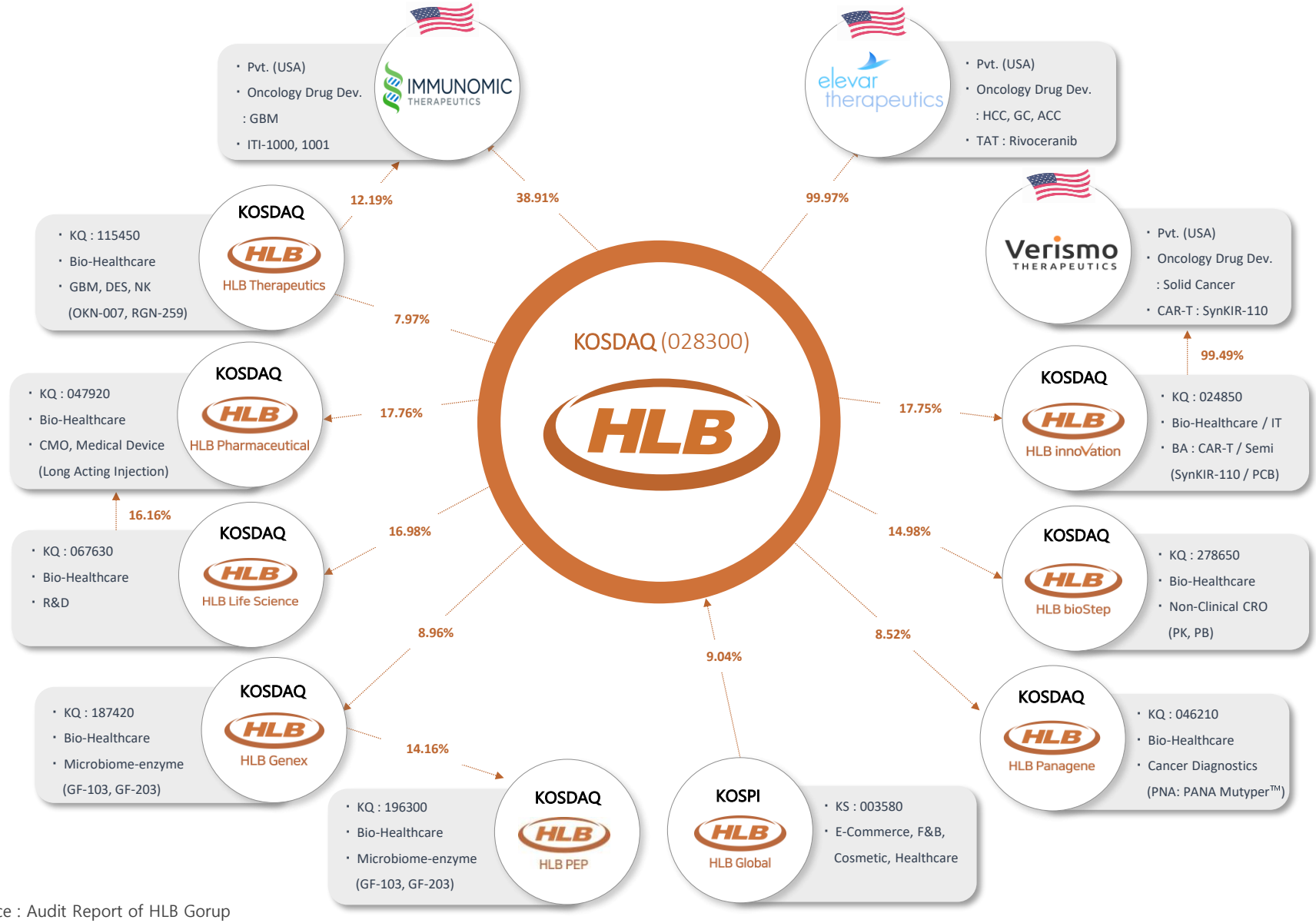

HLB
Human Life Better
2025 Update

DNA of Breakthrough

Human Life Better

「 New Drugs · CRO · CMO · Diagonistics · HealthCare 」

Our Goal is Advancing Innovation Therapy for Human Life Better



Source : Audit Report of HLB Gorup

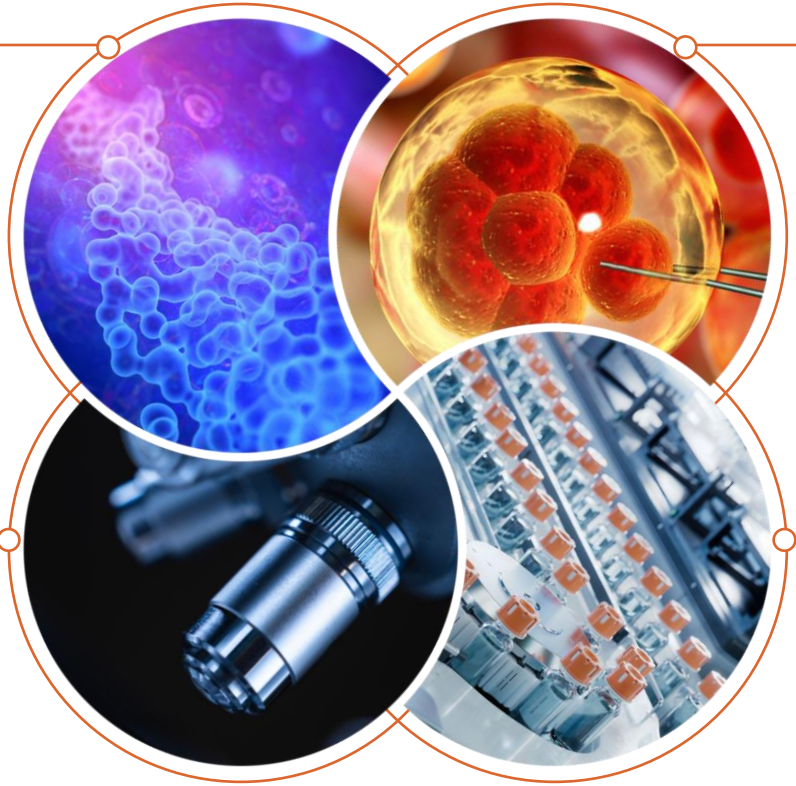
Helping People Life Better by Diversified Therapy

Oncology Drugs

- **Rivoceranib | Liver Cancer**
- ITI-1000,1001 | GBM
- OKN-007 | GBM
- SynKIR-100 | Solid Cancer(CAR-T)
- Pyorotinib | Breast Cancer

Other Therapy

- RGN-259 | Neurotrophic Keratopathy
- BleeFix® | Hemostasis
- NT-1 (5HT2AR) | Dystonia
- NT-3 (Gav3.1) | Parkinson's Disaease



Long Acting Injectable

- Apixaban | Anticoagulant
- Semaglutide | Obesity
- Liraglutide | Obesity

Cancer Diagnostics

- PNAClamp™ | Colorectal cancer
- PANAMutyper™ | Lung cancer
- OncoTector™ | Lung cancer
- PANA RealTyper™ | Cervical cancer
- PANA qPCR™ | Tuberculosis
- PANAMAX 48, 16™ | Virus

Source : HLB Group

HLB Group Main Pipelines Landscape

COMPANY	INDICATION	DRUGS	SITE	PHASE (PHASE 1 / PHASE 2 / PHASE 3 / NDA Sub / Approval)	Remarks
elevar therapeutics	HCC 1st	**Rivoceranib** +Camrelizumab	Global	■ ■ ■ ■ □	FDA Orphan drug Designation — CRL(2nd)
	GC 3rd / 4th	**Rivoceranib**	Global	■ ■ ■ □ □	FDA Orphan drug Designation
	ACC 1st	**Rivoceranib**	US, KR	■ ■ □ □ □	FDA Orphan drug Designation
	GC 2nd	**Rivoceranib** +Pacitaxel	US	■ ■ □ □ □	
	CRC 3rd	**Rivoceranib** +Lonsurf	US	■ □ □ □ □	
	iCCA	**RLY-4008**	US	■ ■ □ □ □	FDA Breakthrough Therapy Designation
Verismo THERAPEUTICS	Blood cancer(CAR-T)	SynKIR-100	Global	■ □ □ □ □	
IMMUNOMIC THERAPEUTICS	GBM (Cell Thearpy)	ITI-1000	Global	■ ■ □ □ □	
	GBM (pDNA)	ITI-1001	Global	■ □ □ □ □	
	Merkel Cell Carcinoma	ITI-3000	Global	■ □ □ □ □	
HLB Therapeutics	NK	**RGN-259**	Global	■ ■ ■ □ □	
	Dry Eye Syndrome	**RGN-259**	Global	■ ■ ■ □ □	

Source : HLB Group

HCC 1st Line Market Players

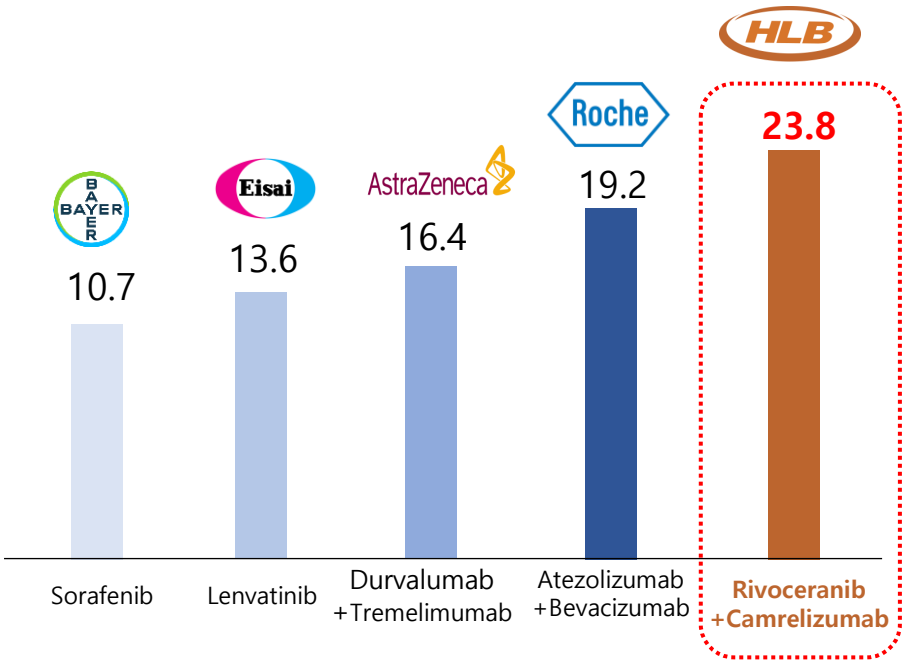
Therapy	Rivoceranib + Camrelizumab	Atezolizumab + Bevacizumab	Tremelimumab + Durvalumab	Lenvatinib	Sorafenib
Patients	**543**	501	782	954	602
Control Group	**Sorafenib**	Sorafenib	Sorafenib	Sorafenib (Inequality)	Placebo
OS	**23.8 vs. 15.2 HR 0.62**	19.2 vs 13.4 HR 0.66	16.4 vs 13.8 HR 0.78	13.6 vs 12.3 HR: 0.92	10.7 vs 7.9 HR: 0.69
PFS	**5.6 vs. 3.7 HR 0.52**	6.8 vs 4.3 HR 0.59	3.8 vs 4.1 HR 0.9	7.4 vs 3.7 HR: 0.66	5.5 vs 2.8
ORR	**25.4% vs. 5.9%**	27.3% vs 11.9%	20.1% vs 5.1%	18.8% vs 6.5%	2% vs 1%
DCR	**78.3% vs. 53.9%**		73.6% vs. 55.3%		43% vs 32%
Market Share	**Target 50%**	52%	25%		
Approval	***CRL Issued**	2020	2022	2018	2007

Source: Clinical Trail Gov.

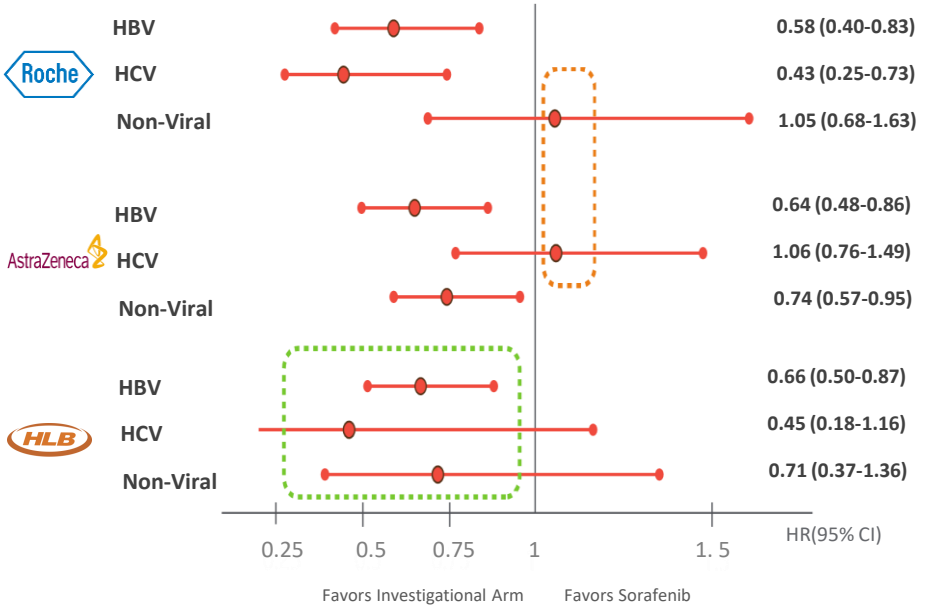
Best-in-Class Clinical Data 1 : OS, Efficacy by Types

OS (Overall Survival) Comparison

(Unit: months)



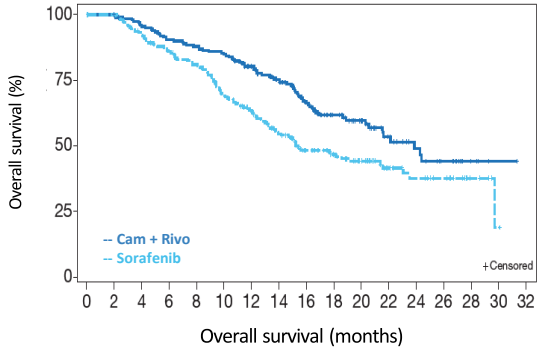
Efficacy By Types of HCC Incidence Factor

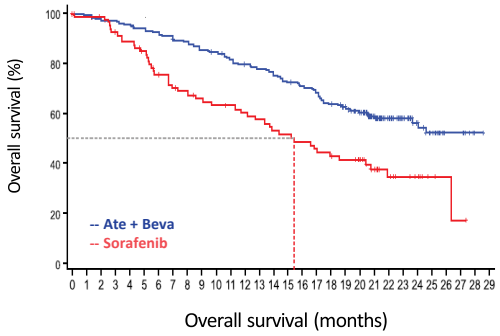


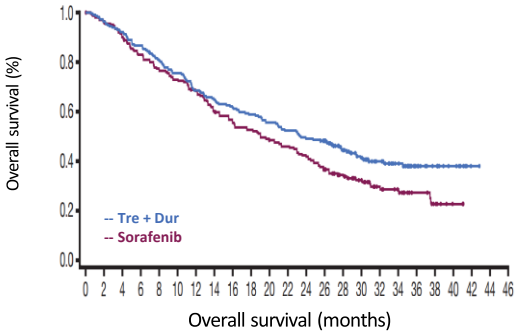
* OS= Overall Survival, HCC= Hepatocellular Carcinoma, HBV= Hepatitis B Virus, HCV= Hepatitis C Virus

Best-in-Class Clinical Data 2 : Overall Survival of ALBI 1, 2 Grade

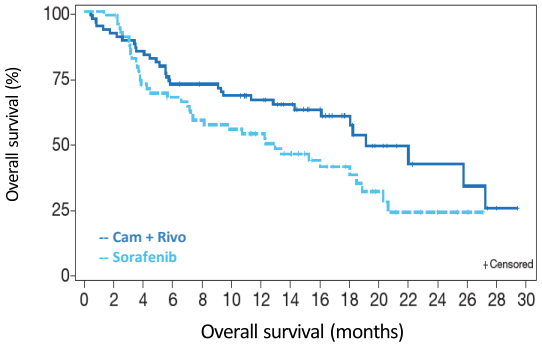
	Rivoceranib + Camrelizumab	Atezolizumab + Bevacizumab	Tremelimumab + Durvalumab
ALBI 1 Grade	ALBI G1 HR: 0.62 (0.47-0.83)	ALBI G1 HR: 0.50 (0.35-0.72)	ALBI G1 HR: 0.79 (0.62-1.01)
	ALBI G2 HR: 0.62 (0.40-1.00)	ALBI G2 HR: 0.92 (0.66-1.29)**	ALBI G2 HR: 0.83 (0.65-1.05)

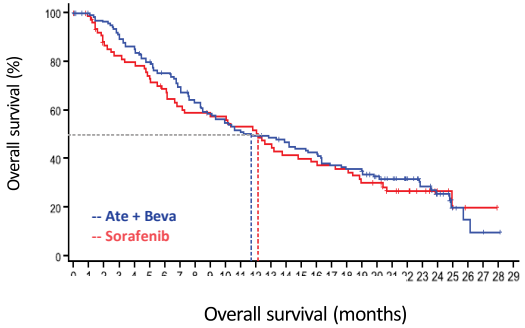


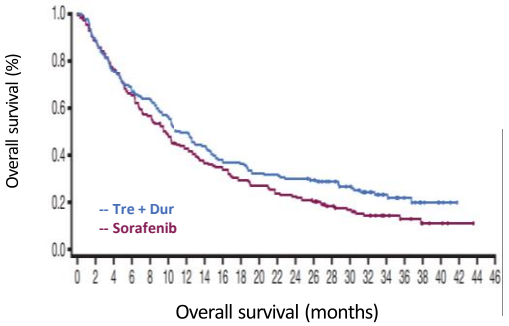




ALBI 2 Grade

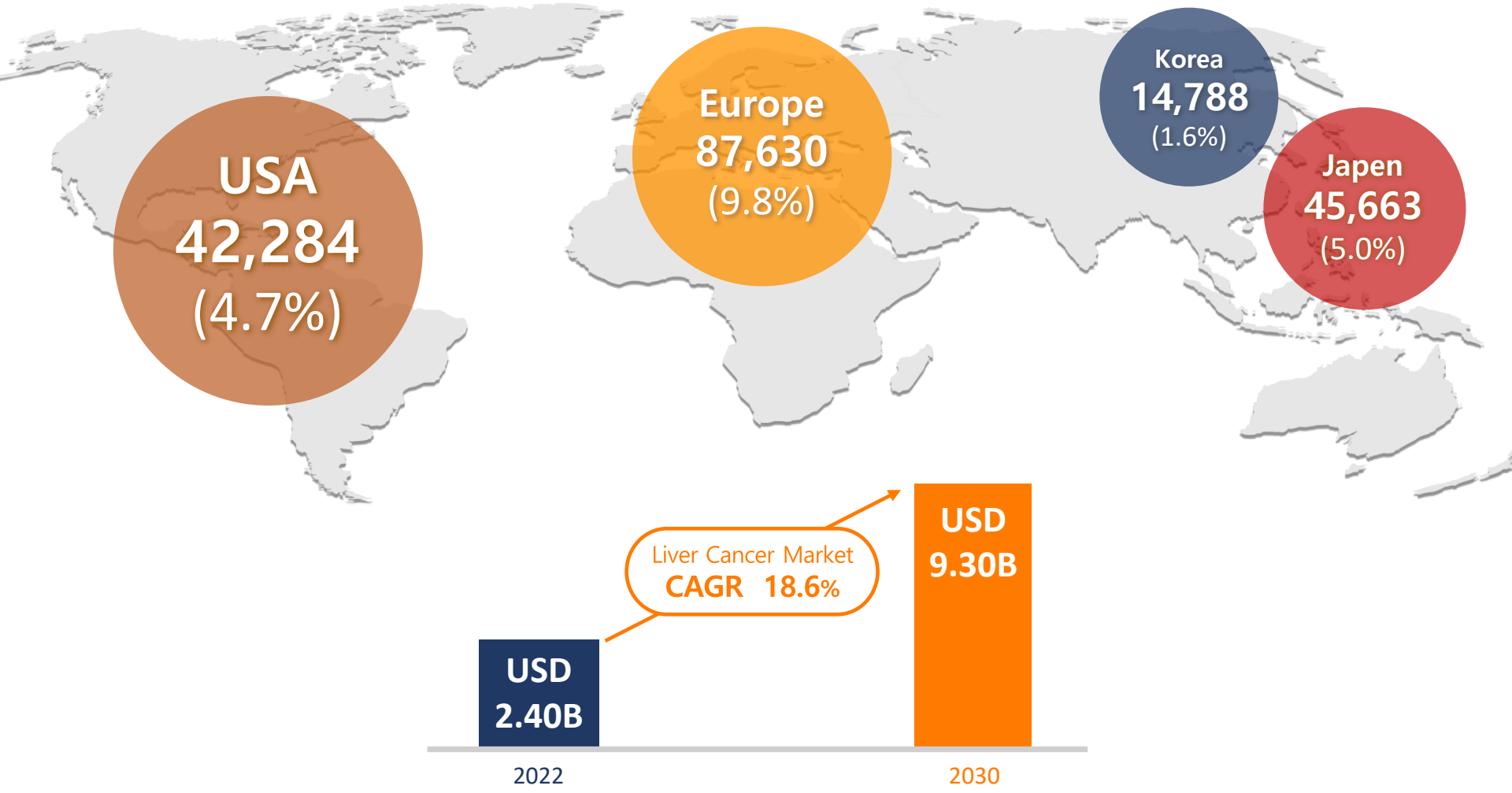






Source: Liver Cancer 2023, Supplementary appendix, Lancet 2023; published online July 24.
ALBI 1/2 Grade is an indicator of the ability of liver function to deteriorate, Grade 2 patients have lower liver function than Grade 1 patients.
**Hazard Ratio (HR) means that the closer to 1.0, the less effective it is.
Source: Abou-Alfa GK, et al. NEJM Evid Published online 6 June 2022. doi: 10.1056/EVIDoa2100070.

Global Liver Cancer Patients Data



Source: WHO, American Cancer Society, World Cancer Research Fund International, Digestive Cancers Europe, Clinical & Molecular Hepatology

Appendix

- Global Academic Data
- CRL Trends
- Development History

Lancet Journal (Published: 2023.07.24)

Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study

Shukui Qin, Stephen L Chan*, Shanzhi Gu, Yuxian Bai, Zhenggang Ren, Xiaoyan Lin, Zhendong Chen, Weidong Jia, Yongdong Jin, Yabing Guo, Xiaohua Hu, Zhiqiang Meng, Jun Liang, Ying Cheng, Jianping Xiong, Hong Ren, Fang Yang, Wei Li, Yajin Chen, Yong Zeng, Alexander Sultanbaev, Monika Pazgan-Simon, Margaryta Pisetska, Davide Melisi, Dmitriy Ponomarenko, Yurii Osypchuk, Ivan Sinielnikov, Tsai-Sheng Yang, Xiao Liang, Chunxia Chen, Linna Wang, Ann-Lii Cheng†, Ahmed Kaseb†, Arndt Vogel†, for the CARES-310 Study Group‡*

Summary

Background Immunotherapy with immune checkpoint inhibitors combined with an anti-angiogenic tyrosine-kinase inhibitor (TKI) has been shown to improve overall survival versus anti-angiogenic therapy alone in advanced solid tumours, but not in hepatocellular carcinoma. Therefore, a clinical study was conducted to compare the efficacy and safety of the anti-PD-1 antibody camrelizumab plus the VEGFR2-targeted TKI rivoceranib (also known as apatinib) versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma.

Methods This randomised, open-label, international phase 3 trial (CARES-310) was done at 95 study sites across 13 countries and regions worldwide. Patients with unresectable or metastatic hepatocellular carcinoma who had not previously received any systemic treatment were randomly assigned (1:1) to receive either camrelizumab 200 mg intravenously every 2 weeks plus rivoceranib 250 mg orally once daily or sorafenib 400 mg orally twice daily. Randomisation was done via a centralised interactive response system. The primary endpoints were progression-free survival, as assessed by the blinded independent review committee per Response Evaluation Criteria in Solid Tumours version 1.1, and overall survival in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of the study drugs. We report the findings from the prespecified primary analysis for progression-free survival and interim analysis for overall survival. This study is registered with ClinicalTrials.gov (NCT03764293).

Findings Between June 28, 2019, and March 24, 2021, 543 patients were randomly assigned to the camrelizumab–rivoceranib (n=272) or sorafenib (n=271) group. At the primary analysis for progression-free survival (May 10, 2021), median follow-up was 7·8 months (IQR 4·1–10·6). Median progression-free survival was significantly improved with camrelizumab–rivoceranib versus sorafenib (5·6 months [95% CI 5·5–6·3] *vs* 3·7 months [2·8–3·7]; hazard ratio [HR] 0·52 [95% CI 0·41–0·65]; one-sided p<0·0001). At the interim analysis for overall survival (Feb 8, 2022), median follow-up was 14·5 months (IQR 9·1–18·7). Median overall survival was significantly extended with camrelizumab–rivoceranib versus sorafenib (22·1 months [95% CI 19·1–27·2] *vs* 15·2 months [13·0–18·5]; HR 0·62 [95% CI 0·49–0·80]; one-sided p<0·0001). The most common grade 3 or 4 treatment-related adverse events were hypertension (102 [38%] of 272 patients in the camrelizumab–rivoceranib group *vs* 40 [15%] of 269 patients in the sorafenib group), palmar-plantar erythrodysaesthesia syndrome (33 [12%] *vs* 41 [15%]), increased aspartate aminotransferase (45 [17%] *vs* 14 [5%]), and increased alanine aminotransferase (35 [13%] *vs* eight [3%]). Treatment-related serious adverse events were reported in 66 (24%) patients in the camrelizumab–rivoceranib group and 16 (6%) in the sorafenib group. Treatment-related death occurred in two patients: one patient in the camrelizumab–rivoceranib group (ie, multiple organ dysfunction syndrome) and one patient in the sorafenib group (ie, respiratory failure and circulatory collapse).

Interpretation Camrelizumab plus rivoceranib showed a statistically significant and clinically meaningful benefit in progression-free survival and overall survival compared with sorafenib for patients with unresectable hepatocellular carcinoma, presenting as a new and effective first-line treatment option for this population.

Funding Jiangsu Hengrui Pharmaceuticals and Elevar Therapeutics.

- "Rivoceranib/Camrelizumab combination therapy has the longest patient survival rate in liver cancer and presents new options for first-line treatments." **by Ghassan K. Abou-Alfa**
  (US Memorial Sloan Kettering Cancer Center)

- "It has demonstrated high efficacy and safety of first-line liver cancer treatment and has high potential to change advanced liver cancer treatment."
  by Stephen Chan (The Chinese University of Hong Kong)

- "The results with high risk-to-treatment benefits support that it may be a new 1st line treatment option in patients with non-interstitial liver cancer who have not received prior systemic therapy." **by Shukui Qin** (Nanjing University in China)

Bayer & Southwestern Texas University (Published: 2023.09.12)

1007P - Network meta-analysis (NMA) of lenvatinib vs key comparators in first-line unresectable hepatocellular carcinoma (uHCC)

Presentation Number 1007P
Speakers David Trueman (London, United Kingdom)
Onsite Poster display date Monday, 23 October 2023

Abstract

Background

This research compared the relative efficacy of lenvatinib monotherapy (mono), a standard of care for treatment of uHCC, versus approved / anticipated comparators. Using inverse probability of treatment weighting (IPTW) and an NMA, updated evidence for lenvatinib mono from LEAP-002, in addition to evidence from REFLECT, were included in the analyses.

Methods

Randomized controlled trials (RCTs) were identified via systematic literature review. REFLECT and LEAP-002 investigated lenvatinib mono in uHCC, with patient-level data available for each, however, only REFLECT had a comparator arm of interest. To utilise all available lenvatinib data, the lenvatinib arm from LEAP-002 was adjusted to match aggregate data for confounding factors from REFLECT using IPTW. Weighted Cox regression including matching variables as covariates were used to derive hazard ratios (HRs) for OS and progression-free survival (PFS) comparing lenvatinib and sorafenib. The estimated HRs were included in fixed-effects Bayesian NMAs to compare lenvatinib and comparators. Scenario analyses explored alternative choices for IPTW estimators.

Results

Eight RCTs (including REFLECT) and adjusted data from LEAP-002, were included in the NMA. Lenvatinib demonstrated a significant improvement in OS compared with sorafenib, and significant improvement in PFS compared with sorafenib, tremelimumab + durvalumab, tislelizumab and durvalumab (Table).

Results

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Table: 1007P

NMA results for OS and PFS – lenvatinib vs comparator

Comparator	OS; median HR (95% CrI)	PFS; median HR (95% CrI)
Sorafenib	0.75 (0.66, 0.86)	0.57 (0.49, 0.66)
Durvalumab	0.88 (0.71, 1.08)	0.55 (0.45, 0.69)
Tislelizumab	0.88 (0.71, 1.11)	0.51 (0.41, 0.65)
Tremelimumab 300 mg + durvalumab	0.97 (0.77, 1.20)	0.63 (0.51, 0.78)
Atezolizumab + bevacizumab	1.14 (0.86, 1.51)	0.87 (0.67, 1.13)
Camrelizumab + apatinib	1.21 (0.92, 1.60)	1.09 (0.82, 1.44)

Bold = significant resultAbbreviations: CrI, credible interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

Conclusions

These results suggest that patients with uHCC treated with lenvatinib mono have similar or significantly improved OS and PFS when compared with other therapies.

Legal entity responsible for the study

Eisai Inc.

Funding

Eisai Inc.

- Eisai, a competitor, presented a paper on OS/PFS HR at ESMO 2023.
- Comparative efficacy analysis of 4 current and anticipated drugs including Rivoceranib/Camrelizumab.

HLB's Treatment is confirmed as Best in Class for OS/PFS HR among key players in HCC 1st line market.

CRL Trends Past 5 Years

24%

Average CRL Rates for NDA Submission

74%

Approval Rates After CRLs

100~224 Days

Estimated Period to Resubmission for HLB

(Nonclinical or Manufacturing)

89%

Approval rate among all CRL issues Related to CMC Issues

(Only 24% approved for Clinical Deficiencies)

Source: WELLS FARGO Research, FDA CRL Deep Dive, June 6, 2024, Source: WELLS FARGO Research, FDA CRL Deep Dive, June 6, 2024

Merck & Daiichi Sankyo CRL Issue Case

Daiichi-Sankyo MERCK News Release

Patritumab Deruxtecan BLA Submission Receives Complete Response Letter from FDA Due to Inspection Findings at Third-Party Manufacturer

The letter did not identify any issues with the efficacy or safety data submitted in the application

BASKING RIDGE, N.J. & RAHWAY, N.J., June 26, 2024 – The U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter (CRL) for the Biologics License Application (BLA) seeking accelerated approval of Daiichi Sankyo (TSE: 4568) and Merck's (known as MSD outside of the United States and Canada) (NYSE: MRK) patritumab deruxtecan (HER3-DXd) for the treatment of adult patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) previously treated with two or more systemic therapies.

The CRL results from findings pertaining to an inspection of a third-party manufacturing facility. The CRL did not identify any issues with the efficacy or safety data submitted.

CRL

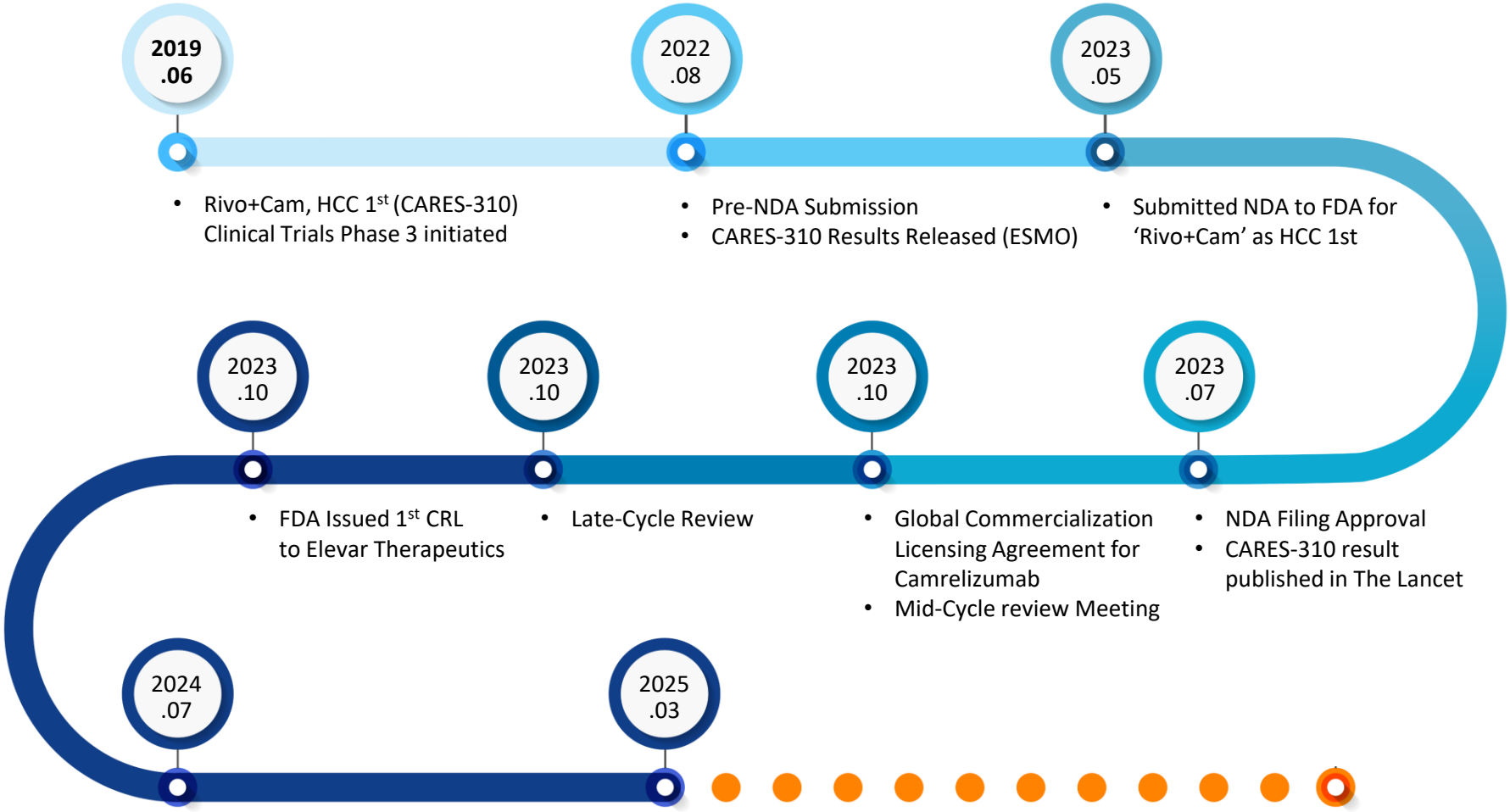
On 6 26, 2024, Merck and Daiichi Sankyo Received a CRL for the BLA Submission of Patritumab Deruxtecan

CRL

Received a CRL Letter Due to 'Facility Issues' ; Preparing for Resubmission Based on FDA Feedback
(Same case with HLB)

Source: WELLS FARGO Research, FDA CRL Deep Dive, June 6, 2024

HCC 1st Treatment(Rivo+Cam) Development History



Thank you