The Role of SCT in the Treatment of MZL

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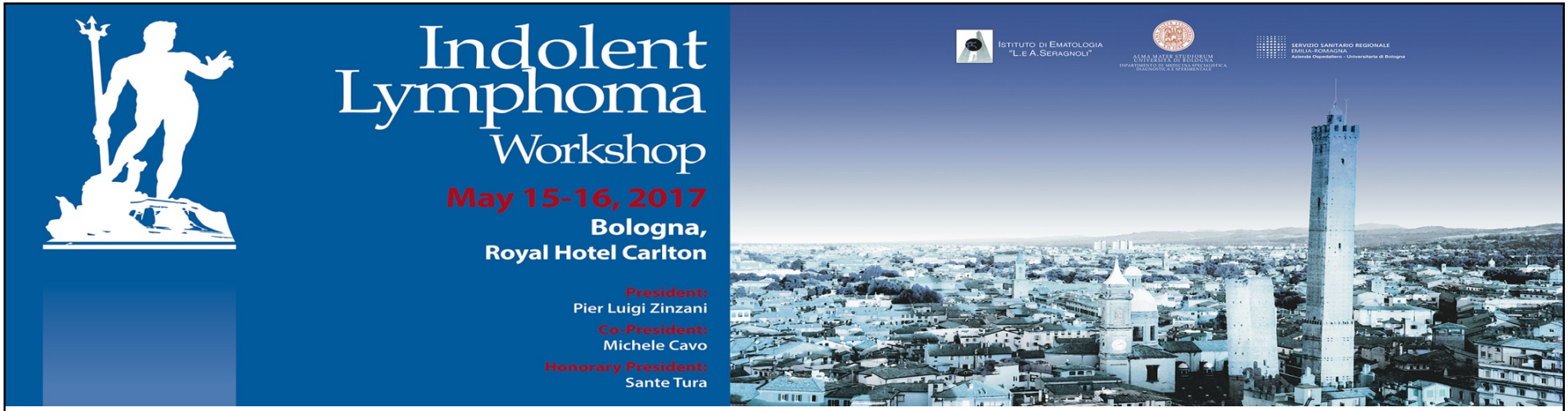


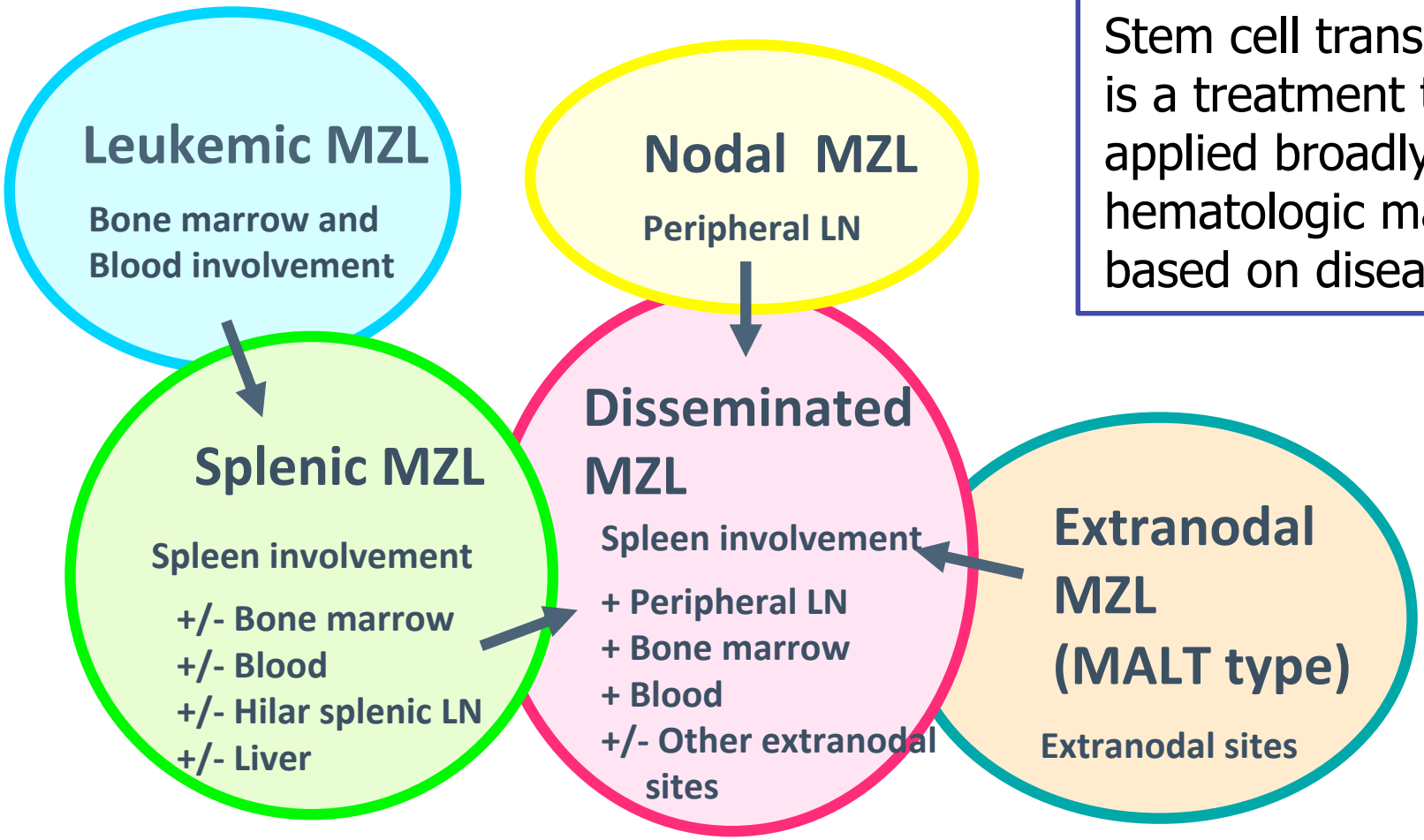
Disclosures of John Kuruvilla

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			X			X	
BMS			X			X	
Janssen	X		X			X	
Merck			X			X	
Roche	X		X			X	
Gilead			X			X	
Seattle Genetics			X			X	

Objectives – Role of SCT in MZL

- Highlight approach to SCT in lymphoma
- Review available data of SCT in MZL
- Propose a strategy for use of SCT in MZL

MZL is a group of related entities



Stem cell transplantation is a treatment that is applied broadly across hematologic malignancies based on disease risk

Thieblemont, *Lancet Oncology* 2004

A MALT lymphoma-specific prognostic index generated from the IELSG-19 dataset

Generation of a MALT lymphoma-specific prognostic model

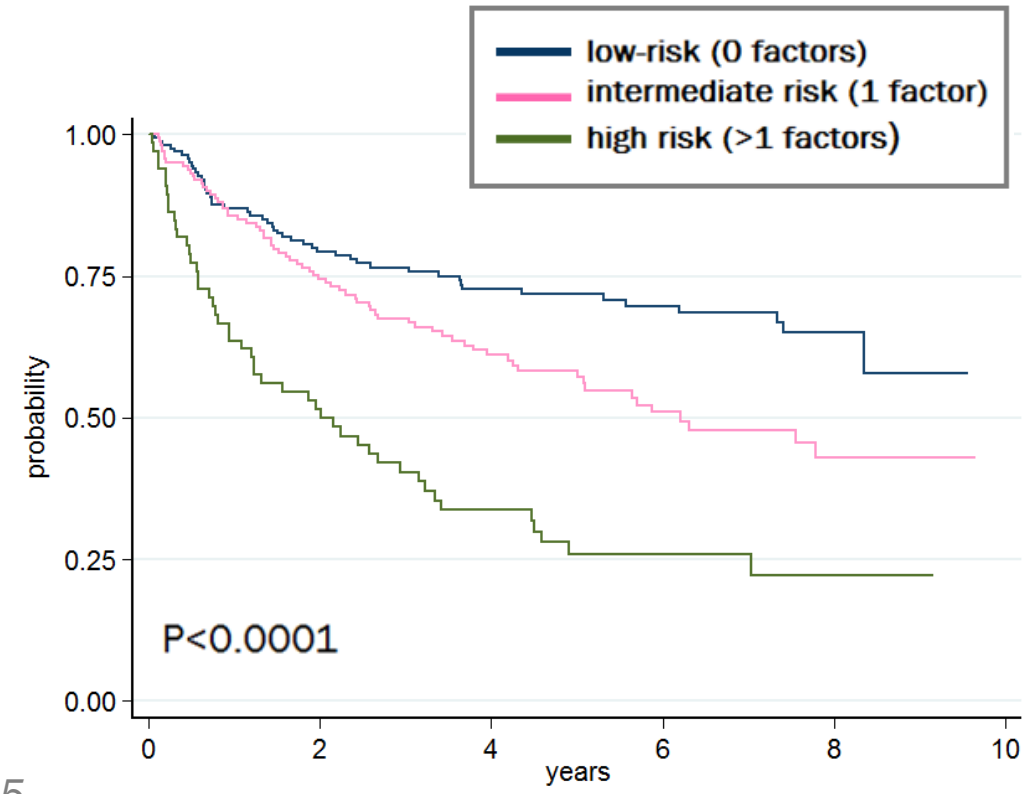
Cox regression

Backward selection using a p<0.05 cut-off

No. of subjects = 391 No. of failures = 168

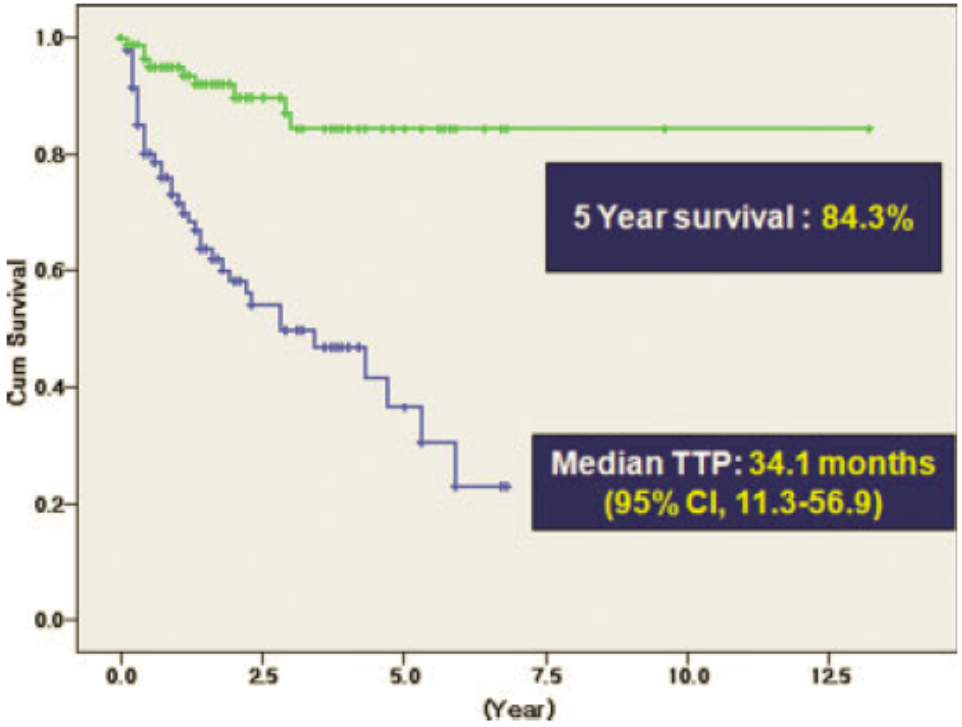
LR chi2(3)= 37.47 Log likelihood = -912.25 Prob > chi2 = 0.0000

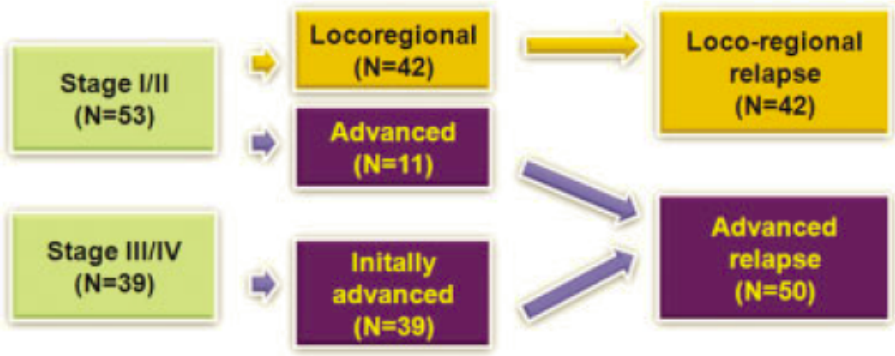
_t	HR	P>|z|	95% C.I.
LDH>N	1.702	0.014	1.111 - 2.608
AGE>70	1.832	0.000	1.324 - 2.535
STAGE>2	1.927	0.000	1.419 - 2.617



C. Thieblemont et al, 13-ICML, Lugano, 2015

Retrospective Korean review of RR-MZL





	N = 92	Median TTP (month)	P [a]	5 year OS (%)	P [a]
Pattern of relapse					
Loco-regional	42	63.4	0.004	97.4	0.039
Advanced	50	23.2		74.1	
Pattern of progression					
Relapsed	85	40.7	0.026	88.1	0.001
Refractory	7	4.1		NR	

- Higher rate of subsequent treatment failure if advanced stage and refractory to prior therapy

Recent results of novel therapy in RR-MZL

Study	N	ORR (%)	PFS (m)	Reference
Everolimus IELSG	30	20	14 (est)	Conconi BJH 2014
Bortezomib IELSG	32	48	25	Conconi Ann Onc 2011
Lenalidomide Austrian	18	61	20+	Kiesewetter Haematologica 2013
Ibrutinib Pharmcyclics	63	48	14	Noy Blood 2017
Idelalisib Gilead	15	47	6.6	Martin ASH Abs 1543, 2015

Application of ASCT in MZL

- MZL is an heterogeneous disease
- Primary therapy outcomes are good for most patients with rituximab-based approaches
  - Higher risk patients can be identified
- Relapsed disease has inferior outcomes and targeted therapies offer reasonable results
  - Long term disease control seems unclear

ASCT – Nebraska Series

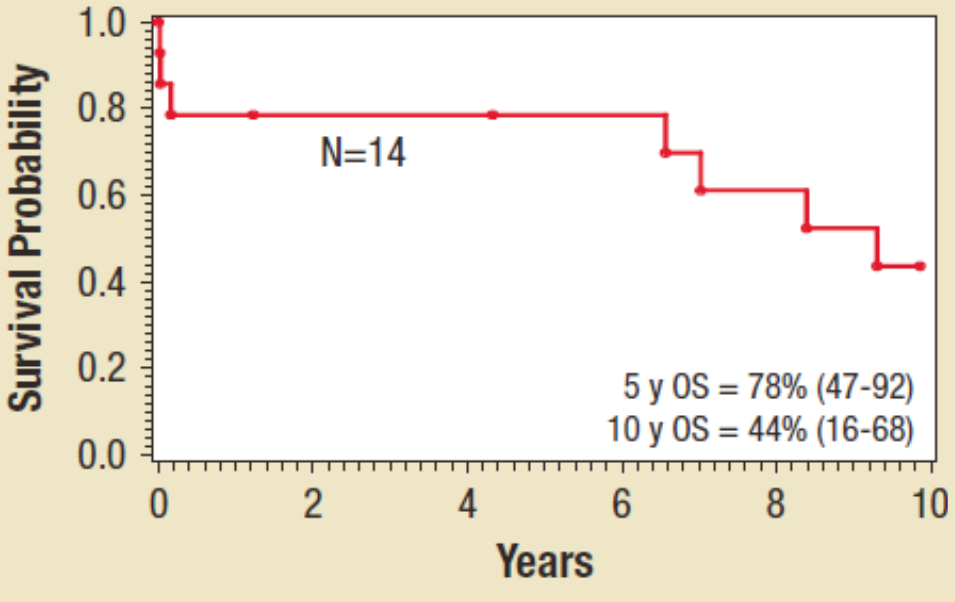
N	14
M:F	9:5
Age m (range)	48 (29-62)
Subtype NMZL MALT SMZL	 5 7 2
Stage I-II III-IV	 4 10
Median prior therapies	2
Status at SCT CR:PR	 3:11

- SCT between Aug 92-Aug 08
- N=13 PBSC
- 100d TRM 3%
- 6m TRM 2%

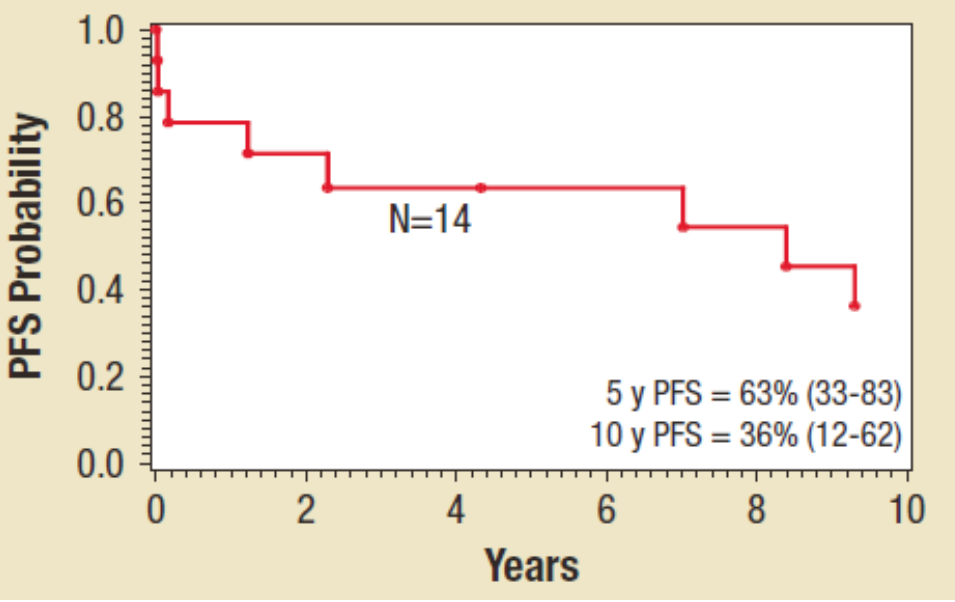
Li, Clin Lym Mye Leuk 2011

ASCT – Nebraska Series

OS



PFS



- Demonstrates feasibility with lower NRM

Li, Clin Lym Mye Leuk 2011

Allogeneic SCT

- No series
- Minimal case reports
  - Most often described as post-SCT recurrence (potentially PTLD)
  - Unknown biology
- No descriptions of GVLy

High Dose Therapy and Autologous Stem Cell Transplantation in Marginal Zone Lymphoma : An EBMT-FIL-GITMO Retrospective Study

Irit Avivi, Luca Arcaini, Virginia Ferretti, Ariane Boumendil, Herve Finel, Cristiana Pascutto, Giuseppe Milone, Francesco Zaja, Devizzi Liliana, Maurizio Musso, Blaise Didier, Gilles Salles, Mohammed Wattad, Emmanuelle Nicolas-Virelizier, Martin Gramatzki, Jean-Henri Bourhis, Denis Caillot, Shannon Haenel, Anette Haenel, Gerhard Held, Catherine Thieblemont, Pavel Jindra, David Pohlreich, François Guilhot, Martin Bornhaeuser, Per T. Ljungman, Christof Scheid, Norbert Ifrah, Christian Berthou, Peter Dreger, Silvia Montoto and Annarita Conconi

Blood 2014 124:2526, manuscript in preparation

EBMT Review

- Eligible for this study were patients with non-transformed nodal, extra-nodal (MALT) or splenic MZL
- aged ≥18 years, who underwent a first ASCT between July 1994 and February 2013
- Reported to the European Society for Blood and Marrow Transplantation (EBMT), to the Fondazione Italiana Linfomi (FIL) or the Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

Avivi et al. Manuscript in preparation

Baseline Characteristics

Characteristic	Whole group n=199
Male sex, n (%)	115 (58)
Age at diagnosis, years median (IQR)	53 (45–57)
Age at ASCT, years median (IQR)	56 (48–60)
N of prior therapies (n=195) median (IQR) **≥3, n (%)**	2 (2-3) 61 (31)
ASCT as front-line therapy, n (%) (n=195)	36 (18)
Year of ASCT, median (IQR) (range)	2006 (2002-2010)
Rituximab treatment at any time prior to ASCT, n (%) (n=195)	**139 (71)**
Rituximab in first-line treatment, n (%) (n=195)	**97 (50)**
Interval diagnosis ASCT, years median (IQR)	2 (0.8-3.9)
Disease status at ASCT, n (%) (n=191) **CR1/PR1** **>CR1/PR1** **SD**	 **74 (39)** 109 (57) 8 (4)
Chemosensitive at ASCT, n (%) (n=196)	187 (95)
Stem cell source, n (%) (n=198) PB	190 (96)
High-dose regimen, n (%) **TBI based** **Chemotherapy based*** **HD ibritumomab tiuxetan**	 18 (9) 178 (89) 3 (2)
Follow-up for surviving patients (years),median (IQR)	5.0 (2.4-7.5)

Avivi et al.

Baseline Characteristics: Subgroups

Characteristic	Whole group	MALT (111)	SMZL (33)	NMZL (55)	P
Male sex, n (%)	115 (58)	67 (60)	14 (42)	34 (62)	0.208
N of prior therapies (n=195) **median (IQR)** **1-2, n (%)** **≥3, n (%)**	 2 (2-3) 134 (69) 61 (31)	 2 (2-3) 72 (65) 38 (35)	 2 (2-3) 21 (64) 12 (36)	 2 (2-2) 41 (79) 11 (21)	 0.596 0.178
ASCT as front-line therapy, n (%) (n=195)	36 (18)	23 (21)	5 (15)	8 (15)	0.714
Year of ASCT, **median** **(IQR)** **(range)**	 2006 (2002-2010) (1994-2013)	 2005 (2000-2009) (1994-2013)	 2009 (2005-2010) (2000-2013)	 2007 (2005-2009) (1995-2011)	0.013
Rituximab treatment at any time prior to ASCT, n (%) (n=195)	**139 (71)**	**69 (62)**	**29 (88)**	**41 (80)**	**0.004**
Rituximab in first-line treatment, n (%) (n=195)	**97 (50)**	**46 (41)**	**21 (64)**	**30 (59)**	**0.026**
Interval diagnosis ASCT, years **median (IQR)**	 2 (0.8-3.9)	 1.6 (0.8-4.2)	 3.0 (1.2-4.6)	 2.3 (0.7-3.7)	 0.381
Disease status at ASCT, **n (%) (n=191)** **CR1/PR1** **>CR1/PR1** **SD**	 74 (39) 109 (57) 8 (4)	 47 (44) 57 (53) 4 (4)	 11 (34) 20 (63) 1 (3)	 16 (31) 32 (63) 3 (6)	 0.576
Follow-surviving patients	5.0 (2.4-7.5)	5.4 (2.8-10.6)	3.3 (1.7-6.3)	4.9 (1.9-7.1)	0.088

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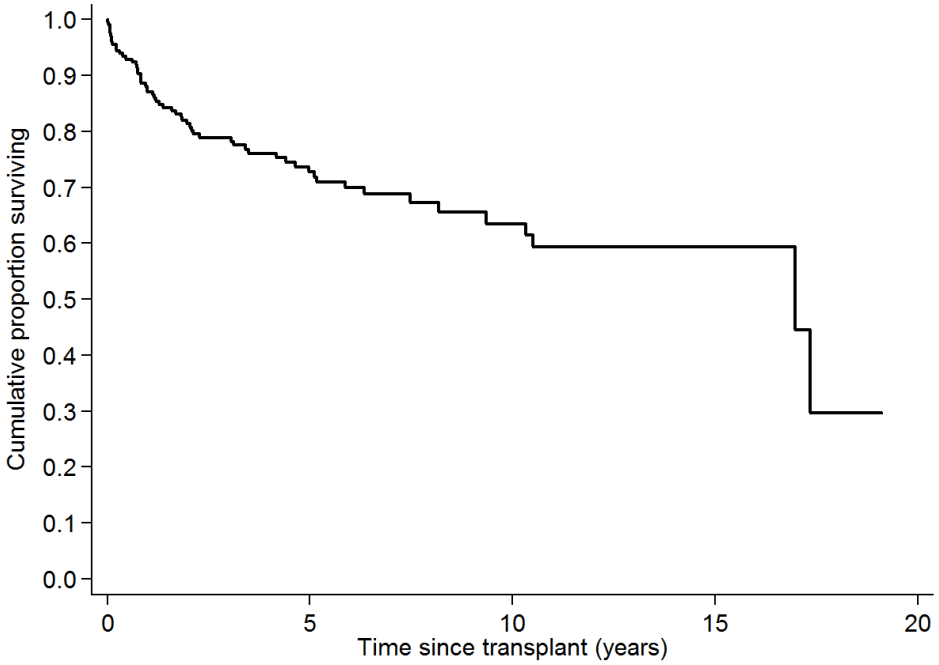
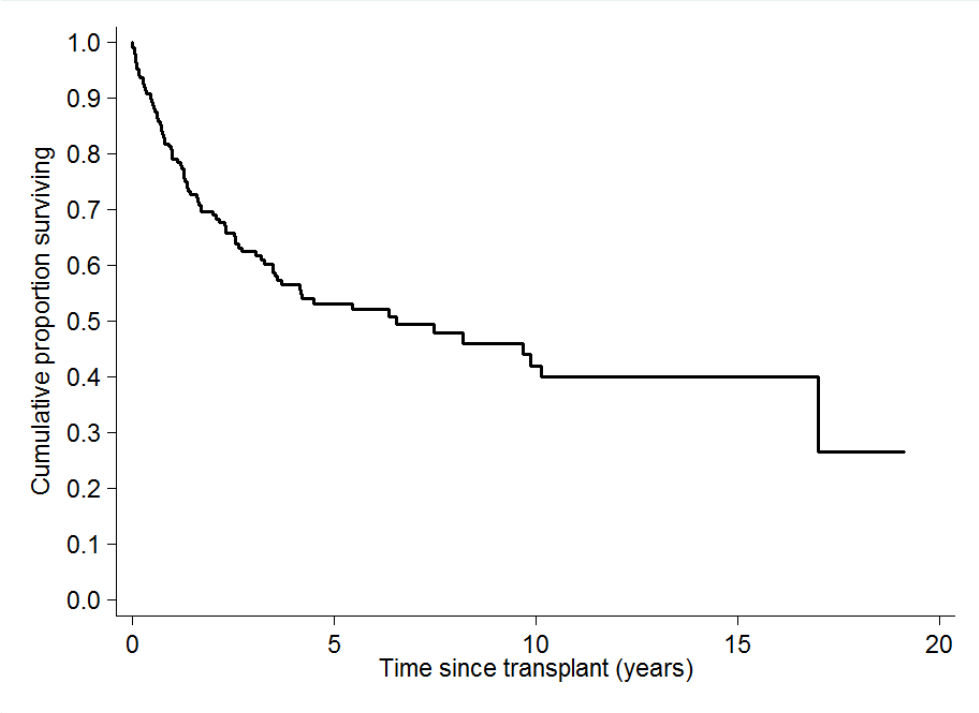
OS and EFS post SCT





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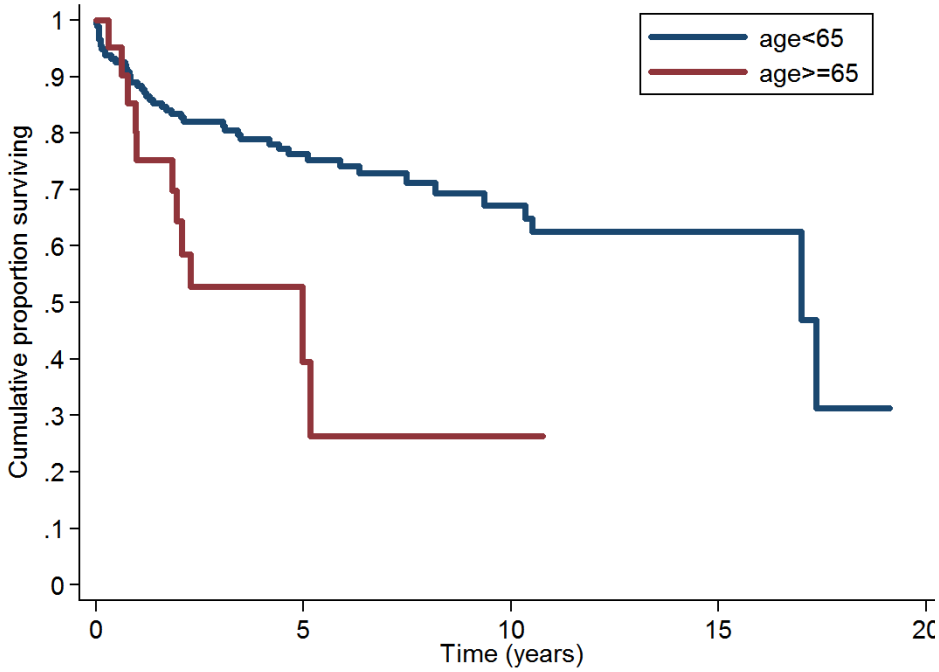
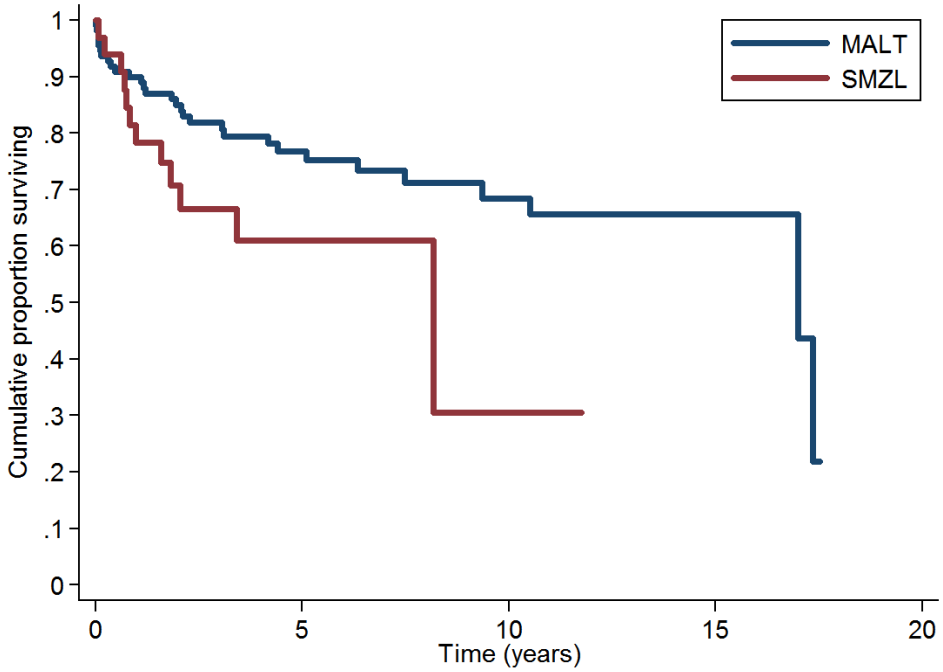
OS by Age and Histologic Subtype





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Multivariate Analysis – OS

	HR	Low	High	p-value
Rituximab before ASCT (yes vs no)	0.50	0.20	1.23	0.131
Age at transplantation (≥65 vs <65)	**2.70**	**1.32**	**5.52**	**0.007**
Time from diagnosis to ASCT (>1 year vs ≤1 year)	1.70	0.87	3.29	0.119
N of prior lines of therapy (>2 vs 1-2)	1.19	0.64	2.19	0.586
Histological diagnosis (NMZL vs MALT)	1.26	0.67	2.37	0.476
Histological diagnosis (SMZL vs MALT)	**2.01**	**1.00**	**4.05**	**0.052**
Chemosensitive disease (yes vs no)	0.65	0.23	1.81	0.409
Conditioning regimen TBI vs HD chemotherapy	0.57	0.20	1.62	0.290
Year of transplant (continuous)	1.03	0.93	1.14	0.590

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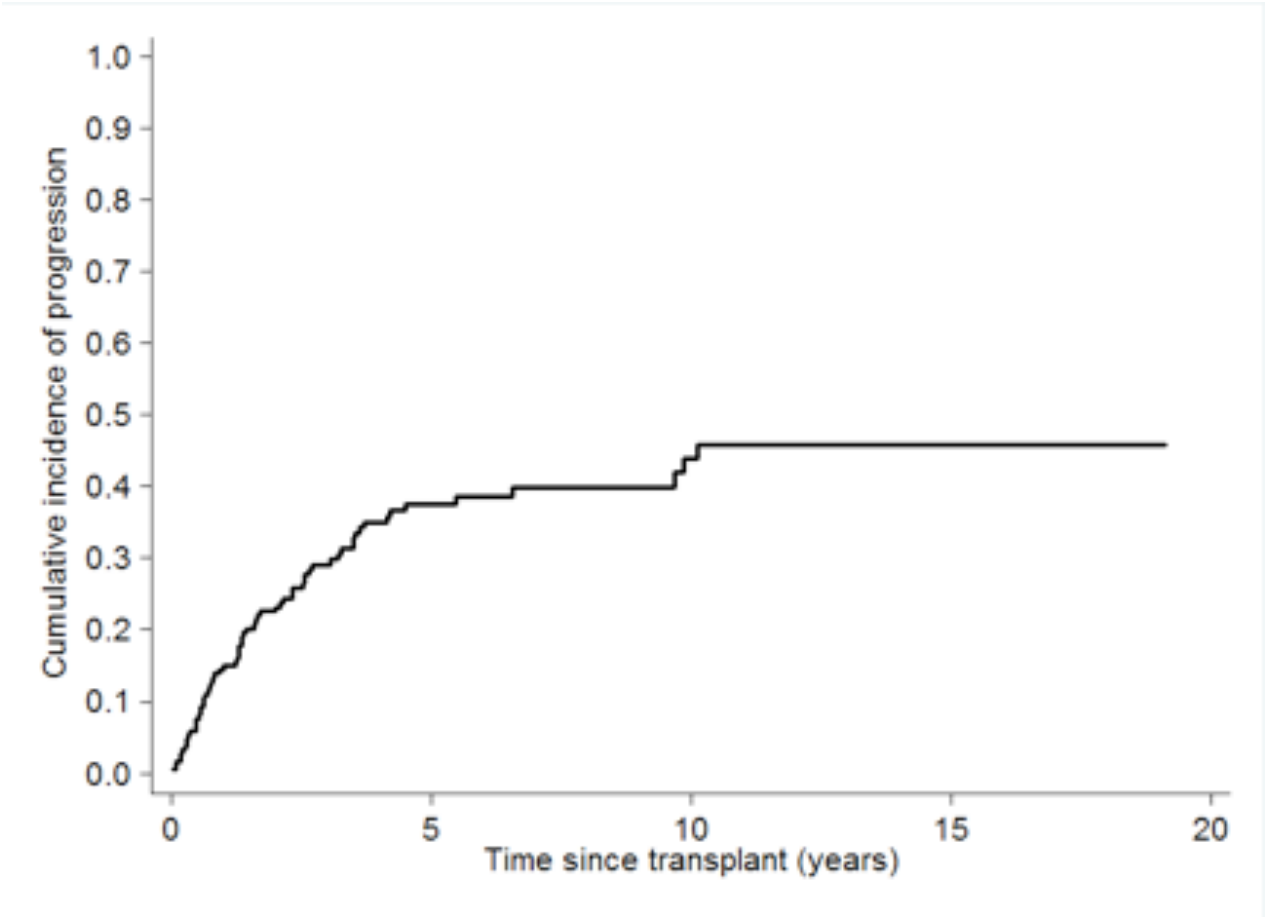
Cumulative Incidence of Relapse



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NRM and Secondary CA

- 5 year non-relapse mortality (NRM) was 9% (95% CI 5-14%)
  - SCT related in ½, non-related in ½
- 5 year secondary malignancy rate was 6% (95% CI 3-10%)
  - Median time to diagnosis 13 months (13.5-91m)
  - 3 tMDS, 1 Mycoses Fungoides, 9 solid tumour

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EBMT Data: Interpretation

- Relatively small sample size with <200 patients post-SCT over almost 20 years
- Only 50% received primary rituximab based therapy and 70% prior rituximab at all
- Procedure appears feasible with reasonable outcomes
- Difficult to draw any conclusions about magnitude of any benefit over non-SCT therapies

Defining a role for SCT in MZL

- SCT as part of primary therapy
  - Data not clearly supportive of this
- SCT in the relapse setting
  - Difficult to suggest blanket approach
  - Could be considered in higher risk population (ie. early treatment failure post rituximab)
- Very little data with allogeneic SCT
- Biology and prospective studies required to better define role of SCT

Conclusions – Role of SCT in MZL

- MZL represents a heterogeneous group of indolent lymphomas
- Patterns of management often generalized from follicular lymphoma
- Specific studies have demonstrated unique biology
- SCT does not appear to be a frequently utilized approach − data are not robust
  - Clinicians will likely continue approaches generalized from FL