STUDY REPORT SYNOPSIS

D419CR00025 OREIOS

A Multicountry, Multicentre, Noninterventional, Retrospective Study to Describe the Real-world Management Outcomes in Patients With Unresectable Hepatocellular Carcinoma

This multicountry, multicentre, noninterventional, real-world, retrospective study is designed to describe the management patterns, clinical characteristics, possible predictors, and survival outcomes in patients with unresectable HCC.

Milestones:	Study Design concept approved - 22-Sep-2020 Final Protocol - 29-Sep-2021 FPFV/Database Start date - Dec 2021 LPLV/ Database End Date -15-Aug-2023 Database Lock - 22-Nov-2023 Database Cleaning and Extraction - 22-Nov-2023 Development of Analytic datasets - 29-Dec-2022 Final Results Tables - 22-Jan-2024 Final Report and Manuscript-Q1 2024
Phase of development:	IV or Retrospective Study
Sponsor:	AstraZeneca
Author:	[redacted]
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This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

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Background/rationale: Liver cancer, ranked sixth globally in 2020, caused 830,180 deaths among 905,677 cases. Hepatocellular carcinoma (HCC), 90% of cases, often results from hepatitis-induced cirrhosis. Surgical resection is limited, prompting systemic therapies. Chemotherapy's low efficacy led to exploring alternatives. Sorafenib initiated molecular targeted therapy, but its limitations spurred new drug developments and led to the approval of regorafenib, lenvatinib, cabozantinib, ramucirumab, pembrolizumab, and nivolumab as second-line therapy in patients with advanced HCC who progressed on sorafenib. Combination therapies like atezolizumab with bevacizumab show promise, and ongoing trials explore additional options, emphasizing the evolving landscape in HCC management.

Patients with unresectable HCC pose a challenge due to heterogeneity and diverse risk factors. Real-world studies identify have identified factors such as performance status, Child-Pugh class, macrovascular invasion (MVI), and AFP levels which predicts response to the treatment. Very few studies have identified the predictors of survival in advanced HCC and further exploration is warranted to optimize clinical decision-making regarding choice of systemic therapies. This multicountry, noninterventional study aims to uncover real-world management patterns, clinical characteristics, survival outcomes, and possible predictors of survival in patients with unresectable HCC. The results of the study may help oncologists in optimal patient selection and systemic therapies for unresectable HCC.

Objectives:

Primary Objective

• To describe the OS rate in patients with unresectable HCC including estimates of survival rates at 6, 12, and 18 months and at 2 years

Secondary Objectives

• To describe the management patterns in patients with unresectable HCC

• To describe the demographic and clinical characteristics of patients with unresectable HCC

Exploratory Objectives

• To describe the survival outcomes associated with different treatment regimens for unresectable HCC

• To estimate the effectiveness of different treatment regimens for unresectable HCC including real-world objective response rate (rwORR) and real-world disease control rate (rwDCR)

• To investigate the correlation between survival outcomes and clinical characteristics, liver function, and underlying disease in unresectable HCC

Study design: This was a multicountry, multicentre, noninterventional, retrospective study.

Data source: Data of 1116 patients were collected retrospectively from their established medical records. The data on different types of treatment received by patients including best supportive care

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(BSC), socio-demographics, and clinico-pathological characteristics was collected from patients' medical records and entered into an electronic data capture system.

Study population: The study population included patients diagnosed with unresectable HCC, who have been treated or are currently receiving treatment outside North America and Europe. Participating countries included were Brazil, Egypt, Hong Kong, India, Kuwait, Oman, Russia, Saudi Arabia, Singapore, South Korea, Taiwan.

Inclusion criteria: Patients who fulfil all the following inclusion criteria were eligible for participation in the study:

1. Adult female or male patients aged ≥18 years or 'adults' according to the age of majority as defined by the local regulations at index diagnosis

2. Patients or legal representatives (unless a waiver was granted) willing and be able to provide informed consent according to local regulations. For deceased patients at study entry, informed consent was not mandatory.

3. Patients with radiologically or histopathologically confirmed diagnosis (at index date) of unresectable BCLC stage B HCC, not considered eligible for initial loco-regional therapy[a] or stage C advanced or metastatic disease, between 01 January 2017 and 31 December 2019.

4. Availability of at least 12 months of follow-up data (from the index date) in the medical records at the participating site, unless patient died within the first 12 months of diagnosis.

[a] loco-regional therapy may have been administered following an initial therapeutic approach of systemic therapy.

Exclusion criteria: Patients who fulfil any of the following exclusion criteria were not eligible for participation in the study:

1. Patients with BCLC stage D HCC at index diagnosis

2. Patients with concomitant cancer, at the time of diagnosis of unresectable HCC, except for the nonmetastatic nonmelanoma skin cancers or in situ or benign neoplasms; a cancer was considered concomitant if it occurs within 5 years of HCC diagnosis.

Statistical methods: According to the objectives, the relevant parameters were summarized descriptively with appropriate statistical methods. Standard imputation methods were used to handle missing/partially entered dates. Time-to-event data was analyzed and plotted using the KM method.

Results:

Sr. No.	Objectives	Results
Primary Objective		
1.	To describe the OS rate in patients with unresectable HCC including estimates of	Median OS for the entire study population was 13.1 months. **Stage B patients:** Median OS was 18.6 months. **Stage C patients:** Median OS was 10.9 months. **Survival Rates for different stages:**

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	survival rates at 6, 12, and 18 months and at 2 years	**At 6 months:** Overall study survival rate was 72.6% (95%CI: 69.9– 75.3), 85.8% (95% CI: 80.9–89.9) for Stage B and 68.8 % (95% CI: 65.6–71.9) Stage C patients. **At 12 months:** Overall study survival rate was 52.1% (95% CI: 49.1–55.1), 66.1 % (95% CI: 59.8–72.0) for Stage B and 48.1 % (95% CI: 44.7–51.5) Stage C patients. **At 18 months:** Overall study survival rate was 40.4% (95% CI: 37.4–43.4), 51.5% (95% CI: 45.0–57.9) for Stage B and 37.1 (95% CI: 33.9–40.5) for Stage C patients. **At 2 years:** Overall study survival rate was 30.6% (95% CI: 27.8– 33.4), 39.1% (95% CI: 32.7– 45.5) for Stage B and 28.1% (95% CI: 25.1–31.4) for Stage C patients. Survival rate was higher for Stage B patients compared to Stage C patients.
Secondary Objectives		
1.1	To describe the management patterns in patients with unresectable HCC - Percentage of patients receiving each of the following standard regimens alone or in combination with other systemic agents in any line of therapy (LOT)	Among 1116 patients enrolled, the distribution of patients receiving the following any Line of Therapy (LOT) (expressed as percentage are): **Tyrosine Kinase Inhibitors:** Sorafenib: 69.1% (95% CI: 66.3–71.8) Lenvatinib: 17.6% (95% CI: 15.4–19.9) Regorafenib: 13.9% (95% CI: 12.0–16.2) Cabozantinib: 5.0% (95% CI: 3.8– 6.5) **Immune Checkpoint Inhibitors:** Nivolumab: 18.9% (95% CI: 16.7– 21.3) Durvalumab: 4.4% (95% CI: 3.3–5.8) Pembrolizumab, Atezolizumab, Tremelimumab (each < 3%) **VEGF-A/VEGF-R Targeting Agents:** Bevacizumab: 0.9% (95% CI: 0.4– 1.6) Ramucirumab: 1.5% (95% CI: 0.9 –2.4) **Combination Therapies:** Atezolizumab + Bevacizumab : 1.8% (1.1–2.8) Durvalumab + Tremelimumab : 1.5% (0.9–2.4 Pembrolizumab + Lenvatinib : 0.9% (0.4–1.6) Nivolumab + Ipilimumab : 0.2% (0.1–0.8) Cabozantinib + Atezolizumab : 0.2% (0.02–0.7) **Systemic anticancer therapy ± hepatic arterial infusion chemotherapy or transarterial chemoembolization (TACE)** Before Index Date • TACE : 22.9% (Conventional TACE (cTACE) : 22.0%; Drug-eluting Bead TACE (DEB-TACE): 0.8% From and after Index Date : • TACE : 20.8% (Conventional TACE (cTACE) : 79.2%; Drug-eluting Bead TACE (DEB-TACE): 1.7%

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<table>
<tr><td></td><td></td><td>Prior local-regional therapy including TACE, history of liver transplantation, surgical resection, and ablation
• Before Index date: 17.8% (95% CI: 15.6–20.2)
• After Index date : 19.6% (95% CI: 17.3–22.1)

Best Supportive Care: 10.8 % (95% CI: 9.0,12.7)</td></tr>
<tr><td>1.2</td><td>Duration of treatment (DOT) for each regimen in any LOT and reasons for discontinuation of regimen (disease-related factors, individual patient factors, resource-related factors [income status and insurance coverage])</td><td>Duration of Treatment (DOT) for Each Regimen in Any LOT:

<table>
<tr><th>Treatment / Parameter</th><th>Tyrosine Kinase Inhibitors</th><th>Immune Checkpoint Inhibitors</th><th>VEGF-A/VEGF-R Targeting Agents</th><th>Combination Therapy</th></tr>
<tr><td>Mean (SD) duration (days)</td><td>200.6</td><td>182.3</td><td>144.6</td><td>177.2</td></tr>
<tr><td>Median duration (days)</td><td>114.0</td><td>69.0</td><td>74.0</td><td>155.0</td></tr>
<tr><td>25th to 75th percentile (Days)</td><td>50.0 – 274.5</td><td>29.0 – 203.0</td><td>40.0 – 125.0</td><td>71.0 – 232.0</td></tr>
<tr><td colspan="5">Most common reasons for discontinuation</td></tr>
<tr><td>Progression of disease (%)</td><td>50.0%</td><td>19.3%</td><td>2.2%</td><td>1.6%</td></tr>
<tr><td>Adverse events (%)</td><td>15.5%</td><td>3.5%</td><td>1.0%</td><td>-</td></tr>
<tr><td>Lost to follow-up (%)</td><td>7.4%</td><td>1.7%</td><td></td><td>0.1%</td></tr>
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</td></tr>
<tr><td>2.</td><td>To describe the demographic and clinical characteristics of patients with unresectable HCC</td><td>Demographic characteristics:

The demographic characteristics of the 1116 patients in the study is detailed below.
Sociodemographic
Gender: Males (83.2%) and Females (16.8%)
Age: Mean Age: 61.7 years; Median age: 63.0 years
Ethnicity: Primarily East Asian (China, Hong Kong, Macau, Taiwan, Japan, Mongolia, North Korea, and South Korea) :50.4%
BMI: Normal (18.5 to 24.9 kg/m²): 46.9%.
Health Insurance: 66.4%
Lifestyle:
Tobacco consumption status : 23.8% were ex-smokers, 14% were current smokers, and 38.5% never smoked.
Alcohol consumption status:
Never consumed: 40.3%;
Current: 10.9% (Occasional consumers: 49.1%; Moderate consumers: 28.7%; Heavy consumer: 19.7%)
Past status: 21.6% (Moderate consumers: 37.3%; Occasional consumers: 29.9%; Heavy consumers: 20.8%)
Clinical Characteristics</td></tr>
</table>

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BCLC Stage at Diagnosis: Stage C (53.4%) and Stage B - 26.8%
AFP Levels: ≤400 ng/mL (47.5%), >400 ng/mL (37.1%)
BLCC stage at any LOT

- TKIs: Stage B : 13.4% ; Stage C : 67. 5%
- Immune checkpoint inhibitors : Stage B : 4.5% ; Stage C : 23.8%
- VEGF-A/VEGF-R : Stage B : 0.2% ; Stage C : 2.2%
- Combination: Stage B : 13.4% ; Stage C : 67.5%

Presence of encephalopathy : 98.9%
Presence of ascites : 79.3%
Child-Pugh Class: Mostly Class A (42.3%), few in Class B (12.0%) and class C (0.5%)
Liver Diseases: ALD (6.45%), NAFLD (2.33%) ; Liver cirrhosis : (3.1%)

AFP levels : AFP <=400 : 47.49%; (AFP)>400 : 37.10%
Hepatitis: HBV : 47.4% ; HCV: 22.5% **Comorbidities:** Diabetes (27.9%), systemic hypertension (34.3%), coronary heart disease: 7.7%
ECOG performance status : ECOG 0 (31.5%); ECOG 1 (48.4%); ECOG 2 (7.4%) ; ECOG 3 (1.5%); ECOG 4 (0.1%)

Exploratory Objective

1. To describe the survival outcomes associated with different treatment regimens for unresectable HCC

Treatment / Parameter	Tyrosine Kinase Inhibitors (OS)	Immune Checkpoint Inhibitors (OS)	VEGF-A/VEGF-R Targeting Agents (OS)	Combination Therapy (OS)
Median OS (95%CI)	13.2 months (12.0 – 14.5)	19.4 months (15.8 – 22.2)	27.0 months (21.2 – 33.8)	23.4 months (14.7 – 28.5)
Survival Rate (95%CI)				
6 months	74.12 (71.09, 76.98)	85.23 (80.90, 88.91)	100.00	92.16 (81.12,97.82)
12 months	53.21 (49.84, 56.56)	64.48 (59.03, 69.72)	81.48 (61.92, 93.70)	70.59 (56.17, 82.51
18 months	40.62 (37.35, 44.02)	52.58 (47.03, 58.19)	77.78 (57.74, 91.38)	58.64 (44.17, 72.42)
2 years	30.85 (27.76, 34.09)	41.10 (35.69, 46.72)	59.26 (38.80, 77.61)	48.53 (34.75, 63.40)

2. To estimate the effectiveness of different treatment regimens for unresectable HCC including - Real-world

PFS at any LOT:

	Overall (N=1116)	**Tyrosine kinase inhibitors**	**Immune checkpoint inhibitors**	**VEGF-A/ VEGF-R targeting agents**	**Combination**
Treatment (n)		891	325	27	51
Number of Events					

[redacted]

progression-free survival (rwPFS), real-world objective response rate (rwORR) and real-world disease control rate (rwDCR)

Progressed n (%)	808 (72.5)	712 (80.0)	291 (89.5)	25 (92.6)	43 (84.3)
Right Censored	306 (27.5)	178 (20.0)	34 (10.5)	2 (7.4)	8 (15.7)
Progression Free Survival (Months)					
Median [b]	6.1	5.3	4.5	7.1	8.0
95% CI for Median	(5.5, 6.7)	(4.8, 6.0)	(4.0, 5.4)	(3.1, 9.3)	(5.0, 14.6)

Overall rwORR:

11(0.1%) patients achieved complete response (CR).
120 (10.8%) patients achieved partial response (PR).
Objective response rate (% responders) for overall study population was 11.7% (95% CI: 9.9, 13.8). ORR was consistent in subgroups with Stage B and Stage C HCC. The objective response rate was highest for combination therapies (25.5%) followed by VEGF-A/VEGF-R Targeting Agents (18.5%), Immune Checkpoint Inhibitors (15.1%), (0.5%), and TKIs (7.1%).

Overall rwDCR:

Among the overall study population, the rwDCR was 40.5% with majority having stable disease (33%), 10.8% having partial response and 0.1% having complete response. DCR was consistent in both Stage B and stage C patients. The disease control rate was highest for combination therapies (70.6%), followed by VEGF-A/VEGF-R Targeting Agents (40.7%), Immune Checkpoint Inhibitors (39.4%), and TKIs (36.6%).

Treatment Regimen	rwORR	rwDCR
Overall	11.7%	40.5%
Tyrosine Kinase Inhibitors	7.1%	36.6%
Immune Checkpoint Inhibitors	15.1%	39.4%
VEGF-A/VEGF-R Targeting Agents	18.5%	40.7%
Combination Therapy	25.5%	70.6%

	Overall (N=1116)	**Tyrosine kinase inhibitors**	**Immune checkpoint inhibitors**	**VEGF-A/ VEGF-R targeting agents**	**Combination**
CR	11 (0.99)	4 (0.45)	6 (1.85)	-	-
PR	120 (10.75)	59 (6.62)	43 (13.23)	5 (18.52)	13 (25.49)
SD	368 (32.97)	274 (30.75)	82 (25.23)	6 (22.22)	25 (49.02)

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3.	To investigate the correlation between survival outcomes and clinical characteristics, liver function, and underlying disease in unresectable HCC.	On multivariate analysis, only AFP Levels (≤400 ng/mL versus >400 ng/mL) - Hazard Ratio: 0.74, p-value: 0.003 and Portal Vein Invasion (no) - Hazard Ratio: 0.67, p-value: 0.004 was found to be significantly associated with overall survival. Patients with AFP Levels (≤400 ng/ml) were shown to have lower risk of mortality. Also, patients without Portal Vein Invasion were shown to have lower risk of mortality

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Publications: None