Supplementary Online Content

Abou-Alfa GK, Shi Q, Knox JJ, Kaubisch A, Niedzwiecki D, Posey J, Tan Jr BR, Kavan P, Goel R, Lammers PE, Bekaii-Saab TS, Tam VC, Rajdev L, Kelley RK, El Dika I, Zemla T, Potaracke RI, Balletti J, El-Khoueiry AB, Harding JH, Suga JM, Schwartz LH, Goldberg RM, Bertagnolli MM, Meyerhardt J, O'Reilly EM, Venook AP. Assessment of treatment with sorafenib plus doxorubicin vs sorafenib alone in patients with advanced hepatocellular carcinoma: phase 3 CALGB 80802 randomized clinical trial. Published online September 5, 2019. *JAMA Oncol*. doi:10.1001/jamaoncol.2019.2792

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

eTable 1 Sorafenib Dose Modifications for Hypertension

Blood Pressure	Sorafenib Dose Modification
Controlled with medication (to <140/90 mmHg	Continue sorafenib
>140/90 and ≤160/100 mmHg	Continue sorafenib. Consider adding or adjusting anti-hypertensive medications (e.g., calcium channel blockers)
Persistent (>160/100 mmHg) or symptomatic hypertension	Interrupt sorafenib. Resume when blood pressure improves to <160/100. If sorafenib is interrupted for ≥3 weeks, discontinue sorafenib
Grade 4	Discontinue all protocol therapy

eTable 2 Sorafenib Dose Modifications for Hand-Foot Skin Reaction HFSR, palmar-plantar erythrodysesthesia

Grade	Apperance	Dose Modification
Grade 2	1st appearance	Interrupt sorafenib until skin toxicity improves to ≤ grade 1, then resume sorafenib at the previous dose level
Grade 2	2nd or 3rd appearance	Interrupt sorafenib until skin toxicity improves to ≤ grade 1, then resume sorafenib at one reduced dose level
Grade 2	4th appearance	Discontinue all protocol therapy
Grade 3	1st or 2nd appearance	Interrupt sorafenib until skin toxicity improves to ≤ grade 1, then resume sorafenib at one reduced dose level
Grade 3	3rd appearance	Discontinue all protocol therapy

Following a full cycle of reduced dose sorafenib with no rash (maculo-papular) or HFSR (palmar-plantar erythrodysesthesia) of ≥ grade 1 severity, the dose of sorafenib may be re-escalated to the previous dose level. (Note: Re-escalation is only allowed in the case of skin toxicity.)

eTable 3 Dose Modifications for Hepatic Toxicity

Patients on full starting doxorubicin dose (60 mg/m^2) and sorafenib 400 mg po twice daily	
Bilirubin 1.3-3.0 mg/dL	Decrease by one dose level all drugs for all subsequent cycles
Bilirubin > 3.0 mg/dL	Discontinue all protocol therapy
Patients on reduced starting doxorubicin dose (30 mg/m^2) and sorafenib 400 mg po daily	
Bilirubin 1.3-3.0 mg/dL	Continue on same starting dose all drugs for all subsequent cycles
Bilirubin > 3.0 mg/dL	Discontinue all protocol therapy

eTable 4 Observed Adverse Events Regardless of Attribution by Grade and Treatment Arm

Adverse Event and Grade	Doxorubicin + Sorafenib (N=167)	Sorafenib (N=171)	p value[1]
General			
Fatigue			0.0084
1	48 (28.7%)	66 (39.1%)	
2	61 (36.5%)	35 (20.5%)	
3	20 (12.0%)	17 (10.1%)	
4	1 (0.6%)	0 (0.0%)	
Cardiology			
Left Ventricular Systolic Dysfunction			0.1187
1	3 (1.8%)	1 (0.6%)	
2	1 (0.6%)	0 (0.0%)	
3	4 (2.4%)	0 (0.0%)	
4	1 (0.6%)	0 (0.0%)	
Ejection Fraction Decreased			0.0021
1	3 (1.8%)	0 (0.0%)	
2	5 (3.0%)	1 (0.6%)	
3	8 (4.8%)	0 (0.0%)	
Hypertension			0.0351
1	17 (10.2%)	16 (9.5%)	
2	30 (18.0%)	34 (20.1%)	
3	8 (4.8%)	23 (13.6%)	
Dermatology			
Palmar-Plantar Erythro-Dysesthesia			0.7096
1	15 (9.0%)	21 (12.4%)	
2	23 (13.9%)	25 (14.8%)	
3	22 (13.3%)	24 (14.2%)	
Skin Ulceration			0.1202
1	7 (4.2%)	2 (1.2%)	
2	2 (1.2%)	6 (3.6%)	
3	1 (0.6%)	0 (0.0%)	
Endocrinology			
Hypothyroidism			0.9996
1	2 (1.2%)	2 (1.2%)	
2	3 (1.8%)	3 (1.8%)	
Gastrointestinal			

Adverse Event and Grade	**Doxorubicin + Sorafenib (N=167)**	**Sorafenib (N=171)**	**p value**[1]
Nausea			0.1069
1	43 (25.9%)	49 (29.0%)	
2	30 (18.1%)	15 (8.9%)	
3	11 (6.6%)	12 (7.1%)	
Oral Mucositis			0.0004[1]
1	36 (21.7%)	19 (11.2%)	
2	14 (8.4%)	9 (5.3%)	
3	15 (9.0%)	4 (2.4%)	
Abdominal Pain			0.4276[1]
1	34 (20.5%)	38 (22.5%)	
2	25 (15.1%)	29 (17.2%)	
3	8 (4.8%)	14 (8.3%)	
Diarrhea			0.4185[1]
1	46 (27.7%)	49 (29.0%)	
2	28 (16.9%)	18 (10.7%)	
3	12 (7.2%)	12 (7.1%)	
Hematology			
Neutropenia			<0.0001[1]
1	5 (3.0%)	5 (3.0%)	
2	15 (9.0%)	5 (3.0%)	
3	21 (12.7%)	1 (0.6%)	
4	40 (24.1%)	0 (0.0%)	
Decreased Platelets Count			<0.0001[1]
1	39 (23.5%)	51 (30.2%)	
2	19 (11.4%)	13 (7.7%)	
3	21 (12.7%)	2 (1.2%)	
4	8 (4.8%)	2 (1.2%)	
Hematuria			0.7983[1]
1	6 (3.6%)	4 (2.4%)	
2	1 (0.6%)	1 (0.6%)	
Epistaxis			0.1966[1]
1	6 (3.6%)	14 (8.2%)	
2	1 (0.6%)	1 (0.6%)	

[1]Chi-Square