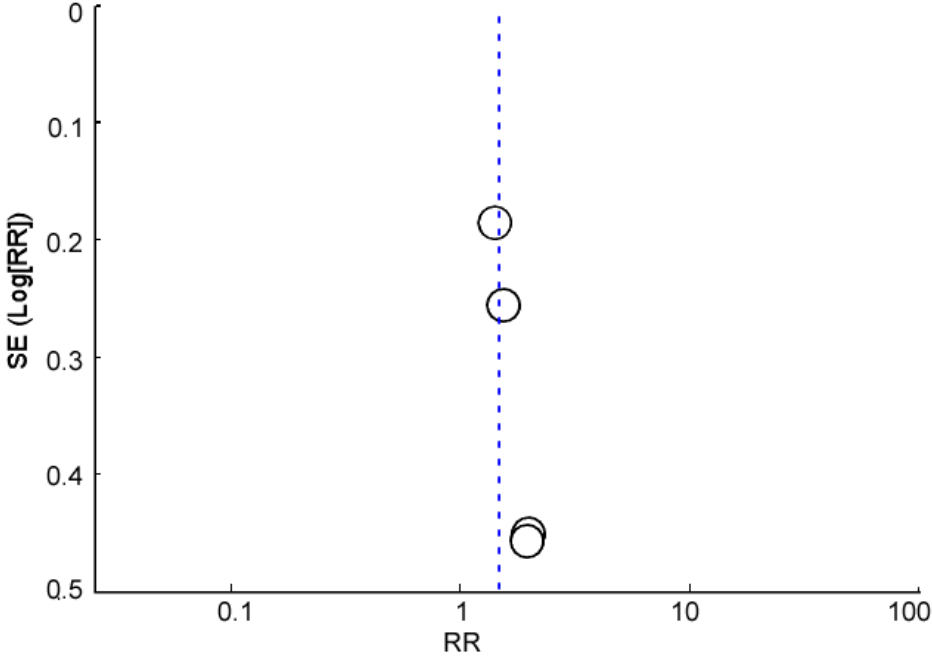


**Supplementary Information for
Outcome Comparison of Allogeneic vs. Autologous Stem Cell Transplantation
in Transformed Low Grade Lymphoid Malignancies: A Systematic Review
and Pooled-Analysis of Comparative Studies**

Seongseok Yun MD, PhD, Nicole D. Vincelette PhD, Ivo Abraham PhD, Soham Puvvada MD,
Faiz Anwer MD

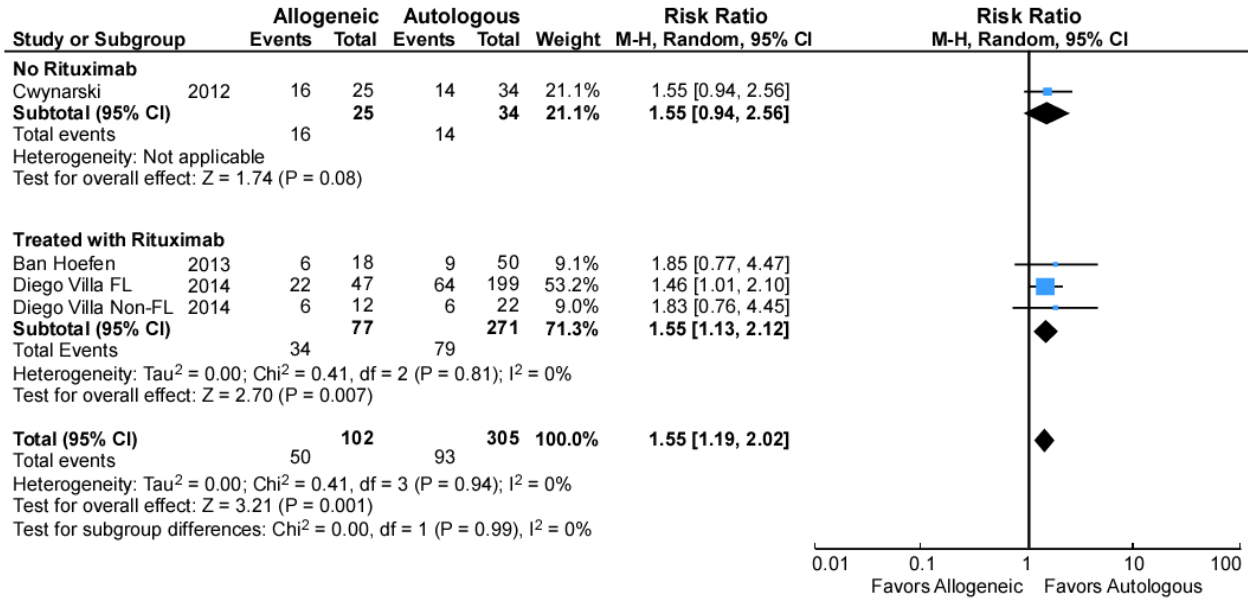
Supplementary Figure 1: Funnel Plot in OS Analysis



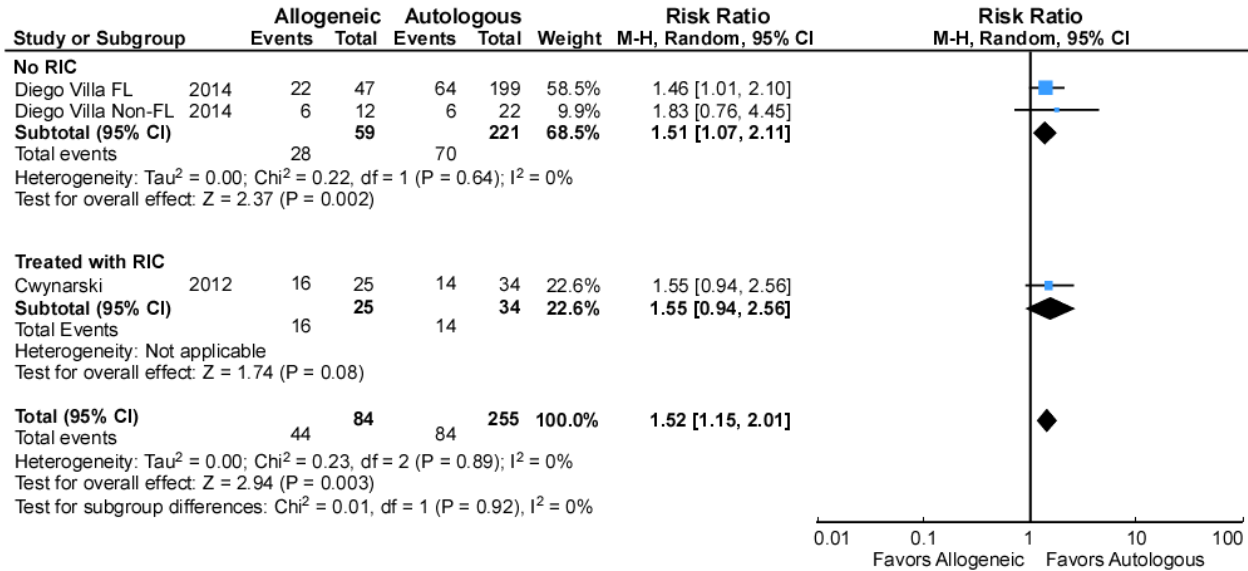
Funnel plot to evaluate the evidence of publication bias.

Supplementary Figure 2: Subgroup Analysis of OS

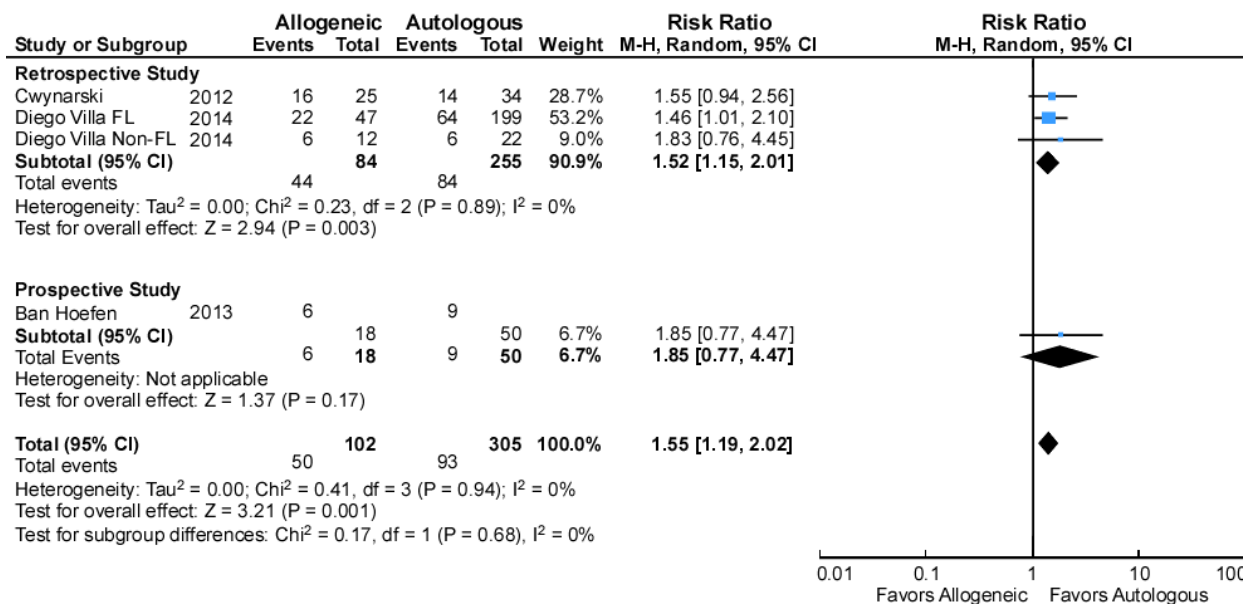
S2A: Rituximab Treatment



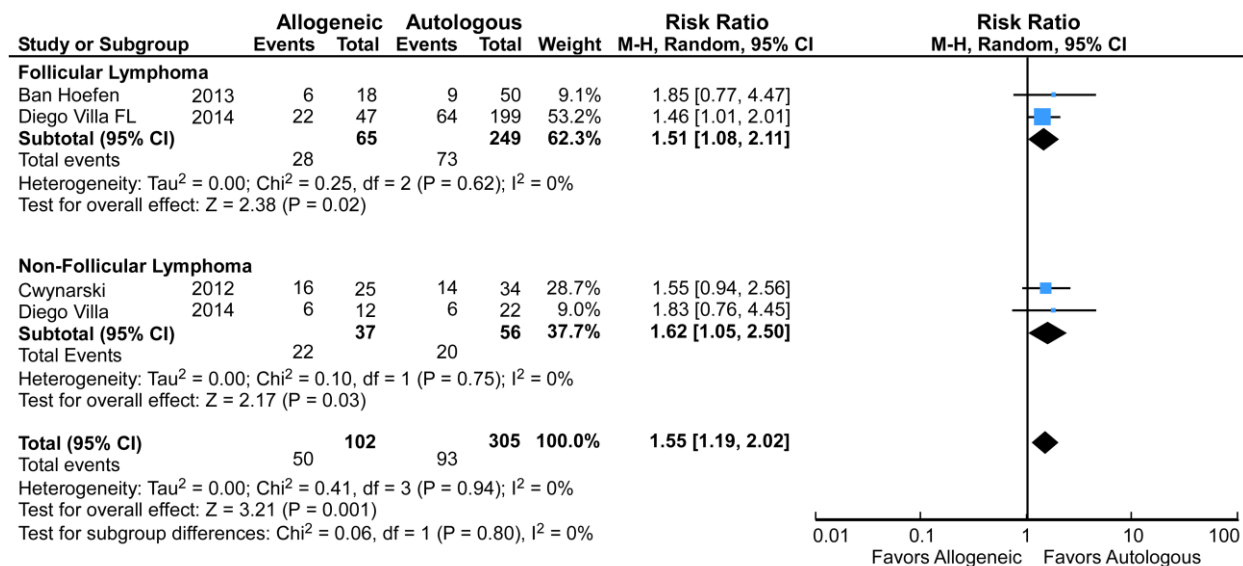
S2B: Reduced Intensive Conditioning



S2C: Study design



S2D: Pathology of initial diagnosis



Forest plots of risk ratios for OS rate from all available data. The size of the data markers (square) corresponds to the weight of the study in the pooled analysis. The effects of interventions are calculated with the random effects model.

Supplementary Table 1: Search Detail in PubMed, EMBASE and Cochrane Database of Systematic Review

Study	Search strategies	No. of Results
PubMed	("allogeneic"[All Fields] OR "autologous" [All Fields]) AND ("low grade lymphoma" [All Fields] OR "indolent lymphoma" [All Fields] OR "chronic lymphocytic leukemia" [All Fields] OR "Transformed" [All Fields]) AND ("controlled" [All Fields] OR "comparative" [All Fields] OR "case" [All Fields]) AND ("0001/01/01"[PDAT]: "2015/10/15"[PDAT]) AND ("humans" [MeSH])	379
EMBASE	<ol style="list-style-type: none"> 1. 'allogeneic' AND 'autologous' AND 'stem cell transplantation' 2. AND ('indolent lymphoma' OR 'low grade lymphoma' OR ' follicular lymphoma' OR 'chronic lymphocytic leukemia' OR 'non Hodgkin lymphoma')/de 3. AND 'transformation' OR 'transformed' 4. AND 'human'/de 	<ol style="list-style-type: none"> 1. 7,573 2. 1,070 3. 102 4. 91
Cochrane Database of Systematic Review	<ol style="list-style-type: none"> 1. 'indolent lymphoma' OR 'low grade lymphoma' OR 'non-Hodgkin lymphoma' 2. 'allogeneic' AND 'autologous' AND 'stem cell transplant' 	<ol style="list-style-type: none"> 1. 1889 2. 241

Initial literature search was performed on 6/30/2014 and search results were lastly updated on 10/15/2015.

Supplementary Table 2: Additional Characteristics of Comparative Studies

Study	Inclusion/exclusion criteria	Pre-SCT chemosensitivity†		Median time from Dx to SCT		Supportive Care	GVHD Prophylaxis	Stem cell source		Purging
		Allo SCT (%)	Auto SCT (%)	Allo SCT (Range)	Auto SCT (Range)			Allo SCT (%)	Auto SCT (%)	
Cwynarski, K. (2012) ¹	CLL with transformation. Age > 18	Sensitive: 16 (60) Resistant: 9 (36) Unknown: 1 (4)	Sensitive: 28 (82) Resistant: 3 (9) Unknown: 3 (9)	N/A	N/A	N/A	ATG Alemtuzumab	BM 2 (8) PBSC 23 (92)	BM 1 (3) PBSC 33 (97)	N/A
Villa, D.‡ (2013) ²	FL (grade I, II and IIIA) with transformation. Age 18-65 at transformation. Prior autologous SCT in allogeneic SCT was allowed (n=2). Exclude discordant or composite histology.	Sensitive: 18 (82) Resistant: 4 (18)	Sensitive: 83 (86) Resistant: 14 (14)	5 (1-18)	5 (0.6-26)	Standard care per individual institutional protocol.	CsA + MTX CsA + MMF FK + MMF FK + MTX CsA only Antithymocyte	BM: 4 (18) PBSC: 17 (77) Cord: 1 (5)	BM: 6 (6) PBSC: 91 (94)	N/A
Ban-Hoefen M. (2013) ³	Indolent lymphoma. Biopsy proven transformation to DLBCL more than 6 months from initial diagnosis of indolent NHL. Excluded grade 3b FL, discordant histology, patients who had prior SCT before transformation.	Sensitive: 12 (67) Resistant: 5 (28) Unknown: 1 (6)	Sensitive: 39 (78) Resistant: 2 (4) Unknown: 9 (18)	188 day (75-565)	174 day (63-1900)	N/A	N/A	N/A	N/A	N/A
Villa, D. (2014) ⁴	Indolent lymphoma with transformation. (65 % of auto SCT was performed as an upfront treatment, 35 % was performed in a relapsed setting).	Sensitive: 10 (85) Resistant: 2 (16)	Sensitive: 22 (100) Resistant: 0 (0)	N/A	N/A	Followed individual institution standards	CsA + MTX CsA + MMF Antithymocyte	BM 8 (67) PBSC 4 (33)	BM 0 (0) PBSC 22 (100)	N/A
Villa, D. (2014) ⁴	Transformed FL	Sensitive: 216 (88) Resistant: 30 (12) N/D	Sensitive: 216 (88) Resistant: 30 (12) N/D	N/A	N/A	Followed individual institution standards	N/A	BM 29 (12) PBSC 215 (87) Cord 2 (1) N/D	BM 29 (12) PBSC 215 (87) Cord 2 (1) N/D	N/A

† Pre-SCT chemosensitive: chemosensitive disease is defined as at least partial remission with induction or salvage chemotherapy. Chemoresistant disease is defined as either stable or progressing disease with induction or salvage chemotherapy. Response was assessed following the 1999 international working group criteria^{5,6}

‡ Data from patients with FL in this study was reused in study performed by Villa, D. *et al.* in 2014. Overall survival, treatment related mortality and relapse rates were analyzed with most updated data which are available.

Abbreviations: chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), stem cell transplantation (SCT), diffuse large B cell lymphoma (DLBCL), anti-thymocyte globulin (ATG), methotrexate (MTX), cyclosporine (CsA), tacrolimus (FK), mycophenolate mofetil (MMF), methylprednisolone (MEP), bone marrow (BM), peripheral blood stem cell (PBSC), no separate report about clinical characteristics between allogeneic and autologous SCT (N/D)

Supplementary Table 3: Risk of Bias Assessment of Prospective Studies According to Cochrane Risk Bias Assessment Tool ⁷

Study	Database	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other Source of Bias †
Ban-Hoefen M. (2013) ³	NCCN NHL	Inadequate (non-randomized)	Inadequate	Inadequate	Inadequate	1. No PFS report 2. No relapse rate report 3. TRM f/u duration unknown	Biased baseline population characteristics

† Other source of bias was evaluated according to the Cochrane risk of bias assessment tool⁷.

‡ Assigned to treatment arm based on the availability of an HLA compatible sibling donor.

Abbreviation: NCCN NHL (National Comprehensive Cancer Network Non-Hodgkin Lymphoma), PFS (progression free survival), TRM (treatment related mortality).

Supplementary Table 4: MOOSE Checklist for the Retrospective Studies ⁸

Study	Background †	Search strategy ‡	Methods	Results	Discussion	Conclusion
Cwynarski, K. (2012) ¹	Hypothesis: clear Study outcomes: adequate Intervention used: allogeneic/autologous SCT Study design: cohort study	Qualifications of search: Investigators Search strategy/database/registry: EBMT Search software: Unclear Use of hand searching: Unclear	Documentation of data classification and coding: Adequate Assessment of confounding: adequate Assessment of study quality: not performed Assessment of heterogeneity: not performed Description of statistical methods: Adequate (Multivariate Cox proportional hazards regression analysis for confounding factors evaluation)	Graphic/table: adequate Subgroup analysis: not performed Indication of statistical uncertainty of findings: adequate	Bias assessment: performed Justification for exclusion: yes	Alternative explanations for observed results: yes (RS may arise through a transformation for the original CLL clone or new/secondary neoplasm) Generalization of the conclusion: yes Guidelines for future research: yes Disclosure of funding source: no
Villa, D. (2013) ²	Hypothesis: clear Study outcomes: missing data for relapse rate Intervention used: allogeneic/autologous SCT/rituximab containing CTx Study design: cohort study	Qualifications of search: Investigators Search strategy/database/registry: CBMTG Search software: Unclear Use of hand searching: Unclear	Documentation of data classification and coding: adequate Assessment of confounding: adequate Assessment of study quality: not performed Assessment of heterogeneity: not performed Description of statistical methods: adequate (Multivariate Cox proportional hazards regression for survival analysis)	Graphic/table: adequate Subgroup analysis: not performed Indication of statistical uncertainty of findings: adequate	Bias assessment: performed Justification for exclusion: yes	Alternative explanations for observed results: yes (prior rituximab treatment) Generalization of the conclusion: yes Guidelines for future research: yes Disclosure of funding source: Canadian Blood and Marrow Transplant Group Small budget Research Grant
Villa, D. (2014) ⁴	Hypothesis: clear Study outcomes: missing data for relapse rate Intervention used: allogeneic/autologous SCT Study design: cohort study	Qualifications of search: Investigators Search strategy/database/registry: International multicenter cohort Search software: Unclear Use of hand searching: Unclear	Documentation of data classification and coding: adequate Assessment of confounding: not performed Assessment of study quality: not performed Assessment of heterogeneity: not performed Description of statistical methods: adequate	Graphic/table: adequate Subgroup analysis: not performed Indication of statistical uncertainty of findings: adequate	Bias assessment: performed Justification for exclusion: yes	Alternative explanations for observed results: yes (prior rituximab treatment) Generalization of the conclusion: yes Guidelines for future research: yes Disclosure of funding source: 2010 Canadian Blood and Marrow Transplant Group Small Budget Research Grant

† Study population is described in table 1.

‡ Search strategy including time period, inclusion and exclusion criteria is described in table 1 and 2.

Abbreviation: CBMTG (Canadian Blood and Marrow Transplant Group), EBMT (European Group for Blood and Marrow Transplantation), CTx (chemotherapy), SCT (stem cell transplant), RS (Richter's syndrome), CLL (chronic lymphocytic leukemia).

Reference

1. Cwynarski K, van Biezen A, de Wreede L, Stilgenbauer S, Bunjes D, Metzner B *et al.* Autologous and allogeneic stem-cell transplantation for transformed chronic lymphocytic leukemia (Richter's syndrome): A retrospective analysis from the chronic lymphocytic leukemia subcommittee of the chronic leukemia working party and lymphoma working party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol* 2012; **30**(18): 2211-2217. doi: 10.1200/JCO.2011.37.4108
2. Villa D, Crump M, Panzarella T, Savage KJ, Toze CL, Stewart DA *et al.* Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. *J Clin Oncol* 2013; **31**(9): 1164-1171. doi: 10.1200/JCO.2012.44.0693
3. Ban-Hoefen M, Vanderplas A, Crosby-Thompson AL, Abel GA, Czuczman MS, Gordon LI *et al.* Transformed non-Hodgkin lymphoma in the rituximab era: analysis of the NCCN outcomes database. *Br J Haematol* 2013; **163**(4): 487-495. doi: 10.1111/bjh.12570
4. Villa D, George A, Seymour JF, Toze CL, Crump M, Lee C *et al.* Favorable Outcomes from Allogeneic and Autologous Stem Cell Transplantation for Patients with Transformed Nonfollicular Indolent Lymphoma. *Biol Blood Marrow Transplant* 2014. doi: 10.1016/j.bbmt.2014.07.015
5. Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH *et al.* Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* 2003; **21**(24): 4642-4649. doi: 10.1200/JCO.2003.04.036
6. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM *et al.* Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999; **17**(4): 1244.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62**(10): 1006-1012. doi: 10.1016/j.jclinepi.2009.06.005
8. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis

Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**(15): 2008-2012.