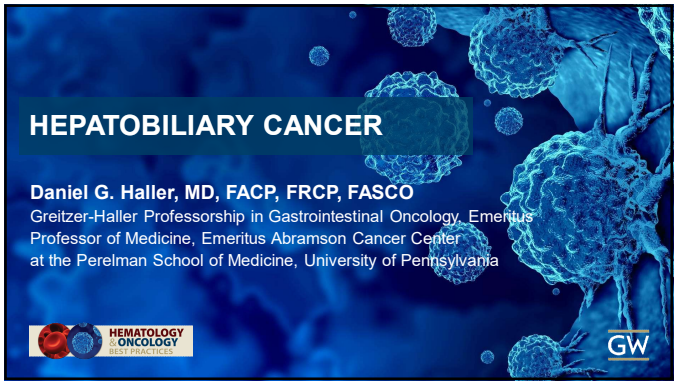


Disclosures

Off-Label Usage
- None

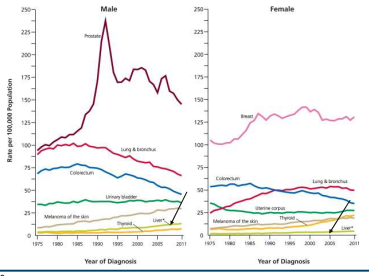
Interests- Speakers Bureau:
- Amgen
- TAIHO
- Lilly
- Exilixis

Hepatobiliary Carcinomas:
ACS 2021 Incidence and Mortality

	Incidence	Mortality
Liver/ Intrahepatic bile duct (~75% HCC)	42,230	30,230
GB/ extrahepatic bile duct	11,980	4,310

ACS Cancer Statistics

Trends in Incidence Rates for Selected Cancers by Sex, United States, 1975 to 2011



CA: A Cancer Journal for Clinicians
Volume 65, Issue 1, pages 5-29, 5 JAN 2015 DOI: 10.3322/caac.21254
http://onlinelibrary.wiley.com/doi/10.3322/caac.21254/full#caac21254-fig-0003

4

ACS Cancer Statistics, 2021

- **New cases:** An estimated 42,230 new cases of liver cancer (including intrahepatic bile duct cancers) will be diagnosed in the US during 2021, approximately three-fourths of which will be hepatocellular carcinoma (HCC). Liver cancer is about 3 times more common in men than in women.
- **Incidence trends:** Liver cancer incidence has more than tripled since 1980; the rate continued to increase by more than 2% per year in women from 2013 to 2017 but has stabilized in men. ~70% of HCCs could be prevented (excess body weight, type 2 diabetes, chronic infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV), heavy alcohol consumption (3 or more drinks per day), and tobacco smoking).
- **Deaths:** An estimated 30,230 liver cancer deaths will occur in 2021.
- **Mortality trends:** Liver cancer mortality rates have doubled since 1980 and continued to increase by 1% per year in women from 2014 to 2018, but have stabilized in men.

CA: A Cancer Journal for Clinicians
Volume 68, Issue 1, pages 5-29, 5 JAN 2015 DOI: 10.3322/caac.21254
http://onlinelibrary.wiley.com/doi/10.3322/caac.21254/full#caac21254-fig-0003

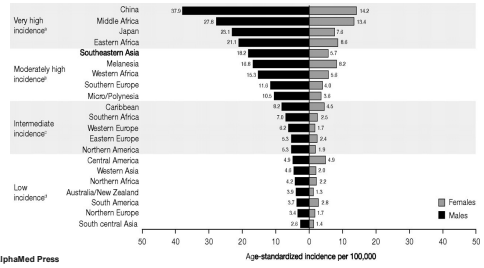
5

Hepatocellular Carcinoma

- Incidence
  - among the most common tumors in the world:
    - Liver cancer in adult men is the fifth most frequently diagnosed cancer worldwide, and is the second leading cause of cancer-related death in the world
  - >800,000 deaths annually
  - wide regional variation
    - highest in Southeast Asia and sub-Saharan Africa
    - epidemiological links to environmental, occupational exposure, life style (NASH)
    - implications for reduction of risk and prevention

6

Global variation in liver cancer incidence rates



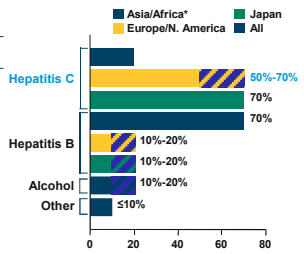
Venook A P et al. *The Oncologist* 2010;15:5-13

Hepatocellular Carcinoma

- Etiology
  - Cirrhosis
    - HBV
    - HCV
    - Alcoholic
    - NASH (Nonalcoholic steatohepatitis)
  - Metabolic diseases
    - hemochromatosis
    - hereditary tyrosinemia
    - alpha-1 antitrypsin deficiency

Risk Factors for HCC Worldwide

% of Patients With Risk Factor in SHARP trial	
Sorafenib (n=299)	Placebo (n=303)
29	27
19	19
26	26
9	10



*Excluding Japan.
Llovet JM et al. *Lancet.* 2003;362:1907-1917. 2. Llovet J et al. *J Clin Oncol.* 2007;25(Suppl 18):LBA1.

Obesity and NASH in HCC

- Obesity is a risk factor for worse outcomes in HCC
- **Metabolic syndrome and HCC: Non-alcoholic steatohepatitis (NASH)-increasing in West**
  - Abdominal obesity
  - Atherogenic dyslipidemia
  - Elevated blood pressure
  - Insulin resistance or glucose intolerance
  - Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor–1 in the blood)
  - Proinflammatory state (e.g., elevated C-reactive protein in the blood)

A Siegel, S Wang, J Yu, E Lim, J Jacobson, R Brown, A Neugut.
College of Physicians and Surgeons

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Hepatocellular Carcinoma

- Hepatitis and HCC: mechanisms
  - Tumors arise in the context of chronic liver-cell injury, inflammation and increased turnover of hepatocytes
  - Viral genome may be integrated in hepatocyte DNA, leading to mutations, deletions, etc.
  - Viral gene products may increase the expression of growth-factor regulating genes involved in malignant transformation

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Statins and HCC

- Population-based cohort study of 260,864 HCV-infected patients enrolled in the Taiwan National Health Insurance Research Database
- Among the 35,023 patients using statins, 1,378 had HCC. Among the 225,841 patients not using statins 26,505 were diagnosed with HCC. A dose-response relationship between statin use and HCC risk was observed.
- Possible mechanisms:
  - statins may exert anti-HCV activity via the inhibition of cholesterol synthesis and HCV replication.
  - statins may limit the development of HCC through the inhibition of products downstream of the mevalonate pathway and disrupt the growth of malignant cells, eventually leading to apoptosis.

Tsan et al, JCO 2013; Shao et al, Medicine 2015 Oct;94(42):e1801
Simon TG, Duberg AS, Aleman S, et al. Lipophilic statins and risk for hepatocellular carcinoma and death in patients with chronic viral hepatitis: results from a nationwide Swedish population. *Ann Intern Med*. doi: 10.7326/M18-2753.

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Hepatocellular Carcinoma

- Pathology
  - Gross
    - nodular
      - most common pattern
    - massive
      - solitary component, occupying one lobe
    - diffusely infiltrating
      - usually associated with cirrhosis

Hepatocellular Carcinoma

- Pathology:
  - Uncommon, favorable forms of hepatocellular carcinoma
    - fibrolamellar
      - younger females
    - pedunculated HCC (subcapsular)
    - "minute" HCC
      - found by accident or by screening
  - Differential diagnosis
    - focal nodular hyperplasia and adenomatous hyperplasia
    - cholangiocarcinoma
    - metastatic tumors

Hepatocellular Carcinoma

- Diagnosis
  - Radiographic techniques
    - ultrasound
      - cheap, reliable, useful for screening
    - CT/MRI
      - useful to determine extent of disease for staging and resectability
  - Biopsy
    - FNA vs core biopsy
    - rare seeding of biopsy track (<1%)
      - May avoid if OLT is being considered

Hepatocellular Carcinoma

- AFP
  - Increased in 80-90% of patients from Far East with HCC
  - Increased in 50-70% of patients from North America and Europe
  - Elevations of greater than 400 are generally considered diagnostic for HCC
  - AFP >400 have poorer prognosis
    - Usual level for stratification in RCTs

Hepatocellular Carcinoma

- General Principles of Screening
  - Identification of high-risk groups
  - Reliable diagnostic tools
    - Ultrasound
    - AFP
  - Cost
  - Compliance
  - Availability of treatment that alters natural history of the disease

Hepatocellular Carcinoma

- **Screening: generally recommended, but**
  - Few large-scale screening trials have been completed to demonstrate efficacy
  - Small studies show anecdotal cases of early HCC resected with curative intent
  - ? Whether all patients with HBV, HCV, hemochromatosis should undergo AFP and US screening, and at what intervals
  - ? Whether early detection prolongs survival in patients who have developed cirrhosis
- **Potential Harms**
  - Up to one-third of patients with cirrhosis may experience physical harms related to false-positive and indeterminate screening results
  - Most harms consist of additional diagnostic exams
  - Severe physical harm (e.g. invasive procedures or procedure-related complications) is rare

RCT in HCC Screening

- 18,816 people, aged 35-59 years with hepatitis B virus infection or a history of chronic hepatitis in urban Shanghai, China. Participants were randomly allocated to a screening (9,373) or control (9,443) group
- Screening group participants were invited to have an AFP test and ultrasonography examination every 6 months.
- HCC mortality rate was significantly lower in the screened group than in controls, being 83.2/100,000 and 131.5/100,000, respectively, with a mortality rate ratio of 0.63 (95%CI 0.41-0.98)

Zhang, et al. J Cancer Res Clin Oncol. 2004 Jul;130(7):417-22.

Screening for HCC

Guideline	EASL[1]	AASLD[2]	JSH[3]	APASL[4]
Definition of high-risk population	•Pts with cirrhosis, Child-Pugh stage A and B •Pts with cirrhosis, Child-Pugh stage C awaiting liver transplantation •Pts without cirrhosis with HBV and an intermediate or high risk of HCC (PAGE-B score ≥ 10a) •Pts without cirrhosis with chronic HCV and bridging fibrosis	•Pts with cirrhosis, Child-Pugh stage A and B •Pts with cirrhosis, Child-Pugh stage C awaiting liver transplantation •Pts without cirrhosis with HBV	•Extremely high-risk pts: o Pts with cirrhosis and HBV •or HCV •High-risk pts: •Non-viral cirrhosis Pts without cirrhosis with •HBV or HCV	•Pts with cirrhosis •Pts without cirrhosis with •HBV: o Asian females > 50 yrs o Asian males > 40 yrs o Africans > 20 yrs o Family history of HCC
Screening interval	Every 6 months	Every 4-8 months	•Every 3-4 months in extremely high-risk pts •Every 6 months in high-risk pts	Every 6 months
Imaging modality	US (performed by experienced personnel)	US	US CT/MRI optional every 6–12 months in extremely high-risk pts	US
Biomarkers	Not recommended	At discretion of provider	AFP AFP-L3 fractions DCP	AFP (+ US)

Hepatitis B Vaccine to Prevent Hepatocellular Cancer: Based on solid evidence, immunizing individuals against hepatitis B would lead to a decrease in the incidence of HCC

- **Study Design:** Evidence obtained from cohort or case-control studies.
- **Internal Validity:** Fair (ecologic control; no direct comparison group).
- **Consistency:** Limited number of studies.
- **Magnitude of Effects on Health Outcomes:** A study in Taiwan shows that vaccination of newborns (the vaccination program includes administration of hepatitis B immunoglobulin at birth, followed by a course of hepatitis B vaccine) of mothers infected with hepatitis B virus was associated with a reduction in the average annual incidence of HCC from 0.70 per 100,000 children between 1981 and 1986 to 0.57 and 0.36 for the time periods of 1986 to 1990 and 1990 to 1994, respectively (P < .01]) Although there was no direct control group, the decline in incidence of HCC over time would unlikely be explained by other causes.

The JAMA Network

From: **Thirty-Year Outcomes of the National Hepatitis B Immunization Program in Taiwan**

JAMA. 2013;310(9):974-976. doi:10.1001/jama.2013.276701

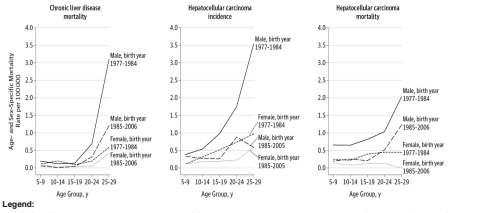

Figure Legend:
Age- and Sex-Specific Mortality and Incidence Rates of Chronic Liver Disease and Hepatocellular Carcinoma for Birth Cohorts Born Before and After the Launch of the Hepatitis B Immunization Program in 1984 in Taiwan

Date of download: 7/13/2016

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Hepatitis C

- The Centers for Disease Control and Prevention (CDC) recommends one-time HCV testing for everyone born from 1945 to 1965
- HCV testing is recommended for those who:
  - Currently injecting drugs
  - Ever injected drugs, including those who injected once or a few times many years ago
  - Have certain medical conditions, including persons:
    - who received clotting factor concentrates produced before 1987
    - who were ever on long-term hemodialysis
    - with persistently abnormal alanine aminotransferase levels (ALT)
    - who have HIV infection
  - Were prior recipients of transfusions or organ transplants, including persons who:
    - were notified that they received blood from a donor who later tested positive for HCV infection
    - received a transfusion of blood, blood components, or an organ transplant before July 1992

cdc.gov/hepatitis/

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Evolving Treatment of Hepatitis C

- NO vaccine.
- Initially, before 2011: IFN+ribavirin
- On July 18, 2019, FDA approved a combination tablet (Vosevi) to treat adults with chronic hepatitis C virus genotypes 1-6 without cirrhosis or with mild cirrhosis. This fixed-dose, combination tablet contains two previously approved drugs—sofosbuvir and velpatasvir—and a new drug, voxilaprevir. Approved for patients who have been previously treated with the direct-acting antiviral drug sofosbuvir.
- Selection is in part based on genotype
- **Goals:** SVR (sustained virologic response): 90% achieve SVR with 8-12 weeks of oral treatment
- **Benefits with newer agents:** high SVR, shorter therapy, oral
- **Downsides:** some treatments restricted to certain genotypes; increased side effects; $$$$...cheapest ~$25,000 for 2 month Rx
- ~10% of HepC patients are under treatment in US
  - ? Impact on HCC in US and ROW (especially Asia)

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Modified Stage System (pTNM)

T0	Tumor not found
T1	1 nodule ≤ 1.9 cm
T2	1 nodule 2.0-5.0 cm; 2 or 3 nodules, all ≤ 3.0 cm
T3	1 nodule > 5.0 cm; 2 or 3 nodules, at least one > 3.0 cm
T4a	4 or more nodules, any size
T4b	Gross intrahepatic portal or hepatic vein involvement

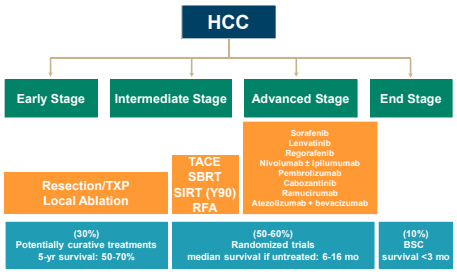
N0 :	No lymph node involvement
N 1 :	Regional (porta hepatis) nodes involved
M0 :	No distant metastasis
M1 :	Metastatic disease • Including extrahepatic portal or hepatic vein involvement

Child's Pugh Score: Liver Cirrhosis

Parameter	Points		
	1	2	3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Bilirubin (mg/dL)	< 2	2 - 3	> 3
Ascites	Absent	Slight	Moderate
Encephalopathy	None	I - II	III – IV
PT (INR)	< 1.7	1.8 – 2.3	> 2.3

Score	A	B	C
Points	5 - 6	7 - 9	10 - 15

HCC Treatment



Llovet JM, & Bruix J, BCLC. *Lancet*, 2003

Treatment of HCC
Role of Liver Transplantation

PROS

- "Cures" underlying disease as well as treating HCC
  - Avoids complications associated with resection in cirrhosis
- Excellent outcome in selected patients
  - Equivalent to benign disease; OLT currently has a 5-year survival of 70-80%
- "Optimal" candidate –Milan, UCSF Criteria
  - Single lesion < 5cm
  - Multiple lesions up to 3 nodules, adding to < 3 cm
- Treatments available for Hepatitis B and C to prevent reinfection

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Treatment of HCC
Role of Liver Transplantation

CONS

- Difficult to accurately stage preoperatively
  - Tumor burden frequently underestimated
- Lack of prospective, randomized studies to determine who is a good candidate
- Limited organ supply
  - Increasing waiting times is associated with tumor growth and patient drop out because of primary liver failure
  - Differential waiting times depending on region

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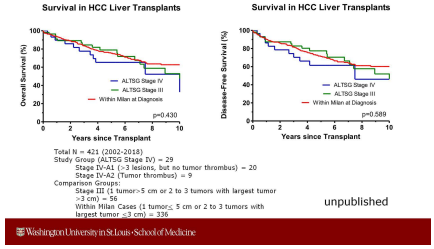
UpDated treatment of HCC and transplant including stage III and IV disease



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Liver Directed Therapies

- Ablation - Radiofrequency, MW ablation, cryotherapy, IRE, PEI
- TransArterial Chemoembolization TACE, cTACE,
- Bland Embolization - TAE
- Radioembolization Sir Spheres and Theraspheres
- Hepatic arterial pump therapy (HAP)
- External Beam (EBRT) and Stereotactic Radiation Therapy (SBRT)

Washington University in St. Louis • School of Medicine

Presented By Maria Doyle at 2019 Gastrointestinal Cancer Symposium

GW 31

CHEMOEMBOLIZATION/TACE

- Developed c.1980 in Japan for treatment of hepatoma
- Procedure has disseminated world-wide for primary and secondary hepatic malignancies

Advantages:

- Tumor ischemia
- Increased drug concentration
- Increased dwell time
- Decreased systemic toxicity
- Wide availability

GW 32

CHEMOEMBOLIZATION

Disadvantages

- Lack of standardization
- Operator dependent
- Difficult to access patients for trials through interventional radiology
- Highest rates of HCC in countries with least mature clinical trials mechanisms

GW 33

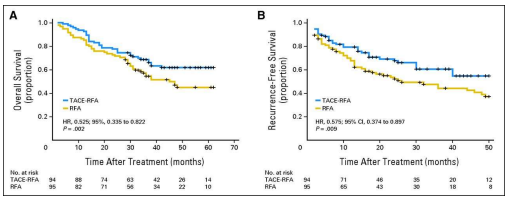
TACE+RFA vs RFA Alone

- A randomized controlled trial was conducted on 189 patients with HCC less than 7 cm at a single tertiary referral center between October 2006 and June 2009. Patients were randomly assigned to receive TACE combined with RFA (TACE-RFA; n = 94) or RFA alone (n = 95). The primary end point was overall survival. The secondary end point was recurrence-free survival, and the tertiary end point was adverse effects.
- **Patients in the TACE-RFA group had better overall survival and recurrence-free survival than patients in the RFA group** (hazard ratio, 0.525; 95% CI, 0.335 to 0.822; P = .002; hazard ratio, 0.575; 95% CI, 0.374 to 0.897; P = .009, respectively).

Peng et al. *JCO* February 1, 2013 vol. 31 no. 4 426-432

TACE+RFA vs RFA Alone

Overall (A) and recurrence-free (B) survival curves for the transcatheter arterial chemoembolization (TACE) plus radiofrequency ablation (RFA) and RFA groups.



Peng Z et al. *JCO* 2013;31:426-432

TACE+RFA vs RFA Alone

- The sample size was small, with a mainly HBV population conducted in a single tertiary center in China, making it difficult to extrapolate these results.
- The selection of patients participating in this study was stringent, and the findings may only be applicable to a relatively small percentage of patients with HCC.
- The study only had two arms without the potential third arm of TACE alone, making it difficult to assess the relative added contribution of TACE or RFA in the TACE-RFA arm.
- Only approximately 50% of lesions were larger than 3 cm and there were no specification on the number of patients with lesion size from 3 to 7 cm; it remained unclear whether the benefits of TACE-RFA were only applicable to smaller lesions (i.e., less than 5 cm), as has been previously suggested

Zhu editorial JCO

A multicenter randomized controlled trial to evaluate the efficacy of SUrgery vs. RadioFrequency ablation for small hepatocellular carcinoma

SURF
Efficacy of SUrgery vs. Radio-Frequency ablation (RFA) on primary hepatocellular carcinoma: a multicenter clinical trial

SURF Trial Group
Namiki izumi
Kiyoshi Hasegawa, Yujiro Nishioka, Tadatoshi Takayama
Naoki Yamanaka, Masatoshi Kudo, Mitsuo Shimada
Masahumi Inomata, Shuichi Kaneko, Hideo Baba
Kazuhiko Koike, Masao Omata, Masatoshi Makuuchi
Yutaka Matsuyama, Norihiro Kokudo

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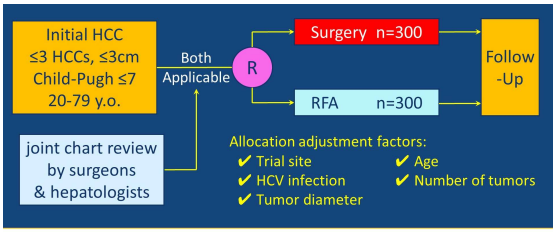
RCT Design (from April 2009)



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Summary of Previous RCTs

Author	Year	Site	Size	Tumor No.	Child -Pugh	n	Conclusion
Chen DS Liang J-D	2005	Taiwan	≤3cm	≤2	A,B	76	NS
Chen M-S Lau WY	2005	Hongkong, Guangzhou	≤5cm	1	A	180	NS
Huang J Zeng Y	2010	Chengdu	≤3cm (Milan)	≤3	A,B	230	Favor (Surgery)
Feng K Dong J	2012	Chongqing	≤4cm	≤2	A,B	168	NS

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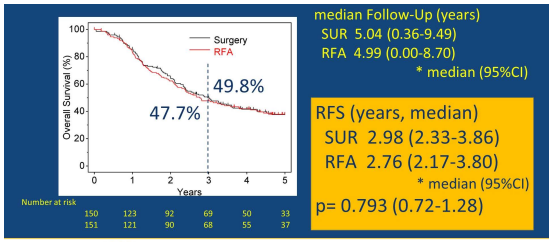
Kaplan-Meier estimate of RFS



median Follow-Up (years)
SUR 5.04 (0.36-9.49)
RFA 4.99 (0.00-8.70)
* median (95%CI)

RFS (years, median)
SUR 2.98 (2.33-3.86)
RFA 2.76 (2.17-3.80)
* median (95%CI)
p= 0.793 (0.72-1.28)

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TACE plus Sorafenib Versus TACE alone for Intermediate or Advanced Stage HCC: A Meta-Analysis

- Pubmed and Embase databases were systematically reviewed for studies published up to November 2013, that compared TACE alone or in combination with sorafenib
- Six studies published from 2011 to 2013, with a total of 1254 patients
- The pooled results showed that TACE combined with sorafenib significantly improved
  - OS (HR=0.65; 95% CI: 0.47-0.89, P=0.007)
  - TTP (HR=0.68; 95% CI: 0.52-0.87, P=0.003)
  - ORR (HR=1.06; 95% CI: 1.01-1.12, P=0.021)
- but did not affect PFS (HR=0.84; 95% CI: 0.62-1.14, P=0.267)
- The incidence of grade III/IV adverse reaction was higher in the TACE plus sorafenib group than in the TACE group

Zhang et al PLoS One 2014 Jun 19;9(6):e100305. doi: 10.1371/journal.pone.0100305

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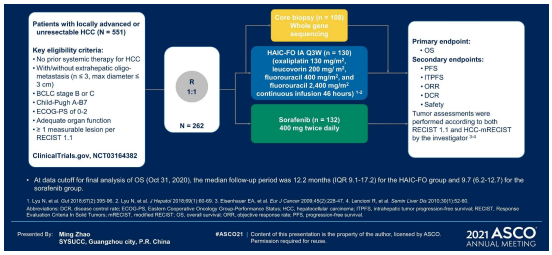
Trial Schema
FOHAIC-1: Randomized, head-to-head, phase 3 clinical trial



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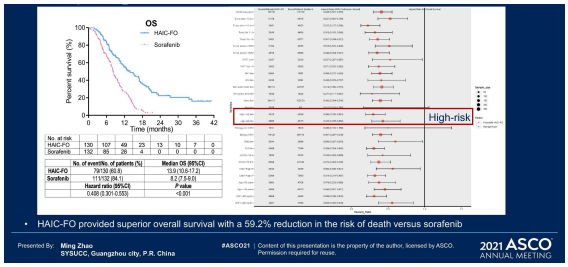
Survivals: Primary Endpoint



- HAIC-FO provided superior overall survival with a 59.2% reduction in the risk of death versus sorafenib

Presented By: Ming Zhao
SYSUCC, Guangzhou city, P.R. China

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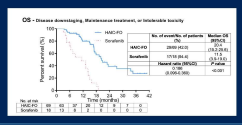
Overall Survivals: Subgroup exploration

Patients with conversion therapy

HAIC-FO vs. Sorafenib:

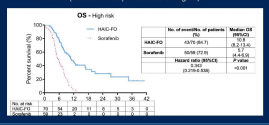
- ✓ Downstaging occurred in 16 (12.3% of 130) patients in the HAIC-FO group comparing 1 (0.8% of 132) in the sorafenib group.
- ✓ Patients with conversion therapies in the HAIC-FO group had significantly longer OS than those in the sorafenib group.



Patients with high-risk factor

HAIC-FO vs. Sorafenib:

- ✓ Proportions of high-risk factors (Vp4-PVTT and/or tumor involvement >50% of the liver) was comparable between the HAIC-FO group and the sorafenib group (53.8% vs. 44.7%, P= 0.139).
- ✓ OS was significantly longer with HAIC-FO; the median OS was 10.8 months (95% CI 8.2-13.4) in the HAIC-FO group and 5.7 months (95%CI 4.4-6.9) in the sorafenib group.



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Conclusions and Future Directions

- Neoadjuvant HAI with FOLFOX has activity in the neoadjuvant setting
- 78/199 (39%) of randomized and evaluable patients had multifocal disease who would not normally go to upfront surgery by current BCLC guidelines
  - Would these patients have done better with locoregional therapy, attempted downstaging for liver transplantation, or modern systemic therapy?
- Patients were enrolled in China and 80% in a single center (>90% CP A, HBV+)
  - Results are provocative but need replication in a global or Western population before HAI can enter routine practice

Presented By: Mark Yarchoan

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Perioperative Strategies in HCC

Strategy	Overview and Current status
Perioperative HAI with FOLFOX	• Downstaging potential, ORR 63.6% (mRECIST) • Anticipated to reduce liver micrometastasis • OS benefit in the neoadjuvant setting and adjuvant setting (NCT03192618)
Neoadjuvant radioembolization	• Downstaging potential (ORR 72.2% by mRECIST in LEGACY Study) • Not anticipated to reduce micrometastasis • No randomized data versus upfront surgery
Neoadjuvant immunotherapy-based regimens	• Some downstaging potential (ORR ~35% by mRECIST with modern systemic therapy) • Anticipated to reduce micrometastasis • Multiple exploratory phase 1 studies demonstrating feasibility but larger studies are needed
Adjuvant immunotherapy	• Multiple P3 studies ongoing (all versus placebo): • EMERALD-2: durvalumab+/-bevacizumab • KN-937: pembrolizumab • CM-9DX: nivolumab • IMBrave050: atezolizumab/bevacizumab

Presented By: Mark Yarchoan

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Problems in Assessing Effectiveness of Systemic Therapy for HCC

- Only patients with advanced HCC, and not amenable to surgery or local treatment, are entered onto systemic therapy
- Underlying liver disease(s)—cirrhosis– may be as, or more, important than HCC for pts. prognosis
- Liver function and drug: metabolism and effects
- Differences in etiology of HCC in different population and studies – inconsistence of study results
- HCC is a heterogeneous disease at the molecular level
- Traditional criteria (methods) for cancer response assessment may be not suitable for HCC: Tumor measurements (RECIST)
  - Especially for radiologic definition of RR, TTF, PFS

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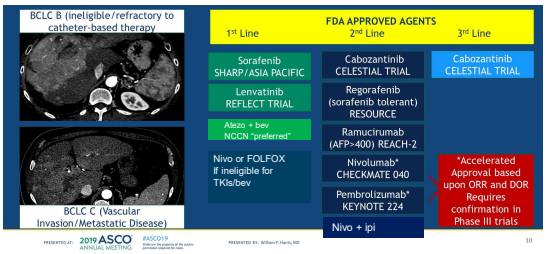
Background: Systemic Therapy for Advanced Hepatocellular Carcinoma



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PRESENTED BY: William P. Harris, MD

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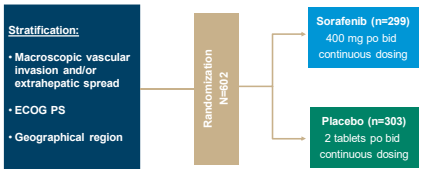
Sorafenib in HCC: Rationale

- Raf kinase is overexpressed and activated in HCC
- Sorafenib is the only approved inhibitor of Raf kinase
- Sorafenib is a multikinase inhibitor of RAF, VEGFR, and other kinases3
- Sorafenib induces apoptosis in HCC xenograft models
- Sorafenib was active in a Phase II trial of patients with advanced HCC and Child-Pugh class A and B liver function status

Phase III SHARP Trial Study Design

- Primary end-points: Overall survival
  Time to symptomatic progression (FHSI8-TSP)
- Secondary end-points: Time to progression (independent review)

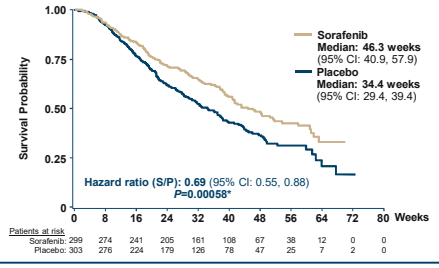


Phase III SHARP Trial Study Design

Design

- International, multicenter Phase III study
- Inclusion criteria:
  - Histology-proven HCC
  - Advanced HCC
  - At least 1 measurable untreated lesion
  - **ECOG 0-2**
  - **Child-Pugh A class**
  - No prior systemic treatment
- Randomization
- Double-blind sorafenib 400 mg bid vs placebo; ratio 1:1
- Accrual: March 2005 to April 2006

Phase III SHARP Trial
Overall survival (Intent-to-treat)



*O'Brien-Fleming threshold for statistical significance was P=0.0077.

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Phase III SHARP Trial
Response assessment (RECIST; Independent review)
Time to symptom progression (FSHI8-TSP)

	Sorafenib (n=299)	Placebo (n=303)
Overall response		
Complete response (CR)	**0**	**0**
Partial response (PR)	**7 (2.3%)**	**2 (0.7%)**
Stable disease (SD)	211 (71%)	204 (67%)
Progression-free rate at 4 mo	**62%**	**42%**
Duration of treatment (median, weeks)	23	19

FSHI8-TSP: No significant differences between treatment groups (P=0.77).

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Comparative trial of Sorafenib Toxicity: Childs A vs B (MSKCC)

	CPA (n=98) %	CPB (n=38) %
Adverse Events	97	97
Serious Adverse Events	52	68
Fatigue	41	37
Hand Foot Skin Reaction	30	13
Diarrhea	59	47
Bilirubin Increase	**18**	**40**
Ascites	**11**	**18**
Encephalopathy	**2**	**11**

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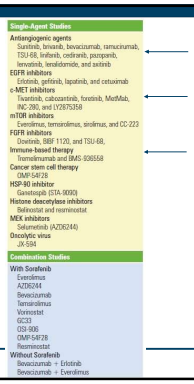
Childs A vs B: Outcomes

	CP A (n=98)	CP B (n=38)
SD (≥ 4 months)	49%	**26%**
TTP	21 weeks	**13 weeks**
OS	41 weeks	**14 weeks**

New Agents in HCC



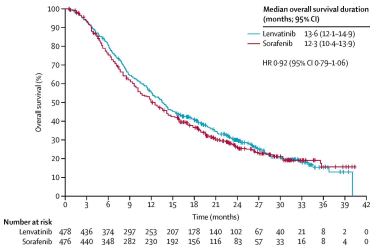
Lenvatinib vs Sorafenib First-line HCC: ASCO 2017

REFLECT trial

- LEN, an inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet derived growth factor receptor α, RET, and KIT
- Randomized, open-label, noninferiority (NI) study; primary endpoint noninferiority for OS
- 1492 Pts enrolled
- 13% Of LEN-treated and 9% of SOR-treated pts discontinued due to adverse events. 33% Of LEN-treated and 39% of SOR-treated pts received second-line therapy
- FDA approved 8/2018

Lancet 2018 Mar 24;391(10126):1163-1173

Lenvatinib vs Sorafenib Primary Endpoint: OS



Kudo,M, et al. *The Lancet* 2018 391, 1163-1173DOI: (10.1016/S0140-6736(18)30207-1)

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Lenvatinib mRECIST Response

	Lenvatinib (n=478)	Sorafenib (n=476)	Effect size (95% CI)	p value
Objective response (%, 95% CI)	194 (40·6%, 36·2–45·0)	59 (12·4%, 9·4–15·4)	OR 5·01 (3·59–7·01)	<0·0001
Complete response	10 (2%)	4 (1%)	..	..
Partial response	184 (38%)	55 (12%)	..	..
Stable disease	159 (33%)	219 (46%)	..	..
Durable stable disease lasting ≥23 weeks	84 (18%)	90 (19%)	..	..
Progressive disease	79 (17%)	152 (32%)	..	..
Unknown or not evaluable	46 (10%)	46 (10%)	..	..

Kudo, M. et al. *Lancet* Volume 391, Issue 10126, 24–30 March 2018, Pages 1163-1173

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Landscape-Second line therapy for HCC

		Total N	PFS benefit	OS benefit	RR
CHECKMATE040 (SINGLE ARM)	Nivolumab*	154	NA	NA median OS =15 mo*	14%
RESOURCE	Regorafenib* v placebo	573 (2:1)	+1.6 mo HR 0·46 (0.37–0.56); p<0·0001	+2.8 mo HR 0.63 (0.50–0.79) p<0.0001)	11%
CELESTIAL**	Cabozantinib* v placebo	707 (2:1)	+3.3 mo HR=0.44 [0.36-0.52]; *P* < 0.001	+2.2 mo HR=0.76 (0.63-0.92) P = 0.0049	4%
REACH1	Ramucirumab* v placebo	565	+0.7mo HR 0.63 [0.52–0.75]; p<0.0001	NO	7%
REACH 2 (AFP≥400)	Ramucirumab* v placebo	292 (2:1)	+1.2 mo HR 0.452 (0.339, 0.603) p< 0.0001	+1.2 mo HR 0.71 (0.531, 0.949); p=0.0199	4.6%
Pooled REACH 1 / 2 (AFP≥400 subgroup)	*Ramucirumab* v placebo*	*542*	*NA*	*+3.1 mo HR 0.694 (0.571, 0.842) P=0.0002*	*NA*

*FDA approved
** included 2nd and 3rd line; 2nd line update: Kelley, et al. Abstr #4088 ASCO 2018

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Ramucirumab (VEGFR2) versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH)

- 565 patients were enrolled, of whom 283 were assigned to ramucirumab and 282 were assigned to placebo. Median overall survival for the ramucirumab group was 9·2 months (95% CI 8·0–10·6) versus 7·6 months (6·0–9·3) for the placebo group (HR 0·87 [95% CI 0·72–1·05]; p=0·14)
- Subsets benefiting: good CP score; elevated AFP ≥400 ng/ml
- **REACH-2: Child-Pugh score <7 (Child-Pugh Class A), Baseline AFP ≥400 nanograms/milliliter. (NCT02435433)**

Zhu, et al. *Lancet Oncol.* Volume 16, No. 7, p859–870, July 2015

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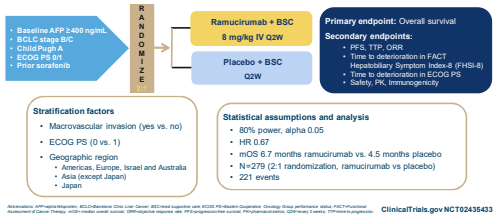
REACH-2 Study Design



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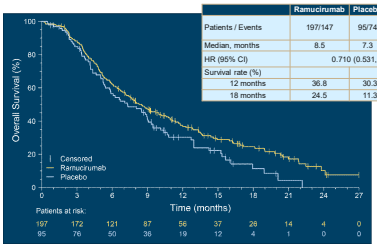
Overall Survival



	Ramucirumab	Placebo	Difference	P-value
Patients / Events	197/147	95/74		
Median, months	8.5	7.3	1.2	
HR (95% CI)	0.710 (0.531, 0.949)			0.0199
Survival rate (%)				
12 months	36.8	30.3	6.5	0.2930
18 months	24.5	11.3	13.2	0.0187

Andrew Zhu, MD, PhD

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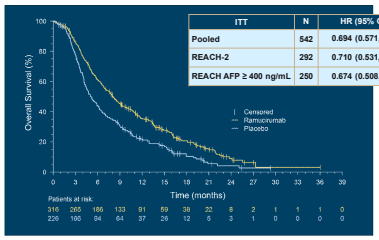
Overall Survival in Pooled Population



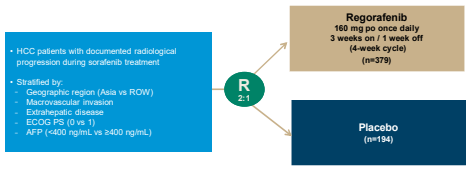
ITT	N	HR (95% CI)	mOS	P-value
Pooled	542	0.694 (0.571, 0.842)	Δ=+3.1 (8.1 vs. 5.0)	0.0002
REACH-2	292	0.710 (0.531, 0.949)	Δ=+1.2 (8.5 vs. 7.3)	0.0199
REACH AFP ≥ 400 ng/mL	250	0.674 (0.508, 0.895)	Δ=+3.6 (7.8 vs. 4.2)	0.0059

Andrew Zhu, MD, PhD

RESORCE [REgorafenib after SORafenib in patients with hepatoCEllular carcinoma]

- The Ang/TIE-2 pathway is considered a key angiogenic signaling pathway. Combined blockage of VEGFR2 and TIE2 signaling with regorafenib may exert more profound antiangiogenic effects than inhibition of VEGF signaling alone
- HCC is a FGFR-enriched tumor
- Additional activity against FGFR, c-kit, and Ret
- Antiangiogenesis beyond progression
- Other hidden pathways

RESORCE Trial Design



- 152 centers in 21 countries in North and South America, Europe, Australia, Asia
- All patients received best supportive care
- Treat until progression, unacceptable toxicity, or withdrawal

Bruix J et al, *Lancet* 2017; 389: 56–66

RESORCE: Efficacy

	Regorafenib n=379	Placebo n=194
Events	232 (61%)	140 (72%)
Censored	147 (39%)	54 (28%)
Median OS (95% CI)	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
HR 0.62 (95% CI: 0.50, 0.78)		
P<0.001 (2-sided)		

	Regorafenib n=379	Placebo n=194
Events	291 (77%)	181 (93%)
Censored	88 (23%)	13 (7%)
Median PFS (95% CI)	3.1 months (2.8, 4.2)	1.5 months (1.4, 1.8)
HR 0.46 (95% CI: 0.37, 0.56)		
P<0.001 (2-sided)		

	mRECIST		RECIST 1.1	
	Regorafenib n=379	Placebo n=194	Regorafenib n=379	Placebo n=194
Response rate	10.6%	4.1%	6.6%	2.6%
	P=0.01 (2-sided)		*P*=0.04 (2-sided)	
Disease control rate	65.2%	36.1%	65.7%	34.5%
	P<0.001 (2-sided)		*P*<0.001 (2-sided)	

Bruix J et al, *Lancet* 2017; 389: 56–66

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Cabozantinib in HCC CELESTIAL trial; ASCO GI 2018

- Cabozantinib: an inhibitor of MET, VEGFR, and AXL
- 707 pts with prior sorafenib; 27% had 2 Rx; primary endpoint OS

	Cabozantinib	Placebo
OS	10.2 mos	8.0 mos
PFS	5.2 mos	1.9 mos
ORR	4%	0.4%

FDA approval: January 2019

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Checkmate 040: Nivolumab Efficacy

	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Objective response*	13 (23%; 13 to 36)	12 (21%; 11 to 34)	10 (20%; 10 to 34)	7 (14%; 6 to 26)	[illegible] (16 to 26)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
Stable disease	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
Progressive disease	13 (23%)	18 (32%)	14 (28%)	23 (45%)	68 (32%)
Not evaluable	1 (2%)	4 (7%)	3 (6%)	0	[illegible] (7%)
Duration of response*					
KM median	8·4 (8·3 to NE)	NR	9·9 (4·5 to 9·9)	NR	9·9 (8·3 to NE)
Ongoing, n/N (%)	8/13 (62%)	7/12 (58%)	8/10 (80%)	5/7 (71%)	[illegible] (69%)
Disease control*	42 (75%; 62 to 86)	35 (61%; 48 to 74)	33 (66%; 51 to 79)	28 (55%; 40 to 69)	138 (64%; 58 to 71)
Disease control with stable disease for ≥6 months	22 (39%; 27 to 53)	22 (39%; 26 to 52)	17 (34; 21 to 49)	18 (35%; 22 to 50)	79 (37%; 30 to 44)
Overall survival					
6 months	89% (77 to 95)	75% (62 to 85)	85% (72 to 93)	84% (71 to 92)	83% (78 to 88)
9 months	82% (68 to 90)	63% (49 to 74)	81% (66 to 90)	70% (55 to 81)	74% (67 to 79)
KM median	NR	13·2 (8·6 to NE)	NR	NR	NR
Progression-free survival*					
KM median	5·4 (3·9 to 8·5)	4·0 (2·6 to 6·7)	4·0 (2·6 to 5·7)	4·0 (1·3 to 4·1)	4·0 (2·9 to 5·4)

Unless otherwise indicated, data are n (%; 95% CI); n (%); months (95% CI); or % (95% CI). HCV=hepatitis C virus. HBV=hepatitis B virus. KM=Kaplan-Meier estimate. NR=not reached. NE=not estimable. RECIST=Response Evaluation Criteria in Solid Tumors. *Determined by investigator assessment using RECIST version 1.1.

Table 4: Nivolumab efficacy in the dose-expansion phase

El-Khoueiry A et al, *Lancet*, online April 2017

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KEYNOTE 240: Study Design

- Key eligibility criteria
  - ≥18 y
  - Pathologically confirmed HCC
  - Progression on or intolerance to sorafenib treatment
  - Child Pugh class A
  - ECOG PS 0-1
  - BCLC Stage C or B disease
  - Predicted life expectancy >3 mo

→ Pembrolizumab 200 mg Q3W for 2y or until PD, intolerable toxicity, withdrawal of consent or investigator decision → Survival follow-up

- Response assessed Q9W
- Primary endpoint: ORR (RECIST v1.1, central review)
- Secondary endpoint: DOR, DCR, PFS, OS, and safety and tolerability

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Response per RECIST version 1.1 by independent central review

	Total N=104
ORR, n (%, 95%CI)*	18 (17, 11-26)
BOR, n (%)†	
CR	1 (1)
PR	17 (16)
SD	46 (44)
PD	34 (33)
No assessment‡	6 (6)
DCR, n (%, 95%CI)§	64 (62, 52-71)
Median time to response, mo (IQR)¶	2.1 (2.1-4.1)
Median DOR, mo (range)¶‖	Not reached (3.1–14.6+)
Response duration ≥9 mo, n (%)¶‖	12 (77)

BOR=best overall response; CR=complete response; DCR=disease control rate; DOR=duration of response; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease.*ORR includes complete and partial responses. †Confirmed best response by independent central review per RECIST version 1.1. ‡Patients without post-baseline assessment on the data cutoff date were considered not assessable for BOR. §Disease control rate includes CR, PR, and SD. ¶Assessed in patients who had a BOR as confirmed CR or PR. ‖From product-limit (Kaplan-Meier) method for censored data, + indicates no PD by the time of last disease assessment.

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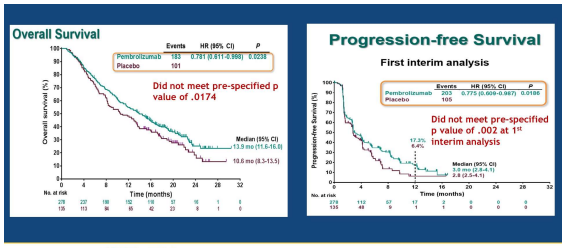
Results: KEYNOTE-240



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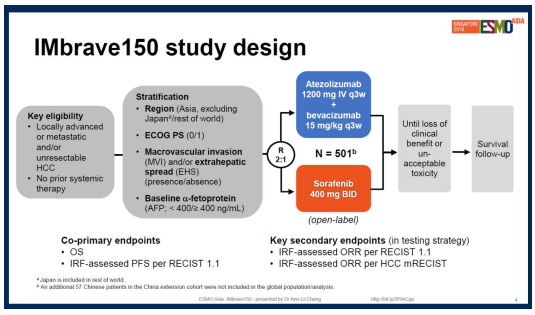
CheckMate 459

- Phase III Study of Nivolumab Versus Sorafenib as First-Line Treatment
- 726 participants
- Primary endpoint: OS
- Failed to meet primary endpoint: HR, 0.85; 95% CI, 0.72-1.02;P= .0752



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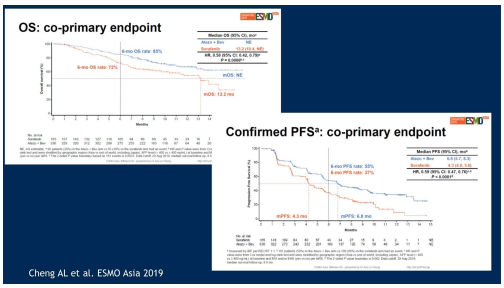
IMbrave50: Positive co-primary endpoints



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CM 040: Ipilimumab + Nivolumab IO doublet: 2nd line

	nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (n=50)	nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (n=49)	nivolumab 3 mg/kg Every 2 Weeks + ipilimumab 1 mg/kg Q6W (n=49)
ORR, n (%)	16 (32)	15 (31)	15 (31)
CR	4 (8)	3 (6)	0
PR	12 (24)	12 (24)	15 (31)
SD	9 (18)	5 (10)	9 (18)
PD	20 (40)	24 (49)	21 (43)
DCR, % (95% CI)	54 (39-68)	43 (29-58)	49 (34-64)
Median OS, mo (95% CI)	23 (9-NA)	12 (8-15)	13 (7-33)
12-mo OS rate, % (95% CI)	61 (46-73)	56 (41-69)	51 (36-64)
24-mo OS rate, % (95% CI)	48 (34-61)	30 (18-44)	42 (28-56)

- Noteworthy OS
- Double the ORR of single agent nivolumab
- Increase TREA- 37% grade 3-4 (rash, pruritis)

(Non-randomised data)

Yau T et al. ASCO 2019 abst 4012

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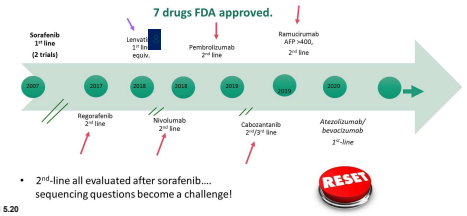
Changing (Busy) Landscape in HCC

- **Multikinase inhibitors:** sorafenib/lenvatinib
  - cabozantanib, regorafenib
- **PD-1 inhibitors**: nivolumab, pembrolizumab
- **PD-L1 inhibitors**: durvalumab and atezolizumab
- **CTLA-4 inhibitors** : Tremelimumab, Ipiluminab
- **mAB**: bevacizumab, ramucirumab



- 2nd-line all evaluated after sorafenib.... sequencing questions become a challenge!

FDA approved 5.20

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Ongoing first-line trials

Combination	Sponsor	Comments
durvalumab vs durv + tremelimumab combo (2 doses) vs sorafenib	AZ	**HIMALAYA**, n=1310, 4 arms, CPA OS Near completion
lenvatinib +pembrolizumab vs lenvatinib + placebo	Merck, Eisai	**LEAP-002**, n=750, CPA OS and PFS Near completion
cabozantinib + atezolizumab vs sorafenib vs cabozantinib	Exelixis, Ipsen	**COSMIC-312**, n=640, 3 arms, CPA 6:3:1 PFS, OS
Nivo 1 + Ipi 3 q 3wks x 4, Nivo 480 q4 vs sorafenib or lenvatinib	BMS	**CHECKMATE 9DW**, n=1084, CPA OS

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Sorafenib as Adjuvant Treatment in the Prevention Of Recurrence of Hepatocellular Carcinoma (STORM) phase 3, double-blind, placebo-controlled trial

- 1,114 patients with HCC judged to have an intermediate (54%) or high (46%) risk of recurrence after surgical resection (81% of patients) or local ablation. The median age of patients was 59 years, 62% were Asian, and 97% had Child-Pugh class A disease
- 400 mg orally twice a day (n = 556) or placebo (n = 558) for a maximum of 4 years. The primary endpoint was RFS; Secondary endpoints included TTR and overall survival OS
- Median RFS in the sorafenib and placebo arms of 33.3 months (95% confidence interval [CI], 27.6-44.0 months) and 33.7 months (95% CI, 27.6-39.0 months), respectively (hazard ratio [HR] = 0.94; 95% CI, 0.78-1.134)
- Median TTR of 38.6 months (95% CI, 30.4 months to not applicable) in the sorafenib arm and 30.3 months (95% CI, 30.3-41.4 months) in the placebo arm (HR = 0.891; 95% CI, 0.735-1.081)
- OS (median OS not reached in either arm; HR = 0.995; 95% CI, 0.761-1.3)

Bruix, et al. *Lancet Oncology*. Volume 16, No. 13, p1344–1354, October 2015

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Biliary Carcinomas

- Gall Bladder
- Biliary duct
  - intrahepatic cholangiocarcinoma
  - proximal (Klatskin's tumor)
  - middle
  - distal (ampullary)

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Background

- Epidemiological data is poor
- Worldwide, there is wide geographic variation
- South America has highest incidence (up to 13/100,000): GB, Peru
- Some European countries, such as Hungary, Poland and Germany have higher incidences (9.2–6.8/100,000)
- Variation in the incidence in Asian countries
  - Japan 11.9/100,000
  - India has been as low as 1/100,000 but is on the rise
    - in Delhi, female incidence is 8.9/100,000
- Female:male ratio is 2.5–3.0:1

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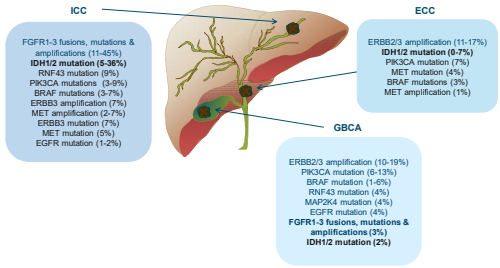
Reasons for Confusion

- Heterogeneous disease
  - Intrahepatic cholangiocarcinoma
  - Extrahepatic biliary tract carcinoma
    - including Klatzkin tumors
  - Gallbladder carcinoma
  - Periampullary carcinoma (?)
- Not all the above are included in each country's statistics
  - ACS puts intrahepatic cholangiocarcinoma with HCC for unclear reasons

Genetic Landscape of Biliary Tract Cancers



Etiology: Biliary Carcinoma

- Cholangiocarcinoma
  - risks include stones, sclerosing cholangitis, UC, PCKD with liver cysts

Biliary Carcinoma

- Gall Bladder
  - most common biliary site
  - associated with gallstones
    - 1% of cholecystectomies have carcinoma
  - increased risks with choledochal cysts
  - polyps increase risk (Peutz-Jegher's)

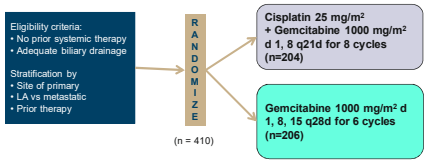
GB Carcinoma

- Treatment
  - surgical cures most often in incidentalomas
  - simple cholecystectomy for stage I and II
  - ? Role of extended (reoperation) in patients with stage III (serosal or N+)
  - ? Role for combined chemoradiation/embolization in patients at high risk of recurrence

Primary Approaches to GC Ca:
Gallbladder cancer: expert consensus statement

- Adequate lymphadenectomy includes assessment of any suspicious regional nodes, evaluation of the aortocaval nodal basin, and a goal recovery of at least six nodes.
- Patients with confirmed metastases to N2 nodal stations do not benefit from radical resection and should receive systemic and/or palliative treatments.
- Primary resection of patients with early T-stage (T1b-2) disease should include en bloc resection of adjacent liver parenchyma.
- **Patients with T1b, T2 or T3 disease that is incidentally identified in a cholecystectomy specimen should undergo re-resection** unless this is contraindicated by advanced disease or poor performance status. Re-resection should include complete portal lymphadenectomy and bile duct resection only when needed to achieve a negative margin (R0) resection.
- **Patients with preoperatively staged T3 or T4 N1 disease should be considered for clinical trials of neoadjuvant chemotherapy.** Following R0 resection of T2-4 disease in N1 gallbladder cancer, patients should be considered for adjuvant systemic chemotherapy and/or chemoradiotherapy.

Gemcitabine ± Cisplatin in Advanced Biliary Tract Cancer: Phase III UK ABC-02 Trial



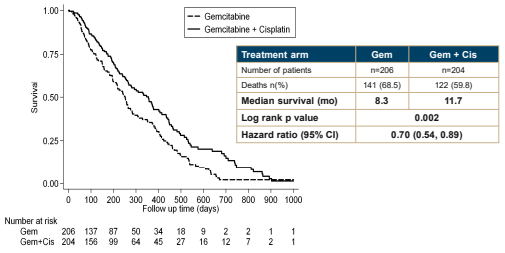
- **Primary endpoint: OS**
- **Secondary endpoints including: PFS, toxicity**

Valle et al. *J Clin Oncol* 2009; 27(suppl):202s (abstract 4503)
N Engl J Med. 2010 Apr 8;362(14):1273-81

Baseline Characteristics of Patients

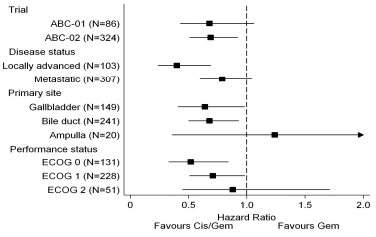
	Gem (n=206)	Cis/Gem (n=204)
Age (yr, median)	63	64
Male/female (%)	48 / 52	47 / 53
Extent of disease Locally advanced / metastatic (%)	23 / 77	27 / 73
Primary site Gallbladder / bile duct / ampulla (%)	37 / 58 / 5	36 / 60 / 4
ECOG Performance score 0 / 1 / 2 (%)	31 / 57 / 12	32 / 54 / 13
Prior therapy		
None (%)	24	25
Biliary stenting (%)	44	46
Surgery (curative / palliative, %)	24 / 20	18 / 19
Radiotherapy (%)	2	1

ABC-02 - Results: Overall Survival (ITT)



Treatment arm	Gem	Gem + Cis
Number of patients	n=206	n=204
Deaths n(%)	141 (68.5)	122 (59.8)
Median survival (mo)	**8.3**	**11.7**
Log rank p value	**0.002**	
Hazard ratio (95% CI)	**0.70 (0.54, 0.89)**	

ABC-02 - Overall Survival
Exploratory Sub-group Analysis



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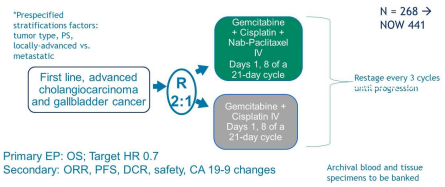
S1815 Study Design



Primary EP: OS; Target HR 0.7
Secondary: ORR, PFS, DCR, safety, CA 19-9 changes

PRESENTED AT: ASCO20 Virtual EDUCATION PROGRAM #ASCO20 PRESENTED BY: Rachna T. Shroff, MD, MS

Activation effective Monday, December 3, 2018; accrual ~2/3 complete

Presented By Rachna Shroff at ASCO 2020 Virtual Education Program

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ABC-06 study design
Phase III, randomised, open-label

Inclusion criteria
- Histo/cytologically verified advanced BTC
- ECOG performance score 0-1
- Progression after 1st-line CisGem
- Max 6 weeks progression to randomisation
- Adequate haematological, renal & hepatic function

R 1:1

Arm A
Active Symptom Control (ASC)
- May include: biliary drainage, antibiotics, analgesia, steroids, anti-emetics etc
- 4-weekly clinical review

Arm B
Active Symptom Control + mFOLFOX
- Chemotherapy every 14 days for up to 12 cycles
- Day 1: Oxaliplatin 85mg/m², L-folinic acid 175 mg (or folinic acid 350 mg), 5 FU 400 mg/m² (bolus), 5 FU 2400 mg/m² 46 hours continuous infusion
- 4-weekly clinical review after chemotherapy
- 3-monthly radiological assessment

Follow up
- **Overall survival** = primary end-point
- Until death or until completion of 12 months after enrolment of the final patient (whichever happened first)

Stratification factors
- **Platinum sensitivity** (yes vs. no; determined from first-line CisGem*)
- **Serum albumin** (<35 vs. ≥35 g/L)
- **Stage** (locally advanced vs. metastatic disease)

*Determined from first-line CisGem: sensitive [progression after three months (90 days) of day 1 of the last cycle of 1st-line CisGem], refractory [progression during 1st-line CisGem], resistant [progression within the first three months (90 days) after completion of day 1 of the last cycle of 1st-line CisGem]. CisGem: cisplatin and gemcitabine; BTC: biliary tract cancer; ECOG: Eastern Cooperative Oncology Group

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19 PRESENTED BY: Dr Angela Lamarca, MD, PhD, MSc Abstract #4003 | ABC-06 study

Presented By Angela Lamarca at 2019 ASCO Annual Meeting

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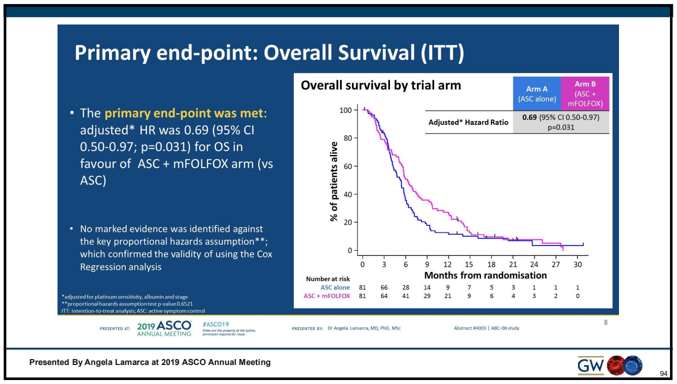
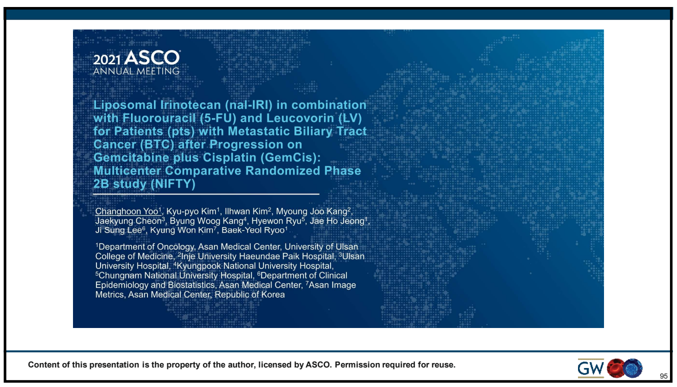
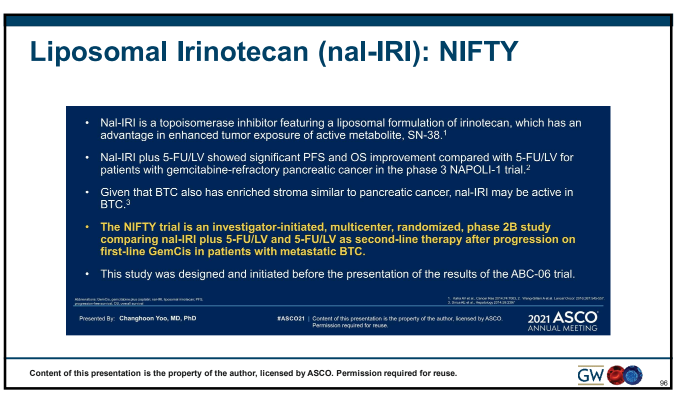
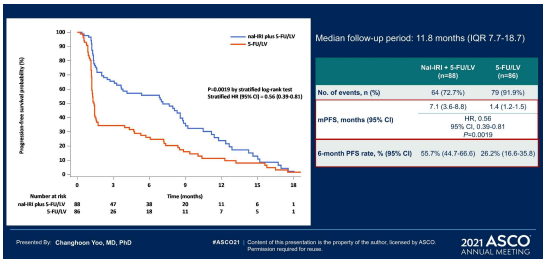






Primary Endpoint: BICR-Assessed PFS



Median follow-up period: 11.8 months (IQR 7.7-18.7)

	Nal-IRI + 5-FU/LV (n=88)	5-FU/LV (n=86)
No. of events, n (%)	64 (72.7%)	79 (91.9%)
mPFS, months (95% CI)	7.1 (3.6-8.8)	1.4 (1.2-1.5)
	HR, 0.56 95% CI, 0.39-0.81 P=0.0019	
6-month PFS rate, % (95% CI)	55.7% (44.7-66.6)	26.2% (16.6-35.8)

Presented By: Changhoon Yoo, MD, PhD

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2021 ASCO ANNUAL MEETING

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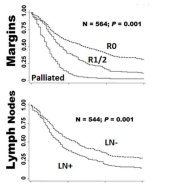
Post-resection patterns of disease relapse

The Christie NHS Foundation Trust | MANCHESTER 1824 The University of Manchester

- **Recurrence rates are similar** Hilar CCA 68% v GBCA 66%[1]
- **Patients with GBC relapse earlier** GBC median 11.5 v hilar CCA 20.3 months, p= 0.007[1]
- **Different recurrence patters** (multivariate analysis)[1]
  - Locoregional: hilar CCA 65% GBC 28%
  - Distant metastases: hilar CCA 36% GBC 72%
- **Survival better with hilar CCA v GBCA** 29 v 20.6 months, p=0.037[1]
- **Involved LNs are adversely prognostic in CCA**[2]
- **Involved margins are adversely prognostic**[2]



How should these differences determine adjuvant strategy?

[1] Jarnagin et al 2003 Cancer 98(8)1689 (MSKCC), [2] De Oliveira et al 2007 Ann Thorac Surg 83(1)1067 (Johns Hopkins)

PRESENTED AT: 2018 Gastrointestinal Cancers Symposium | #GI18

Presented By Juan Valle at 2018 Gastrointestinal Cancers Symposium

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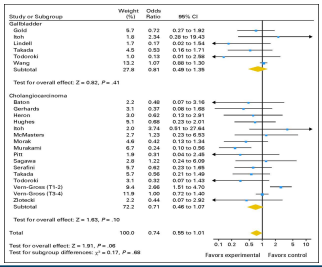
Adjuvant Therapy of Bile Duct Tumors: 6712 pts with CT, XRT, CT+XRT



Those receiving CT or CRT derived statistically greater benefit than RT alone (OR, 0.39, 0.61, and 0.98,respectively; *P* = .02).

The greatest benefit for AT was in those with LN-positive disease (OR, 0.49; *P* = .004) and R1 disease (OR, 0.36; *P* = .002).

Horgan A M et al. *JCO* 2012;30:1934-1940

JOURNAL OF CLINICAL ONCOLOGY

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NCCN guidelines intrahepatic cholangiocarcinoma

The Christie NHS Foundation Trust | The University of Manchester

National Comprehensive Cancer Network®

Post-resection status

	Treatment options
No residual local disease (R0 resection)	• Observe • Clinical trial • **Fluoropyrimidine-based or gemcitabine-based Cx**
Microscopic margins (R1) **or positive regional nodes**	• Clinical trial • **Fluoropyrimidine chemo-Rx** • **Fluoropyrimidine-based or gemcitabine-based Cx**
Residual local disease (R2 resection)	• Clinical trial • Fluoropyrimidine-based or gemcitabine-based Cx • Loco-regional therapy • Best supportive care

Surveillance

- Multi-phasic abdominal/pelvic CT/MRI with IV contrast and chest CT +/- contrast
- Every 6 months for 2 years (if clinically indicated)
- Then annually up to 5 years

No longer true

*"There are **no randomised Phase III** clinical trial data to support a standard **adjuvant regimen**"*

Adapted from NCCN Guidelines Version 4.2017

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Adjuvant Therapy of Bile Duct Tumors

	SWOG S0809 (U.S.)	PRODIGE 12 (France)	BILCAP (U.K.)
Design	Single-arm phase 2	Randomized phase 3	Randomized phase 3
Treatment	Gemcitabine/capecitabine + capecitabine/XRT	Gemcitabine/oxaliplatin versus observation	Capecitabine versus observation
n	79	196	440
BTC tumor type	Gallbladder 32% Perihilar 48% Distal 20% Intrahepatic 0%	Gallbladder 19% Perihilar 8% Distal 28% Intrahepatic 45%	Gallbladder 18% Perihilar 28% Distal 35% Intrahepatic 19%
Positive margin (%)	32	15	38
Positive lymph nodes (%)	N/A	37	54
Endpoint/summary	•Two-year OS 65% •Treatment well tolerated •R0/R1 OS similar at 35 and 34 months	•RFS similar between treatment and control groups (p = 0.47) •Treatment well tolerated based on QOL	•ITT median OS 51 versus 36 months (p = 0.097) •Per protocol analysis median OS 53 versus 36 months (p = 0.028)

BTC = biliary tract cancer; XRT = external beam radiation therapy; OS = overall survival; RFS = recurrence free survival; QOL = quality of life; ITT = intention to treat

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BILCAP | design

The Christie NHS Foundation Trust | The University of Manchester

- Developed by the Hepatobiliary group, UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group in March 2005

- ICC, Hilar CC, muscle-invasive GBC, Lower common bile duct CC
- Radical & macroscopically complete surgery
- ECOG PS 0-2
- No prior treatment
- Adequate organ function
- Randomisation within 3 months

N=360 patients

R → 1:1

Observation

Capecitabine
1250mg/m^2 capecitabine twice a day, days 1-14 of a 3 weekly cycle for 24 weeks (8 cycles)

Primary endpoint; OS

Secondary endpoints; relapse-free survival, toxicity, QoL, health economics

Primrose *et al* (ASCO 2017) J Clin Oncol 35 (15) 4006

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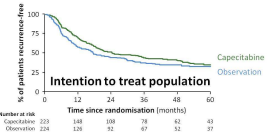
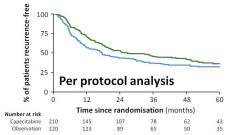
BILCAP | improved recurrence-free survival

The Christie NHS Foundation Trust



Number at risk

Capecitabine	223	148	108	78	62	43
Observation	224	126	92	67	52	37



Number at risk

Capecitabine	210	145	107	78	62	43
Observation	220	123	89	65	50	35

Treatment	Median RFS (95% CI)	24 months HR (95% CI)
Capecitabine	24.6 months (18.9-36.7)	0.76 (0.58-0.99)
Observation	17.6 months (12.8-27.6)	p=0.039

Treatment	Median RFS (95% CI)	24 months HR (95% CI)
Capecitabine	25.9 months (19.8-46.3)	0.71 (0.54-0.92)
Observation	17.6 months (12.0-23.8)	p=0.011

[10 patients excluded in per-protocol analysis from capecitabine arm who did not receive capecitabine]

Primrose et al (ASCO 2017) J Clin Oncol 35 (15) 4006

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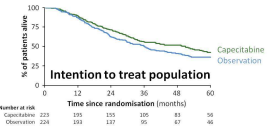
BILCAP | overall survival

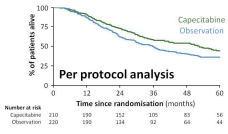
The Christie NHS Foundation Trust

>80% patients followed-up for 36 months



Number at risk

Capecitabine	223	195	155	105	83	56
Observation	224	193	137	95	67	46



Number at risk

Capecitabine	210	190	152	105	83	56
Observation	220	190	134	92	64	44

Treatment	Median OS (95% CI)	HR (95% CI)
Capecitabine	51.1 months (34.6-59.1)	0.81 (0.63-1.04)
Observation	36.4 months (29.7-44.5)	p=0.097

Treatment	Median OS (95% CI)	HR (95% CI)
Capecitabine	52.7 months (40.3-NR)	0.75 (0.58-0.97)
Observation	36.1 months (29.6-44.2)	p=0.028

Sensitivity analyses adjusting for further prognostic factors (nodal status, disease grade, gender) **HR 0.70** (95% CI 0.55-0.91) **p=0.007**

Primrose et al (ASCO 2017) J Clin Oncol 35 (15) 4006

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dMMR and PD-1 in Biliary Cancers

- Mismatch repair deficiency (MRD)/MSI is a feature of many cancers at a frequency of approximately 1 in 30 patients independent of tumor histology. Tumors with MRD are deficient in the repair of specific DNA replication errors and as a result accumulate hundreds to thousands of mutations per tumor genome
  - **MSI-H present in 5-15% of biliary tumors**
- Phase 2 study to evaluate the activity of pembrolizumab; co-primary endpoints were response and progression-free survival rate at 20 weeks in previously treated patients
- endometrial: 9; pancreatic: 4; **ampullary: 4; biliary: 3;** small bowel: 3; gastric: 3; thyroid: 1; prostate: 1; sarcoma: 1
- Objective response and disease control rates were 48% (14/29, 95% confidence interval: 29-67%) and 72% (21/29), respectively. Twenty of 29 patients remain on treatment due to clinical benefit. Median overall Survival (OS) and progression-free survival (PFS) were 21 months and not reached (NR).
- 5/23/17: FDA gave accelerated approval for pembrolizumab for MSI-H tumors, independent of organ site

Le, et al. *N Engl J Med* 2015; 372:2509-2520; *J Clin Oncol* 34, 2016 (suppl; abstr 3003)

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Non-Randomised CPI data in BTC: Uncertainty with variable response data so far, IO biomarkers inadequate

study	Eligibility/ population	ORR/ PFS	Preliminary data comments
KN-158[2] Pembrolizumab	MSI-H N=9	37% (MSI-H)	Consistent with KN-16
KN-28[1] Pembrolizumab	PD-L1+ BTC screened, pretreated N=24	17% (PD-L1+) DOR 5-9 mo.	Screened 89 for 42% PD-L1. Asian patients
KN-158[2] Pembrolizumab	Unselected MSS, pretreated N=104	6% / 2 mo. Med OS 9 mo.	N=61 PD-L1+, 7% RR N=34 PD-L1- , 3% RR
Nivolumab BTC[3]	Unselected pretreated N=54 (45 evaluable)	22% /4 mo. OS 14 mo.	Responders were MSS US patients (63% IHCCA) Biomarker pending.
Nivolumab [4]	30 pt post chemo 30 pt combined with CisGem (chemo naive)	3% 37%	Pt had Lynch (chemo alone ~25%) Non-rand. Japanese pts

1. Bang Y-J et al. ESMO 2015 abstract #525. 2. Ueno, M ESMO 2018 abst 625. 3. Kim R et al JCO 2019. 4. Ueno M et al Lancet GH 2019

Presented By Jennifer Knox at 2020 Gastrointestinal Cancer Symposium

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Ongoing Randomised Trials with CPI in BTC

- Adding on to up-front SOC chemo

Combination	Sponsor	Comment
Pembrolizumab +CisGem vs CisGem NCT04003636	Merck	**Keynote-966** Phase III, n=788 Co- PFS/OS
Durvalumab + CisGem vs placebo + CisGem NCT03875235	AZ	**Topaz1** Phase III, n=474 OS
Durvalumab/Tremelimumab Gem, CisGem combos NCT03473574	AIO-Studien-gGmbH / AZ	**IMMUCHEC** Rand phase II -5 arms ORR
Nivolumab +CisGem vs Nivolumab + Ipilumimab NCT03101566	U of Mich.	Rand phase II N=64, 6-mo. PFS

Others: Multiple trials underway: combinations, dual blockade, local therapies
Biomarker validation: PD-L1 + thresholds etc.

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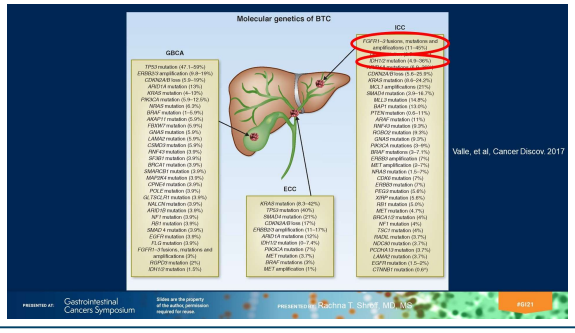

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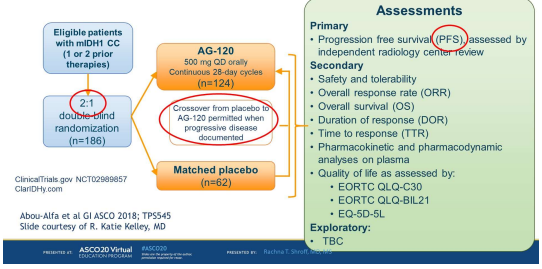
Phase III ClarIDHy Trial Design

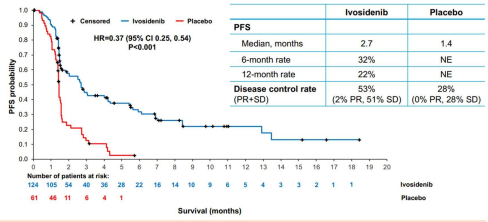


AG-120: selective, potent inhibitor of mutant IDH1) Lancet Oncol 2020 Jun;21(6):796-807

Presented By Rachna Shroff at ASCO 2020 Virtual Education Program

ClarIDHy: PFS by IRC

Abou-Alfa et al ESMO 2019



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

NE=not estimable; PR=partial response; SD=stable disease.

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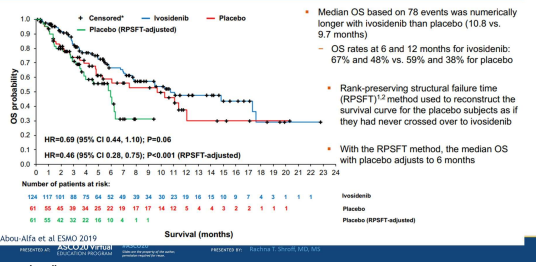
ClarIDHy: OS by intent-to-treat (ITT)



- Median OS based on 78 events was numerically longer with ivosidenib than placebo (10.8 vs. 9.7 months)
  - OS rates at 6 and 12 months for ivosidenib: 67% and 48% vs. 59% and 38% for placebo
- Rank-preserving structural failure time (RPSFT)[1,2] method used to reconstruct the survival curve for the placebo subjects as if they had never crossed over to ivosidenib
- With the RPSFT method, the median OS with placebo adjusts to 6 months

Abou-Alfa et al ESMO 2019

FDA approval pending

Presented By Rachna Shroff at ASCO 2020 Virtual Education Program

Final results from a phase 2 study of infigratinib (BGJ398), an FGFR-selective tyrosine kinase inhibitor, in patients with previously-treated advanced cholangiocarcinoma containing *FGFR2* fusions/rearrangements

Milind Javle,[1] Sameek Roychowdhury,[2] Robin Kate Kelley,[3] Saeed Sadeghi,[4] Teresa Macarulla,[5] Karl-Heinz Weiss,[6] Dirk-Thomas Waldschmidt,[7] Lipika Goyal,[8] Andrew Zhu,[8] Ivan Borbath,[9] Anthony El-Khoueiry,[10] Mitesh Borad,[11] Wei Peng Yong,[12] Philip A. Philip,[13] Michael Bitzer,[14] Surbpong Tanasanvimon,[15] Ai Li,[16] Amit Pande,[16] Harris S. Soifer,[16] Stacie Peacock Shepherd,[16] Susan Moran,[16] Tanios S Bekaii-Saab,[11] Ghassan K Abou-Alfa[17]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]Ohio State Comprehensive Cancer Center/James Cancer Hospital, Columbus, OH, USA [3]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [4]David Geffen School of Medicine at UCLA; [5]Hospital Vall d'Hebron, Barcelona, Spain; [6]University Hospital Heidelberg, Heidelberg, Germany; [7]Klinikum der Universitaet zu Köln, Cologne, Germany; [8]Massachusetts General Hospital, Boston, MA, USA; [9]Cliniques Universitaires St Luc, Brussels, Belgium; [10]USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA, USA; [11]Mayo Clinic, Scottsdale, AZ, USA; [12]National University Cancer Institute Singapore, Singapore; [13]Karmanos Cancer Institute, Detroit, MI, USA; [14]University Hospital Tübingen, Tübingen, Germany; [15]Chulalongkorn University, Bangkok, Thailand; [16]QED Therapeutics Inc., San Francisco, CA, USA; [17]Memorial Sloan Kettering Cancer Center, New York, New York, USA

ASCO GI 2021

Presented By Milind Javle at 2021 Gastrointestinal Cancers Symposium

GW 112

Clinical activity of infigratinib in advanced/metastatic cholangiocarcinoma

Per blinded independent central review	N=108
Objective response rate (confirmed), % (95% CI)	**23.1** (15.6–32.2)
Complete response, n (%)	1 (0.9)
Partial response, n (%)	24 (22.2)
Stable disease, n (%)	66 (61.1)
Progressive disease, n (%)	11 (10.2)
Unknown, n (%)	6 (5.6)
Best overall response (confirmed/unconfirmed), % (95% CI)	**34.3** (25.4–44.0)
Median time to response, months (range)	**3.6** (1.4–7.4)
Disease control rate, % (95% CI)	**84.3** (76.0–90.6)
Median duration of response, months (range)	**5.0** (0.9–19.1)
Median progression-free survival, months (95% CI)	**7.3** (5.6–7.6)
PFS (event free) rate at 4 month, % (95% CI)	75.2 (65.2–82.7)
Median overall survival, months (95% CI)	**12.2** (10.7–14.9)
Per investigator assessment	
Objective response rate (confirmed), % (95% CI)	**30.6** (22.1–40.2)
Median duration of response, months (range)	**6.0** (5.2–9.0)

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GW 113

Clinical activity of infigratinib by prior lines of therapy

	Patients with ≤1 line of prior therapy (n=50)	Patients with ≥2 lines of prior therapy (n=58)
Objective response rate (confirmed), % (95% CI)	**34.0** (21.2–48.8)	**13.8** (6.1–25.4)
Complete response, n (%)	0	1 (1.7)
Partial response, n (%)	17 (34.0)	7 (12.1)
Stable disease, n (%)	27 (54.0)	39 (67.2)
Progressive disease, n (%)	4 (8.0)	7 (12.1)
Unknown, n (%)	2 (4.0)	4 (6.9)
Best overall response (confirmed/unconfirmed), % (95% CI)	**42.0** (28.2–56.8)	**27.6** (16.7–40.9)
Duration of response in confirmed responders, months (95% CI)	5.6 (3.7–9.5)	4.9 (3.7–NE)
Disease control rate, % (95% CI)	**88.0** (75.7–95.5)	**81.0** (68.6–90.1)
Median progression-free survival, months (95% CI)	**7.3** (5.6–9.3)	**7.4** (5.6–7.7)

Response evaluated by blinded independent central review — Interim analysis (n=108)

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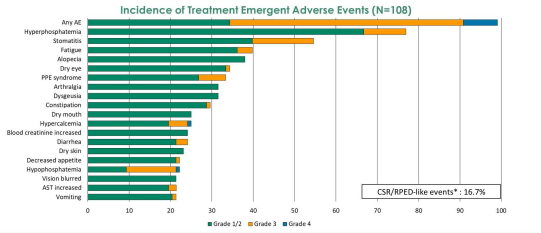
GW 114

Infigratinib safety profile
Most common treatment-emergent adverse events (> 20%)



*Central serous retinopathy (CSR)/retinal pigment epithelial detachment (RPED)-like events included the following terms: chorioretinopathy; subretinal fluid; serous retinal detachment; and detachment of retinal pigment epithelium, macular detachment, and retinopathy

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GW 115

When to perform NGS in Cholangiocarcinoma

- Practical considerations in screening for genetic alterations in cholangiocarcinoma
- T.S. Bekaii-Saab
- Annals of Oncology open access 4/2021

GW 116

On April 17, 2020, the Food and Drug Administration granted accelerated approval to pemigatinib (PEMAZYRE, Incyte Corporation) for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.
The FDA also approved the FoundationOne® CDX (Foundation Medicine, Inc.) as a companion diagnostic for patient selection.

GW 117

Thank You