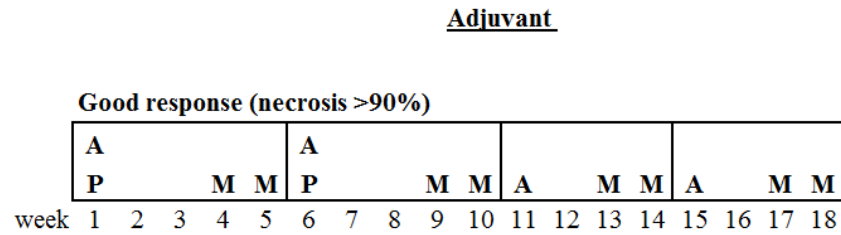
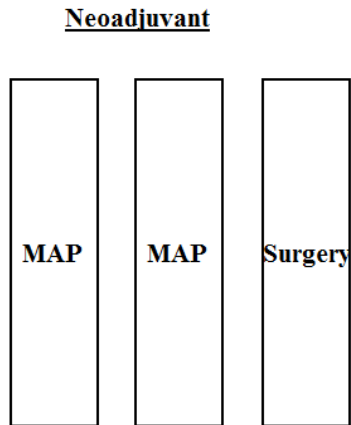


Supplementary Fig. S1.



M= methotrexate 12 g/m²/day
 A* = doxorubicin 90 mg/m²/day
 A= doxorubicin 37.5 mg/m²/day on day 1 and 2
 P= cisplatin 60 mg/m²/day on day 1 and 2
 I* = ifosfamide 2.8 g/m²/day for 5 days
 I= ifosfamide 3 g/m²/day for 3 days

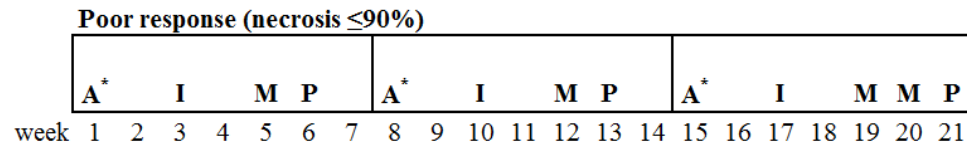
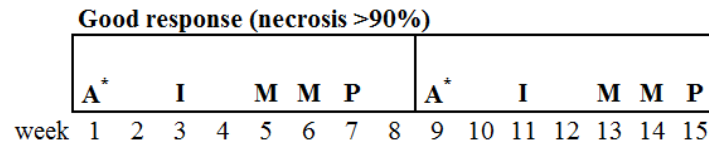
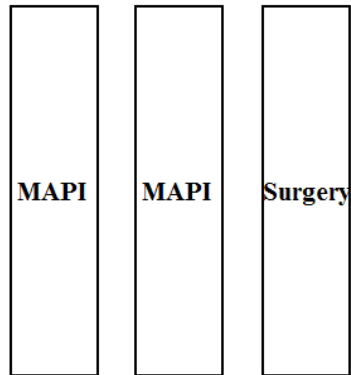
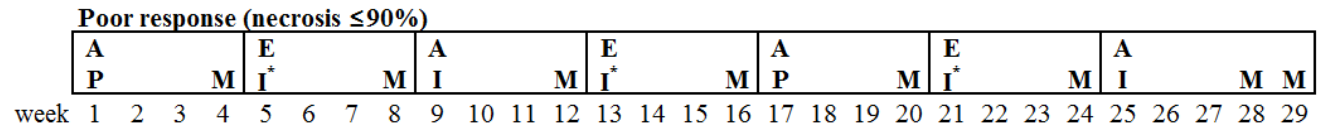


Fig. S1. Treatment scheme of the two adjuvant regimens. Treatment was tailored according to the histologic response of surgical specimens. For MAP therapy (upper panel), cisplatin (P), doxorubicin (A), and methotrexate (M) were given at the time points and doses depicted in the figure for a total of four courses in patients showing a good response. For those with a poor response, ifosfamide at two dose levels (I or I^{*}) and etoposide (E) were added to P, A, and M, and they were given as shown in the figure for a total of seven courses. For MAPI therapy (lower panel), doxorubicin at a higher dose than A (A^{*}), I, M, and P were administered at the time points and doses displayed in the figure for a total of two courses in patients showing a good response. For those with a poor response, A^{*}, I, M, and P were administered as shown in the figure for a total of three courses.

Supplementary Fig. S2.

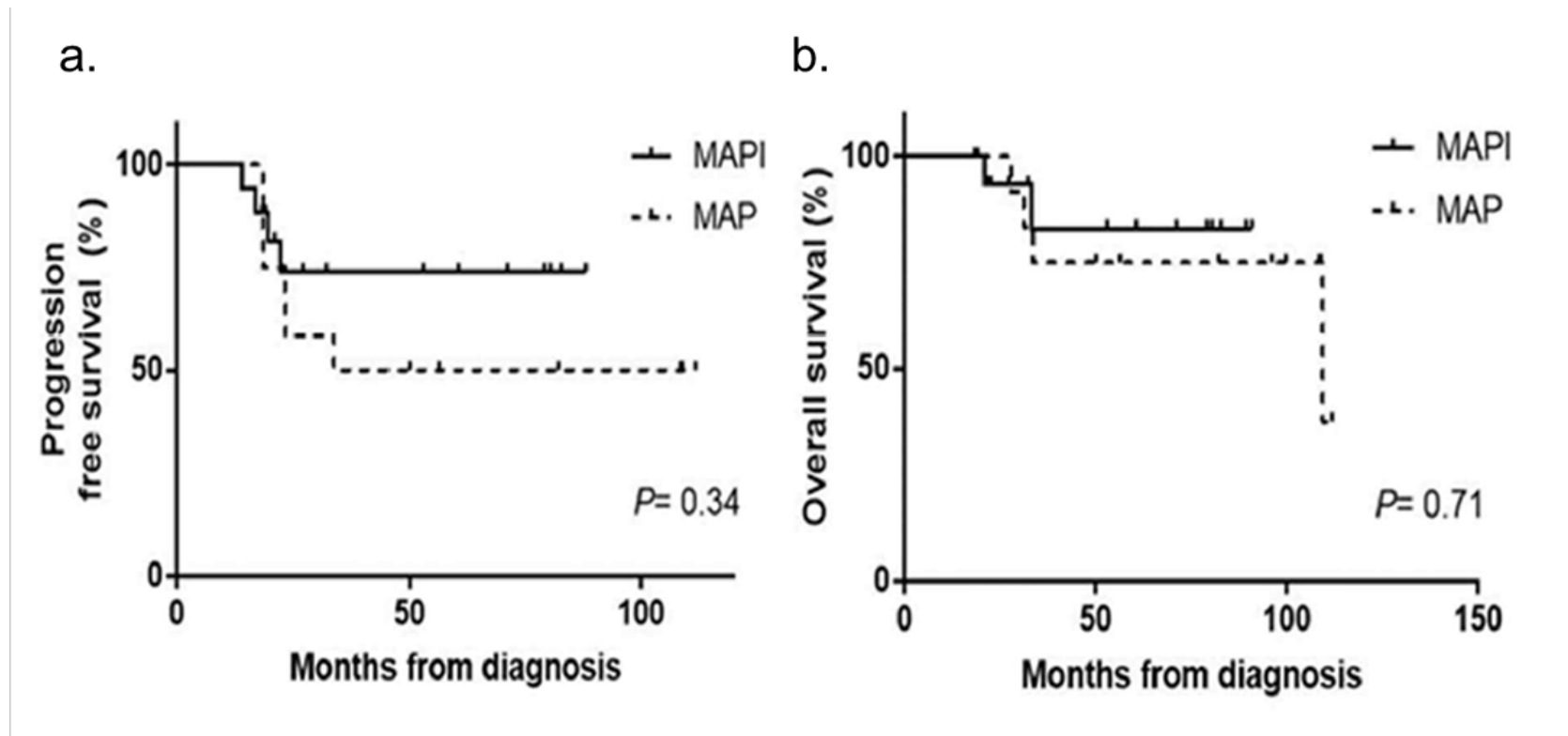


Fig. S2. Survival outcomes. Progression free survival (a) and overall survival (b) calculated by the Kaplan-Meier method. Ticks represent censored patients ($n = 29$).

Supplementary Table S1. Variables associated with histologic response

Variables		<i>p</i>	Univariate	
			OR	95% CIs
Regimen	MAP	Reference		
	MAPI	0.12	3.36	0.71-15.85
Sex	Male	Reference		
	Female	0.64	1.43	0.32-6.32
Age \geq 18 years		0.09	1.14	0.98-1.33
Tumor location in the limb primaries	Non-proximal	Reference		
	Proximal	0.63	1.59	0.24-10.57
Histology	Osteoblastic	Reference		
	Chondroblastic	0.80	1.46	0.08-25.81
Days from the start of chemotherapy to operation		0.38	1.02	0.97-1.08
Tumor volume \geq 200 mL		0.17	3.75	0.56-25.12

MAPI, methotrexate, doxorubicin, cisplatin, and ifosfamide; MAP, methotrexate, doxorubicin, and cisplatin; OR, odds ratio; CIs, confidence intervals.

Supplementary Table S2. Variables included in the univariate analysis for survival outcome

Variables		Progression-free survival			Overall survival		
		<i>p</i>	HR	95%CI	<i>p</i>	HR	95%CI
Regimen	MAP	ref			ref		
	MAPI	0.642	0.751	0.225-2.507	0.718	1.392	0.231-8.378
Sex, boys	Female	ref			ref		
	Male	0.118	2.898	0.763-11.009	0.201	4.192	0.467-37.640
Age, older		0.828	0.989	0.898-1.090	0.990	0.999	0.872-1.145
Stage	<4	ref			ref		
	4	0.015	4.423	1.339-14.604	0.035	10.590	1.177-95.241
Pathologic fracture	No	ref			ref		
	Yes	0.575	1.808	0.228-14.356	0.977	1.035	0.098-10.912
Primary site	Limb	ref			ref		
	Others	0.481	0.477	0.061-3.741	0.550	0.039	0-1647.088
Tumor origin in long bone	Non-proximal	ref			ref		
	Proximal	0.004	6.609	1.828-23.896	0.111	4.032	0.727-22.370
Histologic type	Osteoblastic	ref			ref		
	Chondroblastic	0.708	0.046	0-473730.227	0.897	0.047	0-5.284E18
Resection margin	Complete	ref			ref		
	Incomplete	0.269	2.408	0.506-11.452	0.595	1.813	0.202-16.280
Tumor volume ≥ 200 ml		0.114	0.274	0.784-9.575	0.288	2.649	0.438-16.008
Histologic response	Good (necrosis $>90\%$)	ref			ref		
	Poor (necrosis $\leq 90\%$)	0.992	0.993	0.296-3.336	0.299	2.461	0.450-13.464

MAPI, methotrexate, doxorubicin, cisplatin, and ifosfamide; MAP, methotrexate, doxorubicin, and cisplatin; HR, Hazard ratio; CIs, confidence intervals.