

Appendix 2- Balance Check after matching

Covariate	Level	Statistics	LOT1 PPx		Parametric P-value*	Standardized Difference
			IV N=179	IT N=179		
Sex	Male	N (Col%)	99 (55.31)	95 (53.07)	0.671	0.045
	Female	N (Col%)	80 (44.69)	84 (46.93)		0.045
Number EN sites	Less than 2 sites	N (Col%)	101 (56.42)	104 (58.1)	0.749	0.034
	2 sites or greater	N (Col%)	78 (43.58)	75 (41.9)		0.034
Renal and/or Adrenal involvement	No	N (Col%)	160 (89.39)	162 (90.5)	0.725	0.037
	Yes	N (Col%)	19 (10.61)	17 (9.5)		0.037
B symptoms	No	N (Col%)	104 (58.1)	95 (53.07)	0.626	0.101
	Yes	N (Col%)	72 (40.22)	81 (45.25)		0.102
	Unknown	N (Col%)	3 (1.68)	3 (1.68)		0.000
NCCN-IPI category	Low	N (Col%)	15 (8.38)	12 (6.7)	0.803	0.064
	Low-intermediate	N (Col%)	76 (42.46)	78 (43.58)		0.023
	High-intermediate	N (Col%)	76 (42.46)	73 (40.78)		0.034
	High	N (Col%)	12 (6.7)	16 (8.94)		0.083
CNS-IPI category	Low	N (Col%)	39 (21.79)	38 (21.23)	0.950	0.014
	Moderate	N (Col%)	87 (48.6)	90 (50.28)		0.034
	High	N (Col%)	53 (29.61)	51 (28.49)		0.025
Testis	No	N (Col%)	162 (90.5)	162 (90.5)	1.000	0.000
	Yes	N (Col%)	17 (9.5)	17 (9.5)		0.000

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			IV N=179	IT N=179		
Double hit positive	No	N (Col%)	166 (92.74)	162 (90.5)	0.445	0.081
	Yes	N (Col%)	13 (7.26)	17 (9.5)		
Double hit evaluable	No	N (Col%)	43 (24.02)	46 (25.7)	0.714	0.039
	Yes	N (Col%)	136 (75.98)	133 (74.3)		
First line of therapy, 2-levels	RCHOP/R-miniCHOP	N (Col%)	120 (67.04)	131 (73.18)	0.204	0.135
	REPOCH/DA-REPOCH	N (Col%)	59 (32.96)	48 (26.82)		
Age		Mean (Std)	57.08 (13.37)	58.22 (13.62)	0.425	0.084

* The parametric p value is calculated by ANOVA for numerical covariates and Chi-Square test for categorical covariates.

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Supplement Table 1: Prophylaxis-related toxicity					
Toxicity - no. (%)	Total (n=1162)	Intrathecal (n=894)	HD-MTX (n=236)	Switched route* (n=32)	
Any documented toxicity	134 (11.5)	54 (6.0)	60 (25.4)	32	100
<i>Category:</i>					
Hematologic	23 (2.0)	12 (1.3)	10 (4.2)	1	(3.1)
Renal impairment	47 (4.0)	5 (0.6)	34 (14.4)	8	(25.0)
Mucositis**	17 (1.5)	6 (0.7)	9 (3.8)	2	(6.3)
Delayed MTX clearance&	27 (2.3)	0 (0)	21 (8.9)	6	(18.8)
Headache	18 (1.5)	17 (1.9)	1 (0.4)	0	(0)
Other neurologic	12 (1.0)	11 (1.2)	1 (0.4)	0	(0)
Other / Not specified#	38 (3.3)	11 (1.2)	12 (5.1)	15	(46.9)
<i>Abbreviations:</i> HD-MTX, high-dose methotrexate. *Includes switching in either direction between intrathecal and intravenous (HD-MTX) administration. **Excludes low-grade mucositis. # Per clinical documentation. & No patients received glucarpidase during the study period.					