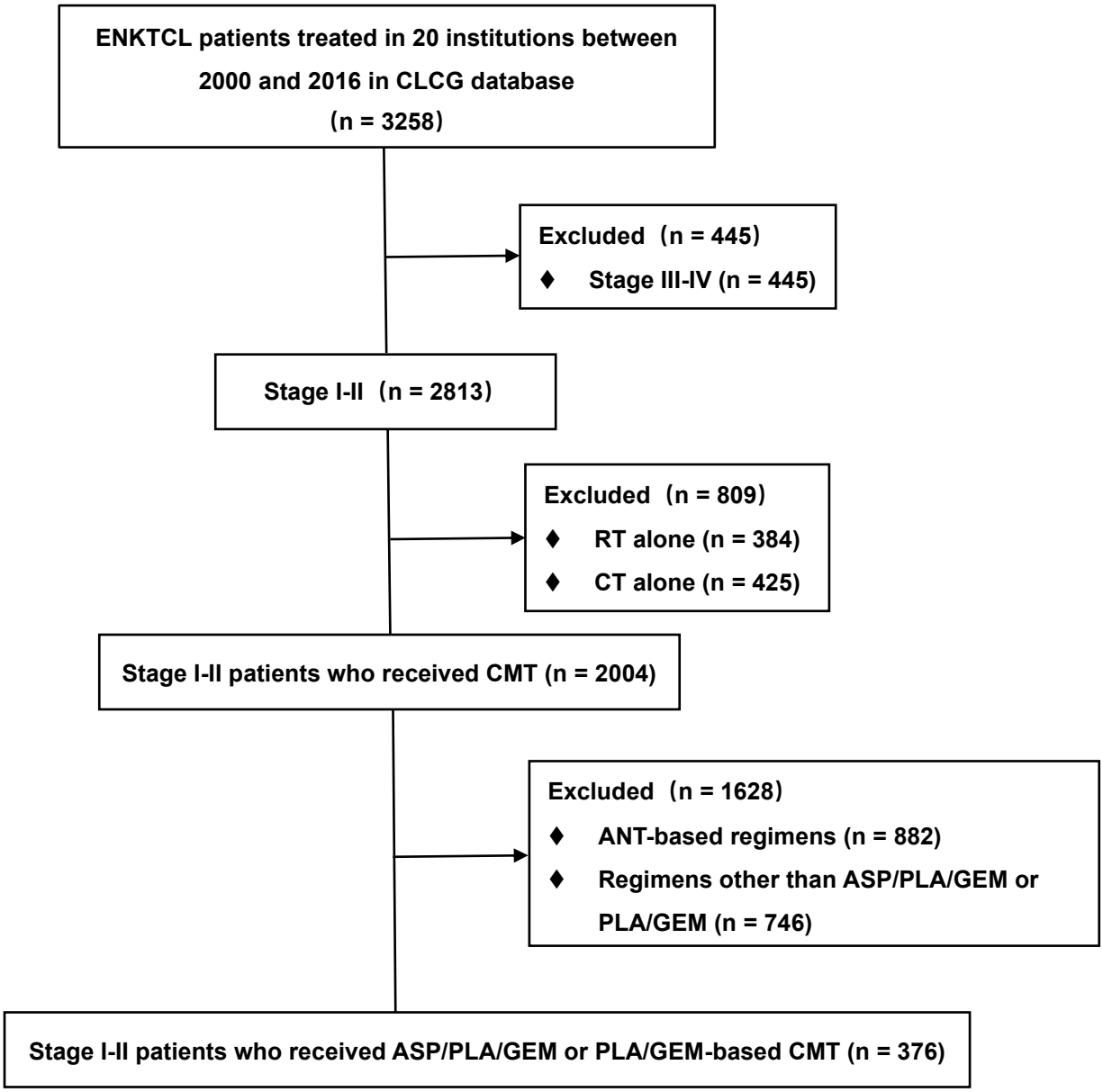
Supplemental table 1. Summary of ASP-based and non-ASP-based regimens in 376 early-stage ENKTCL patients who received combined-modality therapy.

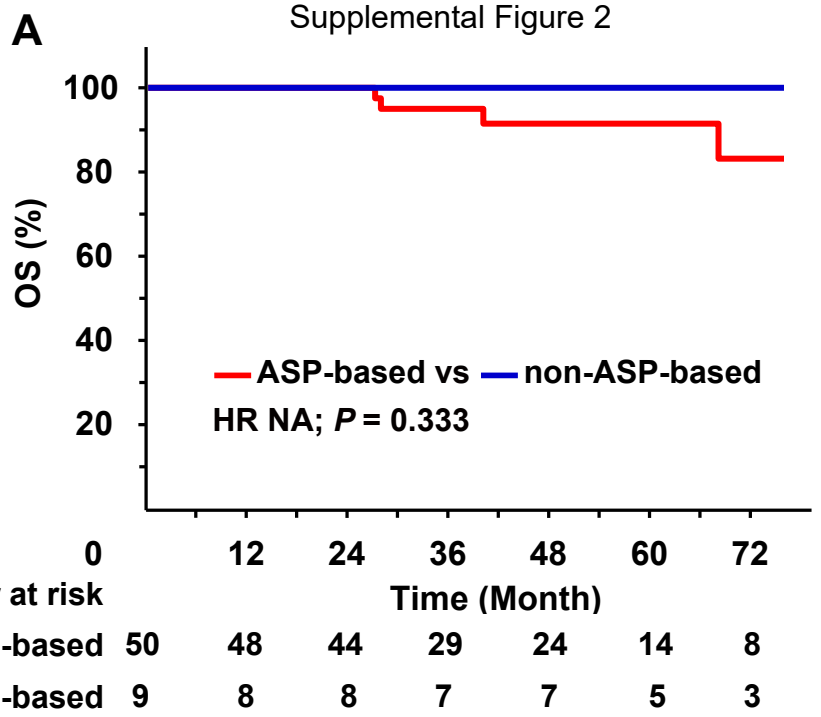
Regimens	Definition and agents	All early-stage patients				Intermediate- and high-risk patients			
		Regimens No. (%)	Cycles ≥4 No. (%)	Cycles ≥3 No. (%)	Cycles Median (IQR)	Regimens No. (%)	Cycles ≥4 No. (%)	Cycles ≥3 No. (%)	Cycles Median (IQR)
ASP-based (ASP/PLA/GEM)	Regimens containing asparaginase, platinum and gemcitabine	286 (76.1)	199 (69.6)	245 (85.7)	4 (3-6)	236 (74.4)	169 (71.6)	204 (86.4)	4 (3-6)
GELOX	Gemcitabine, oxaliplatin, L-asparaginase	119 (31.6)	79 (66.4)	100 (84.0)	4 (3-6)	102 (32.2)	72 (70.6)	86 (84.3)	4 (3-6)
P-GEMOX	Pegaspargase, gemcitabine, oxaliplatin	113 (30.1)	83 (73.5)	101 (89.4)	4 (3-6)	92 (29.0)	69 (75.0)	83 (90.2)	4 (3.8-6)
GDP-L	Gemcitabine, dexamethasone, cisplatin, L-asparaginase	41 (10.9)	27 (65.9)	34 (82.9)	4 (3-6)	34 (10.7)	22 (64.7)	29 (85.3)	4 (3-6)
DDGP	Gemcitabine, pegaspargase, cisplatin, dexamethasone	13 (3.5)	10 (76.9)	10 (76.9)	4 (3-5)	8 (2.5)	6 (75.0)	6 (75.0)	4.5 (2.5-5.8)
Non-ASP-based (PLA/GEM)	Regimens containing platinum and gemcitabine	90 (23.9)	72 (80.0)	80 (88.9)	4 (4-5)	81 (25.6)	65 (80.2)	72 (88.9)	4 (4-5)
GDP	Gemcitabine, dexamethasone, cisplatin	73 (19.4)	61 (83.6)	66 (90.4)	4 (4-5)	66 (20.8)	56 (84.8)	60 (90.9)	4 (4-5)
GEMOX	Gemcitabine, oxaliplatin	9 (2.4)	8 (88.9)	8 (88.9)	4 (4-6)	7 (2.2)	6 (85.7)	6 (85.7)	4 (4-6)
GP	Gemcitabine, cisplatin	8 (2.1)	3 (37.5)	6 (75.0)	3 (2-4)	8 (2.5)	3 (37.5)	6 (75.0)	3 (2-4)

Abbreviations: ENKTCL, extranodal nasal-type natural killer/T-cell lymphoma; ASP, asparaginase; IQR, interquartile range; PLA, platinum; GEM, gemcitabine

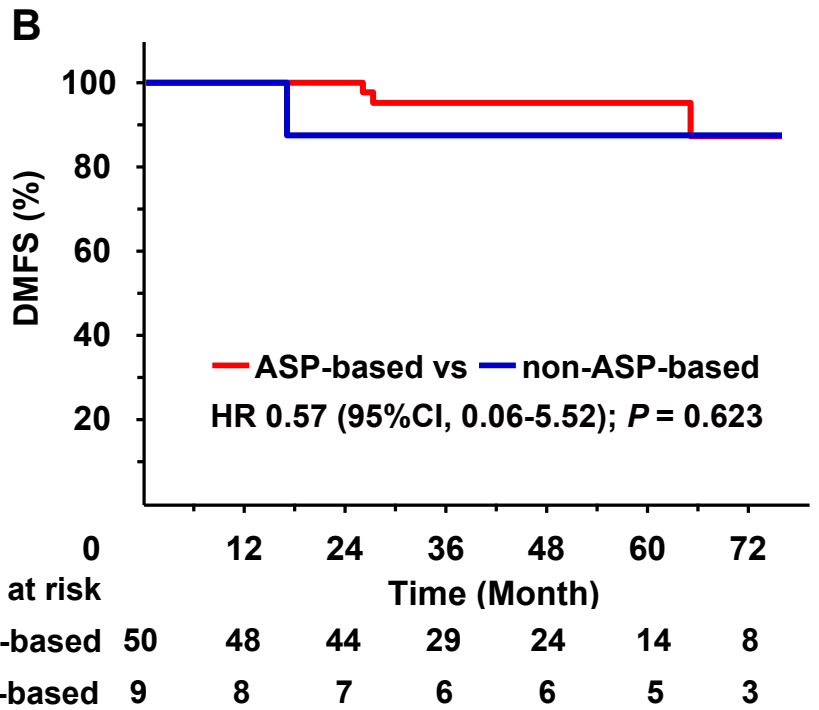
Supplemental Figure 1



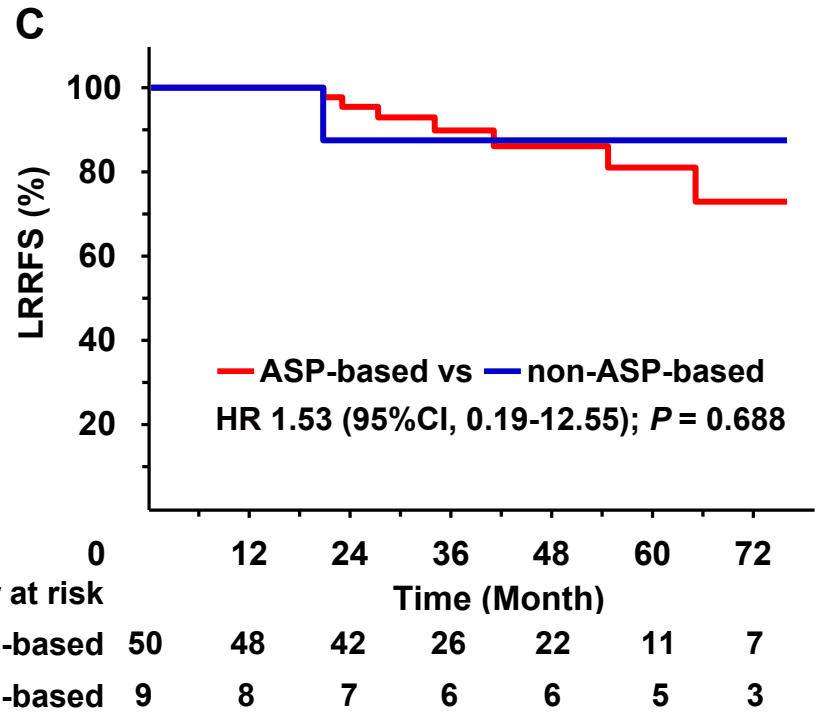
Supplemental Figure 2



Number at risk							
ASP-based	50	48	44	29	24	14	8
non-ASP-based	9	8	8	7	7	5	3



Number at risk							
ASP-based	50	48	44	29	24	14	8
non-ASP-based	9	8	7	6	6	5	3



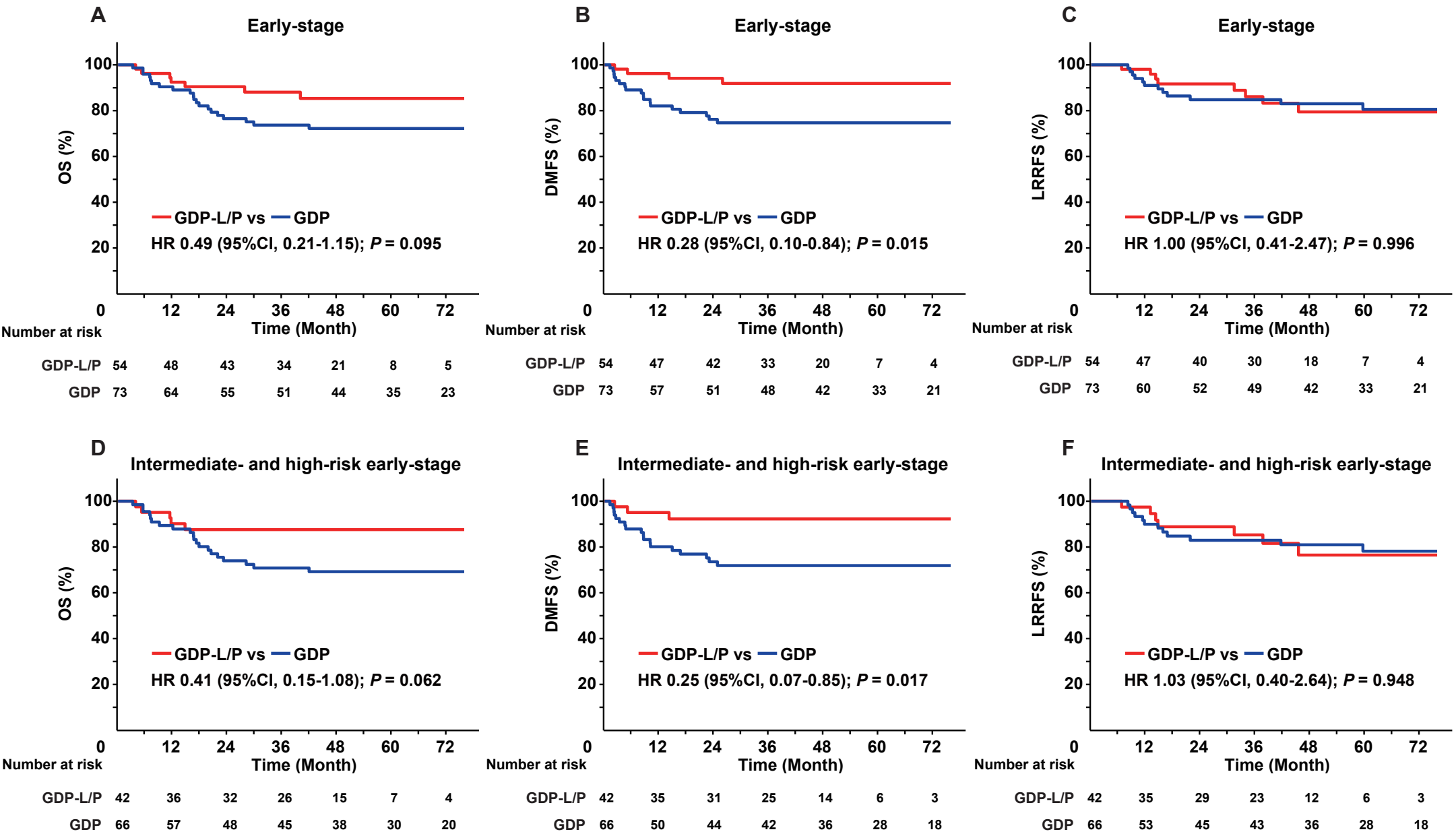
Number at risk							
ASP-based	50	48	42	26	22	11	7
non-ASP-based	9	8	7	6	6	5	3

Supplemental Figure 3

Bounding factor		OR_{ASP-U} in all early-stage patients													
		1.0	1.1	1.2	1.3	1.4	1.5	1.8	2.0	2.2	2.5	3.0	3.5	4.0	5.0
HR_{OS-U}	1.00	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.03, 0.92)	0.52 (0.30, 0.92)
	0.95	0.52 (0.30, 0.92)	0.52 (0.30, 0.92)	0.52 (0.30, 0.93)	0.53 (0.30, 0.93)	0.53 (0.30, 0.93)	0.53 (0.31, 0.94)	0.53 (0.31, 0.94)	0.53 (0.31, 0.94)	0.53 (0.31, 0.95)	0.54 (0.31, 0.95)	0.54 (0.31, 0.95)	0.54 (0.31, 0.95)	0.54 (0.31, 0.96)	0.54 (0.31, 0.96)
	0.90	0.52 (0.30, 0.92)	0.53 (0.30, 0.93)	0.53 (0.31, 0.94)	0.53 (0.31, 0.94)	0.54 (0.31, 0.95)	0.54 (0.31, 0.95)	0.55 (0.31, 0.97)	0.55 (0.32, 0.97)	0.55 (0.32, 0.98)	0.55 (0.32, 0.98)	0.56 (0.32, 0.99)	0.56 (0.32, 0.99)	0.56 (0.33, 1.00)	0.57 (0.33, 1.00)
	0.85	0.52 (0.30, 0.92)	0.53 (0.30, 0.93)	0.54 (0.31, 0.95)	0.54 (0.31, 0.96)	0.55 (0.32, 0.97)	0.55 (0.32, 0.97)	0.56 (0.32, 0.99)	0.57 (0.33, 1.00)	0.57 (0.33, 1.01)	0.58 (0.33, 1.02)	0.58 (0.34, 1.03)	0.59 (0.34, 1.04)	0.59 (0.34, 1.04)	0.59 (0.34, 1.05)
	0.80	0.52 (0.30, 0.92)	0.53 (0.31, 0.94)	0.54 (0.31, 0.96)	0.55 (0.32, 0.97)	0.56 (0.32, 0.99)	0.56 (0.33, 1.00)	0.58 (0.33, 1.02)	0.59 (0.34, 1.04)	0.59 (0.34, 1.05)	0.60 (0.35, 1.06)	0.61 (0.35, 1.07)	0.61 (0.35, 1.08)	0.62 (0.36, 1.09)	0.62 (0.36, 1.10)
	0.75	0.52 (0.30, 0.92)	0.54 (0.31, 0.95)	0.55 (0.32, 0.97)	0.56 (0.32, 0.99)	0.57 (0.33, 1.01)	0.58 (0.33, 1.02)	0.60 (0.34, 1.06)	0.61 (0.35, 1.07)	0.61 (0.35, 1.09)	0.62 (0.36, 1.10)	0.64 (0.37, 1.12)	0.64 (0.37, 1.14)	0.65 (0.38, 1.15)	0.66 (0.38, 1.17)
	0.70	0.52 (0.30, 0.92)	0.54 (0.31, 0.96)	0.56 (0.32, 0.99)	0.57 (0.33, 1.01)	0.58 (0.34, 1.03)	0.59 (0.34, 1.05)	0.62 (0.36, 1.10)	0.63 (0.36, 1.12)	0.64 (0.37, 1.14)	0.65 (0.38, 1.16)	0.67 (0.39, 1.18)	0.68 (0.39, 1.20)	0.69 (0.40, 1.22)	0.70 (0.40, 1.24)
	0.65	0.52 (0.30, 0.92)	0.55 (0.31, 0.97)	0.57 (0.33, 1.00)	0.58 (0.34, 1.03)	0.60 (0.35, 1.06)	0.61 (0.35, 1.09)	0.64 (0.37, 1.14)	0.66 (0.38, 1.17)	0.67 (0.39, 1.19)	0.69 (0.40, 1.22)	0.71 (0.41, 1.25)	0.72 (0.42, 1.27)	0.73 (0.42, 1.29)	0.74 (0.43, 1.32)
	0.60	0.52 (0.30, 0.92)	0.55 (0.32, 0.98)	0.58 (0.33, 1.02)	0.60 (0.35, 1.06)	0.62 (0.36, 1.10)	0.64 (0.37, 1.12)	0.67 (0.39, 1.19)	0.69 (0.40, 1.23)	0.71 (0.41, 1.25)	0.73 (0.42, 1.29)	0.75 (0.43, 1.33)	0.77 (0.44, 1.36)	0.78 (0.45, 1.38)	0.8 (0.46, 1.41)
	0.55	0.52 (0.30, 0.92)	0.56 (0.32, 0.99)	0.59 (0.34, 1.05)	0.62 (0.36, 1.09)	0.64 (0.37, 1.14)	0.66 (0.38, 1.17)	0.71 (0.41, 1.25)	0.73 (0.42, 1.30)	0.75 (0.43, 1.33)	0.78 (0.45, 1.37)	0.80 (0.46, 1.42)	0.82 (0.48, 1.46)	0.84 (0.48, 1.48)	0.86 (0.50, 1.52)
	0.50	0.52 (0.30, 0.92)	0.57 (0.33, 1.00)	0.61 (0.35, 1.07)	0.64 (0.37, 1.13)	0.67 (0.39, 1.18)	0.69 (0.40, 1.23)	0.75 (0.43, 1.33)	0.78 (0.45, 1.38)	0.80 (0.46, 1.42)	0.83 (0.48, 1.47)	0.87 (0.50, 1.53)	0.89 (0.51, 1.58)	0.91 (0.53, 1.61)	0.94 (0.54, 1.66)
	0.45	0.52 (0.30, 0.92)	0.58 (0.33, 1.02)	0.63 (0.36, 1.11)	0.67 (0.38, 1.18)	0.70 (0.40, 1.24)	0.73 (0.42, 1.29)	0.80 (0.46, 1.42)	0.84 (0.48, 1.48)	0.87 (0.50, 1.53)	0.90 (0.52, 1.59)	0.94 (0.54, 1.67)	0.97 (0.56, 1.72)	1.00 (0.58, 1.76)	1.03 (0.59, 1.82)
	0.40	0.52 (0.30, 0.92)	0.59 (0.34, 1.05)	0.65 (0.38, 1.15)	0.70 (0.40, 1.24)	0.74 (0.43, 1.31)	0.78 (0.45, 1.38)	0.87 (0.50, 1.53)	0.91 (0.53, 1.61)	0.95 (0.55, 1.67)	0.99 (0.57, 1.75)	1.04 (0.60, 1.84)	1.08 (0.62, 1.91)	1.11 (0.64, 1.96)	1.14 (0.66, 2.02)
	0.35	0.52 (0.30, 0.92)	0.61 (0.35, 1.08)	0.68 (0.39, 1.20)	0.74 (0.43, 1.31)	0.80 (0.46, 1.41)	0.84 (0.49, 1.49)	0.95 (0.55, 1.68)	1.00 (0.58, 1.77)	1.05 (0.60, 1.85)	1.10 (0.63, 1.95)	1.16 (0.67, 2.06)	1.21 (0.70, 2.14)	1.24 (0.72, 2.20)	1.29 (0.75, 2.29)
	0.30	0.52 (0.30, 0.92)	0.63 (0.36, 1.12)	0.72 (0.42, 1.28)	0.80 (0.46, 1.42)	0.87 (0.50, 1.53)	0.92 (0.53, 1.64)	1.06 (0.61, 1.87)	1.13 (0.65, 1.99)	1.18 (0.68, 2.09)	1.25 (0.72, 2.21)	1.33 (0.77, 2.35)	1.39 (0.80, 2.45)	1.43 (0.83, 2.53)	1.49 (0.86, 2.64)
	0.25	0.52 (0.30, 0.92)	0.66 (0.38, 1.17)	0.78 (0.45, 1.38)	0.88 (0.51, 1.56)	0.97 (0.56, 1.71)	1.04 (0.60, 1.84)	1.21 (0.70, 2.15)	1.30 (0.75, 2.30)	1.37 (0.79, 2.43)	1.46 (0.84, 2.58)	1.56 (0.90, 2.76)	1.63 (0.94, 2.89)	1.69 (0.98, 2.99)	1.77 (1.02, 3.13)
	0.20	0.52 (0.30, 0.92)	0.71 (0.41, 1.25)	0.87 (0.50, 1.53)	1.00 (0.58, 1.77)	1.11 (0.64, 1.97)	1.21 (0.70, 2.15)	1.44 (0.83, 2.56)	1.56 (0.90, 2.76)	1.65 (0.95, 2.93)	1.77 (1.02, 3.13)	1.91 (1.10, 3.37)	2.01 (1.16, 3.55)	2.08 (1.20, 3.68)	2.18 (1.26, 3.86)

Bounding factor		OR_{ASP-U} in intermediate- and high-risk early-stage patients													
		1.0	1.1	1.2	1.3	1.4	1.5	1.8	2.0	2.2	2.5	3.0	3.5	4.0	5.0
HR_{OS-U}	1.00	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)
	0.95	0.45 (0.25, 0.80)	0.45 (0.25, 0.80)	0.45 (0.25, 0.81)	0.46 (0.25, 0.81)	0.46 (0.25, 0.81)	0.46 (0.25, 0.81)	0.46 (0.26, 0.82)	0.46 (0.26, 0.82)	0.46 (0.26, 0.82)	0.46 (0.26, 0.83)	0.47 (0.26, 0.83)	0.47 (0.26, 0.83)	0.47 (0.26, 0.83)	0.47 (0.26, 0.83)
	0.90	0.45 (0.25, 0.80)	0.45 (0.25, 0.81)	0.46 (0.25, 0.81)	0.46 (0.26, 0.82)	0.46 (0.26, 0.83)	0.47 (0.26, 0.83)	0.47 (0.26, 0.84)	0.48 (0.26, 0.84)	0.48 (0.27, 0.85)	0.48 (0.27, 0.85)	0.48 (0.27, 0.86)	0.49 (0.27, 0.86)	0.49 (0.27, 0.87)	0.49 (0.27, 0.87)
	0.85	0.45 (0.25, 0.80)	0.46 (0.25, 0.81)	0.46 (0.26, 0.82)	0.47 (0.26, 0.83)	0.47 (0.26, 0.84)	0.48 (0.26, 0.85)	0.49 (0.27, 0.86)	0.49 (0.27, 0.87)	0.49 (0.27, 0.88)	0.50 (0.28, 0.88)	0.50 (0.28, 0.89)	0.51 (0.28, 0.90)	0.51 (0.28, 0.91)	0.51 (0.29, 0.91)
	0.80	0.45 (0.25, 0.80)	0.46 (0.26, 0.82)	0.47 (0.26, 0.83)	0.48 (0.26, 0.85)	0.48 (0.27, 0.86)	0.49 (0.27, 0.87)	0.50 (0.28, 0.89)	0.51 (0.28, 0.90)	0.51 (0.28, 0.91)	0.52 (0.29, 0.92)	0.53 (0.29, 0.93)	0.53 (0.29, 0.94)	0.53 (0.30, 0.95)	0.54 (0.30, 0.96)
	0.75	0.45 (0.25, 0.80)	0.46 (0.26, 0.82)	0.48 (0.26, 0.84)	0.48 (0.27, 0.86)	0.49 (0.27, 0.88)	0.50 (0.28, 0.89)	0.52 (0.29, 0.92)	0.53 (0.29, 0.93)	0.53 (0.30, 0.95)	0.54 (0.30, 0.96)	0.55 (0.31, 0.98)	0.56 (0.31, 0.99)	0.56 (0.31, 1.00)	0.57 (0.32, 1.01)
	0.70	0.45 (0.25, 0.80)	0.47 (0.26, 0.83)	0.48 (0.27, 0.86)	0.49 (0.27, 0.88)	0.51 (0.28, 0.90)	0.51 (0.29, 0.91)	0.54 (0.30, 0.95)	0.55 (0.30, 0.97)	0.56 (0.31, 0.99)	0.57 (0.31, 1.01)	0.58 (0.32, 1.03)	0.59 (0.33, 1.04)	0.59 (0.33, 1.06)	0.60 (0.34, 1.07)
	0.65	0.45 (0.25, 0.80)	0.47 (0.26, 0.84)	0.49 (0.27, 0.87)	0.51 (0.28, 0.90)	0.52 (0.29, 0.92)	0.53 (0.29, 0.94)	0.56 (0.31, 0.99)	0.57 (0.32, 1.02)	0.58 (0.32, 1.03)	0.60 (0.33, 1.06)	0.61 (0.34, 1.09)	0.62 (0.35, 1.11)	0.63 (0.35, 1.12)	0.64 (0.36, 1.14)
	0.60	0.45 (0.25, 0.80)	0.48 (0.27, 0.85)	0.50 (0.28, 0.89)	0.52 (0.29, 0.92)	0.54 (0.30, 0.95)	0.55 (0.31, 0.98)	0.58 (0.32, 1.04)	0.60 (0.33, 1.07)	0.61 (0.34, 1.09)	0.63 (0.35, 1.12)	0.65 (0.36, 1.16)	0.66 (0.37, 1.18)	0.68 (0.38, 1.20)	0.69 (0.38, 1.23)
	0.55	0.45 (0.25, 0.80)	0.48 (0.27, 0.86)	0.51 (0.28, 0.91)	0.53 (0.30, 0.95)	0.56 (0.31, 0.99)	0.57 (0.32, 1.02)	0.61 (0.34, 1.09)	0.63 (0.35, 1.13)	0.65 (0.36, 1.16)	0.67 (0.37, 1.19)	0.70 (0.39, 1.24)	0.71 (0.40, 1.27)	0.73 (0.40, 1.29)	0.74 (0.41, 1.32)
	0.50	0.45 (0.25, 0.80)	0.49 (0.27, 0.87)	0.53 (0.29, 0.93)	0.55 (0.31, 0.98)	0.58 (0.32, 1.03)	0.60 (0.33, 1.07)	0.65 (0.36, 1.16)	0.68 (0.38, 1.20)	0.70 (0.39, 1.24)	0.72 (0.40, 1.28)	0.75 (0.42, 1.33)	0.77 (0.43, 1.37)	0.79 (0.44, 1.40)	0.81 (0.45, 1.44)
	0.45	0.45 (0.25, 0.80)	0.50 (0.28, 0.89)	0.54 (0.30, 0.96)	0.58 (0.32, 1.03)	0.61 (0.34, 1.08)	0.63 (0.35, 1.13)	0.69 (0.39, 1.23)	0.73 (0.40, 1.29)	0.75 (0.42, 1.33)	0.78 (0.43, 1.39)	0.82 (0.45, 1.45)	0.84 (0.47, 1.50)	0.86 (0.48, 1.53)	0.89 (0.49, 1.58)
	0.40	0.45 (0.25, 0.80)	0.51 (0.28, 0.91)	0.56 (0.31, 1.00)	0.61 (0.34, 1.08)	0.64 (0.36, 1.14)	0.68 (0.38, 1.20)	0.75 (0.42, 1.33)	0.79 (0.44, 1.40)	0.82 (0.45, 1.45)	0.86 (0.48, 1.52)	0.90 (0.50, 1.60)	0.93 (0.52, 1.66)	0.96 (0.53, 1.70)	0.99 (0.55, 1.76)
	0.35	0.45 (0.25, 0.80)	0.53 (0.29, 0.94)	0.59 (0.33, 1.05)	0.64 (0.36, 1.14)	0.69 (0.38, 1.22)	0.73 (0.40, 1.30)	0.82 (0.46, 1.46)	0.87 (0.48, 1.54)	0.91 (0.50, 1.61)	0.95 (0.53, 1.69)	1.01 (0.56, 1.79)	1.05 (0.58, 1.86)	1.08 (0.60, 1.91)	1.12 (0.62, 1.99)
	0.30	0.45 (0.25, 0.80)	0.55 (0.30, 0.97)	0.63 (0.35, 1.11)	0.69 (0.38, 1.23)	0.75 (0.42, 1.33)	0.80 (0.44, 1.42)	0.92 (0.51, 1.63)	0.98 (0.54, 1.73)	1.02 (0.57, 1.82)	1.08 (0.60, 1.92)	1.15 (0.64, 2.04)	1.20 (0.67, 2.13)	1.24 (0.69, 2.20)	1.29 (0.72, 2.29)
	0.25	0.45 (0.25, 0.80)	0.57 (0.32, 1.02)	0.68 (0.38, 1.20)	0.76 (0.42, 1.35)	0.84 (0.46, 1.49)	0.90 (0.50, 1.60)	1.05 (0.58, 1.87)	1.13 (0.63, 2.00)	1.19 (0.66, 2.11)	1.26 (0.70, 2.24)	1.35 (0.75, 2.40)	1.41 (0.79, 2.51)	1.46 (0.81, 2.60)	1.53 (0.85, 2.72)
	0.20	0.45 (0.25, 0.80)	0.61 (0.34, 1.09)	0.75 (0.42, 1.33)	0.87 (0.48, 1.54)	0.96 (0.54, 1.71)	1.05 (0.58, 1.87)	1.25 (0.69, 2.22)	1.35 (0.75, 2.40)	1.43 (0.80, 2.55)	1.53 (0.85, 2.72)	1.65 (0.92, 2.93)	1.74 (0.96, 3.09)	1.80 (1.00, 3.20)	1.89 (1.05, 3.36)

Supplemental Figure 4



Supplemental Figure 1. CONSORT diagram. Abbreviations: ENKTCL, extranodal nasal-type natural killer/T-cell lymphoma; CLCG, China Lymphoma Collaborative Group; RT, radiotherapy; CT, chemotherapy; CMT, combined-modality therapy; ANT, anthracycline; ASP, asparaginase; PLA, platinum; GEM, gemcitabine.

Supplemental Figure 2. OS, DMFS and LRRFS stratified by chemotherapy regimens in low-risk early-stage patients. OS (A), DMFS (B) and LRRFS (C) of ASP-based regimens vs. non-ASP-based regimens in low-risk patients. Abbreviations: OS, overall survival; DMFS, distant metastasis-free survival; LRRFS, locoregional recurrence-free survival; ASP, asparaginase.

Supplemental Figure 3. Magnitudes of the joint bounding factor for different combinations of the OR_{ASP-U} and the HR_{OS-U} for all early-stage patients and intermediate- to high-risk patients. Columns correspond to increasing imbalance in unmeasured confounders between treatment groups. Rows correspond to increasing adverse effect of unmeasured confounders on overall survival. The entries in the table represent HR (with 95% CI) of ASP-based regimens versus non-ASP-based regimens in presence of unmeasured confounders with a given combination of imbalance (OR_{ASP-U}) and impact on overall survival (HR_{OS-U}). The present sensitivity analysis allows for testing the treatment effect of ASP-based regimens versus non-ASP-based regimens in presence of unmeasured confounders with varying combination of imbalance between treatment groups and impact on overall survival. The HR is

colored as significant (blue), nonsignificant (orange), and reverse treatment effect (red), respectively. Abbreviations: OR, odd ratio; HR, hazard ratio; ASP, asparaginase (L-asparaginase, or pegaspargase).

Supplemental Figure 4. Sensitivity analysis of GDP-ASP vs. GDP. OS (A), DMFS (B) and LRRFS (C) of GDP-L/P vs. GDP in early-stage patients. OS (A), DMFS (B) and LRRFS (C) of GDP-L/P vs. GDP in intermediate- and high-risk early-stage patients. Abbreviations: OS, overall survival; DMFS, distant metastasis-free survival; LRRFS, locoregional recurrence-free survival; GDP (gemcitabine, dexamethasone, cisplatin); ASP, asparaginase (L-asparaginase or pegaspargase); GDP-L (gemcitabine, dexamethasone, cisplatin and L-asparaginase); GDP-P (gemcitabine, cisplatin, dexamethasone, pegaspargase); HR, hazard ratio; CI, confidence interval.