

Table SI: Extranodal sites at baseline

Site	Present		Absent	
	N	CNS relapses (%)	N	CNS relapses (%)
Bone	164	6 (3.7)	525	13 (2.5)
Liver	67	1 (1.5)	622	18 (2.9)
Small bowel or Colon	66	2 (3.0)	623	17 (2.7)
Lung	57	3 (5.3)	632	16 (2.5)
Gastric or Oesophageal	47	2 (4.3)	642	17 (2.6)
Pleural	47	2 (4.3)	642	17 (2.6)
Renal	47	4 (8.5)	642	15 (2.3)
Muscle	41	3 (7.3)	648	16 (2.5)
Peritoneum or Omentum	30	1 (3.3)	659	18 (2.7)
Pancreas	28	1 (3.6)	661	18 (2.7)
Skin or Subcutaneous	25	2 (8.0)	664	17 (2.6)
Testis	21	0	668	19 (2.8)
Thyroid	21	0	668	19 (2.8)
Adrenal	19	1 (5.3)	670	18 (2.7)
Tonsil	15	0	674	19 (2.8)
Pericardial or Cardiac	11	0	678	19 (2.8)
Breast	10	0	679	19 (2.8)
Parotid	9	0	680	19 (2.8)
Tongue base	9	0	680	19 (2.8)
Intervertebral	7	0	682	19 (2.8)
Nasopharynx	7	1 (14.3)	682	18 (2.6)
Ovary	6	0	683	19 (2.8)
Sinus	4	0	685	19 (2.8)
Bladder	4	0	685	19 (2.8)
Uterus	4	0	685	19 (2.8)
Crus of diaphragm	3	0	686	19 (2.8)
Dural	2	0	687	19 (2.8)
Trachea/Larynx	2	0	687	19 (2.8)
Ureter	2	0	687	19 (2.8)
Gallbladder	2	0	687	19 (2.8)
Orbit	2	0	687	19 (2.8)
Epidural	2	0	687	19 (2.8)
Prostate	2	0	687	19 (2.8)
Peripheral nerve	1	0	688	19 (2.8)
Vagina	1	0	688	19 (2.8)
Aorta	1	0	688	19 (2.8)
Palate	1	0	688	19 (2.8)

Table SII: Univariable and adjusted risk of CNS relapse – according to CNS prophylaxis and CNS-IPI excluding patients receiving HDMTX

Factor	Events/N	Univariable (complete cases)*		Adjusted	
		HR (95% CI)	p-value	HR (95% CI)	p-value
IT CNS prophylaxis					
No	12/550	1.00	0.098	1.00	0.98
Yes	5/98	2.35 (0.83 – 6.69)		0.98 (0.31 – 3.15)	
IT CNS IPI					
0-3	5/399	1.00	<0.001	1.00	0.003
4	5/148	3.15 (0.91 – 10.90)		3.15 (0.91 – 10.96)	
5	3/82	4.75 (1.12 – 20.19)		4.78 (1.06 – 21.60)	
6	4/19	38.61 (9.98 – 149.45)		38.95 (8.92 – 170.07)	

Factor	Events/N	Univariable (complete cases)* HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
CNS prophylaxis					
No	12/550	1.00	0.09	1.00	0.58
Yes	5/98	2.49 (0.88 – 7.08)		1.38 (0.45 – 4.31)	
CNS IPI					
0-3	5/399	1.00	<0.001	1.00	0.036
4	5/148	2.76 (0.80 – 9.55)		2.69 (0.78 – 9.34)	
5	3/82	3.31 (0.79 – 13.85)		3.02 (0.69 – 13.18)	
6	4/19	21.35 (5.72 – 79.64)		18.90 (4.70 – 76.10)	
Patients alive and PFS free at 6 months					
CNS prophylaxis					
No	9/439	1.00	0.76	1.00	0.70
Yes	2/80	1.27 (0.27 – 5.86)		0.72 (0.14 – 3.72)	
CNS IPI					
0-3	4/338	1.00	0.016	1.00	0.29
4	4/118	2.34 (0.63 – 8.72)		2.37 (0.63 – 8.90)	
5	1/54	1.34 (0.16 – 11.50)		1.41 (0.16 – 12.66)	
6	2/9	13.71 (2.65 – 70.96)		14.74 (2.46 – 88.36)	

*i.e. excludes patients with missing CNS scores, this includes 1 patient with a CNS event.

Table SIII: CNS relapses: patient characteristics and CNS prophylaxis received.

Patient number	Age at diagnosis (years)	CNS IPI	>1 Extranodal	Number of extranodal sites	Extranodal sites	CNS prophylaxis	Site of progression	Time to progression (years)
1	74.6	6	Y	3	pancreas, kidney, bowel	Nil	CNS PD	1.62
2	75.3	5	Y	2	stomach, bowel	Nil	CNS AND SYSTEMIC PD	0.36
3	79.0	1	N	1	nasal cavity	IV and IT MTX	CNS PD	1.08
4	80.2	5	Y	2	subcutaneous, bone	Nil	CNS AND SYSTEMIC PD	0.40
5	80.9	4	N	1	liver	Nil	CNS PD	0.78
6	71.4	5	Y	2	skin, muscle	Nil	CNS AND SYSTEMIC PD	0.69
7	73.0	4	Y	3	bone, muscle, pleura	IT MTX	CNS PD	0.74
8	78.0	6	Y	2	bone, renal	IT MTX	CNS PD	0.15
9	83.5	1	N	0	nil	Nil	CNS PD	0.91
10	85.1	3	N	1	pleural	Nil	CNS AND SYSTEMIC PD	2.49
11	70.1	6	Y	2	adrenal, lung	IT MTX	CNS PD	0.27
12	70.1	2	N	1	muscle	Nil	CNS PD	2.43
13	83.5	4	N	1	bone	IT MTX	CNS PD	0.39
14	81.6	6	Y	5	renal, lung, bone, omentum, gastric	IT MTX	CNS PD	0.91
15	75.7	1	N	1	bone	Nil	CNS PD	5.90
16	82.3	4	N	0	Nil	Nil	CNS PD	1.17
17	86.0	4 or 5*	N	1	renal	Nil	CNS AND SYSTEMIC PD	1.19
18	75.5	3	N	1	pulmonary	Nil	CNS PD	0.34
19	75.5	4	N	0	nil	Nil	CNS AND SYSTEMIC PD	0.58

Abbreviations: CNS: central nervous system; PD: progressive disease; IT: intrathecal; IV: intravenous; MTX: methotrexate. *LDH unknown