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Guidelines

Multidisciplinary treatment of hepatocellular carcinoma in 2023: Italian practice Treatment Guidelines of the Italian Association for the Study of the Liver (AISF), Italian Association of Medical Oncology (AIOM), Italian Association of Hepato-Bilio-Pancreatic Surgery (AICEP), Italian Association of Hospital Gastroenterologists (AIGO), Italian Association of Radiology and Clinical Oncology (AIRO), Italian Society of Pathological Anatomy and Diagnostic Cytology (SIAPeC-IAP), Italian Society of Surgery (SIC), Italian Society of Gastroenterology (SIGE), Italian Society of Medical and Interventional Radiology (SIRM), Italian Organ Transplant Society (SITO), and Association of Patients with Hepatitis and Liver Disease (EpaC) – Part II – Non-surgical treatments

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ABSTRACT

Worldwide, hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death. The remarkable improvements in treating HCC achieved in the last years have increased the complexity of its management. Following the need to have updated guidelines on the multidisciplinary treatment management of HCC, the Italian Scientific Societies involved in the management of this cancer have promoted the drafting of a new dedicated document. This document was drawn up according to the GRADE methodology needed to produce guidelines based on evidence. Here is presented the second part of guidelines, focused on the multidisciplinary tumor board of experts and non-surgical treatments of HCC.

1. Introduction

This report summarizes the recommendations of Clinical Practice Guidelines regarding non-surgical treatments of Hepatocellular Carcinoma (HCC) [1], drawn up according to the GRADE methodology [2] and promoted by the following scientific societies: Italian Association for the Study of the Liver (AISF), Italian Association of Medical Oncology (AIOM), Italian Association of Hepato-Bilio-Pancreatic Surgery (AICEP), Italian Association of Hospital Gastroenterologists (AIGO), Italian Association of Radiology and Clinical Oncology (AIRO), Italian Society of Pathological Anatomy and Diagnostic Cytology (SIAPeC-IAP), Italian Society of Surgery (SIC), Italian Society of Gastroenterology (SIGE), Italian Society of Medical and Interventional Radiology (SIRM), Italian Organ Transplant Society (SITO), and Association of Patients with Hepatitis and Liver Disease (EpaC).

Current knowledge on treatment of HCC is translated into relevant practical recommendations following the rules and the methodology indicated by the Centro Nazionale per l'Eccellenza delle Cure (CNEC) and the Istituto Superiore di Sanità (ISS).

The guideline developers, designated by the above-mentioned scientific societies, identified key questions that health care providers are frequently faced with in the management of patients with HCC.

2. Background

HCC is a common cause of cancer-related mortality and morbidity worldwide [3,4] with variable, but on average still poor prognosis [5], that in the vast majority of cases occurs in patients with chronic liver disease, usually in the cirrhotic stage [6,7]. Early detection of HCC, increasing the percentage of early-stage tumors, expands the rate of patients amenable to curative treatments, favorably impacting overall survival [8,9].

In recent years, the therapeutic armamentarium of HCC has been remarkably enriched with new effective techniques and strategies, leading to the need of a management involving different specialists [10,11]. Indeed, prediction of outcome and treatment choice are particularly complex as they must consider the underlying liver disease and comorbidities, which condition treatment feasibility and have an inherent competing mortality risk [12].

In this line, in the first part of these Clinical Practice Guidelines, the Panel underlines the fundamental role of the Multidisciplinary Board in the management of patients with HCC [10,13].

3. Methods for developing the guideline

Twenty-two experts indicated by the above-mentioned scientific societies, plus 2 delegates of the EpaC patient association, selected by collegial discussion the key questions and draw up guidelines. This document was arranged according to the rules of the CNEC of the Italian Ministry of Health. The key questions were developed according to the Population, Intervention, Comparison, Outcomes (PICO) acronym. For each PICO question, the literature on MEDLINE/Pubmed, Embase and Cochrane Library databases was systematically searched with both Thesaurus terms and free text. A further hand-search was performed on the bibliography of articles and previously published guidelines.

Recommendations were formulated applying the GRADE approach [2] according to the CNEC manual [14]. All aspects concerning questions, assessment of evidence and conclusions were discussed among panel members and voted. Before voting, members declared their potential conflict of interest (COI) relevant to the PICO question, and only those without COI voted. The online GRADEpro GDT tool was used to develop questions, assess evidence, and make decisions [15]. The certainty of evidence was assessed applying the tool for Risk of Bias in randomized trials (RoB) as suggested by Cochrane [16], and the Newcastle-Ottawa scale for non-randomized studies [17].

Certainty of evidence, significance and consequence are reported in Table 1 [1].

The Panel provided justifications for the final recommendations (strong pro, conditional pro, conditional against, and strong against), including relevant considerations on implementation, monitoring and evaluation indicators, and priorities for research.

4. PICO questions and recommendations

Table 2 summarizes PICO questions about Non-Surgical treatment, Recommendations, Certainty of evidence, and Strength of

Table 1
Graduation of certainty of Evidence [1].

Certainty of Evidence	Significance	Consequence
High	High degree of confidence in the results	It is very likely that the true treatment effect is similar to the estimated one
Moderate	Fair degree of confidence in the results	The true treatment effect is likely to be similar to the estimated one but there is the possibility that the effect is different
Low	Results not very credible	Confidence in the estimate of the effect is limited: the true effect could be substantially different from the estimated one
Very Low	Data examined totally unreliable	Confidence in the estimate of the effect is very limited: it is likely that the true effect is substantially different from the estimated one

recommendation of Clinical Practice Guidelines for the management of Hepatocellular Carcinoma (HCC).

In this document [1] many recommendations show "Very Low" or "Low" in term of Certainty in evidence. This is particularly true for PICOs related to locoregional treatments for which recommendations often derive from observational studies (that, according to the GRADE's approach, start as low-quality evaluation of evidence). In fact, devices usually do not require positive RCTs to be registered.

1. **In patients with compensated cirrhosis and single intermediate-sized (3.1–5 cm) unresectable HCC, is the combined treatment of percutaneous ablation + intra-arterial therapy versus ablation alone indicated?**

Although liver transplantation (LT) remains the ideal treatment for cirrhotic patients with HCC [10], ineligibility to LT due to several reasons, the limited availability of grafts and the growing and improved efficacy of therapeutic alternatives to transplantation have led to consider resection and locoregional therapies as first-line options for some of these patients [10,13].

For patients with compensated cirrhosis and unresectable single HCC of intermediate size (3.1–5 cm), the panel believes that the data emerging from the two available studies do not allow the conclusion that the use of the combined treatment TACE + percutaneous ablation is preferable to ablation alone. Although the combination therapy is now used in clinical practice, in particular situations, the panel underlines the scarcity and low quality of data comparing the two methods.

One randomized controlled trial (RCT) [18] and one propensity score adjusted observational study [19] were considered. The RCT showed a non-significant relative risk (RR) for survival at 1 year (RR 1.12, 95 % CI 0.93–1.36) and at 3 years (RR 1.22, 95 % CI 0.93–1.59) [18]. The observational study showed a Hazard Ratio (HR) of 0.49 (95 % CI 0.35–0.69 for the risk of death in favor of the combined treatment; the HR was 0.50 (95 % CI 0.38–0.66) for the risk of death or progression [19].

Moreover, based on the lack of pertinent data in the literature, the panel members considered that the balance between desirable and undesirable effects, and cost effectiveness, cannot be defined with certainty.

Clinical recommendation: **In patients with compensated cirrhosis and single unresectable intermediate-sized (3.1–5 cm) HCC, the panel suggests not using the combined treatment of intra-arterial therapy and percutaneous ablation versus ablation alone.**
Certainty in evidence: Very low.
Strength of recommendation: Conditional against combined treatment.

2. **In patients with liver cirrhosis (maximum Child-Pugh score B7) with not transplantable, unresectable, multifocal HCC and without intrahepatic vascular invasion or extrahepatic tumor spread, is transarterial chemoembolization (TACE) with DC-beads indicated compared to conventional TACE?**

Cirrhotic patients (maximum Child-Pugh score B7) with not transplantable, unresectable multifocal HCC without portal invasion and extrahepatic extension are treated with transarterial embolization (TAE) or chemoembolization (TACE) treatments [20] if more radical treatment are excluded [10,21]. There are two main chemoembolization techniques: a) conventional TACE (cTACE), that involves the preliminary infusion of a chemotherapeutic agent emulsified with Lipiodol®, followed by the temporary occlusion of the tumor arterial supply by infusion of absorbable gelfoam particles; b) DEB-TACE, that involves the infusion in the tumor arteries of permanent embolizing microspheres (DC beads) preloaded with the chemo agent. A meta-analysis of both randomized and observational studies published up to 2015 highlights the non-superiority of DEB-TACE over cTACE in terms of tumor response and survival [22].

After literature review, we included 6 randomized controlled trials (RCTs) [23–28] including a total of 645 patients, of whom 73.8 % were male and with a mean age of 66.6 years.

These studies have shown:

- a disease control rate at 1 month of 93 % in both patients undergoing cTACE and in those undergoing DEB-TACE (RR 1, 95 % CI 0.94–1.07);
- a 6-month disease control rate of 67 % in patients undergoing cTACE and 73 % in patients undergoing a DEB-TACE (RR 1.09, 95 % CI 0.95–1.26)
- a 2-year mortality rate of 43.5 % in patients undergoing cTACE and 36 % in patients undergoing DEB-TACE (RR 0.82, 95 % CI 0.65–1.04).

Moreover, the members of the Panel felt that the balance of desirable and undesirable effects, and cost-effectiveness evaluations [29–31], favors neither the intervention nor the comparator.

Clinical recommendation: **In patients with liver cirrhosis (maximum Child-Pugh score B7) with not transplantable, unresectable multifocal HCC and without intrahepatic vascular invasion or extrahepatic tumor spread, the panel suggests using DC-bead TACE or conventional TACE, according to the local availability of treatment.**
Certainty in evidence: Very low.
Strength of recommendation: Conditional for equivalence.

3. **In patients with HCC, not eligible for surgical and/or ablative treatment, is the treatment with TACE followed by radiotherapy rather than TACE alone indicated?**

In the field of hepato-oncology there is growing interest for the use of radiotherapy (RT) in combination with TACE, both as a pre-established combination and as sequential therapy after repeated TACEs.

A systematic review evaluating the efficacy of adding 3D conformal RT to TACE included 11 RCTs with a total of 632 participants [32]. A second systematic review, including 8 studies for a total of 1030 participants, evaluated the effectiveness of adding to TACE any type of radiotherapy [33]. The median follow-up was 12 months (range 2–38 months) in the first, while it was not reported

Table 2
PICO questions, Recommendations, Certainty of evidence, and Strength of recommendation about non-Surgical treatment, of Clinical Practice Guidelines for the management of Hepatocellular Carcinoma (HCC).

PICO		Recommendation	Certainty of evidence	Strength of recommendation
1	In patients with compensated cirrhosis and single intermediate-sized (3.1–5 cm) unresectable HCC, is the combined treatment of percutaneous ablation + intra-arterial therapy versus ablation alone indicated?	In patients with compensated cirrhosis and single unresectable intermediate-sized (3.1–5 cm) HCC, the panel suggests not using the combined treatment of intra-arterial therapy and percutaneous ablation versus ablation alone.	Very low	Conditional against combined treatment
2	In patients with liver cirrhosis (maximum Child-Pugh score B7) with not transplantable, unresectable, multifocal HCC and without intrahepatic vascular invasion or extrahepatic tumor spread, is transarterial chemoembolization (TACE) with DC-beads indicated compared to conventional TACE?	In patients with liver cirrhosis (maximum Child-Pugh score B7) with not transplantable, unresectable multifocal HCC and without intrahepatic vascular invasion or extrahepatic tumor spread, the panel suggests using DC-bead TACE or conventional TACE, according to the local availability of treatment.	Very low	Conditional for equivalence
3	In patients with HCC not eligible for surgical and/or ablative treatment, is treatment with TACE followed by radiotherapy rather than TACE alone indicated?	In patients with HCC not eligible for surgical and/or ablative treatment, the panel suggests TACE followed by radiotherapy instead of TACE alone	Low	Conditional in favor of TACE followed by radiotherapy
4	In patients with Child-Pugh class A cirrhosis and unresectable single ≤8 cm or multifocal HCC, without ascites, portal invasion and extrahepatic tumor spread, transarterial radioembolization (TARE) is indicated compared to conventional transarterial chemoembolization (cTACE) or transarterial chemoembolization with microspheres (DEB-TACE)?	In patients with Child-Pugh class A cirrhosis and unresectable single ≤8 cm or multifocal HCC, without ascites, portal invasion and extrahepatic tumor spread, the panel suggests not performing TARE compared to cTACE or DEB-TACE	Very low	Conditional against TARE
5	In patients with compensated cirrhosis and HCC technically eligible (by size and number of lesions) for surgical treatment, but excluded from it due to contraindications, is the treatment with external (stereotactic) radiotherapy indicated compared to alternative therapies (thermal ablation, TACE, TARE or systemic therapy)?	In patients with compensated cirrhosis and HCC technically eligible (by size and number of lesions) for surgical treatment, but excluded from them due to other contraindications, the panel suggests using external (stereotactic) radiotherapy compared to alternative therapies.	Very low	Conditional in favor of radiotherapy
6	In Child-Pugh class A patients with intermediate or advanced BCLC stage HCC who are not eligible for surgical or loco-regional treatments (or in whom these approaches have failed), is systemic therapy with sorafenib/lenvatinib indicated instead of best supportive care (BSC)?	For Child-Pugh class A patients with intermediate or advanced or BCLC stage HCC who are not eligible for surgery or loco-regional treatment (or in whom these approaches have failed), the panel recommends the use of sorafenib/lenvatinib instead of BSC.	Sorafenib: high Lenvatinib: moderate	Strong in favor of systemic therapy
7	In Child-Pugh class A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments (or in whom these approaches have failed), is treatment with lenvatinib indicated compared to sorafenib?	In Child-Pugh class A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments (or in whom these approaches have failed), the panel suggests using sorafenib or lenvatinib according to the local drug availability.	Moderate	Conditional for equivalence
8	In Child-Pugh B patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments, is the use of sorafenib or lenvatinib indicated instead of best supportive care?	In Child-Pugh B patients with intermediate or advanced stage HCC not eligible for surgical or loco-regional treatments, the panel suggests not using sorafenib or lenvatinib instead of BSC alone.	Low	Conditional against sorafenib/lenvatinib
9	In Child-Pugh class A patients with HCC progressing to sorafenib therapy, is a second-line treatment with regorafenib indicated instead of best supportive care?	For Child-Pugh class A patients with HCC progressing on sorafenib therapy, provided that they tolerated this treatment, the panel suggests using regorafenib instead of BSC.	Moderate	Conditional in favor of regorafenib
10	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatments (or in whom these approaches have failed), progressing on or intolerant to sorafenib, and even in progression on post-sorafenib treatment, is cabozantinib indicated instead of best supportive care?	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatment (or in whom this approach has failed), progressing on or intolerant to sorafenib, and even after failure of a post-sorafenib systemic therapy, the panel suggests using cabozantinib.	Moderate	Conditional in favor of cabozantinib

(*continued on next page*)

Table 2 (*continued*)

PICO		Recommendation	Certainty of evidence	Strength of recommendation
11	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatments (or in whom these approaches have failed), progressing on or intolerant to sorafenib, and with alpha-fetoprotein ≥400 ng/ml, is ramucirumab indicated instead of best supportive care?	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatments (or in whom these approaches have failed), progressing on or intolerant to sorafenib, and with alpha-fetoprotein ≥400 ng/ml, the panel suggests considering ramucirumab instead of best supportive care.	Low	Conditional in favor of ramucirumab
12	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments, is the atezolizumab + bevacizumab combination indicated as first-line systemic therapy compared to sorafenib?	In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments, the panel suggests using the combination atezolizumab + bevacizumab as first-line systemic therapy.	High	Conditional in favor of atezolizumab + bevacizumab

GRADE Working Group grades of evidence:.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

in the second study. Both reviews showed a significant reduction in mortality at 1, 2 and 3 years in patients treated with TACE combined with RT compared to patients treated with TACE alone at 1, 2 and 3 years (RR 0.54, CI 95 % 0.44–0.66; RR 0.68, CI 95 % 0.60–0.78 and RR 0.80, CI 95 % 0.73–0.88, respectively).

However, the Panel points out that these results should be interpreted with high caution, as most of the evidence derive from studies that were carried out exclusively on Asian populations (which is not the main population in Italy) and show a significant heterogeneity in terms of sample size, selection criteria, stratification of the tumor stage and design of the study. In addition, the Panelists emphasize the need that this technique is used only in centers with extensive experience in liver radiotherapy and with adequate technical equipment.

Clinical recommendation: **In patients with HCC not eligible for surgical and/or ablative treatment, the panel suggests TACE followed by radiotherapy instead of TACE alone.**
Certainty in evidence: Low.
Strength of recommendation: Conditional in favor of TACE followed by radiotherapy.

4. **In patients with Child-Pugh class A cirrhosis and unresectable single ≤8 cm or multifocal HCC, without ascites, portal invasion and extrahepatic tumor spread, transarterial radioembolization (TARE) is indicated compared to conventional transarterial chemoembolization (cTACE) or transarterial chemoembolization with microspheres (DEB-TACE)?**

Patients with well compensated cirrhosis (Child-Pugh class A) with unresectable single (≤8 cm) or multifocal HCC, without portal invasion and extrahepatic extension, can undergo locoregional bridging treatments aimed at controlling the disease or reducing its extension to meet the transplant criteria [34]. TARE offers the opportunity to lead tumor necrosis not through ischemia (like TACE) but through the local irradiation of neoplastic cells [35].

Two meta-analyses were found, one including only randomized controlled trials (RCTs) [36] and one also accepting prospective cohort studies and retrospective studies [37]. Both reviews suffer from important methodological weaknesses and, therefore, were solely used as source of primary study references. Eventually, 4 RCTs [38–41] with a total of 169 patients were considered.

These studies shown:

- a 1–3-year mortality rate of 69 % in patients undergoing TACE, and 63 % in patients undergoing TARE (RR 0.91, 95 % CI 0.56–1.49);
- a treatment response rate of 92 % with TACE, and 87 % with TARE (RR 0.95, 95 % CI 0.87–1.04);
- a stable disease rate in 60 % with TACE, and 45 % with TARE (RR 0.77, 95 % CI 0.38–1.58);
- a disease progression rate of 36 % with TACE, and 13 % with TARE (RR 0.35, 95 % CI 0.08–1.49).
- the occurrence of serious adverse events of 47 % with TACE, and 48 % with TARE (RR 1.01, 95 % CI 0.48–2.12).

Notably, a recent position paper suggests the use of TARE even in very early (BCLC-0) and early (BCLC-A) stages if surgical and other locoregional curative treatments are contraindicated [42]. This recommendation is based on the results of the LEGACY retrospective multicenter study [43]. Nevertheless, TARE does not result cost-effective compared to TACE in patients with HCC in BCLC-A or BCLC-B stage [44,45].

Clinical recommendation: **In patients with Child-Pugh class A cirrhosis and unresectable single ≤8 cm or multifocal HCC, without ascites, portal invasion and extrahepatic tumor spread, the panel suggests not performing TARE compared to cTACE or DEB-TACE.**
Certainty in evidence: Very low.
Strength of recommendation: Conditional against TARE.

5. **In patients with compensated cirrhosis and HCC technically eligible (by size and number of lesions) for surgical treatment, but excluded from it due to contraindications, is the treatment with external (stereotactic) radiotherapy indicated compared to alternative therapies (thermal ablation, TACE, TARE or systemic therapy)?**

Stereotactic body radiation therapy (SBRT) represents a modern and advanced technique of radiotherapy which allows to deliver, with high precision and in a few sessions, ablative doses of radiation to the tumor, sparing the surrounding healthy tissues. SBRT is currently used for the treatment of various primary and secondary tumors.

We found one observational study comparing SBRT with TACE [46], 3 studies comparing SBRT with resection [47–49], and 7 studies comparing SBRT with radiofrequency thermal ablation (RFA) [50–56]. All these studies presented propensity-score-adjusted results.

The first study included 190 patients with HCC stage BCLC A who were not amenable to or who had refused resection and/or radiofrequency ablative therapy, of whom 95 were treated with TACE and 95 with SBRT [46]. The analysis of the results adjusted with propensity score matching showed a comparable survival between the two treatments at 1, 3 and 5 years. Furthermore, SBRT was associated with a lower rate of both local recurrence at 1 year (RR 1.24, 95 % CI 1.06–1.45) and 5 years (RR 1.54, 95 % CI 1.12–2.12) and intrahepatic recurrence at 1 year (RR: 1.35, 95 % CI 1.10–1.66) and 5 years (RR 2.35, 95 % CI 1.44–3.84).

Studies [47–49] have shown comparable overall survival and progression-free survival (PFS) between patients undergoing SBRT and those undergoing surgical resection; while in studies comparing SBRT vs RFA, SBRT led to an equal survival but a better local control of the disease at 1, 2, 3 and 5 years than RFA [50–56].

However, it is important to note that the overall certainty of the evidence was judged by the Panel to be very low, as it derives from observational studies and with important limitations such as the risk of bias, imprecision, and poor generalizability. Most studies were indeed carried out exclusively on Asian populations and show a significant heterogeneity in terms of sample size, selection criteria, stratification of the tumor stage and design of the study. Therefore, their results should be interpreted with great caution. Lastly, the Panel emphasizes the need for this technique to be used only in centers with extensive experience in liver radiotherapy, and with adequate technical equipment.

Clinical recommendation: **In patients with compensated cirrhosis and HCC technically eligible (by size and number of lesions) for surgical treatment, but excluded from them due to other contraindications, the panel suggests using external (stereotactic) radiotherapy compared to alternative therapies.**

Certainty in evidence: Very low.

Strength of recommendation: Conditional in favor of radiotherapy.

6. **In Child-Pugh class A patients with intermediate or advanced BCLC stage HCC who are not eligible for surgical or loco-regional treatments (or in whom these approaches have failed), is systemic therapy with sorafenib/lenvatinib indicated instead of best supportive care?**

Patients with HCC diagnosed at advanced stage o even in previous stage but unsuitable for or not responding to locoregional therapy have a poor outcome [5,6]. Nevertheless, these patients, provided that they have a compensated cirrhosis, benefit from systemic therapy based on immunotherapy or multi-kinase inhibitors (TKIs) [57].

Currently, based on the results of RCTs, two orally administered TKIs are available for the treatment of HCC: a) sorafenib, that blunts tumor cell proliferation and tumor angiogenesis, and induces apoptosis; b) lenvatinib, that obtain the same effects by targeting VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor α, RET and KIT.

We found 2 phase III RCTs comparing sorafenib vs. placebo: the SHARP trial [58] and the Asia-Pacific trial [59]. In total, they enrolled 828 participants with a mean age of 61.5 years; 83 % were male; 96.7 % were in Child-Pugh class A and 86 % were in BCLC stage C. Of them, 60.4 % had vascular invasion and 56 % had extrahepatic disease. The median duration of sorafenib treatment was 4 months. Treatment with sorafenib resulted in a prolongation of overall survival of approximately 3 months in the SHARP study and approximately 2 months in the Asian study compared to placebo.

The efficacy of the drug was thereafter validated by the positive results found in clinical practice studies and by meta-analyses for individual and pooled data [60–64].

A multicenter RCT (154 centers in 20 countries) of non-inferiority, the REFLECT study, compared lenvatinib vs sorafenib [65]. It enrolled 954 participants, with a mean age of 61.3 years; 84.5 % were male; 99.2 % were in Child-Pugh class A and 79.5 % had a BCLC stage C HCC. Of them, 20.9 % had neoplastic portal invasion and 61.4 % had extrahepatic disease. The median duration of treatment was 4 months. Patients with tumor extension >50 % of liver volume, involvement of the hepatic duct or the trunk of the portal vein were excluded. Seventy percent of enrolled patients were Asian. Patients were randomized to receive lenvatinib 12 mg daily if body weight was ≥60 kg or 8 mg if body weight was <60 kg. Sorafenib was administered at the standard dose of 400 mg twice daily. Both drugs were administered until disease progression or unacceptable toxicity.

The REFLECT study demonstrated the non-inferiority of lenvatinib compared to sorafenib in terms of overall survival: 13.6 months (95 %CI 12.1–14.9) and 12.3 months (95 % CI 10.4–13.9), respectively (HR 0.92, 95 %CI 0.79–1.06). The secondary endpoint, PFS, was in favor of lenvatinib (7.4 months, 95 %CI 6.9–8.8 vs. 3.7 months, 95 %CI 3.6–4.6; HR 0.66, 95 %CI 057–0.77).

We also identified and analyzed 4 observational studies concerning the comparison between lenvatinib and sorafenib, in which the propensity score matching was used to control baseline differences between groups [66–69]. A total of 1540 participants were included in these 4 studies, 79 % were male, the mean age was 64 years, 92 % were in Child-Pugh class A, and 69 % in BCLC stage C. Observational studies confirmed RCT results in terms of survival and PFS.

Adverse events

In RCTs, the treatment with sorafenib was overall well tolerated although treatment discontinuation due to adverse events was more than double in subjects treated with sorafenib than in those undergoing placebo (RR: 2.37, 95 % CI 1.32–4.25). The most common adverse events are hand-foot skin reaction (HFSR), diarrhea and asthenia. Dermatological adverse events in the first two months of treatment correlates with a better prognosis [61].

The REFLECT study [65] showed that lenvatinib was equally tolerated compared to sorafenib. The percentage of subjects with at least one grade ≥3 adverse event was not significantly different in both the randomized (RR 1.13, 95 %CI 1.04–1.22) [65,70] and observational studies (pooled RR 0.99, 95 % CI 0.84–1.18) [66–69], as well as the percentage of patients who discontinued treatment due to adverse events (RCT: RR 1.46, 95 %CI 1.01–2.10; observational studies: pooled RR 0.84, 95 %CI 0.40–1.76). The most common adverse events of lenvatinib are hypertension, diarrhea, anorexia, weight loss, asthenia, HFSR and proteinuria.

Management of side effects associated with lenvatinib are similar to that described for sorafenib.

The occurrence of adverse events such as hypertension, diarrhea, proteinuria, and hypothyroidism herald a better prognosis [70].

All previous cost-effectiveness analyses [71–78] of sorafenib versus placebo and versus lenvatinib are invalidated due to recent great drop of sorafenib price.

Clinical recommendation: **For Child-Pugh class A patients with intermediate or advanced or BCLC stage HCC who are not eligible for surgery or loco-regional treatment (or**

in whom these approaches have failed), the panel recommends the use of sorafenib/lenvatinib instead of BSC.

Certainty in Evidence: Sorafenib: High. Lenvatinib: Moderate.

Strength of recommendation: Strong in favor of systemic therapy.

7. **In Child-Pugh class A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments (or in whom these approaches have failed), is treatment with lenvatinib indicated compared to sorafenib?**

The only study included is the multicenter non-inferiority phase III REFLECT RCT [65] (for more details on the study design, outcomes, adverse events, and cost-effectiveness see PICO n. 6).

Evaluation of health-related quality of life (HRQOL) [79] support the use of lenvatinib in this setting.

Adverse events

For the study of adverse events, a meta-analysis of observational studies was also considered [80]. It included 4 studies for a total of 542 patients, 84 % of whom were male, with an age range of 56–74 years; 55 % to 95 % of cases were in Child-Pugh class A. In two studies, BCLC stage C was reported in 45 % and 50 % of cases, respectively, while information was missed in the remaining studies.

No difference between lenvatinib and sorafenib in terms of severe adverse event rate was observed (OR 1.31, 95 %CI 0.82–2.09). Pooled rates of SAEs were 38.2 % and 36.1 % with lenvatinib and sorafenib, respectively; hand-foot syndrome, diarrhea and hypertension were the most frequently observed events.

An Italian multicenter observational study was also considered [69]. It enrolled 288 patients, 80 % of whom were male, 57 % were aged <70 years, 93.5 % were in Child-Pugh class A, and 75 % in BCLC stage C. Overall, 97.3 % and 97.9 % experienced at least one (any grade) AE in lenvatinib and sorafenib arm, respectively. HFSR and diarrhea were significantly more frequent in patients treated with sorafenib, while hypertension and fatigue were significantly more frequent in patients treated with lenvatinib. Treatment dose reduction was performed both in 28.5 % of patients treated with lenvatinib and sorafenib.

Clinical recommendation: **In Child-Pugh class A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments (or in whom these approaches have failed), the panel suggests using sorafenib or lenvatinib according to the local drug availability.**

Certainty in Evidence: Moderate.

Strength of recommendation: Conditional for equivalence.

8. **In Child-Pugh B patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments, is the use of sorafenib or lenvatinib indicated instead of best supportive care?**

We considered 2 RCTs comparing sorafenib vs best supportive care (BSC) [81,82] and a systematic review of observational studies [83]. No studies assessing lenvatinib outcome were found.

In the BOOST trial [81] only 35 patients were randomized as the study was stopped due to the low accrual rate. The median overall survival was 4.9 months (95 % CI 1.2–5.6) with sorafenib, and 3.5 months (95 % CI 1.3–5.3) with BSC.

The second RCT - PRODIGE 21 [82] - is a multicenter, multi-arm phase II study comparing sorafenib vs pravastatin vs sorafenib+pravastatin vs BSC. For the analysis of interest, the sorafenib and BSC arms were evaluated. The median survival was 3.8 months (95 %CI 2.4–6.5) with sorafenib, and 3.5 months (95 %CI 2.2–5.4) with BSC.

The systematic review [83] evaluated the efficacy and safety of sorafenib in patients with advanced stage HCC belonging to Child-Pugh class A (6820 patients) or B (1684 patients). The median survival of Child-Pugh B patients treated with sorafenib was 4.6 months (95 %CI were not calculated due to the lack of data), while in Child-Pugh A patients it reached 8.8 months. Overall, 35 % of sorafenib-treated Child-Pugh B patients developed grade 3–4 adverse events (same percentage observed in treated Child-Pugh A patients (OR 0.95, 95 %CI 0.73–1.23).

Clinical recommendation: **In Child-Pugh B patients with intermediate or advanced stage HCC not eligible for surgical or loco-regional treatments, the panel suggests not using sorafenib or lenvatinib instead of BSC alone**.

Certainty in evidence: Low.

Strength of Recommendation: Conditional against sorafenib/lenvatinib.

9. **In Child-Pugh class A patients with HCC progressing to sorafenib therapy, is a second-line treatment with regorafenib indicated instead of best supportive care?**

In the studies assessing the results of second-line systemic therapy after tumor progression on sorafenib, the overall survival of the placebo group is approximately 8 months [84–88].

Regorafenib is an orally administered multikinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, metastasis, and tumor immunity. We considered the international multicenter phase III RCT RESORCE [89], which randomized 573 patients to receive regorafenib or placebo in a 2:1 ratio. The primary endpoint was overall survival.

Regorafenib was tested in patients with preserved liver function (Child-Pugh class A), ECOG PS 0–1, and with tumor progressing on sorafenib. The drug was administered at a dose of 160 mg per day for 21 days, in cycles lasting at least 28 days (the last week of suspension) and continued until disease progression or intolerable toxicity. Patients had to be tolerant to sorafenib at a dose of at least 400 mg/day for at least 20 of the last 28 days prior to randomization, a pre-requisite which excluded from the RCT those who had suspended sorafenib due to toxicity. The mean patient's age was 63 years, 88 % were male, Child-Pugh class was A in 97.5 %, and BCLC stage C in 87.5 %. The median duration of sorafenib treatment (7.8 months) and median time since discontinuation of prior therapy (1.4 months) were similar in the two treatment arms. The median duration of regorafenib treatment was 3.6 months. A statistically significant increase in overall survival from 7.8 months with placebo (95 %CI 6.3–8.8) to 10.6 months with regorafenib (95 %CI 9.1–12.1) (HR=0.63, 95 %CI 0.50–0.79) was observed. PFS by mRECIST criteria was 3.1 months (95 % CI 2.8–4.2) with regorafenib vs 1.5 months with placebo (95 %CI 1.4–1.6) (HR 0.43, 95 %CI 0.35–0.52). The median time to progression was 3.2 months (95 %CI 2.9–4.2) with regorafenib vs. 1.5 months (95 %CI 1.4–1.6) with placebo (HR 0.41, 95 % CI 0.34–0.51). The objective response rate by mRECIST criteria was 11 % with regorafenib and 4 % with placebo (RR 2.56, 95 %CI 1.22–5.36).

Adverse events

Regorafenib was overall well tolerated. The most frequent grade 3–4 adverse events were hypertension (15 %), HFSR (13 %), asthenia (9 %) and diarrhea (3 %). Therapy-related serious adverse events occurred in 10 % with regorafenib and 3 % with placebo (RR 4.03, 95 % CI 1.61–10.05). The discontinuation rate due to therapy-related adverse events was 10 % with regorafenib and 4 % with placebo (RR 2.88, 95 % CI 1.31–6.31).

The phase IV observational study REFINE [90,91] reports the safety data of regorafenib in the first 500 patients enrolled. The drug was used as second- or third-line treatment in patients not responders to sorafenib. The most frequent adverse events of any grade were HFSR (30 %), diarrhea (21 %) and decreased appetite (14 %).

Two cost-effectiveness studies were considered [92,93]. In both studies, regorafenib was not found to be cost-effective compared to BSC.

Clinical recommendation: **For Child-Pugh class A patients with HCC progressing on sorafenib therapy, provided that they tolerated this treatment, the panel suggests using regorafenib instead of BSC.**

Certainty in Evidence: Moderate.

Strength of recommendation: Conditional in favor of regorafenib.

10. **In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatments (or in whom these approaches have failed), progressing on or intolerant to sorafenib, and even in progression on post-sorafenib treatment, is cabozantinib indicated instead of best supportive care?**

Cabozantinib is a multikinase inhibitor with antiangiogenic action (throughout the inhibition of VEGF receptors) as well as on the MET (hepatocyte growth factor receptor protein) pathways and on the TAM-kinase family (TYRO3, AXL, MER). The CELESTIAL study [94] is a double-blind multicenter phase III RCT which enrolled 707 patients in Child-Pugh class A, with advanced or intermediate HCC (in the latter case not eligible for loco-regional treatment), already treated with sorafenib, which could have been followed by an additional line of therapy, and in progression on at least one line of therapy. Patients were randomized in a 2:1 ratio to receive oral cabozantinib at a dose of 60 mg/day or placebo. The mean patient's age was 64 years, 83 % were male, Child-Pugh class was A in 98 % of patients, BCLC stage was C in 90 % of cases, 29.3 % had vascular invasion and 78 % extrahepatic disease. The median duration of sorafenib treatment was 5 months, and the median time since discontinuation of therapy was 1.3 months. The median duration of cabozantinib treatment was 3.8 months.

Cabozantinib improved median overall survival to 10.2 months (95 %CI 9.1–12.0) compared with 8.0 months (95 % CI 6.8–9.4) found in placebo-treated patients (HR 0.76, 95 %CI 0.63–0.92). Median PFS, calculated using RECIST 1.1 criteria, was 5.2 months (95 % CI 4.0–5.5) with cabozantinib vs. 1.9 months with placebo (95 %CI 1.9–1.9) (HR 0.44, 95 %CI 0.36–0.52).

Adverse events

Grade 3–4 adverse events were observed in 68 % of cabozantinib-treated patients and 36 % of placebo-treated patients. The most frequent were skin toxicity (17% vs. 0 % patients), hypertension (16% vs. 2 %), increased AST (12% vs. 7 %), asthenia (10% vs. 4 %) and diarrhea (10% vs. 2 %). Serious adverse events occurred in 50 % of cabozantinib-treated patients and 37 % of placebo-treated patients (RR 1.36, 95 % CI 1.12 - 1.64). The rate of grade 3–4 adverse events was 67 % with cabozantinib and 36 % with placebo (RR 1.86, 95 % CI 1.50 - 2.31). The discontinuation rate due to therapy-related adverse events was 16 % with cabozantinib and 3 % with placebo (RR 5.51, 95 %CI 2.58 - 11.76).

The occurrence of any grade dermatologic toxicity or grade 3 or higher arterial hypertension has been found to correlate with a better prognosis [95].

A case series study of 88 patients recruited in 11 centers in Switzerland, Austria, and Germany [96] reports safety data of cabozantinib used as second- or third-line treatment. The most frequent grade ≥3 adverse events were diarrhea (8.8 %) and asthenia (4.4 %). The study does not report cases of discontinuation of treatment due to adverse events. In a second case series of 96 patients recruited by 15 Italian centers [97], the frequency of grade 3–4 adverse events was 42.7 %. The most frequent adverse events were asthenia (6.3 %), skin toxicity (6.3 %), ALT elevation (6.3 %) and hypertension (4.2 %).

Clinical recommendation: **In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatment (or in whom this approach has failed), progressing on or intolerant to sorafenib, and even after failure of a post-sorafenib systemic therapy, the panel suggests using cabozantinib**.

Certainty in Evidence: Moderate.

Strength of recommendation: Conditional in favor of cabozantinib.

11. **In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatments (or in whom these approaches have failed), progressing on or intolerant to sorafenib, and with alpha-fetoprotein ≥400 ng/ml, is ramucirumab indicated instead of best supportive care?**

Ramucirumab is a human IgG1 monoclonal antibody that inhibits VEGFR2 ligand activation. Two phase III RCTs were considered: the REACH [98] and the REACH-2 [99]. They were multicenter studies that randomized a total of 857 patients to ramucirumab or placebo. The REACH-2 study [99] enrolled patients in Child-Pugh class A, with advanced or intermediate HCC (in the latter case not eligible for loco-regional treatment), with serum AFP levels ≥400 ng/mL and who were treated with sorafenib. This study found its rationale in the result of the previous REACH study [98], in which the drug did not achieved the primary objective of survival in the totality of patients, but a post-hoc analysis had revealed a significant benefit compared to placebo in patients with AFP ≥400 ng/mL. In the REACH-2 study patients were randomized in a 2:1 ratio to receive ramucirumab (8 mg/kg IV every 2 weeks) or placebo.

The cumulative analysis including the REACH study patients with AFP ≥ 400 ng/mL and the REACH-2 study, for a total of 542 participants, demonstrated a median survival of 8.1 months with ramucirumab and 5 months with placebo (HR 0.69, 95 %CI 0.57 - 0.84). The drug was also superior to placebo in terms of PFS (HR 0.57, 95 %CI 0.47 - 0.69), and complete or partial response (RR 6.08, 95 % CI 1.42 - 26.05) [98,99].

Adverse events

There was an increased risk of grade 3–4 adverse events (RR 1.12, 95 % CI 0.95–1.31) and a remarkably increased risk of treatment discontinuation due to adverse events (RR 3.45, 95 % CI 1.81-6.58). The most frequent adverse events were arterial hypertension (13 % with ramucirumab vs. 5 % with placebo), hyponatremia (6% vs. 0 %), increased AST (3% vs. 5 %), reversible proteinuria (2% vs. 0 %) and ascites (4% vs 0 %).

Ramucirumab is not reimbursed by the Italian National Health System.

Clinical recommendation: **In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for loco-regional treatments (or in whom these approaches have failed), progressing on or intolerant to sorafenib, and with alpha-fetoprotein ≥400 ng/ml, the panel suggests considering ramucirumab instead of best supportive care.**

Certainty in evidence: Low.
Strength of Recommendation: Conditional in favor of ramucirumab

12. **In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments, is the atezolizumab+bevacizumab combination indicated as first-line systemic therapy compared to sorafenib?**

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7–1. The effect of this drug on patients with HCC was studied in combination with the anti-angiogenic drug bevacizumab, a recombinant humanized monoclonal antibody that binds to and inhibits the biological activity of vascular endothelial growth factor (VEGF). This combination increases the efficacy of bevacizumab on VEGF inhibition [100,101]. Indeed, in a phase Ib study, this combination resulted in a longer PFS than atezolizumab monotherapy in treatment-naïve, unresectable patients with HCC [102].

The multicenter phase III RCT, designated IMbrave150 [103,104], enrolled patients with preserved hepatic function (Child-Pugh class A), but ineligible for any surgical or loco-regional treatment (at diagnosis or after previous treatment failure). This trial randomized 501 patients in a 2:1 ratio to receive 1200 mg of atezolizumab plus 15 mg/kg of bevacizumab i.v. every 3 weeks or sorafenib (400 mg twice daily) until disease progression or unacceptable toxicity. For the reported increased risk of bleeding associated to bevacizumab, a gastroscopy was considered mandatory for entry into the study. Stratification factors were geographic origin (Asia excluding Japan vs. rest of the world), macrovascular invasion, extrahepatic disease, AFP level (discriminant value 400 ng/ml), and ECOG PS (0 vs 1). The mean age of the participants was 65 years, 82.5 % were male, 100 % were Child Pugh class A and 81.5 % were BCLC stage C. Portal invasion was present in 37.5 % and extrahepatic disease in 6 % of cases. The median follow up was 8.6 months.

This study demonstrated a significant survival benefit of atezolizumab + bevacizumab compared to sorafenib (HR = 0.58, 95 %CI 0.42–0.79). Median PFS was 6.8 months (95 %CI 5.7–8.3) with the combination vs. 4.3 months (95 %CI 4.0–5.6) with sorafenib (HR = 0.59; 95 %CI 0.47–0.76). The objective radiological response rate, according to RECIST 1.1 criteria with independent review of radiological presentation, was 27.3 % (95 % CI 22.5–32.5) with atezolizumab + bevacizumab vs. 11.9 % (95 % CI 7.4–18.0) with sorafenib (RR 2.30, 95 % CI 1.45–3.64). A complete response was observed in 6 % of patients treated with the combination. Disease control rate was also superior with the combination (73.6% vs. 55.3 %) (RR stable disease: 1.07, 95 %CI 0.8 −1.33).

The updated results of the trial with a longer follow-up (median 15.6 months; range 0–28.6) confirmed the superiority of the combination [105]. Median OS was 19.2 months (95 CI 17.0–23.7) with the combination vs. 13.4 months (95 %CI 11.4–16.9) with sorafenib (HR 0.66, 95 %CI 0.52–0.85), while median PFS was 6.9 (95 %CI 5.7–8.6) and 4.3 (95 %CI 4.0–5.6) months, respectively (HR 0.65, 95 %CI 0.53–0.81). The objective radiological response and disease control rates were higher with atezolizumab + bevacizumab than whit sorafenib.

Adverse events

Grade 3–4 adverse events occurred in 56.5 % of patients treated with the combination and 55.1 % of those on sorafenib (RR 1.03, 95 %CI 0.86–1.22). The most frequent AEs, observed in the atezolizumab + bevacizumab arm, were hypertension (29.8 %; grade 3–4 in 15.2 %), asthenia (20.84 %; grade 3–4 in 2.4 %) and proteinuria (20.1 %; grade 3–4 in 3.0 %). Bleeding from the upper gastrointestinal tract was observed in 7 % of cases treated with the combination. The tolerability profile did not change with a longer follow-up [105]. The median time to deterioration of the quality of life (measured by EORTC QLQ-C30 questionnaire) was significantly longer in the atezolizumab + bevacizumab arm (11.3 vs 3.6 months; risk of deterioration: HR 0.63, 95 %CI 0.46–0.85).

Three cost-effectiveness studies were identified [106–108]. Their analysis showed that the combination cannot be considered cost-effective in all scenarios taken into consideration.

Clinical recommendation: **In Child-Pugh A patients with intermediate or advanced BCLC stage HCC not eligible for surgical or loco-regional treatments, the panel suggests using the combination atezolizumab + bevacizumab as first-line systemic therapy**.
Certainty in evidence: survival: High.
Strength of recommendation: Conditional in favor of atezolizumab + bevacizumab

5. Future perspective

According to recent published Italian Association for the Study of the Liver (AISF) Position Paper [11] and Policy Review from the AISF HCC Special Interest Group [10], the multidisciplinary management of virus-related HCC should consider the close interplay between antiviral treatment, treatment of portal hypertension, reduction of the risk of decompensation and benefit in terms of survival. Furthermore, it is important to highlight the survival benefit of adjuvant therapy with DAAs in patients with prior history of HCC and HCV-related cirrhosis [57,109].

It is to note that alternative tools to assess liver function (i.e., albumin-bilirubin [ALBI] score) have showed to be more granular prediction of liver function and it has been suggested that they may replace the Child-Pugh classification [42].

Non-surgical treatment for HCC can involve different modalities and can be tailored according to the degree of liver function, patient's status (Performance Status, frailty, comorbidities), tumor stage and the availability of different techniques. The number of effective options for systemic treatment of HCC is rapidly increasing [110,111], opening to the possibility of developing sequential treatments [112] with different classes of drugs which have different mechanisms of action.

So, future updated Guidelines should evaluate: 1) The comparison between Lenvatinib versus Atezolizumab plus Bevacizumab in first line systemic therapy of patients with intermediate or advanced stage HCC not eligible for surgical or loco-regional treatments; 2) the role of the combination with Tremelimumab plus Durvalumab for advanced HCC [110] (that at the time of the redaction of this document, it is not yet approved by the Agenzia Italiana del Farmaco and reimbursed by the Italian health system); 3) the potential role of Atezolizumab plus Bevacizumab in Child-Pugh B patients with intermediate or advanced stage HCC not eligible for surgical or loco-regional treatments; and 4) the role of different second-line strategies after first-line therapy with Atezolizumab plus Bevacizumab (where RCTs are still ongoing).

Moreover, the increasing efficacy of systemic therapy is opening the road toward the "conversion therapy" of HCC patients that is the possibility to use downstream surgical or locoregional treatments [10] (Fig. 1). On the other hand, the net health benefit (for example, using the incremental safety-effectiveness ratio - ISER) [112,113] of these new strategies needs to be evaluated. In this line, decompensation-free survival should be reported and included as endpoint in trial designs of non-surgical therapies [11,12].

Finally, future studies should well assess the role of intermediate surrogate endpoints [114] for the design of HCC trials.

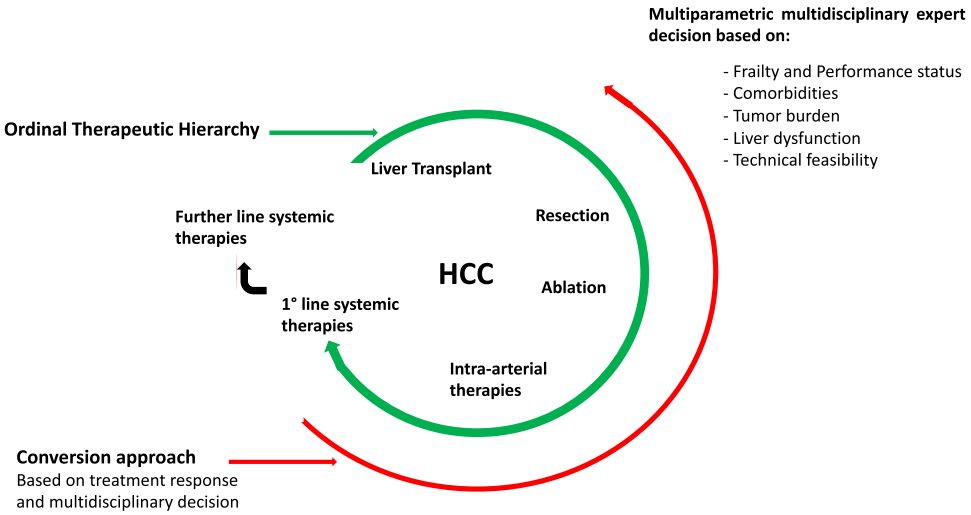

Fig. 1. Proposed treatment approach for patients with Hepatocellular Carcinoma, according to Therapeutic Hierarchy and multiparametric multidisciplinary expert evaluation.

Conflict of interest

Giuseppe Cabibbo: Bayer, Eisai, Ipsen, MSD, AstraZeneca, Roche.
Bruno Daniele: Astrazeneca, IPSEN, EISAI, MSD, Roche, Amgen, Incyte, Sanofi
Mauro Borzio: none
Andrea Casadei-Gardini: AstraZeneca, Bayer, Eisai, Incyte, Ipsen, IQVIA, MSD, Roche, Servier
Umberto Cillo: none
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