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Supplemental Tables for:
Optimal Avapritinib Treatment Strategies for Patients with Metastatic or Unresectable Gastrointestinal Stromal Tumors
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Table S1. Protocol-specified dose-modification guidelines

Toxicity	Modification
General	
Grade 1 or 2	No dose modification required
Grade 3 or 4 of any duration	Hold until event is grade ≤2 or has returned to baseline, then resume by reducing the dose by 100 mg less than the current dose If the patient is already receiving a dose of 100 mg, and continued treatment is considered in the best medical interest of the patient due to the underlying GIST, treatment may be resumed at 100 mg, after the adverse event has improved to grade ≤2
Cognitive effects	
Grade 1 with only mild impairment	No dose modification required if the investigator considers it in the best medical interest of the patient to continue treatment. Written documentation that continuation of treatment is in the best medical interest of the patient must be provided to the sponsor
Grade 1, other than mild impairment	Interrupt dosing for 7 days, and resume dosing without dose reduction The dosing interruption may be repeated if the impairment continues to worsen after resuming dosing; however, repeated dosing interruption is not required, and should be balanced with the need to treat the underlying GIST If dosing will be resumed after interruption or continued without interruption, written documentation that resumption or continuation of treatment is in the best medical interest of the patient must be provided to the sponsor
Grade 2	Interrupt dosing for a minimum of 7 days Resume dosing with a dose reduction of 100 mg when the cognitive effect has improved to grade ≤1, or while still at grade 2, if continued treatment is considered in the best medical interest of the patient due to the underlying GIST If the patient is already receiving a dose of 100 mg, and continued treatment is considered in the best medical interest of the patient due to the underlying GIST, treatment may be resumed at 100 mg If dosing will be resumed after interruption, written documentation that resumption of treatment is in the best medical interest of the patient must be provided to the sponsor
Grade 3 or 4	Interrupt dosing for a minimum of 14 days Resume dosing with a dose reduction of 100 mg when the cognitive effect has improved to grade ≤1, or when it has improved to grade 2, if continued treatment is considered in the best medical interest of the patient due to the underlying GIST If the patient is already receiving a dose of 100 mg, and continued treatment is considered in the best medical interest of the patient due to

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	the underlying GIST, treatment may be resumed at 100 mg, after the cognitive effect has improved to grade ≤2 or lower If dosing will be resumed after interruption, written documentation that resumption of treatment is in the best medical interest of the patient must be provided to the sponsor
Intracranial bleeding	
Grade 1	Interrupt dosing for a minimum of 7 days, and re-image brain Resume dosing without dose reduction if the bleed is stable or improving and continued treatment is considered in the best medical interest of the patient due to the underlying GIST If dosing will be resumed after interruption, written documentation that resumption of treatment is in the best medical interest of the patient must be provided to the sponsor
Grade 2	Interrupt dosing for a minimum of 14 days and re-image brain Resume dosing with a dose reduction of 100 mg when the intracranial bleeding has improved to grade ≤1, or while still at grade 2, if continued treatment is considered in the best medical interest of the patient due to the underlying GIST If the patient is already receiving a dose of 100 mg and continued treatment is considered in the best medical interest of the patient due to the underlying GIST, treatment may be resumed at 100 mg If dosing will be resumed after interruption, written documentation that resumption of treatment is in the best medical interest of the patient must be provided to the sponsor
Grade 3 or 4	Permanently discontinue avapritinib treatment

Abbreviation: GIST, gastrointestinal stromal tumor.

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Table S2. Presentation of *Common Terminology Criteria for Adverse Events* (CTCAE) [1] cognitive effects adverse events

Cognitive effect	Presentation
Memory impairment	
Grade 1	Mild memory impairment that does not interfere with daily performance
Grade 2	Moderate memory impairment that limits daily activities
Grade 3	Severe memory impairment that limits both daily activities and self-care
Cognitive disorder	
Grade 1	Mild cognitive disability that does not interfere with daily performance
Grade 2	Moderate cognitive disability that interferes with daily performance, but the patient remains capable of independent living
Grade 3	Severe cognitive disability resulting in a significant impairment of daily performance
Confusional state	
Grade 1	Mild disorientation
Grade 2	Moderate disorientation that limits daily performance
Grade 3	Severe disorientation that limits both daily activities and self-care
Grade 4	Life-threatening consequences requiring urgent intervention
Grade 5	Death
Encephalopathy	
Grade 1	Mild symptoms
Grade 2	Moderate symptoms that limit daily activities
Grade 3	Severe symptoms that limit both daily activities and self-care
Grade 4	Life-threatening consequences requiring urgent intervention
Grade 5	Death

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Table S3. All-cause AEs by age among patients starting with avapritinib 300 mg

	<65 years (*n* = 102)		≥65 years (*n* = 65)	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
AE[a], n (%)	101 (99.0)	66 (64.7)	65 (100)	55 (84.6)
Nausea	65 (63.7)	1 (<1.0)	38 (58.5)	1 (1.5)
Fatigue	48 (47.1)	1 (<1.0)	40 (61.5)	9 (13.8)
Anemia	46 (45.1)	24 (23.5)	41 (63.1)	27 (41.5)
Diarrhea	38 (37.3)	2 (2.0)	32 (49.2)	6 (9.2)
Decreased appetite	34 (33.3)	3 (2.9)	27 (41.5)	1 (1.5)
Periorbital edema	33 (32.4)	1 (<1.0)	31 (47.7)	1 (1.5)
Vomiting	33 (32.4)	2 (2.0)	25 (38.5)	2 (3.1)
Face edema	30 (29.4)	0 (0)	8 (12.3)	0 (0)
Increased lacrimation	26 (25.5)	0 (0)	25 (38.5)	0 (0)
Hair color changes	24 (23.5)	0 (0)	9 (13.8)	0 (0)
Blood bilirubin increased	23 (22.5)	5 (4.9)	14 (21.5)	3 (4.6)
Abdominal pain	22 (21.6)	7 (6.9)	19 (29.2)	4 (6.2)
Constipation	19 (18.6)	1 (<1.0)	19 (29.2)	2 (3.1)
Headache	19 (18.6)	0 (0)	8 (12.3)	1 (1.5)
Hypokalemia	18 (17.6)	3 (2.9)	12 (18.5)	4 (6.2)
Edema peripheral	17 (16.7)	1 (<1.0)	28 (43.1)	0 (0)
Dysgeusia	16 (15.7)	0 (0)	14 (21.5)	0 (0)
Dizziness	14 (13.7)	1 (<1.0)	13 (20.0)	0 (0)
Weight decreased	13 (12.7)	1 (<1.0)	14 (21.5)	1 (1.5)
Hypophosphatemia	13 (12.7)	2 (2.0)	11 (16.9)	6 (9.2)
Dyspepsia	12 (11.8)	0 (0)	15 (23.1)	0 (0)
Pyrexia	12 (11.8)	0 (0)	10 (15.4)	0 (0)
Dyspnea	11 (10.8)	1 (<1.0)	16 (24.6)	3 (4.6)
Pleural effusion	10 (9.8)	1 (<1.0)	11 (16.9)	1 (1.5)
Hypomagnesemia	5 (4.9)	0 (0)	15 (23.1)	1 (1.5)
Cough	4 (3.9)	0 (0)	10 (15.4)	0 (0)
Cognitive effects	40 (39.2)	1 (<1.0)	38 (58.5)	4 (6.2)
Memory impairment	25 (24.5)	0 (0)	20 (30.8)	1 (1.5)
Cognitive disorder	11 (10.8)	1 (<1.0)	10 (15.4)	0 (0)
Confusional state	4 (3.9)	0 (0)	7 (10.8)	2 (3.1)
Encephalopathy	0 (0)	0 (0)	1 (1.5)	1 (1.5)
Intracranial bleeding	3 (2.9)	1 (<1.0)	1 (1.5)	1 (1.5)
Intracranial hemorrhage	2 (2.0)	1 (<1.0)	1 (1.5)	1 (1.5)
Subdural hematoma	1 (<1.0)	0 (0)	0 (0)	0 (0)
Cerebral hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)

The cutoff date for these analyses was April 2, 2019.
[a]Preferred Terms for any-grade AEs reported in ≥15% of patients in either dose group.
Abbreviation: AE, adverse event.

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Table S4. Correlation between patient characteristics and cognitive effects. Univariable logistic regression of cognitive events in patients who started on avapritinib 300 mg

Patient characteristics	Description	Odds ratio (95% CI)	*p* value
Race	White (*n* = 114)	Reference	
	Nonwhite (*n* = 38)	1.288 (0.613–2.706)	.603
	Unknown (*n* = 15)	1.061 (0.353–3.185)	.904
Gender	Male (*n* = 103)	Reference	
	Female (*n* = 64)	1.035 (0.548–1.954)	.916
Baseline ECOG performance status	0 (*n* = 66)	Reference	
	1 (*n* = 96)	0.583 (0.308–1.104)	.841
	2 (*n* = 5)	0.266 (0.028–2.505)	.350
Number of prior TKIs	<4	Reference	
	≥4	1.016 (0.521–1.982)	.963
Total duration of prior TKI use, years	167	0.987 (0.913–1.067)	.747

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.

Table S5. Summary of cognitive effects in patients starting with avapritinib 300 mg

	Patients (*n* = 167)				
	AE incidence				AEs leading to permanent treatment discontinuation
	Grade 1	Grade 2	Grade 3	Total[a]	
Cognitive effects, *n* (%)	47 (28.1)	15 (9.0)	5 (3.0)	67 (40.1)	10 (6.0)
Memory impairment	36 (21.6)	8 (4.8)	1 (<1.0)	45 (26.9)	1 (<1.0)
Cognitive disorder[b]	12 (7.2)	8 (4.8)	1 (<1.0)	21 (12.6)	5 (3.0)
Confusional state	7 (4.2)	2 (1.2)	2 (1.2)	11 (6.6)	2 (1.2)
Encephalopathy	0	0	1 (<1.0)	1 (<1.0)	2 (1.2)

[a]No patient experienced grade 4 or 5 cognitive effects.
[b]Cognitive disorders leading to permanent treatment discontinuation included acute psychotic episode, worsening cognitive disturbances, mental status change, and delirium.
Abbreviation: AE, adverse event.

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References

1. National Institutes of Health and National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. 2009. Available at https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf. Accessed March 4, 2020.