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Supplemental Materials for

Canadian evidence-based guidelines for the first-line treatment of chronic lymphocytic leukemia

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Supplemental Table 1: Patient Fitness Evaluation

Study	Subgroup analysis
CLL8 **FCR vs FC** **[1]**	• No difference in OS or PFS by age. • Increased grade ¾ toxicities in patients ≥ 65 years • Increased grade ¾ toxicities with moderate/high-grade comorbidity in at least one organ system vs low-grade comorbidity (81% vs 66%; $p < 0.001$)
CLL10 **BR vs FCR** **[2]**	• PFS longer with FCR in patients < 65 years, but not in patients ≥ 65 years. • No difference in PFS between FCR and BR in patients with CIRS 4-6 or > 1 CIRS item. • Increased risk of infection with FCR for patients ≥ 65 years (47.7% vs 20.6%; $p < 0.001$)
CLL4/5 **metaanalysis** **[3]**	• Patients with ≥ 2 comorbidities had shorter median OS than patients with < 2 comorbidities (71.7 months vs 90.2 months; $p < 0.001$); significant in both younger (CLL4) and older (CLL5) patients) • Specific comorbidities predicting overall survival could not be identified • Comorbidities did not influence myelotoxicity, infection or any SAEs. • Doses of study drugs were more frequently reduced in patients with ≥ 2 comorbidities vs < 2 comorbidities (40% vs 31%; $P < 0.05$)
Metaanalysis [4]	• Fludarabine does not confer significant benefit in PFS nor OS to adults ≥ 70 years • A trend toward poorer OS with fludarabine versus chlorambucil in subgroup ≥ 70 years • Addition of rituximab to fludarabine-containing regimens significantly improves both PFS and OS in younger and older patients
FCR **[5, 6]**	• Age ≥ 70 years independently associated with inferior response to FCR • Patients ≥ 70 years less likely to complete 6 cycles of therapy (46% vs 79%; $p < 0.001$) • Dose reductions more common in patients > 60 years • CrCl 30-70mg/ml: more cytopenias, dose reductions and early treatment discontinuations.

Study	Subgroup analysis
F arm of CALGB 9011 [7]	• No association between age (≥ 70 vs < 70 years) and incidence of hematologic toxicity or infection during cycle 1 of treatment • Strong association between CrCl and time-to-toxicity endpoint. • Patients with CrCl < 80 ml/min had increased incidence of toxicity during treatment course (*P* < 0.0001)
BR [8]	• No difference in PFS for patients with CrCl ≥ 70 ml/min vs CrCl < 70 ml/min • No difference in PFS for patients ≥ 70 years vs < 70 years
PCR [9, 10]	• No difference in PFS for patients ≥ 70 years vs < 70 years • No difference in number of treatment cycles, dose reductions, or grade ¾ toxicities for patients ≥ 70 years vs < 70 years • No difference in PFS in patients with CrCl ≥ 70 ml/min vs CrCl < 70 ml/min

BR, bendamustine+rituximab; Clb, chlorambucil; CrCl, Creatinine clearance; F, fludarabine; FC, fludarabine+cyclophosphamide; FCR, fludarabine+cyclophosphamide+rituximab; GCLLSG, German CLL Study Group; OS, overall survival; PCR, pentostatin+cyclophosphamide+rituximab; PFS, progression free survival

Supplemental Table 2: RCTs – First-line Chemotherapy (pre-rituximab)

Reference	Treatment	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[11-13] CALGB 9011	F vs Clb	62 months	Median age: 63 years (32-89) ECOG: 0-2	509	ORR: 63% vs 37%, $p < 0.001$ CR: 20% vs 4%, $p < 0.001$	Median: 20 months vs 14 months, $p < 0.001$ At 4 years: 21% vs 6%, $p < 0.001$	Median: 66 months vs 56 months, $p = 0.1$ At 8 years: 31% vs 19%, $p = 0.07$	All: 55% vs 44% $p = 0.05$ Major infection: 29% vs 17%; $p = 0.008$ Secondary malignancies similar in F vs Clb, except t-MN > in F arm
[14] **LRF CLL4**	FC vs F vs Clb	N/R	Median age: 65 years (35-86)	777	ORR: 94% vs 80% vs 72% $p < 0.0001$ (FC vs F) $p = 0.04$ (F vs Clb) CR: 38 % vs 15% vs 7% $p < 0.0001$ (FC vs F) $p = 0.006$ (F vs Clb)	At 5 years: 36% vs 10% vs 10% $p < 0.00005$ (FC vs F) NS (F vs Clb)	NS	Neutropenia: 56% vs 41% vs 28%, $p < 0.0001$ Admission (> 1day): 38% vs 36% vs 22% $p < 0.0001$ Nausea/vomiting: 53% vs 28% vs 33%, $p < 0.0001$
[15] **NAIT-E2997**	F vs FC	N/R	Median age: 61 years (33-86) PS > 2 ECOG 0-2	278	ORR: 59.5% vs 74.3% $p = 0.013$ CR: 4.6% vs 23.4% $p < 0.001$	Median: 19.2 months vs 31.6 months, $p < 0.0001$	NS	All: 33% vs 50 %, $p = 0.007$ No difference in severe infection

Reference	Treatment	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[16] **GCLLSG-CLL4**	F vs FC	N/R	Age: ≤ 65 years Median age: 58 years ECOG 0-2	375	ORR: 83% vs 94% $p = 0.01$ CR: 7% vs 24% $p < 0.001$	Median: 20 months vs 48 months, $p = 0.001$	At 3 years: 80.7% vs 80.3%, NS	All: 54% vs 72.6%, $p = 0.001$ Myelotoxicity: 40% vs 64%, $p = 0.001$ Leukocytopenia: 26% vs 56%, $p < 0.001$ No difference in rate of infection
[17] **GCLLSG-CLL5**	F vs Clb	N/R	Age: 65-80 years Median age: 70 years ECOG: 0-2	193	ORR: 72% vs 51%, $p = 0.003$ CR: 7% vs 0% $p = 0.01$ TTF: 18 months vs 11 months $p = 0.004$	Median: 18 months vs 19 months, NS	Median: 64 months vs 46 months, NS	Myelotoxicity: 42% vs 23% $p = 0.005$
[18, 19]	Clb vs B	54 months	Age: ≤ 75 years WHO PS: 0-2	319	ORR: 31% vs 68%, $p < 0.0001$ CR: 10.8% vs 21%, p N/R Median TTNT: 10.1 months vs 31.7 months, $p < 0.0001$	Median: 8.8 months vs 21.2 months, $p < 0.0001$ Difference sustained in patients < 65 years and ≥ 65 years	Median: 78.8 months vs NR, NS	Neutropenia: 10.6% vs 23%, p = N/R Leukopenia: 1.3% vs 14.3%, p = N/R

Reference	Treatment	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[20]	F vs CAP vs CHOP	70 months	Age: < 75 Years Median age: N/R	938	ORR: 71% vs 58% vs 71%, *p* < 0.0001 (for F vs CAP and CHOP vs CAP) CR: 40% vs 15% vs 30%, *p* = 0.003 (for F vs CAP and CHOP vs CAP)	Median: 31.7 months vs 27.7 months vs 29.5 months, *p* = 0.09	Median: 69 months vs 70 months vs 67 months, NS	Neutropenia: 38% vs 30% vs 38%, *p* = 0.06 Thrombocytopenia 15% vs7% vs 8%, *p* = 0.003 Alopecia: 0 vs 15% vs 16%, *p* < 0.0001
[21]	Clb+theo vs Clb	48 months (mean)	Median age: Clb+theo: 58 years (44-76) Clb: 61 years (40-74)	210	PR: 35.7% vs 34.9%, *p* = N/R CR: 25.7% vs 12.8%, *p* = 0.01	Median : 44 months vs 30 months , *p* = 0.006	Median : 56 months vs 55 months, *p* = 0.371	Rates of toxicities N/R
[22, 23] PALG-CLL2	2-CdA vs 2-CdAC vs 2-CdACM	N/R	Median age: 2-CdA: 61 years (28-81) 2-CdAC: 62 years (28-80) 2-CdACM: 59 (33-79) WHO-PS <4	508	ORR: 78% vs 83% vs 80%, *p* = 0.1 (2-CdA vs 2-CdAC), *p* = 0.4 (2-CdA vs 2-CdACM) CR: 21% vs 29% vs 36%, *p* = 0.08 (2-CdA vs 2-CdAC), *p* = 0.004 (2-CdA vs 2-CdACM)	Median: 23.5 months vs 22.4 months vs 23.6 months, *p* = 0.49	Median: 51.2 months vs NR vs NR, *p* = 0.73	Neutropenia: 20% vs 32% vs 38%, *p* = 0.01 (2-CdA vs 2-CdaC) *p* = 0.004 (2-CdA vs 2-CdACM)

Reference	Treatment	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[24]	2-CdAP vs ClbP	N/R	Median age: 2-CdA+P: 61 years (31-92) Clb+P: 62 years (31-88) WHO-PS <4	229	ORR: 87% vs 57%, *P* = 0.0001 CR: 47% vs 12%, *p* = 0.0001	At 24 months: 46% vs 33% *p* = 0.01	At 24 months: 78% vs 82%, *p* = 0.6	Neutropenia (all): 23% vs 11%, *p* = 0.02 Infection (all): 56% vs 40%, *p* = 0.02
[25] PALG-CLL3	2-CdAC vs FC	38 months	Median age: 2-CdAC: 58 years (37-81) FC: 59 years (27-81) WHO-PS <4	395	ORR: 88% vs 82%, *p* = 0.11 CR: 47% vs 46% *p* = 0.25	Median: 2.34 years vs 2.27 years, *p* = 0.51	4-year estimate: 62.4% vs 60.6%, *p* = 0.16	Neutropenia: 20% vs 21%, *p* = 0.81 Thrombocytopenia: 12% vs 11%, *p* = 0.62 Infections: 28% vs 27%, *p* = 0.84
[26] CAM307	A vs Clb	24.6 months	Median age: A: 59 years (35-86) Clb: 60 years (36-83) WHO PS 0-2	297	ORR: 83% vs 55%, *p* < 0.0001 CR: 24% vs 2%, *p* < 0.0001	HR: 0.58, 95% CI (0.43-0.77) *p* = 0.0001	Median: NR vs NR	Infusion-related: 15.7% vs 0

2-CdA, cladribine; 2-CdAC, cladribine+cyclophosphamide; 2-CdACM, cladribine+cyclophosphamide+mitoxantrone; 2-CdAP, cladribine+prednisone; A, alemtuzumab; B, bendamustine; CAP, cyclophosphamide+prednisone+doxorubicin; CHOP, cyclophosphamide+vincristine+prednisone+doxorubicin; Clb, chlorambucil; Clb+theo, chlorambucil+theophylline; ClbP, chlorambucil+prednisone; CR, complete response rate; F, fludarabine; FC, fludarabine+cyclophosphamide; GCLLSG, German CLL Study Group; N/R, not reported; NR, not reached; NS, not significant; Ob, obinutuzumab; Obs, observation; Of, ofatumumab; ORR, overall response rate; OS, overall survival; PC, pentostatin+cyclophosphamide; PCOf, pentostatin+cyclophosphamide+ofatumumab; PCR, pentostatin+cyclophosphamide+rituximab; PFS, progression free survival; PR, partial response rate RCT, randomized controlled trial; Theo, theophylline

Supplemental Table 3: Phase II Studies – First-line Therapy

Chemoimmunotherapy								
Reference	**Treatment**	**Median Follow up**	**Patients**	**N**	**Response**	**PFS**	**OS**	**Toxicity (Grade ≥ 3)**
[5, 6, 27]	FCR	12.8 years	Median age: 57 years (17-86)	300	ORR: 95% CR: 72%	Median: 6.4 years At 12.8 years: 30.9%	Median: 12.7 years At 6 years: 77%	Neutropenia:52% Infection:2% 2nd cancers in 101 patients
[28, 29]	FCR-lite	N/R	Median age: 58 (36-85)	63	ORR : 93% CR : 73%	At 5 years : 66.9%	At 5 years : 85.5%	Infection: 6% MDS: 3 patients
[30]	FCR-lite+Len	17.4 months	Median age: 62.5 years (42-75) ECOG 0-2	20	ORR: 90% CR: 75%	At 17.4 months: 95%	At 17.4 months: 95%	Leukopenia: 20.3% Neutropenia: 51.6%
[31]	FCR + GM-CSF	56 months	Median age: 55 years (35-77) ECOG 0-2	60	ORR: 100% CR: 75%	Median: NR	Median: NR	Neutropenia: 83% Infection: 16%
[32]	FCR-M	38.5 months	Age: < 70 years ECOG 0-2	30	ORR: 93% CR: 83%	Median: NR	Median: NR	Neutropenia: 67% No infection requiring hospitalization
[33]	FCR-A	25 months	Median age: 59 years (42-69)	60	ORR: 92% CR: 70%	Median: 38 months	Median: NR	Neutropenia: 33% Infection: 11%
[34]	FER	34 months	Median age: 65	38	ORR: 95% CR: 63%	Median: 61 months	Median:NR	Neutropenia: 56% No infection (grade ≥ 3)
[35, 36]	FR-con FR-seq	117 months	Median age: 65 years (36-86) CALGB PS ≤3	104	ORR: FR-con:90% FR-seq:77% CR: FR-con:33% FR-seq:15%	At 5 years (all): 28% Median (all): 42 months	At 5 years (all): 71% Median (all): 85 months	Neutropenia: 76% vs 39%

Reference	Treatment	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[37]	FA	nr	Age ≤ 60 years Presence of high-risk genetic features	45	ORR: 95% CR: 30%	At 3 years: 42.5%	At 3 years: 79.9%	Neutropenia: 33% Infection: 11%
[9, 10]	PCR	26 months	Median age: 63 years (38-80) ≥ 70 years: 28% ECOG ≤3	64	ORR: 91% CR: 41%	Median: 32.6 months	Median: NR	All: 55% Neutropenia:44%
[38]	PCOf	24 months	Median age: 65 (50-83) ECOG ≤2	48	ORR: 96% CR: 46%	At 24 months: 89%	Median: NR	Hematologic toxicity: 27% Nonhematologic toxicity: 23%
[39]	PCOf	22 months	Age ≥ 65 Median age: 72 years (65-83) ECOG 0-2 CIRS ≤ 6 CrCl ≥ 70 ml/min	47	ORR: 89.4% CR: 51.1%	Median: NR At 24 months: 69%	Median: NR At 24 months: 97.9%	Neutropenia: 53.2% Hospitalization: 6.4%
[40]	P+R	14 months	Median age: 65 (45-81) ECOG ≤3	33	ORR: 76% CR: 27%	24 months: 89%	Median: NR	Hematologic toxicity: 12% Nonhematologic toxicity: 15%
[8]	BR	27 months	Median age: 64 years (34-78) ECOG ≤2	117	ORR: 88% CR: 23%	Median EFS: 33.9 months	Median: NR At 27 months: 90.5%	Hematologic toxicity: 52.1% Nonhematologic toxicity: 41.6%
[41]	ClbR	30 months	Median age: 70 years (43 to 86) Median no. of comorbidities: 7 (0-20)	100	ORR: 84% CR: 10%	Median: 23.5 months	Median: NR At 30 months: 84%	Neutropenia and lymphopenia: 41% Leukopenia: 23% Anemia: 19% Thrombocytopenia: 18%

Monoclonal Antibody therapy

Reference	Treatment	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[42]	R+GM-CSF	79 months	Age: ≥ 70 years	40	ORR: 59%	Median: 15 months	At 7 years: 67%	2 patients experienced serious infection
[43]	Ob (1000) Ob (2000)	20.3 months	Median age: 67 years (34-91) ECOG ≤ 2	80	ORR: 49% vs 67% $p = 0.08$ CR: 5% vs 20% $p < 0.05$	At 18 months: 59% vs 83%	Median: NR	All: 55.0% vs 65% Neutropenia: 30% vs 31.6%
[44]	AR-st AR-lo	24.6 months	Median age: 76 years (67-92) ECOG ≤ 2	25	ORR: 90% CR: 45%	Median: AR-st:12.8 months AR-lo:23.3 months	Median: NR	Neutropenia: AR-st:75% AR-lo:47% $p = 0.15$
[45]	AR	58.3 months	Median age: 58 years (28-80) ECOG ≤ 2	30	ORR: 70% CR: 23%	At 58.3 months: 80%	Median: NR	Neutropenia: 30%

Lenalidomide

Reference	Treatment	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[46, 47]	Len	48 months	Age ≥ 65 Median age: 71 years (65-84) ECOG 0-3	60	ORR: 65% CR: 15%	At 2 years: 60% Median: NR	At 4 years: 82%	Neutropenia: 88% Thrombocytopenia: 47% Severe infection: 13% 1 fatality
[48, 49]	Len	53.2 months	Median age: 60 years (33-78) ECOG 0-3	25	ORR: 72% CR: 20%	At 3 years: 64.6% Median: 40.4 months	At 3 years: 85.3%	Neutropenia: 72% Thrombocytopenia: 28% Severe infection: 36%

Reference	Treatment	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[50]	Len+R	20 months	Arm A: < 65 years Median: 57 years (45-64) Arm B: ≥ 65 years Median: 70 years (65-80) ECOG 0-2	Arm A: 40 Arm B: 29	Arm A: ORR: 95% CR: 20% Arm B: ORR: 79% CR: 10%	Arm A median: 19 months Arm B median: 20 months	Median: NR	Neutropenia: Arm A: 53% Arm B: 66%

A, alemtuzumab; AR, alemtuzumab+rituximab; BR, bendamustine+rituximab; ClbR, chlorambucil+rituximab; CR, complete response rate; CrCl, Creatinine clearance; FCA, fludarabine+cyclophosphamide+alemtuzumab; FCR, fludarabine+cyclophosphamide+rituximab; FR, fludarabine+rituximab; GM-CSF, granulocyte macrophage colony stimulating factor; Len, lenalidomide; Len+R, lenalidomide+rituximab; N/R, not reported; NR, not reached; NS, not signifiacnt Ob, obinutuzumab; Obs, observation; ORR, overall response rate; OS, overall survival; PC, pentostatin+cyclophosphamide; PCOf, pentostatin+cyclophosphamide+ofatumumab; PCR, pentostatin+cyclophosphamide+rituximab; PFS, progression free survival; P+R, pentostatin+rituximab

Supplemental Table 4: RCTs - Maintenance Drug Therapy After First-line Treatment

Reference	Induction Therapy	Maintenance Therapy	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[51]	FCR (71%) BR (21%) Other (8%) First-line (80%) Second-line (20%)	R (maint) vs Obs	33.4 months	Median age: 63 years (35-85) ECOG 0-1 CR, Cri, or PR after induction	263	Conversion of PR to CR or Cri: 13% vs 2%	Median: 47.0 months vs 35.5 months *p* = 0.00077 Median TNT: NR vs 47.3 months P=0.0051	NR	Neutropenia: 21% vs 11% Infection: 20% vs 8%

Reference	Induction Therapy	Maintenance Therapy	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[52] (Abstract)	FCR (4 cycles)	R (maint) vs Obs	43.6 months	Age ≥ 65 years; Median age: 71.3 years Fit, no del(17p) PR or CR after induction	409	N/R	Median: 59.3 months vs 49.0 months *p* = 0.0011 At 3 years: 83.0% vs 64.2%	At 3 years: 92.6% vs 87.2%	Hematological toxicity: 6.9% vs 1.9% *p* = 0.027 Infections: 18.8% vs 10.1% *p* = 0.036
[53]	FCR, BR, or FC	Len (maint) vs Obs	17.9 months (Recruitment closed prematurely due to poor accrual)	Median age: 64 years (57-69) High risk: ≥ intermediate MRD + IGHV-U or TP53 aberration CR, Cri, or PR after induction	85	MRD status at cycle 12: Negative (7% vs 0); Intermediate (48% vs 22%); Positive (44% vs 78%)	Median: NR vs 13.3 months	NE	Neutropenia: 34% vs 6% GI disorders: 13% vs 0 Infections: 15% vs 9%

BR, bendamustine+rituximab; Con, consolidation; CR, complete response rate; Cri, complete response with incomplete blood count recovery; FCR, fludarabine+cyclophosphamide+rituximab; IGHV-U, unmutated IGHV gene; Len, lenalidomide; Maint, maintenance; MRD, minimal residual disease; N, number of patients; N/R, not reported; NE, not evaluable; NR, not reached; Obs, observation; ORR, overall response rate; OS, overall survival; PCOf, pentostatin+cyclophosphamide+ofatumumab; PFS, progression free survival; PR, partial response rate; R, rituximab; TFS, treatment-free survival

Supplemental Table 5: Phase II Studies – Maintenance and/or Consolidation Drug Therapy After First-line Treatment

Reference	Induction Therapy	Maintenance Therapy	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[54, 55]	FCR-M	R (maint)	48.7 months	Median age: 60 (35-70) CR or PR after induction	64	CR (MRD-neg): 40.6% CR (MRD-pos): 40.6% PR: 4.8% TF: 14% Improved response: 21%	At 4 years: 74.8% Median: NR	At 4 years: 93.7% Median: NR	2 deaths due to adverse events Serious infection: 25%
[56]	FR	R (con + maint) vs Obs	26 months	Median age: 60 (35-70) CR or PR (MRD-pos) after induction: R or Obs MRD-neg: Obs	71 MRD-pos:28 R vs 18 Obs MRD-neg: 25 Obs	N/R	At 5 years: 87% vs 32% $p = 0.001$	At 5 years: 90% for all patients	Few SAEs
[57]	ClbR	R (maint) vs Obs	34.9 months	Age ≥ 60 Median age: 70 (61-84) CR, CRi or PR after induction	66 randomized to R or Obs post-induction	ORR: 55.9% vs 34.4% P= 0.079 (Among 50 PR/nPR randomized after induction, ORR: 56.7% vs 26.7% $p = 0.027$)	Median: 38.2 vs 34.7 months At 3 years: 48.6% vs 31.8% $p = 0.07$	N/R	SAEs equal across both arms; only one R-related event (neutropenia)

Reference	Induction Therapy	Maintenance Therapy	Median Follow up	Patients	N	Response	PFS	OS	Toxicity (Grade ≥ 3)
[58]	FR (4 cycles)	A (con)	41 months	Median age: 60 (40-80) Rai II-IV requiring treatment ECOG 0-2	34 started Ale, only 20 completed prescribed dose	ORR: 76% CR: 21%	Median: 42 months At 4 years: 47%	At 4 Years: 82%	Neutropenia: 12% Thrombocytopenia: 9% Infusion-related: 21% Infection: 21%
[59, 60]	FR	A (con)	36 months	CR, PR or SD after induction	58 received A consolidation	ORR: 90% CR: 57% 61% of patients achieving PR after induction attained CR after A; 42% became MRD-neg	Median: 36 months 2 years: 72%	2 years: 86%	7 patient deaths due to infection following A consolidation
[61]	PCOf	Of (con)	33 months	ECOG 0-2 CR or PR after induction	28	ORR: 96% CR:32% 25% had improvement in depth of response after Of con	Median TFS: NR TFS at 36 months: 84%	N/R	2 deaths due to sepsis Neutropenia: 42% Infection: 6%
[62]	PCR	Len (con)	37 months		34 initiated Len consolidation	24% improved response with Len CR: 38.3 after induction to 52.99 after Len	Median TFS: NR TFS at 37 months: 75%	At 37 months : 86.4%	Hematologic toxicity : 65%

A, alemtuzumab; ClbR, chlorambucil+rituximab; Con, consolidation; CR, complete response rate; Cri, complete response with incomplete blood count recovery; FCR-M, fludarabine+cyclophosphamide+rituximab+mitoxantrone; FR, fludarabine+rituximab;
Len, lenalidomide; Maint, maintenance; N, number of patients; N/R, not reported; NR, not reached; Obs, observation; Of, ofatumumab; ORR, overall response rate; OS, overall survival; PCOf, pentostatin+cyclophosphamide+ofatumumab; PFS, progression free survival; PR, partial response rate; R, rituximab; TFS, treatment-free survival

Supplemental Table 6: RCTs – Autologous Transplant After First-line Treatment

Reference	Patients	Treatment	N	EFS	OS	Toxicity (Grade ≥ 3)
[63]	1st and 2nd line, response after induction	After 1st or 2nd line treatment (various): Obs vs ASCT	223	5 years: 24% vs 42% $p < 0.001$	5 years: 84.3% vs 85.5% NS	Low rates of grade3/4 toxicity in each group
[64]	1st line, CR after induction	CHOP/F -> Obs vs CHOP/F -> ASCT	105	3 years: 35.5% vs 79.8% $p = 0.003$	3 years: 97.8% vs 95.7% NS	Low rates of grade3/4 toxicity in each group
[64]	1st line, PR after induction	CHOP/F -> DHAP -> FC vs CHOP/F -> DHAP -> ASCT	94	3 years: 48.9% vs 44.4% NS	3 years: 87.0% vs 81.7% NS	Low rates of grade3/4 toxicity in each group
[65]	1st line, CR after induction	CHOP + CHOP maintenance vs CHOP + ASCT	82	Median: 22 vs 53 months $p < 0.0001$	Median: 104.7 months vs 107.4 months NS	Secondary malignancies: 15% vs 13% Infection: 11.5% vs 34.5% (1 fatal) p = N/R
[66]	< 65 years Binet Stage B or C 1st line treatment + con/maint	FCR + R maintenance vs FCR + (HDT + ASCT)	96	5 years: 65.1 months vs 60.4 months NS	5 years: 88.1% vs 88% NS	Bacterial infection: 19% vs 35.4% $p = 0.067$ Treatment related deaths: 6% vs 6%

ASCT, autologous stem cell transplant; CHOP, cyclophosphamide+vincristine+prednisone+doxorubicin; Con, consolidation; CR, complete response rate; EFS, event-free survival; FCR, fludarabine+cyclophosphamide+rituximab; HDT, high-dose therapy; Maint, maintenance; N/R, not reported; NS, not significant; Obs, observation; OS, overall survival; PR, partial response rate RCT, randomized controlled trial.

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