

Appendix

Supplemental Table 1

All grade 1 and 2 attributable toxicities seen on both strata 1 (A) and 3 (B).

A. Stratum 1

PBTC-29B Stratum 1	Grade			
	1		2	
	N	%	N	%
Toxicity				
Abdominal pain	4	16	.	.
Alanine aminotransferase increased	11	44	.	.
Alkaline phosphatase increased	7	28	.	.
Alopecia	3	12	.	.
Anemia	17	68	.	.
Aspartate aminotransferase increased	11	44	2	8
CPK increased	9	36	7	28
Cheilitis	2	8	.	.
Chills	2	8	.	.
Constipation	4	16	.	.
Cough	3	12	.	.
Creatinine increased	.	.	2	8
Diarrhea	11	44	.	.
Dizziness	3	12	.	.
Dry skin	9	36	4	16
Edema limbs	4	16	2	8
Ejection fraction decreased	.	.	2	8
Fatigue	10	40	2	8
Fever	2	8	.	.
Headache	5	20	.	.
Hyperglycemia	5	20	.	.
Hyperkalemia	2	8	.	.
Hypernatremia	2	8	.	.
Hypoalbuminemia	12	48	2	8
Hypocalcemia	5	20	.	.
Hypokalemia	8	32	.	.
Hypomagnesemia	10	40	.	.
Hyponatremia	3	12	.	.
Hypophosphatemia	4	16	.	.
Lymphocyte count decreased	6	24	.	.

PBTC-29B Stratum 1	Grade			
	1		2	
	N	%	N	%
Lymphocyte count increased	.	.	2	8
Metabolism and nutrition disorders - Other	2	8	.	.
Nausea	6	24	.	.
Neutrophil count decreased	2	8	4	16
Paronychia	2	8	4	16
Platelet count decreased	3	12	.	.
Pruritus	3	12	.	.
Rash acneiform	10	40	3	12
Rash maculo-papular	8	32	3	12
Skin and subcutaneous tissue disorders - Other	5	20	3	12
Skin infection	.	.	4	16
Vomiting	8	32	.	.
White blood cell decreased	7	28	.	.

B. Stratum 3

PBTC-29B Stratum 3	Grade			
	1		2	
	N	%	N	%
Toxicity				
Abdominal pain	8	32	.	.
Alanine aminotransferase increased	7	28	.	.
Alkaline phosphatase increased	3	12	.	.
Alopecia	3	12	.	.
Anemia	8	32	2	8
Anorexia	3	12	.	.
Aspartate aminotransferase increased	12	48	.	.
CPK increased	12	48	6	24
Constipation	5	20	.	.
Cough	4	16	.	.
Creatinine increased	2		2	8
Diarrhea	12	48	4	16
Dizziness	2	8	.	.
Dry eye	2	8	.	.
Dry skin	11	4	4	16
Edema limbs	6	24	.	.
Ejection fraction decreased	.	.	4	16
Epistaxis	4	16	.	.
Eye disorders - Other	2	8	.	.
Fatigue	14	56	2	8
Gastrointestinal disorders - Other	3	12	.	.
Headache	7	28	.	.
Hyperglycemia	5	20	.	.
Hyperkalemia	2	8	.	.
Hypernatremia	2	8	.	.
Hypertension	8	32	2	8
Hypoalbuminemia	14	56	3	12
Hypocalcemia	4	16	.	.
Hypokalemia	4	16	.	.
Hypomagnesemia	8	32	.	.
Hyponatremia	2	8	.	.
Hypophosphatemia	3	12	.	.
Investigations - Other	2	8	.	.
Lymphocyte count decreased	10	40	2	8

PBTC-29B Stratum 3	Grade			
	1		2	
	N	%	N	%
Metabolism and nutrition disorders - Other	3	12	.	.
Mucositis oral	4	16	.	.
Nail infection	2	8	.	.
Nausea	14	56	.	.
Neutrophil count decreased	4	16	4	16
Pain	2	8	.	.
Paronychia	2	8	11	44
Platelet count decreased	5	20	.	.
Pruritus	5	20	.	.
Rash acneiform	10	40	6	24
Rash maculo-papular	9	36	6	24
Rectal hemorrhage	2	8	.	.
Skin and subcutaneous tissue disorders - Other	13	52	4	16
Skin infection	.	.	2	8
Stomach pain	3	12	.	.
Vomiting	13	52	.	.
Weight gain	.	.	3	12
White blood cell decreased	11	44	.	.

Supplemental Table 2

Grade 3 and 4 toxicities divided by stratum 1 (A) and stratum 3 (B).

A: Stratum 1

PBTC-29B Stratum 1	Grade			
	3		4	
	N	%	N	%
<u>Toxicity</u>				
Alanine aminotransferase increased	1	4	.	.
CPK increased	4	16	.	.
Diarrhea	1	4	.	.
Headache	1	4	.	.
Lymphocyte count decreased	.	.	1	4
Neutrophil count decreased	3	12	.	.
Paronychia	1	4	.	.
Rash acneiform	2	8	.	.
Rash maculo-papular	2	8	.	.
Tooth infection	1	4	.	.
Weight gain	1	4	.	.

B: Stratum 3

PBTC-29B Stratum 3	Grade	
	3	
	N	%
<u>Toxicity</u>		
CPK increased	1	4
Diarrhea	1	4
Ejection fraction decreased	1	4
Gastric hemorrhage	1	4
Paronychia	2	8
Rash maculo-papular	3	12
Skin infection	1	4

Supplemental Table 3

Dose reduction on stratum 1 (A) and stratum 3 (B)

A: Stratum 1

Accession Number	Assigned Dose (selumetinib mg/m ² /dose BID)	Course when the reduction occurred	Reduced Dose (selumetinib mg/m ² /dose BID)	Toxicity
6	25	1.4	20	G3 rash
40	25	1.13	20	G3 rash
	25	1.19	15	G3 ALT increased
44	25	1.3	20	G3 CPK
49	25	1.3	20	G3 CPK
58	25	1.6	20	G2 intolerable headache
60	25	1.23	20	G3 paronychia
75	25	1.3	20	G3 rash
90	25	1.24	20	G3 tooth infection
91	25	1.12	20	G3 rash
93	25	1.2	20	G2 intolerable rash

B: Stratum 3

Accession Number	Assigned Dose (selumetinib mg/m ² /dose BID)	Course when the reduction occurred	Reduced Dose (selumetinib mg/m ² /dose BID)	Toxicity
7	25	1.7	20	G3 rash and G2 intolerable paronychia
21	25	1.1	20	G2 intolerable rash
26	25	1.21	20	G3 rash
32	25	1.9	20	G3 skin infection.
47	25	1.8	20	G3 rash
59	25	1.9	20	G3 rash
63	25	1.17	20	G3 rash
83	25	1.13	20	G2 intolerable paronychia

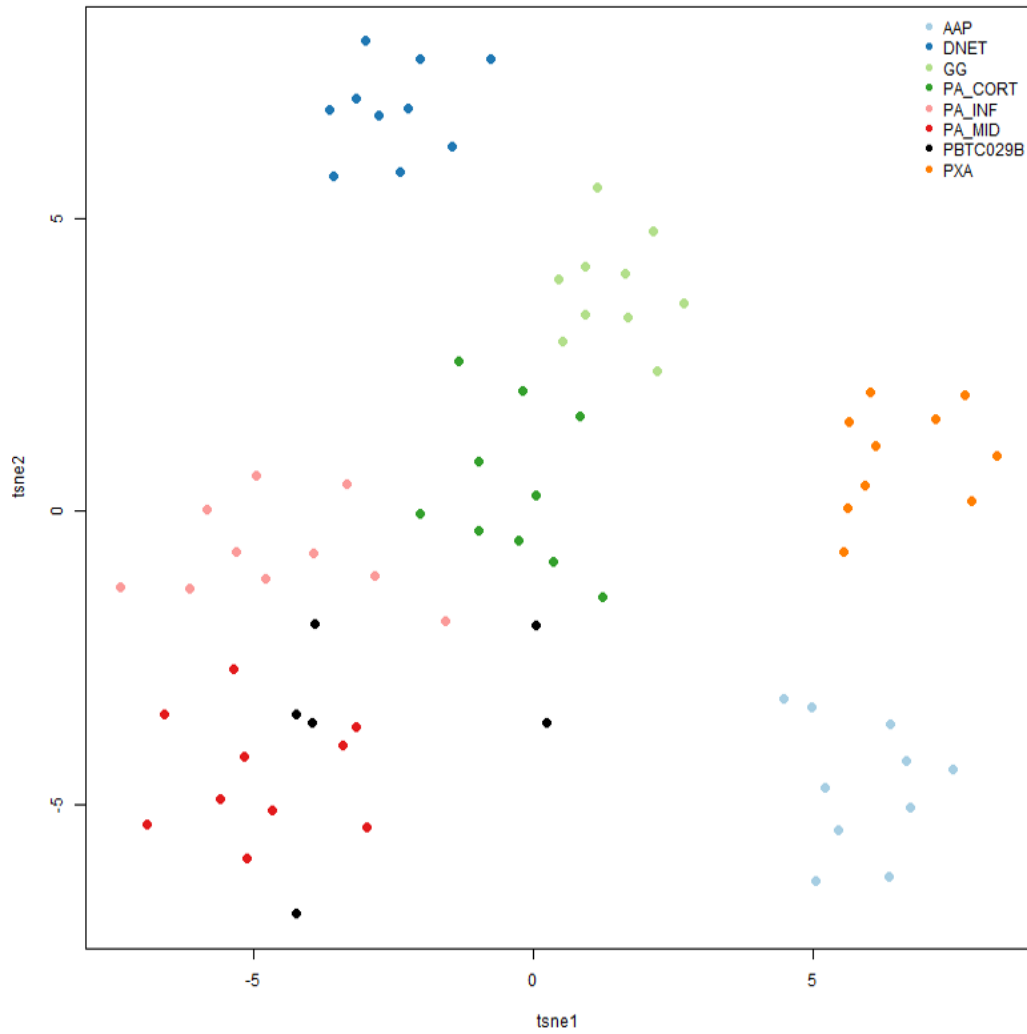
Supplemental Table 4

Recruiting sites, number of eligible and evaluable patients recruited, and name of the responsible Principle Investigator

		Stratum 1	Stratum 3	All
		N	N	N
Institution	Local Principle Investigator			
CCHMC	Fouladi, Maryam	3	4	7
CHLA	Dhall, Girish	3	.	3
Chicago	Fangusaro, Jason	6	4	10
Children's DC	Packer, Roger	2	3	5
Duke	Kreissman, Sue	2	2	4
MSKCC	Dunkel, Ira	.	3	3
Pittsburgh	Pollack, Ian	1	7	8
St. Jude	Qaddoumi, Ibrahim	4	1	5
Stanford	Fisher, Paul	3	.	3
Texas Children	Baxter, Patricia	.	1	1
UCSF	Banerjee, Anurudha	1	.	1
All		25	25	50

Supplemental Figure 1

Visualization of DNA methylation array data by t-distributed stochastic neighbor embedding. Samples from PBTC-029B strata 1 and 3 (black dots) were compared with reference profiles of molecularly defined glioma/glioneuronal tumor groups. All analyzed trial samples showed similarities with pilocytic astrocytoma.



*AAP, anaplastic astrocytoma with piloid features; DNET, dysembryoplastic neuroepithelial tumor; GG, ganglioglioma; PA_CORT, cortical pilocytic astrocytoma; PA_INF, infratentorial pilocytic astrocytoma; PA_MID, midline pilocytic astrocytoma; PXA, pleomorphic xanthoastrocytoma.