

Supplemental Tables for: “Neoadjuvant treatment with angiogenesis-inhibitor dovitinib prior to local therapy in hepatocellular carcinoma: a phase 2 study - F.J. Sherida H. Woei-A-Jin, *et al.*”

Supplemental Table 1. Full list of inclusion and exclusion criteria	
Inclusion criteria	
1.	Hepatocellular carcinoma diagnosis based on cytology, histology or multi-phasic contrast-enhanced computed tomography (CT) showing typical vascular hallmarks of HCC (hypervascularity in arterial phase, washout in portal venous or delayed phase)
2.	HCC stage 0, A or B according to Barcelona Clinic Liver Cancer staging classification (i.e. T1-3N0M0 according to 8 th edition UICC staging system without impaired cancer-related ECOG performance status (PS))
3.	Patients eligible for local therapy, i.e. radiofrequency ablation, chemo-embolization, or surgical resection
4.	ECOG PS 0, 1, or 2 (however, no cancer-related symptoms: i.e. cancer-related PS 0)
5.	Age \geq 18 years old
6.	At least one unidimensional measurable lesion. Lesions must be measured by CT-scan or MRI-scan.
7.	Patients must have adequate bone marrow, liver and renal function: <ul style="list-style-type: none"> • Absolute neutrophil count (ANC) \geq $1.5 \times 10^9/L$ • Platelets \geq $75 \times 10^9/L$ • Hemoglobin \geq 6.0 mmol/L • Serum total bilirubin: \leq 1.5 x ULN • Modified Child-Pugh score \leq 6 points, i.e. Child-Pugh class A or well-compensated liver disease, with no encephalopathy at time of screening. • ALT and AST \leq 3.0 x ULN (with or without liver metastases) • Serum creatinine \leq 1.5 x ULN or serum creatinine $>$ 1.5 – 3 x ULN if calculated creatinine clearance is \geq 30 mL/min according to the Cockcroft-Gault equation.
8.	Life expectancy of at least 3 months
9.	Patients who give a written informed consent obtained according to local guidelines
Exclusion criteria	
1.	Presence or suspicion of brain metastases
2.	Another primary malignancy within 3 years prior to study drug initiation, with the exception of adequately treated in-situ carcinoma of the uterine cervix, non-melanoma skin cancer and superficial bladder tumors (Ta, Tis and T1)
3.	Anticancer therapy \leq 4 weeks prior to study drug initiation
4.	Treatment with targeted therapy (e.g. sunitinib, sorafenib, pazopanib) within 2 weeks prior to study drug initiation
5.	Incomplete recovery of side effects from previous HCC treatments or interventions.
6.	Patients who have undergone major surgery (e.g. thoracic, abdominal or pelvic), open biopsy or significant traumatic injury \leq 4 weeks prior to starting of the study drug, or patients who have undergone minor procedures \leq 1 week prior to starting study drug.
7.	The following concurrent severe and/or uncontrolled medical conditions: <ul style="list-style-type: none"> • Impaired cardiac function or clinically significant cardiac diseases, including any of the following: <ol style="list-style-type: none"> a. History or presence of serious uncontrolled ventricular arrhythmias b. Clinically significant resting bradycardia c. LVEF assessed by 2-D echocardiogram $<$ 50% or multiple gated acquisition scan $<$ 45% d. Any of the following within 6 months prior to starting of the study drug: myocardial infarction, severe/unstable angina pectoris, coronary artery bypass graft, congestive heart failure, cerebrovascular accident, transient ischemic attack, pulmonary embolism. e. Uncontrolled hypertension defined by a SBP \geq 160 mm Hg and/or DBP \geq 100 mm Hg, with or without anti-hypertensive medication(s) • Impairment of gastrointestinal function or disease that may significantly alter absorption of dovitinib (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) • Known diagnosis of human immunodeficiency virus infection (HIV testing is not mandatory) • Patients who are receiving anticoagulation treatment with therapeutic doses of warfarin at time of screening • Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. uncontrolled infection or diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol.
8.	Pregnant or lactating women
9.	Women of child-bearing potential, not employing two forms of highly effective contraception.
10.	Fertile males not willing to use contraception, as stated above.
11.	Patients unwilling or unable to comply with the protocol

* AST = aspartate transaminase. ALT = alanine transaminase. DBP = diastolic blood pressure. HCC = hepatocellular carcinoma. LVEF = left ventricular ejection fraction. ULN = upper limit of normal. SBP = systolic blood pressure.

Supplemental Table 2. Dovitinib-related toxicity management guidelines

Hypertension	
SBP <160 and/or DBP <100 mHg	Maintain dose level
SBP ≥160 and/or DBP ≥100 mHg	Delay study treatment. Restart in conjunction with standard antihypertensive medication if BP is controlled: maintain or reduce dose at investigator's discretion.
Urgent intervention indicated	Discontinue dovitinib permanently
Other cardiovascular events	
Grade 1-2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then reduce 1 dose level
Grade 4	Discontinue study treatment
Diarrhea (despite max. anti-diarrheic treatment)	
Grade 1	Maintain dose level
Grade 2	Omit dose until resolved to ≤ grade 1, then restart at current dose level. If diarrhea returns as ≥ grade 2, then omit until resolved to ≤ grade 1, then reduce 1 dose level.
Grade 3-4	Omit dose until resolved to ≤ grade 1, then reduce 1 dose level
Nausea / Vomiting (despite max. anti-emetic treatment)	
Grade 1	Maintain dose level
Grade 2	Omit dose until resolved to ≤ grade 1, then restart at current dose level. If nausea returns as ≥ grade 2, then omit until resolved to ≤ grade 1, then reduce 1 dose level.
Grade 3	Omit dose until resolved to ≤ grade 1, then reduce 1 dose level
Neutropenia	
Grade 1-2	Maintain dose level
Grade 3-4	Omit dose until resolved to ≤ grade 2. Maintain dose level if resolved by ≤ 7 days. If resolved by > 7 days after suspending dovitinib, reduce 1 dose level.
Thrombocytopenia	
Grade 1	Maintain dose level
Grade 2	Maintain dose level
Grade 3-4	Omit dose until resolution to ≤ grade 1. Maintain dose level if resolved by ≤ 7 days. If resolved by > 7 days after suspending dovitinib, reduce 1 dose level.
Febrile neutropenia ≥ Grade 3	Omit dose until resolved, then reduce 1 dose level
Hemolytic anemia ≥ Grade 3	Discontinue study treatment permanently
Lymphopenia ≥ Grade 3	Requires dose interruption until resolved to ≤ grade 1, then reduce 1 dose level
Serum creatinine	
Grade 1-2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then reduce 1 dose level
Grade 4	Discontinue study treatment permanently
Bilirubin	
Grade 1	Maintain dose level
Grade 2	Maintain dose level
Grade 3-4	Discontinue study treatment permanently
AST or ALT*	
Grade 1-2	Maintain dose level
Grade 3-4	Omit dose until resolved to ≤ grade 1 and reduce 1 dose level. Discontinue permanently if ALT or AST elevations > 3x upper limit of normal recur.
Hand-foot syndrome	
Grade 1-2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then reduce 1 dose level
Grade 4	Discontinue study treatment permanently
Other clinically significant AEs	
Grade 1-2	Maintain dose level
Grade 3 (except hyperlipidemia)	Omit dose until resolved to ≤ grade 1, then maintain dose level or reduce 1 dose level at the discretion of the investigator
Grade 4	Omit dose until resolved to ≤ grade 1, then maintain dose level or reduce 1 dose level at the discretion of the investigator

Two dose reductions are allowed: 500 mg to 400 mg, and 400 mg to 300 mg. In case of dose interruption >21 days, the patient must be discontinued from the study. * AST = aspartate transaminase. ALT = alanine transaminase. BP = blood pressure.

Supplemental Table 3. Radiographic tumor response to 1 cycle dovitinb (N = 24)				
	BCLC stage 0 <i>N = 3</i>	BCLC stage A <i>N = 10</i>	BCLC stage B <i>N = 9</i>	BCLC stage C† <i>N = 2</i>
RECIST 1.1.				
Complete response	-	-	-	-
Partial response	1 (33%)	-	1 (11%)	-
Stable disease	2 (67%)	10 (100%)	8 (89%)	2 (100%)
Progressive disease	-	-	-	-
mRECIST				
Complete response	2 (67%)	-	1 (11%)	-
Partial response	-	7 (70%)	1 (11%)	-
Stable disease	1 (33%)	2 (20%)	7 (78%)	2 (100%)
Progressive disease	-	-	-	-
Not evaluable	-	1 (10%)	-	-

Abbreviations: BCLC: Barcelona Clinic Liver Cancer. HCC: hepatocellular carcinoma. (m)RECIST: (modified) Response Evaluation Criteria in Solid Tumors.

† Following study enrollment and dovitinib treatment, 2 patients in retrospect already had BCLC stage C at inclusion: one patient had extensive mesentery metastases at laparoscopy following tumor rupture prior to inclusion and one patient had aspecific 1-3 mm lung nodules, one of which later turned out to be a lung metastasis. This however does not preclude tumor response assessment according to RECIST 1.1 and mRECIST since all patients were systemic treatment-naive.

Supplemental Table 4. Treatment-emergent adverse events with frequencies $\geq 10\%$				
Adverse events	Any grade N (%)	Grade 1-2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Hypertension	19 (79)	6 (25)	13 (54)	0 (0)
Fatigue	18 (75)	12 (50)	6 (25)	0 (0)
Diarrhea	15 (63)	13 (54)	2 (8)	0 (0)
Nausea	11 (46)	10 (42)	1 (4)	0 (0)
Abdominal pain	10 (42)	9 (38)	1 (4)	0 (0)
Headache	10 (42)	9 (38)	1 (4)	0 (0)
Dysphonia	7 (29)	7 (29)	0 (0)	0 (0)
Myalgia	6 (25)	6 (25)	0 (0)	0 (0)
Dizziness	5 (21)	5 (21)	0 (0)	0 (0)
Dyspnea	5 (21)	5 (21)	0 (0)	0 (0)
Fever	5 (21)	5 (21)	0 (0)	0 (0)
Rash	5 (21)	5 (21)	0 (0)	0 (0)
Vomiting	5 (21)	5 (21)	0 (0)	0 (0)
Weight loss	5 (21)	5 (21)	0 (0)	0 (0)
Cough	4 (17)	4 (17)	0 (0)	0 (0)
Dry mouth	4 (17)	4 (17)	0 (0)	0 (0)
Palmar-plantar erythrodysesthesia	4 (17)	4 (17)	0 (0)	0 (0)
Confusion	3 (13)	1 (4)	1 (4)	1 (4)
Oral mucositis	3 (13)	2 (8)	1 (4)	0 (0)
Anorexia (decreased appetite)	3 (13)	3 (13)	0 (0)	0 (0)
Constipation	3 (13)	3 (13)	0 (0)	0 (0)
Pruritus	3 (13)	3 (13)	0 (0)	0 (0)
Laboratory abnormalities				
Thrombocytopenia	13 (54)	8 (33)	5 (21)	0 (0)
Elevated alanine transferase	13 (54)	12 (50)	1 (4)	0 (0)
Elevated aspartate transferase	12 (50)	9 (38)	3 (13)	0 (0)
Elevated total bilirubin	8 (33)	6 (25)	2 (8)	0 (0)
Hypertriglyceridemia	7 (29)	6 (25)	1 (4)	0 (0)
Leukopenia	3 (13)	2 (8)	1 (4)	0 (0)
Lymphopenia	3 (13)	2 (8)	1 (4)	0 (0)