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original contributions

Application of ASCO Value Framework to Treatment Advances in Hepatocellular Carcinoma

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QUESTION ASKED: Could a recognized value framework supported by ASCO be used to objectively compare the potential benefit across available hepatocellular carcinoma (HCC) therapies to inform treatment decision making?

SUMMARY ANSWER: Of the 22 studies identified, HCC therapies that were Food and Drug Administration (FDA)-approved (n = 9) showed longer overall survival (median 10.7 *v* 7.9 months, $P < .01$) and higher ASCO net health benefit scores (+18.4 *v* −5.7 scores, $P < .01$) compared with those that were not approved (n = 13).

WHAT WE DID: We undertook an umbrella review to identify notable licensing trials of novel drugs for systemic treatment of HCC from ClinicalTrials.gov. Studies assessing surgery, locoregional therapies, noncancer-directed therapies, and adjuvant therapies were excluded. Data related to FDA drug approval, study design, outcomes, and toxicities were extracted from oncology meeting abstracts, published trials on PubMed, and the FDA website. ASCO Value Framework Net Health Benefit Score version 2 (ASCO-NHB v2) scores were computed, and the overall scores along with important trial end points were compared between drugs that were FDA-approved versus not approved. ESMO-Magnitude of Clinical Benefit Scale version 1.1 scores were also computed as secondary analysis.

WHAT WE FOUND: The nine FDA-approved therapies for HCC have higher mean net health benefit scores than those that were not FDA-approved (Fig). The application of ASCO-NHB v2 and other patient-oriented scoring systems could be used to compare and sequence future therapies for HCC.

BIAS, CONFOUNDING FACTOR(S), REAL-LIFE IMPLICATIONS: Even validated scoring systems intended as patient-oriented approach are subjected to inadequate side effect reporting, different study designs, heterogeneous study populations, and variable journal reporting standards. How data are presented in published tables and figures can influence how ASCO-NHB v2 is scored by a researcher. Nevertheless, the trends gleaned from a carefully computed analysis here can still formulate a value-based estimate that can be used to compare and sequence the many HCC treatment options available now (Fig).

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ASSOCIATED CONTENT

See accompanying editorials on pages 164 and 167

Data Supplement

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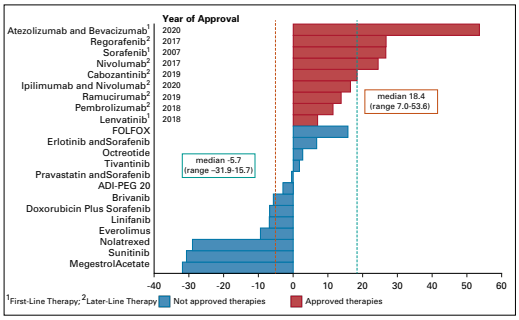

FIG. ASCO framework net health scores for FDA-approved and not FDA-approved therapies.

VALUE IN CANCER CARE

original contributions

Application of ASCO Value Framework to Treatment Advances in Hepatocellular Carcinoma

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abstract

BACKGROUND Determination of the comparative efficacy of one therapy over another for hepatocellular carcinoma (HCC) can be challenging. Application of a recognized value framework to published studies could objectively compare the potential benefit across available therapies.

MATERIALS AND METHODS An umbrella review of phase III trials for HCC therapies was performed. ASCO Value Framework Net Health Benefit Score version 2 (ASCO-NHB v2) scores, the primary analysis, and European Society of Medical Oncology Magnitude of Clinical Benefit Scale version 1.1 scores, the secondary analysis, were computed using selected drug registration trials. Both scores were compared between drugs that were Food and Drug Administration (FDA)-approved by 2020 and those that were not.

RESULTS Of the 22 studies identified, nine were FDA-approved and 13 were not. Across 22 trials, the median overall survival (OS) was 9.2 months (range, 1.9-16.4 months), with a median gain of 0.35 month (range, 2.3-3.3 months). HCC therapies that were FDA-approved showed longer OS (median 10.7 *v* 7.9 months, $P < .01$) and higher ASCO NHB scores (+18.4 *v* −5.7 scores, $P < .01$). The median gain in OS was 2.2 months in the approved treatments compared with −0.3 months in the unapproved group, with no difference in progression-free survival between the two groups.

CONCLUSION The nine FDA-approved therapies for HCC have higher mean NHB score than those that were not FDA-approved. The application of ASCO-NHB v2 and other proposed value frameworks could examine data of future therapies for HCC through a patient-oriented approach.

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BACKGROUND

Worldwide, hepatocellular carcinoma (HCC) is one of the main causes of cancer-related deaths. In the United States, the incidence of HCC has been on the rise over the past 2 decades,[1] with a projected increase in annual cases to 38,353 in 2020 and to 56,229 by 2030.[2] Historically, patients with intermediate and advanced stage HCC according to the Barcelona Clinic Liver Cancer criteria had a poor overall prognosis, with the expected median survival of 13.8 months and 2.9 months, respectively.[3] For those with metastatic disease, portal vein thrombosis, or persistent disease after prior locoregional therapies, systemic treatment is currently recommended.[4] Efforts in drug development have persevered since the 2000s, but only one standard option, sorafenib, was approved to the market prior to the 2010s.[5] Since 2017, immunotherapy checkpoint inhibitors, oral tyrosine kinase inhibitors, and antivascular endothelial growth factor biologics have all quickly become viable treatment options.[6] However, the optimal treatment sequence and combination remain uncertain.

Although all the evidence-based systemic treatment options have demonstrated either survival advantage or promising objective response rates (RRs) in their respective drug registration trials, few have been compared head-to-head. Such analysis is often limited by cross-trial comparisons and shift in epidemiological patterns, where the study population and design could not be well matched and simply compared. Furthermore, comparative effectiveness research has not considered previous therapies that seemed promising initially but later failed in their respective registration trials.

The ASCO and European Society of Medical Oncology (ESMO) value frameworks have been previously

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proposed to systematically assess the value and patient-oriented benefit for cancer therapies approved by regulatory agencies.[7,8] The ESMO value framework was tested only for studies that achieved statistically significant primary end point results and may not apply to negative, yet important, studies. On the other hand, the scores calculated from the ASCO framework algorithm account for negative studies and can provide a quantitative perspective of the patient-oriented benefit balanced with potential treatment toxicities regardless of statistical significance in this study. To date, little is known regarding the specific risk-benefit ratio informed by the ASCO value framework for systemic treatment options available for HCC.

We hypothesize that the ASCO value framework, additionally supplemented by ESMO value assessment, can be applied to novel drugs for the treatment of HCC, and its application could inform treatment decision making in sequencing, choosing, and combining novel drug therapies for HCC.

MATERIALS AND METHODS

Overview

We undertook an umbrella review to identify notable licensing trials of novel drugs for the treatment of HCC. We included studies regardless of primary end point outcome, to compare the magnitude of patient-oriented benefit, suggest sequences of existing treatments, and explore potential shortcomings of current value framework analysis that could become problematic in future trials for novel HCC drug candidates.

Literature Search and Selection

We performed searches for HCC trials on ClinicalTrials.gov, which is a publicly available, comprehensive web-based database maintained by the National Library of Medicine and National Institute of Health. Studies were initially selected based on the search word by hepatocellular carcinoma. The following filters were then applied to the search interventional trials, phase III trials, and starting date after January 1, 2000. The following recruitment status options were also applied: completed, active not recruiting, active recruiting, unknown, or terminated. The names and registration numbers of the trials were then used to identify primary source data from PubMed, ASCO meeting abstract lists, and ESMO meeting abstract lists. The initial literature search was conducted on October 10, 2019.

All studies with publicly available publications or meeting presentations by January 31, 2020, were then reviewed for data extraction. Subsequent news releases and published reports after the data cutoff date were not considered. Only randomized controlled trials testing a novel, first-in-disease cancer-directed systemic therapy compared with the former standard-of-care were selected. Randomized phase II trial without a definite control arm was considered if the Food and Drug Administration (FDA) accepted the trial for drug approval. Studies assessing surgery, locoregional therapies, or noncancer-directed therapies were excluded. Studies assessing neoadjuvant, perioperative, and adjuvant therapies were also excluded. Only one licensing trial was selected for each drug, with preference for first-line treatment, favorable results, and study in North America. Some excluded studies may meet multiple exclusions. At least two reviewers completed the literature search and agreed upon the selected trials (E.Y.C., A.A., and A.K.).

Data Extraction

For every published trial, we collected data related to the drug, study design, study dates, primary and secondary end points, and FDA drug approval status. FDA drug approval status was verified by using publicly available FDA website.[8a] Each drug was categorized as either approved or not approved by the FDA at the time of manuscript submission.

Ipilimumab with nivolumab, which was approved on March 11, 2020, based on a multicohort randomized phase II study was reported in 2019 instead of a fully published phase III trial.[9] Atezolizumab with bevacizumab combination was categorized as approved despite being under FDA priority review at the data cutoff date because substantial data from a randomized phase III trial were already publicly available prior to 2020.[10] It was later approved on May 29, 2020. Nivolumab was categorized as the second-or-later line to match the current FDA indication in the accelerated approval specification despite data taken from the postmarking first-line HCC phase III trial.[11] Nivolumab, ipilimumab-nivolumab, and atezolizumab with bevacizumab did not have fully published manuscripts by January 31, 2020, and their data were taken from conference abstracts.[9-11] The ASCO Value Framework Net Health Benefit Score version 2 (ASCO-NHB v2) was applied to every drug using the most updated published clinical trial. The ESMO-Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1) was also applied for sensitivity analysis.

The primary end point was the NHB score per ASCO-NHB v2, which is the sum of numerical scores from (1) the regimen's clinical benefit based on published end points, (2) toxicity profile, and (3) potential bonuses for the tail of the curve, symptom palliation, quality-of-life improvement, and treatment-free intervals. Additional input from cost was not done given no publicly available price label existed for newly FDA-approved therapies and drugs not approved to the market.

The secondary end point was the ESMO-MCBS v1.1. Specific rules regarding the end points and quality of life were followed to input magnitude of clinical benefit (MCB) grades from a five-point scale (1-5). ESMO-MCBS v1.1 was not chosen as primary end point because it was not validated for negative studies and did not account for toxicities in the

scoring system. All the scores were computed and agreed upon by at least two reviewers (E.Y.C., M.C., and C.D.).

All extracted data were publicly available online, contained no direct protected health information, and thus did not meet criteria to be submitted to the local institutional review board. All data were taken from ClinicalTrials.gov and the 22 published drug registration trials, which are all detailed in the Data Supplement. Notable excluded phase III trials are also listed in the same table.

Data Analysis

The ASCO-NHB v2 NHB scores were compared between drugs that were approved and those that were not approved using the Mann-Whitney test. The ESMO-MCBS v1.1 grades in the sensitivity analysis were compared using Fisher's Exact test. Study-specific end points, such as overall survival (OS), progression-free survival (PFS), and RR, were also compared between the two groups. Time to progression was used in place for PFS if PFS was not reported in the study. For the treatment sequence analysis, the drugs that were FDA-approved were organized by drug class (small-molecule targeted agent, immunotherapy, and antivascular endothelial growth factor biologic) and then by line of therapy to calculate possible cumulative scores over time for every possible scenario, assuming that a hypothetical patient could get approximately two drug combinations over their disease course. Descriptive calculations and specific statistical testing were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC), but all figures were created using Microsoft Excel and Microsoft PowerPoint.

RESULTS

We identified 1,809 trials in HCC on October 10, 2019, and 1,566 were immediately excluded by planned filters because of trial type, start date, and recruitment status. One phase II trial was added back because it received FDA approval. Then, an additional 222 trials were excluded after detailed record review (Data Supplement). A total of 22 distinct trials of systemic treatments for HCC were selected. Of the 22 drugs or drug combinations tested in these registration trials, six trials have since received FDA regular approval, three trials with accelerated approval, and 13 not meeting standards for FDA approval (Table 1). Fifteen were first-line treatment for advanced HCC, whereas seven were second-line treatment. Four were noninferiority rather than superiority analysis studies, and 10 used blind placebo with best supportive care rather than any active therapies in the control arm. Collectively, in these 22 trials, the median OS was 9.2 months (range, 1.9-16.4 months) and the median gain in OS advantage was 0.35 month (range, 2.3-3.3 months) (Table 1).

HCC treatments that are FDA-approved have demonstrated longer OS (median 10.7 *v* 7.9 months, $P < .01$), higher ASCO NHB scores (+ 18.4 *v* − 5.7 scores, $P < .01$), and higher ESMO MCB grades ($P < .01$) compared with those that are not approved by the FDA (Table 2). Collectively, across the entire heterogeneous study population, the median OS gain is + 2.2 months in the approved FDA treatments compared with − 0.3 months in the unapproved treatments (Table 2). There is no difference with regard to PFS between the two groups, but a modest difference

TABLE 1. General Characteristics of Selected Drug Registration Trials for the Treatment of HCC

N = 22	n (%)
Drug approval	
FDA regular approval	6 (27%)
FDA accelerated approval	3 (14%)
No FDA indication	13 (59%)
Drug class (N = 23)[a]	
Cytotoxic chemotherapy	3 (13%)
Small-molecule targeted agent	13 (57%)
Immunotherapy checkpoint inhibitor	4 (17%)
Biologic targeted agent	2[a] (9%)
Enzymatic targeted agent	1 (4%)
Line of therapy	
First line	15 (68%)
Second-or-later line	7 (32%)
Study sample size	524 (148-1,155)[b]
Blinding	
Double-blind	12 (55%)
Open-label	10 (45%)
Analysis	
Superiority	17 (77%)
Noninferiority	4 (18%)
Multiple cohort, no control	1 (5%)
Control arm	
Placebo	10 (45%)
Sorafenib	9 (41%)
Doxorubicin	2 (9%)
None	1 (5%)
End points	
OS hazard ratio (n = 21)	0.93 (0.58-1.33)[b]
Median OS duration (mo, n = 20)	9.2 (1.9-16.4)[b]
Median OS gain (mo, n = 20)	0.35 (−2.3 to 3.3)[b]
Median time to progression or PFS duration (n = 20)	3.5 (2.1-7.4)[b]
RR (n = 21)	7.9% (0%-32%)[b]

Abbreviations: FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; RR, response rate.

[a]Atezolizumab with bevacizumab combination was counted twice as both immunotherapy and biologic targeted agents.

[b]Median (range).

TABLE 2. Comparison of Study End Points and Value Frameworks Between Drugs That Were Approved and Not Approved

Median (Range)	Approved (n = 9)	Not Approved (n = 13)	*P*
Study end points			
OS hazard ratio (n = 21)	0.74 (0.58-0.92)[a]	1.05 (0.80-1.33)	<0.01
Median OS duration (mo, n = 20)	10.7 (8.5-16.4)[b]	7.9 (1.9-10.7)	<0.01
Median OS gain (mo, n = 20)	2.2 (1.2-3.3)[b]	−0.3 (−2.3 to 1.4)	<0.01
Median PFS duration (n = 20)	4.5 (2.8-7.4)[a]	3.3 (2.1-5.4)[c]	0.16
RR (n = 21)	15% (2%-32%)	6.7% (0%-13%)[c]	<0.05
ASCO-NHB v2 framework			
Net health scores	18.4 (7.0-53.6)	−5.7 (−31.9 to 15.7)	<0.01
ESMO-MCBS v1.1 grading			
Score 1	1[d]	13	<0.01
Score 3	7	0	
Score 4	1	0	

Abbreviations: ASCO-NHB v2, ASCO Value Framework Net Health Benefit Score version 2; ESMO-MCBS v1, European Society of Medical Oncology Magnitude of Clinical Benefit Scale version 1.1; OS, overall survival; PFS, progression-free survival; RR, response rate.

[a]n = 8.

[b]n = 7.

[c]n = 12.

[d]Ramucirumab.

between RR was observed (15% *v* 6.7%, $P < .05$). Although all nine FDA-approved drugs have positive NHB scores, four of the 13 not approved drugs also have positive NHB scores (Fig 1). They are 5-fluorouracil and oxaliplatin, erlotinib with sorafenib, octreotide, and tivantinib. Interestingly, the atezolizumab with bevacizumab combination has NHB scores well above the median compared with other FDA-approved therapies (Fig 1). A similar depiction of ESMO grades across all 22 drugs is given in the Data Supplement.

As a means to evaluate whether the ASCO-NHB v2 may provide some insight into how HCC treatment could be sequenced, we evaluated the cumulative score of two lines of treatments assuming that a high combined score could reflect a possible sequence. We inferred that HCC first-line therapy would include sorafenib, lenvatinib, or atezolizumab with bevacizumab, followed by a second-line targeted agent that could be regorafenib, cabozantinib, ramucirumab, or a checkpoint inhibitor. Given these parameters, the sequence with the highest ASCO NHB scores observed was atezolizumab with bevacizumab followed by either regorafenib or cabozantinib (Table 3). Finally, the Data Supplement summarizes ongoing clinical trials of interest we have noted in our literature search where the ASCO-NHB v2 could be applied in the future once phase III trial data are made publicly available.

DISCUSSION

Current FDA-approved therapies for HCC overall demonstrated higher NHB scores based on the value framework set forth by ASCO-NHB v2 compared with those that did not receive FDA approval. However, four of the unapproved therapies yielded positive values that seemed to be in the same numerical range as some of the approved therapies. These results support the need to devise a meaningful threshold to differentiate novel drugs that have significant, rather than incremental, NHBs. This threshold could be considered for important health policy decisions such as postmarketing approval fulfillments, physician uptake, insurance coverage, and price negotiations. For example, one study proposed threshold scores of 40 or less as low benefit.[12] However, such assignment would discredit eight of the nine currently FDA-approved therapies; in fact, atezolizumab with bevacizumab would be the only drug combination declared as having substantial NHB. Indeed, this highlights the fundamental problem of applying these scoring systems to assign value when dealing with data derived from heterogeneous patient populations, different therapeutics using varying mechanisms of action, a spectrum of trial designs, and the underlying different biologic subtypes.

Our analysis using these frameworks suggests that any potential treatment sequences that included atezolizumab and bevacizumab would result in the highest NHB scores and perhaps with substantial clinical value. Previously, a cost-effectiveness analysis supported lenvatinib over sorafenib, with more quality-adjusted life-years gained and a total of $23,719 potentially saved per patient.[13] Regarding second-line treatment, studies of cabozantinib, ramucirumab, and regorafenib have all shown only modest clinical benefit and a lack of overall cost-effectiveness.[14-17] Nivolumab with or without ipilimumab and pembrolizumab all have not yet fulfilled the accelerated approval requirements

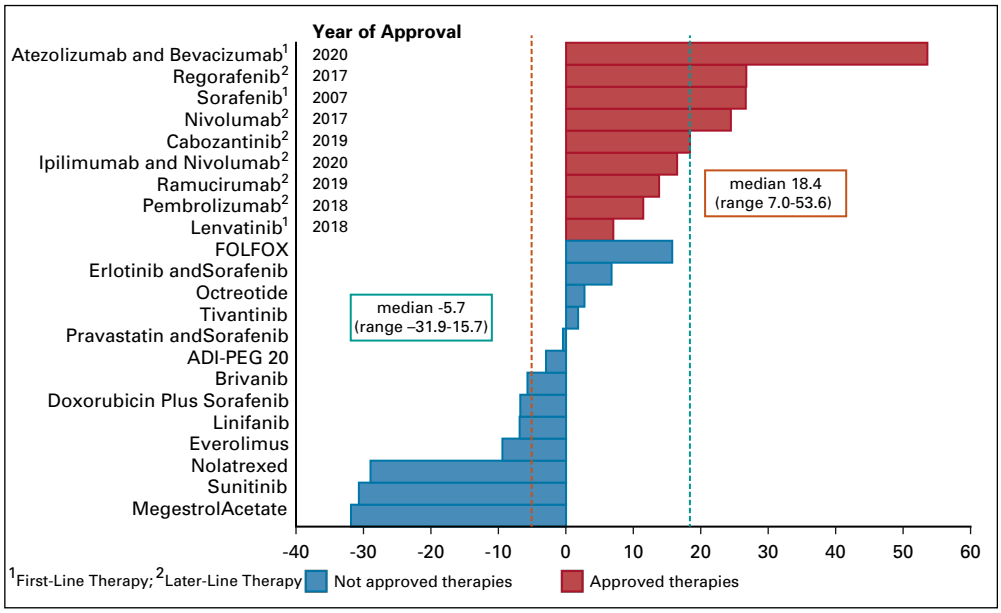

FIG 1. ASCO framework net health scores for FDA-approved and not FDA-approved therapies. FDA, Food and Drug Administration; FOLFOX, fluorouracil and oxaliplatin.

for the FDA, and cost-effectiveness research regarding these therapies is likely not yet published. Individual assessments of each drug using these frameworks may be more interpretable than applying scores to hypothetical sequences and combinations. A number of promising randomized phase III trials using FDA-approved agents as combinations are ongoing, and future analysis using value framework applied to those trials could be helpful.

Several inherent challenges in using ASCO and ESMO value frameworks need to be addressed for future applications. First, these frameworks consider both subjective side effect reporting and surrogate end points and as such do not always correlate well with definite OS benefit.[18] They also do not integrate laboratory data; clinically meaningful lab abnormalities such as low albumin, low sodium, low glucose, and elevated bilirubin could be captured to adequately evaluate clinical toxicities seen in HCC therapies. However, both scales do have good concordance and have previously demonstrated to be informative in assessing FDA-approved therapies across cancer types.[12] Such methods could be applied to future HCC systemic treatment combinations, including ongoing drug registration

TABLE 3. Cumulative Scores If Two Lines of Therapies Were Used in the Treatment Sequence for HCC

First Line	Second Line	Cumulative ASCO Scores	Cumulative ESMO Scores
Atezolizumab and bevacizumab	Regorafenib	80.34	7
Atezolizumab and bevacizumab	Cabozantinib	71.97	7
Sorafenib	Regorafenib	53.4	6
Sorafenib	Nivolumab	51.11	6
Sorafenib	Cabozantinib	45.03	6
Sorafenib	Ipilimumab and nivolumab	43.13	6
Sorafenib	Ramucirumab	40.45	4
Sorafenib	Pembrolizumab	38.11	6
Lenvatinib	Regorafenib	33.74	6
Lenvatinib	Nivolumab	31.45	6
Lenvatinib	Cabozantinib	25.37	6
Lenvatinib	Ipilimumab and nivolumab	23.47	6
Lenvatinib	Ramucirumab	20.79	4
Lenvatinib	Pembrolizumab	18.45	6

Abbreviations: ESMO, European Society of Medical Oncology; HCC, hepatocellular carcinoma.

trials listed in the Data Supplement, as well as locoregional therapies such as radioembolization, transarterial chemoembolization, and stereotactic body radiation therapy to better validate these frameworks for HCC.

Second, these frameworks are vulnerable to biases in published literature. The reporting of efficacy could be limited by data cutoff dates with no long-term survival data available. The reporting of side effects is also different from one journal to another, and more detailed reporting of negative clinical side effects can reduce overall framework scoring. One reasonable solution is to use only toxicities reported from the package insert approved by the FDA. Third, some trials were first-line in treatment-naïve patients, and other trials were second-line after prior therapy, thereby influencing the magnitude of benefit in the respective outcome assessments. Fourth, some studies were designed to have noninferiority (eg, lenvatinib) instead of superiority analyses (eg, sorafenib), and some had placebo instead of active treatment in the control arm, which one could see in the Data Supplement. These study design differences influenced the positive benefit scores given to each drug. For example, Keynote-240 compared pembrolizumab with placebo, whereas CheckMate-459 compared nivolumab with sorafenib. Given that toxicity scores are relative to comparator (eg, placebo or sorafenib), the NHB score was more negatively affected by toxicity when scoring Keynote-240. Other study design differences such as blinding, sample size, and duration of follow-up could also influence components of the ASCO net health scores. We do also note that our ESMO clinical benefit scale assessments seemed more conservative compared with the published ESMO score cards,[12a] but we minimized bias by incorporating at least two reviewers for trial selection and individual therapy assessment.

Finally, our study was limited by three trials with data from conference abstracts, but we felt, given the significant findings, their inclusion was necessary. It is possible that additional data from these studies and those listed in the Data Supplement, possibly with subsequent FDA decisions, will become available during manuscript review. We encourage others to continue such analysis in HCC and other cancer types with emerging treatment advances.

Overall, we demonstrated that the three first-line and six second-line FDA-approved therapies for HCC in our data set have higher NHB scores, based on a recognized value framework from ASCO, compared with formerly abandoned therapies in the early drug development for HCC. Some concerns remain regarding some of the drugs with low clinical benefit scores and low cost-effectiveness when applied to broad patient populations. Small differences in RR or PFS between drugs that succeeded and those that failed highlight the importance of scoring systems that include assessments of longevity, morbidity, and treatment tolerability. Although these findings may curb enthusiasm for RR or PFS to be used as the definitive end point in future HCC trials, their role as a secondary end point or an outcome for any promising early phase trials remains logical.[19,20] Importantly, patients with HCC could develop hepatic decompensation and complications regardless of radiologic improvement.

Therefore, a comprehensive evaluation of the patients' long-term clinical status, both quantity and quality of life, will ultimately determine the true value of the drugs we have for HCC. The application of ASCO value framework with ESMO grading as supplemental analysis presented here is an initial step of how we can closely examine data of future treatment options for HCC in a patient-oriented approach as more therapeutic agents and treatment combinations become commercially available.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Application of ASCO Value Framework to Treatment Advances in Hepatocellular Carcinoma

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