Characteristics, Systemic Treatments and Outcomes in Patients with Advanced Hepatocellular Carcinoma: A Systematic Literature Review

Abdalla Aly[1], Sarah Ronnebaum[2], Eleanor Lucas[2], Dipen Patel[2], Yunes Doleh[1], Fernando Concha-Benavente[1]

[1]AstraZeneca, Gaithersburg, MD; [2]Pharmerit International, Bethesda, MD

Introduction

- Liver cancer is the sixth-most common diagnosed cancer and fourth-most common cause of death worldwide.[1]
- Hepatocellular carcinoma (HCC) accounts for ~80% of all liver cancer cases, making HCC a major cause of cancer and cancer-related deaths.[2,3]
- The prognosis of HCC is poor, with a 2-year overall survival (OS) rate of approximately 25%.[4]
- Patients with HCC are often diagnosed in advanced disease stages, when potentially curative options are not feasible or not recommended.[5]
- The National Comprehensive Cancer Network (NCCN) recommends 2 agents (sorafenib, lenvatinib) in the first-line (1L) setting and 5 agents (regorafenib, cabozantinib, ramucirumab, pembrolizumab, nivolumab) in the second-line (2L) setting (**Table 1**).[6]
- Despite the use of sorafenib and other NCCN-recommended systemic therapies, the median OS (mOS) of patients diagnosed with advanced stage HCC is approximately 12 months.[7]

Table 1. Systemic Therapies Recommended by NCCN[6]

	1L	2L
Recommended Therapies	Sorafenib Lenvatinib	Cabozantinib Nivolumab Pembrolizumab Ramucirumab Regorafenib Sorafenib (after 1L lenvatinib)

Objective

- To describe the characteristics, treatments, and clinical outcomes of patients with advanced HCC enrolled in interventional trials administering systemic therapies.

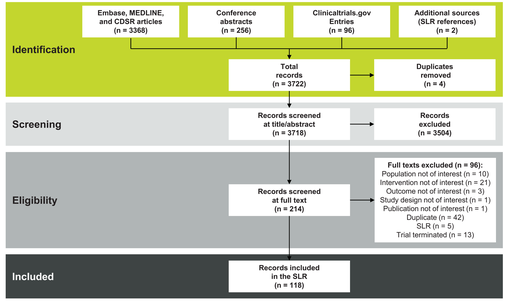
Methods

- A systematic literature review was performed to identify relevant trials describing the efficacy and safety of systemic therapies used for patients with advanced HCC.
- A predefined search strategy was used to search articles and specific conferences published 2008-2018 in Embase, MEDLINE, and Cochrane Database of Systematic Reviews, and registered trials from Clinicaltrials.gov.
- Records describing trials terminated due to lack of efficacy/safety and trials describing loco-regional HCC treatment were excluded.
- The review of citations and data extraction was performed by 2 reviewers with adjudication at each step.
- Treatments were identified as the following:
  - Placebo/none: placebo or best supportive care
  - NCCN guideline-recommended therapies: alone or in combination with another agent (**Table 1**)
  - Non-recommended therapies: all other active therapies
- Survival was measured as median progression-free survival (mPFS) and median overall survival (mOS).
- Tumor response was measured as overall response rate (ORR) and disease control rate (DCR)
- Safety was measured as the incidence of treatment-emergent adverse events (TEAEs) that were Grade 3+, serious, or leading to discontinuation; incidence of commonly reported specific TEAEs was also measured.
- Weighted means based on study arm size were calculated for all numerical outcomes of interest based on 1L or 2L status.

Results

- A total of 3,718 records were identified through the systematic search, of which 118 trials (103 articles, 9 conference abstracts, 6 Clinicaltrials.gov entries) were reviewed (**Figure 1**).

Figure 1. PRISMA Study Identification Flow Chart



- The 118 trials included 45 1L and 73 2L trials, comprising 155 total trial arms: 67 1L trial arms and 88 2L trial arms (**Table 2**).

Table 2. Trial Characteristics for Systemic Treatments in Advanced HCC

No. of Trials or Trial Arms (%)	1L	2L	Total
Trials	**45**	**73**	**118**
Trial phases			
Phase 1	3 (7)	13 (18)	16 (14)
Phase 2	32 (71)	45 (62)	77 (65)
Phase 3	7 (16)	9 (12)	16 (14)
Not reported	3 (7)	6 (8)	9 (8)
Trial design			
Single arm	27 (60)	58 (79)	85 (72)
Dosing study	1 (2)	2 (3)	3 (3)
Comparison against different active therapy	12 (27)	3 (4)	15 (13)
Comparison against placebo	2 (4)	10 (14)	12 (10)
Comparison against best supportive care	3 (7)	0 (0)	3 (3)
Trial location			
Multi-country	21 (47)	24 (33)	45 (38)
China	6 (13)	6 (8)	12 (10)
Japan	6 (13)	18 (25)	24 (20)
South Korea	1 (2)	3 (4)	4 (3)
United States	11 (24)	22 (30)	33 (28)
Staging system(s) used			
BCLC	22 (49)	33 (45)	55 (47)
TNM	10 (22)	23 (32)	33 (28)
CLIP	6 (13)	6 (8)	12 (10)
Okuda	2 (4)	1 (1)	3 (3)
None of the above	16 (36)	26 (36)	42 (36)
Trial arms	**67**	**88**	**155**
Placebo/none	5 (7)	10 (11)	15 (10)
NCCN recommended therapies	37 (55)	18 (20)	45 (29)
NCCN non-recommended therapies	25 (37)	60 (68)	85 (55)

- Patients in 1L and 2L cohorts were generally similar in terms of demographics, disease characteristics, HCC etiology, and previous resection or loco-regional treatment (**Table 3**).

Table 3. Patient Characteristics for Systemic Treatment Trials in Advanced HCC

Category	Characteristic	1L	2L
Demographic characteristics	Median age, years	60	64
	Male, %	84	83
Disease characteristics, %	Vascular invasion	33	28
	Extrahepatic spread	58	66
	Portal vein thrombosis	34	18
	ECOG 0/1	98	99
	Child Pugh A	94	90
	BCLC C	81	81
	BCLC B or C	98	99
HCC etiology, %	Hepatitis B	45	39
	Hepatitis C	24	28
	Alcoholism/alcoholic cirrhosis	15	21
	Other cirrhosis	56	59
	NASH	6	7
Previous HCC treatment, %	Resection	29	40
	Ablation	13	19
	Radiation	8	14
	Liver-directed therapy	42	63

Results represent weighted means based on trial arm sample size.

Tumor Response

- Among all active therapy arms, the weighted mean tumor response was:
  - ORR, 9% (1L) and 8% (2L)
  - DCR, 57% (1L) and 55% (2L)
- Tumor response rates appeared higher for recommended therapies versus non-recommended therapies in 2L but not 1L patients.

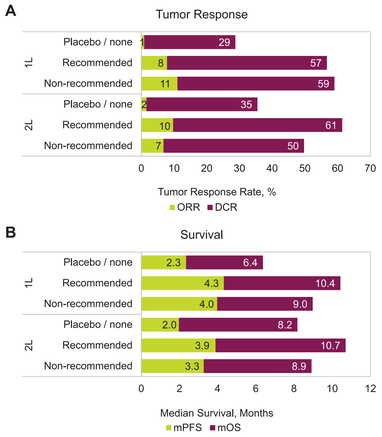
Survival

- Among all active therapy arms, the weighted mean survival was:
  - mPFS, 4.2 months (1L) and 3.5 months (2L)
  - mOS, 10.0 months (1L) and 9.6 months (2L)
- Both mPFS and mOS appeared longer for recommended therapies vs non-recommended therapies in both 1L and 2L patients.

Safety

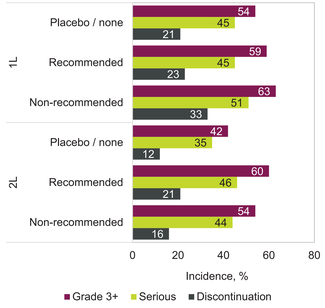
- Among all active therapy arms, the weighted mean incidence of any TEAE was:
  - Grade 3 or higher, 60% (1L) and 55% (2L)
  - Serious, 46% (1L) and 44% (2L)
  - Leading to discontinuation, 26% (1L) and 18% (2L)
- The incidence of any Grade 3+, serious, or discontinuation-related TEAEs appeared similar between recommended and non-recommended therapy arms (**Figure 3**).

Figure 2. Tumor Response and Survival



A, tumor response rates; B, progression-free and overall median survival.
Abbreviations: DCR, disease control rate; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate.
ORR = complete response + partial response.
DCR = complete response + partial response + stable disease.
Results represent weighted means based on trial arm sample size. "Recommended" refers to NCCN-recommended therapies.

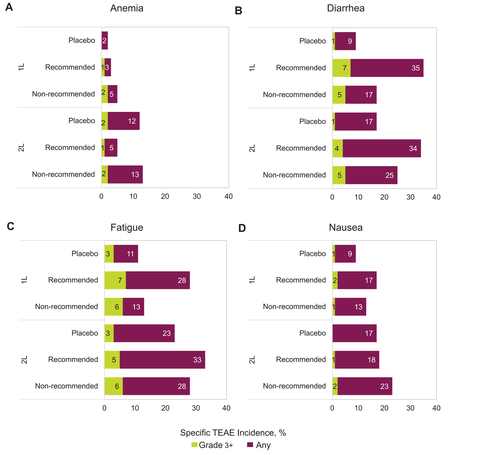
Figure 3. Incidence of Any TEAEs



Results represent weighted means based on trial arm sample size. "Recommended" refers to NCCN-recommended therapies. "Grade 3+" refers to the NCI Common Terminology Criteria for Adverse Events.[8]

- The most frequently reported individual TEAEs were anemia, diarrhea, fatigue, and nausea.
- Although these TEAEs were common across treatments, most patients experienced mild or moderate severity events (i.e., less than Grade 3; **Figure 4**).

Figure 4. Incidence of Specific TEAEs



Incidence of A, anemia; B, diarrhea; C, fatigue; D, nausea. Results represent weighted means based on trial arm sample size. "Recommended" refers to NCCN-recommended therapies. "Grade 3+" refers to the NCI Common Terminology Criteria for Adverse Events.[8]

Discussion

- Patients with advanced HCC treated with systemic agents face relatively poor prognosis, with recommended therapies providing less than 1 year survival on average.
- Approximately one-fifth of patients discontinue trials due to adverse events.
- Current recommended therapies do not appear to provide a substantial benefit in overall safety.
- There is a major unmet need for systemic therapies to treat patients with advanced HCC that have improved efficacy and greater tolerability.

Disclosures

AA, YD, and FC-B are employees and stockholders of AstraZeneca. SR, EL, and DP are employees of Pharmerit International, which received funding by AstraZeneca to conduct the review.

References

1. Global Cancer Observatory. Liver. 2018; http://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf.
2. Murata S, et al. *Eur Radiol*. 2009;19(8):2016-2023.
3. Wallace MC, et al. *Expert Rev Gastroenterol Hepatol*. 2015;9(6):765-779.
4. Golabi P, et al. *Medicine*. 2017;96(9):e5904-e5904.
5. Tan D, et al. *Aliment Pharmacol Ther*. 2013;38(7):703-712.
6. National Comprehensive Cancer Network. Hepatobiliary cancers - version 3.2019. 2019.
7. Llovet JM, et al. *Nat Rev Clin Oncol*. 2018;15(10):599-616.
8. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Supported by AstraZeneca