New Systemic Treatment Options for Hepatobiliary Cancers

Presented by Robin Kate Kelley, MD

ABSTRACT

Multiple systemic therapy options now exist for unresectable and metastatic hepatocellular carcinoma (HCC). Atezolizumab + bevacizumab is the preferred first-line regimen, and although many second-line treatment options have recently been added to the NCCN Guidelines, none have been studied after atezolizumab + bevacizumab (all post-sorafenib), and therefore optimal sequence has yet to be established. Multiple new combination regimens with immune checkpoint inhibitors are also being studied in advanced-stage HCC. In biliary tract cancer (BTC), gemcitabine + cisplatin remains the preferred first-line regimen. FOLFOX is the preferred regimen in the second line. Multiple targeted therapy options are now available in second-line BTC for patients with tumors harboring specific mutations, and these therapeutic targets may guide future treatment sequence and combinations for BTCs.

J Natl Compr Canc Netw 2021;19(5.5):633–635
doi: 10.6004/jnccn.2021.5015

Worldwide, the incidence of hepatobiliary cancers is increasing. In the United States, liver cancer is one of the few malignancies with a significantly increasing rate of mortality compared with other common cancers, according to Robin Kate Kelley, MD, Associate Professor, Clinical Medicine, UCSF Helen Diller Family Comprehensive Cancer Center. “Liver cancer is the third or fourth leading cause of cancer death worldwide based on GLOBOCAN estimates,” she said at the NCCN 2021 Virtual Annual Conference.¹ “Its impact is not to be understated.”

Most hepatocellular carcinomas (HCCs) are caused by an underlying liver injury due to toxins, such as alcohol, or viruses, such as hepatitis B virus (HBV) or hepatitis C virus (HCV). “But a very important cause of increasing rates of HCC is nonalcoholic fatty liver disease,” she said. Biliary tract cancer (BTC) is more uncommon, but is showing the same increasing incidence seen with HCC.² The etiology of BTC is similar to that of HCC, and includes underlying liver inflammation and injury, but other causes also include fluke infection and hereditary cancer (in ~15% of cases).

First-Line Therapy for HCC

Sorafenib was the first agent to show a meaningful survival benefit in HCC.³ In 2007, sorafenib became the preferred first-line therapy in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Hepatocellular Carcinoma, as well as the standard of care worldwide. After a host of clinical trial failures, sorafenib remained the only systemic therapy agent with a 2A or higher recommendation in the NCCN Guidelines

until 2017. But according to Dr. Kelley, a lot has changed since then.

Data from the REFLECT trial, where patients were enrolled to either lenvatinib or sorafenib, were the first to show lenvatinib provided a meaningful survival benefit in HCC.⁴ In this randomized phase III trial, median overall survival (OS) showed a trend in favor of lenvatinib over sorafenib, leading to the adoption of lenvatinib as another first-line therapy option, based on its noninferiority to sorafenib. “Around that same time, we began to study immune checkpoint inhibitors [ICIs] for advanced HCC, based on the premise that HCC occurs in an immune-suppressed microenvironment and has many features in common with other solid tumors that respond to ICIs,” explained Dr. Kelley.⁵

The first important trial of ICIs in advanced HCC was the CheckMate 040 trial of nivolumab,⁶ in which patients were divided according to etiology (uninfected, HCV-infected, or HBV-infected). “This was a very important design because it ensured that any signal of immune-related hepatitis or hepatotoxicity could be captured according to etiology and risk,” she noted. Beyond its acceptable safety in this phase I/II trial, nivolumab also showed a signal for efficacy, with durable, meaningful responses in approximately 15% to 20% of patients and occasional complete responses.

The CheckMate 040 data led to an important phase III trial, CheckMate 459, of first-line nivolumab versus sorafenib.⁷ “This was a negative study, but it signaled that a subset of patients benefit from nivolumab, with objective responses in 15% and complete responses in 4%,” she said. “These responses were durable, and health-

related quality of life also favored nivolumab over sorafenib.” According to Dr. Kelley, these “provocative” findings prompted the rationale for combining ICIs with antiangiogenic agents in HCC.

In the randomized phase III IMbrave150 trial,⁸ atezolizumab + bevacizumab led to a significant OS benefit compared with sorafenib in patients with locally advanced or metastatic and/or unresectable HCC who had no prior systemic therapy. The doublet also significantly improved the co-primary endpoint of progression-free survival, and achieved objective responses in 27% of patients.

Updated results presented at the 2021 ASCO Gastrointestinal Cancers Symposium showed mature survival data,⁹ with a median OS of 19.2 months for the combination arm versus 13.4 months for sorafenib (hazard ratio, 0.66), and a median progression-free survival of 6.9 versus 4.3 months (hazard ratio, 0.65). “With the more mature data, we see objective responses in 30% of patients, and 8% with complete responses; that’s a really meaningful number of patients,” she noted.

These data led to the FDA approval of combination atezolizumab + bevacizumab as a first-line therapy. It is now the preferred first-line therapy for advanced HCC in patients with Child-Pugh class A liver function and no high-risk features for bleeding.

Second-Line Therapy for HCC

“It’s important to recognize that second-line therapy is used in a meaningful number of patients,” said Dr. Kelley. “Historically, I think we felt that patients with HCC were only able to receive one therapy before progression and death. But with modern therapies, we see a substantial number of patients who are proceeding to receive second and later lines of therapy.” Options for second-line therapy in HCC are listed in the NCCN Guidelines.

Second-line systemic therapies with level 1 evidence include regorafenib, which improved OS after progression on sorafenib,¹⁰ and cabozantinib, which improved OS in the second or third line after treatment with sorafenib.¹¹ Another agent to show improvement in survival over placebo was ramucirumab, which improved OS as second-line therapy after sorafenib in patients with an elevated alpha-fetoprotein (AFP) level ≥ 400 ng/mL.¹² “Importantly, this is the first biomarker-selected therapy for HCC that requires patients to have elevated AFP levels, which may be a biomarker for increased dependence on angiogenic therapies,” she said.

However, according to Dr. Kelley, second-line therapy in HCC still requires a great amount of research, because none of the approved agents have been studied after combination atezolizumab + bevacizumab in the first line. “All of these second-line therapies are based on data post-sorafenib, and the optimal sequence of these agents has not yet been established,” she noted.

A selection of ICIs (either as monotherapy or in combination) have received accelerated FDA approvals in the second-line setting based on earlier levels of data in phase I/II studies: nivolumab,¹³ pembrolizumab,¹⁴ and nivolumab in combination with the CTLA-4 inhibitor ipilimumab.¹⁵ She noted, however, that the role of ICI monotherapy after atezolizumab + bevacizumab is still unclear. “We do not yet have biomarkers of response to identify which patients are most likely to respond to one regimen over another,” she said.

What Lies Ahead?

A host of pivotal trials in HCC are ongoing, particularly in the first-line setting. According to Dr. Kelley, the 4 trials listed in Table 1 could change first-line standard-of-care options in HCC.

Studies of ICIs are also ongoing in the adjuvant setting in patients with Child-Pugh class A disease who are at high risk for HCC recurrence after resection or ablation (ClinicalTrials.gov identifiers: NCT03847428, NCT033-83458, NCT04102098, NCT03867084). Currently, there is no role for adjuvant therapy after resection or ablation in HCC.

“Lastly, an important point to look forward to in the field is the combination of ICIs with local therapies, such as transarterial chemoembolization [TACE], in intermediate-stage HCC,” she noted. “There are many ongoing randomized phase II or III trials looking at immunotherapy monotherapy or in combination with TACE versus TACE alone to determine if we can improve outcomes in the intermediate space” (NCT03778957, NCT04340193).

Systemic Therapy for Advanced BTCs

Until very recently, few systemic therapy options existed for BTC. Until 2019, gemcitabine + cisplatin (GEMCIS) was the only systemic therapy guideline recommendation supported by randomized clinical trial data, and no “Principles of Systemic Therapy” option was needed in the NCCN Guidelines until 2020, owing to the paucity of options. However, just like in HCC, substantial progress has been made in BTC over the past several years.

The ABC-02 trial established GEMCIS as the global standard of care, and it remains the preferred first-line regimen in advanced BTC.¹⁶ However, randomized phase III trials are ongoing in the first line, including SWOG 1815, which combines GEMCIS $\pm$ nab-paclitaxel (NCT037-68414), in addition to ongoing studies of a GEMCIS backbone with or without ICIs, and FGFR inhibition in *FGFR2* fusions.

In second-line BTC, leucovorin/fluorouracil/oxaliplatin (FOLFOX) is the preferred regimen, per results from the ABC-06 trial,¹⁷ but according to Dr. Kelley, finding more active therapies in second and later lines of therapy for BTC remains an area of unmet need. “Before 2019, we really had no established second-line therapy

Table 1. Ongoing Pivotal ICI + TKI/ICI Combination Trials for First-Line Advanced HCC

Combination Arm	Control Arm(s)	Design	Sample Size	Primary Endpoints	ClinicalTrials.gov Identifier
Pembrolizumab + lenvatinib	Lenvatinib	2-arm RP3	750	PFS, OS	NCT03713593
Cabozantinib + atezolizumab	Sorafenib or cabozantinib	3-arm RP3	740	PFS, OS	NCT03755791
Nivolumab + ipilimumab	Sorafenib or lenvatinib	2-arm RP3	650	OS	NCT04039607
Durvalumab ± tremelimumab	Sorafenib	3-arm RP3	1,504	OS	NCT03298451

Abbreviations: HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; RP3, randomized phase III trial; TKI, tyrosine kinase inhibitor.

after GEMCIS,” she noted. “FOLFOX was certainly an improvement compared with active supportive care, but also not aspirational in terms of where we’d like to be in the field.”

But where the field is really evolving, she said, is in looking beyond standard chemotherapy to new therapeutic targets in BTC. “As we learn more about the underlying biology of these tumors, we see that the biology according to anatomy varies quite substantially, and we can see different driver mutations according to the site of the tumor,” she explained. “I think this is the future of intrahepatic cholangiocarcinoma in particular, with its preponderance of targetable aberrations.” Multiple targeted therapy options are now available in the second line, including inhibitors of *FGFR2*, *IDH1*, *BRAF*, and *NTRK* in

patients harboring mutations, and pembrolizumab in patients with microsatellite instability–high/mismatch repair deficiency.¹⁸

“But the big challenge is that randomized trials/comparative data will always be limited by the very small sample sizes of these rare subpopulations,” she said, adding that tumor mutation profiling is now warranted to guide treatment decisions, particularly in patients with advanced or high-risk disease.

Disclosures: Dr. Kelley has disclosed serving as a scientific advisor for Exact Sciences, Genentech/Roche, and Merck; and receiving consulting fees from Gilead, Genentech/Roche, and Ipsen.

Correspondence: Robin Kate Kelley, MD, UCSF Helen Diller Family Comprehensive Cancer Center, 550 16th Street, Box 3211, San Francisco, CA 94143. Email: katie.kelley@ucsf.edu

References

- Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
- Saha SK, Zhu AX, Fuchs CS, et al. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. *Oncologist* 2016;21:594–599.
- Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–390.
- Kudo M, Finn RS, Qin S. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163–1173.
- Cancer Genome Atlas Research Network. Comprehensive and integrative genomic characterization of hepatocellular carcinoma. *Cell* 2017;169:1327–1341.e23.
- El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017;389:2492–2502.
- Yau T, Park JW, Finn RS, et al. CheckMate 459: a randomized, multi-center phase 3 study of nivolumab vs sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma. *Ann Oncol* 2019;30(Suppl 5):v851–934.
- Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020;382:1894–1905.
- Finn RS, Qin S, Ikeda M, et al. IMbrave150: updated overall survival data from a global, randomized, open-label phase III study of atezolizumab + bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma [abstract]. Presented at the 2021 Gastrointestinal Cancers Symposium; January 15–17, 2021. Abstract 267.
- Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;389:56–66.
- Abou-Alfa GK, Meyer T, Cheng A, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med* 2018;379:54–63.
- Zhu AX, Kang Y, Yen C, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α -fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019;20:282–296.
- El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017;389:2492–2502.
- Finn RS, Ryoo B, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol* 2020;38:193–202.
- Yau T, Kang Y, Kim T, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. *JAMA Oncol* 2020;6:e204564.
- Valle J, Wasan H, Palmer DH. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362:1273–1281.
- Lamarca A, Palmer DH, Wasan HS, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol* 2021;22:690–701.
- Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017;357:409–413.