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The safety and efficacy of lenvatinib combined with TACE and PD-1 inhibitors (Len-TAP) versus TACE alone in the conversion resection for initially unresectable hepatocellular carcinoma: Interim results from a multicenter prospective cohort study

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Background: Surgical resection is the main treatment for hepatocellular carcinoma (HCC) in China. While more than 70% of HCC are in the intermediate or advanced stages at diagnosis and are unresectable; For those patients, transarterial chemo-embolization (TACE) is the main conversion therapy to improve the resectability rate and to diminish postoperative relapse. But its success rate is only about 10%; Both Lenvatinib and PD-1 inhibitors (immune checkpoint inhibitors) are indicated for unresectable HCC. The purpose of this study was to assess the safety and efficacy of Lenvatinib combined with TACE and PD-1 inhibitors (Len-TAP) alone as conversion therapy for patients with initially unresectable HCC.

Table: 715P

|                | Len-TAP, n (%) | TACE, n (%) | P value |
|----------------|---------------|------------|---------|
| Baseline       |               |            |         |
| Age, years     | 64±11.0       | 58.8±8.6   | 0.163   |
| Gender (male)  | 68 (95.8)     | 62 (87.3)  | 0.070   |
| Etiology       |               |            |         |
| HBV            | 60 (84.5)     | 56 (78.9)  | 0.419   |
| HCV            | 1 (1.4)       | 3 (4.2)    |         |
| ECOG PS        |               |            |         |
| 0              | 64 (90.1)     | 66 (93.0)  | 0.546   |
| 1              | 7 (9.9)       | 5 (7.0)    |         |
| BCLC stage     |               |            |         |
| A              | 30 (42.3)     | 31 (43.7)  | 0.865   |
| B              | 41 (57.7)     | 40 (56.3)  |         |
| C              |               |            |         |
| AEs            |               |            |         |
| Grade 3 AEs    | 38 (53.5)     | 13 (18.3)  | <0.001  |
| Outcomes       |               |            |         |
| Median PFS, days | 531±182      | 224±33.3   | <0.001  |
| Conversion resection rate | 36 (50.7) | 11 (15.5) | <0.001  |
| mRECIST  ORR   | 56 (78.9)     | 12 (16.9)  | <0.001  |
| DCR            | 67 (94.4)     | 41 (57.7)  | <0.001  |
| RECIST 1.1 ORR| 27 (38.0)     | 5 (7.0)    | <0.001  |
| DCR            | 61 (93.0)     | 20 (28.1)  | <0.001  |

Methods: This is a multicenter, prospective, cohort study. Key Eligibility Criteria:18-70 years old; HCC confirmed by radiographic or histology; No systemic treatment history; BCLC stage B/C. The conversion therapy includes Len-TAP (Lenvatinib followed by TACE and Camrelizumab/Sintilimab) and TACE alone. Their adverse events (AEs), response rate, conversion-resection rate, and survival outcome were compared.

Results: From October 2020 to March 2022, 71 patients were enrolled in both groups. Until April 2022, the Len-TAP group had a higher rate of Grade 3 AEs (P<0.001), there were no level 4 or 5 TRAEs in both groups. At 16±1.1 weeks, OS were based on mRECIST was 78.9% and 16.9% in the Len-TAP and TACE groups (P<0.001). The Len-TAP group had a better conversion resection rate (50.7% vs 15.5%; P<0.001) than TACE group. The median PFS were 331.8±22 and 244±33.3 days (P<0.001), and the 1 year OS rate was 93.3% and 64.3% (P<0.001) in the Len-TAP and TACE groups.

Conclusions: Lenvatinib combined with TACE and PD-1 inhibitors was safe and effective, which can improve resectability rate and prolong overall survival for patient with uHCC.

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Impact of COVID-19 pandemic on clinical outcomes in hepatocellular carcinoma: A multicentre cohort study

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Background: Hepatocellular carcinoma (HCC) accounts for 90% of all liver cancer cases and is the fifth most common form of cancer. HCC remains the second most common cause of cancer-related death. Patients with early-stage disease may be treated surgically with resection, liver transplantation, or percutaneous ablation with current treatment. COVID-19 pandemic has caused severe disruption of healthcare services worldwide and has interrupted patients’ access to essential services. During the first wave, many healthcare services were shut to all but emergencies. However, the immediate and long-term impact of COVID-19 on clinical outcomes in HCC are unknown. In this study, we aimed to determine the indirect impact of COVID-19 health service utilisation on HCC outcomes.

Methods: A prospective cohort study was conducted from March 15 until June 30 2020. Patients were enrolled from 8 tertiary hospitals in the UK and Germany with dedicated HCC management services. All patients with current or past HCC who were discussed at a multidisciplinary meeting (MDT) were identified. Hospital medical records, HCC MDT notes and hospital HCC databases were used to gather patient demographic and HCC related clinical data. Presence of the COVID-19 pandemic was operationalised as the time period during which the first wave of COVID-19 pandemic was present in the UK. Any delay to treatment (DTT) and the effect on survival at 1 year were reported. Any delay to treatment (DTT) and the effect on survival at 1 year were reported.

Results: The median time from MDM discussion to commencement of treatment was 49 days (IQR 26-83), with 70.1% of patients commencing treatment after 31 days of the first wave of COVID-19 pandemic. Any delay to treatment (DTT) and the effect on survival at 1 year were reported. Any delay to treatment (DTT) and the effect on survival at 1 year were reported.

Results: During the first wave of COVID-19 pandemic, severe delays in HCC treatment. However, DTT did not translate to reduced survival. Longer follow is important given the delay to therapy in those receiving curative therapy.
Effectiveness and safety of TACE in combination with TIS and LEN in patients with uHCC.

Conclusions: Preliminary analysis showed that TACE combined with TIS and LEN showed a considerable efficiency with relatively high ORR and a tolerable safety profile in uHCC treatment.

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Prognosis-related molecular subtypes and immune features associated with hepatocellular carcinoma

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Background: Bioinformatics tools were used to identify prognosis-related molecular subtypes and biomarkers of hepatocellular carcinoma (HCC).

Methods: The TCGA datasets and GEO datasets (GSE14520, GSE76427, and GSE25097) were screened for differentially expressed genes (DEGs) between HCC and normal tissues. DEGs in the same direction across the four datasets were analyzed for enrichment. Non-negative matrix decomposition to identify subtypes of HCC with different prognosis. Cox regression and Kaplan-Meier curve analyses were performed to identify overlapping DEGs associated with survival defined as prognosis-related genes. An area under the curve > 0.80 of genes used to construct random survival forest and least absolute shrinkage and selection operator (LASSO) models to identify feature genes. We constructed a Gaussian mixture model (GMM) to identify feature genes with ability to diagnose HCC recurrence. Key gene associated with OS were determined by univariate Cox regression analysis. Nomograms mode was used to evaluate the predictive power. The mutation and methylation of key gene were analyzed in TCGA. The relative levels of immune cell infiltration were determined by single-sample gene set enrichment.

Results: Four datasets identified 3,330 DEGs in the same direction that were involved in cell cycle, and FOKO signaling pathway. Subtype C2 showing better overall survival than subtype C1. Seven feature genes (SORBS2, DHR51, SLC16A2, RCLI, IGFALS, GNA14, and FANCI) that may be involved in HCC occurrence and prognosis. A univariate Cox model identified FANCI as a key gene involved mainly in the cell cycle, and mismatch repair. FANCI had two mutation sites and may undergo methylation. ssGSEA showed that Th2 and Th cells are significantly high-infiltrated in HCC patients.

Conclusions: We defined two molecular subtypes of HCC that are associated with different prognosis, and we identified FANCI as a good prognostic indicator in HCC.

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