Supplementary Material

Cobimetinib in Pediatric and Young Adult Patients with Relapsed or Refractory Solid Tumors (iMATRIX-cobi): A Multicenter, Phase I/II Study

Tanya Trippett[1*] · Helen Toledano[2] · Quentin Campbell-Hewson[3] · Arnauld Verschuur[4] · Anne-Marie Langevin[5] · Isabelle Aerts[6] · Lisa Howell[7] · Soledad Gallego[8] · Claudia Rossig[9] · Amy Smith[10] · Darshak Patel[11†] · Leonardo R. Pereira[12] · Sravanthi Cheeti[13] · Luna Musib[13‡] · Katherine E. Hutchinson[14] · Clare Devlin[15] · Ronald Bernardi[16] · Birgit Geoerger[17]

[1] Memorial Sloan Kettering Cancer Center, Department of Pediatrics, New York, NY, USA
[2] Schneider Children's Medical Center, Department of Pediatric Hematology-Oncology and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[3] The Great North Children's Hospital, Department of Paediatric and Adolescent Oncology, Newcastle Upon Tyne, UK
[4] Timone Children's Hospital, Assistance Publique-Hopitaux de Marseille, Pediatric Oncology, Marseille, France
[5] UT Health San Antonio, Department of Pediatrics, San Antonio, TX, USA
[6] Institut Curie, PSL Research University, Oncology Center SIREDO, Paris, France
[7] Alder Hey Children's NHS Foundation Trust, Paediatric Oncology, Liverpool, UK
[8] Hospital Universitari Vall d'Hebron, Paediatric Oncology, Barcelona, Spain
[9] University Children's Hospital Muenster, Pediatric Hematology and Oncology, Muenster, Germany
[10] Haley Center for Children's Cancer and Blood Disorders, Orlando-Health Arnold Palmer Hospital for Children, Orlando, FL, USA
[11] F. Hoffmann-La Roche Ltd, Product Development, Biometrics, Biostatistics, Mississauga, ON, Canada
[12] Roche Products Ltd, Product Development Safety, Welwyn, UK
[13] Genentech, Inc., Clinical Pharmacology, South San Francisco, CA, USA
[14] Genentech, Inc., Oncology Biomarker Development, South San Francisco, CA, USA
[15] Roche Products Ltd, Product Development Oncology, Welwyn, UK
[16] Genentech, Inc., Product Development Oncology, South San Francisco, CA, USA

[17] Gustave Roussy Cancer Center, Department of Pediatric and Adolescent Oncology, Université Paris-Saclay, INSERM U1015, Villejuif, France
[†]Current affiliation: IQVIA, Mississauga, ON, Canada
[‡]Current affiliation: Gilead Sciences, Foster City, CA, USA

***Corresponding author:** Tanya Trippett, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY10065, USA. Phone: +1 212-639-8267; E-mail: trippet1@MSKCC.ORG

Definition of Dose-Limiting Toxicities

Dose-limiting toxicities (DLTs) were defined as any of the following events occurring during the DLT assessment window and considered by the investigator to be related or possibly related to cobimetinib:

- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] <0.5 x 10^9 cells/L) for > 7 days
- Grade ≥ 4 neutropenia with documented infection
- Febrile neutropenia (ANC < 500 cells/mm^3 with a single temperature of > 38.3 °C or a sustained temperature of ≥ 38 °C for > 1 h)
- Grade ≥ 4 (i.e., life-threatening) anemia of any duration
- Grade ≥ 4 thrombocytopenia for > 48 h or any thrombocytopenia requiring a platelet transfusion, with the following exception: patients who have undergone autologous stem cell transplant or ^{131}I-metaiodobenzylguanidine therapy, grade ≥ 4 thrombocytopenia for > 7 days or any thrombocytopenia requiring a platelet transfusion on two or more separate dates will be considered a DLT
- Grade ≥ 3 thrombocytopenia with bleeding
- Elevation of serum hepatic transaminase (alanine aminotransferase or aspartate aminotransferase) to ≥ 5 x upper limit of normal (ULN); for patients with elevated hepatic transaminase levels at baseline as a result of liver metastases, hepatic transaminase ≥ 5 × baseline and < 10 × baseline for > 3 days, or any hepatic transaminase ≥ 10 × baseline, will be considered a DLT
- Serum bilirubin elevation to ≥ 3 x ULN
- For patients reliably able to report visual symptoms: grade ≥ 2 visual disturbance that does not resolve to grade ≤ 1 within 72 h after interruption of cobimetinib
- Retinal pathology of any grade, or grade ≥ 2 uveitis or iritis
- Grade ≥ 2 hemorrhage of any type
- Intracranial hemorrhage of any grade
- Grade ≥ 4 creatine phosphokinase (CPK) elevation
- Rhabdomyolysis of any grade; rhabdomyolysis includes elevations of CPK in conjunction with either clinical features (such as muscle pain, signs of renal failure, dark red or brown urine) or with laboratory evidence of renal insufficiency (including grade ≥ 2 increased creatinine or creatinine clearance [or radioisotope glomerular filtration rate] < 70 mL/min/1.73 m^2), or investigator judgement that a clinical scenario is consistent with rhabdomyolysis
- Grade ≥ 2 ventricular dysfunction or symptomatic congestive heart failure

- Reduction in left ventricular ejection fraction below 50% (or shortening fraction below 28%) AND either symptomatic heart failure or a ≥ 10% relative reduction from baseline measurement. Note: The relative reduction must be ≥ 10% of baseline function, not an absolute decrease of ≥ 10 percentage points
- Grade ≥ 4 (i.e., life-threatening) vomiting or diarrhea of any duration
- Grade ≥ 3 non-hematologic, non-hepatic, non-ocular adverse event, with the following exceptions, which will not be considered DLTs: grade ≥ 3 diarrhea or rash that resolves to grade ≤ 2 within 7 days after interruption of cobimetinib; grade 3 fever; grade 3 mucositis or stomatitis that resolves to grade ≤ 2 within 3 days; grade ≥ 3 nausea or vomiting that responds to standard-of-care therapy within 3 days; grade 3 fatigue lasting ≤ 3 days; or grade 3 laboratory abnormalities that are asymptomatic and considered by the investigator not to be clinically significant.

Patients who missed ≥ 5 doses, or who discontinued treatment prior to completing the assessment window for reasons other than a DLT, were non-evaluable for dose-escalation and assessment of the maximum tolerated dose and were replaced.

Table S1 Dose-limiting toxicities during dose escalation

Dose and formulation	Tumor type	Adverse event	Onset	Duration	Most extreme NCI CTCAE grade	Action taken with study drug	Outcome
1.0 mg/kg tablet	LGG (chiasmatic glioma)	Headache	Day 23	12 days	3	Interrupted	Recovered/resolved
	LGG (optic pathway glioma)	Retinal detachment	Day 9	50 days	2	Withdrawn	Recovered/resolved
0.6 mg/kg suspension	LGG (pilocytic astrocytoma)	Chorioretinopathy	Day 13	50 days	1	Interrupted	Recovered/resolved
1.33 mg/kg suspension	LGG (pilomyxoid astrocytoma grade II)	Chorioretinopathy	Day 8	8 days	2	Interrupted	Recovered/resolved
			Day 22	–	4	Withdrawn	Not recovered/not resolved
	LGG (optic pathway glioma)	Serous retinal detachment	Day 6	7 days	1	Interrupted	Recovered/resolved
	Plexiform neurofibroma	Pigment epithelial detachment	Day 111	–	1	None	Recovering/resolving

LGG low-grade glioma, *NCI CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events

Table S2 Safety summary by age group and study stage

Patients with events, *n* (%)	2 – < 6 years (*n* = 10)	6 – < 12 years (*n* = 31)	12 – < 18 years (*n* = 14)	≥ 18 years (*n* = 1)	Dose escalation tablet (*n* = 18)	Dose escalation suspension (*n* = 26)	Dose expansion (*n* = 12)
AE	10 (100)	31 (100)	14 (100)	1 (100)	18 (100)	26 (100)	12 (100)
Leading to treatment withdrawal	0	2 (7)	4 (29)	0	1 (6)	4 (15)	1 (8)
Leading to dose modification/interruption	3 (30)	11 (36)	4 (29)	1 (100)	4 (22)	12 (46)	3 (25)
Treatment-related AE	9 (90)	28 (90)	12 (86)	1 (100)	16 (89)	23 (89)	11 (92)
Leading to treatment withdrawal	0	2 (7)	4 (29)	0	1 (6)	4 (15)	1 (8)
Leading to dose modification/interruption	1 (10)	6 (19)	4 (29)	1 (100)	3 (17)	8 (31)	1 (8)
SAE	4 (40)	9 (29)	4 (29)	1 (100)	6 (33)	6 (23)	6 (50)
Leading to treatment withdrawal	0	0	1 (7)	0	0	0	1 (8)
Leading to dose modification/interruption	2 (20)	4 (13)	0	1 (100)	1 (6)	3 (12)	3 (25)
Related to study treatment	0	2 (7)	1 (7)	1 (100)	1 (6)	1 (4)	2 (17)
Fatal AE	0	0	0	0	0	0	0
AE of special interest[a]	5 (50)	12 (39)	7 (50)	1 (100)	6 (33)	13 (50)	6 (50)

AE adverse event, *SAE* serious adverse event

[a]Serous retinopathy-related AEs, retinal vein occlusion AEs, rhabdomyolysis, or creatine phosphokinase elevation, rash, potential drug-induced liver injury as defined by Hy's Law, left ventricular dysfunction, any new malignancy including cutaneous squamous cell and basal cell. Multiple occurrences of the same AE in one individual are counted only once, except for the 'AE' row, in which multiple occurrences of the same AE are counted separately.

Table S3 Available molecular testing information provided by enrolling sites with best overall response per tumor type

Tumor type (*n*)	Test findings (*n*)	Best confirmed overall response, *n*				Not evaluable	Not collected
		PR	SD	PD	Non-CR/PD		
LGG (32)	*KIAA1549-BRAF* fusion or other tandem duplication of *BRAF* (15)		12	1	1	1	
	BRAF V600E mutation (1)			1			
	BRAF mutation not specified (1)			1			
	BRAF copy number amplification (1)			1			
	NF1 truncating mutation (1)	1					
	Other mutation in *RAS/RAF/MEK/ERK* pathway gene not specified (4)		2	2			
	No mutation identified in a *RAS/RAF/MEK/ERK* pathway gene (5)[a]	1	2	1			1
	Unknown / not provided (4)	1	2				1
HGG (5)	No mutation identified in a *RAS/RAF/MEK/ERK* pathway gene (1)[a]			1			
	Unknown / not provided (4)			3		1	
NF1-associated neurofibroma (12)	*NF1* mutation not specified (3)		3				
	Unknown / not provided (9)		9				
MPNST (2)	Other mutation in *RAS/RAF/MEK/ERK* pathway gene not specified (1)			1			
	No mutation identified in a *RAS/RAF/MEK/ERK* pathway gene (1)[a]		1				

ATRT (1)	Other mutation in *RAS/RAF/MEK/ERK* pathway gene not specified (1)		1	
Metastatic mediastinal yolk sac tumor (1)	*RAS* mutation (1)			1
Neuroblastoma (1)	Unknown / not provided (1)		1	
Liposarcoma (1)	Unknown / not provided (1)	1		
DNET in Noonan syndrome (1)	Unknown / not provided (1)	1		

ATRT atypical teratoid/rhabdoid tumor, *CR* complete response, *DNET* dysembryoplastic neuroepithelial tumor, *HGG* high-grade glioma, *LGG* low-grade glioma, *MPNST* malignant peripheral nerve sheath tumor, *NF1* neurofibromatosis type 1, *PCR* polymerase chain reaction, *PD* progressive disease, *PR* partial response, *SD* stable disease

[a]Lack of a noted MAPK pathway gene alteration possibly influenced by type and scope of testing performed at an enrolling site, or due to lack of reporting by site to the Sponsor, as systematic reporting was not required (see Table S4 for additional information).

Table S4 Available molecular test results and test types as provided by enrolling sites

Tumor type (n)	Test findings (*n*)	Test type (*n*)
LGG (32)	*KIAA1549-BRAF* fusion or other tandem duplication of *BRAF* (15)	PCR-based (5) FISH (4) NGS (3) Other test not specified (3)
	BRAF V600E mutation (1)	FISH (1)
	BRAF mutation not specified (1)	FISH (1)
	BRAF copy number amplification (1)	Other test not specified (1)
	NF1 truncating mutation (1)	Other test not specified (1)
	Other mutation in *RAS/RAF/MEK/ERK* pathway gene not specified (4)	FISH (1) Other test not specified (3)
	No mutation identified in a *RAS/RAF/MEK/ERK* pathway gene (5)	FISH (2) NGS (1) Other test not specified (2)
	Unknown / not provided (4)	
HGG (5)	No mutation identified in a *RAS/RAF/MEK/ERK* pathway gene (1)	Other test not specified (1)
	Unknown / not provided (4)	
NF1-associated neurofibroma (12)	*NF1* mutation not specified (3)	NGS (3)
	Unknown / not provided (9)	
MPNST (2)	Other mutation in *RAS/RAF/MEK/ERK* pathway gene not specified (1)	Other test not specified (1)
	No mutation in *RAS/RAF/MEK/ERK* pathway genes (1)	NGS (1)
ATRT (1)	Other mutation in *RAS/RAF/MEK/ERK* pathway gene not specified (1)	PCR-based (1)
Metastatic mediastinal yolk sac tumor (1)	*RAS* mutation (1)	NGS (1)
Neuroblastoma (1)	Unknown / not provided (1)	
Liposarcoma (1)	Unknown / not provided (1)	
DNET in Noonan's syndrome (1)	Unknown / not provided (1)	

ATRT atypical teratoid/rhabdoid tumor, *DNET* dysembryoplastic neuroepithelial tumor, *FISH* fluorescence in situ hybridization, *HGG* high-grade glioma, *LGG* low-grade glioma, *MPNST* malignant peripheral nerve sheath tumor, *NF1* neurofibromatosis type 1, *NGS* next-generation sequencing, *PCR* polymerase chain reaction

Fig. S1 Comparison of pharmacokinetic profiles between the dose-escalation and expansion cohorts.

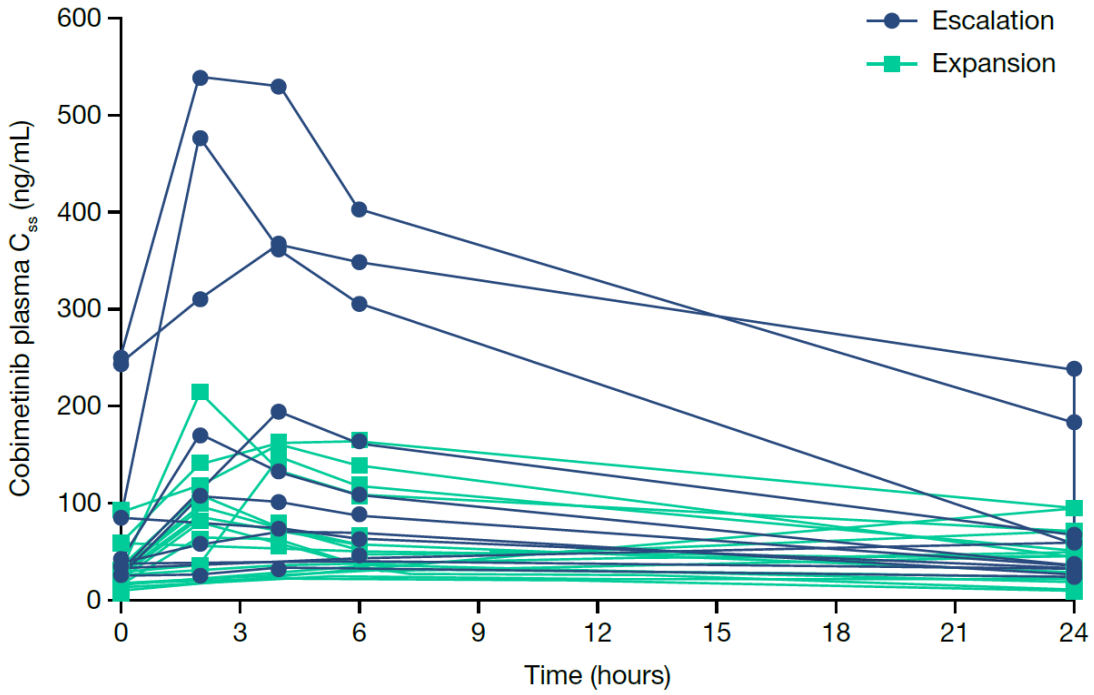
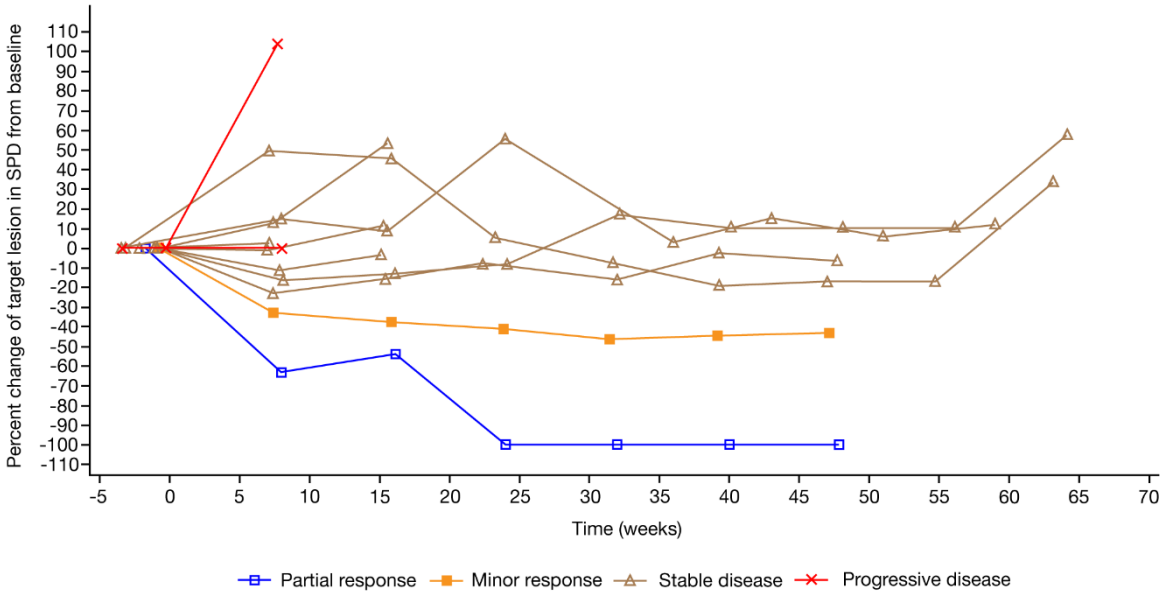
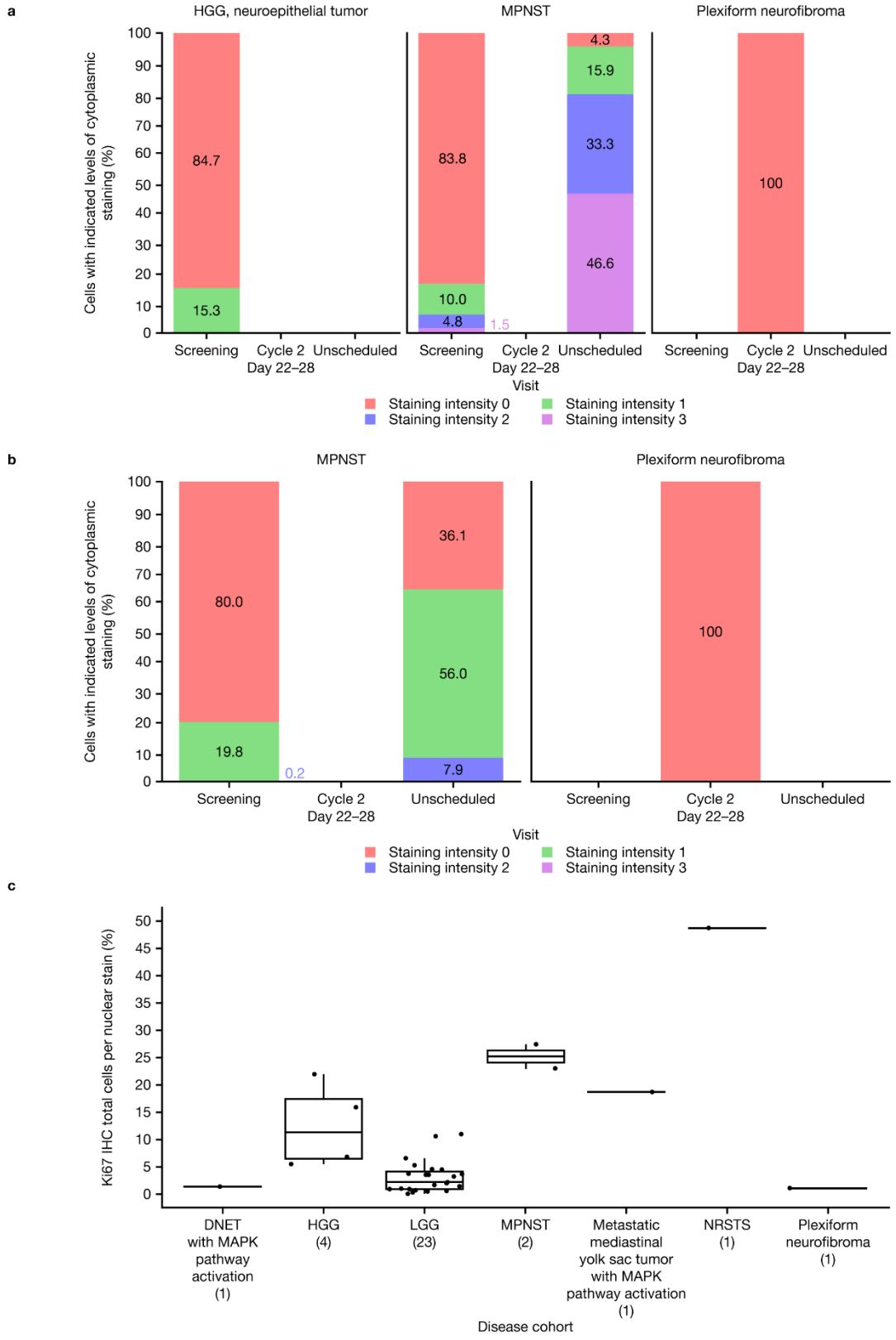


Fig. S2 Spider plot for patients with LGG in the expansion cohort by RANO.



LGG low-grade glioma, *SPD* sum of product diameters, *RANO* Response Assessment in Neuro-Oncology

Fig. S3 IHC staining for (**a**) pERK1/2 (*n* = 3), (**b**) pMEK1/2 (*n* = 2 at baseline and/or during study treatment), and (**c**) Ki67 for evaluable tumor tissue specimens (*n* = 33).



DNET dysembryoplastic neuroepithelial tumor, *HGG* high-grade glioma, *IHC* immunohistochemistry, *LGG* low-grade glioma, *MAPK* mitogen-activated protein kinase, *MPNST* malignant peripheral nerve sheath tumor, *NRSTS* non-rhabdomyosarcoma soft tissue sarcoma

With the exception of three specimens (one HGG and two MPNST), all baseline Ki67 nuclear expression scores were < 20%. Median percent nuclear Ki67 expression was 10.8% in HGG (*n* = 4), 2.0% in LGG (*n* = 23), and 25.3% in MPNST (*n* = 2).