Sorafenib (SOR) Combined With Nivolumab (NIVO) In Advanced Hepatocellular Carcinoma (HCC): Safety And Efficacy In A Dose Escalation Cohort

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BACKGROUND

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide.[1] The incidence and mortality of HCC are rising significantly in the United States.[2] Anti-angiogenic therapies including the tyrosine kinase inhibitor (TKI) sorafenib (SOR) demonstrate activity in advanced HCC, though objective response rates and duration of response are modest.[3] Immune checkpoint inhibition (CPI) with PD-1 inhibitors such as nivolumab (NIVO) or pembrolizumab can achieve durable objective responses in 15-18% of patients but low rates of disease control.[4,5] The combination of VEGF-targeted therapy with the monoclonal antibody bevacizumab with the PD-L1 inhibitor, atezolizumab, improved overall survival (OS) and progression-free survival (PFS) over standard SOR in a phase III trial[6]. This phase II trial (NCT# 03439891) examines the combination of SOR and NIVO in unresectable HCC patients, with Child Pugh A or B7 liver function, without prior systemic therapy. We present here results from the dose escalation cohort (Part 1) of this study.

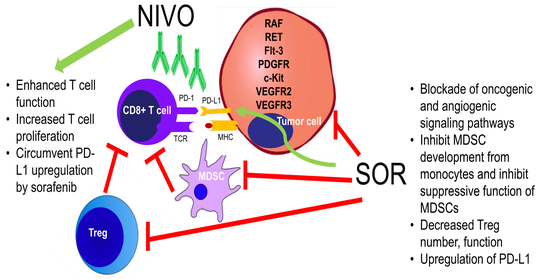
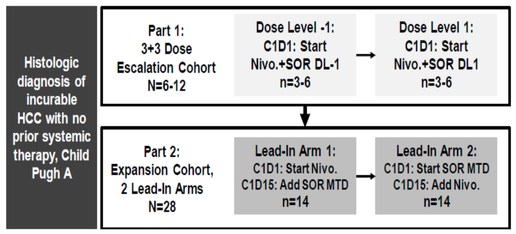


Figure 1: Diagram of possible mechanisms of synergism between SOR and NIVO. Treg = Foxp3$^+$ regulatory T-cells, MDSC = myeloid-derived suppressor cells.

TRIAL DESIGN

Table 1. Trial Design: After determination of maximum tolerated dose (MTD) of SOR in combination with NIVO, patients will enroll to Arm 1 then Arm 2 sequentially.



Primary Endpoints:

- Part 1: MTD of SOR in combination with standard dose NIVO
- Part 2: Overall response rate by RECIST 1.1

- Major Inclusion Criteria:
  - Unresectable histologically confirmed HCC, not amenable to curative treatment
  - Child-Pugh A or B7 liver function, ECOG 0-1, Age >18 years
  - Disease measurable by RECIST 1.1
  - Adequate organ function including total bilirubin <2.0
  - HBV infection allowed with appropriate anti-viral prophylaxis
  - Portal hypertension with adequate endoscopic surveillance
- Major Exclusion Criteria:
  - Prolonged systemic steroids; autoimmune disease
  - Fibrolamellar or mixed HCC-cholangiocarcinoma histology
  - Co-infection with HBV and HCV or HDV
  - Uncontrolled hypertension

Table 2. Part 1 Dose Levels: Toxicity will be graded by NCI CTCAE v.4.03. If no Dose-Limiting Toxicity (DLTs) for 3 pts at Dose Level 0, will escalate to Dose Level 1. QOD = every other day. BID = twice daily. DL= Dose Level.

Drug	Dose Level -1	Dose Level 0 (starting dose)	Dose Level 1
	n =3-6 (if >1 DLT at DL0)	n = 3-6	n = 0-6
Sorafenib	400 mg PO QOD	400 mg PO daily	400 mg PO BID
Nivolumab	240 mg IV Q2 weeks over 30 minutes		

RESULTS

Table 3. Baseline patient characteristics by SOR starting dose level. A total of 11 patients have been treated in Part 1 at UCSF.

Demographic		SOR starting dose level	
		DL 0	DL 1
		n=6	n=5
Mean age, years (SD)		64.3 (4.5)	66 (11.4)
Male, n (%)		5 (83.3)	3 (60)
Race, n (%)			
	White	3 (50)	1 (20)
	Black or African American	1 (16.7)	0
	Asian	2 (33.3)	4 (80)
	American Indian or Alaska Native	0	0
Ethnicity			
	Non-Hispanic	6 (100)	4 (80)
	Hispanic or Latino	0	1 (20)
Viral status			
	HBV+*	3 (50)	4 (80)
	HCV+*	3 (50)	1 (20)
	Non-viral	1 (16.7)	1 (20)
ECOG at enrollment			
	0	5 (83.3)	1 (20)
	1	1 (16.7)	4 (80)
BCLC			
	BCLC B	1 (16.7)	1 (20)
	BCLC C	5 (83.3)	4 (80)
AFP ≥ 400 ng/mL, n (%)		1 (16.7)	2 (40)

*Two patients (one in DL0, one in DL1) had both HBV+ and HCV+

Table 4. DLTs by SOR starting dose level.

	SOR starting dose level	
	DL 0	DL 1
	n=6	n=5
Cycles received, median (range)	4.5 (3-8)	3 (1-4)
Patients with ≥1 DLT, n (%)	1 (16.7)	2 (40)
DLTs	Grade 3 rash	Grade 3 hyperbilirubinemia, Grade 3 ascites, Grade 3 fatigue

Table 5. Treatment-related adverse events (TrAE) by grade for Part 1 (n=11), DL0 and DL1 combined. TrAEs were listed if they occurred in >10% of patients.

Adverse event, n (%)	Grade 1 or 2	Grade 3 or 4	Any grade
Rash	8 (72.7)	1 (9.1)	9 (81.8)
Increased alanine aminotransferase	4 (36.4)	0	4 (36.4)
Increased aspartate aminotransferase	4 (36.4)	0	4 (36.4)
Palmar-plantar erythrodysesthesia syndrome	1 (9.1)	3 (27.3)	4 (36.4)
Decreased appetite/anorexia	3 (27.3)	0	3 (27.3)
Fatigue	2 (18.2)	1 (9.1)	3 (27.3)
Hoarseness	3 (27.3)	0	3 (27.3)
Hypertension	2 (18.2)	1 (9.1)	3 (27.3)
Diarrhea	2 (18.2)	0	2 (18.2)
Dry skin	2 (18.2)	0	2 (18.2)
Dyspepsia	2 (18.2)	0	2 (18.2)
Hyperbilirubinemia	1 (9.1)	1 (9.1)	2 (18.2)
Headache	2 (18.2)	0	2 (18.2)
Hypoalbuminemia	2 (18.2)	0	2 (18.2)
Hyponatremia	1 (9.1)	1 (9.1)	2 (18.2)
Myalgia	2 (18.2)	0	2 (18.2)
Nausea	2 (18.2)	0	2 (18.2)
Pruritus	2 (18.2)	0	2 (18.2)
Weight loss	2 (18.2)	0	2 (18.2)

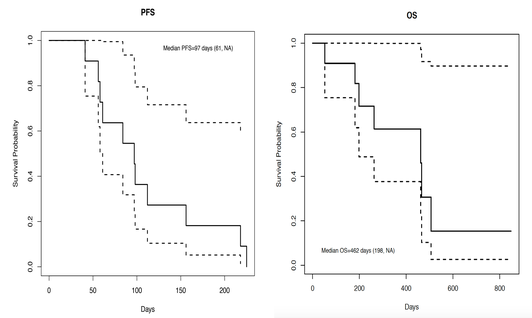
Table 6. Immune-related adverse events (IrAE) by grade for Part 1 (n=11). IrAEs were listed if they occurred in >10% of patients.

Immune-related adverse event, n (%)	Grade 1 or 2	Grade 3 or 4	Any grade
Rash	8 (72.7)	0	8 (72.7)
Increased alanine aminotransferase	4 (36.4)	0	4 (36.4)
Increased aspartate aminotransferase	4 (36.4)	0	4 (36.4)
Fatigue	2 (18.2)	1 (9.1)	3 (27.3)
Decreased appetite	3 (27.3)	0	3 (27.3)
Pruritus	2 (18.2)	0	2 (18.2)
Myalgia	2 (18.2)	0	2 (18.2)
Dyspepsia	2 (18.2)	0	2 (18.2)
Diarrhea	2 (18.2)	0	2 (18.2)
Hyponatremia	1 (9.1)	1 (9.1)	2 (18.2)

- In addition to IrAEs occurring in >10% patients, there was one case each of grade 2 hypothyroidism, grade 2 esophagitis, and grade 3 keratoacanthoma, possible or probably related to nivolumab.
- Systemic steroids were required for treatment of irAE in 2 (18.2%) of 11 patients.

Table 7. Response rates and survival estimates for Part 1 (n=11).

Best overall response, n (%)	
Complete response (CR)	0
Partial response (PR)	1 (9.1)
Stable disease (SD)	4 (36.4)
Progressive disease (PD)	5 (45.5)
Not evaluable (NE)	1 (9.1)
Response rate, n (%)	
Objective response rate (CR/PR)	1 (9.1)
Disease control rate (CR/PR/SD)	5 (45.5)
Kaplan-Meier estimate of median duration of SD, days (95% confidence intervals)	
Progression-free survival (PFS)	97 (61-NA)
Overall survival (OS)	462 (198 -NA)



NA = not reached.

CONCLUSIONS

- MTD was DL0: SOR 400 mg once daily in combination with NIVO 240 mg IV Q2 weeks.
- Adverse events and IrAEs occurred in similar frequency to SOR and NIVO as historical rates for each drug as monotherapy.[3,4]
- One partial response occurred in DL0.
- Part 2 (Dose Expansion) of this pilot study is now ongoing with inclusion of a second study site.
- Peripheral blood mononuclear cells (PBMC) and optional biopsies will be studied to examine immune profile on each drug as monotherapy and in sequential combination in each Arm of the expansion cohort.

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