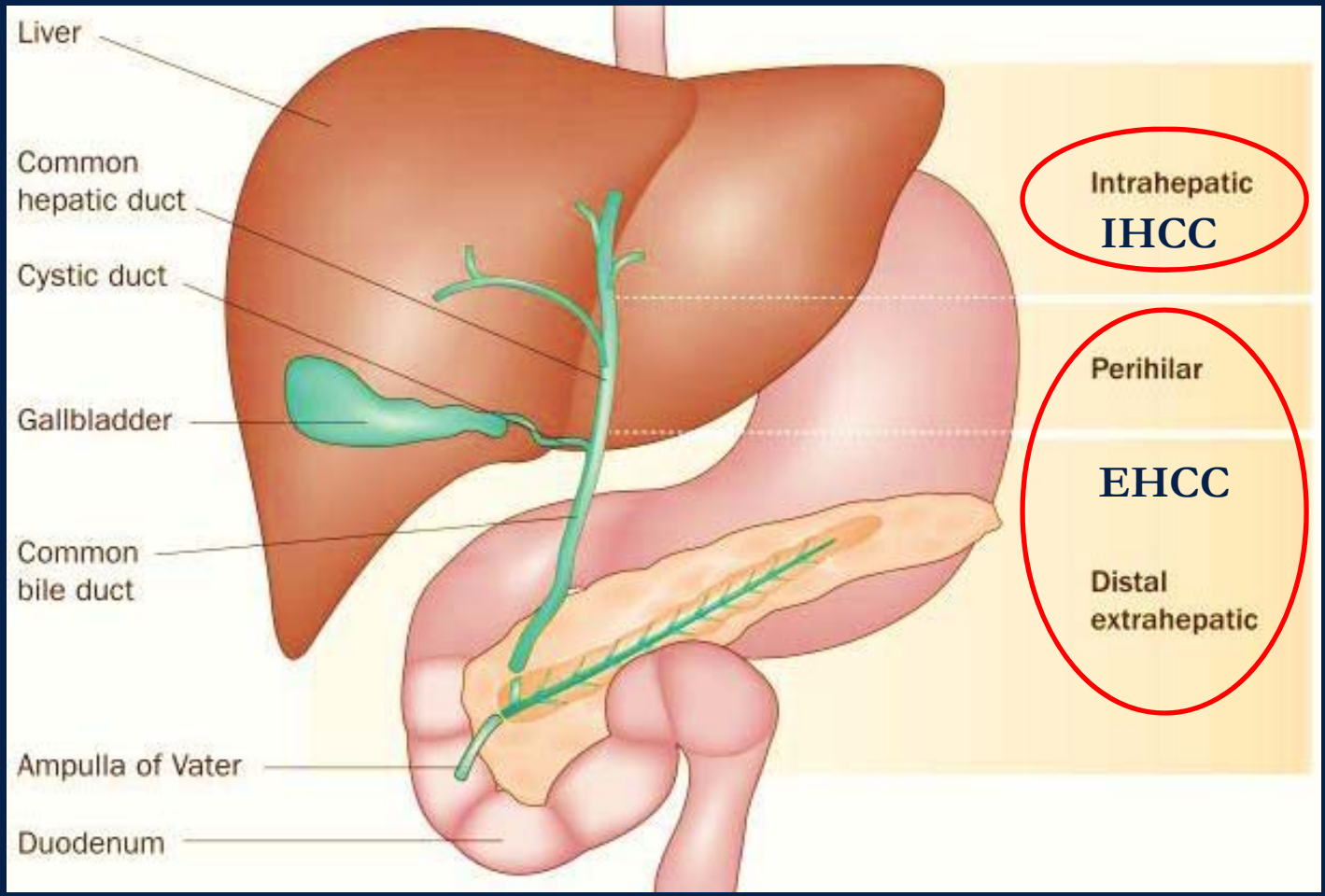


Mortality: 745,500 deaths worldwide in 2012

GLOBOCAN 2012

UCSF

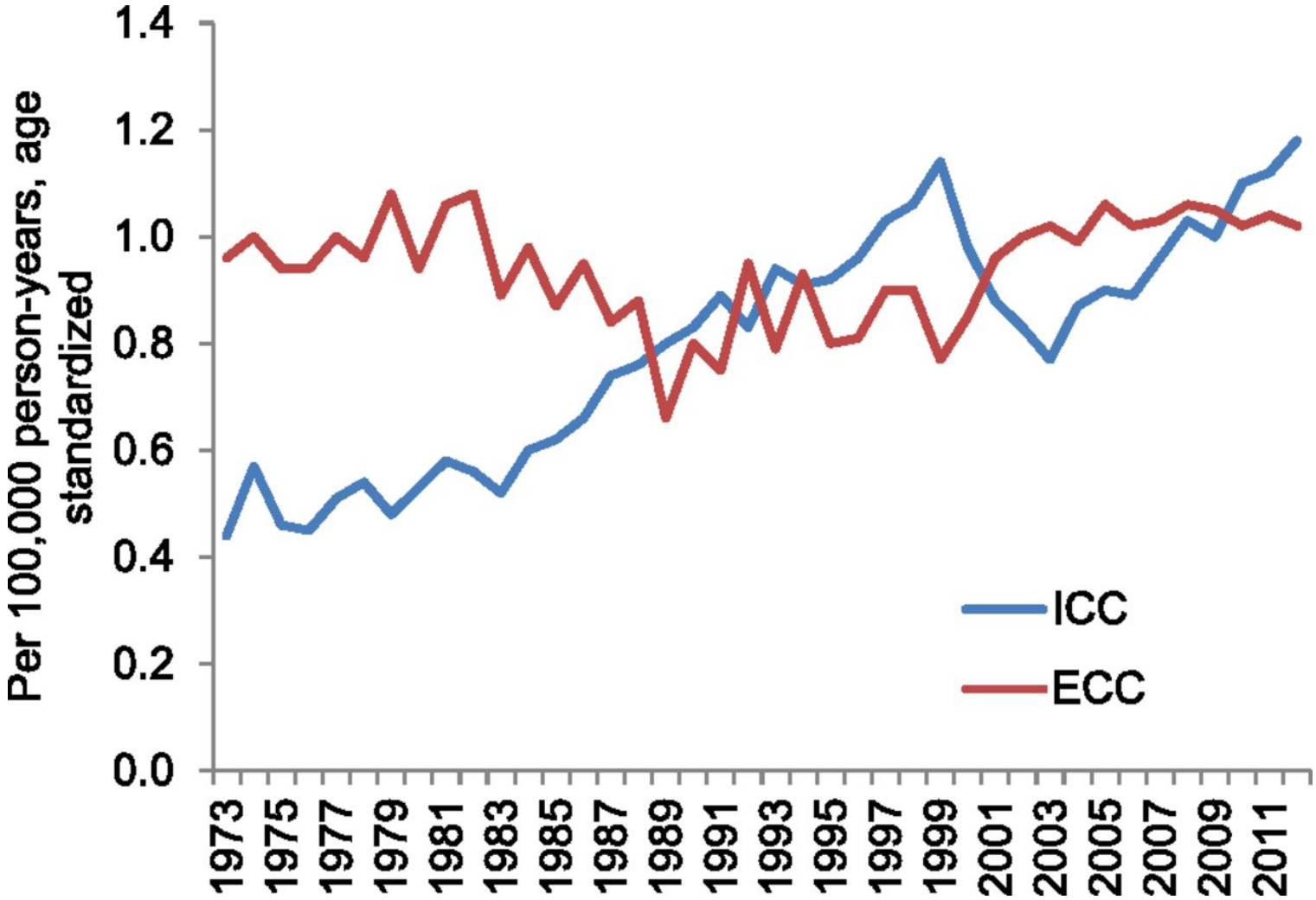
Anatomic Classification of Liver and Biliary Tract Cancers



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

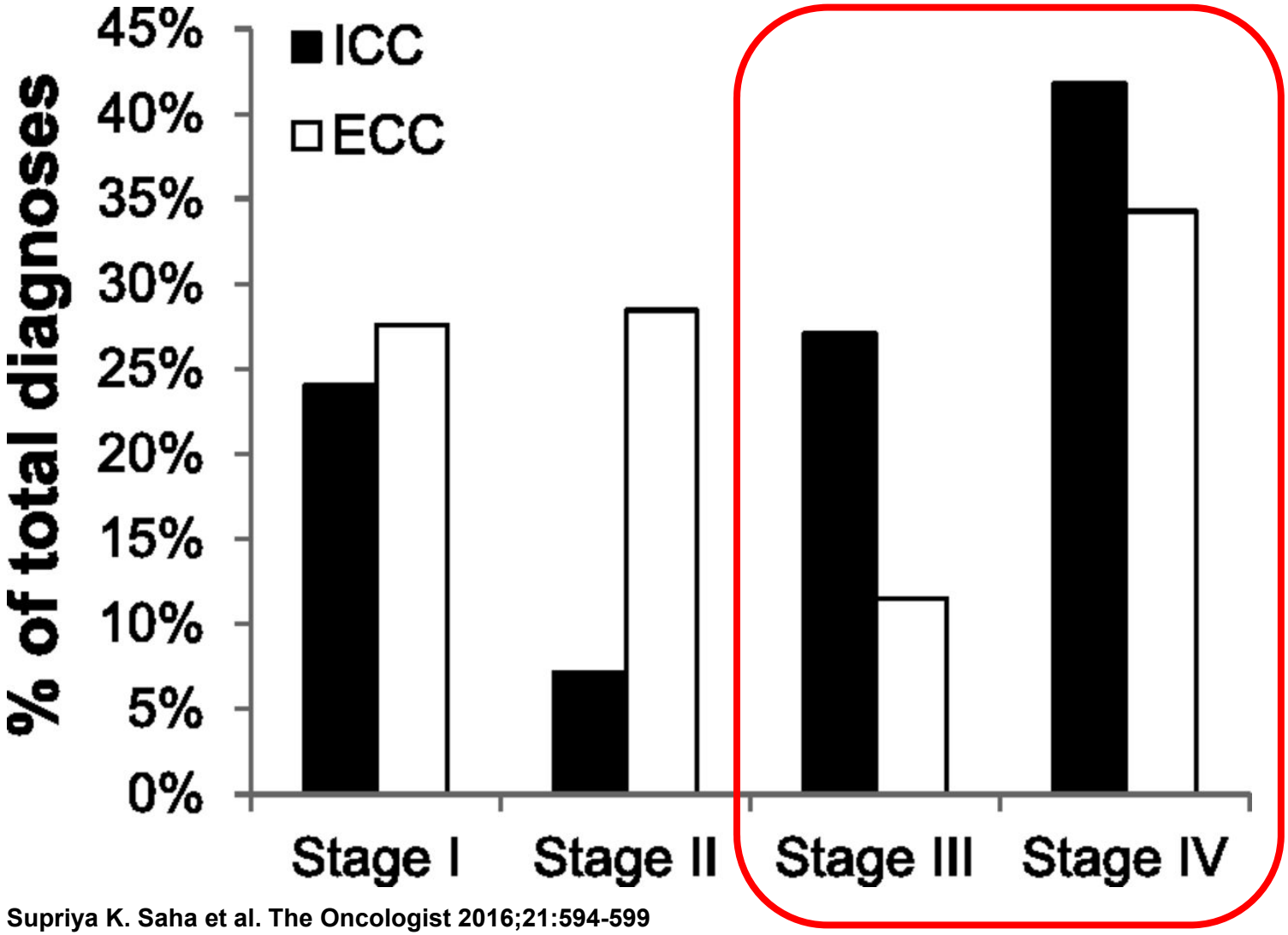
UCSF

Age-adjusted incidence of intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma, 1973–2012



Supriya K. Saha et al. The Oncologist 2016;21:594-599

Stage distribution at diagnosis of ICC and ECC, 2004–2010



Supriya K. Saha et al. The Oncologist 2016;21:594-599

The Oncologist

Prognosis CCA

Intrahepatic bile duct cancer

Stage	5-year relative survival
Localized	15%
Regional	6%
Distant	2%

Extrahepatic bile duct cancer

Stage	5-year relative survival
Localized	30%
Regional	24%
Distant	2%

www.cancer.org

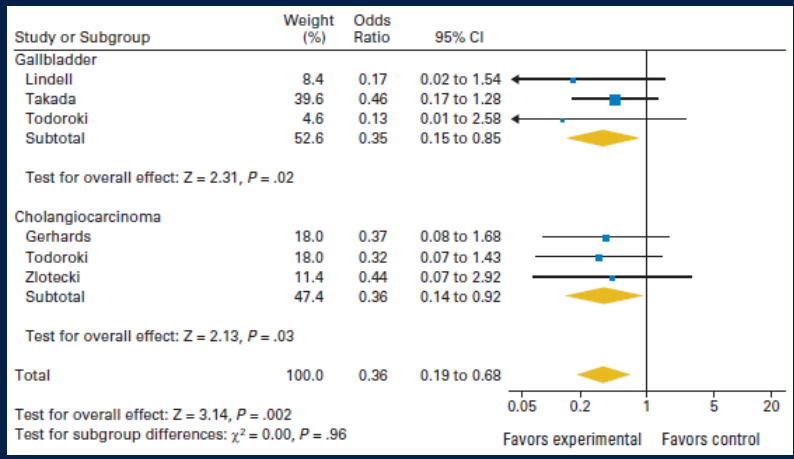
Current Treatments: Localized CCA

- Surgery
  - Resection
  - Transplant may be an option in selected cases of perihilar CCA
- Consider adjuvant therapy with:
  - Chemotherapy?
  - Radiation/chemoradiation?

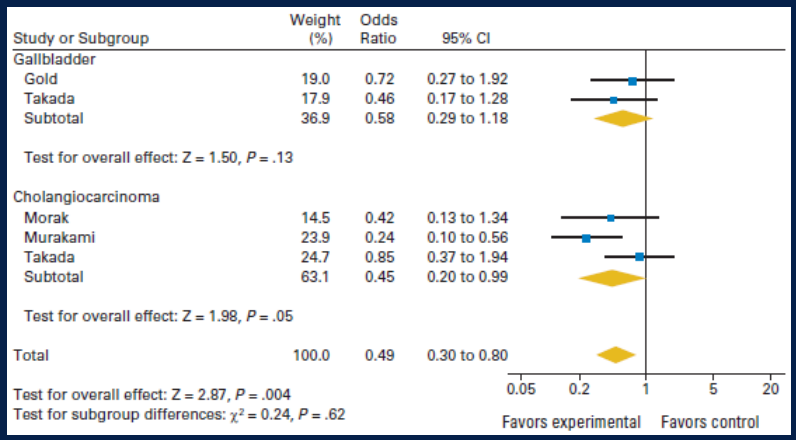
Is there a role for adjuvant therapy after surgery for localized CCA?

- Meta-analysis of 6712 patients after curative surgery for CCA:
  - Any adjuvant therapy in overall population: OR 0.74, p=0.06
    - Node-positive (A) : OR 0.49, p=0.004; chemotherapy or chemoRT > RT alone
    - Margin-positive (B): OR 0.36, p=0.002; chemotherapy or chemoRT > RT alone
    - IHCC subset data are limited
  - Optimal chemotherapy/RT regimen remains unknown

A. Node-positive population



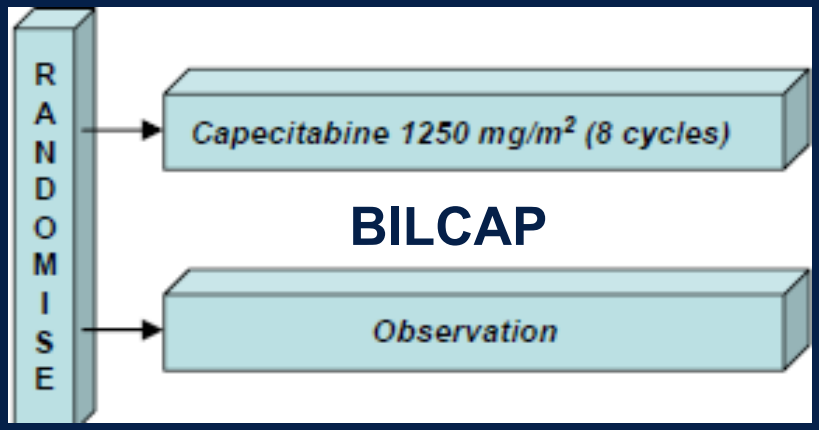
B. Margin-positive population



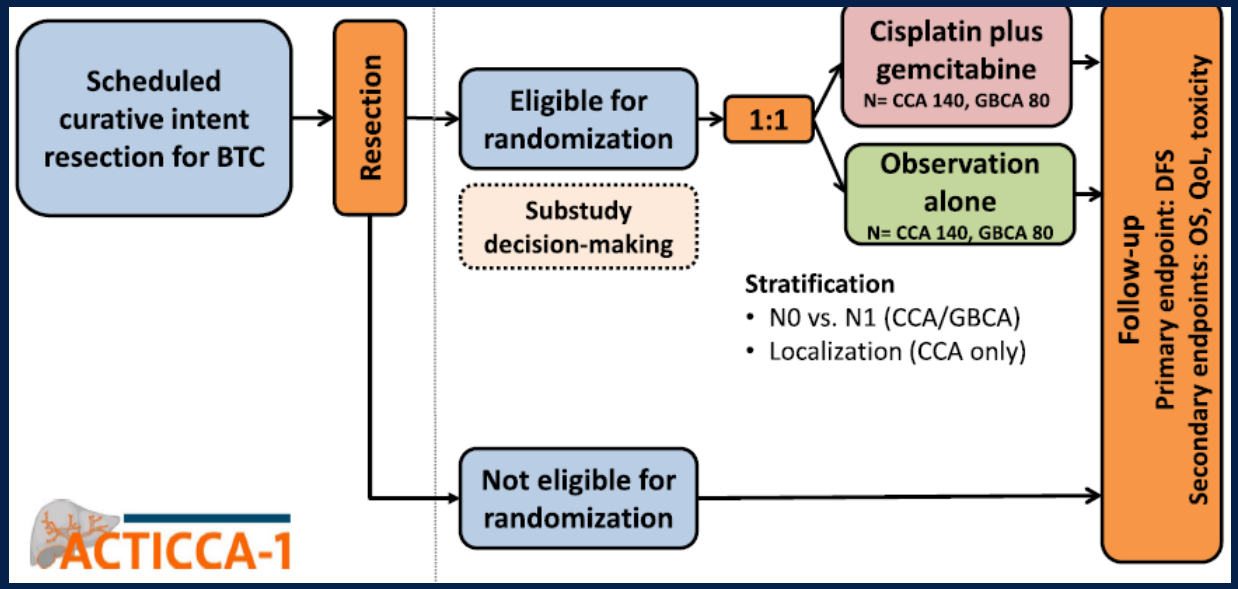
Horgan et al J Clin Oncol 30(16) 2012

UCSF

Ongoing Randomized Adjuvant Studies



- BILCAP (UK): Capecitabine
  - Report expected ASCO 2017
- ACCTICA-1 (UK): GEMCIS
- UNICANCER (France): GEMOX



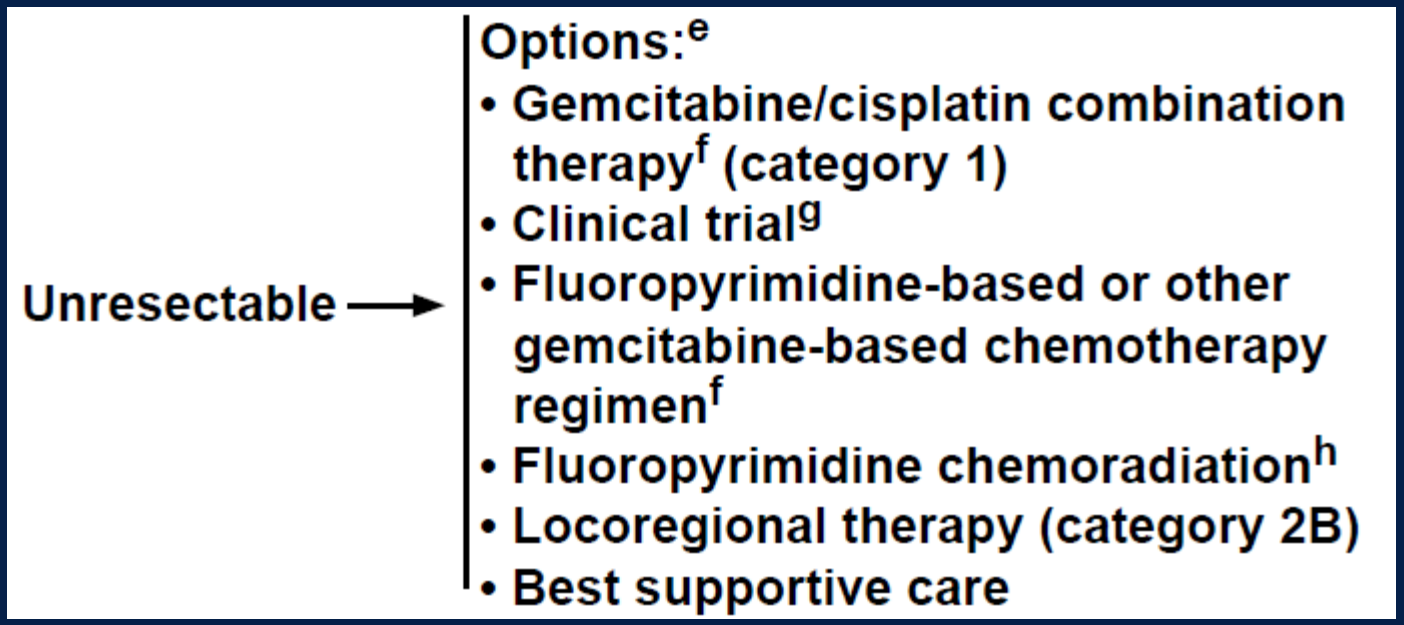
Stein et al BMC Cancer 15 2015; Bridgewater et al ASCO 2011 abstr. 4125

UCSF

Current Treatments: Locally-Advanced, Unresectable CCA

- Generally treat as metastatic disease with chemotherapy
- Consider liver-directed treatments:
  - Radiation/chemoradiation
  - Ablative or arterial therapies for IHCC?

National Comprehensive Cancer Network (NCCN): Guidelines for Locally-Advanced, Unresectable IHCC, EHCC



- Multiple loco-regional modalities available, limited prospective data
- Choice of modality and sequence is based upon individual patient tumor and comorbidity characteristics, institutional capabilities and expertise

Role of Radiation in Locally-Advanced, Unresectable IHCC: NRG GI-001 Trial Ongoing

REGISTER	Gemcitabine/Cisplatin x 3	**Evaluate to confirm no progression:** **Patients without progression, will be randomized**	**STRATIFY**	Tumor size (≤ 6cm vs. > 6cm) Satellite lesions (Yes vs. no)	**RANDOMIZE**	**Arm 1**: Gem/Cis x 1 -> Liver-directed Radiation Therapy -> Gem/Cis x 4 (Maintenance gemcitabine may be given after completion of Gem/Cis)* Vs. **Arm 2:** Gem/Cis x 5 (Maintenance gemcitabine may be given after completion of Gem/Cis)*

- Ongoing NCI trial for unresectable IHCC, activated 9/2014
- Radiation therapy: Proton, stereotactic, or intensity-modulated
- Target accrual 182

UCSF

Current Treatments: Metastatic CCA

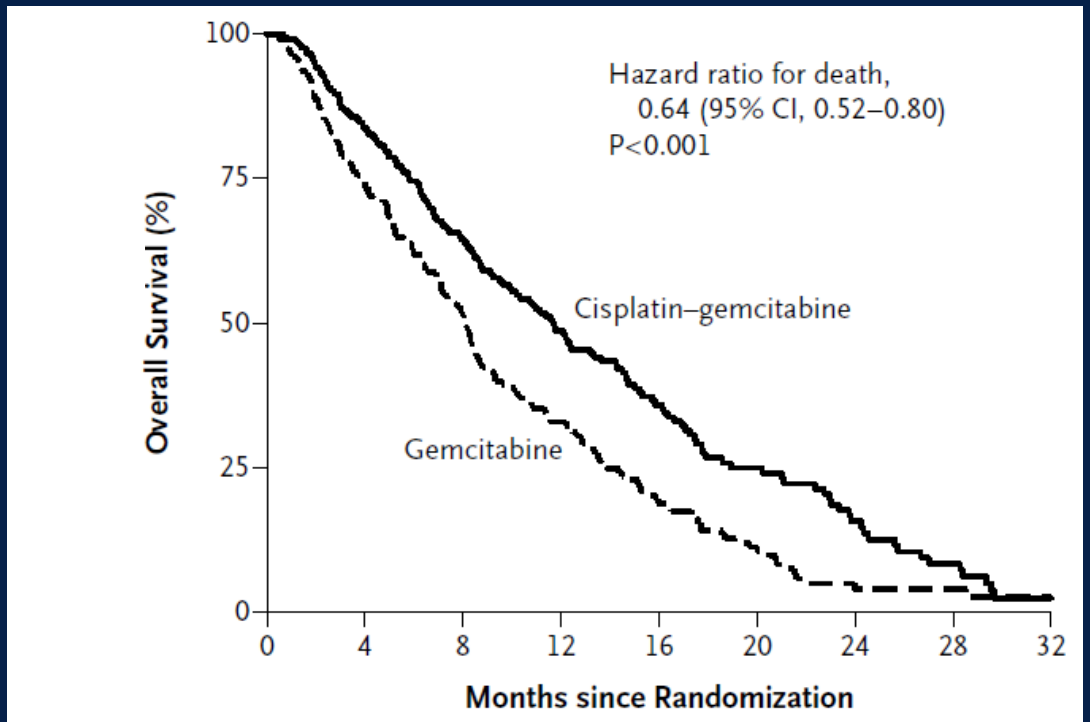
- Before 2010: No established "1st-line" chemotherapy; gemcitabine (GEM) or 5-FU regimens commonly used
- In 2010: ABC-02 trial showed combination of gemcitabine plus cisplatin ("GEMCIS") was superior to GEM alone
- In 2016: Still no standard 2nd line therapy
  - 5FU-based regimens are commonly used such as capecitabine (Xeloda), FOLFIRI, 5-FU; irinotecan; taxanes; response rates are modest

Valle et al NEJM 362(14) 2010; Hezel and Zhu Oncologist 13(4) 2008; Brieu et al Cancer 121(18) 2015

UCSF

ABC-02 Trial: Established GEMCIS as 1st-Line Therapy for Advanced Biliary Cancers

- Randomized phase 3 trial GEMCIS vs. GEM:
  - 37 centers in UK NCRN
  - N=397, randomized 1:1
- Results:
  - Partial response rate: 25.5% vs. 14.8% (NR)
  - Progression-free survival (PFS) 8.0 vs. 5.0 mos. (p<0.001)
  - mOS: 11.7 vs. 8.1 mos., HR 0.64 (p<0.001)



No. at Risk									
Gemcitabine	206	151	97	53	28	15	4	3	2
Cisplatin–gemcitabine	204	167	120	76	51	28	17	8	2

Valle et al NEJM 362(14) 2010

UCSF

2016: Still no established ≥ 2nd-line therapy for advanced CCA…

- No current labeled 2nd line therapy
- Retrospective studies:
  - N=603 patients across 17 French centers:
    - Only 32% received 2nd line therapy
    - Most common regimens were 5-FU-based
    - **Median 2nd-line progression-free survival (mPFS2) 3.2 months**
    - Median 2nd-line overall survival (mOS) 6.7 months
  - N=56 patients at M.D. Anderson Cancer Center:
    - **mPFS2 2.7 months**
    - mOS2 13.8 months
- ABC-06 trial is ongoing in UK: 2nd-line FOLFOX versus best supportive care

Brieu et al Cancer 121(18) 2015
; Rogers et al J Gastrointest Oncol 5(6) 2014

UCSF

Challenges to Finding New Treatments in Cholangiocarcinoma

- Complex anatomy
- Competing comorbidity of organ dysfunction
  - E.g. biliary obstruction, cirrhosis, viral hepatitis
- Heterogeneous tumor and microenvironment biology
  - "One-size-fits-all"/unselected clinical trial designs are inadequate in highly heterogeneous populations
  - Therapeutic targets not well understood

Complex Anatomy: Location Impacts Tumor Genetics in 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

What are the clinical implications?

- There are subgroups defined by tumor mutations, pathway aberrations, and/or viral microenvironment within biliary cancers
- Some may be prognostic
- Some of these mutations may be driver oncogenes amenable to targeted therapies

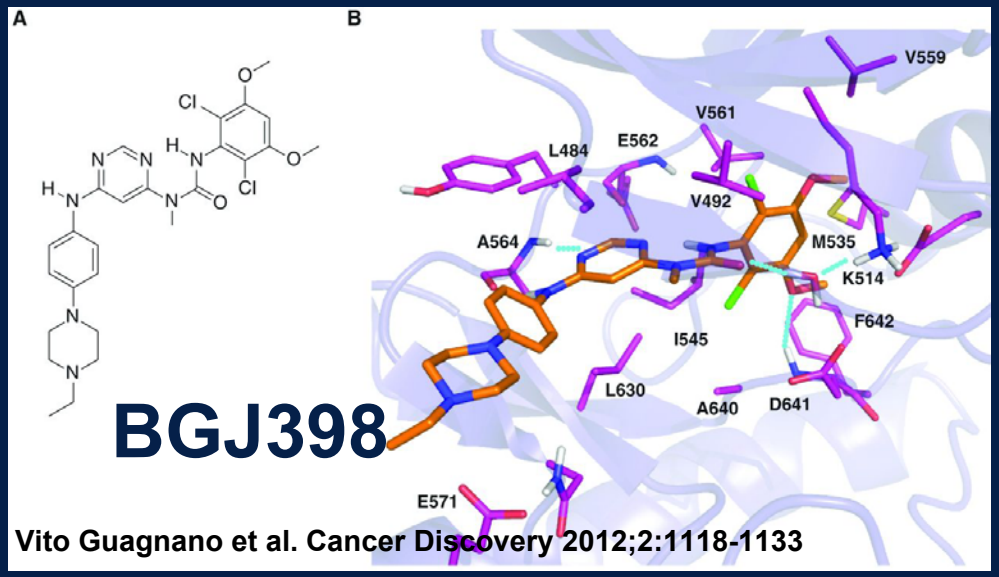
Need to define clinical and biologic subpopulations in cholangiocarcinoma clinical research …and in future treatment decisions?

Emerging Therapeutic Targets in Biliary Tract 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
Immune activation	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)
  - TAS-120 (Taiho)
  - Others

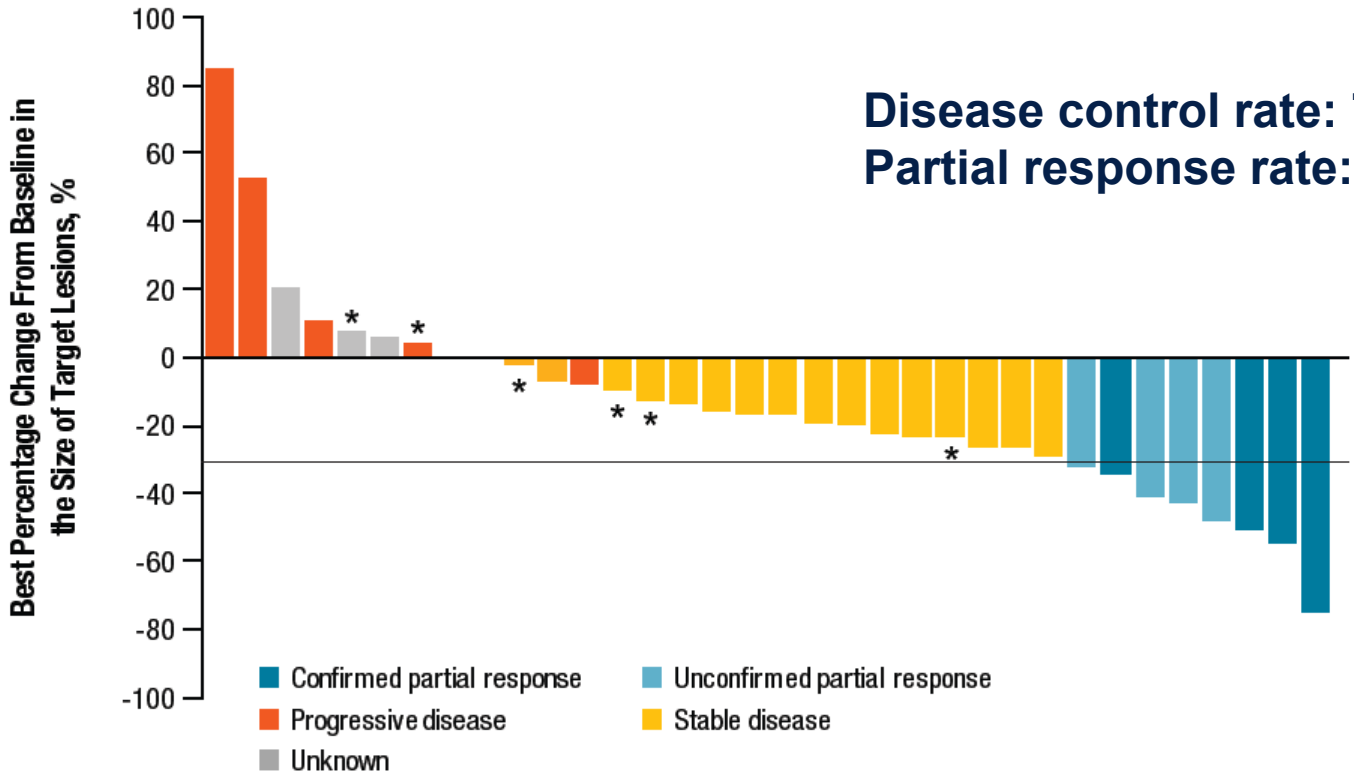


Vito Guagnano et al. Cancer Discovery 2012;2:1118-1133

UCSF

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]).

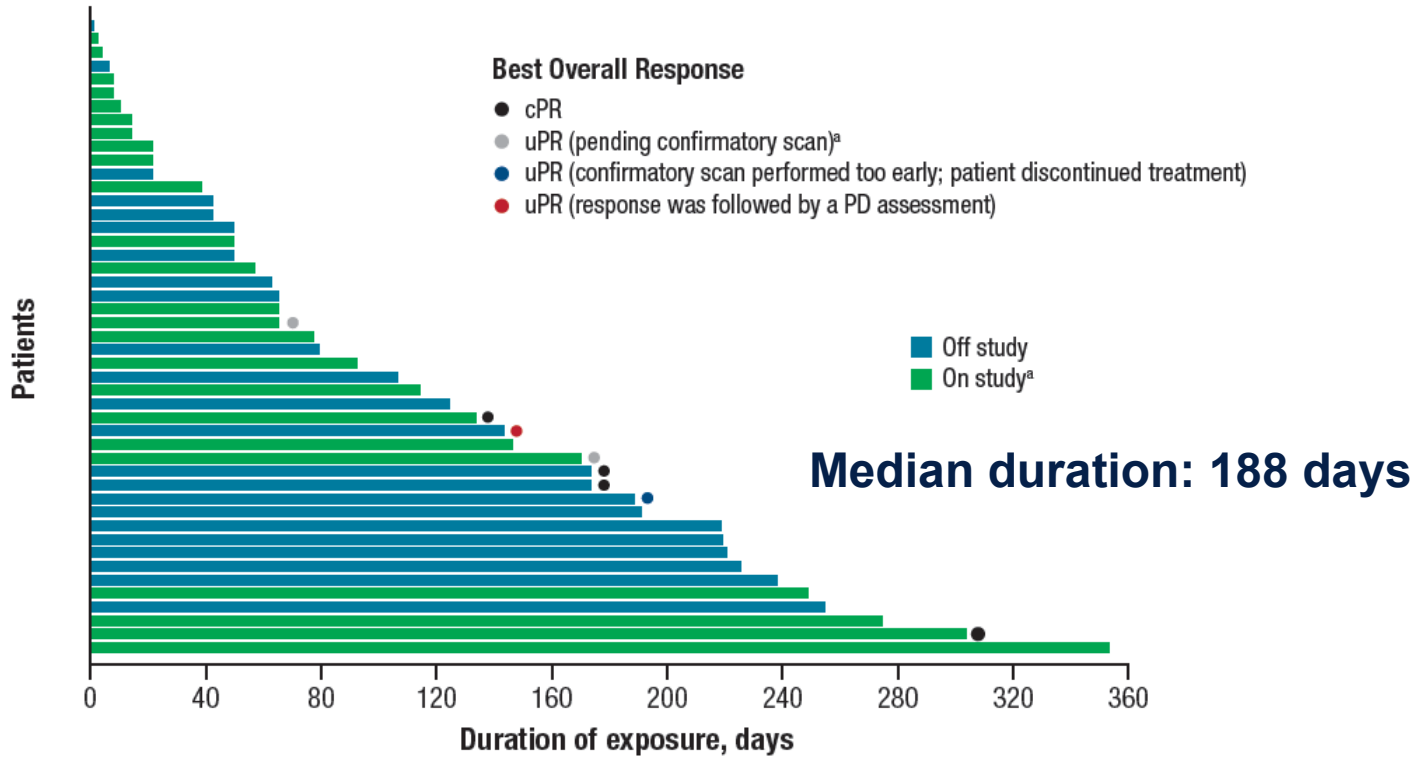
[b] Patients marked with an asterisk had *FGFR2* mutations (n = 2) or amplification (n = 3), or *FGFR3* amplification (n = 1). All other patients had *FGFR2* fusions (n = 28).

Javle et al GI ASCO 2016

UCSF

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

UCSF

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

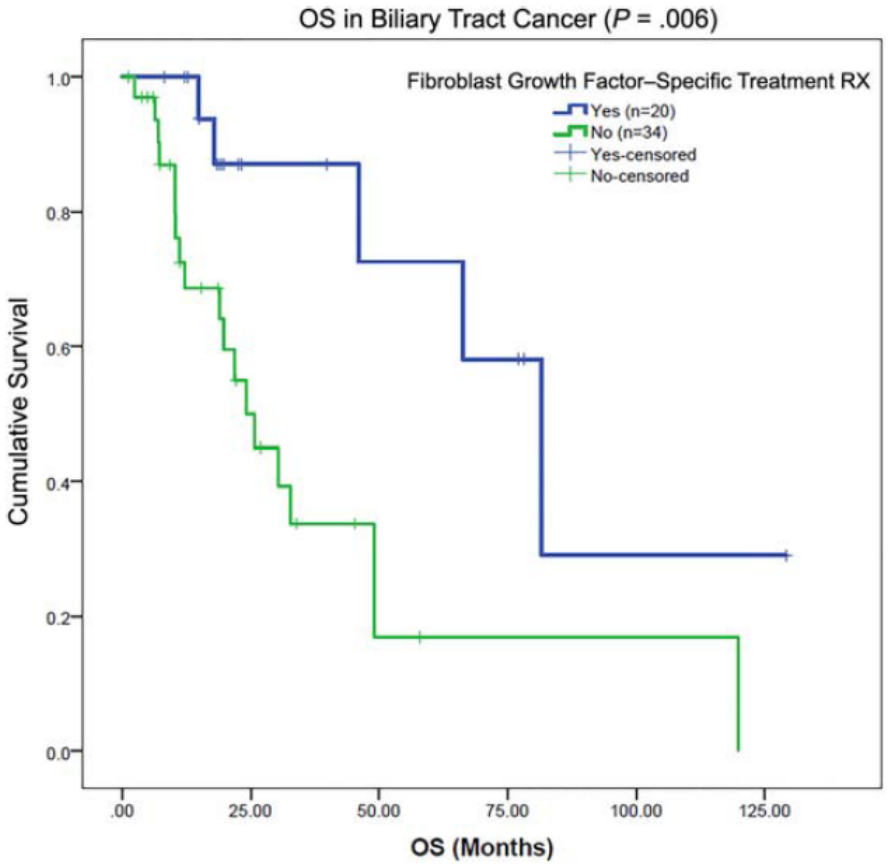
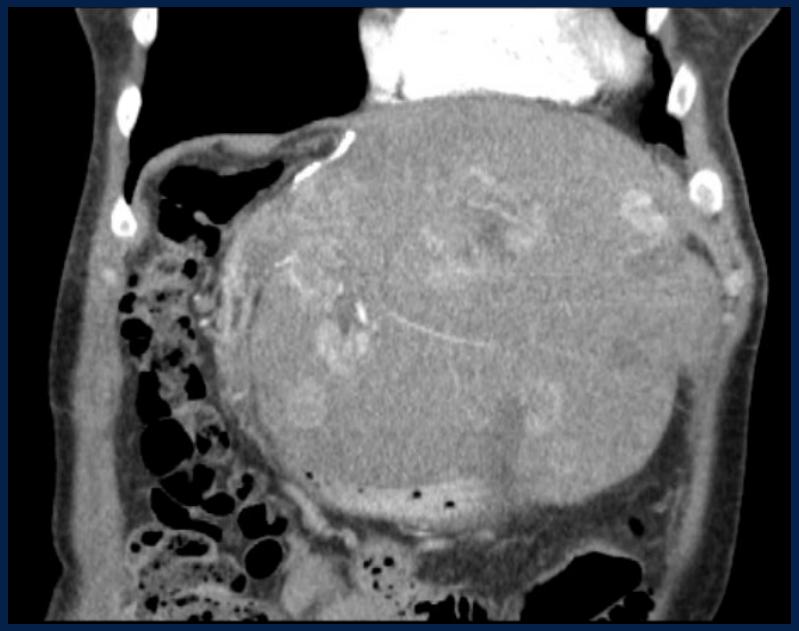


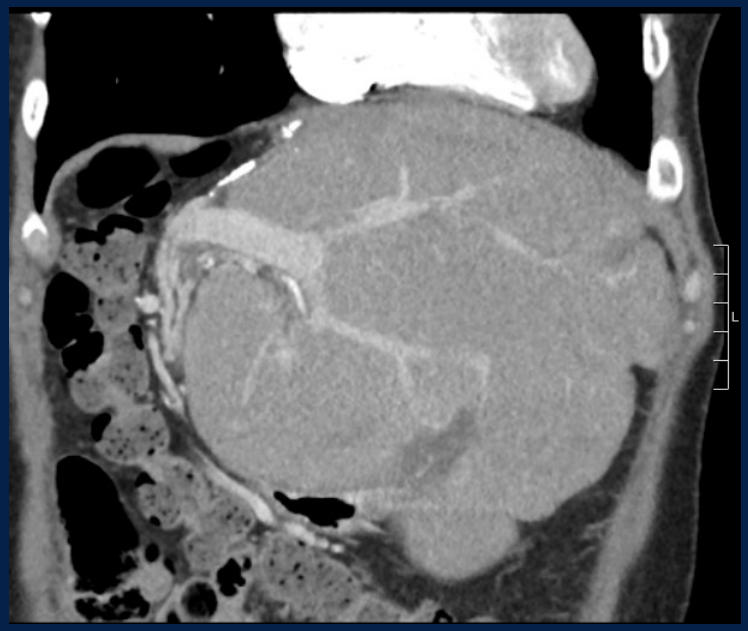
Figure 6. Kaplan-Meier curves of overall survival (OS) for 54 patients with a fibroblast growth factor receptor pathway genetic aberration with (n = 20) and without (n = 34) fibroblast growth factor receptor–specific treatment.

Javle et al Cancer epub Sep 13, 2016

UCSF

Case: FGFR2-BICC1 fusion IHCC Patient Treated with FGFR Inhibitor

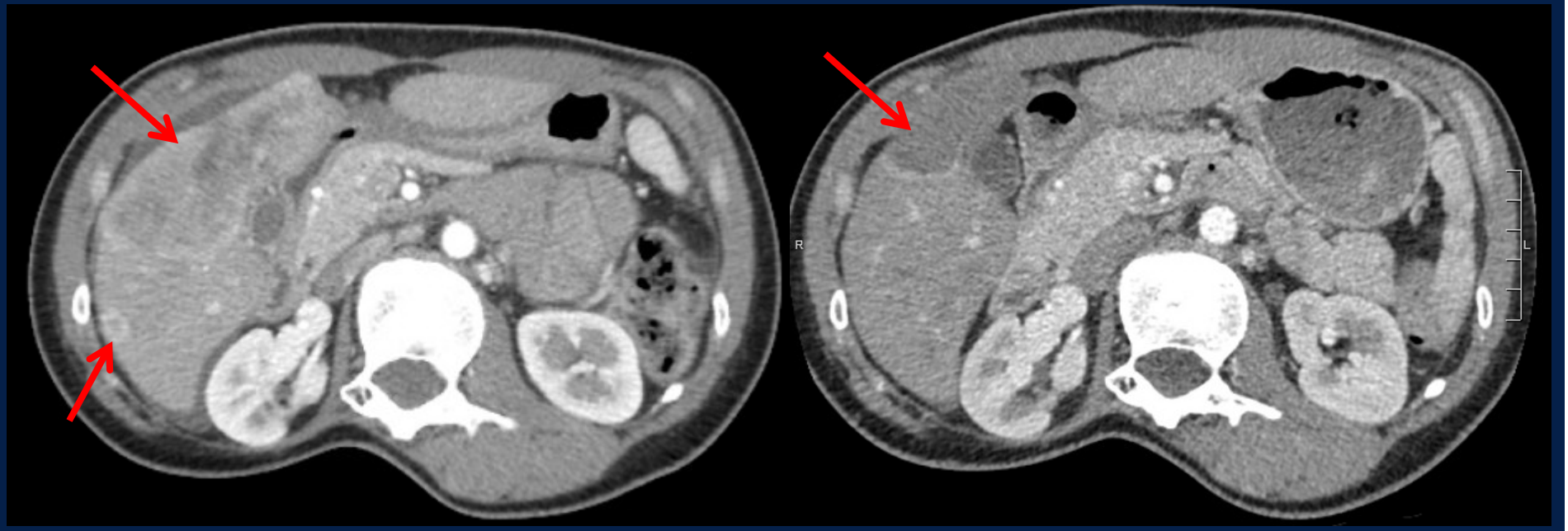




- 1/2016: Multifocal IHCC lesions
- 8/2016: Prolonged partial response, 57% reduction in multifocal liver tumors

UCSF

Another Case: FGFR2-BICC1 fusion IHCC Patient Treated with FGFR Inhibitor



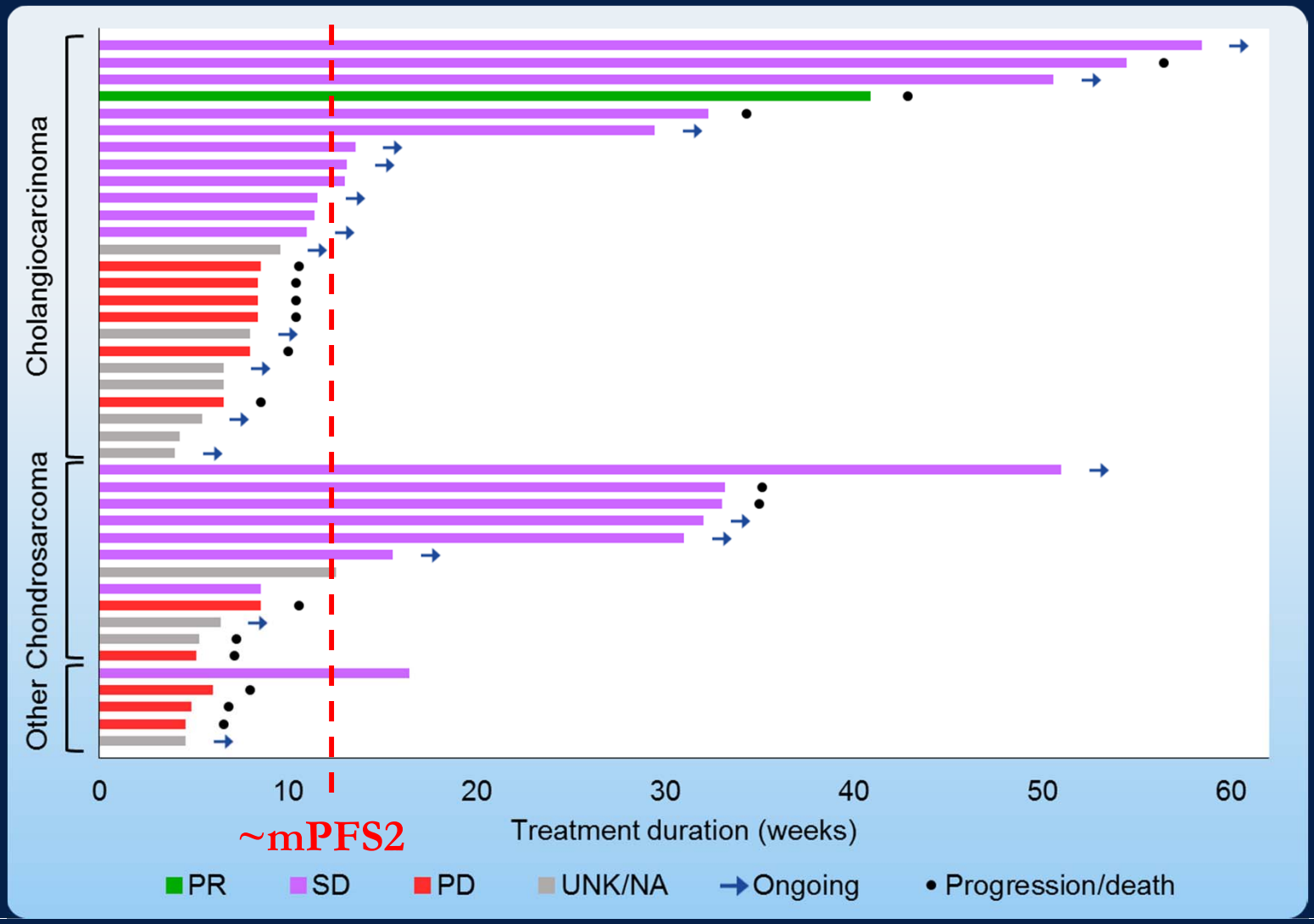
- 9/2016: Multifocal metastatic IHCC
- 11/2016: ~60% reduction after 2 months on treatment

UCSF

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

Prolonged Tumor Control on AG-120 in IDH1-Mutant IHCC

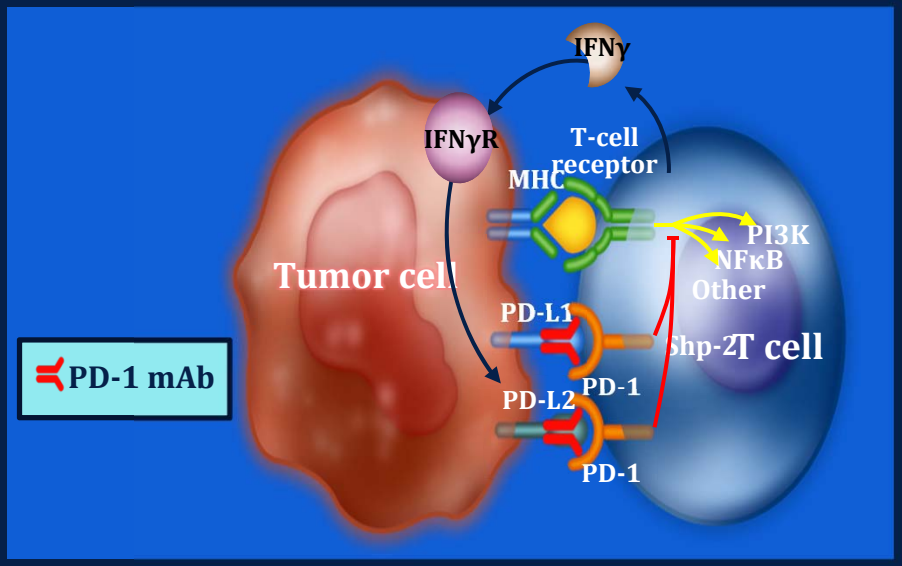


Burris et al AACR/NCI/EORTC 2015

UCSF

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



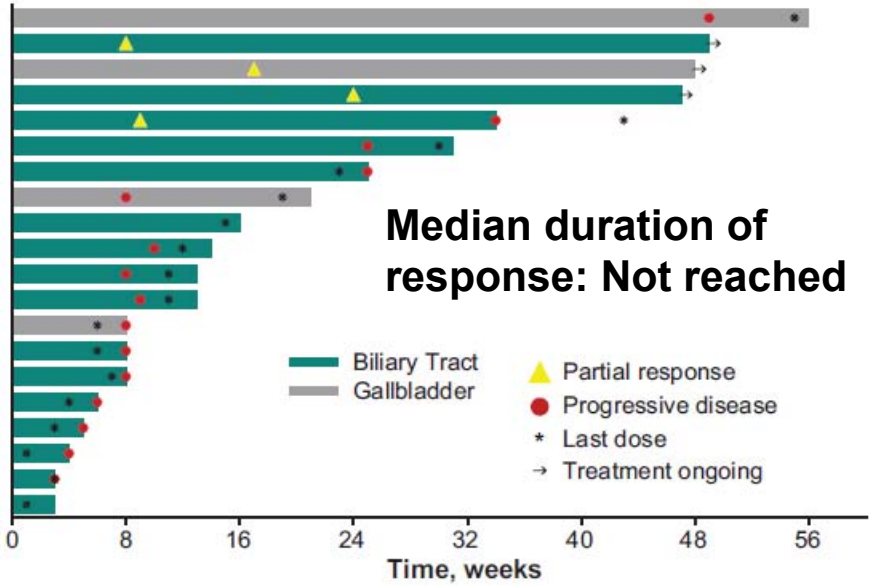
- **Early results in biliary cancer cohorts are promising…**

UCSF

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

- Screened 87 patients:
  - 41% tumor PD-L1+
  - Enrolled 24
- 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).

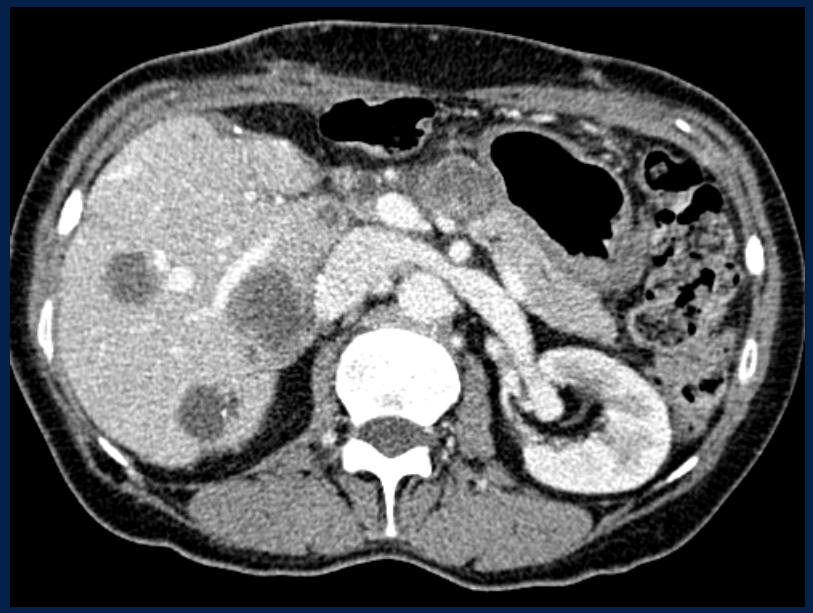


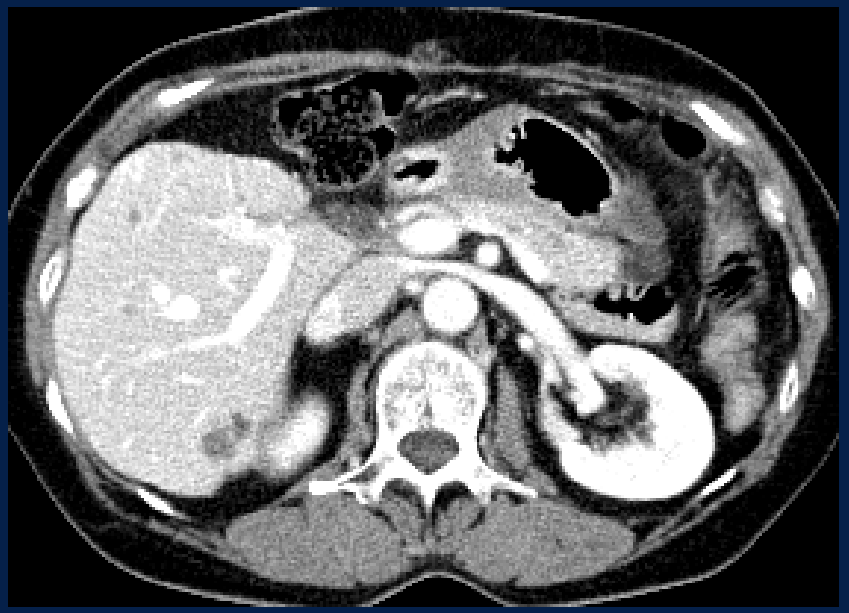
Bang et al ESMO 2015, Abstract 525

UCSF

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

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

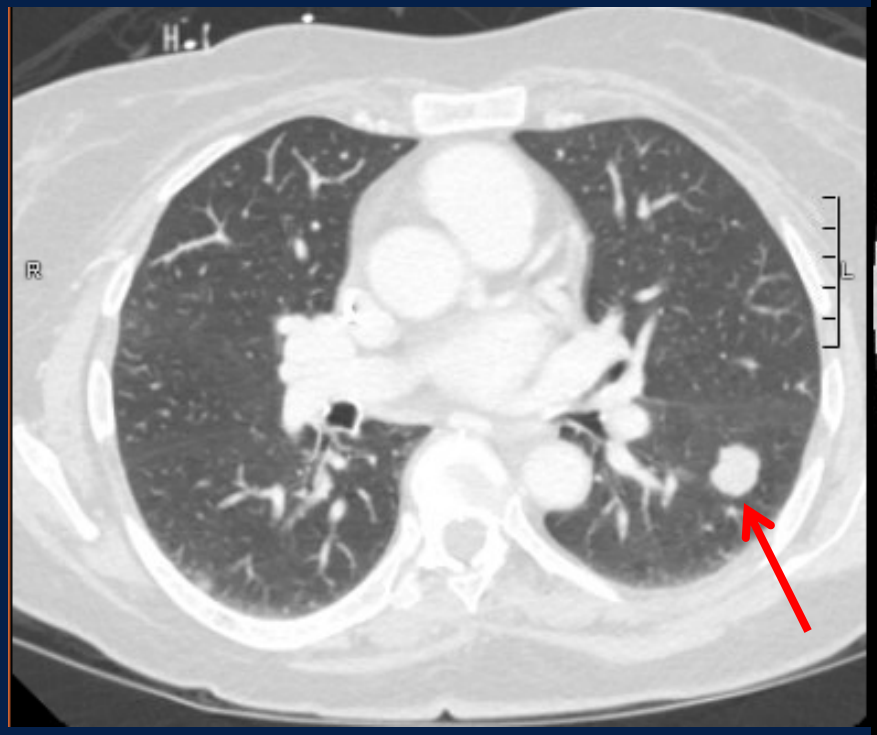




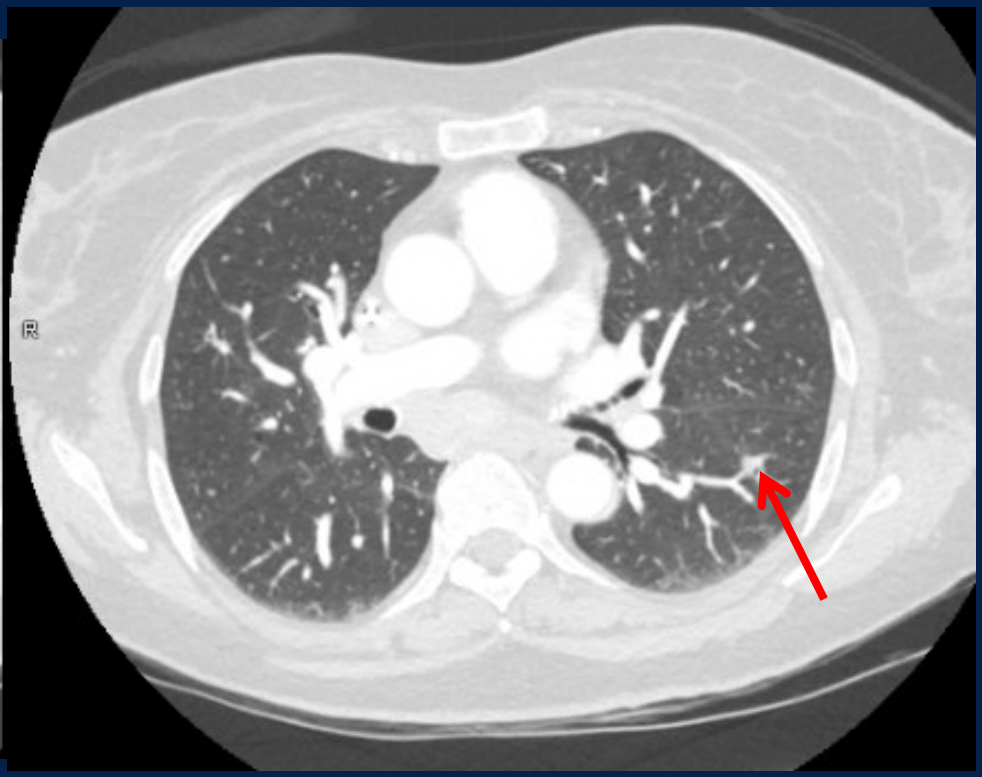
- Treated with 2nd line clinical trial of PD-1 inhibitor
- Prolonged response ("super-responder"); completed 2 years on treatment, no toxicity; now off treatment since 6/2016, no recurrence as of 11/2016

UCSF

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



- 6/2016: Started immunotherapy clinical trial



- 10/2016: ~15% reduction overall tumor burden

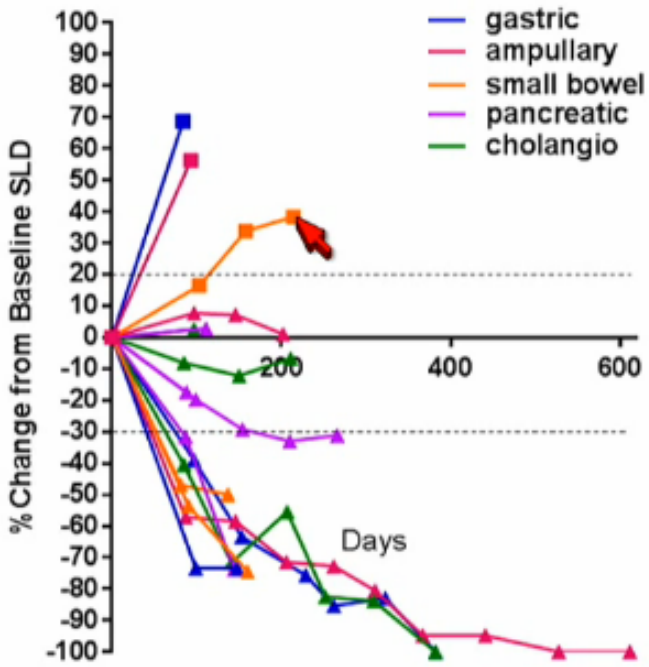
UCSF

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/transcriptional signatures?
- Combination strategies for PD-1/-L1 inhibitors:
  - CTLA-4 inhibitors, other immunotherapy agents
  - Chemotherapy?
  - Local therapies such as radiation, arterial therapies, ablation?

Mismatch-Repair Deficient (MSI-High) Tumors Respond to PD-1/PD-L1 Inhibition

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

UCSF

Summary and Conclusions

- Adjuvant chemotherapy or chemoradiation benefit not yet established, but should be considered if node+ or positive margins
  - Ongoing trials: BILCAP (report expected 6/2017), ACCTICA-1, UNICANCER
- Standard 1st-line therapy for locally-advanced and metastatic cholangiocarcinoma is ABC-02 regimen of gemcitabine plus cisplatin
- There is no standard 2nd line therapy
  - Ongoing trial ABC-06: FOLFOX versus best supportive care
- Targeted molecular/immune approaches show promise in subsets:
  - Pivotal clinical trials of FGFR2 and IDH1 inhibitors now ongoing
  - Immunotherapy trials ongoing, high response rates in MSI-high

Acknowledgments

- Colleagues in Hepatology/GI, Surgery, IR, Radiation Oncology, Radiology, and basic sciences…
- The Bili Project Foundation, Inc.
- Cholangiocarcinoma Foundation
- Our patients and their families