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School of Medicine

HCC and Biliary Cancers
Time to Overcome Challenges

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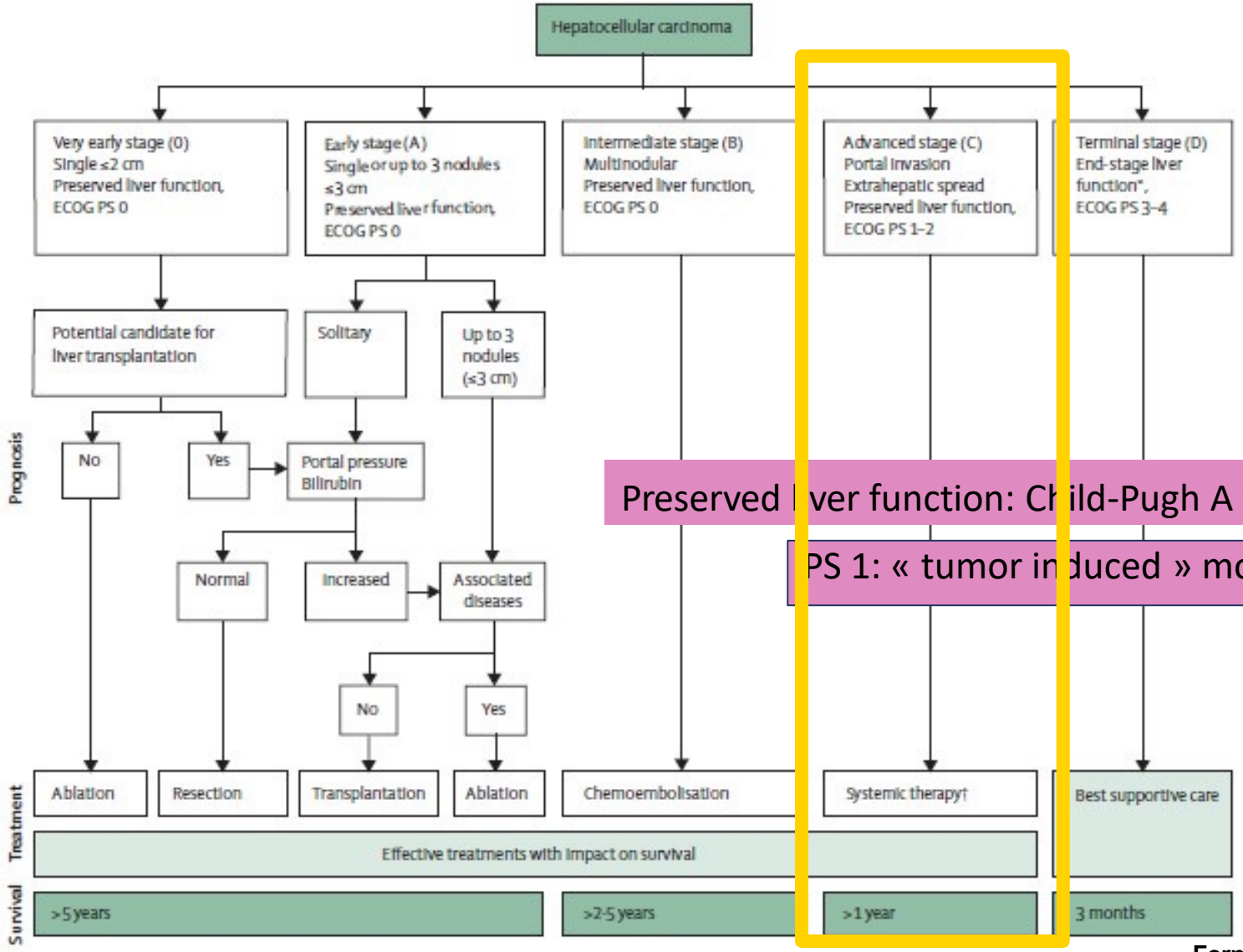
Wake Forest School of Medicine

HCC

HCC: Treatment

The BCLC staging system is recommended for prognostic selection and treatment assignment



Preserved liver function: Child-Pugh A without ascites

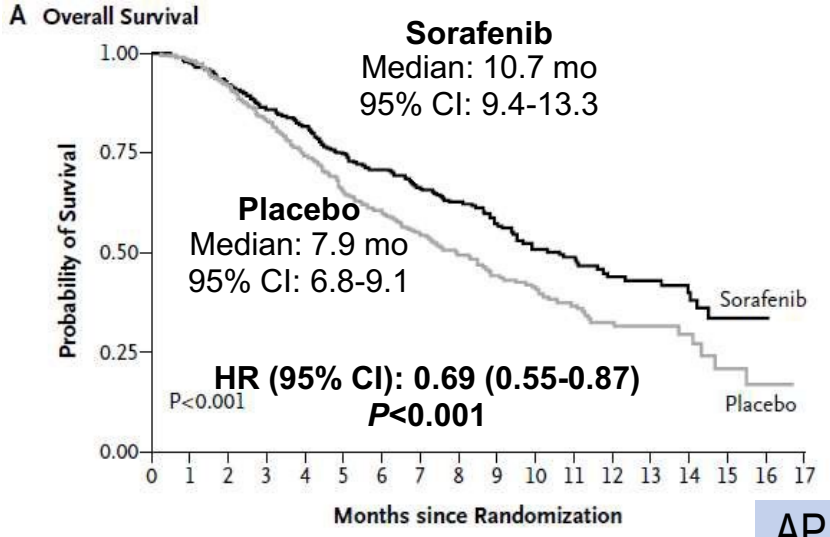
PS 1: « tumor induced » modification in PS

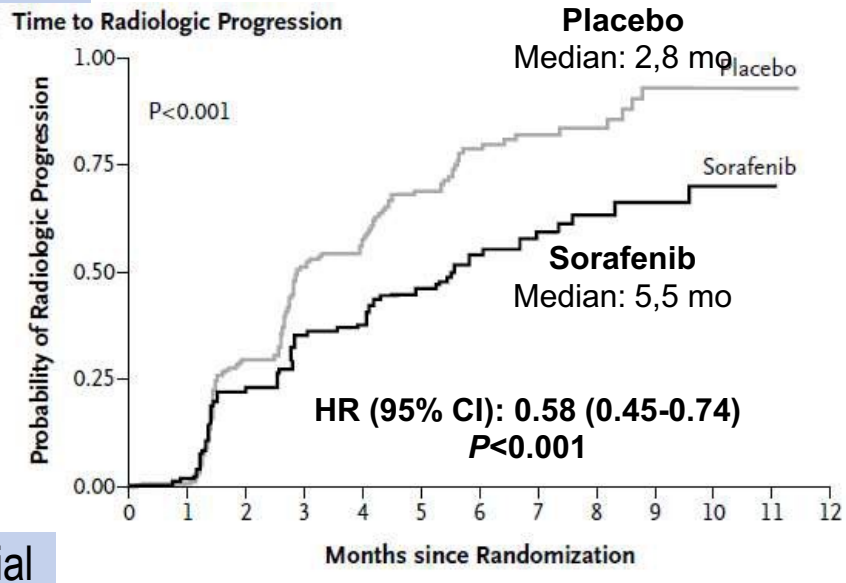
Forner A, et al. Lancet 2018

Sorafenib
Sharp and AP trials

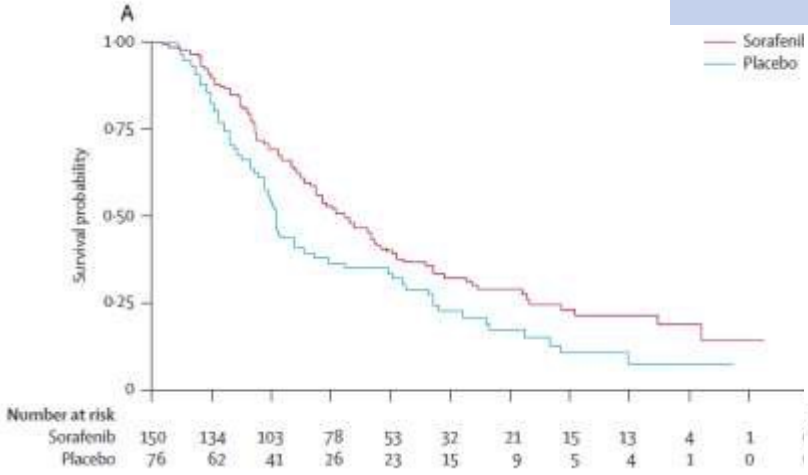
Sorafenib

SHARP trial

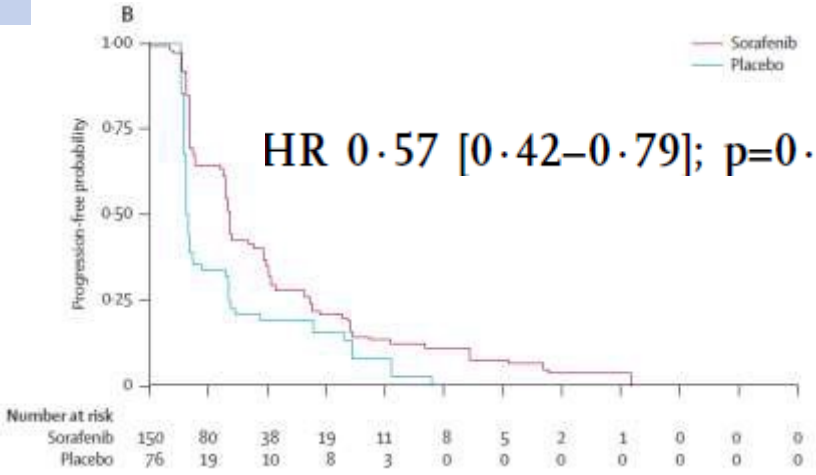




AP trial



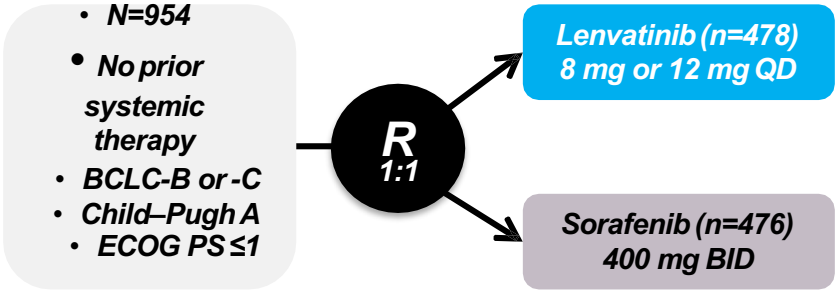
[HR] 0·68 [95% CI 0·50–0·93]; p=0·014)



HR 0·57 [0·42–0·79]; p=0·0005)

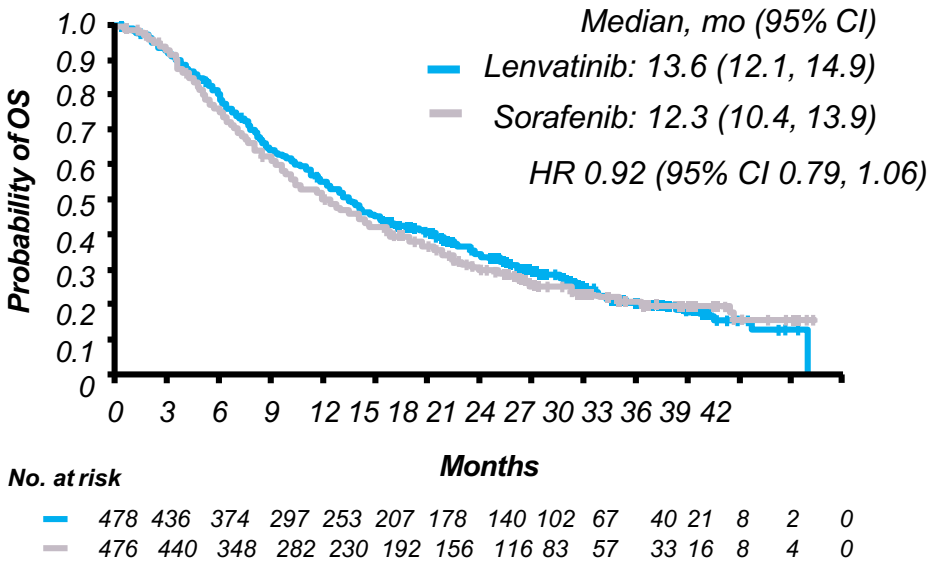
Llovet JM, et al N Engl J Med 2008; Bruix J, et al J Hepatol 2012; Chen AL, et al Lancet Oncol 2009.

Lenvatinib
REFLECT Study



BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; R, randomized; TTP, time to progression.
Kudo M, et al. *Lancet* 2018;391:1163–1173.

Overall survival



Non-inferiority, open-label study design

Patients with ≥50% liver occupation, clear bile duct invasion, or main portal vein invasion were excluded

Primary endpoint: OS

Secondary endpoints: PFS, TTP, ORR

IMBrave150 – Updated

Atezolizumab 1200 mg IV q3w + bevacizumab 15 mg/kg q3w

Sorafenib 400 mg BID

	AtezoBev	Sorafenib	p	HR
OS (months)	19.2	13.4	<0.001	0.66
PFS (months)	6.9	4.3	<0.001	
RR (%)	30 (8%CR)	11		

Cheng et al, J of Hepatol 2022

HIMALAYA
Durvalumab + Tremelimumab vs Sorafenib

Tremelimumab 300 mg IV
X 1 dose
+
Durvalumab
1500 mg q4w

Sorafenib
400 mg BID

	Treme/Durva	Sorafenib	p	HR
OS (months)	16.4	13.8	<0.0035	0.78
PFS (months)	3.78	4.04	NS	
RR (%)	20	5		

Abou-Alfa et al NEJM Evidence 2022

COSMIC-312:
Cabozantinib + Atezolizumab vs Sorafenib

	Cabo/Atezo	Sorafenib	p	HR
OS (months)	15.4	15.5	NS	0.9 (0.69-1.18)
PFS (months)	6.8	4.2	0.0012	0.63
RR (%)	11	4		

Kelley et al, Lancet Oncol 2022

LEAP-002
Lenvatinib + Pembrolizumab vs Lenvatinib

	Lenva/Pembro	Lenva	p	HR
OS (months)	21.2	19.0	0.227 (NS)	0.84
PFS (months)	8.2	8.0	0.0012	0.63
24-month Surv %	43.7	40		
RR %	26.1	17.5		

Subgroup analysis favored combo in high-risk features:
MVI or EHD (HR = 0.78)
Elevated AFP(HR = 0.67).

Finn et al LBA 34 ESMO 2022

Camrelizumab + rivoceranib (apatinib) vs sorafenib

	Camre/Rivo	Sorafenib	p	HR
OS (months)	22.1	15.2	<0.001	0.62
PFS (months)	5.6	3.7	<0.001	0.52
RR %	25.4	5	<0.001	

Support that camrelizumab + rivoceranib as another first-line treatment option for unresectable HCC.

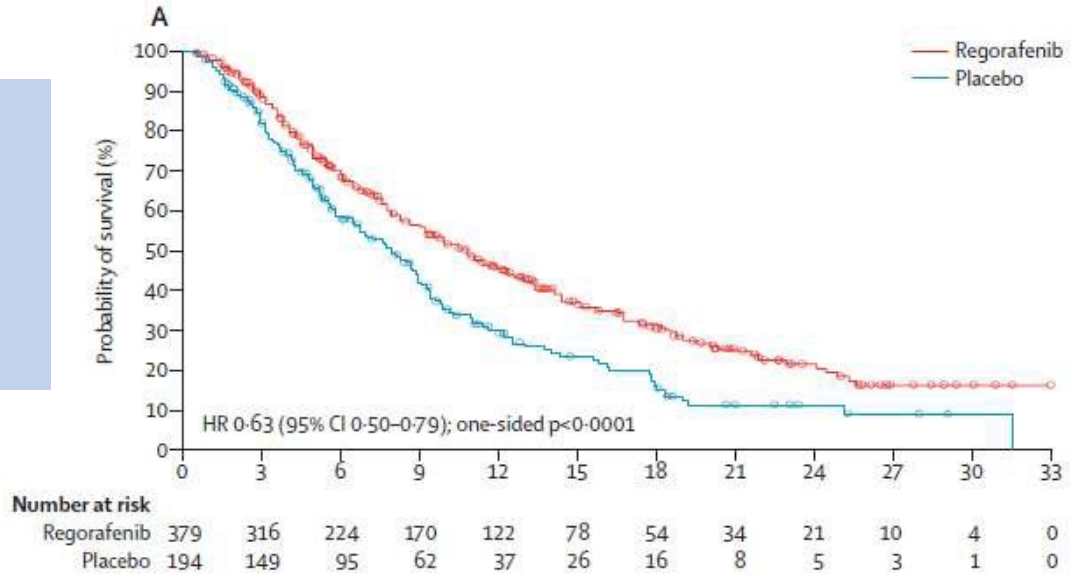
Qin S et al LBA35 ESMO 2022

Second-Line

Regorafenib
RESORCE trial
Second line after sorafenib:

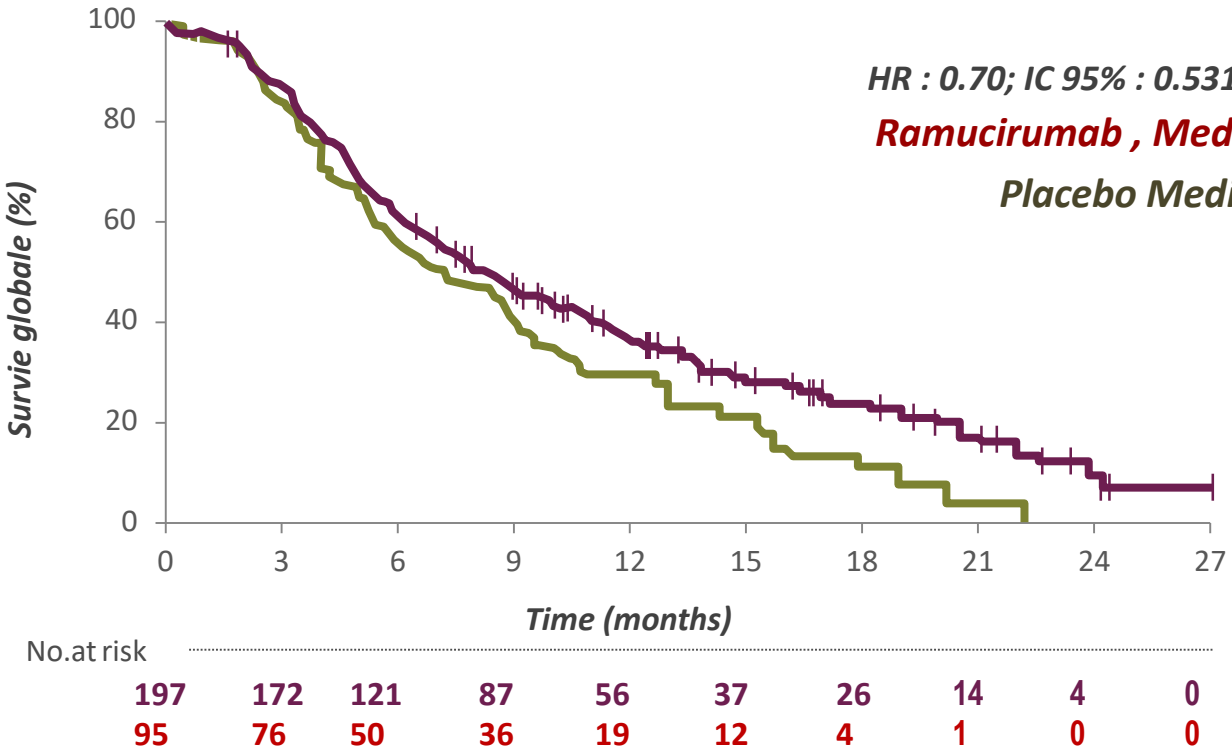
- RESORCE trial:
  - Progression during sorafenib
  - In patients who tolerated well sorafenib (> 400 mg/d , 20 d / month)
  - 160 mg/QD 3 weeks on 1 week off

	Regorafenib	HR:	Placebo
mOS	10.6 m	0.63	7.8 m
mTTP	3.2 m	0.44	1.5 m
ORR	10.6%		4.1%
DCR	65.2%		36.1%



Bruix J, et al. Lancet 2016

REACH-2 : Overall survival, AFP level > 400 ng/mL



HR : 0.70; IC 95% : 0.531 – 0.949, p=0.0199

Ramucirumab , Median : 8.5 months

Placebo Median : 7.3 months

Zhu AX, et al., Lancet Oncol 2019;20:282-96

Cabozantinib
CELESTIAL Trial

- *N=707*
- *Child–Pugh A*
- *ECOG PS ≤1*
- *Up to 2 prior therapies*
- *Progressed on 1 systemic therapy*

R 2:1

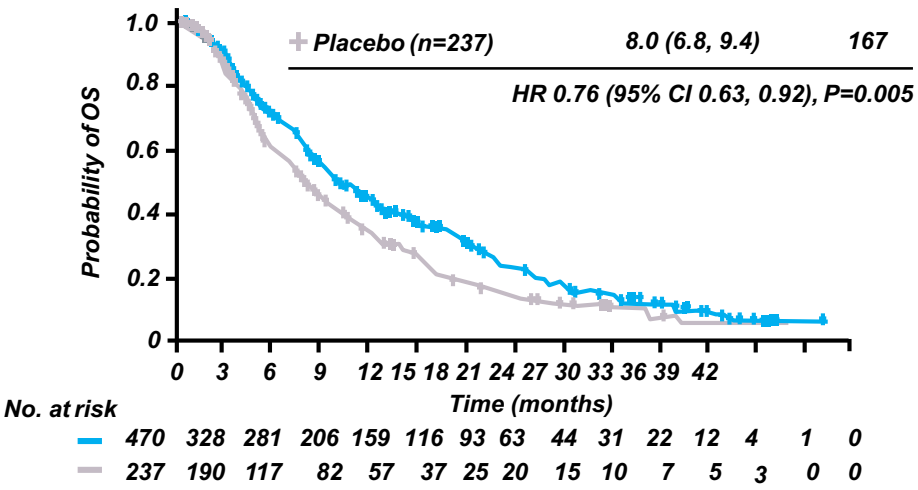
- *Cabozantinib (n=470) 60 mg QD*
- *Placebo (n=237) QD*

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR
- 27% of patients had 2 prior regimens

Overall survival

	Median OS, mo (95% CI)	No. of deaths
Cabozantinib (n=470)	10.2 (9.1, 12.0)	317
Placebo (n=237)	8.0 (6.8, 9.4)	167

HR 0.76 (95% CI 0.63, 0.92), P=0.005



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; R, randomized.
Abou-Alfa G, et al. N Engl J Med 2018;379:54–63.

Abou-Alfa G, et al. N Engl J Med 2018;379:54–63.

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2022
Hepatocellular Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy

Preferred Regimens

- Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)[a,b,c,1]
- Tremelimumab-actl + durvalumab (category 1)[b,2]

Other Recommended Regimens

- Sorafenib (Child-Pugh Class A [category 1] or B7)[d,e,3,4]
- Lenvatinib (Child-Pugh Class A only)[5,6] (category 1)
- Durvalumab[b,7]
- Pembrolizumab[b,8] (category 2B)

Useful in Certain Circumstances

- Nivolumab[b,9] (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) Child-Pugh Class A or B) (category 2B)

Subsequent-Line Therapy[f] if Disease Progression[g]

Options

- Regorafenib (Child-Pugh Class A only) (category 1)[h,10]
- Cabozantinib (Child-Pugh Class A only) (category 1)[i,11]
- Ramucirumab (AFP ≥400 ng/mL and Child-Pugh Class A only) (category 1)[i,12]
- Lenvatinib (Child-Pugh Class A only)
- Sorafenib (Child-Pugh Class A or B7)[d,e]

Other Recommended Regimens

- Nivolumab + ipilimumab (Child-Pugh Class A only)[b,i,13]
- Pembrolizumab (Child-Pugh Class A only) (category 2B)[b,j,k,14-16]

Useful in Certain Circumstances

- Nivolumab (Child-Pugh Class B only)[b,j,17-20] (category 2B)
- Dostarlimab-gxly[b,j,l,21,22] for MSI-H/dMMR tumors (category 2B)
- For *RET* gene fusion-positive tumors:
  - Selpercatinib (category 2B)[23]

[a] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[b] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[c] Patients on atezolizumab + bevacizumab should have adequate endoscopic evaluation and management for esophageal varices within approximately 6 months prior to treatment or according to institutional practice and based on the assessment of bleeding risk.
[d] See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[e] Caution: There are limited safety data available for patients with Child-Pugh Class B or C liver function and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, et al. J Clin Oncol 2009;27:1800-1805). The impact of sorafenib on patients potentially eligible for transplant is unknown.
[f] Larotrectinib and entrectinib are treatment options for patients with hepatocellular carcinoma that is NTRK gene fusion positive. (Drilon A, et al. N Engl J Med 2018;378:731-739; Doebele RC, et al. Lancet Oncol 2020;21:271-282.)
[g] There are no comparative data to define optimal treatment after first-line systemic therapy.
[h] The data reflect use on or after sorafenib in patients who previously tolerated sorafenib at a dose of at least 400 mg per day.
[i] The data reflect use on or after sorafenib.
[j] For patients who have not been previously treated with a checkpoint inhibitor because there is a lack of data for subsequent use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[k] Pembrolizumab is a recommended treatment option for patients with or without MSI-H HCC.
[l] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Biliary Cancer

Prospective, National, Multicenter Phase 3 Study: ABC-02 Schema

Eligible patients (n = 400[a])

+ QoL

Randomized 1:1

(stratified by center, primary site, PS, prior therapy and locally advanced vs metastatic)

Arm A

Gem *1000 mg/m²*
D1,8,15 q 28d
24 weeks (6 cycles)

Arm B

Cisplatin *25 mg/m²*
+ Gem *1000 mg/m²*
D1,8 q 21d
24 weeks (8 cycles)

Primary endpoint OS

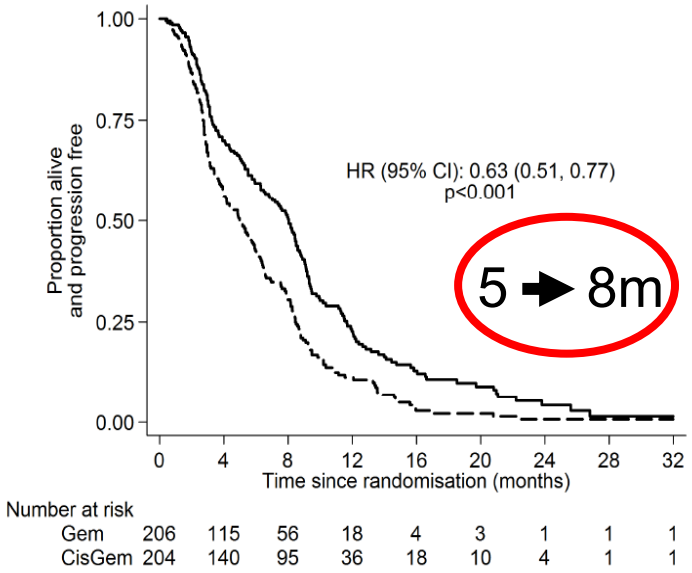
Inclusion criteria:

- Histologically / cytologically verified, non-resectable or recurrent/metastatic CCC, GB, or ampullary carcinoma
- Adequate biliary drainage, no uncontrolled infection
- ECOG PS 0-2
- LFTs: bilirubin ≤ 1.5 x ULN, ALT/ AST/ alk phos ≤ 3 x ULN (≤ 5 if liver metastases)
- No prior systemic treatment[b]
- Consenting informed-patients

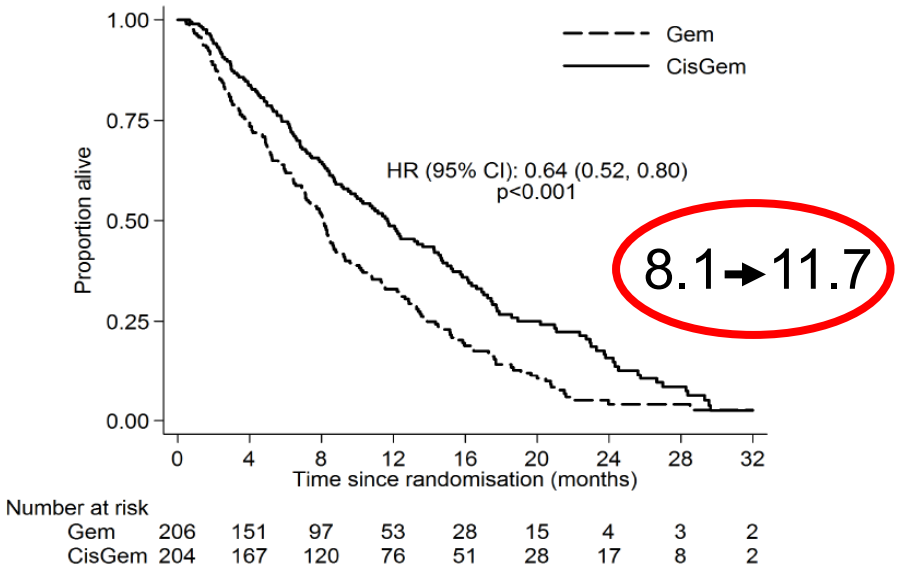
[a] Including 86 patients in ABC-01.
[b] Allowed: palliative surgery, relapse following curative surgery, PDT, radiotherapy with documented progression.
Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

ABC-02 Results

Progression-free Survival (ITT)

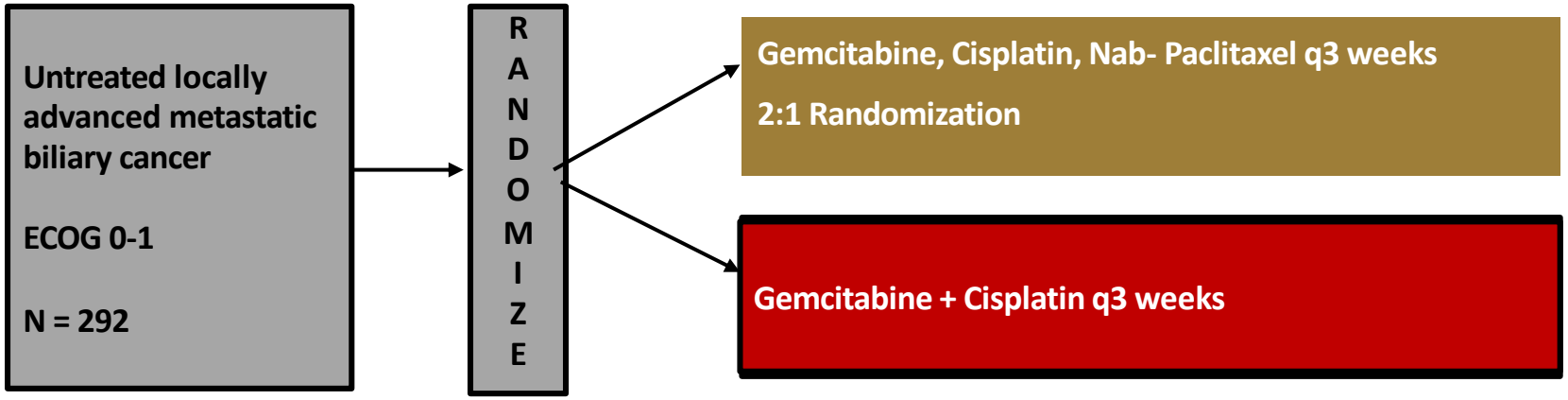


Overall Survival (ITT)



Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

Phase 3 SWOG 1815



Primary endpoint: overall survival
Secondary: ORR, PFS, DCR, Safety, Ca 19-9 response

	NabGemDDP	GEMDDP	p
OS (months)	14	12.7	.65
PFS (months)	8.2	6.4	.43
RR (%)	31	22	

Shroff R et al: LBA490, ASCO GI 2023

TOPAZ-1 Study

- 685 chemo naïve for met, locally advanced or metastatic BTC (ICC, ECC, and GBC)
- ECOG PS 1
- Randomized 1:1 Gem/DDP +/- Durvalumab or Placebo up to 8 cycles. Follower by D or P to progression

Oh D-Y et al NEJM Evid. June 1, 2022

TOPAZ-1 Efficacy Results

	GEM/DDP/D (n=341)	GEM/DDP/P (n=343)	HR (C.I.) [P Value]
mOS (months)	12.8	11.5	0.8 (0.66-0.97) [0.021]
PFS (months)	7.2	5.7	0.75(0.63-0.89) [0.001]
ORR (%)	26.7	18.7	
DCR	85.3	82.6	
Survival 24 months %	24.9	10.4	

Oh D-Y et al NEJM Evid. June 1, 2022

TOPAZ-1 Toxicity

- No clear additional Non-immune Toxicity
- Immune mediated toxicity G 3 or G4 were infrequent;
  - Pneumonitis (0.3%), Dermatitis (.9%), hepatic (0.6 %).

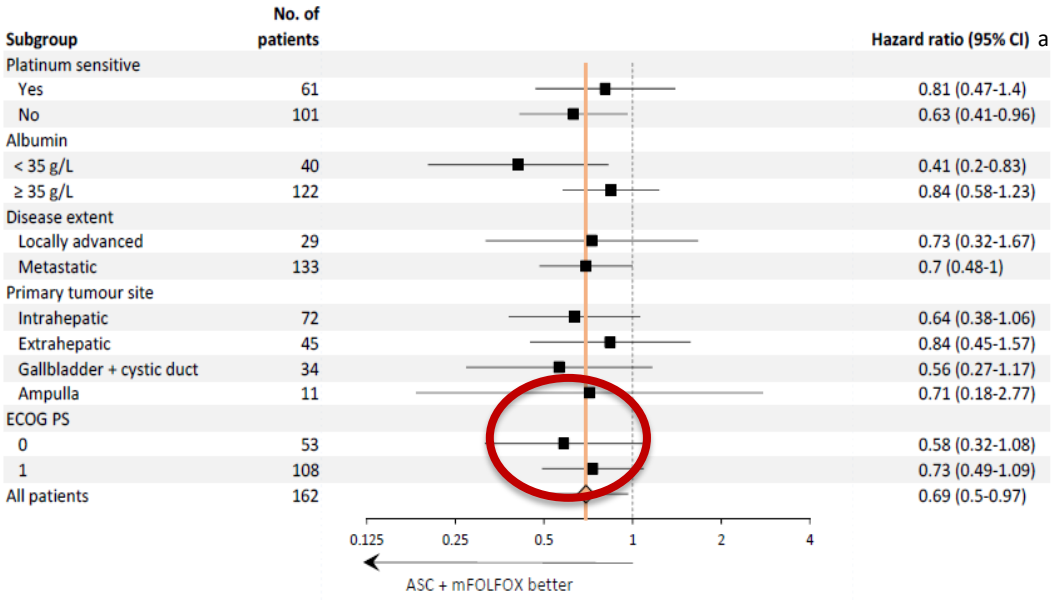
Oh D-Y et al NEJM Evid. June 1, 2022

Second Line

ABC-06: Active Symptom Control ± mFOLFOX

- ASC ± mFOLFOX in ABC after prior gemcitabine/cisplatin therapy
- 162 patients were randomized (1:1)
  - 44% intrahepatic, 28% extrahepatic, 21% gallbladder, and 7% ampullary
- Median OS: 5.3 mo ASC vs. 6.2 mo combo (adjusted HR 0.69 [95% CI 0.50-0.97]; *P* = 0.031)
  - 6-month survival rate: 35.5% vs 50.6%
  - 12-month survival rate: 11.4% vs 25.9%
- Grade 3/4 toxicities were reported in 32 (39%) and 48 (59%) patients in the ASC alone and combination groups, respectively

Supgroup Analyses All Favor the Combination Over ASC Alone

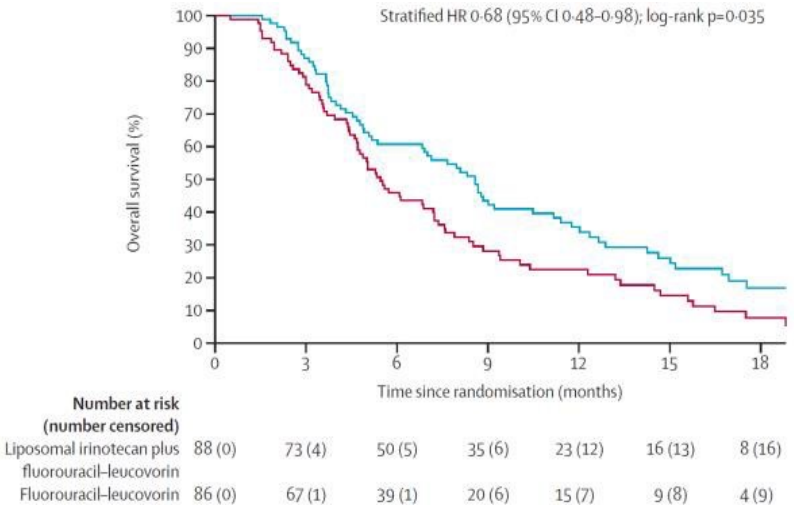


[a] HRs are adjusted for platinum sensitivity, albumin and stage.

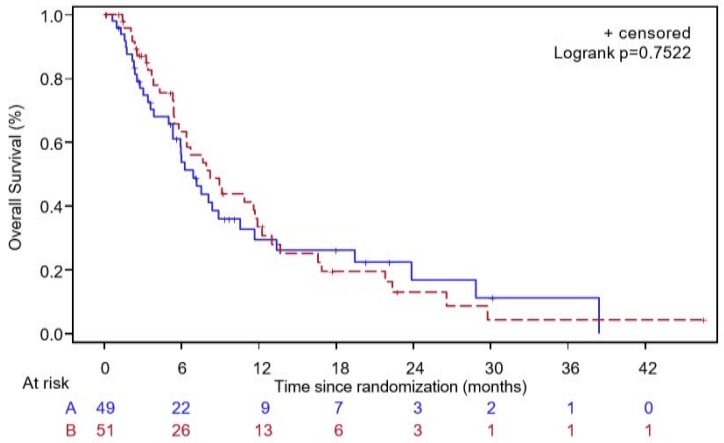
ASC, active symptom control.

Lamarca A, et al. *J Clin Oncol* 2019;37,(suppl; abstr 4003).

Liposomal Irinotecan + 5FU



Yoo et al. The Lancet Oncology 22, 1560



Vogel et al. ESMO 2022, Abstr. 53

Targets

- Specific
  - IDH-1 mutations
  - FGFR2 fusions
  - BRAF
  - Her-2
- Tumor agnostic
  - NTRK fusions
  - MMR-deficiency

IDH-1

Ivosidenib Phase 1 and Phase 3 Studies

Phase 1 Study

CCA, chondrosarcoma, glioma, others [NCT02073994]

CCA cohort[1]: n = 73 [dose escalation (n = 24); dose-expansion 500 mg QD (n = 49)]

No DLTs; drug-related AEs: fatigue, nausea, diarrhea, vomiting

Activity:

Median PFS 3.8 months

6-month PFS: 40.1%

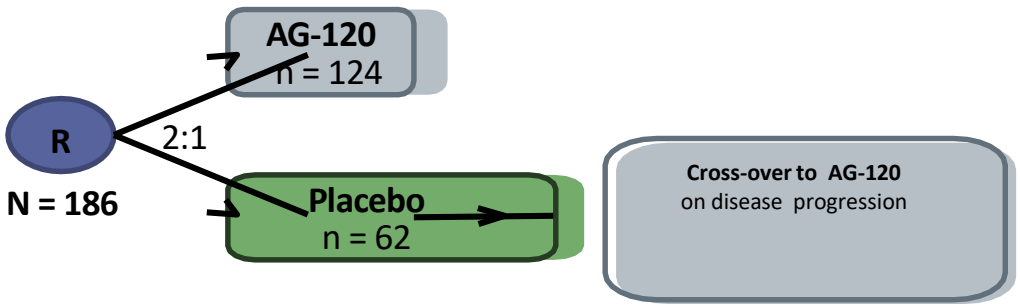
12-month PFS: 21.8%

RR 5% (4 PRs)

OS: 13.8 m

Phase 3 Study (ClarIDHy)

Second-line, placebo- controlled
[NCT02989857][2]



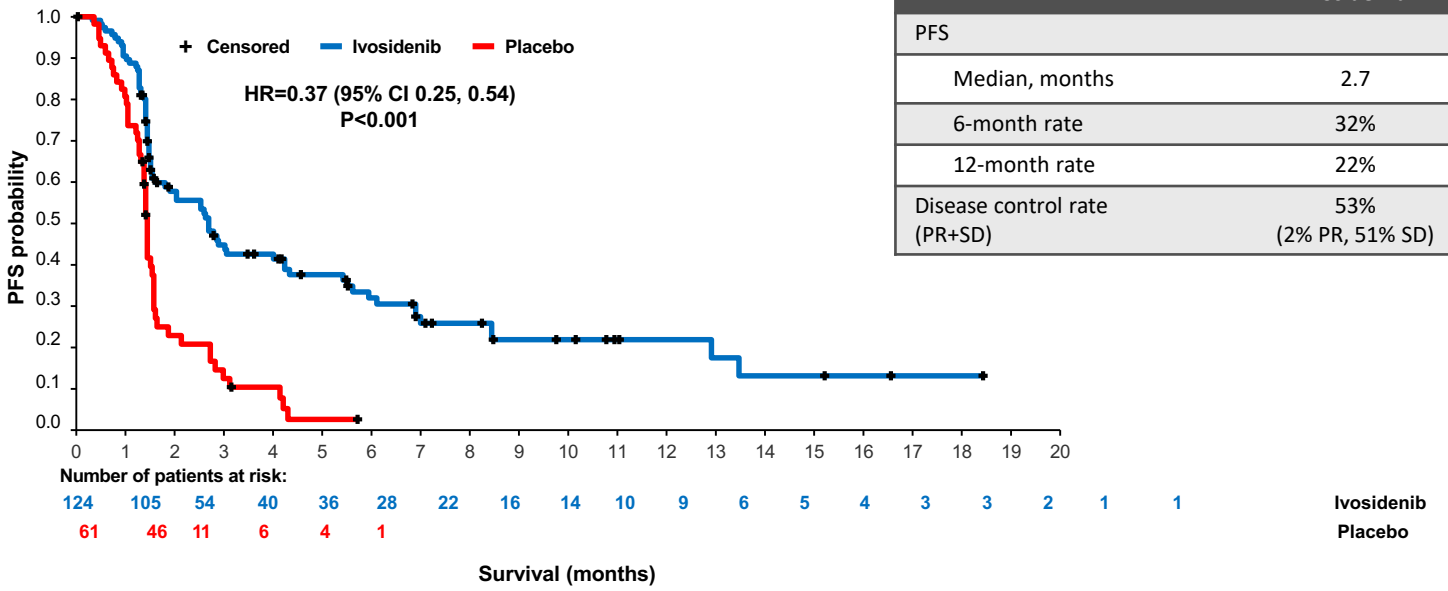
AG-120 is a first-in-class, potent, oral inhibitor of the mutant IDH1 enzyme

IDH1 Mutations

- IHCCA (22%)
- Chondrosarcoma (50%)
- Glioma (80%)

Abou-Alfa, GK. Lancet Oncol, 2020

ClarIDHy: PFS by IRC



	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.

- mOS (months; adjusted for cross-over): 10.8 vs 6 months (9.7 months unadjusted)

Abou-Alfa, GK. Lancet Oncol, 2020

- FGFR2 Fusions

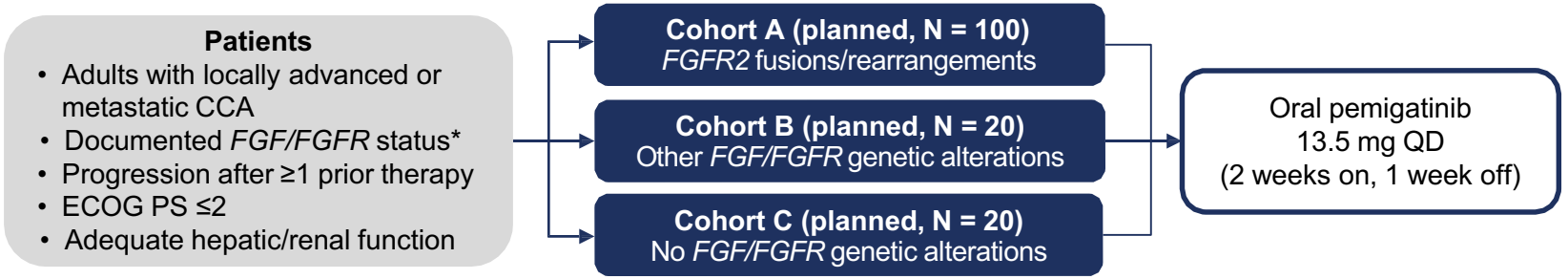
  At the time of initial diagnosis, CA19-9 was < 35U/mL in 42.6% of pts.

  Bone metastases were observed in 41 (30.6%) pts with advanced disease

Goyal et al ASCO 2020

FIGHT-202 STUDY DESIGN

- Phase 2 open-label, single-arm study evaluating the efficacy and safety of pemigatinib in patients with previously treated locally advanced or metastatic CCA (NCT02924376)
  - Sites opened in the United States, Europe, Middle East, and Asia



FGFR2

- Physiologic roles: cell proliferation, differentiation, migration, angiogenesis
- Approx. 10-15% IHCCA
- FGFR fusions: ligand independent activation of FGFR

Abou-Alfa, GK. Lancet Oncol, 2020

CONCLUSIONS

- 56 unique *FGFR2* fusion genes were observed in cohort A (*FGFR2* fusions or rearrangements).
- In cohort A, pemigatinib treatment resulted in
  - ORR of 35.5% with durable responses
  - Median PFS of 6.9 months
- A phase 3 study is ongoing in the first-line setting to evaluate pemigatinib versus gemcitabine plus cisplatin in patients with CCA and *FGFR2* fusions or rearrangements (NCT03656536)

Phase II study of infigratinib cholangio *FGFR2* gene fusion/rearrangement

- 108 pts advanced/metastatic CCA post ≥1 line of systemic therapy
- Infigratinib 125 mg orally for 21 days of each 28-day cycle
  - ORR 23.1% (1 CR/24PRs). DOR 5 months
  - TEAEs any grade: hyperphosphatemia (76.9%), eye disorders (67.6%), stomatitis (54.6%), and fatigue (39.8%).
  - A phase III infigratinib versus gem/DDP is ongoing in the front-line setting

Javie M: JCO 2021, 39(suppl 3):265

Other FGFR Inhibitors in Development

- **Futibatinib (TAS-120): i**rreversible FGFR1–4 inhibitor
  - RR 41.7% (FGFR2 fusion)
  - Duration of response 9.7 months AND mPFS was 9.0 months
- **Derazantinib; ARQ 087**
  - RR 20.7%
- ICP-192 (gunagratinib)
  - Preclinical studies demonstrated potential to overcome resistance to first generation agents

Goyal et al, AACR 2021 DOI: 10.1158/1538-7445

The Phase 2 Dabrafenib and trametinib: BRAF ^{V600E}-mutated BTC Rare Oncology Agnostic Research (ROAR) basket trial

- *BRAF* mutations have been reported in approximately 5%-7% of iCCAs; these mutations may be enriched in iCCA vs other types of biliary cancers
- **Phase 2 study in 43 pts**
  - **ORR 47% (95% CI, 31–62)** – central review
  - Duration of response: 9 months (95% CI, 6–14)
  - PFS: 9 months (95% CI, 5–10)
  - OS: 14 months (95% CI, 10–33)

Subbiah V, et al. *Lancet Oncol.* 2020;21:1234–43.

Targeting HER-2

- **Pertuzumab and trastuzumab: phase 2a study**
  - 39 patients previously treated HER2 amplification, HER2 overexpression, or both
  - RR 23 %

- **Zanidatamab – HER-2 bispecific antibody**
  - 20 patients (11 gallbladder cancers, 5 intra- and 4 extra-hepatic cholangiocarcinoma)
  - RR 47%; median duration of response 6.6 months

- **Neratinib, a pan-HER irreversible tyrosine kinase inhibitor**
  - 25 pts with activating somatic HER2 mutations (GB 40%, ICC24%, EHCC20%, AV 16%)
  - RR 12% and PFS 2.8 months

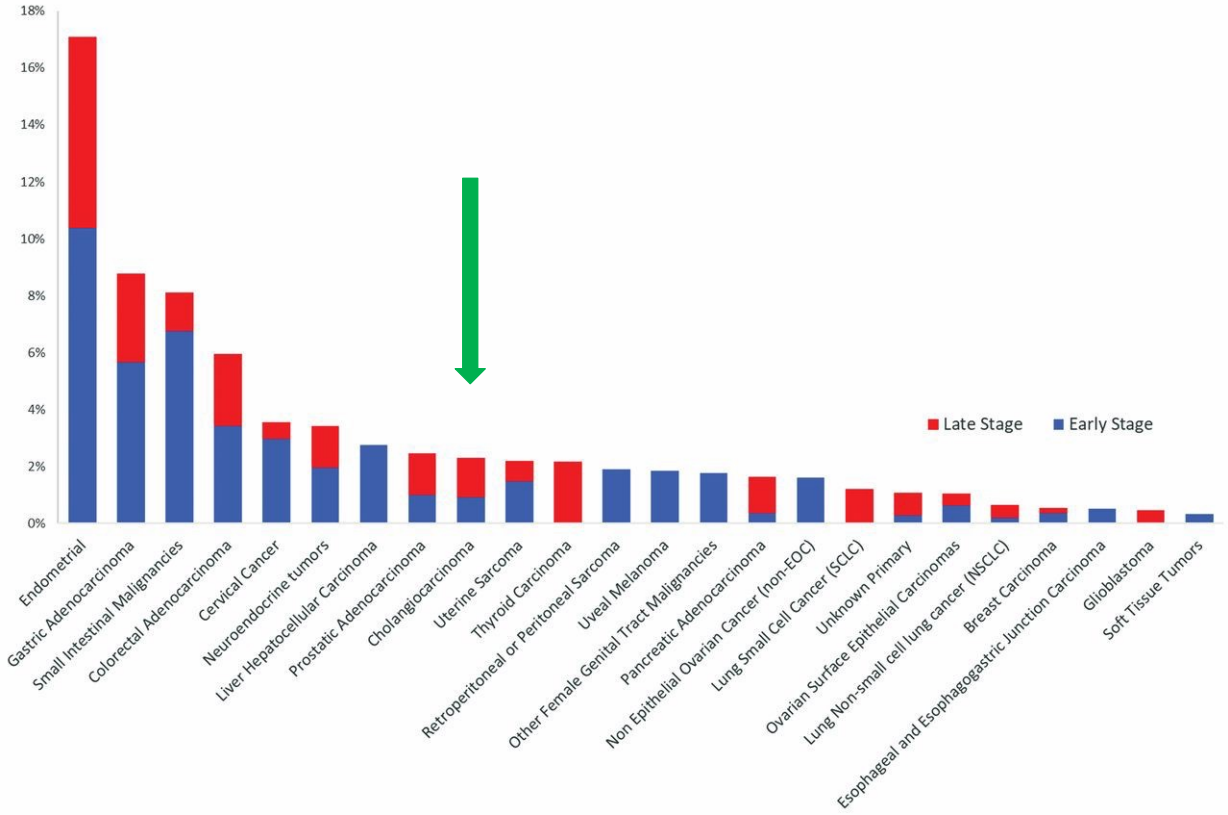
Javle Lancet Oncol 2021
Meric-Bernstam ASCO GI 2021
Harding et al ASCO GI 2021

Targeting HER-2

- Trastuzumab deruxtecan
- 30 pts recurrent or unresectable: 22 HER2+(10 IHC 3+ and 12 IHC 2+) and 8 HER2-low (6 IHC 2+ and 2 IHC1+)
- RR 36.4% and 12.5%. PFS 5.1 and 3.2 months
- DOR in Her 2 +: 7.4 months
- ILD: ≥ Grade 3 12.5%

Ohba A et al: A 4006, ASCO 2022

MSI-High Frequency: Multiple Cancers



Le, D et al. Science, 2017

Immune Biomarkers in Biliary Cancers

- MMR deficiency
  - KEYNOTE-16: Biliary tract cancers; RR 53%, 21% CR
  - KEYNOTE-158: Cholangiocarcinoma RR 37% (N= 9)
- Tumor mutation burden (TMB)
  - >10 mutations/Mb 3.5- 5.5% - highest in gallbladder cancer

Le, DT. NEJM, 2015. Silva, VW. CCO, 2016. Lee, H. Ther Adv Gastroenterol, 2017. Diaz, L. ESMO, 2017, Abstr 386P

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2022
Biliary Tract Cancers

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Gemcitabine + cisplatin[4] (category 1)
- Durvalumab + gemcitabine + cisplatin (category 1)[d,e,5]

Other Recommended Regimens

- 5-fluorouracil + oxaliplatin
- 5-fluorouracil + cisplatin (category 2B)
- Capecitabine + cisplatin (category 2B)
- Capecitabine + oxaliplatin
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Gemcitabine + cisplatin + albumin-bound paclitaxel[1] (category 2B)
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,10,11]
- For *RET* gene fusion-positive tumors:
  - Pralsetinib (category 2B)[12]
  - Selpercatinib for CCA (category 2B)[13]

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[g]

Preferred Regimens

- FOLFOX[14]

Other Recommended Regimens

- FOLFIRI[15] (category 2B)
- Regorafenib[16] (category 2B)
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)[17]
- Durvalumab + gemcitabine + cisplatin (category 2B)[e,h,5]
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,h,10,11]
  - Dostarlimab-gxly[e,h,i,18,19] (category 2B)
- For TMB-H tumors:
  - Pembrolizumab[e,f,h,20]
- For *BRAF*-V600E mutated tumors
  - Dabrafenib + trametinib[21,22]
- For CCA with *FGFR2* fusions or rearrangements:
  - Pemigatinib[23]
  - Infigratinib[24]
  - Futibatinib[25]
- For CCA with *IDH1* mutations
  - Ivosidenib[26,27]
- For *RET* gene fusion-positive tumors:
  - Selpercatinib for CCA[13]
  - Pralsetinib (category 2B)[12]
- For HER2-positive tumors:
  - Trastuzumab[j] + pertuzumab[28]
- Nivolumab[e,h,29] (category 2B)
- Lenvatinib + pembrolizumab[e,h,30] (category 2B)

[d] Durvalumab + gemcitabine + cisplatin is also a recommended treatment option for patients who developed recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[f] There are limited clinical trial data to support pembrolizumab in this setting. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med 2019;25:744-750.
[g] Treatment selection depends on clinical factors including previous treatment regimen/agent and extent of liver dysfunction.
[h] For patients who have not been previously treated with a checkpoint inhibitor because there is a lack of data for subsequent use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[i] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
[j] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References
Continued

Thanks for the attention!
Questions???