

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378-90.

SUPPLEMENTARY APPENDIX A: DEFINITIONS AND DESCRIPTIONS OF INSTRUMENTS

Table A1. Definitions of ECOG Performance Status¹⁵ Reproduced with permission from Lippincott Williams and Wilkins, on behalf of Wolters Kluwer Healthcare and the American Journal of Clinical Oncology

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair for more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Table A2. Child–Pugh Classification.^{16,17} Copyright 1973, copyright British Journal of

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Measure	Score*		
	1 point	2 points	3 points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time, sec (seconds prolonged)	<4	4–6	>6
Encephalopathy grade [†]	None	1–2	3–4

* Child–Pugh A: 5 or 6 points; Child–Pugh B: 7–9 points; Child–Pugh C: >9 points

[†] Encephalopathy grades were defined as follows; grade 0: normal consciousness,

personality, neurological examination, electroencephalogram; grade 1: restless, sleep disturbed,

irritable/agitated, tremor, impaired handwriting, 5 cps (cycles per second) waves; grade 2:

lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves; grade 3:

somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves; grade 4:

unrousable coma, no personality/behavior, decerebrate, slow 2–3 cps (cycles per second) delta activity

Table A3. Definitions of Best Response According to RECIST.¹⁸ Copyright 2007, reproduced with permission from Oxford University Press and the Journal of the National Cancer Institute

Best response	Change in sum of longest diameter
Complete response	Disappearance; confirmed at 4 weeks
Partial response	30% decrease; confirmed at 4 weeks
Stable disease	Neither partial response nor progressive disease criteria met
Progressive disease	20% increase; no complete response, partial response or stable disease documented before increased disease

Table A4. FACT Hepatobiliary Symptom Index (FHSI-8).¹⁹ Copyright 2007, reproduced

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Below is a list of statements that other people with your illness have said are important. By circling one number per line, please indicate how true each statement has been for you during the past 7 days

		Not at all	A little bit	Somewhat	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
CNS7	I have pain in my back	0	1	2	3	4
HI7	I am fatigued	0	1	2	3	4
Hep2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep8	I have discomfort or pain in my stomach	0	1	2	3	4

* Note that higher scores represent deterioration

Table A5. BCLC Staging System.⁴ Copyright 2007, reproduced with permission from

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BCLC stage					
	Very early stage (0)	Early stage (A)	Intermediate stage (B)	Advanced stage (C)	Terminal stage (D)
Child-Pugh	A	A-B	A-B	A-B	C
classification					
Performance status	0	0	0	1-2	>2
Hepatocellular carcinoma (HCC)	1 HCC <2cm Carcinoma in situ	1 HCC or 3 nodules <3cm	Multinodular	Portal invasion, N1, M1	Terminal stage

APPENDIX B: DOSE REDUCTION GUIDELINES

Doses will be delayed or reduced for clinically significant hematologic and other toxicities that are related to protocol therapy. If a patient experiences several toxicities and there are conflicting recommendations, the recommended dose adjustment that reduces the dose to the lowest level will be used. All dose modifications will follow predefined dose levels:

Dose level 1: 400 mg (2x200 mg) administered orally (po) twice daily (bid)

Dose level 2: 400 mg (2x200 mg) po every day

Dose level 3: 400 mg (2x200 mg) po every two days

If further dose reduction is required, the patient should be discontinued from the study. Also, at the discretion of the investigator, the dose may be re-escalated to 400 mg po bid after the resolution of the adverse event.

Table B1. Sorafenib dose delay and modification guidelines for non-dermatological toxicities		
Grade	Dose delay	Dose modification
<i>Hematologic toxicities</i>		
Grade 0-2	Treat on time	No change
Grade 3	Treat on time	Decrease one dose level
Grade 4	Delay [†] until ≤grade 2	Decrease one dose level
<i>Non-hematologic toxicities (except skin toxicity)[†]</i>		
Grade 0-2	Treat on time	No change
Grade 3	Delay [†] until ≤grade 2	Decrease one dose level [‡]
Grade 4	Off protocol therapy	Off protocol therapy

* If no recovery after 30-day delay, treatment will be discontinued unless patient is deriving clinical benefit

[†] Also excludes nausea/vomiting that has not been premedicated, and diarrhea

[‡] If more than two dose reductions are required, treatment will be discontinued

Table B2. Sorafenib dose delay and modification guidelines for dermatological toxicities[*]			
Grade		During a course of therapy	Dose for next cycle
Grade 1		Maintain dose level	Maintain dose level
Grade 2	1st appearance	Interrupt until resolved to grade 0–1	Maintain dose level
	2nd appearance	Interrupt until resolved to grade 0–1	400 mg every day

	3rd appearance	Interrupt until resolved to grade 0–1	400 mg every 2 days
	4th appearance	Discontinue treatment permanently	
Grade 3	1st appearance	Interrupt until resolved to grade 0–1	400 mg every day [†]
	2nd appearance	Interrupt until resolved to grade 0–1	400 mg every two days
	3rd appearance	Discontinue treatment permanently	

* Patients experiencing hand–foot skin reaction should have their signs and symptoms graded

according to the following system: grade 1: numbness, dysesthesia/paresthesia, tingling, painless

swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal

activities; grade 2: painful erythema and swelling of the hands and/or feet and/or discomfort affecting

the patient’s activities; grade 3: moist desquamation, ulceration, blistering or severe pain of the hands

and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities

of daily living. Other skin toxicities will be graded according to CTCAE v3.0 Common Terminology

Criteria for Adverse Events version 3.0.

[†] For patients who require a dose reduction for grade 3 rash or hand–foot skin reaction, the dose of study drug may be increased to the starting dose after one full cycle of therapy has been administered at the reduced dose without the appearance of rash or hand–foot skin reaction grade ≥ 1 .

APPENDIX C: DESCRIPTION OF TREATMENT-EMERGENT ADVERSE EVENTS

Table C1. Incidence of Treatment-emergent Adverse Events.

Adverse event*	Sorafenib (N = 297)			Placebo (N = 302)			P-value for between-	
	Incidence (%) at grade						group comparison	
	Any	3	4	Any	3	4	Any	3–4
Overall incidence	98	39	6	96	24	8	0.47	0.04
Constitutional symptoms								
Fatigue	46	9	1	45	12	2	1.00	0.11
Fever	10	<1	0	10	0	0	1.00	0.50
Weight loss	30	2	0	10	1	0	<0.001	0.54
Dermatology/skin								
Alopecia	14	0	0	2	0	0	<0.001	–
Dry skin	10	0	0	6	0	0	0.05	–
Hand–foot skin reaction	21	8	0	3	1	0	<0.001	<0.001
Pruritus	14	<1	0	11	<1	0	0.46	1.00
Rash/desquamation	19	1	0	14	0	0	0.15	0.06
Gastrointestinal								
Anorexia	29	3	0	18	3	<1	0.001	1.00
Ascites	22	6	<1	24	10	1	0.56	0.10
Constipation	14	0	0	10	0	0	0.17	–
Diarrhea	55	10	<1	25	2	0	<0.001	<0.001
Nausea	24	1	0	20	3	0	0.24	0.26
Vomiting	15	2	0	11	2	0	0.18	0.57
Hepatobiliary								
Liver dysfunction	11	2	1	8	2	1	0.13	0.82
Lymphatics								
Edema, limb	16	3	0	18	0	0	0.51	0.004

Pain								
Pain, abdomen NOS	31	9	0	26	5	1	0.15	0.21
Pain, back	13	2	0	13	3	<1	1.00	0.45

*National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 adverse events reported for at least 10% of patients in either treatment arm. NOS = not otherwise specified.

Table C2. Incidence of Serious Treatment-emergent Adverse Events

Serious adverse event *	Incidence (%)	
	Sorafenib (N = 297)	Placebo (N = 302)
Overall incidence	52	54
Blood/bone marrow		
Hemoglobin	3	2
Cardiac general		
Cardiac ischemia/infarction	3	1
Death		
Death not associated with CTCAE term, disease progression NOS	19	20
Constitutional symptoms		
Fatigue	2	3
Constitutional symptoms – other	1	2
Gastrointestinal		
Ascites	5	4
Diarrhea	5	2
Dehydration	3	<1
Hemorrhage/bleeding		
Gastrointestinal hemorrhage, esophageal varices	2	4
Gastrointestinal hemorrhage, peritoneal cavity	0	2
Upper gastrointestinal hemorrhage NOS	1	2
Hepatobiliary		
Liver dysfunction	7	5
Hepatobiliary – other	4	5
Metabolic/laboratory		
Bilirubin (hyperbilirubinemia)	2	1
Pain		
Pain, abdomen NOS	2	3
Renal/genitourinary		

Renal failure

<1

3

*Adverse events that resulted in death, were life threatening, required hospitalization or prolongation of existing hospitalization, resulted in a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, required medical or surgical intervention to prevent any of these outcomes, or were determined by the investigator to be medically important event, reported for at least 2% of patients in either treatment arm. CTCAE = Common Terminology Criteria for Adverse Events; NOS = not otherwise specified.