C Subgroup Analysis No. of No. of Hazard Ratio (95% CI) Subgroup Patients Events All patients 529 77 0.35 (0.22-0.56) Eligible patients 498 72 0.32 (0.20-0.51) Sex Female 173 19 0.30 (0.12-0.77) Male 0.40 (0.23-0.67) 356 58 Age <60 yr 314 51 0.32 (0.18-0.56) 26 0.44 (0.20-0.97) ≥60 yr 215 ECOG performance-status score 0.26 (0.14-0.47) 335 46 0.61 (0.29-1.27) 1 or 2 194 31 Rai stage 0.35 (0.18-0.65) 0 to II 301 41 III or IV 228 0.38 (0.19-0.74) 36 Beta, microglobulin level Elevated 265 48 0.26 (0.14-0.48) Normal 259 29 0.56 (0.26-1.20) Splenomegaly 0.36 (0.19-0.70) No 311 39 Yes 218 38 0.32 (0.17-0.63) Lymphadenopathy No 159 16 0.44 (0.14-1.42) Yes 370 61 0.35 (0.21-0.59) Dohner classification Chromosome 11a22.3 deletion 117 22 0.24 (0.10-0.62) Trisomy 12 97 10 0.73 (0.19-2.89) 106 18 0.78 (0.29-2.04) Normal Chromosome 13q deletion 179 19 0.22 (0.08-0.60)

0.12

0.25

0.50

1.00

Ibrutinib-Rituximab Better Chemoimmunotherapy Better

0.44 (0.14-1.36)

0.26 (0.14-0.50)

2.00

4.00

14

41

114

281

IGHV mutation

Yes

No