SUPPLEMENTARY APPENDIX

Table S1: Chemotherapy Schema

Patients receiving radiation therapy for local control

Cycle	1	2	3	4	5	6	7	8
Week	0	3	6	9	12	15	18	21
Drugs	Ifos Doxo Dxrz* Mesna G-CSF/ Neulasta	Ifos Doxo Dxrz Mesna G-CSF/ Neulasta	Ifos Etop Mesna G-CSF/ Neulasta	Ifos Etop Mesna G-CSF/ Neulasta	Ifos Etop Mesna G-CSF/ Neulasta	Ifos Etop Mesna G-CSF/ Neulasta	Ifos Doxo Dxrz Mesna G-CSF/ Neulasta	Ifos Doxo Dxrz Mesna G-CSF/ Neulasta

Patients not receiving radiation therapy for local control

Cycle	1	2	3	4	5	6	7	8
Week	0	3	6	9	12	15	18	21
Drugs	Ifos Doxo Dxrz Mesna G-CSF/ Neulasta	Ifos Doxo Dxrz Mesna G-CSF/ Neulasta	Ifos Etop Mesna G-CSF/ Neulasta	Ifos Etop Mesna G-CSF/ Neulasta	Ifos Doxo Dxrz Mesna G-CSF/ Neulasta	Ifos Doxo Dxrz Mesna G-CSF/ Neulasta	Ifos Etop Mesna G-CSF/ Neulasta	Ifos Etop Mesna G-CSF/ Neulasta

Dxrz =Dexrazoxane 375 mg/ m^2/ dose IV over 15-30 minutes immediately prior to Doxo on days 1, 2

*Dexrazoxane use was not mandatory and was administered per institutional guidelines.

Doxo =Doxorubicin 37.5 mg/ m^2/ dose IV over 15 minutes on days 1, 2

Ifos =Ifosfamide 1,800 mg/ m^2/ dose IV over 60 minutes on days 1, 2, 3, 4, 5

Etop = Etoposide 100 mg/ m^2/ dose IV over 60 minutes on days 1, 2, 3, 4, 5

Mesna =Mesna 360 mg/ m^2/ dose IV, first dose over 60 minutes (with Ifos) and doses 2-8 over 15 minutes every 3 hours on days 1, 2, 3, 4, 5 with Ifos. Other standard mesna dosing regimens including oral administration of mesna (360 mg/ m2 PO q 3hr supplied as scored 400mg tablets), used at participating institutions, were also permissible.

G-CSF = Filgrastim 5µg/kg/dose SC daily starting 24-36 hours after last dose of chemotherapy until post-nadir ANC ≥1,500/µl, or peg-filgrastim (neulasta™) for patients weighing ≥ 45kg: 6mg SC x 1 dose starting 24 hours after completion of chemotherapy.

Institutional guidelines could be used for hydration and preparation and administration of the standard chemotherapy and supportive care agents

Table S2: On Study Evaluation

	Prior to therapy	Prior to cycles	During treatment cycles
History and Physical exam	X	All Cycles	
Phenotypic analysis	X		
CBC, differential	X	All cycles	Weekly to twice weekly[@]
PT,PTT, fibrinogen	X		
Electolytes[§], Ca, Mg, Phos	X	All cycles	Weekly
Liver function tests[¶]	X	All cycles	Weekly
Urine pregnancy test	X	3,5,7	
MUGA or ECHo	X	Pre cycle 3 doxo	
Chest X-ray	X	As clinically indicated	
Plain film of primary disease	X	As clinically indicated	
CT of chest	X	Cycles 3,5,7	
MRI of primary	X	Cycles 3,5,7	
^{18}FDG-PET	X	Cycle 5	
Cr Cl*	X		
Urinalysis	X	All cycles [¥]	
Serum proteomics	X	Cycles 5**, 7	
Tumor specimen	X	Cycle 5 (if surgery for local control)	

@ Monitor CBC twice weekly once ANC ≤1,000/μL until ANC recovers to ≥500/μL

§ Na, K, CL, CO_2, BUN, creatinine, glucose

¶ ALT, AST, bilirubin, alkaline phosphatase, LDH

* IF serum creatinine abnormal

¥ Frequency of urinalysis during ifosfamide treatment will follow institutional guidelines

**After recovery from cycle 4

Table S3. Evaluation of patients based on response after cycle 4

Stratum	NF1 MPNST	Sporadic MPNST
Response evaluation post cycle 4	28	9
Complete Response (CR)	-	-
Partial Response (PR)	5	4
Stable Disease (SD)	20	4
Progressive Disease (PD)	3	1
Initial tumor size > 5cm*		
PR	3	3
SD	19	3
PD	3	1
Initial tumor size < 5cm*		
PR	2	1
SD	1	1
PD	0	0
Metastatic disease at diagnosis (stage 4)		
PR	1	2
SD	10	2
PD	0	0
Non-metastatic disease at diagnosis (stage 3)		
PR	4	2
SD	10	2
PD	3	1
≥33 years old		
PR	3	4

SD	10	2
PD	1	1

*largest diameter

Table S4: Central pathology evaluation of tumor samples prior to treatment

		NF1 (n= 26)	Sporadic (n= 11)
Location	Central	6	2
	Nerve plexus	3	0
	Trunk	10	6
	Head and Neck	2	0
	Retroperitoneal	1	0
	Proximal limb	2	1
	Distal limb	2	1
	Metastasis	0	1
Arising from Neurofibroma	Yes	13	0
	No	5	9
	Unclear	8	2
Histologic Variant	Conventional	15	7
	Perineural	1	0
	Epithelioid	0	2
	Divergent (Triton)	1	0
	Mixed histology	9	2
Extracellular mucin	0	14	6
	1	9	3
	2	3	1
	3	0	1
Intravascular invasion		7	2

Cellularity	low moderate high	0 5 21	0 4 7
Cellular pleomorphism	1 2 3	9 14 3	4 5 2
Nuclear atypia	1 2 3	4 17 5	1 5 5
Nuclear chromatin	bland hyperchromatic vesicular hyperchromatic/vesicular	1 19 3 3	2 3 6 0
Macronucleoli		8	5
Max #mitoses per 10x HPF		44	44
Atypical mitoses		4	4
Small cells (high NC ratio)	absent 1-10% 10-50%	20 1 4	7 1 3
Necrosis	absent 1-10% 10-50% >50%	5 8 10 3	1 2 5 3

Nuclear pseudopalisading		6	3
IMMUNOHISTOCHEMISTRY			
s100		17+ (of 23)	8+ (of 11)
Leu-7		12+ (of 23)	4 (of 11)
EMA		3 (of 21)	3 (of 11)
Desmin		6 (of 23)	0 (of 11)
p53		16 (of 22)	10(of 11)
Ki67 (MIB-1)		Mean: 31%	Mean: 50%
EGFR		19 (of 21)	8 (of 11)
FISH			
EGFR (7p12) amplification		3 (of 20)	1 (of 8)
TOPO2A (17q21-q22) amplification		5 (of 19)	2 (of 10)
Her2/Neu (17q11-q12) amplification		2 (of 18)	0 (of 10)
Cyclin D1 (11q13) amplification		1 (of 19)	2 (of 9)
c-MYC (8q24) amplification		5 (of 20)	0 (of 8)
N-MYC (2p24) amplification		3 (of 16)	1 (of 6)
NF1 (17q11) deletion		7 (of 19)	0 (of 9)

p16 (9p21) deletion		10 (of 14)	3 (of 6)
RB (13q14) deletion		1 (of 17)	2 (of 10)
p53 (17q13) deletion		6 (of 19)	2 (of 9)