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A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Non-Surgical Management of Advanced Hepatocellular Carcinoma

B.M. Meyers, J. Knox, R. Cosby, R. Beecroft, K. Chan, N. Coburn, J. Feld, D. Jonker, A. Mahmud, J. Ringash and the Gastrointestinal Disease Site Group

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For information about this document, please contact Brandon Meyers or Jennifer Knox, the lead authors, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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PUBLICATIONS RELATED TO THIS REPORT

1. Baldassarre FG, Baerlocher M, Beecroft R, Dawson L. Focal Tumour ablation: thermal ablation of hepatocellular carcinoma and metastases from colorectal carcinoma: evidence summary [Internet]. Cancer Care Ontario; 2014 Jul [cited 2014 Jul 28]. Available from: https://www.cancercare.on.ca/.

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Non-Surgical Management of Advanced Hepatocellular Carcinoma

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

The objective of this guideline is to make recommendations regarding the non-surgical treatment of advanced hepatocellular carcinoma (HCC).

TARGET POPULATION

These recommendations apply to adults with locally advanced and advanced HCC, Barcelona Clinic Liver Cancer Stage B and higher, who are not suitable for transplant or surgery.

INTENDED USERS

Intended users of the guideline are clinicians involved in the care of patients who have HCC; specifically, medical oncologists, radiation oncologists, interventional radiologists, hepatologists, and surgical oncologists.

RECOMMENDATIONS

Recommendation 1
• There is insufficient evidence for or against the use of TEA, TAE, RFA, TARE, SBRT, or DEB-TACE instead of TACE, which has been the conventional standard of care, in patients with intermediate-stage HCC or higher to improve survival. Decisions regarding treatment should be made on a case-by-case basis. Each case should be evaluated separately at a multidisciplinary cancer conference (MCC) that includes medical oncologists, radiation oncologists, surgical oncologists, hepatologists, and interventional radiologists. Short-term follow-up data indicate that TARE may result in less toxicity than TACE but longer-term follow-up data are not available.
Qualifying Statements for Recommendation 1
• For the treatment of intermediate-stage or greater HCC, treatment decisions will depend largely on Child-Pugh score, location of disease, volume of disease, and the number of lesions. • Typically, patients with early-stage disease not amenable to surgery may be treated with RFA or one of the other local/regional therapies. If that treatment fails, they may be treated with TACE for some of their lesions but may also be treated with other local/regional therapies for specific other lesions. • Failure to benefit from prior local/regional therapies should trigger early consideration of systemic treatments. • In addition, recent abstract data from the large international OPTIMIS [1] study show an improvement in overall survival (OS) for patients with an early start to sorafenib therapy at the time of meeting standard TACE ineligibility compared with no sorafenib at that time of TACE ineligibility. This study also demonstrates that in a real-world

experience, deviations from treatment guidelines for TACE and not starting sorafenib (systemic therapy) are common and detrimental. In addition, patient selection is extremely important for TACE. Comorbidities, liver function (beyond Childs Pugh A) and patient performance status (ex. ECOG) need to be thoroughly assessed.

- The decision to stop TACE and move on to systemic therapy can be challenging and should be made on a case-by-case basis at an MCC. Treating patients who were not responsive to TACE or are TACE ineligible may make them ineligible to benefit from systemic therapy.
- Further randomized data would be required to make more definitive statements about the use of local/regional therapies compared with TACE.

Recommendation 2

- There is insufficient evidence to support the addition of sorafenib to local/regional therapies to improve survival in patients with intermediate or higher stage HCC.

Qualifying Statements for Recommendation 2

- Following failure of local therapies, suitable patient (Child-Pugh A, Eastern Cooperative Oncology Group Performance Status [ECOG PS] 0-2) should be considered for treatment with systemic therapy.

Recommendation 3

- There are currently two tyrosine kinase inhibitors (sorafenib and lenvatinib) recommended as first-line single-agent systemic therapy that have survival benefits.
- There is no evidence to support the use of sorafenib or lenvatinib in combination with other agents with respect to objective outcomes (OS, objective response rate, toxicity) in patients with advanced HCC.

Qualifying Statements for Recommendation 3

- It should be noted that in the lenvatinib trial [2] patient inclusion criteria were stricter than in the SHARP [3] sorafenib trial with respect to performance status (ECOG PS 0-1 in the lenvatinib trial vs. ECOG PS 0-2 in SHARP) and main portal vein thrombosis (excluded in the lenvatinib trial vs. included in SHARP).
- Since the side effect profiles of sorafenib and levanitinib differ, it is conceivable that if a patient does not tolerate one drug in the first-line setting, they could be switched to the other drug prior to progression.
- A phase III trial of nivolumab vs. sorafenib (CheckMate 459) is ongoing and this recommendation should be revisited once the data from this trial are available.

Recommendation 4

- There are currently two tyrosine kinase inhibitors (regorafenib and cabozantinib) given as second-line therapy after sorafenib that have survival benefits and are treatment options for patients with advanced HCC with preserved liver function and who are otherwise well.

Qualifying Statements for Recommendation 4

- The modest survival benefit of these drugs needs to be weighed against the side effects incurred.
- For second-line therapy, the cabozantinib trial included patients who did not tolerate sorafenib, whereas in the regorafenib trial, patients were required to tolerate a minimum dose of 400 mg for ≥ 21/28 days previously. None of the second-line trials specifically address lenvatinib; however, for patients who progress on lenvatinib, either second-line agent is reasonable.
- Since the side effect profiles of regorafenib and cabozantinib differ, it is conceivable that if a patient does not tolerate one drug in the second-line setting, they could be switched to the other drug prior to progression.
- There are no data at this time to guide immunotherapy either before or following a tyrosine kinase inhibitor.
- There are no data on sequential tyrosine kinase inhibitors beyond second line.
- CheckMate 040 [4] is a non-comparative phase 1/2 dose escalation study and therefore not eligible for inclusion in the evidence for this guideline. However, in this trial nivolumab had a safety profile that was manageable and a promising response rate. Health Canada has approved the use of nivolumab as second-line treatment based on the response rate in this study. There is a Health Canada indication for nivolumab but it is not currently funded at present for those who are intolerant to sorafenib or who have progressed on sorafenib.
- This recommendation may need to be updated with respect to the use of ramucirumab in those with high alpha-fetoprotein levels once the REACH-2 trial data have been fully published.

Recommendation 5

- The treatment of hepatitis B virus (HBV) is recommended for patients with advanced HCC who are hepatitis B surface antigen positive as it prevents reactivation of HBV and progression of liver disease in general.
- There is no evidence for or against the eradication of hepatitis C virus (HCV) in patients with advanced HCC.

Qualifying Statements for Recommendation 5

- The data addressing the oncologic effects of treating HBV are weak and it is unlikely that there will be randomized data to address this issue in the future.
- In the Xu et al. [5] study, patients with *reactivated* HBV who received antiviral rescue therapy had significantly better survival than those who did not want rescue therapy (median OS, 23.7 months vs. 8.6 months; p=0.023).
- There are currently no ongoing trials to address the issue of the eradication of HCV in patients with advanced HCC.
- The evidence for the use of interferon to eradicate HCV in patients with HCC is confounded by its anti-tumour effects. It is impossible to parse out whether improvements in patients with HCC are owing to the eradication of HCV or directly owing to the anti-tumour effects.
- Interferon is no longer used to eradicate HCV. Direct-acting antivirals are now used.
- HCC patients who are HCV positive have better survival than HCC patients who are HBV positive when treated with sorafenib.
- It is unknown if there are survival differences in HCV and HBV populations when treated with TACE, TAE, or TEA.
- Patients who are HBV and/or HCV positive should be seen by a hepatologist or gastroenterologist to manage their underlying liver disease.

GLOSSARY

LOCAL THERAPIES

- RFA - radiofreqency ablation
- SBRT - stereotactic body radiation therapy
- TEA - transarterial ethanol ablation

REGIONAL THERAPIES

- cTACE – conventional transarterial chemoembolization
- DEB-TACE – drug eluting bead transarterial chemoembolization
- SIRT – selective internal radiation therapy (same as TARE)
- TAE - bland transarterial embolization
- TARE - transarterial radioembolization

DEFINITIONS (http://www.cancer.ca/en/cancer-information/cancer-type/liver/staging/?region=qc)

- Barcelona Clinic Liver Cancer (BCLC) Stage B (Intermediate Stage)
    - Child-Pugh A or B
    - Multifocal disease but tumours are not causing symptoms.
    - ECOG = 0

- Barcelona Clinic Liver Cancer (BCLC) Stage C (Advanced Stage)
    - Child-Pugh A or B
    - Tumour(s) have grown into blood vessels or there has been spread to other body sites. Tumour(s) are causing symptoms.
    - ECOG = 1 or 2

Non-Surgical Management of Advanced Hepatocellular Carcinoma

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

The objective of this guideline is to make recommendations regarding the non-surgical treatment of advanced hepatocellular carcinoma (HCC).

TARGET POPULATION

These recommendations apply to adults with locally advanced and advanced HCC, Barcelona Clinic Liver Cancer (BCLC) Stage B (intermediate stage) and higher, who are not suitable for transplant or surgery.

INTENDED USERS

Intended users of the guideline are clinicians involved in the care of patients who have HCC; specifically, medical oncologists, radiation oncologists, interventional radiologists, hepatologists, and surgical oncologists.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1
• There is insufficient evidence for or against the use of TEA, TAE, RFA, TARE, SBRT, or DEB-TACE instead of TACE, which has been the conventional standard of care, in patients with intermediate-stage HCC or higher to improve survival. Decisions regarding treatment should be made on a case-by-case basis. Each case should be evaluated separately at a multidisciplinary cancer conference (MCC) that includes medical oncologists, radiation oncologists, surgical oncologists, hepatologists, and interventional radiologists. Short-term follow-up data indicate that TARE may result in less toxicity than TACE but longer-term follow-up data are not available.
Qualifying Statements for Recommendation 1
• For the treatment of intermediate-stage or greater HCC, treatment decisions will depend largely on Child-Pugh score, location of disease, volume of disease, and the number of lesions. • Typically, patients with early-stage disease not amenable to surgery may be treated with RFA or one of the other local/regional therapies. If that treatment fails, they may be treated with TACE for some of their lesions but may also be treated with other local/regional therapies for specific other lesions. • Failure to benefit from prior local/regional therapies should trigger early consideration of systemic treatments. • In addition, recent abstract data from the large international OPTIMIS [1] study show an improvement in overall survival (OS) for patients with an early start to sorafenib therapy at the time of meeting standard TACE ineligibility compared with no sorafenib at that time of TACE ineligibility. This study also demonstrates that in a real-world experience, deviations from treatment guidelines for TACE and not starting sorafenib (systemic therapy) are common and detrimental. In addition, patient selection is extremely important for TACE. Comorbidities, liver function (beyond Childs Pugh A) and patient performance status (ex. ECOG) need to be thoroughly assessed.

- The decision to stop TACE and move on to systemic therapy can be challenging and should be made on a case-by-case basis at an MCC. Treating patients who were not responsive to TACE or are TACE ineligible may make them ineligible to benefit from systemic therapy.
- Further randomized data would be required to make more definitive statements about the use of local/regional therapies compared with TACE.

Key Evidence for Recommendation 1

- Overall, head-to-head comparisons of these local therapies with TACE are generally small and of moderate to poor quality.

Interpretation of Evidence for Recommendation 1

- There was agreement among the Working Group members that there was insufficient evidence regarding the use of alternative local or regional therapies instead of TACE.

Recommendation 2

- There is insufficient evidence to support the addition of sorafenib to local/regional therapies to improve survival in patients with intermediate or higher stage HCC.

Qualifying Statements for Recommendation 2

- Following failure of local therapies, suitable patient (Child-Pugh A, Eastern Cooperative Oncology Group Performance Status [ECOG PS] 0-2) should be considered for treatment with systemic therapy.

Key Evidence for Recommendation 2

- The evidence for the addition of sorafenib to local or regional therapies is either non-existent (TEA, TAE, and SBRT) or negative.
- No randomized data for the addition of sorafenib to TARE exist. Retrospective [6] and case-controlled [7] studies are quite small and contradictory.
- Survival was not affected by the addition of sorafenib to conventional TACE (p=0.790) [8].
- Survival was not affected by the addition of sorafenib to DEB-TACE in both the SPACE (hazard ratio [HR], 0.898; 95% confidence interval [CI], 0.606 to 1.330; p=0.295) [9] and TACE 2 (HR, 0.91; 95% CI, 0.67 to 1.24; p=0.57) [10] trials.

Interpretation of Evidence for Recommendation 2

- There was agreement among the Working Group members that the evidence was clear that the addition of sorafenib to local/regional therapies is not effective. This recommendation is generalizable to the entire target population.

Recommendation 3

- There are currently two tyrosine kinase inhibitors (sorafenib and lenvatinib) recommended as first-line single-agent systemic therapy that have survival benefits.
- There is no evidence to support the use of sorafenib or lenvatinib in combination with other agents with respect to objective outcomes (OS, objective response rate [ORR], toxicity) in patients with advanced HCC.

Qualifying Statements for Recommendation 3

- It should be noted that in the lenvatinib trial [2] patient inclusion criteria were stricter than in the SHARP [3] sorafenib trial with respect to performance status (ECOG PS 0-1 in the lenvatinib trial vs. ECOG PS 0-2 in SHARP) and main portal vein thrombosis (excluded in the lenvatinib trial vs. included in SHARP).
- Since the side effect profiles of sorafenib and levanitinib differ, it is conceivable that if a patient does not tolerate one drug in the first-line setting, they could be switched to the other drug prior to progression.
- A phase III trial of nivolumab vs. sorafenib (CheckMate 459) is ongoing and this recommendation should be revisited once the data from this trial are available.

Key Evidence for Recommendation 3

- Kudo et al. [2] demonstrated that lenvatinib is non-inferior to sorafenib with respect to survival (HR, 0.92; 95% CI, 0.79 to 1.06).
- The original sorafenib trial demonstrated that sorafenib is associated with longer median OS compared with placebo (HR, 0.69, 95% CI, 0.55 to 0.87, $p<0.001$) [3].

Interpretation of Evidence for Recommendation 3

- There was agreement among the Working Group members that the evidence regarding this recommendation is of high quality and high certainty. The use of sorafenib or lenvatinib as first-line treatment is associated with increased survival at the cost of incurred side effects. The benefits of using one of these two single agents outweigh the risks.
- Although the Working Group looked at survival, local control, quality of life, and toxicity, OS was considered to be the most important outcome. The Working Group was unanimous in their opinion that most patients would also value the increased survival benefit associated with the use of sorafenib or lenvatinib, although patient input was not sought.

Recommendation 4

- There are currently two tyrosine kinase inhibitors (regorafenib and cabozantinib) given as second-line therapy after sorafenib that have survival benefits and are treatment options for patients with advanced HCC with preserved liver function and who are otherwise well.

Qualifying Statements for Recommendation 4

- The modest survival benefit of these drugs needs to be weighed against the side effects incurred.
- For second-line therapy, the cabozantinib trial included patients who did not tolerate sorafenib, whereas in the regorafenib trial, patients were required to tolerate a minimum dose of 400 mg for ≥ 21/28 days previously. None of the second-line trials specifically address lenvatinib; however, for patients who progress on lenvatinib, either second-line agent is reasonable.
- Since the side effect profiles of regorafenib and cabozantinib differ, it is conceivable that if a patient does not tolerate one drug in the second-line setting, they could be switched to the other drug prior to progression.
- There are no data at this time to guide immunotherapy either before or following a tyrosine kinase inhibitor.
- There are no data on sequential tyrosine kinase inhibitors beyond second line.
- CheckMate 040 [4] is a non-comparative phase 1/2 dose escalation study and therefore not eligible for inclusion in the evidence for this guideline. However, in this trial nivolumab had a safety profile that was manageable and a promising response rate. Health Canada has approved the use of nivolumab as second-line treatment based on the response rate in this study. There is a Health Canada indication for nivolumab but it is not currently funded at present for those who are intolerant to sorafenib or who have progressed on sorafenib.
- This recommendation may need to be updated with respect to the use of ramucirumab in those with high alpha-fetoprotein (AFP) levels once the REACH-2 trial data have been fully published.

Key Evidence for Recommendation 4

- Regorafenib combined with best supportive care (BSC) had significantly better survival than placebo/BSC in the RESORCE trial (HR, 0.63; 95% CI, 0.50 to 0.79, p<0.0001) [11].
- Cabozantinib had significantly better survival than placebo in the CELESTIAL trial (HR, 0.76; 95% CI, 0.63 to 0.92; p=0.005) [12].

Interpretation of Evidence for Recommendation 4

- There was agreement among the Working Group members that the evidence regarding this recommendation is of high quality and high certainty. The use of using regorafinib or cabozantinib as second-line treatment is associated with increased survival at the cost of incurred side effects. The benefits of using one of these single agents outweigh the risks.
- Although the Working Group looked at survival, local control, quality of life, and toxicity, OS was considered to be the most important outcome. The Working Group was unanimous in their opinion that most patients would also value the increased survival benefit associated with the use of regorafenib or cabozantinib, although patient input was not sought.
- The evidence regarding regorafenib and cabozantinib is generalizable to the entire target population.

Recommendation 5

- The treatment of hepatitis B virus (HBV) is recommended for patients with advanced HCC who are hepatitis B surface antigen positive as it prevents reactivation of HBV and progression of liver disease in general.
- There is no evidence for or against the eradication of hepatitis C virus (HCV) in patients with advanced HCC.

Qualifying Statements for Recommendation 5

- The data addressing the oncologic effects of treating HBV are weak and it is unlikely that there will be randomized data to address this issue in the future.
- In the Xu et al. [5] study, patients with *reactivated* HBV who received antiviral rescue therapy had significantly better survival than those who did not want rescue therapy (median OS, 23.7 months vs. 8.6 months; p=0.023).
- There are currently no ongoing trials to address the issue of the eradication of HCV in patients with advanced HCC.
- The evidence for the use of interferon to eradicate HCV in patients with HCC is confounded by its anti-tumour effects. It is impossible to parse out whether improvements in patients with HCC are owing to the eradication of HCV or directly owing to the anti-tumour effects.
- Interferon is no longer used to eradicate HCV. Direct-acting antivirals are now used.
- HCC patients who are HCV positive have better survival than HCC patients who are HBV positive when treated with sorafenib.
- It is unknown if there are survival differences in HCV and HBV populations when treated with TACE, TAE, or TEA.
- Patients who are HBV and/or HCV positive should be seen by a hepatologist or gastroenterologist to manage their underlying liver disease.

Key Evidence for Recommendation 5

- In the Xu et al. [5] study, survival of patients with HBV was significantly better in those receiving antiviral treatment in addition to sorafenib compared with those receiving sorafenib alone (16.47 months vs. 13.10 months; p=0.03).
- Three studies [13-15] demonstrated that survival was significantly better in patients receiving HBV antiviral treatment in addition to TACE compared with those receiving TACE alone.

Interpretation of Evidence for Recommendation 5

- There was agreement among the Working Group members that the evidence regarding HBV is of high quality and high certainty. There is a lack of evidence regarding HCV.
- Although the Working Group looked at survival, local control, quality of life, and toxicity, OS was considered to be the most important outcome. The Working Group was unanimous in their opinion that most patients would also value the increased survival benefit associated with the eradication of HBV, although patient input was not sought.
- The evidence is generalizable to the entire target population.

FURTHER QUALIFYING STATEMENTS

None.

IMPLEMENTATION CONSIDERATIONS

The Working Group considered the recommendations provided above to be the ideal standard of care and would be feasible to implement. Furthermore, they may improve current health inequities by ensuring the same standards of care for all patients no matter where they are treated in Ontario. Thus, there is the potential for better outcomes for patients with HCC across the province. The recommendations would not require a significant change to the current system. The Working Group believed the outcomes valued in this guideline would align well with patient values and patients would view these recommendations as acceptable. Moreover, the Working Group believed that the interpretation of the evidence provided in this guidance document would align with the interpretation of most members of the clinical community.

RELATED GUIDELINES

- Baldassarre FG, Baerlocher M, Beecroft R, Dawson L. Focal tumour ablation: thermal ablation of hepatocellular carcinoma and metastases from colorectal carcinoma: evidence summary [Internet]. Cancer Care Ontario; 2014 Jul [cited 2014 Jul 28]. Available from: https://www.cancercare.on.ca/.

Non-Surgical Management of Advanced Hepatocellular Carcinoma

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

BACKGROUND FOR GUIDELINE

The current standard of practice for the treatment of advanced HCC, especially as it pertains to local treatments, varies according to hospital and local expertise. Furthermore, there has not been much head-to-head comparison of these techniques. The Gastrointestinal Disease Site Group (GI DSG) decided that a guideline to help standardize care across Ontario was warranted.

GUIDELINE DEVELOPERS

This guideline was developed by the GI DSG (Appendix 1). The project was led by a small Working Group of the GI DSG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology, radiation oncology, interventional radiology, hepatology, surgical oncology, and health research methodology. Other members of the GI DSG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 2, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [16,17]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [18] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine if an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.
- General databases: MEDLINE and EMBASE

The guideline search included guidelines published in 2013 and later. Practice guideline databases and guideline developer websites did not yield any relevant guidelines. The MEDLINE and EMBASE searches yielded 7987 hits in total of which 388 underwent full-text review; none were considered suitable for endorsement or adaptation. The guideline search strategy can be found in Appendix 3. A summary of these results of the guideline search can be found in Figure 4-1.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the DSG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other

potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS

The GI DSG would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Laurie Elit, Ted Hong, Donna Maziak, Sheila McNair, Morris Sherman, Emily Vella for providing feedback on draft versions.
- Jillian Sing for conducting a data audit.
- Sara Miller for copy editing.

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Section 4: Systematic Review

INTRODUCTION

The incidence of liver cancer has been steadily increasing in Canadian men and women between 1992 and 2013 [19]. Specifically, the incidence has increased by 3.1% and 2.1% in males and females, respectively. This rising incidence may partially be attributed to immigration from regions where exposure to liver cancer risk factors such as hepatitis B, hepatitis C, and aflatoxin are much more common [19]. The mortality from liver cancer has also been steadily increasing. Between 1992 and 2012, mortality increased by 2.8% in males and 1.7% in females in Canada [19]. HCC accounts for approximately 72% of all liver cancers in Canada. This disease is a global health problem, accounting for 5.6% of all new cancer cases and 9.1% of all cancer deaths worldwide in 2012 [20]. In Ontario in 2017, there was an estimated 970 new-incident cases of liver cancer (39.1% of the estimated new-incident liver cancer cases in Canada) and 520 deaths from liver cancer (42.6% of the estimated liver cancer deaths in Canada) [19]. The five-year age-standardized observed survival for 2006 to 2008 for liver cancer was 17% (95% CI, 16% to 19%) for males and females combined [19].

Resection and transplantation are the foundations for cure for HCC; however, most patients are diagnosed at an advanced stage precluding these curative treatments. Non-curative treatments are usually TACE and, in the case of advanced disease, sorafenib. Other treatments are available but their efficacy compared with TACE and sorafenib are not well known. The purpose of this guideline is to review the current evidence for all treatment options for advanced, unresectable HCC.

The Working Group of the GI DSG developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTION(S)

This guidance document examined the evidence to answer the following questions in patients with locally advanced or advanced HCC (BCLC Stage B or higher):

1) What are benefits of other local therapies (transarterial ethanol ablation [TEA], bland transarterial embolization [TAE], radiofrequency ablation [RFA], transarterial radioembolization [TARE], stereotactic body radiation therapy [SBRT] and drug eluting bead transarterial chemoembolization [DEB-TACE]) versus transarterial chemoembolization (TACE)?

2) What is the benefit of the addition of sorafenib to local therapies (TEA, TAE, RFA, TARE, SBRT, TACE, DEB-TACE)?

3) What is the benefit of other systemic treatment regimens versus sorafenib?

4) What is the benefit of the eradication of viral hepatitis (HCV and/or HBV) in patients with advanced HCC?

5) What is the benefit of second-line systemic therapy following sorafenib?

6) Is there a survival difference in HCV populations compared with HBV populations compared with non-viral populations when treated with sorafenib?

7) Is there a survival difference in HCV populations compared with HBV populations compared with non-viral populations when treated with TACE, TAE, or TEA?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews.

- Databases searched: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews
- Years covered for Question 1 – 2000 to present
- Years covered for Question 2 to Question 7 – 2005 to present
- Search terms: See Appendix 3
- Selection criteria: English-language systematic review that covered any of the current guideline questions.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) [21] tool to determine whether or not existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base.

Search for Primary Literature

A relevant systematic review was available for the TARE versus TACE part of Question 1 and one relevant systematic review was available for Question 6. A search for primary studies was undertaken from the point in time at which this systematic review was ended until July 2018 in MEDLINE and EMBASE. The newer relevant primary studies are included for this question.

No relevant systematic review was available for all the other comparisons in Question 1 or for any of the other questions. Therefore, a search for primary studies was undertaken. If more than one publication was available for a given trial only the most recent publication was included.

Literature Search Strategy

Please see Appendix 3 for the primary literature search strategy for each question. The MEDLINE and EMBASE databases were searched from 2000 to July 2018 for Question 1 and from 2005 to July 2018 for Questions 2 through 7. In addition abstracts from ASCO 2018 were searched for relevant studies.

Study Selection Criteria and Process

Question 1 - What are benefits of other local therapies (transarterial ethanol ablation [TEA], bland transarterial embolization [TAE], radiofrequency ablation [RFA], transarterial radioembolization [TARE], stereotactic body radiation therapy [SBRT] and drug eluting bead transarterial chemoembolization [DEB-TACE]) versus transarterial chemoembolization (TACE)?

Inclusion Criteria
- English language
- Adult patients with locally advanced or advanced HCC at BCLC Stage B (intermediate stage) or higher who are not suitable for transplant or surgery
- Includes a comparison of interest:
    - TEA vs. TACE
    - TAE vs. TACE
    - RFA vs. TACE
    - TARE vs. TACE
    - SBRT vs. TACE
    - DEB-TACE vs. TACE
- Includes at least one outcome of interest (OS, local control, progression-free survival [PFS], quality of life [QOL], toxicity)
- Randomized controlled trials (RCTs) (if available). If RCTs not available, other comparative studies
- N=30 minimally

Exclusion Criteria
- Case studies, commentaries, editorials

Question 2 - What is the benefit of the addition of sorafenib to local therapies (TEA, TAE, RFA, TARE, SBRT, TACE, DEB-TACE)?

Inclusion Criteria
- English language
- Adult patients with locally advanced or advanced HCC at BCLC Stage B (intermediate stage) or higher who are not suitable for transplant or surgery
- Includes a comparison of interest:
    - TEA + Sorafenib vs. TEA
    - TAE + Sorafenib vs. TAE
    - RFA + Sorafenib vs. RFA
    - TARE + Sorafenib vs. TARE
    - SBRT + Sorafenib vs. SBRT
    - TACE + Sorafenib vs. TACE
    - DEB-TACE + Sorafenib vs. DEB-TACE
- Includes at least one outcome of interest (OS, local control, PFS, QOL, toxicity)
- RCTs (if available). If RCTs not available, other comparative studies
- N=30 minimally

Exclusion Criteria
- Case studies, commentaries, editorials

Question 3 - What is the benefit of other systemic treatment regimens versus sorafenib?

Inclusion Criteria
- English language
- Adult patients with locally advanced or advanced HCC at BCLC Stage B (intermediate stage) or higher who are not suitable for transplant or surgery or standard evidence-based locoregional therapies
- Comparison of other systemic therapy to sorafenib
- Includes at least one outcome of interest (OS, local control, PFS, QOL, toxicity)
- Randomized trials in which N=30 minimally

Exclusion Criteria
- Case studies, commentaries, editorials

Question 4 - What is the benefit of the eradication of viral hepatitis (HCV and/or HBV) in patients with advanced HCC?

Inclusion Criteria
- English language
- Adult patients with locally advanced or advanced HCC at BCLC Stage B (intermediate stage) or higher who are not suitable for transplant
- Comparison of treating viral infection vs. not treating viral infection
- Includes at least one outcome of interest (OS, local control, PFS, QOL, toxicity)
- Comparative studies in which N=30 minimally

Exclusion Criteria
- Case studies, commentaries, editorials

Question 5 - What is the benefit of second-line systemic therapy following sorafenib?

Inclusion Criteria
- English language
- Adult patients with locally advanced or advanced HCC at BCLC Stage B (intermediate stage) or higher who are not suitable for transplant or surgery and who have failed, either by progression or intolerance, first-line therapy with sorafenib
- Second-line systemic treatment vs. no second-line systemic treatment
- Includes at least one outcome of interest (OS, local control, PFS, QOL, toxicity)
- Randomized controlled trials in which N=30 minimally

Exclusion Criteria
- Case studies, commentaries, editorials

Question 6 - Is there a survival difference in HCV populations compared with HBV populations compared with non-viral populations when treated with sorafenib?

Inclusion Criteria
- English language
- Adult patients with locally advanced or advanced HCC at BCLC Stage B (intermediate stage) or higher with HCV or HBV and who have undergone systemic therapy with sorafenib
- HBV patients vs. HCV patients vs. non-viral patients
- Includes at least one outcome of interest (OS)
- RCTs or subgroup analyses within randomized trials in which N=30 minimally

Exclusion Criteria
- Case studies, commentaries, editorials

Question 7 - Is there a survival difference in HCV populations compared with HBV populations compared with non-viral populations when treated with TACE, TAE, or TEA?

Inclusion Criteria
- English language
- Adult patients with locally advanced or advanced HCC at BCLC Stage B (intermediate stage) or higher with HCV or HBV and who have been treated with TACE, TAE, or TEA.
- Second-line systemic treatment vs. no second-line systemic treatment
- HBV patients vs. HCV patients vs. non-viral patients
- Includes at least one outcome of interest (OS)
- RCTs or subgroup analyses within randomized trials in which N=30 minimally.

Exclusion Criteria
- Case studies, commentaries, editorials

A review of the titles and abstracts that resulted from the search was independently conducted by one reviewer (RC). For those items that warranted full-text review, one reviewer reviewed each item (RC) for all questions. If there was any question regarding eligibility of a given study, two reviewers (RC and BMM) reviewed each item in collaboration.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data from the included systematic review and primary studies were extracted by one member of the Working Group (RC). All extracted data and information were subsequently audited by an independent auditor.

RCTs were assessed for quality and potential bias using the Cochrane Risk of Bias tool (chapter 8.5) (http://handbook.cochrane.org/) and all non-RCTs were assessed using the Cochrane Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) tool (https://sites.google.com/site/riskofbiastool/). Systematic reviews were evaluated using the AMSTAR tool [21].

Ratios, including hazard ratios (HR), were expressed with a ratio <1.0 indicating that the intervention was numerically greater than the control on that particular variable. This may or may not indicate statistical significance.

Synthesizing the Evidence

Meta-analyses were not conducted. There were not enough studies in any given question or part of a question to warrant the use of meta-analysis.

RESULTS

Search for Existing Systematic Reviews

A search for systematic reviews uncovered 5423 documents. Of these, 374 underwent full-text review and two [22,23] were retained (Table 4-1).

Search for Primary Literature

A search for primary literature was conducted for all questions. For the TARE versus TACE part of Question 1 and for Question 6, the literature search was an update from where the systematic review left off.

Literature Search Results

For the individual study literature search there were 37,645 hits. Of these, 863 underwent a full-text review and 72 were retained. Included in this search was one relevant pooled analysis, which was retained. For a summary of the full literature search results (including guidelines and systematic reviews), please refer to Figure 4-1, which is a flow diagram depicting the inclusion and exclusion of all studies for this guidance document. A summary of all included studies can be found in Table 4-1.

Figure 4-1. Literature search results flow diagram.

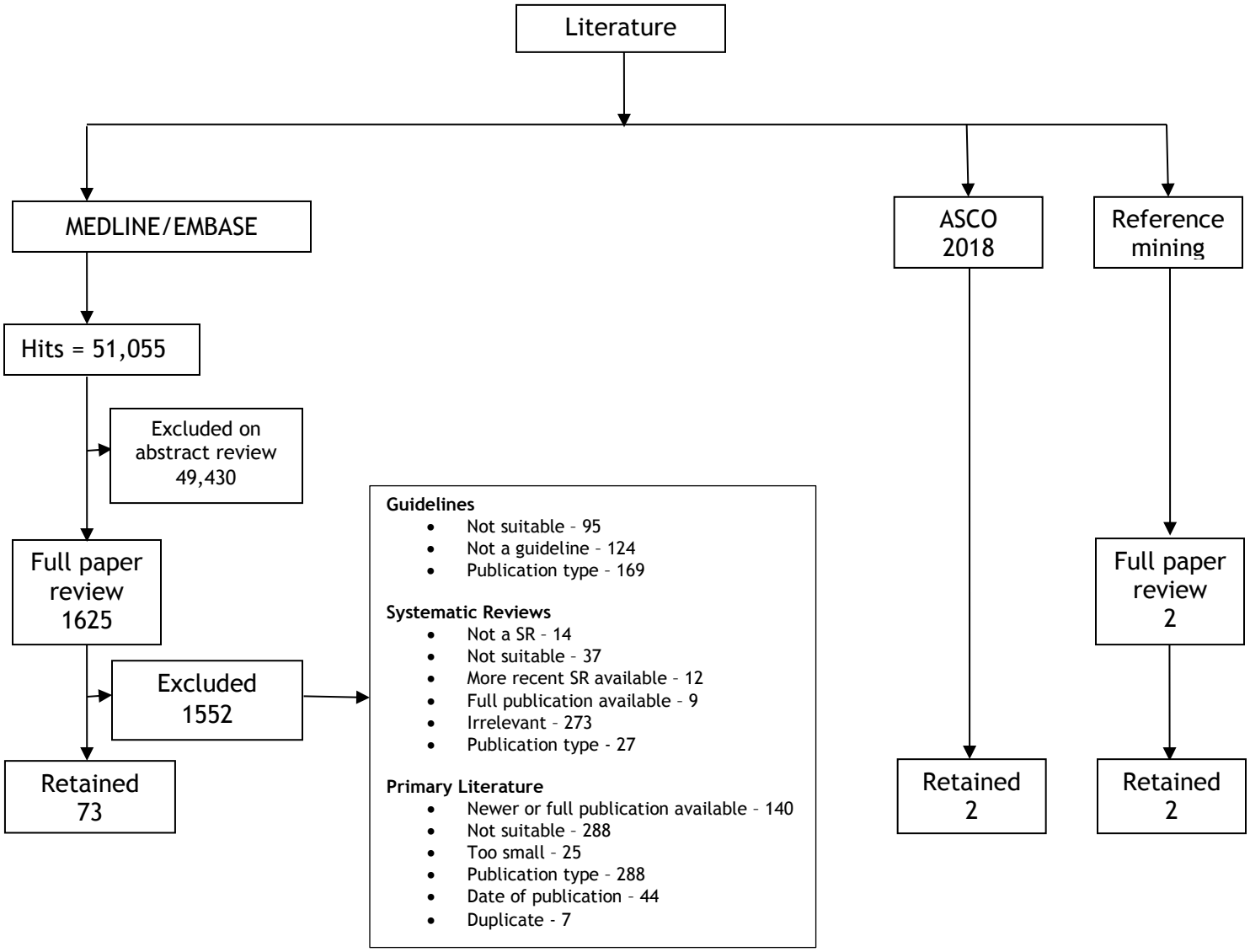

Table 4-1. Studies selected for inclusion.

QUESTION	GLs[a]	SRs	PRIMARY STUDIES					REFERENCES
	GLs RETAINED	SRs RETAINED	HITS	FULL-TEXT REVIEW	STUDIES RETAINED	ASCO 2018	REFERENCE MINING	
Q1 – Local Therapy vs. TACE			12551					
• TEA vs. TACE	0	0		2	1	0	0	25
• TAE vs. TACE	0	0		21	4	0	0	26–29
• RFA vs. TACE	0	0		23	2	0	0	79,80
• TARE vs. TACE	0	1		60	2	0	0	22,81,82
• SBRT vs. TACE	0	0		11	0	0	0	NA
• DEB-TACE vs. TACE	0	0		83	4	0	0	30-33
• Other	0	0		11	0	0	0	NA
Q2 – Local Therapy + Sor vs. Local Therapy			2426					
• TEA + Sor vs. TEA	0	0		0	0	0	0	NA
• TAE + Sor vs. TAE	0	0		0	0	0	0	NA
• RFA + Sor vs. RFA	0	0		7	1	0	0	34
• TARE + Sor vs. TARE	0	0		23	2	0	0	6,7
• SBRT + Sor vs. SBRT	0	0		6	0	0	0	NA
• TACE + Sor vs. TACE	0	0		121	3	1	0	8,35-37
• DEB-TACE + Sor vs. DEB-TACE	0	0		22	2	0	0	9,10
• Other	0	0		12	0	0	0	NA
Q3 – Sor vs. other systemic therapy /	0	0	8373	178	23	0	0	2,38-59
Q5 – Second-line systemic therapy after Sor	0	0			18	1	1	11,12,61-78
Q4 – Eradication of HCV/HBV	0	0	10225	209	7	0	1	5,13-15,60,83-85
Q6 – Survival difference in HCV/HBV after Sor	0	1	1525	45	1[b]	0	0	23,24
Q7 – Survival difference in HCV/HBV after TACE, TAE, or TEA	0	0	2545	29	1	0	0	86

[a]See Section 3

[b]One pooled analysis

Abbreviations: DEB-TACE=drug eluting bead transarterial chemoembolization; GL=guideline; HBV=hepatitis B virus; HCV=hepatitis C virus; NA=not applicable; RFA=radiofrequency ablation; SBRT=stereotactic body radiation therapy; Sor=sorafenib; SR=systematic review; TACE=transarterial chemoembolization; TAE=bland transarterial embolization; TARE=transarterial radioembolization; TEA=transarterial ethanol ablation.

Study Design and Quality

Various study designs are included in this guidance document. All systematic reviews were assessed using AMSTAR [21] (see Table 4-2). RCTs were assessed using the Cochrane Risk of Bias tool (chapter 8.5) (http://handbook.cochrane.org/) (see Table 4-3) and all non-RCTs were assessed using Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) tool (https://sites.google.com/site/riskofbiastool/) (see Table 4-4).

Systematic Reviews

All systematic reviews used in this guidance document were assessed using the AMSTAR tool [21]. Two systematic reviews and one pooled analysis were evaluated. One systematic review scored well [22]. The other systematic review [23] did not score as well. It is difficult to determine whether the items scored as 'no' were simply a matter of not reporting that information in the manuscript. The Jackson et al. [24] individual patient data pooled analysis did not score well on the AMSTAR tool as it is not actually a systematic review. Therefore, several of the AMSTAR items are not applicable to this type of study (Table 4-2).

Table 4-2. Evaluation of included systematic reviews using AMSTAR.

ITEM	Lobo et al. 2016 [22]	Shao et al. 2015 [23]	Jackson et al. 2017 [24]
1. Was an 'a priori' design provided?	Y	Y	Y
2. Was there duplicate study selection and data extraction?	Y	Y	NA
3. Was a comprehensive literature search performed?	Y	N	NA
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	N	N	NA
5. Was a list of studies (included and excluded) provided?	N	N	N
6. Were the characteristics of the included studies provided?	Y	Y	Y
7. Was the scientific quality of the included studies assessed and documented?	Y	N	Y
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	N	N
9. Were the methods used to combine the findings of the studies appropriate?	Y	Y	Y
10. Was the likelihood of publication bias assessed?	Y	N	N
11. Was the conflict of interest stated?	Y	Y	Y
TOTAL AMSTAR POINTS	9	5	5

Abbreviations: N=no; NA=not applicable; Y=yes

Randomized Controlled Trials

Forty-seven RCTs published in 62 manuscripts [2,8-13,15,25-78] were included in this guidance document and were assessed using Cochrane's Risk of Bias tool (chapter 8.5) (http://handbook.cochrane.org/) (Table 4-3). Many of the included RCTs could not be assessed on at least one element of the risk of bias tool as the information needed was not discussed in the publication. This was particularly evident in abstracts, which have only a very limited amount of information reported. These items were therefore rated as 'unclear'. Overall, there were only five RCTs: REACH [62], Bruix et al. [11], Santoro et al. [75], Rimassa et al. [76] and Abou-Alfa et al. [12] that scored 'low' on all domains and could undoubtedly be classified as having a low risk of bias. Twenty-four RCTs [9,10,12,13,15,27,28,34-36,44,46,47,49-51,53,54,57,59,61,68,74,77,78] were considered to have an unclear risk of bias as at least one of the domains was rated as 'unclear'. It is conceivable that either this is a reporting issue or that this is both a reporting and methodological issue, resulting in an unknown risk of bias. Therefore, these studies are given the overall evaluation of 'unclear' risk of bias. Eighteen RCTs [2,8,25,26,29-33,37,38,43,45,48,52,55,56,58,60] were considered to have a serious risk of bias because one domain was rated as 'high'. In 17 of these trials this was owing to a lack of blinding of participants and personnel and in one case this evaluation was owing to a lack of blinding of the outcome assessment (Table 4-3).

Non-Randomized Controlled Studies

This guidance document includes 12 non-RCTs [5-7,14,79-86] that were each assessed using Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) tool (https://sites.google.com/site/riskofbiastool/). This tool assesses each trial on seven domains of bias (Table 4-4) as well as an overall assessment of risk of bias. Two of the studies were only available in abstract form and therefore were assessed as 'no information' as there was not enough information in the abstracts to evaluate risk of bias [6,7]. Seven of the studies [6,7,14,81,82,85,86] did not report on their funding. Overall, each included non-randomized study (that was not in abstract form) was assessed as having a moderate risk of bias.

Table 4-3: Evaluation of included randomized controlled trials using Cochrane's Risk of Bias tool.

Question	Comparison	Study	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
			Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Sources of Bias
Local Therapy vs. TACE	TEA vs. TACE	Yu 2014 [25]	Low	Low	High	Low	Low	Low	Low
	TAE vs. TACE	Llovet 2002 [26]	Low	Low	High	Unclear	Low	Low	Low
		Meyer 2013 [27]	Unclear	Low	Unclear	Unclear	Low	Low	Low
	TAE vs. DEB-TACE	Malagari 2010 [28]	Unclear	Low	Unclear	Unclear	Low	Low	Low
		Brown 2016 [29]	Low	Low	High	Low	Low	Low	Low
	DEB-TACE vs. TACE	PRECISION V 2010/2011 [30,31]	Low	Low	High	Low	Low	Low	Low
		van Malenstein 2011 [32]	Unclear	Unclear	High	Unclear	Low	Low	Low
		Golfieri 2014 [33]	Low	Low	High	Unclear	Low	Low	Low
Local Therapy + Sorafenib vs. Local Therapy	RFA + Sor vs. RFA alone	Kan 2015 [34]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
	TACE + Sor vs. TACE alone	Kudo 2011 [8]	Unclear	Unclear	Unclear	High	Low	Low	Low
		Sansonno 2012 [35]	Unclear	Low	Low	Unclear	Low	Low	Low
		Kudo 2018 [36]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
		Park 2018 [37]	Unclear	Unclear	High	Unclear	Unclear	Low	Unclear
	DEB –TACE + Sor vs. DEB-TACE alone	SPACE Trial 2016 [9]	Unclear	Unclear	Low	Unclear	Low	Low	Low
		TACE2 2017 [10]	Low	Low	Low	Unclear	Low	Low	Low
First-Line Sorafenib vs. other systemic therapy	Lifinanib vs. Sor	Cainap 2015 [38]	Unclear	Unclear	High	Unclear	Low	Low	Low
	Lenvatinib vs. Sor	Kudo 2018 [2], Han 2017 [39], Vogel 2017 [40-42]	Low	Low	High	Unclear	Low	Low	Low
	Sunitinib vs. Sor	Cheng 2013 [43]	Unclear	Low	High	Unclear	Low	Low	Low
	Nintedanib vs. Sor	Yen 2018 [44]	Low	Low	Unclear	Unclear	Low	Low	Low
		Palmer 2015 [45]	Unclear	Unclear	High	Unclear	Unclear	Low	Unclear
	Brivanib vs. Sor	BRISK-FL 2013 [46]	Unclear	Low	Low	Unclear	Low	Low	Low
	Capecitabine vs. Sor	Wahab 2012 [47]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
	Doxorubicin + Sor vs. Sor	Soradox 2015 [48]	Unclear	Unclear	High	Unclear	Unclear	Low	Unclear
		Abou-Alfa 2016 [49]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
	GEMOX + Sor vs. Sor	GONEXT 2013a,b [50,51]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
	Tigatuzumab +Sor vs. Sor	Cheng et al. 2015 [52]	Low	Low	High	Unclear	Low	Low	Low
	MAP + Sor vs. Sor + Pbo	Ciuleanu 2016 [53]	Unclear	Unclear	Low	Low	Low	Low	Low
	Everolimus + Sor vs. Sor	Koeberle 2016 [54]	Unclear	Unclear	Low	Low	Low	Low	Low
	AEG35156 + Sor vs. Sor	Lee 2016 [55]	Unclear	Unclear	High	Unclear	Low	Low	Low
	BEV + Erlotinib vs. Sor	Thomas 2018 [56]	Unclear	Unclear	High	Unclear	High	Low	Low
	Erlotinib + Sor vs. Sor	SEARCH 2015 [57]	Low	Low	Low	Unclear	Low	Low	Low
	Pravastatin + Sor vs. Sor	PRODIGE 21 2018 [58]	Unclear	Unclear	High	Unclear	Low	High	Unclear
	Resminostat + Sor vs. Sor	Kudo 2017 [59]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Eradication of Viral Hepatitis	HBV – TACE ± Antiviral Therapy	Jang 2006 [60]	Low	Unclear	High	Unclear	Low	Low	Low
		Li 2009 [13]	Low	Low	Unclear	Unclear	Low	Low	Low
		Xu 2014 [15]	Low	Unclear	Unclear	Unclear	Low	Low	Low

Second-Line Systemic Therapy following Sorafenib	ADI-PEG 20+BSC vs. Pbo+BSC	Abou-Alfa 2018 [61]	Unclear	Unclear	Low	Unclear	Low	High	Low
	RAM + BSC vs. Pbo + BSC	REACH [62-67]	Low	Low	Low	Low	Low	Low	Low
		REACH-2 [68]	Unclear	Unclear	Low	Unclear	Unclear	Low	Low
	Regorafinib +BSC vs Pbo+BSC	RESORCE [11,69-71]	Low	Low	Low	Low	Low	Low	Low
	Cabozantinib vs. Pbo	Abou-Alfa 2018 [12]	Low	Low	Low	Unclear	Low	Low	Low
	S-1 vs. Pbo	S-CUBE 2016, 2017 [72,73]	Low	Low	Low	Low	Low	Low	Low
	BRIV + BSC vs. Pbo + BSC	BRISK-PS 2013 [74]	Unclear	Low	Low	Unclear	Low	Low	Low
	Tivantinib vs. Pbo	Santoro 2013 [75]	Low	Low	Low	Low	Low	Low	Low
		Rimassa 2018 [76]	Low	Low	Low	Low	Low	Low	Low
	RO5137382/GC33 vs. Pbo	Yen 2014 [77]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
	Everolimus+BSC vs. Pbo +BSC	Zhu 2014 [78]	Low	Low	Low	Unclear	Low	Low	Low

Abbreviations: BEV=bevacizumab; BRIV= brivanib; BSC=best supportive care; DEB-TACE=drug eluting bead transarterial chemoembolization; GEMOX=gemcitabine + oxsaliplatin; HBV=hepatitis B virus; MAP=mapatumumab; RAM=ramucirumab; RFA=radiofrequency ablation; SBRT=stereotactic body radiation therapy; Sor=sorafenib; TACE=transarterial chemoembolization; TAE=bland transarterial embolization; TARE=transarterial radioembolization; TEA=transarterial ethanol ablation.

Table 4-4: Evaluation of included non-randomized controlled studies using Cochrane's Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ROBINS-I).

Question	Comparison	Study	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Funding[b]	Overall
Local Therapy vs. TACE	RFA vs. TACE	Chok 2006 [79]	Mod	Low	Low	Low	Low	See below[b]	Low	Low	Mod
		Nouso 2017 [80]	Mod	NI	Low	Low	Low	See below[b]	Low	Low	Mod
	TARE vs. TACE	Soydal 2016 [81]	Mod	Low	Low	Low	Low	See below[b]	Low	NI	Mod
	TARE vs. DEB-TACE	Akinwande 2016 [82]	Mod	Low	Low	Low	Low	See below[b]	Low	NI	Mod
Local Therapy + Sorafenib vs. Local Therapy	TARE + Sor vs. TARE alone	Ma 2014 [6]	NI	Low	Low	NI	NI	See below[b]	NI	NI	NI
		Maccauro 2014 [7]	NI	NI	Low	NI	NI	See below[b]	Low	NI	NI
Eradication of Viral Hepatitis	HCV – TACE ± Antiviral Therapy	Yu 2018 [83]	Mod	Mod	Low	Low	Low	See below[b]	NI	Low	Mod
	HBV – Sor ± Antiviral Therapy	Xu 2015 [5]	Mod	Low	Low	Low	Low	See below[b]	Low	Low	Mod
		Yang 2015 [84]	Mod	Low	Low	Low	Low	See below[b]	Low	Low	Mod
	HBV – TACE ± Antiviral Therapy	Toyoda 2012 [14]	Mod	Low	Low	Low	Low	See below[b]	Low	NI	Mod
		Zhou 2015 [85]	Mod	Low	Low	Low	Low	See below[b]	Low	NI	Mod
Survival Difference in HCV, HBV and non-viral populations when treated with TACE, TAE or TEA	HBV vs. HCV vs. HBV + HCV vs. no viral hepatitis	Chen 2014 [86]	Mod	Low	Low	Low	Low	See below[b]	Low	NI	Mod

Abbreviations: DEB-TACE=drug eluting bead transarterial chemoembolization; HBV=hepatitis B virus; HCV=hepatitis C virus; Mod=moderate; NI=no information; Sor=sorafenib; TACE=transarterial chemoembolization; TAE=bland transarterial embolization; TARE=transarterial radioembolization; TEA=transarterial ethanol ablation

[a]Low risk for mortality and survival; No information for other outcomes

[b]Low risk = non-industry funding.

Outcomes

Question 1: What are benefits of other local therapies (TEA, TAE, RFA, TARE, SBRT, and DEB-TACE) versus TACE?

TEA vs. TACE

One RCT comparing TEA to TACE was retained [25]. It was terminated early for futility after an interim analysis of the first 98 patients enrolled. OS was not significantly different between the TEA and TACE study arms (24.3 months vs. 20.1 months; p=0.513). Time to progression (TTP) and PFS were also similar between the study arms (p=0.128 and p=0.16, respectively). With respect to treatment-related toxicity, fever occurred more in the TEA arm (p=0.017) whereas vomiting occurred more in the TACE arm (p=0.001). Within 12 months of randomization, tumour response (complete responses and partial responses) were not significantly different between the two treatment arms.

TAE vs. TACE

Two small RCTs comparing TAE to TACE were retained [26,27]. One study was stopped early for futility [26] and one study was stopped early for slow accrual [27]. OS was not significantly different between the TAE and TACE study arms in either of the two trials. PFS was reported in the two trials and there was no significant difference between the study arms. Grade 3/4 toxicity was significantly better in the TAE arm of only one study [27]. QOL was only reported on in one study [27] and there was no significant difference between the arms (Table 4-5).

TAE vs. DEB-TACE

Two RCTs comparing TAE to DEB-TACE were retained [28,29]. TTP was only reported in one study [28] and was significantly longer in the DEB-TACE arm (9.05 vs. 10.6 months; p=0.008). ORR was also significantly better in DEB-TACE arm but only at nine months' follow-up in the Malagari et al. trial [28] (Table 4-5). The difference was gone by 12 months. ORR was not significantly different in the two arms of the Brown et al. [29] trial.

RFA vs. TACE

No RCTs comparing RFA to TACE were found. In the absence of any RCT data, two retrospective studies were retained [79,80]. Chok et al. [79] conducted a small, single-centre study of 91 participants. One- and two-year OS was similar between the study arms (p=0.21). Median TTP in the RFA and TACE arms was also similar (10.4 months vs. 9.5 months; p=0.95). Patients treated with RFA had a significantly higher complication rate than those treated with TACE (28% vs. 10%; p=0.04). Nouso et al. [80] conducted a study in two hospitals in Japan (N=167). OS was significantly longer in the RFA arm compared with the TACE arm (p<0.001); however, the participants in the two study arms were not equivalent. Those in the RFA arm had significantly fewer tumours, smaller tumours, and earlier BCLC B stage (i.e., more BSLC B1 and B2 vs. B3). After propensity score matching, the difference in OS was not maintained (p=0.067) [80].

TARE vs. TACE

One systematic review that included five retrospective studies was retained [22]. In addition, one retrospective study published after the search date for the systematic review was retained [81]. In the Lobo et al. [22] systematic review, there was no difference in OS up to four years (HR, 1.06; 95% CI, 0.81 to 1.46; p=0.567). Soydal et al. [81] also found no survival difference in the TARE and TACE arms. There was no difference in ORR between

study arms in either of these papers [22,81]. There were no differences in toxicity in any of the papers except for significantly less pain and less fatigue in the TARE arm (both $p<0.01$) in the systematic review [22] (Table 4-6).

TARE vs. DEB-TACE

One retrospective study of TARE versus DEB-TACE was retained [82]. Akinwande et al. [82] includes both a pooled cohort analysis as well as a matched cohort analysis (see Table 4-6). These authors report significantly better median OS in the DEB-TACE arm in both the pooled cohort and the matched cohort analyses. There were no significant differences between the study arms with respect to ORR or toxicity (Table 4-6).

SBRT vs. TACE

No studies comparing SBRT to TACE were found.

DEB-TACE vs. TACE

Three RCTs in four papers comparing DEB-TACE to conventional TACE (cTACE) were retained [30-33]. There were no significant differences between the two types of TACE for survival [33], TTP [33], or ORR at six months post intervention [30,33]. All of these trials reported toxicity results. PRECISION V reported toxicity results in a separate publication [31]. There were no significant differences between the study arms for most toxicities and serious adverse events (SAEs). One exception was liver enzyme levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), which were significantly more elevated in cTACE than DEB-TACE in the two studies that reported on this outcome [31,32]. The PRECISION V study authors [31] also report a small but significant drop in left ventricular ejection fraction in the cTACE compared with DEB-TACE.

Table 4-5. Outcomes from included studies regarding TAE versus TACE.

STUDY	DESIGN	TREATMENT ALLOCATION	N	OS (months)	PFS (months)	TTP (months)	ORR N (%)	TOXICITY N (%)	QOL	TERMINATED EARLY
TAE versus TACE										
Llovet 2002 [26]	RCT	TAE TACE Control	37 40 35	25.3 28.7 17.9 TAE vs. TACE =NR	NR	NR	16 (43) 14 (35) NR TAE vs. TACE =NR	7 (19) 11 (28) NR TAE vs. TACE =NR	NR	Yes, for futility
Meyer 2013 [27]	RCT	TAE sTACE	42 44	17.3 16.3 p=ns	7.2 7.5 p=ns	NR	9 (23.7) 18 (41.9) p=ns per protocol	Grade 3/4 NR (63.5) NR (83.7) p=0.019	p=ns for all scales	Yes, for slow accrual
TAE versus DEB-TACE										
Brown 2016 [29]	RCT	TAE DEB-TACE	51 50	19.6 20.8 p=ns	6.2 2.8 p=ns	NR	3 (5.9) 3 (6.0) p=ns	p=ns on all measures	NR	No
Malagari 2010 [28]	RCT	TAE DEB-TACE	41 43	NR NR p=ns	NR	9.05 10.6 p=0.008	At 9 months 13 (31.7) 22 (55) p=0.04	NR NR p=ns	NR	No

Abbreviations: DEB-TACE=drug eluting bead transarterial chemoembolization; NR=not reported; ns=not signficant; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QOL=quality of life; RCT=randomized controlled trial; sTACE=sequential TACE; TACE=transarterial chemoembolization; TAE=bland transarterial embolization; TTP=time to progression

Table 4-6. Outcomes from included studies regarding TARE versus TACE.

STUDY	DESIGN	TREATMENT ALLOCATION	N	OS (months)	PFS (months)	TTP (months)	ORR N(%)	TOXICITY N (%)	QOL
TARE versus TACE									
Lobo 2016 [22]	SR (5 retro studies)	TARE TACE	269 284	Up to 4 years NR NR (HR; 1.06, 95% CI:0.81-1.46; p=0.567)	NR	NR	NR NR p=ns	p=ns for all toxicities except pain[a] and fatigue[b]	NR
Soydal 2016 [81]	Retro	 TARE TACE	 40 40	mean 39 31 p=0.014	NR	NR	NR	NR NR p=0.32	NR
TARE versus DEB-TACE									
Akinwande 2016 [82]	Retro (Pooled Cohort)	 TARE DEB-TACE	 67 291	median 9 15 p<0.0001 (log-rank)	 5 15 p<0.0001 (log-rank)	NR	 21(34) 108 (41) p=ns	(Grade ≥3) 5 (4.0) 27 (4.5) p=ns	NR
	Retro (Matched Cohort)	 TARE DEB-TACE	 48 48	median 4 13 p<0.0077 (log-rank)	 5 6 p=ns (log-rank)	NR	 16 (35) 22 (47) p=ns	(Grade ≥3) 5 (6) 7 (7) p=ns	NR

[a]Significantly less pain with TARE (p<0.01)
[b]Significantly less fatigue following TARE (p<0.01)
Abbreviations: CI=confidence interval; DEB-TACE=drug eluting bead transarterial chemoembolization; HR=hazard ratio; NR=not reported; ns-not signficant; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QOL=quality of life; SR=systematic review; TACE=transarterial chemoembolization; TARE=transarterial radioembolization; TTP=time to progression

Table 4-7. Outcomes from included studies regarding DEB-TACE versus cTACE.

STUDY	DESIGN	TREATMENT ALLOCATION	N (evaluated)	OS (months)	TTP (months)	ORR N (%)	TOXICITY N (%)
PRECISION V 2010/2011 [30,31]	RCT (Phase II)	DEB-TACE cTACE	102 (93) 110 (108)	NR	NR	at 6 months 48 (51.6) 47 (43.5) p=0.11	SAEs* 19 (20.4) 21 (19.4) p=0.86 ALT & AST post-procedure increase less in DEB-TACE than cTACE (p<0.001 for each) Postembolization Syndrome 23 (24.7) 28 (25.9) p=NR Cardiotoxicity small drop in LVEF in cTACE p=0.038
Van Malenstein 2011 [32]	RCT (Phase II)	DEB-TACE cTACE	16 14	NR	NR	NR	Grade 3/4 4 (25) 8 (57) p=NR ALT Day 1 post-procedure 59.9 IU/L 128.2 IU/L p=0.003 AST Day 1 post-procedure 120.5 IU/L 225.5 IU/L p=0.007
Golfieri 2014 [33]	RCT	DEB-TACE cTACE	89 88	1-year 86.2 83.5 2-year 56.8 55.4 p=0.949	Median 9 9 p=0.766	At 6 months 76.1 75.7 p>0.999	Post-procedural pain 22 (24.7) 63 (71.6) p=0.001 All other AEs p=ns

*Treatment-related SAEs with 30 days of treatment

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; cTACE = conventional transarterial chemoembolization; DEB-TACE=drug eluting bead transarterial chemoembolization; LVEF=left ventricular ejection fraction; NR=not reported; ORR=objective response rate; OS=overall survival; RCT=randomized controlled trial; SAE=serious adverse events; TTP=time to progression

Question 2: What is the benefit of the addition of sorafenib to local therapies (TEA, TAE, RFA, TARE, SBRT, TACE, and DEB-TACE)?

TEA + Sorafenib vs. TEA

No studies comparing TEA plus sorafenib versus TEA were found.

TAE + Sorafenib vs. TAE

No studies comparing TAE plus sorafenib versus TAE were found.

RFA + Sorafenib vs. RFA

One trial comparing RFA plus sorafenib versus RFA was retained [34]. This study included 62 patients. One-, two-, and three-year recurrence rates were significantly higher in the RFA-alone arm ($p<0.01$). Median TTP was significantly longer in the RFA plus sorafenib arm (17.0 months vs. 6.1 months, $p<0.05$). There were no serious toxicities in the RFA arm. However, 8.1% and 6.5% of patients in the combination arm experienced a Grade 3 increase in ALT and AST, respectively.

TARE + Sorafenib vs. TARE

No RCTs comparing TARE plus sorafenib versus TARE were found. However, two abstracts (one retrospective study and one case-control study) were retained. Ma et al. [6] conducted a retrospective study of 55 patients in one centre. Median survival in the combined arm was significantly higher than in the TARE-only arm (21.0 months vs. 7.0 months; $p=0.003$). Adverse effects were reported in one patient in the combined treatment arm and in six patients in the TARE-only arm. However, severities of the toxicities were not reported. Maccauro et al. [7] conducted a case control study of 15 cases and 30 controls. There were no significant differences between the groups on any reported outcome including median PFS, median OS, and ORR.

SBRT + Sorafenib vs. SBRT

No studies comparing SBRT plus sorafenib versus SBRT were found.

TACE + Sorafenib vs. TACE

Four trials comparing TACE plus sorafenib versus TACE were retained [8,35-37]. Kudo et al. [8] conducted a phase III trial of 458 participants with unresectable HCC. Median TTP was not significantly different in the two arms of the trial (HR, 0.87; 95% CI, 0.70 to 10.9; $p=0.252$). Median OS was also not significantly different in the two arms of the study ($p=0.790$). The incidence of drug-related adverse events (AEs) were higher in the TACE/sorafenib arm (18%) compared with the TACE/placebo arm (9%) but no p-value is reported. Sansonno et al. [35] conducted a smaller trial of 80 intermediate-stage HCC participants. There was a significantly longer TTP in the TACE/sorafenib arm compared with the TACE/placebo arm (9.2 months vs. 4.9 months, $p<0.001$). There were more drug-related AEs in the TACE/sorafenib arm; however, no p-values are reported. In 2018 Kudo et al. [36] conducted a trial of 256 participants with unresectable HCC in 33 centres. Median PFS was significantly longer in the TACE/sorafenib arm compared with the TACE-alone arm (25.2 months vs. 13.5 months; HR, 0.56; 95% CI, 0.38 to 0.83; $p=0.004$). Park et al. [37] conducted a phase III trial of 330 participants with advanced HCC. Median OS was not significantly different in the two study arms (HR, 0.91; 95% CI, 0.69 to 1.21; $p=0.290$). However, both median TTP (HR, 0.67; 95% CI, 0.53 to 0.85; $p=0.003$) and median PFS (HR, 0.73; 95% CI, 0.59 to 0.91; $p=0.01$) significantly favoured the TACE/sorafenib arm.

DEB-TACE + Sorafenib vs. DEB-TACE

Two trials comparing DEB-TACE plus sorafenib versus DEB-TACE were retained [9,10]. The SPACE trial [9] included 307 patients with intermediate-stage HCC. TTP was not significantly different in the two study arms (HR, 0.797; 95% CI, 0.588 to 1.080; p=0.072). OS was also not significantly different in the two study arms (HR, 0.898, 95% CI, 0.606 to 1.330; p=0.295). ORR was 35.7% in the DEB-TACE/sorafenib arm and 28.1% in the DEB-TACE/placebo arm (p=NR). The TACE 2 trial [10] included 399 patients and was terminated early for futility. Median PFS (HR, 0.99; 95% CI, 0.77 to 1.27; p=0.94) and median OS (HR, 0.91; 95% CI, 0.67 to 1.24; p=0.57) were not significantly different in the two study arms.

Question 3: What is the benefit of other systemic treatment regimens versus sorafenib?

Single Drugs versus Sorafenib Alone

Linifanib vs. Sorafenib

One phase III trial of linifanib versus sorafenib was retained [38]. This phase III trial of 1035 patients was terminated early for futility. This study was designed for both non-inferiority and superiority analyses. Overall, the study did not meet the OS non-inferiority boundary set. Therefore, linifanib was neither non-inferior nor superior to sorafenib. Median OS was similar in both study arms (HR, 1.046; 95% CI, 0.896 to 1.221; p=ns). Median TTP was significantly longer in the linifanib arm (HR, 0.759; 95% CI, 0.643 to 0.895; p=0.001) as was median PFS (HR, 0.813; 95% CI, 0.697 to 0.948; p=0.008). ORR was 10.1% in the linifanib arm and 6.1% in the sorafenib arm (p=0.018) (Table 4-8). Grade 3/4 toxicities that were significantly greater in the linifanib arm were hypertension, fatigue, hepatic encephalopathy, asthenia, ascites, thrombocytopenia, hypokalemia, vomiting, and hypoglycemia. Increased ALT occurred significantly more often in the sorafenib arm.

Lenvatinib vs. Sorafenib

A phase III non-inferiority trial of lenvatinib versus sorafenib reported in one full publication [2] and four abstracts were retained [39-42]. This trial enrolled 954 patients. The data indicate that lenvatinib is non-inferior to sorafenib with respect to median OS (HR, 0.92; 95% CI, 0.79 to 1.06). Median PFS (HR, 0.66; 95% CI, 0.57 to 0.77, p<0.0001), median TTP (HR, 0.63; 95% CI, 0.53 to 0.73, p<0.0001) and ORR (24.1% vs 9.2%, p<0.0001) were all significantly better in the lenvatinib arm (Table 4-8). It should be noted that this trial had very strict inclusion criteria. Specifically, only those with ECOG PS 0-1 were included and those with main portal vein thrombosis were excluded. This limits the generalizability of the results. Subgroup analysis demonstrated that median OS was similar in the two study arms in HBV-positive participants in general (HR, 0.83; 95% CI, 0.68 to 1.02) and in HBV-positive participants from the Asia-Pacific (HR, 0.82; 95% CI, 0.66 to 1.02) [39]. Health-related QOL was reported in three abstracts [40-42]. Lenvatinib was significantly better with respect to role-function (p=0.0098), pain (p=0.006), diarrhea (p<0.0001), body image (p=0.0041), and nutrition (p=0.006).

Sunitinib vs. Sorafenib

One phase III trial that compared sunitinib to sorafenib alone was retained [43]. This study was terminated early for futility and safety. There were no significant differences between the sunitinib and sorafenib study arms with respect to median OS (7.9 months vs. 10.2 months; p=0.9990), median TTP (4.1 months vs. 3.8 months; p=0.8312) and median PFS (3.6 months vs. 3.0 months; p=0.8785) (Table 4-8). Grade 3/4 AEs occurred in 82.1% of

patients in the sunitinib arm and 74.2% of patients in the sorafenib arm. Fatal AEs occurred in 17.5% of the sunitinib patients and 15.3% of the sorafenib patients.

Nintedanib vs. Sorafenib

Two very similar phase II trials comparing nintedanib and sorafenib were retained; one conducted in Asia [44] and the other conducted in Europe [45]. The European trial was only available as a conference abstract. Investigator-assessed TTP was similar in both treatment arms in the Asian (HR, 1.21; 95% CI, 0.73 to 2.01) and European (HR, 1.05; 95% CI, 0.63 to 1.76) trials. OS was also similar in both treatment arms in the Asian (HR, 0.94; 95% CI, 0.59 to 1.49) and European (HR, 1.05; 95% CI, 0.63 to 1.76) trials (Table 4-8). Median PFS, which was only reported in the Asian study [44], was similar in the two trial arms (HR, 1.19; 95% CI, 0.73 to 1.93). More patients in the sorafenib arm had grade 3 or greater AEs in both trials (84% vs. 56%; p=NR and 90% vs. 68%; p=NR) (Table 4-8).

Brivanib vs. Sorafenib

One phase III noninferiority trial (BRISK-FL) of brivanib versus sorafenib was retained [46]. The trial did not demonstrate non-inferiority of brivanib compared with sorafenib. There were no significant differences between the two arms of the trial for median OS (HR, 1.07; 95.8% CI, 0.94 to 1.23; p=0.31), median TTP (HR, 1.01; 95% CI, 0.88 to 1.16; p=0.85) or ORR (OR, 1.45; 95% CI, 0.99 to 2.13; p=0.057) (Table 4-8). The incidence of grade 3/4 AEs were similar in the brivanib and sorafenib arms (67% vs. 65%). QOL after 12 weeks of treatment declined compared with baseline in both groups but declined more in the brivanib arm (p=0.0002).

Capecitabine vs. Sorafenib

One abstract of a phase II trial of capecitabine versus sorafenib was retained [47]. Median OS was significantly longer in the sorafenib arm compared with the capecitabine arm (7.05 months vs. 5.07 months, p<0.016) and median PFS was significantly longer in the sorafenib arm as well (6 months vs. 4 months, p<0.005). ORR was 14.5% and 3% in the sorafenib and capecitabine arms, respectively (Table 4-8). The incidence of hand-foot skin reaction was greater in the sorafenib arm and the incidence of hyperbilirubinemia was greater in the capecitabine arm (p=NR for both AEs).

Drug Combinations versus Sorafenib Alone

Doxorubicin/Sorafenib vs. Sorafenib

Two trials, reported in abstract form only, comparing doxorubicin/sorafenib versus sorafenib alone were retained [48,49]. Soradox [48] was a small trial of 30 patients. There was no significant difference between the combination arm and the sorafenib-only arm for both median TTP (7.11 months vs. 8.45 months; p=0.96) and OS (6.97 months vs. 19.8 months; p=0.14) (Table 4-8). Grade 3/4 toxicities were similar in the two study arms. CALGB 80802 [49] was a larger study of doxorubicin/sorafenib versus sorafenib alone. This study was supposed to accrue 480 patients but was terminated early for futility after the accrual of 346 patients. There was no significant difference between the combination arm and the sorafenib only arm for both median OS (9.3 months vs. 10.5 months; p=NR) and median PFS (3.6 months vs. 3.2 months; p=NR) (Table 4-8). There were more hematologic AEs in the combination arm compared with the sorafenib alone arm (37.8% vs. 8.1%; p=NR) whereas non-hematologic AEs were similar in each arm (63.6% vs. 61.5%; p=NR).

Gemcitabine + Oxaliplatin (GEMOX)/Sorafenib vs. Sorafenib

Two abstracts of the GONEXT trial that compared GEMOX/sorafenib to sorafenib alone were retained [50,51]. Both abstracts, published in 2013, contain the same information. Median PFS was numerically longer in the combination arm compared with the sorafenib-alone arm (6.2 months vs. 4.6 months). Median OS was also numerically longer in the combination arm (13.5 months vs. 13.0 months). No p-values are reported for either outcome. ORR was 16% in the combination arm and 9% in the sorafenib-alone arm (p=NR) (Table 4-8). Grade 3/4 neutropenia, fatigue, and thrombocytopenia were all higher in the combination arm (p=NR).

Tigatuzumab/Sorafenib vs. Sorafenib

One three-arm phase II trial that compared tigatuzumab/sorafenib (two different dose arms) to sorafenib alone was retained [52]. The authors report many pair-wise comparisons but use no correction factor to account for the extra comparisons. TTP was similar between all three study arms (p=ns for all comparisons) as was median OS (p=ns for all comparisons) (Table 4-8).

Mapatumumab/Sorafenib vs. Sorafenib/Placebo

One phase II trial of mapatumumab/sorafenib versus sorafenib/placebo was retained [53]. There were no significant differences between the study arms for median TTP (HR, 1.192; 95% CI, 0 to 1.737; p=0.74), median PFS (HR, 1.066; 90% CI, 0 to 1.430) or OS (HR, 1.195; 90% CI, 0 to 1.651; p=0.78) (Table 4-8). AEs were similar in the two trial arms.

Everolimus/Sorafenib vs. Sorafenib

One phase II trial of everolimus/sorafenib versus sorafenib alone was retained [54]. The combination and sorafenib alone arms were similar with respect to median PFS (5.7 vs. 6.6 months; p=NR), median TTP (6.3 months vs. 7.6 months; p=NR) and median OS (12 months vs. 10 months; p=NR). ORR was 10% in the combination arm (all partial responses) and 0% in the sorafenib arm (Table 4-8). QOL was significantly worse for those in the combination arm for physical well-being (p=0.02) and mood (p=0.02) for the first 12 weeks.

AEG35256/Sorafenib vs. Sorafenib

One small phase II trial of AEG35256/sorafenib versus sorafenib alone was retained [55]. The combination and sorafenib arms were similar with respect to median PFS (4.0 months vs. 2.6 months; p=NR), median OS (6.5 months vs. 5.4 months; p=NR) and ORR (9.7% vs. 0%; p=NR) (Table 4-8). Overall, the incidence of AEs was higher in the combination arm compared with the sorafenib arm (p=NR for any AE).

Bevacizumab/Erlotinib vs. Sorafenib

One phase II trial comparing bevacizumab/erlotinib to sorafenib was retained [56]. OS was not significantly different between the study arms (HR, 0.92; 95% CI, 0.57 to 1.47) (Table 4-8). SAEs were similar in the two study arms (11% per cycle vs. 14% per cycle; p=NR).

Erlotinib/Sorafenib vs. Sorafenib/Placebo

One phase III trial of erlotinib/sorafenib versus sorafenib/placebo (SEARCH trial) was retained [57]. The two arms were similar with respect to median OS (HR, 0.929; 95% CI, 0.781 to 1.106; p=0.408), median TTP (HR, 1.135; 95% CI, 0.944 to 1.366; p=0.18) and ORR (6.6% in the erlotinib/sorafenib arm vs. 3.9% in the sorafenib/placebo arm; p=0.102) (Table 4-8). AE rates were similar in the two study arms.

Pravastatin/Sorafenib vs. Sorafenib

One abstract of a phase II trial comparing pravastatin/sorafenib to sorafenib alone in CHILD B cirrhotic participants who had HCC was retained [58]. Median PFS and median OS were not significantly different in the study arms (p=NR) (Table 4-8). Toxicity was similar in the study arms.

Resminostat/Sorafenib vs. Sorafenib

One abstract of a phase II trial of 170 participants comparing resminostat/sorafenib and sorafenib was retained [59]. Median TTP (2.8 months vs. 2.8 months, HR, 0.984; p=NR) and median OS (p=NR) were not significantly different in the study arms (Table 4-8).

Table 4-8. Outcomes from included studies regarding other systemic treatments versus sorafenib

STUDY	TREATMENT ALLOCATION	N (evaluated)	MEDIAN OS (months)	MEDIAN TTP (months)	MEDIAN PFS (months)	ORR N(%)	TERMINATED EARLY?
SINGLE DRUGS VERSUS SORAFENIB ALONE							
LINIFANIB VS. SORAFENIB							
Cainap 2015 [38]	Linifanib Sorafenib	514 (510) 521 (519)	9.1 9.8 HR, 1.046; 95% CI, 0.896 to 1.221 p=ns	5.4 4.0 HR, 0.759; 95% CI, 0.643 to 0.895 p=0.001	4.2 2.9 HR, 0.813; 95% CI, 0.697 to 0.948 p=0.008	10.1% 6.1% p=0.018	Yes, for futility
LENVATINIB VS. SORAFENIB							
Kudo 2018 [2]	Lenvatinib Sorafenib	478 476	13.6 12.3 HR, 0.92; 95% CI, 0.79 to 1.06 p=NR	8.9 3.7 HR, 0.63; 95% CI, 0.53 to 0.73 p<0.0001	7.4 3.7 HR, 0.66; 95% CI, 0.57 to 0.77 p<0.0001	115 (24) 44 (9) p<0.0001	No
Han 2017 [39] *abstract*	**HBV-positive participants** Lenvatinib Sorafenib	 259 244	 13.4 10.2 HR, 0.83; 95% CI, 0.68 to 1.02 p=NR				
	HBV-positive Asia-Pacific participants Lenvatinib Sorafenib	 218 208	 13.1 9.4 HR, 0.82; 95% CI, 0.66 to 1.02 p=NR				
SUNITINIB VS. SORAFENIB							
Cheng 2013 [43]	Sunitinib Sorafenib	530 544	7.9 10.2 HR, 1.30; 95% CI, 1.13 to 1.50 p=0.9990	4.1 3.8 HR, 1.13; 95% CI, 0.98 to 1.31 p=0.8312	3.6 3.0 HR, 1.13; 95% CI, 0.99 to 1.30 p=0.8785	NR	Yes, for futility and safety

STUDY	TREATMENT ALLOCATION	N (evaluated)	MEDIAN OS (months)	MEDIAN TTP (months)	MEDIAN PFS (months)	ORR N(%)	TERMINATED EARLY?
NINTEDANIB VS. SORAFENIB							
Yen 2018 [44]	Nintedanib Sorafenib	63 32	10.2 10.7 HR, 0.94; 95% CI, 0.59 to 1.49 p=NR	2.8 3.7 HR, 1.21; 95% CI, 0.73 to 2.01 p=NR	2.7 3.7 HR, 1.19; 95% CI, 0.73 to 1.93 p=NR	NR	No
Palmer 2015 [45] *abstract*	Nintedanib Sorafenib	62 31	11.9 11.4 HR, 0.88; 95% CI, 0.52 to 1.47 p=NR	Investigator Assessed 5.5 3.8 HR, 1.05; 95% CI, 0.63 to 1.76 p=NR	NR	NR	No
BRIVANIB VS. SORAFENIB							
BRISK-FL 2013 [46]	Brivanib Sorafenib	577 (575) 578 (575)	9.5 9.9 HR, 1.07; 95.8% CI, 0.94 to 1.23 p=0.3116	4.2 4.1 HR, 1.01; 95% CI, 0.88 to 1.16 p=0.8532	NR	12% 9% p=0.569	No
CAPECITABINE VS. SORAFENIB							
Wahab 2012 [47] *abstract*	Capecitabine Sorafenib	N total 52	5.07 7.05 p<0.016	NR	4 6 p<0.005	3.0% 14.5% p=NR	No
DRUG COMBINATIONS VERSUS SORAFENIB ALONE							
DOXORUBICIN + SORAFENIB VS. SORAFENIB							
Soradox Trial 2015 [48] *abstract*	Doxorubicin + Sorafenib Sorafenib	15 (11) 15 (12)	6.97 19.8 p=0.14	7.11 8.45 p=0.96	NR	NR	No
CALGB 80802 2016 [49] *abstract*	Doxorubicin + Sorafenib Sorafenib	173 173	9.3 10.5 p=NR	NR	3.6 3.2 p=NR	NR	Yes, for futility
GEMOX + OXALIPLATIN + SORAFENIB VS. SORAFENIB							
GONEXT Trial 2013 [50,51] *abstracts*	GEMOX + Sorafenib Sorafenib	In total 94 (83)	13.5 13.0 p=NR	NR	6.2 4.6 p=NR	16% 9% p=NR	No
TIGATUZUMAB + SORAFENIB VS. SORAFENIB							
Cheng 2015 [52]	Tigatuzumab (6/2mg/kg) + Sor Tigatuzumab (6/6mg/kg) + Sor Sorafenib	53 (53) 55 (54) 55 (55)	8.2 12.2 8.2 All pair-wise comparisons; p=ns	3.0 3.9 2.8 All pair-wise comparisons; p=ns	NR	5.7% 14.8% 10.9%	No

STUDY	TREATMENT ALLOCATION	N (evaluated)	MEDIAN OS (months)	MEDIAN TTP (months)	MEDIAN PFS (months)	ORR N(%)	TERMINATED EARLY?
MAPATUMUMAB + SORAFENIB VS. SORAFENIB/PLACEBO							
Ciuleanu 2016 [53]	Mapatumumab + Sorafenib Sorafenib + Placebo	50 51	10.0 10.1 NR HR, 1.195; 90%CI, 0 to 1.651 p=0.7823	4.1 5.6 HR, 1.192; 95% CI, 0 to 1.737 p=0.7382	3.2 4.2 HR, 1.066; 90%CI, 0 to 1.43 p=NR	NR	No
EVEROLIMUS + SORAFENIB VS. SORAFENIB							
Koeberle 2016 [54]	Everolimus/Sorafenib Sorafenib	60 (50) 46 (43)	12 10 p=NR	NR	5.7 6.6 p=NR	6(10) 0 (0) p=NR	No
AEG35256 + SORAFENIB VS. SORAFENIB							
Lee 2016 [55]	AEG35256/Sorafenib Sorafenib	31 17	6.5 5.4	NR	4.0 2.6	3(9.7) 0(0.0)	No
BEVACIZUMAB + ERLOTINIB VS. SORAFENIB							
Thomas 2018 [56]	Bevacizumab/Erlotinib Sorafenib	47 43	8.6 8.6 HR, 0.92; 95% CI, 0.57 to 1.47 p=NR	NR	NR	15% 9% p=NR	No
ERLOTINIB + SORAFENIB VS. SORAFENIB + PLACEBO							
SEARCH 2015 [57]	Erlotinib/Sorafenib Sorafenib/Placebo	362 (362) 358 (355)	9.5 8.5 HR, 0.929; 95% CI, 0.781 to 1.106 p=0.408	3.2 4.0 HR, 1.135; 95% CI, 0.944 to 1.366 p=0.18	NR	6.6% 3.9% p=0.102	No
PRAVASTATIN/SORAFENIB VS. SORAFENIB							
Blanc 2018 [58] *abstract*	Pravastatin Sorafenib	40 41	4.0 3.8 p=NR	NR	3.4 3.2	NR	No
RESMINOSTAT/SORAFENIB VS. SORAFENIB							
Kudo 2017 [59] *abstract*	Resminostat Sorafenib	N total 170	NR NR p=NR (but ns)	2.8 2.8 HR, 0.984	NR	NR	No

Abbreviations: CI=confidence interval; GEMOX= gemcitabine/oxaliplatin; HBV=hepatitis B virus; HR=hazard ratio; NR=not reported; ns=not significant; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Question 4: What is the benefit of the eradication of viral hepatitis (HCV and/or HBV) in patients with advanced HCC?

Hepatitis C – TACE with or without Antiviral Therapy

One retrospective study investigating the use of antiviral therapy after treatment of HCV-associated HCC with non-curative treatment (almost all TACE) was retained [83]. In this small study of 95 participants, OS was significantly better in those who received antiviral therapy compared with those that did not (p=0.003). The two arms in this study were not equivalent. It should be noted that participants who did not receive antiviral therapy had worse liver function prior to treatment than those who did get antiviral therapy [83].

Hepatitis B – Sorafenib with or without Antiviral Therapy

Two retrospective papers that compared the effect of sorafenib with or without antiviral therapy in HBV patients were retained [5,84]. Both of these studies were of similar size (151 patients and 130 patients, respectively). The antivirals used in the Xu et al. [5] trial included lamivudine, entecavir, and adefovir. They reported that median OS was significantly better in the antiviral arm compared with the sorafenib-alone arm (16.47 months vs. 13.10 months; p=0.03). The antivirals used in the Yang et al. [84] trial included lamivudine, adefovir, dipivoxil, and entecavir. They also reported better OS in the antiviral arm; however, it was not significantly better (12.0 months vs. 8.3 months; p=0.058). Both studies report that PFS was not significantly different in the study arms. Subgroup analysis by Xu et al. [5] found that median OS was significantly better in the patients who were BCLC stage C and taking antiviral therapy compared with those who were not taking antiviral therapy (p=0.01). There was no OS difference in BCLC stage B patients who took or did not take antiviral therapy. Moreover, OS was significantly better in patients who had HBV-DNA levels ≥200 IU/mL and were taking antiviral therapy as compared with those not taking antiviral therapy. There was no OS difference in patients who had HBV-DNA levels <200 IU/mL who took or did not take antiviral therapy. Subgroup analysis by Yang et al. [84] found that patients who had a high viral load (HBV-DNA $>10^4$ copies/mL and not on antiviral therapy had the poorest OS at 6.2 months (p<0.001).

Hepatitis B – TACE with or without Antiviral Therapy

Five studies comparing TACE with antiviral therapy to TACE alone were retained [13-15,60,85]. Three of these were randomized trials [13,15,60] and two were retrospective studies [14,85]. Zhou et al. [85] included early- and advanced-stage participants but only the results of the advanced-stage participants are reported here. Four studies reported survival data [13-15,85] and in three cases survival was significantly greater in the patients being pre-emptively treated with antiviral therapy [13-15]. Zhou et al. [85] reported that there was no significant difference in OS between the antiviral and non-antiviral groups in their study (8.4 months vs. 7.4 months; p=0.219 log-rank). One study reported mortality data [60]. Mortality rates were similar in the Jang et al. [60] study although no p-value was reported. Li et al. [13] found that median disease-free survival was significantly longer in the antiviral arm compared with the control arm (23.6 months vs. 20.3 months). Similarly, median TTP was significantly longer in the lamivudine arm compared with the control arm (8.2 months vs. 4.3 months) [15]. There was no difference in PFS in the one study that reported this outcome [14] (Table 4-9).

Table 4-9. Outcomes from included studies regarding TACE treatment with or without antiviral therapy in patients with advanced HBV-related HCC.

STUDY	DESIGN	ANTIVIRAL THERAPY USED	TREATMENT ALLOCATION	N (evaluated)	OS (months)	Mortality N (%)	DFS (months)	PFS (months)	TTP (months)	Deterioration of Hepatic Function (%)
Jang 2006 [60]	RCT	Lamivudine	Antiviral Therapy Control	38 (36) 38 (37)	NR	4 (11.1) 3 (8.1) p=NR	NR	NR	NR	NR
Li 2009 [13]	RCT	Interferon-α	Antiviral Therapy Control	108 (108) 108 (108)	Median 29 26 p=0.003 log-rank	NR	Median 23.6 20.3 p=0.027 log-rank	NR	NR	NR
Toyoda 2012 [14]	Retro	Nucleoside Analogues	Antiviral Therapy Control	21 60	1-year 89.5% 72.6% 3-year 66.8% 27.5% 5-year 40.5% 14.3% p=0.0051	NR	NR	NR NR p=0.2556	NR	NR
Xu 2014 [15]	RCT	Lamivudine	Antiviral Therapy Control	92 89	1-year 83% 60% 2-year 69% 48% 3-year 58% 48% p=0.002	NR	NR	NR	Median 8.2 4.3 p=0.005	NR
Zhou 2015 [85]	Retro	Entecavir or Lamivudine	Antiviral Therapy Control	57 96	8.4 7.4 p=0.219 log-rank	NR	NR	NR	NR	NR

Abbreviations: DFS=disease-free survival; HBV=hepatitis B virus; HCC-hepatocellular carcinoma; NR=not reported; OS=overall survival; PFS=progression-free survival; RCT=randomized controlled trial; Retro=retrospective; TACE=transarterial chemoembolization; TTP=time to progression

Question 5: What is the benefit of second-line systemic therapy following sorafenib?

ADI-peg 20/BSC vs. Placebo/BSC

One phase III trial of second-line ADI-peg 20 plus BSC versus placebo plus BSC was retained [61]. There were no significant differences between the study arms with respect to median OS (HR, 1.022; 95% CI, 0.847 to 1.233; p=0.884) and median PFS (HR, 1.175; 95% CI, 0.964 to 1.432; p=0.075) (Table 4-10).

Ramucirumab/BSC vs. Placebo/BSC

Three full publications [62,63,67] and three abstracts [64-66] of the REACH trial were retained as well as one abstract [68] of the REACH-2 trial (Table 4-10). REACH is a phase III trial that compared second-line ramucirumab plus BSC to placebo plus BSC. Each of these REACH trial publications report different outcomes. Kudo et al. [62] reports the main findings of the REACH trial. There was no significant difference between the groups with respect to median OS (HR, 0.87; 95% CI, 0.72 to 1.05; p=0.14). The ramucirumab arm was significantly better than the placebo arm with respect to median PFS (HR, 0.63; 95% CI, 0.52 to 0.75; p<0.0001), median TTP (HR, 0.59; 95% CI, 0.49 to 0.72; p<0.0001) and ORR (7% vs <1%, p<0.0001). Median OS was significantly better in the ramucirumab arm in a prespecified subgroup of patients who had a baseline AFP concentration ≥400 ng/mL (HR, 0.67; 95% CI, 0.51 to 0.90; p=0.006 (log-rank)) (Table 4-10). An analysis of the interaction between the treatment effect and baseline AFP concentration demonstrated that the effect of treatment occurred over a large range of elevated baseline AFP levels. Although no p-values are reported, ascites, hypertension, asthenia, and thrombocytopenia occurred more often in the ramucirumab arm whereas increased AST, hyperbilirubinemia, and increased blood bilirubin occurred more often in the placebo group. Chau et al. [63] reported on patient-focused outcomes from the REACH trial using the FACT Hepatobiliary Symptom Indexes. There were no significant differences between the two arms of the study. Therefore, treatment with ramucirumab did not lead to any improvement or impairment with respect to symptoms or patient functioning.

Zhu et al. [64] analyzed REACH patients by Child-Pugh score and found that patients with lower Child-Pugh scores had a greater benefit with ramucirumab treatment. Specifically, PFS was significantly better in the ramucirumab arm only in those patients with a Child-Pugh score of 5 (HR, 0.587; 95% CI, 0.47 to 0.74; p<0.0001) (Table 4-10). OS was only better in those patients with a baseline AFP level ≥400 ng/mL and lower Child-Pugh scores of 5 (HR, 0.611; 95% CI, 0.43 to 0.87; p=0.0058) and 6 (HR, 0.64; 95% CI, 0.42 to 0.98; p=0.0384).

Blanc et al. [65] analyzed REACH patients by albumin-bilirubin grade. There were no significant OS differences based on albumin-bilirubin grade. However, there was a significant improvement in OS in those patients with albumin-bilirubin grade 1 and baseline AFP ≥400 ng/mL (HR, 0.60; 95% CI, 0.38 to 0.94; p=0.03) (Table 4-10).

Okusaka et al. [66] conducted ad hoc retrospective analyses based on liver disease etiology. Overall, there were no significant differences in OS between the treatment arms in participants who were HBV positive or in participants who were HCV positive. However, HBV participants who had baseline AFP levels ≥400 ng/mL had significantly better OS in the ramucirumab arm compared with the placebo arm (6.6 months vs. 4.0 months; HR, 0.67; p=0.04).

Kudo et al. [67] conducted a subgroup analysis of Japanese participants (N=93) in the REACH trial. Median OS was significantly better in the ramucirumab arm compared with placebo (12.9 months vs. 8.0 months, HR, 0.62; 95% CI, 0.39 to 0.99; p=0.0416). Similarly, median PFS was significantly better in the ramucirumab arm compared with placebo (4.1

months vs. 1.7 months, HR, 0.45; 95% CI, 0.28 to 0.71; p=0.0004). There was no difference in response rates between the study arms.

REACH-2 [68] was a phase III RCT of ramucirumab versus placebo/BSC in patients with elevated AFP (≥400 ng/mL) following first-line sorafenib. Median OS (HR, 0.710; 95% CI, 0.53 to 0.95; p=0.0199) and median PFS (HR, 0.452; 95% CI, 0.34 to 0.60, p<0.0001) were both significantly better in the ramucirumab arm compared with placebo. There was no significant difference in ORR (Table 4-10).

Regorafenib/BSC vs. Placebo/BSC

One full publication [11] (Bruix et al., 2017) and three abstracts [69-71] of the RESORCE trial were retained. This was a phase III RCT of regorafenib/BSC versus placebo/BSC. The authors [11] reported significantly better median OS (HR, 0.63; 95% CI, 0.50 to 0.79, p<0.0001), median PFS (HR, 0.46; 95% CI, 0.37 to 0.56, p<0.0001) and median TTP (HR, 0.44; 95% CI, 0.36 to 0.55, p<0.0001) in the regorafenib arm of the trial. ORR was also significantly better in the regorafenib arm (11% vs. 4%; p=0.0047). Updated OS results are very similar to the primary analysis (HR, 0.61; 95% CI, 0.50 to 0.75; p<0.0001) [69]. Grade 3/4 toxicity was greater in the regorafenib arm overall (67% vs. 39%) including hand-foot skin reaction (13% vs. 1%), diarrhea (3% vs. 0%), fatigue (9% vs. 5%), and hypertension (15% vs. 5%). No p-values are reported [11] (Table 4-10). All measures of QOL were similar in the two treatment arms [70]. Subgroup analysis of Chinese participants indicates better median OS, PFS, and TTP in the regorafenib arm compared with placebo [71] (Table 4-10).

Cabozantinib vs. Placebo

One full publication of the phase III CELESTIAL trial of second- or third-line cabozantinib versus placebo was retained [12]. Median OS (HR, 0.76; 95% CI, 0.63 to 0.92; p=0.005), median PFS (HR, 0.44; 95% CI, 0.36 to 0.52, p<0.001) and ORR (4% vs. <1%; p=0.009) were significantly better in the cabozantinib arm (Table 4-10). Grade 3/4 toxicity was greater in the cabozantinib arm compared with the placebo arm (68% vs. 36%) including for hand-foot skin reaction (17% vs. 0%), hypertension (16% vs. 2%), fatigue (10% vs. 4%), and diarrhea (10% vs. 2%). No p-values are reported (Table 4-10).

S-1 vs. Placebo

One full publication [73] and one abstract [72] of the S-CUBE trial, a phase III RCT that compared second-line S-1, which is not available in North America, to placebo in patients with advanced HCC who were sorafenib-refractory, were retained (Table 4-10). The main results of the S-CUBE trial demonstrate that there are no significant differences between the S-1 and placebo study arms with respect to median OS (HR, 0.86; 95% CI, 0.67 to 1.10; p=0.220) and ORR (5% vs. 1%; p=0.068). However, median PFS was significantly greater in the S-1 arm (HR, 0.60; 95% CI, 0.46 to 0.77; p<0.0001) [73]. Using predictive enrichment strategy analysis, Kudo et al. [72] were able to identify a group of high-response patients. These are patients who are TNM stage III, Iva, or IVb, Child-Pugh A, and have lower levels of AFP and PIVKA-II. Within this population, median OS was significantly longer in the S-1 group (HR, 0.69; 95% CI, 0.51 to 0.93; p=0.0156 (Table 4-10).

Brivanib/BSC vs. Placebo/BSC

One full publication of the BRISK-PS trial, in which second-line brivanib/BSC was compared with placebo/BSC, was retained [74]. OS was not significantly different between the two study arms (HR, 0.89; 95% CI, 0.69 to 1.15; p=0.3307). However, TTP was significantly longer in the brivanib arm (HR, 0.56; 95% CI, 0.42 to 0.76; p<0.001) and ORR was significantly greater in the brivanib arm compared with placebo (10% vs. 2%; p=0.0030) (Table

4-10). Grade 3/4 AEs were higher in the brivanib arm compared with placebo but it is unknown which AEs, if any, were significantly higher in the brivanib arm as no p-values are reported.

Tivantinib vs. Placebo

One full publication of a phase II trial of second-line tivantinib versus placebo was retained [75] Median TTP was significantly longer in the tivantinib arm as compared with placebo (HR, 0.64; 90% CI, 0.43 to 0.94; p=0.04). This significant difference may be an artifact owing to the use of a 90% rather than a 95% confidence interval. Median PFS and median OS were similar in the two treatment arms. There were no complete responses and only one partial response in the tivantinib arm (Table 4-10). AEs occurred with similar frequency in the two arms of the study with the exception of hematological AEs, which occurred more frequently in the tivanitinib arm (p=NR for all AEs). These authors also conducted a subgroup analysis of 37 patients who had high MET expression. Although not powered for this analysis, results indicate significantly longer median OS, median TTP, and median PFS in the tivantinib group compared with placebo (see Table 4-10). These results could be spurious given the fact that those receiving tivantinib were more likely to have an ECOG score of 0 than those receiving placebo and those receiving tivantinib were less likely to have distant metastases than those receiving placebo.

One full publication of a phase III trial of second-line tivantinib versus placebo in MET-high patients was retained [76]. Median OS (HR, 0.97; 95% CI, 0.75 to 1.25; p=0.81), median PFS (HR, 0.96; 95% CI, 0.75 to 1.22; p=0.72) and TTP (HR, 0.96; 95% CI, 0.74 to 1.25; p=0.76) were similar in the tivantinib and placebo arms (see Table 4-10).

RO5137382/GC33 vs. Placebo

One abstract of a phase II RCT of second-line RO5137382/GC33 vs. placebo was retained [77]. There were no significant differences between the study drug and placebo with respect to PFS (2.6 months vs. 1.5 months; p=0.87), OS (6.8 months vs. 6.7 months; p=0.97) or TTP (2.9 months vs. 1.7 months; p=0.85) (Table 4-10).

Everolimus/BSC vs. Placebo/BSC

One full publication of a phase III trial of second-line everolimus/BSC vs. placebo/BSC was retained [78]. There was no significant difference in median OS between the study arms (HR, 1.05; 95% CI, 0.86 to 1.27; p=0.68). Similarly, there was no significant difference in TTP between the study arms (HR, 0.93; 95% CI, 0.75 to 1.15; p=not calculated). ORR was higher in the everolimus arm (2.2% vs. 1.6%) although no p-value is provided (Table 4-10). AEs occurred more frequently in the everolimus arm (70.9% vs. 47.4%) as did SAEs (52.2% vs. 35.2%). No p-values are reported.

Table 4-10. Outcomes from included studies regarding the benefit of second-line systemic therapy following sorafenib

STUDY	TREATMENT ALLOCATION	N (evaluated)	MEDIAN OS (months)	MEDIAN TTP (months)	MEDIAN PFS (months)	ORR N (%)	TERMINATED EARLY?
ADI-peg 20 + BSC VS. PLACEBO + BSC							
Abou-Alfa 2018 [61]	ADI-peg 20 + BSC Placebo + BSC	424 211	7.8 7.4 HR, 1.022; 95% CI, 0.847 to 1.233; p=0.884	NR	2.6 2.6 HR, 1.175; 95% CI, 0.964 to 1.432; p=0.075	2 (<1.0) 6 (2.8) p=NR	No
RAMUCIRUMAB + BSC VS. PLACEBO + BSC							
REACH - Zhu 2015 [62]	Ramucirumab + BSC Placebo + BSC	283 (277) 282 (276)	9.2 7.6 HR, 0.87; 95% CI, 0.72 to 1.05; p=0.14	3.5 2.6 HR, 0.59; 95% CI, 0.49 to 0.72; p<0.0001	2.8 2.1 HR, 0.63; 95% CI, 0.52 to 0.75; p<0.0001	20 (7) 2 (<1.0) p<0.0001	No
REACH – Zhu 2015 [64] *abstract*	Ramucirumab + BSC Placebo + BSC (Child-Pugh subgroup analysis)	177 180	**Child-Pugh=5** HR, 0.796; 95% CI, 0.62 to 1.02; p=0.0647		**Child-Pugh=5** HR, 0.587; 95% CI, 0.47 to 0.74; p<0.0001		
REACH – Blanc 2016 [65] *abstract*	Ramucirumab + BSC Placebo + BSC (ALBI subgroup analysis)	91 in total	**ALBI 1** **AFP≥400ng/mL** 9.4 4.9 HR, 0.60; 95% CI, 0.38 to 0.94; p=0.03				
REACH – Okusaka 2017 [66] *abstract*	Ramucirumab + BSC Placebo + BSC (etiology subgroup analysis)	HepB 209 in total HepC 154 in total	8.2 5.4 HR, 0.79; p=0.11 9.2 8.8 HR, 0.95; p=0.79				
REACH – Kudo 2017 [67]	Ramucirumab + BSC Placebo + BSC (Japanese subgroup analysis)	45 48	12.9 8.0 HR, 0.621; 95% CI, 0.39 to 0.99; p=0.0416		4.1 1.7 HR, 0.449; 95% CI, 0.28 to 0.71; p=0.0004		

STUDY	TREATMENT ALLOCATION	N (evaluated)	MEDIAN OS (months)	MEDIAN TTP (months)	MEDIAN PFS (months)	ORR N (%)	TERMINATED EARLY?
REACH-2 2018 [68] *abstract*	Ramucirumab Placebo + BSC	197 95	8.5 7.3 HR, 0.710; 95% CI, 0.53 to 0.95; p=0.0199		2.8 1.6 HR, 0.452; 95% CI, 0.34 to 0.60; p<0.0001	NR (4.6) NR (1.1) p=0.1156	No
REGORAFENIB + BSC VS. PLACEBO + BSC							
Bruix 2017 [11]	Regorafenib + BSC Placebo + BSC	379 194	10.6 7.8 HR, 0.63; 95% CI, 0.50 to 0.79; p<0.0001	3.2 1.5 HR, 0.44; 95% CI, 0.36 to 0.55; p<0.0001	3.1 1.5 HR, 0.46; 95% CI, 0.37 to 0.56, p<0.0001	40(11) 8(4) p=0.0047	No
Han 2017 [71] *abstract*	Regorafenib + BSC Placebo + BSC	104 52	7.9 4.9 HR, 0.65; 95% CI, 0.43 to 0.99; p=0.023	2.8 1.4 HR, 0.36; 95% CI, 0.24 to 0.54; P<0.001	2.8 1.4 HR, 0.37; 95% CI, 0.25 to 0.53; p<0.001	NR (4) NR (2) p=NR	
CABOZANTINIB VS. PLACEBO							
Abou-Alfa 2018 [12]	Cabozantinib Placebo	470 237	10.2 8.0 HR, 0.76; 95% CI, 0.63 to 0.92; p=0.005	NR	5.2 1.9 HR, 0.44; 95% CI, 0.36 to 0.52; p<0.001	18(4) 1(<1) p=0.009	Yes, for efficacy
S-1 VS. PLACEBO							
S-CUBE 2017 [73]	S-1 Placebo	222 111	11.1 11.2 HR, 0.86; 95% CI, 0.067 to 1.10; p=0.220	2.6 1.4 HR, 0.59; 95% CI, 0.46 to 0.76; p<0.0001	2.6 1.4 HR, 0.60; 95% CI, 0.46 to 0.77; p<0.0001	12(5) 1(1) p=0.068	No
S-CUBE 2016 [72] *abstract*			**High Response Patients**				
	S-1 Placebo	219 in total	14.0[a] 12.3[a] HR, 0.69; 95% CI, 0.51 to 0.93; p=0.0156	NR	NR		No

STUDY	TREATMENT ALLOCATION	N (evaluated)	MEDIAN OS (months)	MEDIAN TTP (months)	MEDIAN PFS (months)	ORR N (%)	TERMINATED EARLY?
BRIVANIB + BSC VS. PLACEBO + BSC							
BRISK-PS – Llovet 2013 [74]	Brivanib + BSC Placebo + BSC	263 (261) 132 (131)	9.4 8.2 HR, 0.89; 95% CI, 0.69 to 1.15; p=0.3307	4.2 2.7 HR, 0.56; 95% CI, 0.42 to 0.76; p<0.001	NR	10 2 p=0.0030	No
TIVANTINIB VS. PLACEBO							
Santoro 2013 [75]	Tivantinib Placebo Tivantinib Placebo	71 36 Subgroup Analysis **MET-high** 37 in total	6.6 6.2 HR, 0.90; 95% CI, 0.57 to 1.40; p=0.63 7.2 3.8 HR, 0.38; 95% CI, 0.18 to 0.81; p=0.01	1.6 1.4 HR, 0.64; 90% CI[b], 0.43 to 0.94; p=0.04 2.7 1.4 HR, 0.43; 95% CI, 0.19 to 0.97; p=0.03	1.5 1.4 HR, 0.67; 95% CI, 0.44 to 1.04; p=0.06 2.2 1.4 HR, 0.45; 95% CI, 0.21 to 0.95; p=0.02	3 0 NR	No
Rimassa 2018 [76]	Tivantinib Placebo	226 114	8.4 9.1 HR, 0.97; 95% CI, 0.75 to 1.25; p=0.81	2.4 3.0 HR, 0.96; 95% CI, 0.74 to 1.25; p=0.76	2.1 2.0 HR, 0.96; 95% CI, 0.75 to 1.22; p=0.72	NR	No
RO5137382/GC33 VS. PLACEBO							
Yen 2014 [77] *abstract*	RO5137382/GC33 Placebo	121 64	6.8 6.7 p=0.99	2.9 1.7 p=0.85	2.6 1.5 p=0.87	NR	No
EVEROLIMUS + BSC VS. PLACEBO + BSC							
Zhu 2014 [78]	Everolimus + BSC Placebo + BSC	362 184	7.6 7.3 HR, 1.05; 95% CI, 0.86 to 1.27; p=0.68	NR NR HR, 0.93; 95% CI, 0.75 to 1.15; p=ns	NR	2.2 1.6 p=NR	No

[a]Converted from days (426.0 days and 375.5 days, respectively)
[b]Note this is a 90% confidence interval
Abbreviations: AFP=alpha-fetoprotein; BSC=best supportive care; CI=confidence interval; Hep=hepatitis; HR=hazard ratio; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TTP=time to progression

Question 6: Is there a survival difference in HCV populations compared with HBV populations compared with non-viral populations when treated with sorafenib?

Two meta-analyses of phase III randomized trials were retained [23,24]. Shao et al. [23] is a systematic review of randomized phase III trials assessing the efficacy of sorafenib as a first-line treatment for advanced HCC. They specifically evaluated the effect of viral status on survival. It includes four trials with a total of 3057 patients up to November 30, 2015. Jackson et al. [24] conducted an individual patient date meta-analysis of three randomized trials (N=3256) in which sorafenib was the control arm and evaluates the effect of viral status on survival. It is not based on a systematic review. Two studies are included in both of these meta-analyses with Shao et al. [23] including two other unique studies and Jackson et al. [24] including one other unique study.

Shao et al. [23] reported that the OS HR for HCV-positive patients (HR, 0.65; 95% CI, 0.53 to 0.80) was better than that of the HCV-negative patients (HR, 0.87; 95% CI, 0.79 to 0.96). This difference is statistically significant (p=0.013). They also reported that OS was significantly better in HCV-positive patients than HBV-positive patients (HR, 0.65; 95% CI, 0.53 to 0.80 vs. HR, 0.92; 95% CI, 0.82 to 1.05; p=0.005).

Jackson et al. [24] evaluated four different groups of patients with respect to sorafenib efficacy: HBV-negative/HCV-negative; HBV-negative/HCV-positive; HBV-positive/HCV-negative; and HBV-positive/HCV-positive. OS was significantly better in the sorafenib arm than in the comparator arm only for the group of patients who were HBV negative and HCV positive (HR, 0.77; 95% CI, 0.63 to 0.96; p=NR). There were no significant differences in the other three groups of patients evaluated.

Question 7: Is there a survival difference in HCV populations compared with HBV populations compared with non-viral populations when treated with TACE, TAE, or TEA?

One retrospective study evaluating survival after TACE in patients stratified according to viral etiology was retained [86]. No studies pertaining to survival after TAE or TEA were found. Patients were grouped by hepatitis status: HBV positive; HCV positive, HBV and HCV positive; and no viral hepatitis. OS in these four groups of patients was not significantly different (p=0.943).

Ongoing, Unpublished, or Incomplete Studies

Transarterial radioembolization versus chemoembolization for the treatment of advanced hepatocellular carcinoma	
Protocol ID:	NCT02729506
Date last modified:	April 5, 2016
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	Time to progression
Accrual:	150 will be accrued
Sponsorship:	King Faisal Specialist Hospital & Research Center
Status:	Recruiting
Comparing re-TACE versus SABR for post-prior-TACE incompletely regressed HCC: a randomized controlled trial (TASABR)	
Protocol ID:	NCT02921139
Date last modified:	February 15, 2018
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	Freedom from local progression
Accrual:	120 will be accrued
Sponsorship:	Dalin Tzu Chi General Hospital
Status:	Recruiting
Transarterial chemoembolization compared with sterotactic body radiation therapy or stereotactic ablative radiation therapy in treating patients with residual or recurrent liver cancer undergone initial transarterial chemoembolization	
Protocol ID:	NCT02762266
Date last modified:	March 1, 2017
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	Median freedom from local progression
Accrual:	160 will be accrued
Sponsorship:	Stanford University
Status:	Recruiting
Transarterial chemoembolization versus stereotactic body radiation therapy for hepatocellular carcinoma (TRENDY)	
Protocol ID:	NCT02470533
Date last modified:	June 2, 2017
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint:	Time to progression
Accrual:	100 will be accrued
Sponsorship:	Erasmus Medical Center
Status:	Recruiting
SBRT or TACE for Advanced HCC	
Protocol ID:	NCT03338647
Date last modified:	November 9, 2017
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint:	Progression
Accrual:	180 will be accrued
Sponsorship:	University of Aarhus
Status:	Recruiting

TACE with or without sorafenib in intermediate stage hepatocellular carcinoma	
Protocol ID:	NCT02529761
Date last modified:	September 21, 2015
Type of trial:	Non-randomized, parallel assignment, active control, open label
Primary endpoint:	Overall survival
Accrual:	330 will be accrued
Sponsorship:	Fourth Military Medical University
Status:	Recruiting

Transarterial chemoembolization (TACE) plus sorafenib versus TACE for advanced hepatocellular carcinoma	
Protocol ID:	NCT02150317
Date last modified:	March 28, 2016
Type of trial:	Randomized, parallel assignment, active control, double blind
Primary endpoint:	Overall survival
Accrual:	180 will be accrued
Sponsorship:	Eastern Hepatobiliary Surgery Hospital
Status:	Recruiting

Chemoembolization with or without sorafenib tosylate in treating patients with liver cancer that cannot be removed by surgery	
Protocol ID:	NCT01004978
Date last modified:	July 19, 2018
Type of trial:	Randomized, parallel assignment, active control, double blind
Primary endpoint	Progression free survival, adverse events, overall survival
Accrual:	400 will be accrued
Sponsorship:	National Cancer Institute (NCI)
Status:	Active, not recruiting

Efficacy evaluation of TheraSphere in patients with inoperable liver cancer (STOP-HCC)	
Protocol ID:	NCT01556490
Date last modified:	March 6, 2018
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall survival
Accrual:	526 enrolled
Sponsorship:	BTG International Inc.
Status:	Active, not recruiting

A randomized, controlled phase III trial of sorafenib with or without cTACE in patients with advanced HCC	
Protocol ID:	NCT01829035
Date last modified:	March 29, 2018
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall survival
Accrual:	339 enrolled
Sponsorship:	National Cancer Center, Korea
Status:	Completed

Sorafenib tosylate with or without stereotactic body radiation therapy in treating patient with liver cancer	
Protocol ID:	NCT01730937
Date last modified:	April 10, 2018
Type of trial:	Randomized, parallel assignment, active control, single blind
Primary endpoint	Overall survival
Accrual:	368 will be accrued
Sponsorship:	National Cancer Institute (NCI)
Status:	Recruiting

E7050 in combination with sorafenib versus sorafenib alone as first-line therapy in patients with hepatocellular carcinoma	
Protocol ID:	NCT01271504
Date last modified:	August 28, 2017
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Adverse events
Accrual:	102 enrolled
Sponsorship:	PharmaBio Development Inc.
Status:	Completed
A study of LY2157299 in participants with advanced hepatocellular carcinoma	
Protocol ID:	NCT02178358
Date last modified:	July 17, 2018
Type of trial:	Randomized, parallel assignment, active control, double blind
Primary endpoint	Overall survival
Accrual:	120 will be accrued
Sponsorship:	Eli Lily and Company
Status:	Active, not recruiting
A study of BBI608 in combination with sorafenib, or BBI503 in combination with sorafenib in adult patients with hepatocellular carcinoma	
Protocol ID:	NCT02279719
Date last modified:	February 12, 2018
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Adverse events, anti-tumour activity
Accrual:	114 will be accrued
Sponsorship:	Boston Biomedical, Inc.
Status:	Recruiting
An investigational immuno-therapy study of nivolumab compared to sorafenib as a first treatment in patients with advanced hepatocellular carcinoma	
Protocol ID:	NCT02576509
Date last modified:	June 5, 2018
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall survival, overall response rate
Accrual:	726 will be accrued
Sponsorship:	Bristol-Myers Squibb
Status:	Active, not recruiting
Hepatocellular carcinoma study comparing vaccina virus based immunotherapy plus sorafenib vs sorafenib alone (PHOCUS)	
Protocol ID:	NCT02562755
Date last modified:	August 6, 2018
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall survival
Accrual:	600 will be accrued
Sponsorship:	SillaJen, Inc.
Status:	Recruiting
The phase III study of icaritin versus sorafenib in PD0-L1 positive advanced hepatocellular carcinoma subjects	
Protocol ID:	NCT03236649
Date last modified:	July 28, 2017
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall survival
Accrual:	200 will be accrued
Sponsorship:	Beijing Shenogen Biomedical Co., Ltd
Status:	Not yet open for recruitment

Metformin plus sorafenib for advanced HCC	
Protocol ID:	NCT02672488
Date last modified:	February 2, 2016
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall survival
Accrual:	82 will be accrued
Sponsorship:	Tianjin Medical University Cancer Institute and Hospital
Status:	Recruiting
An immune-therapy study to evaluate the effectiveness, safety and tolerability of nivolumab or nivolumab in combination with other agents in patients with advanced liver cancer (CheckMate040)	
Protocol ID:	NCT01658878
Date last modified:	August 1, 2017
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Safety, objective response rate
Accrual:	620 will be accrued
Sponsorship:	Bristol-Myers Squibb
Status:	Recruiting
Efficacy, safety, and pharmacokinetic of MSC2156119J in Asian subjects with hepatocellular carcinoma	
Protocol ID:	NCT01988493
Date last modified:	May 17, 2018
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Adverse events, time to progression
Accrual:	90 enrolled
Sponsorship:	Merck KGaA
Status:	Active, not recruiting
Study of SECOX versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma (HCC)	
Protocol ID:	NCT02716766
Date last modified:	May 25, 2017
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Time to progression
Accrual:	138 will be accrued
Sponsorship:	The University of Hong Kong
Status:	Recruiting
Efficacy and safety of donafenib in patients with advanced hepatocellular carcinoma	
Protocol ID:	NCT02645981
Date last modified:	August 3, 2018
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall survival
Accrual:	668 enrolled
Sponsorship:	Suzhou Zelgen Biopharmaceuticals Co., Ltd
Status:	Active, not recruiting

Sorafenib Tosylate with or without doxorubicin hydrochloride in treating patients with locally advanced or metastatic liver cancer	
Protocol ID:	NCT01015833
Date last modified:	July 25, 2018
Type of trial:	Randomized, parallel assignment, active control, single blind
Primary endpoint	Overall survival
Accrual:	356 enrolled
Sponsorship:	National Cancer Institute (NCI)
Status:	Active, not recruiting
A phase I/II trial of nintedanib in Asian hepatocellular carcinoma patients	
Protocol ID:	NCT00987935
Date last modified:	March 10, 2016
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Time to Progression
Accrual:	134 enrolled
Sponsorship:	Boehringer Ingelheim
Status:	Completed
Phase I/II comparison of efficacy and safety of BIBF 1120 and sorafenib in patients with advanced hepatocellular carcinoma	
Protocol ID:	NCT01004003
Date last modified:	October 26, 2017
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Time to Progression
Accrual:	125 enrolled
Sponsorship:	Boehringer Ingelheim
Status:	Completed
Randomized trial sorafenib-pravastatin versus sorafenib alone for the palliative treatment of Child-Pugh A hepatocellular carcinoma	
Protocol ID:	NCT01903694
Date last modified:	May 12, 2014
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Response
Accrual:	474 will be accrued
Sponsorship:	Centre Hospitalier Dijon
Status:	Completed
Efficacy and safety study of sorafenib plus pravastatin to treat advanced hepatocarinoma (ESTAHEP-2010)	
Protocol ID:	NCT01418729
Date last modified:	September 20, 2017
Type of trial:	Randomized, parallel assignment, active control, double blind
Primary endpoint	Overall survival
Accrual:	216 enrolled
Sponsorship:	Hospital Donostia
Status:	Completed
A study of atezolizumab in combination with bevacizumab compared with sorafenib in patients with untreated locally advanced or metastatic hepatocellular carcinoma (IMbrave150)	
Protocol ID:	NCT03434379
Date last modified:	August 1, 2018
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall Survival, Objective Response
Accrual:	480 will be accrued
Sponsorship:	Hoffmann-La Roche
Status:	Recruiting

Phase 3 study of BGB-A317 versus sorafenib in patients with unresectable HCC	
Protocol ID:	NCT03412773
Date last modified:	June 28, 2018
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall survival
Accrual:	660 will be accrued
Sponsorship:	BeiGene
Status:	Recruiting
Study of durvalumab and tremelimumab as first-line treatment in patients with unresectable hepatocellular carcinoma (HIMALAYA)	
Protocol ID:	NCT03298451
Date last modified:	July 26, 2018
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall Survival
Accrual:	1200 will be accrued
Sponsorship:	AstraZeneca
Status:	Recruiting
A study of dovitinib versus sorafenib in adult patients with hepatocellular carcinoma (HCC) as a first line treatment	
Protocol ID:	NCT01232296
Date last modified:	December 4, 2015
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall survival
Accrual:	162 enrolled
Sponsorship:	Novartis Pharmaceuticals
Status:	Completed
Phase 2, randomized, double-blind, placebo-controlled of the efficacy and safety of CF102 in hepatocellular carcinoma (HCC)	
Protocol ID:	NCT02128958
Date last modified:	March 27, 2018
Type of trial:	Randomized, parallel assignment, placebo control, double blind
Primary endpoint	Overall survival
Accrual:	78 will be accrued
Sponsorship:	Can-Fite BioPharma
Status:	Recruiting
A study to assess the efficacy and safety of enzalutamide in subjects with advanced hepatocellular carcinoma	
Protocol ID:	NCT02528643
Date last modified:	August 2, 2018
Type of trial:	Randomized, parallel assignment, placebo control, double blind
Primary endpoint	Overall survival
Accrual:	165 enrolled
Sponsorship:	Medivation, Inc.
Status:	Active, not recruiting
Study of pembrolizumab (MK-3475) vs. best supportive care in participants with previously systematically treated advanced hepatocellular carcinoma (MK-3475-240/KEYNOTE-240)	
Protocol ID:	NCT02702401
Date last modified:	November 9, 2017
Type of trial:	Randomized, parallel assignment, placebo control, double blind
Primary endpoint	Overall survival, progression free survival
Accrual:	408 will be accrued
Sponsorship:	Merck Sharp & Dohme Corp.
Status:	Active, not recruiting

Efficacy and safety doxorubicin transdrug study in patients suffering from advanced hepatocellular carcinoma (ReLive)	
Protocol ID:	NCT01655693
Date last modified:	October 5, 2017
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall survival
Accrual:	390 will be accrued
Sponsorship:	Onxeo
Status:	Active, not recruiting
A study of LY2157299 in participants with hepatocellular carcinoma	
Protocol ID:	NCT01246986
Date last modified:	May 31, 2018
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Time to progression
Accrual:	235 will be accrued
Sponsorship:	Eli Lilly and Company
Status:	Active, not recruiting
Study of apatinib after systemic therapy in patients with hepatocellular carcinoma (AHELP)	
Protocol ID:	NCT02329860
Date last modified:	July 4, 2017
Type of trial:	Randomized, parallel assignment, placebo control, double blind
Primary endpoint	Overall survival
Accrual:	400 will be accrued
Sponsorship:	NanJing PLA 81 Hospital
Status:	Active, not recruiting
Study of pembrolizumab (MK-3475) or placebo given with best supportive care in Asian participants with previously treated advanced hepatocellular carcinoma (MK-3475-394/KEYNOTE-394)	
Protocol ID:	NCT03062358
Date last modified:	July 25, 2018
Type of trial:	Randomized, parallel assignment, placebo control, double blind
Primary endpoint	Overall survival
Accrual:	330 will be accrued
Sponsorship:	Merck Sharp & Dohme Corp.
Status:	Recruiting
A randomized double-blind, placebo-controlled Japanese phase III trial of ARQ 197 in hepatocellular carcinoma (HCC) (JET-HCC)	
Protocol ID:	NCT02029157
Date last modified:	October 9, 2017
Type of trial:	Randomized, parallel assignment, placebo control, double blind
Primary endpoint	Progression free survival
Accrual:	386 enrolled
Sponsorship:	Kyowa Hakko Kirin Co., Ltd
Status:	Recruiting
Trial of ARQ 197 in patients with unresectable hepatocellular carcinoma (HCC) who have failed one prior systemic therapy	
Protocol ID:	NCT00988741
Date last modified:	February 28, 2013
Type of trial:	Randomized, parallel assignment, placebo control, double blind
Primary endpoint	Time to Progression
Accrual:	107 enrolled
Sponsorship:	ArQule
Status:	Completed

A study of RO5137382 (GC33) in patients with advanced or metastatic hepatocellular carcinoma	
Protocol ID:	NCT01507168
Date last modified:	November 2, 2016
Type of trial:	Randomized, parallel assignment, placebo control, double blind
Primary endpoint	Progression Free Survival
Accrual:	186 enrolled
Sponsorship:	Hoffmann-La Roche
Status:	Completed

DISCUSSION

The majority of patients with newly diagnosed HCC are not eligible for curative therapies, including local or regional ablative therapies, hepatic resection, or transplant. Previous guidelines have reviewed the evidence for local or regional ablative therapies [87,88]. In this guideline, we reviewed the current evidence for all treatment options for advanced, unresectable HCC. We focused on three areas: TACE, systemic therapies, and treatment of underlying hepatitis B and C.

TACE

In the initial management of HCC, small and/or isolated lesions (BCLC A) can be treated by a number of therapies (i.e., most commonly TEA, TAE, RFA). We searched the literature to determine whether local/regional therapies have been compared in the setting of more advanced disease to TACE. We were unable to clearly find data for or against the use of TEA, TAE, RFA, TARE, SBRT, or DEB-TACE compared with TACE. The majority of studies found were small and moderate to poor quality. Treatment decisions need to occur in a multidisciplinary setting given the number of subspecialists involved. Following the treatment of local or regional therapies, there is no evidence to support the addition of sorafenib following this. The majority of these studies also tended to be small and of moderate to poor quality. Following failure of local or regional therapies, patients suitable for systemic therapy should be considered for treatment.

Systemic Therapies

For patients who are either ineligible for local or regional therapies or have progressed following them, the number of systemic therapies now available has increased since earlier in the decade. At present, there are RCT data showing that the tyrosine kinase inhibitors sorafenib and lenvatinib have OS improvements in this setting. In addition, the PD-L1 nivolumab is being compared with sorafenib in an active clinical trial (NCT0257650).

In the second-line setting, both regorafenib and cabozantinib have received approval by the US Food and Drug Administration (FDA) (the latter based on abstract publication only). In addition, nivolumab has received provisional approval (FDA/Health Canada) based on response rates seen.

Treatment of Hepatitis B/C

Treatment of underlying hepatitis is an important consideration and should be left in the hands of subspecialists with expertise in this area such as hepatologists. Patients with surface antigen-positive hepatitis B should be treated owing to the fact that it prevents reactivation of hepatitis B and overall progression of liver disease. On the other hand, there is currently no evidence for the treatment of hepatitis C in advanced HCC.

CONCLUSIONS

There is no evidence for or against the use of local or regional interventions other than TACE for the treatment of intermediate-stage or greater HCC. Furthermore, there is no evidence to support the addition of sorafenib to any local or regional therapy. Single-agent sorafenib or lenvatinib are recommended for first-line systemic treatment of intermediate-stage HCC. Regorafenib or cabozantinib provide survival benefits when given as second-line treatment after progression on sorafenib. HBV eradication is recommended in those with advanced HCC.

Non-Surgical Management of Advanced Hepatocellular Carcinoma

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 2). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 27 members of the GDG Expert Panel, 22 members cast votes and no one abstained, for a total of 81% response in October 2018. Of those that cast votes, 22 approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. Change the wording of Recommendations 1 and 2 from "There is *no* evidence for…" to "There is *insufficient* evidence for…".	We have made this wording change.
2. Identify which interventions are 'local' and which are 'regional'.	We have made this more explicit.
3. Suggestion that an update should be done in 2-3 years as immune therapy will almost certainly supplant sorafenib and lenvantinib by then.	No changes were needed as a mechanism already exists for evaluating the relevancy and currency of documents on an annual basis and subsequently updating when needed.
4. Address the results of REACH-2 in the recommendations.	A Qualifying Statement was added to Recommendation 4 regarding REACH-2.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in August 2018. The RAP approved the document August 20, 2018. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. Questions not framed entirely in PICO terms	We have added in a statement indicating that all questions pertain to patients with advanced HCC.
2. Discuss the strengths and weaknesses of the guideline as well as the risks and side effects of the interventions.	We have included this information in the discussion as suggested.
3. Is TACE the standard of care? If so, it should be stated in Recommendation 1.	We have modified this recommendation.
4. Add in a table with the many acronyms and what they mean for each intervention covered in this guideline.	We have added in a glossary at the end of Section 1.
5. Be explicit that Barcelona Stage B is the same as Intermediate stage.	We have clarified this.

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Four targeted peer reviewers from Ontario, California, and Massachusetts who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Two agreed to be the reviewers (Appendix 2). Two responses were received. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.					2
2. Rate the guideline presentation.				1	1
3. Rate the guideline recommendations.					2
4. Rate the completeness of reporting.			1		1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	
6. Rate the overall quality of the guideline report.				2	
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			1	1	
8. I would recommend this guideline for use in practice.				1	1
9. What are the barriers or enablers to the implementation of this guideline report?	• Poor recognition of TACE failure. • Lack of access to drugs and technologies.				

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. A comment that no definition of TACE failure was provided.	We have added a qualifying statement to address the challenge in defining TACE failure.
2. An observation that a trial of TARE vs. sorafenib (SIRveNIB) was missing from the guideline.	This comparison was not a question of interest in this guidance document.
3. A comment that immunotherapy studies were not included in the guideline	This was not a question of interest in this guidance document. It may become germane in future updates of this guideline and would be included at that time.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All medical oncologists, radiation oncologists and surgical oncologists in the PEBC database were contacted by email to inform them of the survey. In addition a presentation was made to the CCO Interventional Oncology Steering Committee to seek volunteers from among the provinces interventional radiology community. Finally, in order to find hepatologists willing to volunteer, the Canadian Association of the Study of the Liver (CASL) was contacted so they could inform the membership about the survey. Of the 141 professionals who were contacted, 140 practiced in Ontario and one practiced in Alberta. Seven stated that they did not have interest in this area, were unavailable to review this guideline at the time, or were retired. Responses were received from 17 of the remaining 134 (12.7%) professionals. The results of the feedback survey from 17 respondents are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number(%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.		1(6)	1(6)	7(41)	8(47)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	1(6)		1(6)	6(35)	9(53)
3. I would recommend this guideline for use in practice.	1(6)		1(6)	5(29)	10(59)
4. What are the barriers or enablers to the implementation of this guideline report?	**BARRIERS** • Toxicity of treatment. • Absence or inadequate funding for drugs, technologies, and/or other resources (eg., healthcare providers with the appropriate expertise). • Lack of evidence on which to make recommendations. • Difficult to find guidelines on the CCO website. **ENABLERS** • Clear and thorough guideline that should be widely disseminated				

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	Responses
1. A comment that RTOG1112 was not mentioned.	This is an ongoing trial of a question not included in this guideline.
2. A suggestion that definitions for BCLC B and BCLC C should be included.	These definitions have been added in.
3. A query regarding the appropriateness of switching between sorafenib and lenvatinib in first-line therapy and regorafenib and cabozantinib in second-line therapy as indicated in the qualifying statements for Recommendations 3 and 4.	These qualifying statements have been amended to be much more specific.
4. A comment that some types of external beam radiation were missing from the guideline.	We did not address the various types of external beam radiation other than SBRT.
5. A comment on the absence of cost information.	This is beyond the scope of this guideline.
6. A comment that this guideline should be disseminated to all HCC MCCs.	The PEBC does not engage in dissemination beyond that which is accomplished through the professional consultation process. There are other groups that deal with dissemination.
7. A comment that access, process, and resource allocation issues were not addressed and should have been the focus of the guideline.	These issues, while important, are beyond the scope of this guideline. However, this guideline is the first step toward addressing these other issues.
8. A comment that it would have been helpful to have input from a patient representative.	The working group agrees and the PEBC is currently starting to implement a process whereby patient representatives are included in working groups.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GI DSG Working Group and approved by the GI DSG Expert Panel and the PEBC RAP.

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Appendix 1. Members of the Non-Surgical Management of Hepatocellular Carcinoma Guideline Development Group

Name	Specialty	Affiliation
Tim Asmis	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Mala Bahl	MO	Trillium Health Partners Mississauga, ON
Robert Beecroft	IR	Mount Sinai Hospital Toronto, ON
Scott Berry	MO	Odette Cancer Centre Toronto, ON
Jim Biagi	MO	Cancer Centre of Southeastern Ontario Kingston, ON
Kelvin Chan	MO	Odette Cancer Centre Toronto, ON
Charles Cho	RO	Stronach Regional Cancer Program Newmarket, ON
Natalie Coburn	SO	Odette Cancer Centre Toronto, ON
Kristopher Dennis	RO	Ottawa Hospital Cancer Centre Ottawa, ON
Mark Doherty	MO	Odette Cancer Centre Toronto, ON
Tarek Elfiki	MO	Windsor Regional Cancer Centre Windsor, ON
Elena Elimova	MO	Princess Margaret Hospital Toronto, ON
Jordan Feld	HEP	Toronto Western Hospital Toronto, ON
Valerie Francescutti	SO	Hamilton General Hospital Hamilton, ON
Rachel Goodwin	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Robert Gryfe	SO	Mt. Sinai Hospital Toronto, ON
Julie Hallet	SO	Odette Cancer Centre Toronto, ON
Nazik Hammad	MO	Cancer Centre of Southeastern Ontario Kingston, ON
Khalid Hirmiz	RO	Windsor Regional Cancer Centre Windsor, ON
Raymond Jang	MO	Princess Margaret Hospital Toronto, ON
Derek Jonker	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Maria Kalyvas	RO	Cancer Centre of Southeastern Ontario Kingston, ON

Paul Karanicolas	SO	Odette Cancer Centre Toronto, ON
Erin Kennedy	SO	Mt. Sinai Hospital Toronto, ON
Jennifer Knox	MO	Princess Margaret Cancer Centre Toronto, ON
Aamer Mahmud	RO	Cancer Centre of Southeastern Ontario Kingston, ON
Richard Malthaner	SO	London Regional Cancer Program London, ON
Brandon Meyers	MO	Juravinski Cancer Centre Hamilton, ON
Fayez Quereshy	SO	Princess Margaret Hospital Toronto Western Hospital Toronto, ON
Jolie Ringash	RO	Princess Margaret Hospital Toronto, ON
Mark Rother	MO	Peel Regional Cancer Centre Mississauga, ON
Gonzalo Sapisochin	SO	Toronto General Hospital Toronto, ON
Stephen Welch	MO	London Regional Cancer Progam London, ON
Raimond Wong	RO	Juravinski Cancer Centre Hamilton, ON
Rebecca Wong	RO	Princess Margaret Hospital Toronto, ON
Youssef Youssef	RO	Durham Regional Cancer Centre Oshawa, ON
Kevin Zbuk	MO	Juravinski Cancer Centre Hamilton, ON
Roxanne Cosby	HRM	Program in Evidence-Based Care McMaster University Hamilton, ON

Abbreviations: HR=health research methodologist; HEP=hepatologist; IR=interventional radiologist; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Appendix 2. Members of the Non-Surgical Management of Hepatocellular Carcinoma Working Group, Expert Panel, Report Approval Panel and Target Reviewers and their COI Declarations.

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors (Working Group), Non-Surgical Management of Hepatocellular Carcinoma Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Members of the Non-Surgical Management of Hepatocellular Carcinoma Working Group

Name	Specialty	Affiliation	Declarations of interest
Brandon Meyers Co-Chair	MO	Juravinski Cancer Centre Hamilton, ON	Has received $5000 or more in a single year to act in a consulting capacity for Eisai. Has received $5000 or more in a single year for other financial support from Sillajen. Therefore total support would be for $10000 or more only in 2019. Has received research grants from Eisai. Has provided expert testimony to pCODR for Eisai.
Jennifer Knox Co-Chair	MO	Princess Margaret Cancer Centre Toronto, ON	Has received research grants from Merck, Astra Zeneca and Pfizer to support investigator initiated trials lead by JK. Was a PI for an Astra Zeneca trial regarding adjuvant HCC (Emerald-2).
Rob Beecroft	IR	Mount Sinai Hospital Toronto, ON	Is a site PI for the STOP HCC trial of TARE + sorafenib vs. sorafenib alone. This trial has completed recruiting.
Kelvin Chan	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest.
Natalie Coburn	SO	Odette Cancer Centre Toronto, ON	Receives salary support as Cancer Care Ontario's Clinical Lead for Patient Reported Outcomes and Symptom Management.
Jordan Feld	HEP	Toronto Western Hospital Toronto, ON	Received consulting fees from: AbbVie. Is an advisory board member for AbbVie. Has received research grants from AbbVie, Gilead Sciences, Janssen, Wako/Fujifilm. Has been a PI for a trial of serum biomarkers for the detection of HCC for Wako-Fujifilm.
Derek Jonker	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Declared they had no conflicts of interest.
Aamer Mahmud	RO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest.
Jolie Ringash	RO	Princess Margaret Hospital Toronto, ON	Declared they had no conflicts of interest.
Roxanne Cosby	HRM	Program in Evidence-Based Care McMaster University Hamilton, Ontario	Declared they had no conflicts of interest.

Abbreviations: HRM=health research methodologist; HEP=hepatologist; IR=Interventional Radiologist; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Members of the Non-Surgical Management of Hepatocellular Carcinoma Expert Panel

Name	Specialty	Affiliation	Declarations of interest
Tim Asmis	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Declared they had no conflicts of interest.
Mala Bahl	MO	Trillium Health Partners Mississauga, ON	Declared they had no conflicts of interest.
Scott Berry	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest.
Jim Biagi	MO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest.
Charles Cho	RO	Stronach Regional Cancer Program Newmarket, ON	Declared they had no conflicts of interest.
Kristopher Dennis	RO	Ottawa Hospital Cancer Centre Ottawa, ON	Declared they had no conflicts of interest.
Mark Doherty	MO	Odette Cancer Centre Toronto, ON	Has received research support from Merck and AstraZeneca.
Tarek Elfiki	MO	Windsor Regional Cancer Centre Windsor, ON	Declared they had no conflicts of interest.
Elena Elimova	MO	Princess Margaret Hospital Toronto, ON	Spouse is a director for global strategy for Merck Vaccines. Is an institution PI of studies for Bristol-Myers Squibb and Astellas.
Valerie Francescutti	SO	Hamilton General Hospital Hamilton, ON	Declared they had no conflicts of interest.
Rachel Goodwin	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Declared they had no conflicts of interest.
Robert Gryfe	SO	Mt. Sinai Hospital Toronto, ON	Declared they had no conflicts of interest.
Julie Hallet	SO	Odette Cancer Centre Toronto, ON	Received speaking honoraria from Ipsen and Novartis for rounds on NETs. Received support from Baxter for the HPB CUSP.
Nazik Hammad	MO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest.
Khalid Hirmiz	RO	Windsor Regional Cancer Centre Windsor, ON	Declared they had no conflicts of interest.
Raymond Jang	MO	Princess Margaret Cancer Centre Toronto, ON	Received research support from Merck, Astra Zeneca, Eli Lilly, Novartis, Boston Biomedical.
Maria Kalyvas	RO	Cancer Centre of Southeastern Ontario Kingston, ON	
Paul Karanicolas	SO	Odette Cancer Centre Toronto, ON	Received speaker honorarium from Sanofi. Received a research grant from Baxter.
Erin Kennedy	SO	Mt. Sinai Hospital Toronto, ON	Declared they had no conflicts of interest.
Richard Malthaner	SO	London Regional Cancer Program London, ON	Declared they had no conflicts of interest.

Fayez Quereshy	SO	Princess Margaret Hospital Toronto Western Hospital Toronto, ON	Declared they had no conflicts of interest.
Mark Rother	MO	Peel Regional Cancer Centre Mississauga, ON	Declared they had no conflicts of interest.
Gonzalo Sapisochin	SO	Toronto General Hospital Toronto, ON	Has received $10,000 from Bayer for Research Support of the UHN Liver Cancer Research Group. Bayer sponsors our meetings every 6 weeks (~$3000/year).
Stephen Welch	MO	London Regional Cancer Progam London, ON	Declared they had no conflicts of interest.
Raimond Wong	RO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest.
Rebecca Wong	RO	Princess Margaret Hospital Toronto, ON	Declared they had no conflicts of interest.
Kevin Zbuk	MO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest.

Abbreviations: MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Members of the Non-Surgical Management of Hepatocellular Carcinoma Report Approval Panel

Name	Specialty	Affiliation	Declarations of interest
Melissa Brouwers	HRM	Program in Evidence-Based Care	Declared they had no conflicts of interest.
Laurie Elit	SO	Juravinski Cancer Centre	Declared they had no conflicts of interest.
Donna Maziak	SO	The Ottawa Hospital	Declared they had no conflicts of interest.

Abbreviations: HRM=health research methodologist; SO=surgical oncologist

Members of the Non-Surgical Management of Hepatocellular Carcinoma Targeted Peer Reviewers

Name	Specialty	Affiliation	Declarations of interest
Morris Sherman	GE	University Health Network	Has been a member of the independent data monitoring committee of the registration trials for regorafenib.
Ted Hong	RO	Massachusetts General Hospital, Harvard Medical School	Has received grants or other research support within the last five years from Bristol-Myers Squibb, Taiho, Astra-Zeneca and Novartis. Has been a principal investigor within the last five years for NCT03482102; NCT00976898; NCT03186898. Has published several opinion pieces related to HCC in the last five years.

GE=gastroenterologist; RO=radiation oncologist

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy.

Appendix 3: Literature Search Strategies for Clinical Practice Guidelines, Systematic Reviews and Primary Literature

Clinical Practice Guidelines

MEDLINE

1. Liver Neoplasms/ or Carcinoma, Hepatocellular/ or HCC.mp.
2. exp Evidence-Based Practice/
3. exp Practice Guideline/
4. guideline.pt.
5. practice parameter$.tw.
6. practice guideline$.mp.
7. (guideline: or recommend: or consensus or standards).ti.
8. (guideline: or recommend: or consensus or standards).kw.
9. or/2-8
10. 1 and 9
11. limit 10 to yr="2013 - 2016"
12. limit 11 to english language

EMBASE

1. exp liver cell carcinoma/ or heptocellular carcinoma.mp.
2. hcc.mp.
3. liver neoplasms.mp. or exp liver tumor/
4. or/1-3
5. exp evidence based practice/
6. exp practice guideline/
7. guideline.pt.
8. practice parameter$.tw.
9. practice guideline$.mp.
10. (guideline: or recommend: or consensus or standards).ti.
11. (guideline: or recommend: or consensus or standards).kw.
12. or/5-11
13. 4 and 12
14. limit 13 to english language
15. limit 14 to yr="2013 - 2016"

Systematic Reviews

MEDLINE

1. Liver Neoplasms/ or carcinoma, hepatocellular/ or HCC.mp.

2. exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw. or (medline or med-line or pubmed or pub-med or embase or cochrane or cancerlit).ab.

3. 1 and 2

4. limit 3 to english language

5. limit 4 to yr="2000 - 2016"

EMBASE

1. exp liver cell carcinoma/ or hepatocellular carcinoma.mp.

2. hcc.mp.

3. liver neoplasms.mp. or exp liver tumor/

4. or/1-3

5. exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw. or (medline or med-line or pubmed or pub-med or embase or cochrane or cancerlit).ab.

6. 4 and 5

7. limit 6 to english language

8. limit 7 to yr="2000 - 2016"

Primary Studies

MEDLINE

1. Liver Neoplasms/ or Carcinoma, Hepatocellular/ or HCC.mp.
2. exp Chemoembolization, Therapeutic/
3. transarterial chemoembolization.mp.
4. transcatheter arterial chemoembolization.mp.
5. exp Catheter Ablation/
6. TACE.mp.
7. DEB-TACE.mp.
8. drug eluting bead$.mp.
9. or/2-8
10. exp Embolization, Therapeutic/
11. transarterial ethanol ablation.mp.
12. TEA.mp.
13. or/10-12
14. bland transarterial embolization.mp.
15. transarterial bland embolization.mp.
16. bland embolization.mp.
17. TAE.mp.
18. or/14-17
19. radiofrequency ablation.mp.
20. RFA.mp.
21. or/19-20
22. transarterial radioembolization.mp.
23. exp Yttrium Radioisotopes/ or exp Yttrium/ or exp Yttrium Isotopes/
24. selective internal radiation therapy.mp.
25. selective internal radiation treatment.mp.
26. SIRT.mp.
27. TARE.mp.
28. or/22-27
29. stereotactic body radiation therapy.mp.
30. stereotactic body radiation treatment.mp.
31. stereotactic ablative radiotherapy.mp.
32. stereotactic ablative radiation treatment.mp.
33. SABR.mp.
34. SBRT.mp.
35. or/29-34
36. sorafenib.mp.
37. nexavar.mp.
38. or/36-37
39. exp Hepatitis B/ or exp Hepatitis, Viral, Human/ or exp Hepatitis C/
40. exp Hepatitis B, Chronic/
41. HBV.mp.
42. exp Hepatitis C, Chronic/
43. HCV.mp.
44. viral hepatitis.mp.
45. or/39-44
46. peginterferon.mp.

47. exp Interferons/
48. exp Antiviral Agents/
49. exp Ribavirin/
50. exp Drug Therapy, Combination/
51. telaprevir.mp.
52. boceprevir.mp.
53. exp Simeprevir/
54. exp Sofosbuvir/
55. daclatasvir.mp.
56. ledipasvir.mp.
57. harvoni.mp.
58. paritaprevir.mp.
59. ombitasvir.mp.
60. dasabuvir.mp.
61. viekira.mp.
62. holkira.mp.
63. exp Ritonavir/
64. grazoprevir.mp.
65. elbasvir.mp.
66. zepatier.mp.
67. or/46-66
68. 9 or 13 or 18 or 21 or 28 or 35
69. 45 and 67
70. 1 and 68
71. limit 70 to english language
72. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
73. 71 not 72
74. animal/ not (exp human/ or humans/)
75. 73 not 74
76. limit 75 to yr="2000 - 2016"
77. 1 and (68 and 38)
78. limit 77 to english language
79. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
80. 78 not 79
81. animal/ not (exp human/ or humans/)
82. 80 not 81
83. limit 82 to yr="2005 - 2016"
84. 1 and 38
85. limit 84 to english language
86. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
87. 85 not 86
88. animal/ not (exp human/ or humans/)
89. 87 not 88
90. limit 89 to yr="2005 - 2016"
91. 1 and 69
92. limit 91 to english language

93. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.

94. 92 not 93

95. animal/ not (exp human/ or humans/)

96. 94 not 95

97. limit 96 to yr="2005 - 2016"

98. 1 and (38 and 45)

99. limit 98 to english language

100. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.

101. 99 not 100

102. animal/ not (exp human/ or humans/)

103. 101 not 102

104. limit 103 to yr="2005 - 2016"

105. 1 and ((9 or 13 or 18) and 45)

106. limit 105 to english language

107. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.

108. 106 not 107

109. animal/ not (exp human/ or humans/)

110. 108 not 109

111. limit 110 to yr="2005 - 2016"

112. exp Chemoembolization, Therapeutic/

113. transarterial chemoembolization.mp.

114. transcatheter arterial chemoembolization.mp.

115. exp Catheter Ablation/

116. TACE.mp.

117. or/112-116

118. drug eluting bead$.mp.

119. DEB-TACE.mp.

120. or/118-119

121. 13 or 18 or 21 or 28 or 35 or 120

122. 1 and 117 and 121

123. limit 122 to english language

124. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.

125. 123 not 124

126. animal/ not (exp human/ or humans/)

127. 125 not 126

128. limit 127 to yr="2000 - 2016"

EMBASE

1. hepatocellular carcinoma.mp. or exp liver cell carcinoma/
2. liver neoplasms.mp. or exp liver tumor/
3. exp liver cell carcinoma/
4. hcc.mp.
5. or/1-4
6. exp chemoembolization/
7. transcatheter arterial chemoembolization.mp.
8. exp catheter ablation/
9. DEB-TACE.mp.
10. drug eluting bead$.mp.
11. TACE.mp.
12. or/6-11
13. embolization.mp. or exp artificial embolization/
14. transarterial ethanol ablation.mp.
15. TEA.mp.
16. or/13-15
17. bland transarterial embolization.mp.
18. transarterial bland embolization.mp.
19. bland embolization.mp.
20. TAE.mp.
21. or/17-20
22. exp radiofrequency ablation/
23. RFA.mp.
24. or/22-23
25. exp yttrium 90/ or transarterial radioembolization.mp. or exp microsphere/
26. selective internal radiation therapy.mp.
27. selective internal radiation treatment.mp.
28. SIRT.mp.
29. TARE.mp.
30. or/25-29
31. exp stereotactic body radiation therapy/
32. stereotactic body radiation treatment.mp.
33. stereotactic ablative radiotherapy.mp.
34. stereotactic ablative radiation treatment.mp.
35. SABR.mp.
36. SBRT.mp.
37. or/31-36
38. sorafenib.mp. or exp sorafenib/
39. nexavar.mp.
40. or/38-39
41. exp hepatitis C/ or exp hepatitis B/ or exp hepatitis/
42. exp virus hepatitis/
43. chronic hepatitis B.mp.
44. HBV.mp. or exp Hepatitis B virus/
45. chronic hepatitis C.mp.
46. exp Hepatitis C virus/ or HCV.mp.
47. or/41-46

48. exp peginterferon/
49. exp interferon/
50. exp antivirus agent/
51. exp ribavirin/
52. exp combination drug therapy/
53. exp telaprevir/
54. exp boceprevir/
55. exp simeprevir/
56. exp sofosbuvir/
57. exp daclatasvir/
58. exp ledipasvir/
59. harvoni.mp. or exp ledipasvir plus sofosbuvir/
60. exp paritaprevir/
61. exp ombitasvir/
62. exp dasabuvir/
63. exp dasabuvir plus ombitasvir plus paritaprevir plus ritonavir/ or viekira.mp.
64. holkira.mp.
65. exp ritonavir/
66. exp grazoprevir/
67. exp elbasvir plus grazoprevir/ or exp elbasvir/
68. zepatier.mp.
69. or/48-68
70. 12 or 16 or 21 or 24 or 30 or 37
71. 47 and 69
72. 5 and 70
73. limit 72 to english language
74. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
75. 73 not 74
76. animal/ not (exp human/ or humans/)
77. 75 not 76
78. limit 77 to yr="2000 - 2016"
79. 5 and (70 and 40)
80. limit 79 to english language
81. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
82. 80 not 81
83. animal/ not (exp human/ or humans/)
84. 82 not 83
85. limit 84 to yr="2005 - 2016"
86. 5 and 40
87. limit 86 to english language
88. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
89. 87 not 88
90. animal/ not (exp human/ or humans/)
91. 89 not 90
92. limit 91 to yr="2005 - 2016"
93. 5 and 71
94. limit 93 to english language
95. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/

96. 94 not 95
97. animal/ not (exp human/ or humans/)
98. 96 not 97
99. limit 98 to yr="2005 - 2016"
100. 5 and (40 and 47)
101. limit 100 to english language
102. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
103. 101 not 102
104. animal/ not (exp human/ or humans/)
105. 103 not 104
106. limit 105 to yr="2005 - 2016"
107. 5 and ((12 or 16 or 21) and 47)
108. limit 107 to english language
109. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
110. 108 not 109
111. animal/ not (exp human/ or humans/)
112. 110 not 111
113. limit 112 to yr="2005 - 2016"
114. exp chemoembolization/
115. transcatheter arterial chemoembolization.mp.
116. exp catheter ablation/
117. TACE.mp.
118. or/114-117
119. drug eluting bead$.mp.
120. DEB-TACE.mp.
121. or/119-120
122. 16 or 21 or 24 or 30 or 37 or 121
123. 5 and 118 and 122
124. limit 123 to english language
125. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
126. 124 not 125
127. animal/ not (exp human/ or humans/)
128. 126 not 127
129. limit 128 to yr="2000 - 2016"