|  |  |
| --- | --- |
| Table S1. Adverse Event (AE) | Dose-Limiting Toxicity Definition  |
| Any AE  | Any Grade 5 toxicity attributed to study treatment  |
| Hematologic  | Any Grade 4 neutropenia lasting more than 7 days  |
|  | Febrile neutropenia  |
|  | Grade 4 thrombocytopenia  |
|  |  |
| Nervous system disorders  | Any Grade ischemia cerobrovascular  |
|  | Any Grade stroke  |
|  | Any Grade transient ischemic attack  |
|  |  |
| Other non-hematologic  | Any non-hematological AEs grade 3 or greater lasting for 14 or more days |
|  | Any non-hematologic laboratory criteria which is Grade > 3 and lasting ≥ 14 days that is of clinical significance (e.g. elevated lipase only qualifies as DLT if it is in the presence of clinical pancreatits)  |

| **Table S2. Demographics and Baseline Characteristics of Hepatocellular Carcinoma patients  (N =12)** |  |
| --- | --- |
|  | 0[Sor 200/Evo 240](N=4) | 1[Sor 200/Evo 480](N=2) | +1a[Sor 200/Evo 340](N=6) | Total(N=12) | p value |
| **Age (years)** |   |   |   |   | 0.35601 |
|     N | 4 | 2 | 6 | 12 |   |
|     Mean (SD) | 72.3 (7.4) | 63.0 (4.2) | 67.8 (10.4) | 68.5 (8.8) |   |
|     Median | 73.0 | 63.0 | 64.0 | 66.0 |   |
|     Range | (63.0-80.0) | (60.0-66.0) | (59.0-86.0) | (59.0-86.0) |   |
|   |   |   |   |   |   |
| **Gender** |   |   |   |   | 0.50002 |
|    Female | 1 (25.0%) | 0 (0.0%) | 0 (0.0%) | 1 (8.3%) |   |
|    Male | 3 (75.0%) | 2 (100.0%) | 6 (100.0%) | 11 (91.7%) |   |
|   |   |   |   |   |   |
| **Race** |   |   |   |   | 0.40912 |
|     White | 2 (50.0%) | 2 (100.0%) | 6 (100.0%) | 10 (83.3%) |   |
|     Black or African American | 1 (25.0%) | 0 (0.0%) | 0 (0.0%) | 1 (8.3%) |   |
|     Native Hawaiian or Other  Pacific Islander | 1 (25.0%) | 0 (0.0%) | 0 (0.0%) | 1 (8.3%) |   |
|   |   |   |   |   |   |
| **ECOG PS** |   |   |   |   | 1.00002 |
|     0 | 0 (0.0%) | 0 (0.0%) | 1 (16.7%) | 1 (8.3%) |   |
|     1 | 4 (100.0%) | 2 (100.0%) | 5 (83.3%) | 11 (91.7%) |   |
|  |  |  |  |  |  |
| **Child Pugh Score** |   |   |   |   | 0.42851 |
|     Mean (SD) | 6.5 (0.6) | 6.0 (1.4) | 5.8 (0.8) | 6.1 (0.8) |   |
|     Median | 6.5 | 6.0 | 6.0 | 6.0 |   |
|     Range | (6.0-7.0) | (5.0-7.0) | (5.0-7.0) | (5.0-7.0) |   |
|  |   |   |   |   |   |
| **Child Pugh Classification** |   |   |   |   | 0.41412 |
|     A | 2 (50.0%) | 1 (50.0%) | 5 (83.3%) | 8 (66.7%) |   |
|     B | 2 (50.0%) | 1 (50.0%) | 1 (16.7%) | 4 (33.3%) |   |
|  |   |   |   |   |   |
| **Bilirubin** |   |   |   |   | 0.72121 |
|     Mean (SD) | 1.3 (0.9) | 0.8 (0.0) | 0.8 (0.5) | 1.0 (0.6) |   |
|     Median | 1.0 | 0.8 | 0.8 | 0.8 |   |
|     Range | (0.6-2.5) | (0.8-0.8) | (0.2-1.5) | (0.2-2.5) |   |
|  |   |   |   |   |   |
| **Albumin** |   |   |   |   | 0.88171 |
|     Mean (SD) | 3.6 (0.4) | 3.3 (0.8) | 3.6 (0.2) | 3.5 (0.4) |   |
|     Median | 3.7 | 3.3 | 3.6 | 3.6 |   |
|     Range | (3.0-3.8) | (2.7-3.8) | (3.2-3.8) | (2.7-3.8) |   |
|  |   |   |   |   |   |
| **AFP** |   |   |   |   | 0.74032 |
|    <= 400 ng/ml  | 1 (25.0%) | 1 (50.0%) | 4 (66.7%) | 6 (50.0%) |   |
|  > 400 ng/ml  | 3 (75.0%) | 1 (50.0%) | 2 (33.3%) | 6 (50.0%) |   |
|  |  |  |  |  |  |
| **Disease Status** |   |   |   |   | 1.00002 |
|     Intrahepatic | 2 (50.0%) | 1 (50.0%) | 2 (33.3%) | 5 (41.7%) |   |
|     Extrahepatic | 2 (50.0%) | 1 (50.0%) | 4 (66.7%) | 7 (58.3%) |   |
|   |   |   |   |   |   |
| **Vascular Invasion** |   |   |   |   | 0.41922 |
|     Yes | 3 (75.0%) | 0 (0.0%) | 2 (33.3%) | 5 (41.7%) |   |
|     No | 1 (25.0%) | 2 (100.0%) | 4 (66.7%) | 7 (58.3%) |   |
|   |   |   |   |   |   |
| **History of Cirrhosis** |   |   |   |   | 1.00002 |
|     Yes | 3 (75.0%) | 2 (100.0%) | 5 (83.3%) | 10 (83.3%) |   |
|     No | 1 (25.0%) | 0 (0.0%) | 1 (16.7%) | 2 (16.7%) |   |
|   |   |   |   |   |   |
| **Hepatitis B** |   |   |   |   | 0.18792 |
|     Yes | 1 (25.0%) | 2 (100.0%) | 1 (16.7%) | 4 (33.3%) |   |
|     No | 3 (75.0%) | 0 (0.0%) | 5 (83.3%) | 8 (66.7%) |   |
|   |   |   |   |   |   |
| **Hepatitis C** |   |   |   |   | 0.13132 |
|     Yes | 2 (50.0%) | 0 (0.0%) | 5 (83.3%) | 7 (58.3%) |   |
|     No | 2 (50.0%) | 2 (100.0%) | 1 (16.7%) | 5 (41.7%) |   |
|   |   |   |   |   |   |
| **Alcohol Related** |   |   |   |   | 0.57582 |
|     Yes | 1 (25.0%) | 0 (0.0%) | 3 (50.0%) | 4 (33.3%) |   |
|     No | 3 (75.0%) | 2 (100.0%) | 3 (50.0%) | 8 (66.7%) |   |
|   |   |   |   |   |   |
| **NASH** |   |   |   |   |   |
|     No | 4 (100.0%) | 2 (100.0%) | 6 (100.0%) | 12 (100.0%) |   |
|   |   |   |   |   |   |
| **Other Etiology** |   |   |   |   |  |
|     No | 4 (100.0%) | 2 (100.0%) | 6 (100.0%) | 12 (100.0%) |   |
|   |   |   |   |   |   |
| **Prior Chemoembolization** |   |   |   |   | 0.34552 |
|     Yes | 0 (0.0%) | 1 (50.0%) | 2 (33.3%) | 3 (25.0%) |   |
|     No | 4 (100.0%) | 1 (50.0%) | 4 (66.7%) | 9 (75.0%) |   |
|   |   |   |   |   |   |
| **Previous Tumor Directed Therapy** |  |   |   |   | 0.26872 |
|     Yes | 0 (0.0%) | 1 (50.0%) | 3 (50.0%) | 4 (33.3%) |   |
|     No | 4 (100.0%) | 1 (50.0%) | 3 (50.0%) | 8 (66.7%) |   |
| 1Kruskal Wallis    2Fisher ExactSor, sorafenib; Evo, evofosfamide; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AFP; alphafeto protein; NASH, Non-alcoholic steatohepatitis |

|  |  |  |  |
| --- | --- | --- | --- |
| Table S3. Best Response by RECIST 1.1  | Dose Level 0 (N=6 Evaluable) | Dose Level 1 (N=5 evaluable) | Dose Level +1a (N=7 evaluable) |
| Best ResponsePR SDPDNot assessed | 1\*\* 500 | 0122\* | 1213\* |
| Confirmed Response Rate | 0/6 (0%) | 0/5 (0%) | 1/7 (14%) – (PR) |

\* Tumor was not assessed due to early discontinuation of trial.

\*\*Unconfirmed

PR, partial response; SD, stable disease; PD, progressive disease

**Figure S1. Progresion-Free Survival All Patients\***



\***Kaplan-Meier analysis was performed**

**Figure S2. Overall Survival All Patients\***



**\*Kaplan-Meier analysis was performed**

**Figure S3. Progression-Free Survival HCC patients\***



**\*Kaplan-Meier analysis was performed**

**Figure S4. Overall Survival HCC patients\***



**\*Kaplan-Meier analysis was performed**