A phase III multicenter, randomized study with Lenalidomide (Revlimid®) maintenance versus observation after intensified induction regimen containing rituximab followed by high dose chemotherapy and Autologous Stem Cell Transplantation as first line treatment in adult patients with advanced Mantle Cell Lymphoma

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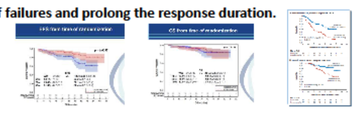
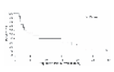
Background and Rationale

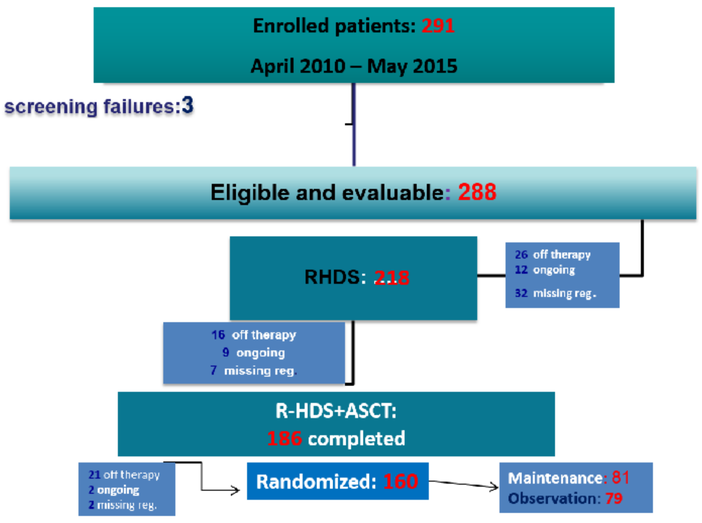
- **In spite of the improvement in disease control obtained with new therapeutic strategies, the rate of relapse and deaths among MCL patients is still high. However, recent studies have shown that maintenance treatment after the achievement of a clinical response may reduce the rate of failures and prolong the response duration.**

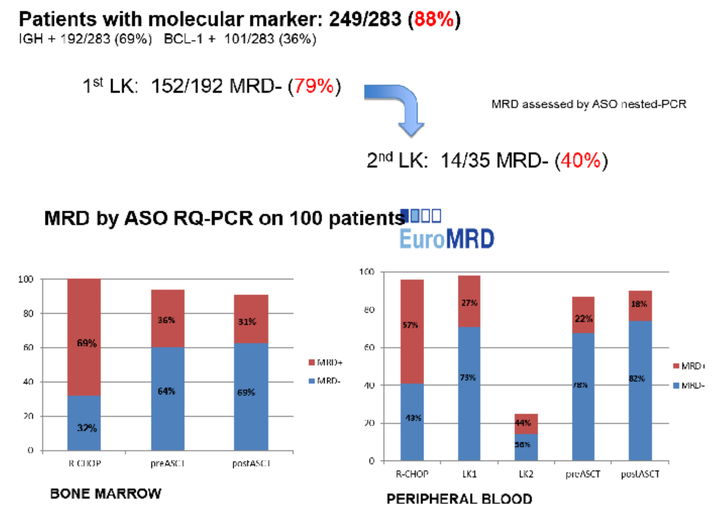


- **Lenalidomide has been shown to be active as a single-agent in relapsing/resistant MCL.**

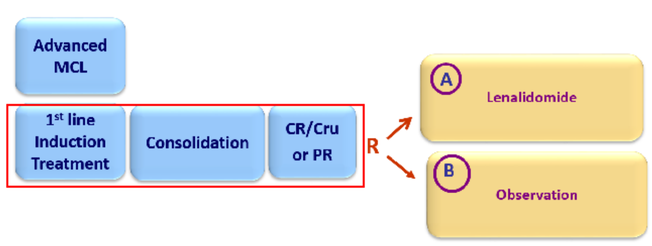


- **The Fondazione Italiana Linfomi (FIL) designed a phase III study (NCT02354313) aimed at evaluating the efficacy and safety of maintenance therapy with lenalidomide after an intensive chemo-immunotherapy with rituximab and ASCT as first line treatment in adult patients with advanced MCL.**





Study Design



Randomization within 120 days after the end of consolidation

Arm A: Lenalidomide, once daily on days 1-21, every 28-days

Arm B: Observation with no any active drugs for MCL

	R-HDS+ASCT n = 288
Median age at randomisation (IQR)	57 (51-62)
Male	228 (79%)
LDH > UNV	81 (31%) (missing=28)
PS ECOG ≥ 1	68 (23%)
Stage III/IV	282 (98%)
MIPI low Intermediate High	131 (51%) 75 (29%) 52 (20%) (missing=30)
Bulky disease (>5 cm)	96 (33%)
BM involvement	209 (76%) (missing=14)

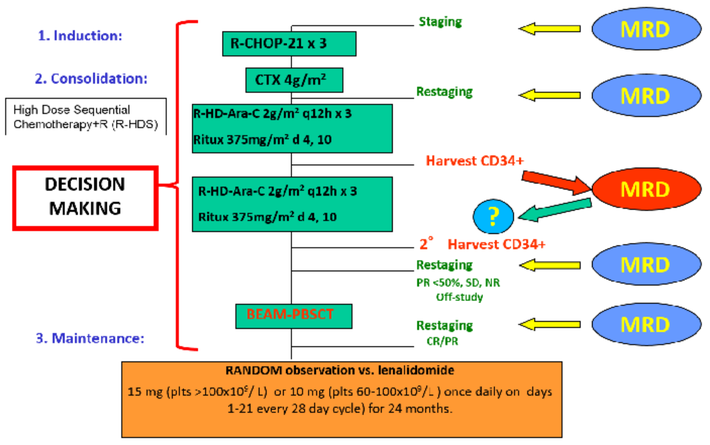
Toxicity

CTC grade 3-4 Haematological	R-HDS+ASCT n =1684 cycles
Neutropenia (Granulocytes)	631(41%)
Anemia (HB)	164(10%)
Thrombocytopenia (PLT)	519 (31%)
CTC grade 3-4 Extrahaematological	**R-HDS+ASCT n = 268 patients**
Gastrointestinal	39(15%)
Cardiac	5 (2%)
Neurological	2 (<1%)
Infection	44(16%)
Toxic deaths	4 (1.6%)

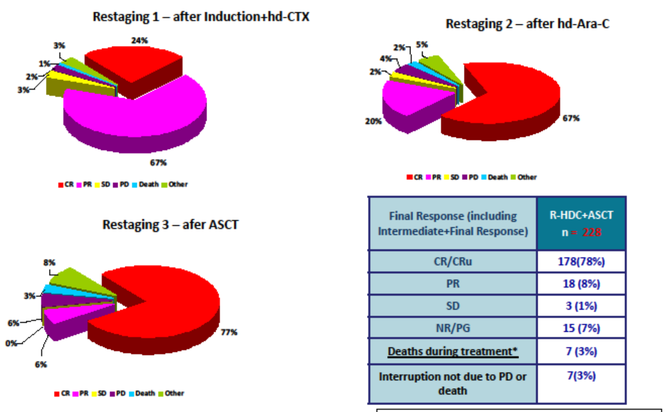
Treatment discontinuation because Aes 63/288 (22%)

*TRD: 0 during R-CHOP induction, 3 during hd-CTX, 1 during hd-ARA-C, 0 post-BEAM+ASCT

Minimal Residual Disease (MRD)



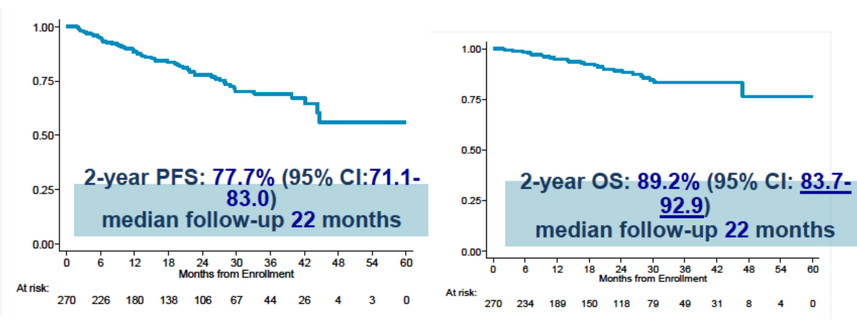
Response

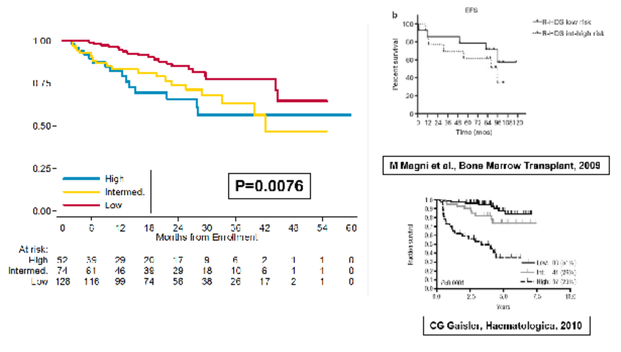


Final Response (including Intermediate+Final Response)	R-HDC+ASCT n = 228
CR/CRu	178(78%)
PR	18 (8%)
SD	3 (1%)
NR/PG	15 (7%)
Deaths during treatment*	7 (3%)
Interruption not due to PD or death	7(3%)

** One not related to treatment: road accident*

Survival





Key Characteristics

✓ International multicenter randomized phase III trial

✓ Adult untreated **MCL with advanced stage**

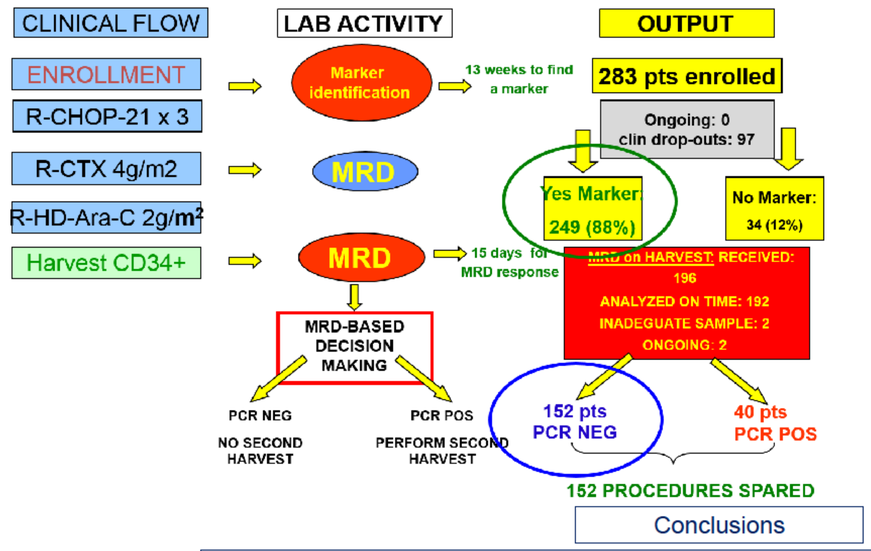
✓ **RANDOMISATION AFTER ASCT**

✓ Evaluation of patients as Intention to Treat. Response criteria according to Cheson et al, JCO, 2007.

✓ Primary end point: **PFS at 30 months from randomization;** PFS (PFS observation after ASCT vs. maintenance with lenalidomide after ASCT, PFS 70%→ 85%); sample size: 150 patients for each arm (alpha: 5%; power 85%; drop-out 30%); two interim analysis at 1/3 and 2/3 of expected events. 47 FIL and 1 international center (Lisbon, Portugal)

✓ Secondary Endpoint: OS, DFS, EFS, **rate of clinical and molecular response**, quality of life, expenses, quality adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER) of the maintenance with lenalidomide vs observation

MRD



	No. Pts	CR	Median F-up	PFS	OS	Toxic deaths
R-HCVAD*	97	87%	3.3 yrs (4.8)**	64-73% (48-60%)	82% (65%)	5%
R-HCVAD**	60	72%	3.8 yrs	5-yr FFs 46%	5-yr OS 73%	5%
R-HCVAD***	49	58%	2 years	2-yr PFS 63%	2-yr OS 76%	2%
R-HDS	28	100%	2.9 yrs	79%	89%	4%
NLG#	160	54%	3.8 yrs	66%	70%	5%
MCL 0208	288	78%	ongoing	2-yr PFS 78%	2-yr OS 89%	1.6%

*29% ** 63% ***50% 14% #37.5% — Of patients did not finish their intended number of cycles because of toxicity or PD

JE Romaguera et al, JCO, 2005; L Fayad and J Romaguera, Clin Lymphoma Myeloma, 2007; **Merli et al, BJH, 2011;*Epner et al, Blood, 2007; AM Gianni et al, Blood, 2003; #6:H. Geisler et al, Blood, 2008*

Conclusions

- High-dose chemotherapy with ASCT followed by lenalidomide maintenance is feasible and safe for patients with advanced MCL in first line of treatment in a multicenter setting.
- The clinical outcome of this ongoing trial is comparable to previous high dose treatments with a manageable toxicity.
- These promising results are supported by the high rate of molecular responses by RQPCR.
- MRD is feasible on time during treatment and may improve the clinical management of this disease sparing probably unnecessary procedures.

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Mantle cell lymphoma

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