Rituximab Maintenance after Chemoimmunotherapy Induction in 1st and 2nd Line Improves Progression Free Survival: Long Term Follow up of the International Randomized AGMT-CLL8/a Mabtenance Trial

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Abstract

Introduction: Results of **Rituximab maintenance after chemoimmunotherapy induction in 1st or 2nd line for 263 patients** from the AGMT-CLL8/a Mabtenance trial NCT01118234 **(Lancet Haematol. 2016)** had been previously presented with a median follow up (FU) of 33.4 months and had shown a PFS benefit. We present an **updated FU of 87.3 months**, including analyses of MRD endpoints and salvage treatment results.

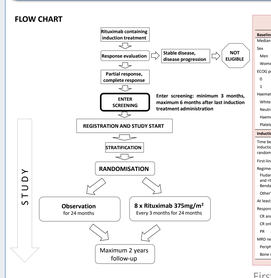
Results: The primary endpoint **PFS benefit of maintenance remained stable and significant over time** with an increase in median PFS from 35.6 months in observation to 46.9 months in the maintenance population (p=0.012). PFS at median FU was 31.1% vs 20.2% in maintenance vs. observation patients, respectively. **The median time to next treatment increased from 53.3 in the observation arm to 78.7 months in the maintenance arm (p=0.01).** The trial was not powered for analysis of OS. We observed no significant benefit in OS with 62.6% in the observation arm vs. 68.4% in the maintenance arm alive at the median FU (p=0.24).

In **exploratory analyses MRD parameters** (MRD from PB or BM, quantitative MRD subgroups) and BMI (as previously published) remained **significant predictors of PFS with longer FU**. The effect of rituximab maintenance was more pronounced in patients with detectable MRD after induction. **MRD-parameters were also highly significant predictors of OS**. A novel parameter of **dynamic assessment of MRD in the first 6 months of observation (or maintenance) was a predictor of PFS, and of OS independent of MRD strata.** .

An analysis of **retreatment outcomes in 144 retreated patients to date showed that the inclusion of novel drugs (any BTKi, Venetoclax or PI3K) in retreatment at any time (n=85 or 59% of retreated patients) led to a highly significant increase in OS (p<0.001)** for the group salvaged with novel drugs in any line of salvage. **Patients in the maintenance arm had a somewhat higher percentage of novel drug treatment (66% vs. 53% in the observation arm) – likely due to the 25.4 months longer time to next treatment in a sensitive period for access to the novel drugs**. Despite this small, but observable difference in usage of or access to novel drugs, no significant OS benefit was observed for maintained patients, likely because a majority of retreated patients had received novel drugs in both arms.

Conclusions: We present longer FU of a trial of rituximab maintenance after remission induction in the chemoimmunotherapy era. With longer FU we observe **stable and meaningful benefits for maintenance in PFS and TTNT**. We can **validate MRD endpoints for PFS and OS prediction** in long follow up and **show novel dynamic MRD endpoints**. Finally, we observe an **enormous increase in OS for the trial group receiving novel drugs in any line of salvage, suggesting that OS benefits may no longer be attainable in trials due to effective salvage options in the current treatment paradigms.**

Introduction: Trial design – CONSORT – Patient Characteristics – PFS (1° EndPoint) with 33.4 Mo FU



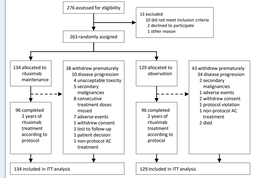
	Rituximab (n=134)	Observation (n=129)
Baseline characteristics (after induction and prior to study entry)		
Median age, year (range, IQR)	63 (33-83, 55-69)	63 (40-85, 58-71)
Sex		
Men	100 (75%)	87 (67%)
Women	34 (25%)	42 (33%)
ECOG performance status		
0	113 (84%)	115 (89%)
1	21 (16%)	14 (11%)
Haematology		
White blood cells, x 10⁹ cells/L	4.1 (3.5-5.2)	4.0 (3.2-5.1)
Neutrophils, x 10⁹ cells/L	2.1 (1.8-3.1)	2.6 (1.9-3.6)
Haemoglobin, g/L	139 (131-149)	140 (131-147)
Platelets, x 10⁹ platelets/L	165 (127-204)	154 (127-191)
Induction therapy (before study entry)		
Time between last infusion of induction therapy and randomisation days	115.5 (100.0-147.0)	107.0 (95.0-133.0)
First-line therapy	103 (77%)	107 (83%)
Regimen		
Fludarabine, cyclophosphamide, and rituximab	95 (71%)	98 (76%)
Bendamustine, and rituximab	28 (21%)	24 (19%)
Other*	11 (8%)	7 (5%)
At least 6 cycles received	99 (74%)	85 (66%)
Response		
CR and CRi	74 (55%)	74 (57%)
CR only	67 (50%)	71 (55%)
PR	60 (45%)	55 (43%)
MRD negativity		
Peripheral blood	70/134 (56%)	65/118 (55%)
Bone marrow	42/134 (36%)	31/111 (28%)

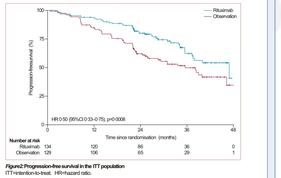
(Table 1 continues in next column)

	Rituximab (n=134)	Observation (n=129)
(Continued from previous column)		
Before induction therapy		
Rai stage		
0/I/II	81/131 (62%)	77/123 (63%)
III/IV	50/131 (38%)	46/123 (37%)
Bulky disease (≥5 cm)	33/119 (28%)	32/117 (27%)
B symptoms	38/112 (34%)	46/106 (43%)
FISH cytogenetic results		
Trisomy 12	14/110 (13%)	19/99 (19%)
Del(11q)	31/111 (28%)	33/103 (32%)
Del(13q)	59/113 (52%)	59/105 (56%)
Del(17p)	17/111 (2%)	5/103 (5%)
Del(11q) and/or del(17p) (mpr-ran)	32/110 (29%)	36/103 (35%)
No cytogenetic abnormalities	20/107 (20%)	19/98 (19%)
Immutated IGVH	56/80 (63%)	56/81 (70%)
CD38-positive	44/95 (46%)	41/94 (44%)
Haematology		
White blood cells, x 10⁹ cells/L	70.0 (30.0-134.4)	82.0 (39.9-144.2)
Haemoglobin, g/L	125 (108-139)	128 (106-139)
Platelets, x 10⁹ platelets/L	157 (109-198)	134 (89-176)
Number of patients with platelets <100 x 10⁹ platelets/L	26 (20%)	32 (26%)

Data are n (%), n/N (%), or median (IQR), unless otherwise stated. CR=complete remission. CRi=CR with incomplete blood count recovery. PR=partial response. ECOG=Eastern Cooperative Oncology Group. MRD=minimal residual disease. FISH=fluorescence in-situ hybridisation. *Other induction regimens comprised cyclophosphamide plus rituximab, fludarabine plus rituximab, cyclophosphamide, and rituximab, rituximab plus chlorambucil, cyclophosphamide, vincristine, and prednisone, and rituximab plus dexamethasone.

Table 1: Patient demographics and baseline characteristics

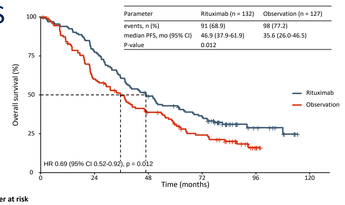




Source: Greil et al Lancet Haematol. 2016

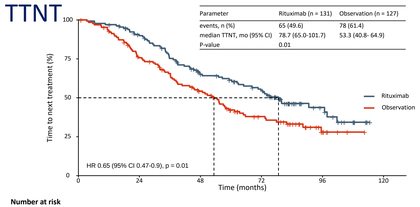
Results I – PFS (Primary EndPoint), TTNT, OS Results with 87.3 Mo (>7a) of FU

PFS



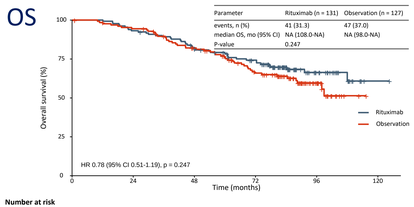
Parameter	Rituximab (n = 132)	Observation (n = 127)
events, n (%)	91 (68.9)	98 (77.2)
median PFS, mo (95% CI)	46.9 (37.3-61.9)	35.6 (26.0-46.5)
P-value	0.012	

TTNT



Parameter	Rituximab (n = 131)	Observation (n = 127)
events, n (%)	65 (49.6)	78 (61.4)
median TTNT, mo (95% CI)	78.7 (65.0-101.7)	53.3 (40.8- 64.9)
P-value	0.01	

OS

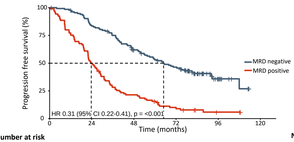


Parameter	Rituximab (n = 131)	Observation (n = 127)
events, n (%)	41 (31.3)	47 (37.0)
median OS, mo (95% CI)	NA (108.0-NA)	NA (98.0-NA)
P-value	0.247	

Results II – Exploratory analyses regarding MRD at Baseline and Dynamic MRD Assessment

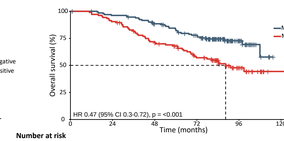
Baseline MRD performance for prediction: whole study population

PFS by PB MRD at baseline



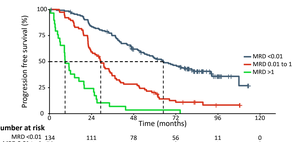
Parameter	MRD negative (n = 134)	MRD positive (n = 105)
events, n (%)	78 (58.2)	96 (91.4)
median PFS, mo (95% CI)	64.9 (54.3-92.0)	23.7 (21.9-29.2)
P-value	<0.001	

OS by baseline PB MRD



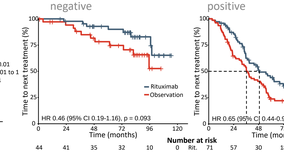
Parameter	MRD negative (n = 133)	MRD positive (n = 105)
events, n (%)	35 (26.3)	50 (47.6)
median OS, mo (95% CI)	NA (108.0-NA)	88.4 (70.7-NA)
P-value	<0.001	

PFS by MRD groups (acc to Boettcher et al.)



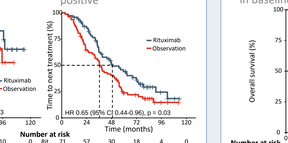
Parameter	MRD <0.01 (n = 134)	MRD 0.01 to 1 (n = 76)	MRD >1 (n = 29)
events, n (%)	78 (58.2)	67 (88.2)	29 (100.0)
median PFS, mo (95% CI)	64.9 (54.3-92.0)	29.2 (23.7-35.7)	8.9 (8.5-19.6)
P-value	<0.001		

TTNT by treatment group (R vs Obs) by baseline BM MRD negative



Parameter	Rituximab (n = 44)	Observation (n = 36)
events, n (%)	8 (18.2)	11 (30.6)
median TTNT, mo (95% CI)	NA (97.8-NA)	NA (95.5-NA)
P-value	0.093	

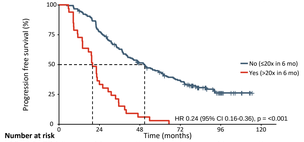
TTNT by treatment group (R vs Obs) by baseline BM MRD positive



Parameter	Rituximab (n = 71)	Observation (n = 77)
events, n (%)	45 (63.4)	61 (79.2)
median TTNT, mo (95% CI)	48.7 (38.8-72.5)	36.3 (31.3-52.3)
P-value	0.03	

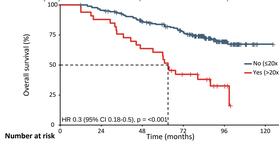
Outcome prediction using dynamic MRD assessment at 6 months

PFS by dynamic PB MRD increase (>20x in 6 months)



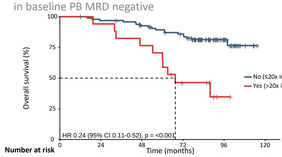
Parameter	No (≤20x in 6 mo) (n = 179)	Yes (>20x in 6 mo) (n = 33)
events, n (%)	122 (68.2)	33 (100.0)
median PFS, mo (95% CI)	50.8 (40.8-61.7)	19.9 (14.0-29.2)
P-value	<0.001	

OS by dynamic PB MRD (>20x in 6 months)



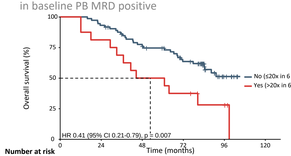
Parameter	No (≤20x in 6 mo) (n = 178)	Yes (>20x in 6 mo) (n = 33)
events, n (%)	48 (27.0)	22 (66.7)
median OS, mo (95% CI)	NA (NA-NA)	63.1 (46.9-NA)
P-value	<0.001	

OS by dynamic PB MRD (>20x in 6 months) in baseline PB MRD negative



Parameter	No (≤20x in 6 mo) (n = 97)	Yes (>20x in 6 mo) (n = 17)
events, n (%)	18 (18.6)	10 (58.8)
median OS, mo (95% CI)	NA (NA-NA)	67.5 (60.0-NA)
P-value	<0.001	

OS by dynamic PB MRD (>20x in 6 months) in baseline PB MRD positive

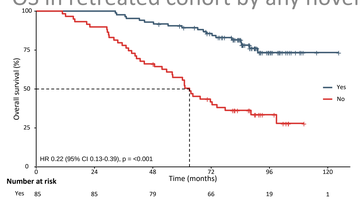


Parameter	No (≤20x in 6 mo) (n = 73)	Yes (>20x in 6 mo) (n = 16)
events, n (%)	30 (41.1)	12 (75.0)
median OS, mo (95% CI)	NA (84.3-NA)	52.8 (33.1-NA)
P-value	0.007	

Results III – Impact of type of retreatment on OS

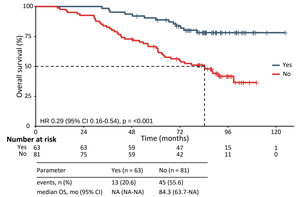
144 Patients were retreated. Novel drugs (BTKi, Venetoclax, Idelalisib) were given/available to 85 patients (59% of all retreated patients) in any following line. Patients in the maintenance arm had a higher percentage of novel drug treatment (66% vs 53% in the observation arm)

OS in retreated cohort by any novel drug in retreatment



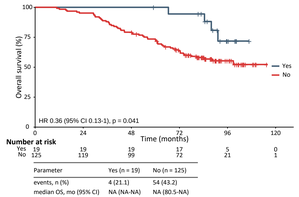
Parameter	Yes (n = 85)	No (n = 59)
events, n (%)	19 (22.4)	39 (66.1)
median OS, mo (95% CI)	NA (NA-NA)	63.1 (53.7-88.4)
P-value	<0.001	

OS in retreated cohort by any BTKi in retreatment



Parameter	Yes (n = 63)	No (n = 81)
events, n (%)	13 (20.6)	45 (55.6)
median OS, mo (95% CI)	NA (NA-NA)	84.3 (63.7-NA)
P-value	<0.001	

OS in retreated cohort by any venetoclax in retreatment



Parameter	Yes (n = 19)	No (n = 125)
events, n (%)	4 (21.1)	54 (43.2)
median OS, mo (95% CI)	NA (NA-NA)	NA (80.5-NA)
P-value	0.041	

Conclusions:

- Benefit of Rituximab remains stable after >7 years
- Two years of Rituximab maintenance delays the next treatment by >2 years
- Baseline MRD (End of induction) and dynamic MRD (>20-fold increase in 6 months) predicts PFS and OS
- Retreating the progressing patients in this trial in a time of arrival of novel drugs shows a massive OS advantage, that likely makes it impossible to see OS benefits in randomized trial in the future