Incontro di aggiornamento sui disordini linfoproliferativi

Protocolli FIL: linfomi mantellari

Torino, 24 novembre 2017

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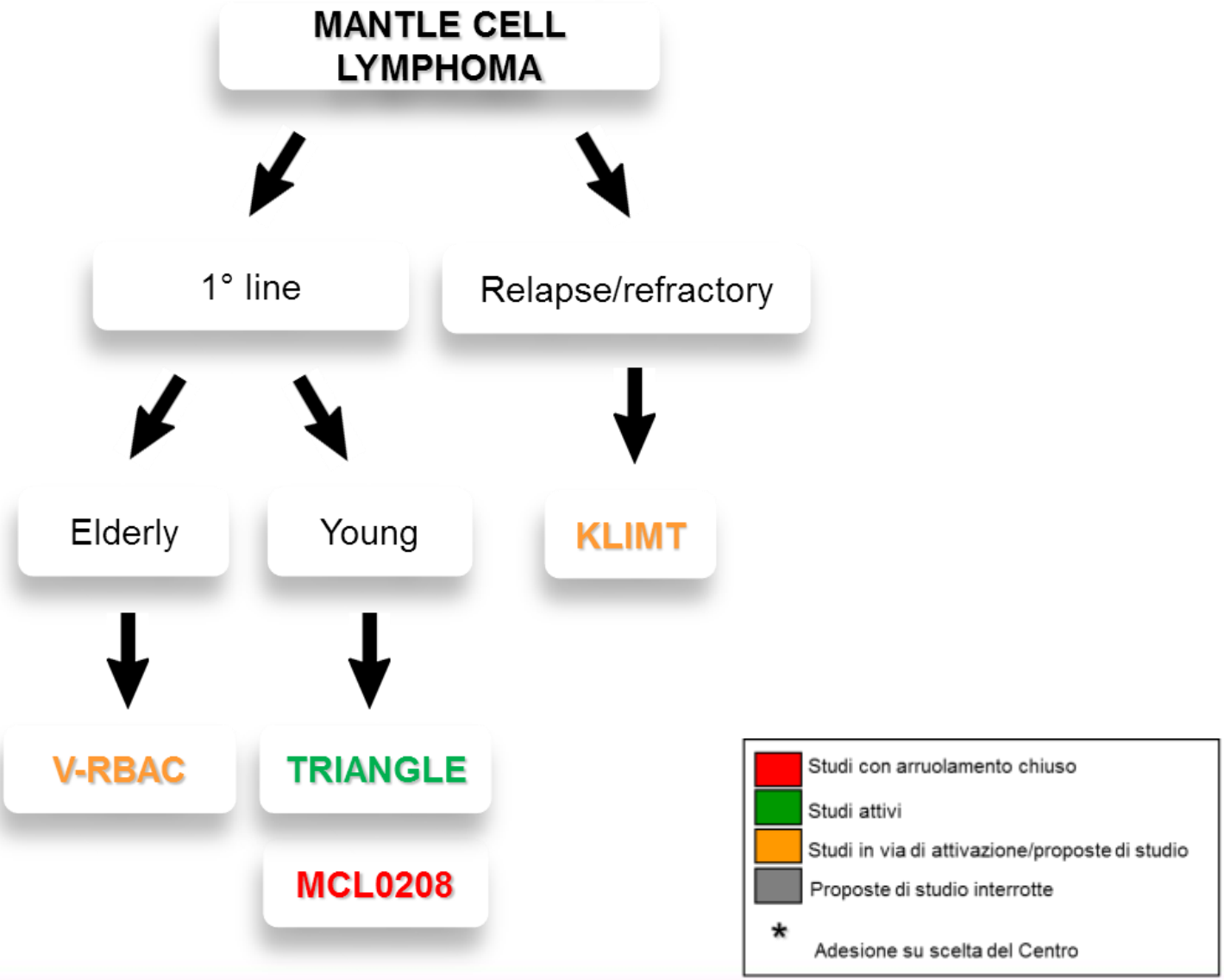
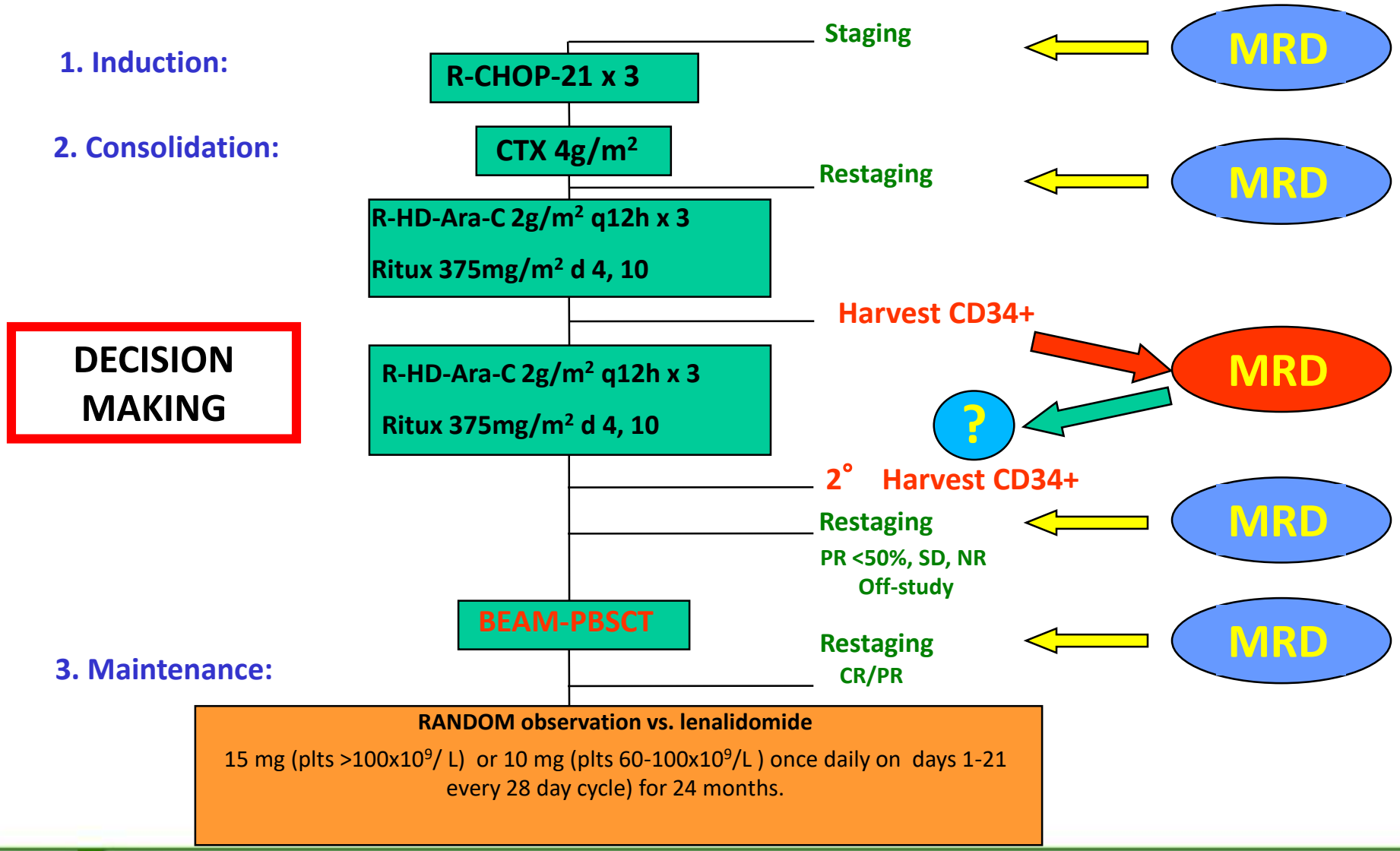
Novara

I protocolli FIL nel linfoma mantellare



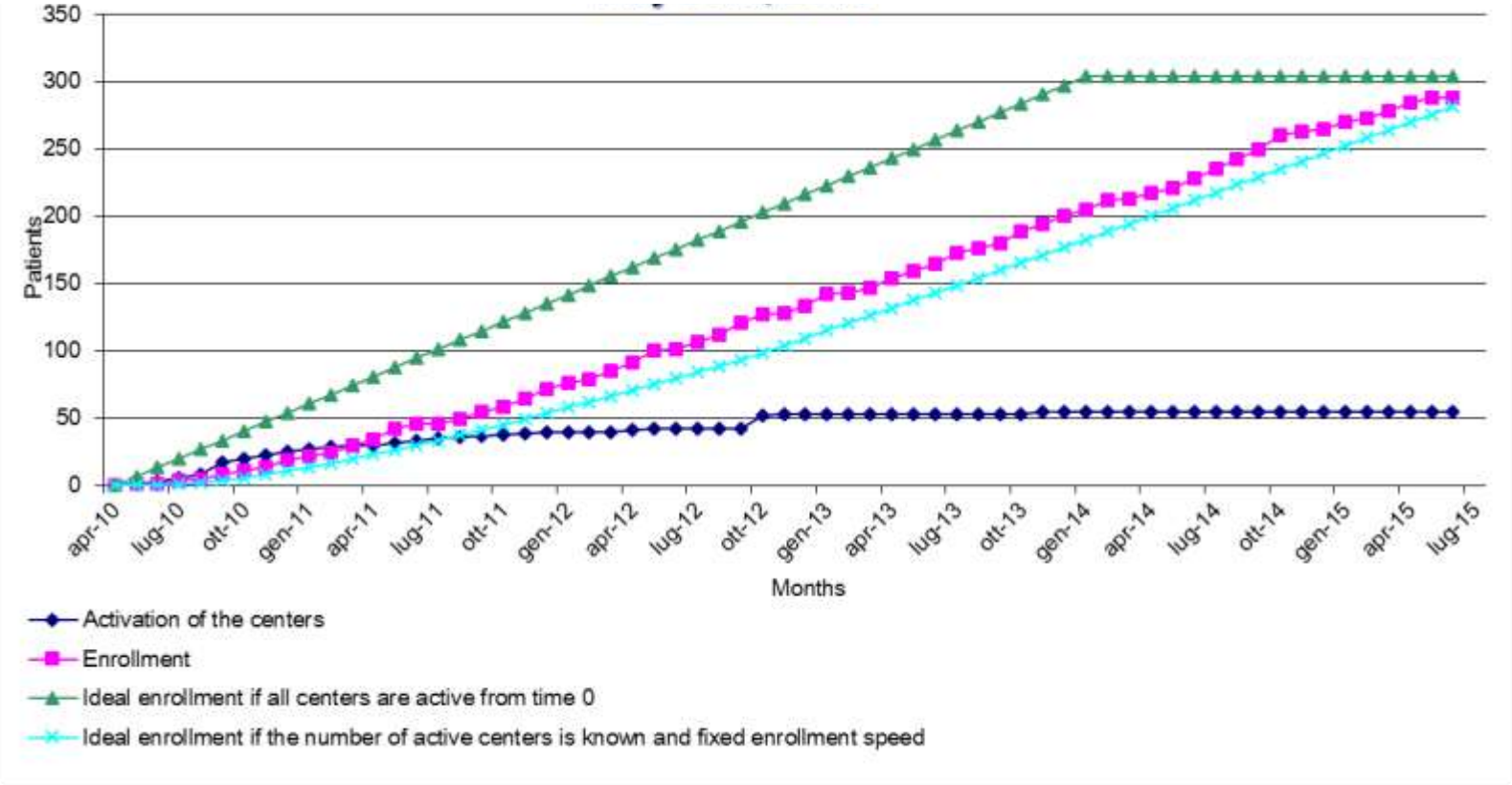
MCL0208: study design



MCL0208. ***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***

- ✓ International multicenter randomized phase III trial
- ✓ Inclusion criteria: adult untreated MCL with advanced stage
- ✓ RANDOMISATION AFTER ASCT
- ✓ Evaluation of patients as Intention to Treat
- ✓ Enrollment: 303 patients from May 2010 to August 2015
- ✓ **Primary end point: PFS at 30 months from randomization PFS (PFS observation after ASCT→maintenance with lenalidomide after ASCT, PFS 70%→ 85%)**
- ✓ Secondary Endpoint: OS, DFS, EFS, Rate and Duration of clinical and molecular response, safety, quality of life, cost, quality adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER) of the maintenance with lenalidomide vs observation.

MCL0208: accrual



First enrollment 04/05/2010

Last enrollment 24/08/2015

MCL0208: accrual per center

Brescia (21 pz)
Pavia (10 pz)
Rozzano (11 pz)
Milano San Raffaele (8 pz)
Monza (6 pz)
Milano Niguarda (10 paz + 1 trasferito a Reggio Calabria)
Milano Ospedale Maggiore (1 pz)

Bolzano (6 pz)

Trieste (2 pz)
Aviano (3 pz)
Udine (3 pz + 1 trasferito poi a Messina)

Treviso (7 pz)
Verona (7 pz)
Venezia Mestre (3 pz)

Alessandria (6 pz)
Torino (Dr. Vitolo) (11 pz)
Torino (Dr.ssa Cavallo) (12 pz)
Cuneo (5 pz)
Novara (4 pz)
Candiolo (2 pz)

Genova
(Prof Gobbi) (9 pz)
Genova
(Prof. Carella) (4 pz)

Reggio Emilia (4 pz)
Modena (8 pz)
Bologna (13 pz)
Rimini (10 pz)
Piacenza (3 pz)
Meldola (3 pz)
Ravenna (4 pz)
Cesena (2 pz)
Parma (5 pz)

Siena (2 pz)
Firenze (8 pz)
Pisa (5 pz)

Terni (2 pz)

Roma La Sapienza (26 pz)
Roma Cattolica (5 pz)
Roma Tor Vergata (1 pz)

Tricase (5 pz)
Lecce (4 pz)
S. Giovanni Rotondo (5 pz)

Sassari (1 pz)
Cagliari (4 pz)
Nuoro (3 pz)

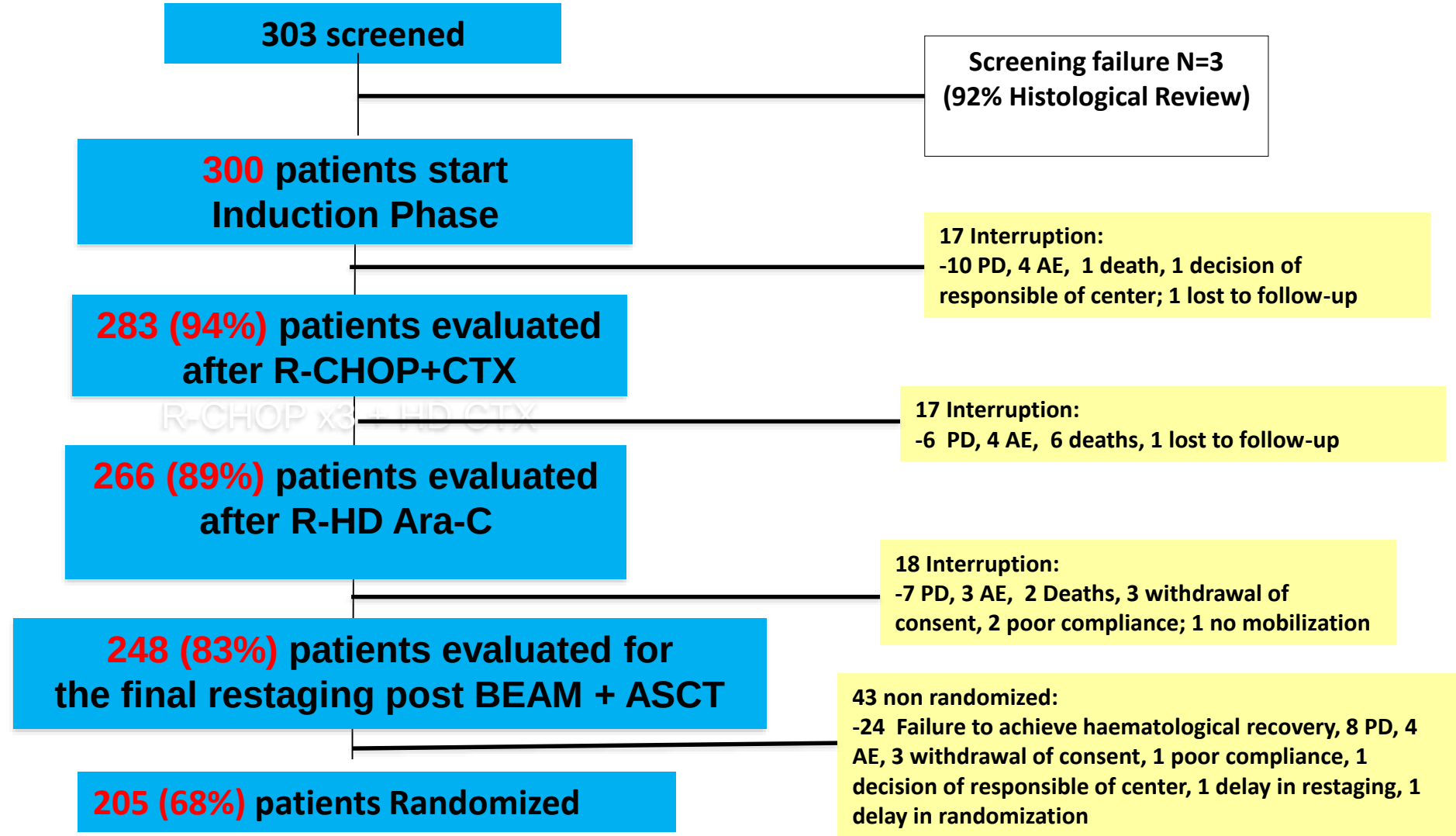
Nocera inferiore (2 pz)

Reggio Calabria (6 pz di cui 1 proveniente da Milano Niguarda)

Messina (2 pz di cui 1 proveniente da Udine)
Palermo (3 pz)

Italian Enrolling centres: 48
Italian Enrolled patients: 289
Portuguese Enrolling Centre: 1
Lisbon (Portugal) Enrolled patients: 11

MCL0208: patient flow



MCL0208: treatment interruptions

64/300 (21%) early treatment interruption not due to PD (31)

Cause	N
Failure to achieve haematological recovery	24
Adverse event	15
Death	9 (1 road accident ; 1 PEA and cardiac arrest on suspected acute pulmonary thromboembolism ; 3 septic shock ; 2 sudden deaths due to cardiovascular arrest; 1 Influence A H1N1 variant during neutropenic phase after second course of HD Cytarabine; 1 Pneumonia/renal Failure in ICU; 1 final cause unknown
No mobilization	1
Withdrawal of consent,	6
Decision of the responsible of the Study	2
Lost to follow-up	2
Poor compliance	3
Serious breach of the protocol	2

MCL0208: clinical characteristics at diagnosis

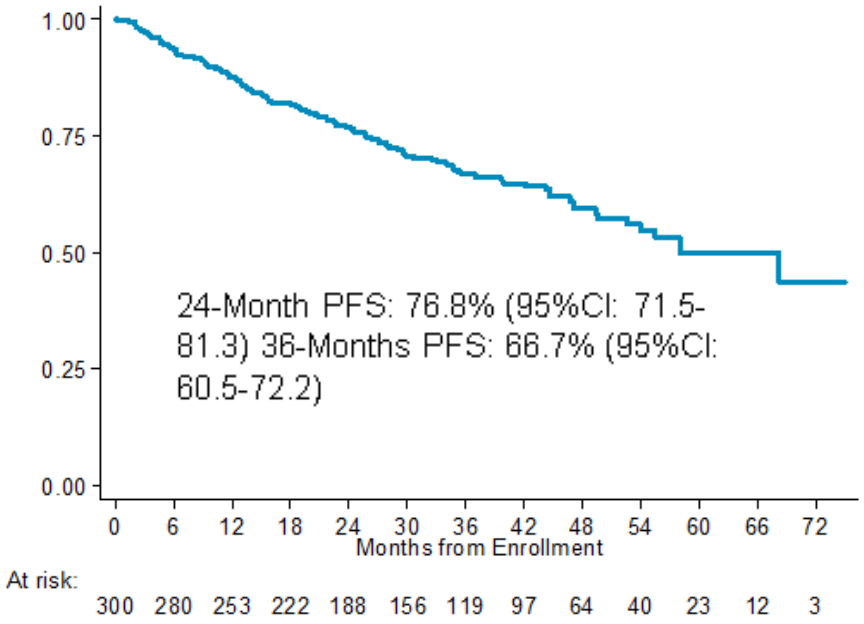
	N=300
Median age at enrollement (IQR)	57 (51-62)
Male	235 (78%)
LDH > UNV	98 (33%)
PS ECOG > 1	69 (23%)
Stage III/IV	293 (97%)
MIPI low	162(54%)
Intermediate	93(31%)
High	45 (15%)
Bulky disease (>5 cm)	98 (33%)
BM involvement	231(79%)
KI67>30%	84/271 (31%) (29 missing)
MIPI-c low	133 (49%)
Low/Int	79 (29%)
High/Int	36 (13%)
High	23 (8%)

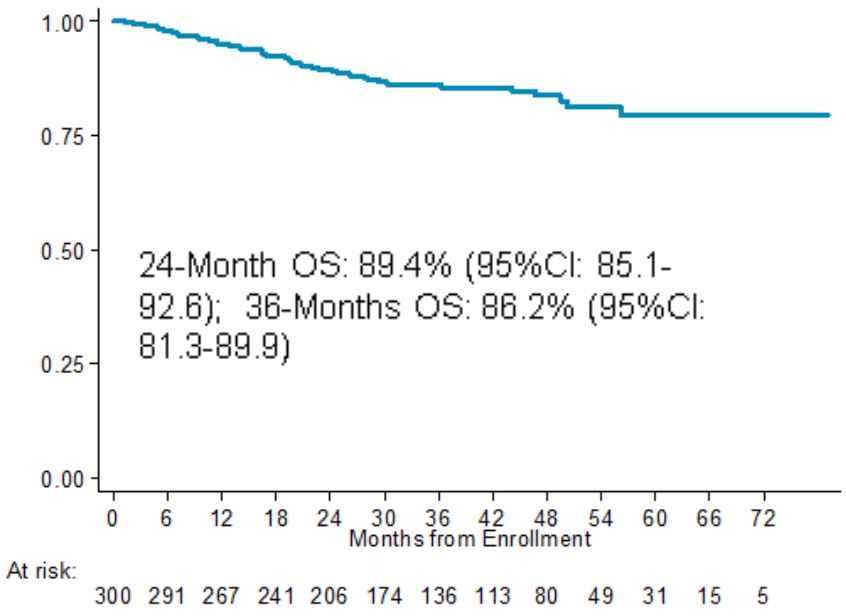
MCL0208: response rate

Final Response (including Intermediate+Final Response)	R-HDS+ASCT n = 300
CR/CRu	234 (78%)
PR	20 (7%)
NR/PG	31 (10%)
Deaths during treatment*	9 (3%)
Interruption not due to PD or death	6(2%)

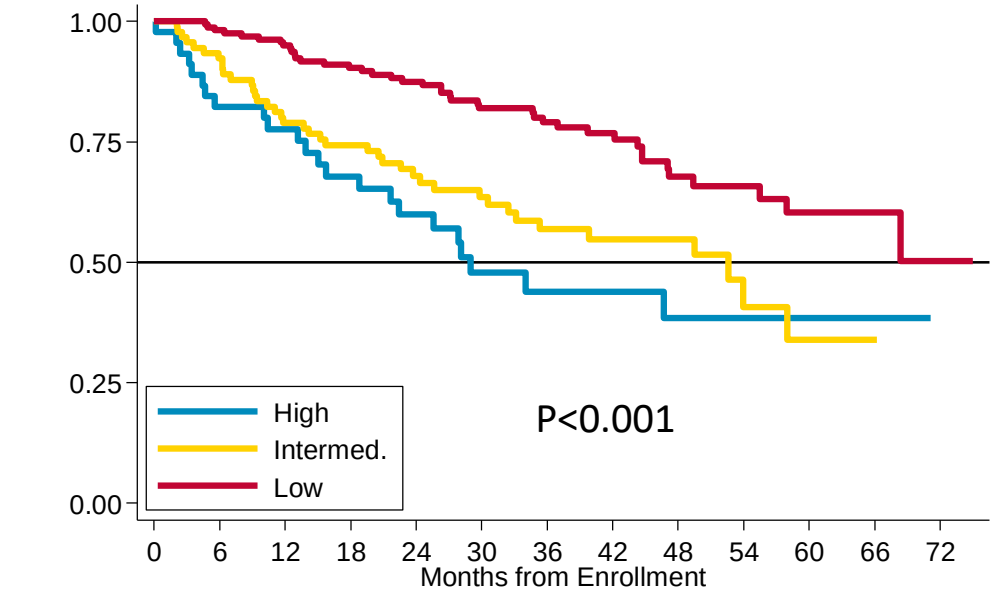
** One not related to treatment: road accident*

MCL0208: PFS and OS



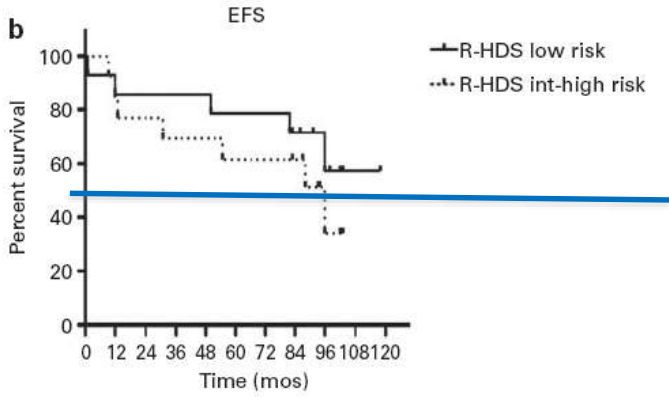


MCL0208: 2y-PFS according to MIPI

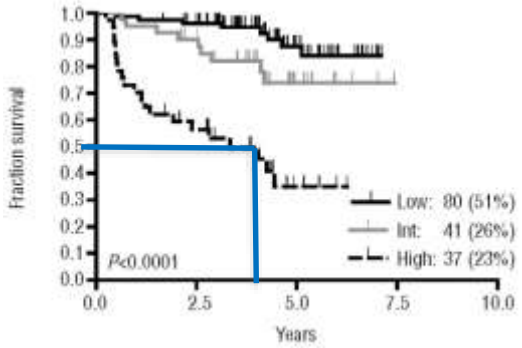


At risk:

High	45	37	32	27	22	13	11	10	6	6	2	2	0
Intermed.	91	84	70	62	48	42	31	26	19	7	3	1	0
Low	161	157	148	131	118	99	76	60	39	27	18	9	3



M Magni et al., Bone Marrow Transplant, 2009



CG Gaisler, blood, 2010

MCL0208: multivariate analysis for PFS

	Univariable		Multivariable	
	HR	p	HR	p
MIPI Interm vs Low	2.05	0.002	1.66	0.037
MIPI High vs Low	2.73	<0.001	1.62	0.111
Male vs Female	1.64	0.088	1.59	0.111
B symptomes	1.92	0.002	1.48	0.075
Bulky disease	1.96	0.001	1.6	0.03
Positive Bone	1.6	0.095	1.28	0.402
Ki67 High	2.1	0.001	1.65	0.03
MIPIc L-I vs L*	1.17	0.572	1.08	0.775
MIPIc H-I vs L*	1.73	0.077	1.17	0.633
MIPIc H vs L*	3.27	<0.001	2.51	0.008

* For Multivariable analysis, MIPI-C effect was not adjusted for MIPI and KI67.

MCL0208: multivariate analysis for OS

	Univariable		Multivariable	
	HR	p	HR	p
MIPI Interm vs Low	3.07	0.003	2.17	0.051
MIPI High vs Low	4.65	<0.001	2.4	0.056
Male vs Female	2.59	0.071	2.37	0.103
B symptomes	2.6	0.002	1.81	0.069
Bulky disease	2.0	0.026	1.54	0.187
Positive Bone	1.42	0.399	0.96	0.918
Ki67 High	4.21	<0.001	2.96	0.002
MIPIc L-I vs L*	1.17	0.752	1.06	0.912
MIPIc H-I vs L*	3.87	0.001	2.72	0.029
MIPIc H vs L*	5.17	0.001	4.00	0.006

* For Multivariable analysis, MIPI-C effect was not adjusted for MIPI and KI67.

MCL0208: results comparison

Regimen	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%
Hermine, 2016^	497	76 vs. 83%	6.1 yrs	5 yr TTF 40 vs 65% 5 yr PFS 45 vs 73	69 vs.76%	3.4% vs .3. 4%
Lyma trial, 2016 §	299	89%	50.2 mo.	4-yr EFS 79% vs. 61%; 4-yr PFS 83% vs. 64	4-yr OS 89% vs. 80%	4% vs. 4%
MCL 0208	300	78%	36 mo	3yr PFS 66.7%	3-yr OS 86.2%	3%

*JE Romaguera et al, JCO, 2005 and ( ) L Fayad and J Ramaguera, Clin Lymphoma Myeloma, 2007; **Merli et al, BJH, 2011;***Epner et al, Blood, 2007; § AM Gianni et al, Blood, 2003; #G:H. Geisler et al, Blood, 2008; ^ O Hermine et al. Lancet , 2016; § S Legouill et al, N Engl J Med, 2017.

MCL0208: timeline

- Enrolment of the first patient: 04/05/2010
- Enrolment of the last patient: 24/08/2015

- 1° Interim Analysis was performed on October 2012 after the occurrence of 20 events. First audio conference of the DSMB: 05/10/2012
- 2° Interim Analysis was performed on April 2017, but 40 events were registered on September 2016. Second audio conference of the DSMB: 27/09/2017
- Sixty events postrandomization have been registered at October 20th, 2017. Therefore, we are ready for the final analysis.

TRIANGLE: inclusion criteria

Autologous **T**ransplantation after a **R**ituximab/**I**brutinib/**A**ra-c containing i**N**duction in **G**eneralized mantle cell **L**ymphoma – a randomized **E**uropean MCL Network trial

- Histologically confirmed diagnosis of MCL according to WHO classification
- Suitable for high-dose treatment including high-dose Ara-C
- Stage II-IV (Ann Arbor)
- Age ≥ 18 years and ≤ 65 years
- Previously untreated MCL
- At least 1 measurable lesion; in case of bone marrow infiltration only, bone marrow aspiration and biopsy is mandatory for all staging evaluations.
- ECOG/WHO Performance Status ≤ 2
- The following laboratory values at screening (unless related to MCL):
  - Absolute neutrophil count (ANC) ≥ 1000 cells/µL
  - Platelets ≥ 100,000 cells/µL
  - Transaminases (AST and ALT) ≤ 3 x upper limit of normal (ULN)
  - Total bilirubin ≤ 2 x ULN unless due to known Morbus Meulengracht [Gilbert-Meulengracht-Syndrome])
  - Creatinine ≤ 2 mg/dL or calculated creatinine clearance ≥ 50 mL/min

TRIANGLE: exclusion criteria

- Major surgery within 4 weeks prior to randomization.
- Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon).
- History of stroke or intracranial hemorrhage within 6 months prior to randomization.
- Requires treatment with strong CYP3A4/5 inhibitors.
- Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of Ibrutinib capsules or put the study outcomes at undue risk.
- Vaccinated with live, attenuated vaccines within 4 weeks prior to randomization.
- Known CNS involvement of MCL.
- Clinically significant hypersensitivity (e.g. anaphylactic or anaphylactoid reactions to the compound of Ibrutinib itself or to the excipients in its formulation).
- Known anti-murine antibody (HAMA) reactivity or known hypersensitivity to murine antibodies.
- Previous lymphoma therapy with radiation, cytostatic drugs, anti-CD20 antibody or interferon except pre-phase therapy according to trial protocol

TRIANGLE: exclusion criteria

- Serious concomitant disease interfering with a regular therapy according to the study protocol:

  - Cardiac (clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart - Association Functional Classification or LVEF below LLN)
  - Pulmonary (e.g. chronic lung disease with hypoxemia)
  - Endocrinological (e.g. severe, not sufficiently controlled diabetes mellitus)
  - Renal insufficiency (unless caused by the lymphoma): Creatinine > 2x normal value and/or creatinin clearance < 50 ml/min)
  - Impairment of liver function (unless caused by the lymphoma): Transaminases > 3x normal or bilirubin > 2,0 mg/dl unless due to morbus Meulengracht (Gilbert-Meulengracht-Syndrome)
- Patients with unresolved hepatitis B or C infection or known HIV positive infection (mandatory test)
- Prior organ, bone marrow or peripheral blood stem cell transplantation
- Concomitant or previous malignancies within the last 3 years other than basal cell skin cancer or *in situ* uterine cervix cancer

TRIANGLE: objectives and endpoint

Primary Objective: To establish one of three study arms as future standard based on the comparison of the investigator-assessed failure-free survival (FFS).

Primary Endpoint: FFS defined as time from start of treatment to stable disease at end of immuno-chemotherapy, progressive disease or death from any cause.

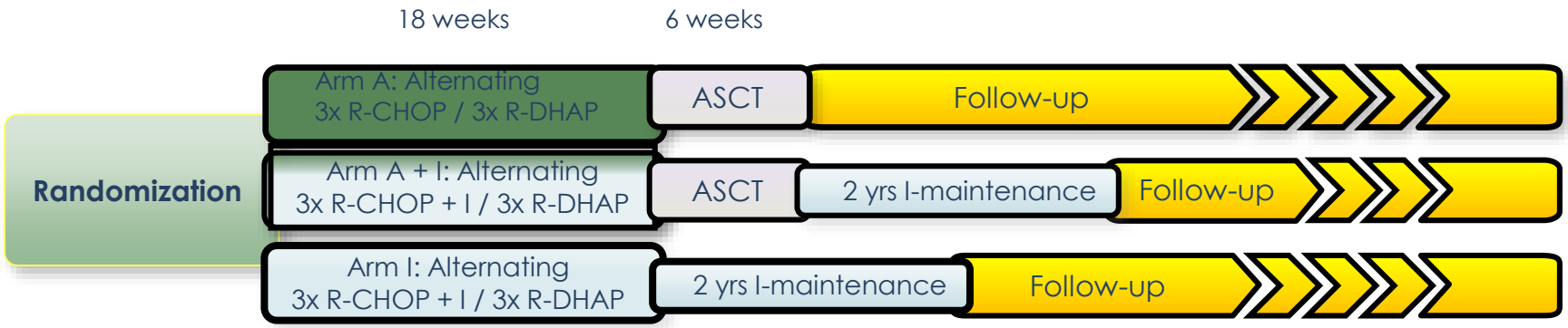
Secondary Objectives

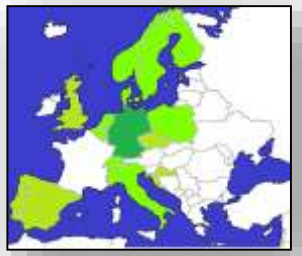
- To compare the efficacy of the three treatment arms in terms of secondary efficacy endpoints
- To determine the safety and tolerability of Ibrutinib during induction immuno-chemotherapy and during maintenance and to compare the safety profile of the three treatment arms in terms of secondary toxicity endpoints

Secondary Efficacy Endpoints

- Overall survival (OS)
- Progression-free survival (PFS) from randomization, from end of induction immuno-chemotherapy in patients with CR or PR at end of induction immuno-chemotherapy and from the staging 6 weeks after end of induction assessment (at month 6)
- Overall response and complete remission rates at midterm, at end of induction and 3 months after end of induction immuno-chemotherapy (at month 6)
- PR to CR conversion rate during follow-up after end of induction immuno-chemotherapy

TRIANGLE: study design

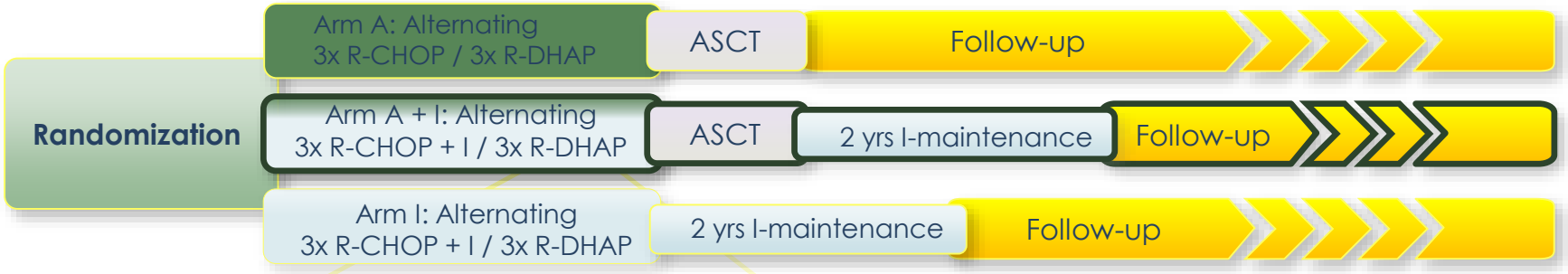




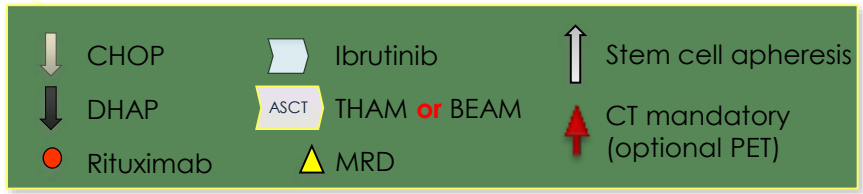
Study design:

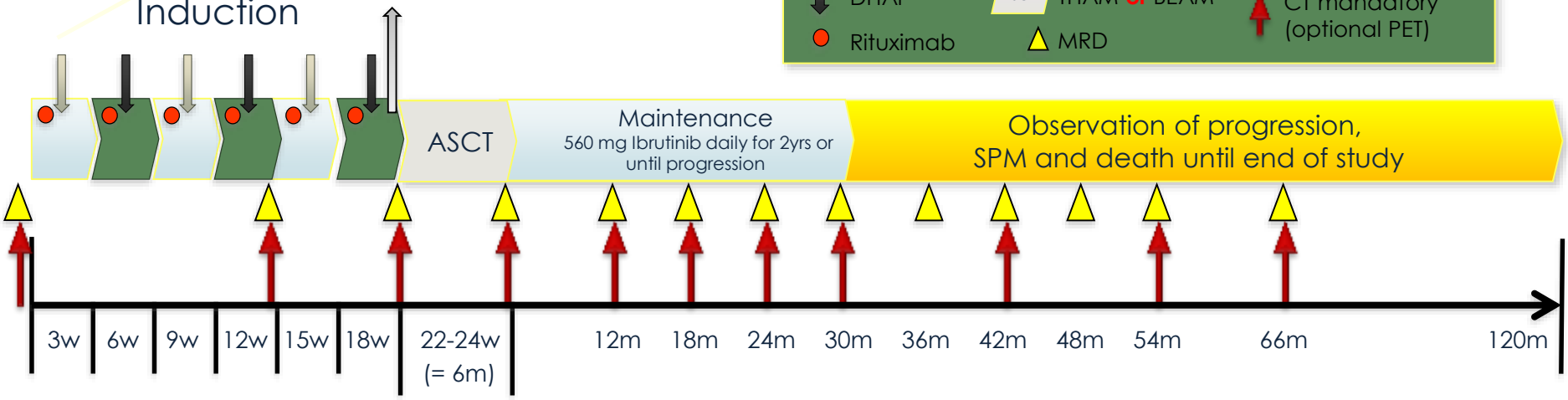
- Randomized, three-arm, parallel-group, open label, international phase III trial
- Up to 870 patients
- Up to 250 sites internationally (34 in Italy)
- Untreated patients (≥ 18 and ≤ 65 years) with mantle-cell lymphoma (MCL)
- The maximal trial duration will be up to 10 years with up to 5 years recruitment.
- The trial may stop earlier based on the result of pre-planned interim analyses.

TRIANGLE: experimental arm A+I

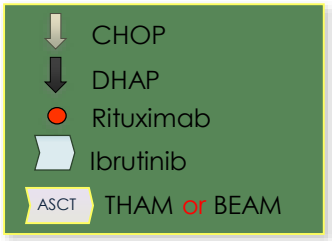


Experimental Arm A + I: R-CHOP + I / R-DHAP followed by ASCT and I-Maintenance





TRIANGLE: therapy, dose (arm A+I)



Arm A + I:

Alternating 3 cycles **R-CHOP+Ibrutinib**/3 cycles R-DHAP induction, followed by ASCT (THAM or BEAM) and 2 years Ibrutinib-Maintenance

R-CHOP (Cycle 1,3,5):

Rituximab 375 mg/m^2	D0 or 1 I.V.
Cyclophosphamide 750 mg/m^2	D 1 I.V.
Doxorubicine 50 mg/m^2	D 1 I.V.
Vincristine 1,4 mg/m^2(max 2mg)	D 1 I.V.
Predniso(lo)ne 100 mg	D 1-5 oral
Ibrutinib 560 mg	**D 1-19 oral**

R-DHAP (Cycle 2,4,6):

Dexamethasone 40 mg	D 1-4 oral or I.V.
Rituximab 375 mg/m^2	D 1 I.V.
Ara-C 2x 2 g/m^2 q12h	D 2 I.V. 3 h
Cisplatine 100 mg/m^2	D1 I.V. 24 h
(alternative Oxaliplatin 130 mg/m^2	D1 I.V.)
G-CSF 5µg/kg	D6 daily SC*

*** G-CSF mandatory in R-DHAP from D6 daily 5µg/kg until recovery of WBC > 2.5 G/l Alternatively pegfilgrastim may be applied once at D6.**

Stem cell apheresis after the last cycle R-DHAP

ASCT conditioning (within 2 weeks after end of induction visit):
THAM or BEAM, stratified per site before trial activation at site

THAM:

TBI 10 Gy	D –7 to –5
Ara-C 2x 1,5 g/m^2 q12h	D –4, –3 I.V. 30 min
Melphalan 140 mg/m^2	D –2 I.V. 1h

BEAM:

BCNU 300 mg/m^2	D –7, I.V. 1h
Etoposide 2x 100 mg/m^2 q12h	D –6 to –3 I.V. 1 h
Cytarabine 2x 200 mg/m^2 q12	D –6 to –3 I.V. 30 min
Melphalan 140 mg/m^2	D –2 I.V. 1h

The availability of BCNU may be challenging in some centers. Instead, TEAM (Thiotepa 5mg/kg twice a day D-7) may be considered based on a retrospective EBMT comparison

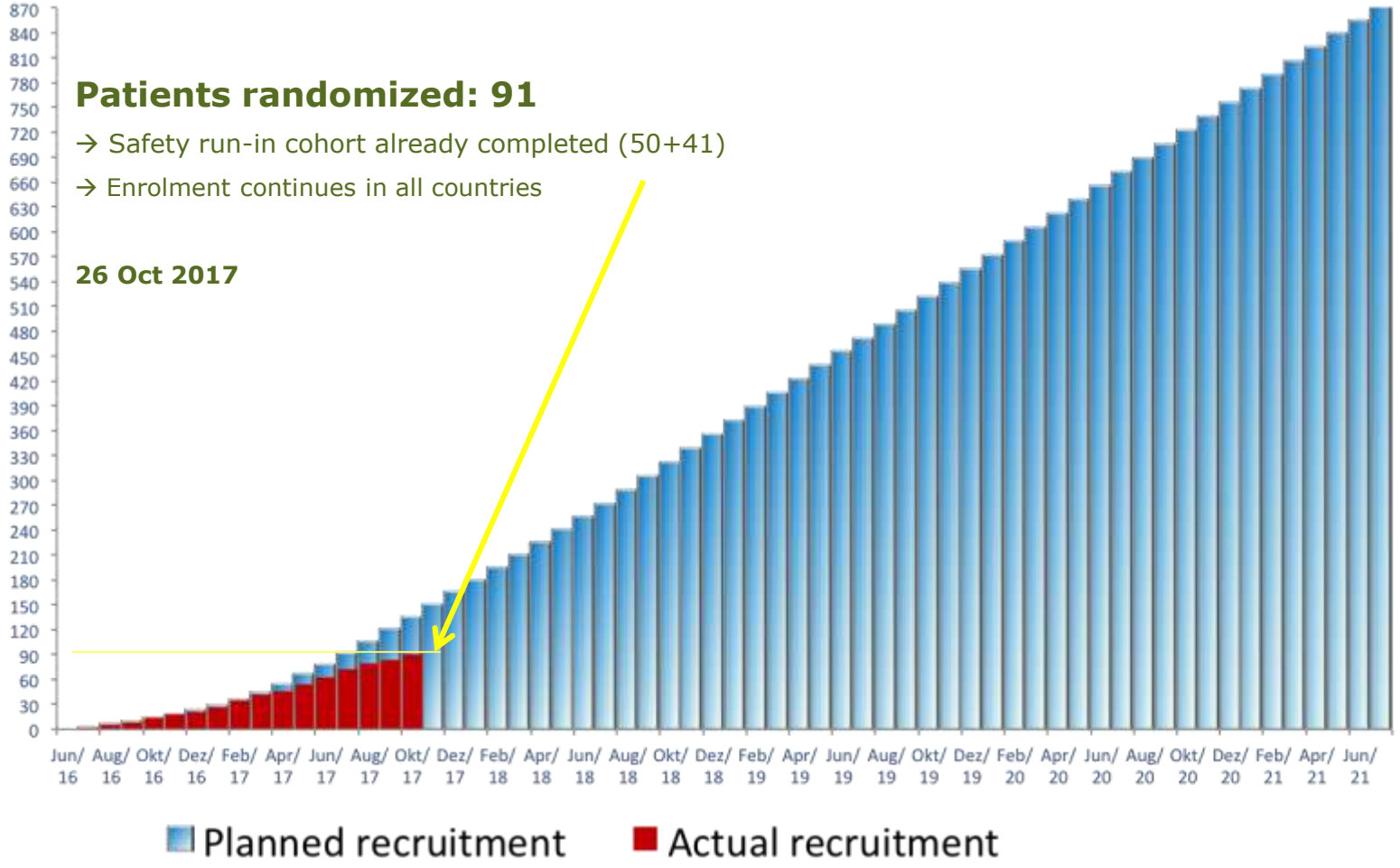
Ibrutinib-Maintenance: Ibrutinib 560 mg (daily, oral) for 2 years, earliest start – week 22 (s. Protocol 7.2.6).

Rituximab maintenance may be added to all 3 study arms depending on national guidelines. (Refer to 7.2.7 for details)

TRIANGLE: frequent issues

- **Hepatitis:** HCV RNA, HBV DNA neg are OK with lamivudine for HBV
- **CNS prophylaxis:** NOT allowed (not recommended worldwide, not studied in combination with Ibrutinib that indeed crosses the blood-brain barrier)
- **Rituximab maintenance:** country-specific decision but MUST be included in all of the three arms. At the last CLA meeting it was decided not to include it for Italian patients. The decision might change in the future
- **Conditioning Regimen:** BEAM (BCNU could be substituted with thiotepa (TEAM) but not with fotemustine). Some countries use a TBI based regimen (THAM)
- **DHAP:** Should be the original DHAP in term of timings, but oxaliplatin 130mg is allowed.

TRIANGLE: recruitment



APPROVAL STATUS IN ITALY (2)

Italian participating centers (n. 34)

	SITE	TITLE	SURNAME PI	NAME PI
1	**Alessandria (coordinatore in Italia)**	Dr.	Ladetto	Marco
2	**Bologna**	Dr.	Stefoni	Vittorio
3	**Bolzano**	Dr.	Mian	Michael
4	**Brescia**	Dr.	Re	Alessandro
5	**Cagliari**	Dr.ssa	Cabras	Maria Giuseppina
6	**Cuneo**	Dr.ssa	Castellino	Claudia
7	**Firenze**	Dr.	Rigacci	Luigi
8	**Genova**	Prof.	Gobbi	Marco
9	**Genova**	Dr.ssa	Congiu	Angela
10	**Meldola (FC)**	Dr.	Musuraca	Gerardo
11	**Milano**	Dr.ssa	Rusconi	Chiara
12	**Milano**	Dr.	Ferreri	Andres
13	**Modena**	Prof.	Narni	Franco
14	**Monza**	Dr.ssa	Bolis	Silvia
15	**Napoli**	Dr.	Pinto	Antonello
16	**Novara**	Prof.	Gaidano	Gianluca
17	**Palermo**	Dr.ssa	Patti	Caterina

	SITE	TITLE	SURNAME PI	NAME PI
18	**Pavia**	Prof.	Arcaini	Luca
19	**Piacenza**	Dr.ssa	Arcari	Annalisa
20	**Pisa**	Prof.	Petrini	Mario
21	**Ravenna**	Dr.ssa	Tani	Monica
22	**Reggio Calabria**	Dr.ssa	Stelitano	Caterina
23	**Reggio Emilia**	Dr.	Merli	Francesco
24	**Rimini**	Dr.ssa	Molinari	Annalia
25	**Roma**	Prof.	Martelli	Maurizio
26	**Roma**	Prof.ssa	Cantonetti	Maria
27	**San Giovanni Rotondo**	Dr.	Cascavilla	Nicola
28	**Torino**	Dr.	Vitolo	Umberto
29	**Torino**	Dr.ssa	Cavallo	Federica
30	**Treviso**	Dr.	Stefani	Piero Maria
31	**Tricase**	Dr.	Pavone	Vincenzo
32	**Udine**	Prof.	Zaja	Francesco
33	**Verona**	Dr.	Benedetti	Fabio
34	**Vicenza**	Dr.	Visco	Carlo

V-RBAC

Clinical Protocol

Rituximab, bendamustine and cytarabine followed by venetoclax (V-RBAC) in high-risk elderly patients with mantle cell lymphoma (MCL)

ID Study: FIL_V-RBAC
EudraCT number: ……..

INVESTIGATOR SPONSOR
Fondazione Italiana Linfomi ONLUS (FIL)

COORDINATING INVESTIGATOR	**Carlo Visco, MD, Vicenza, IT**
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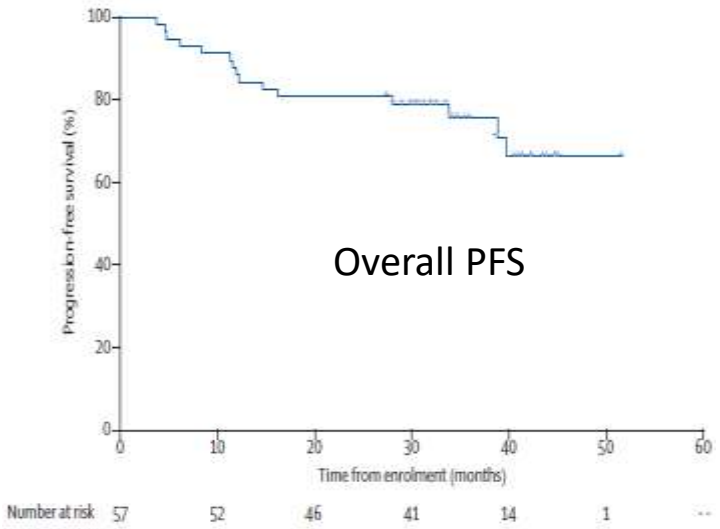
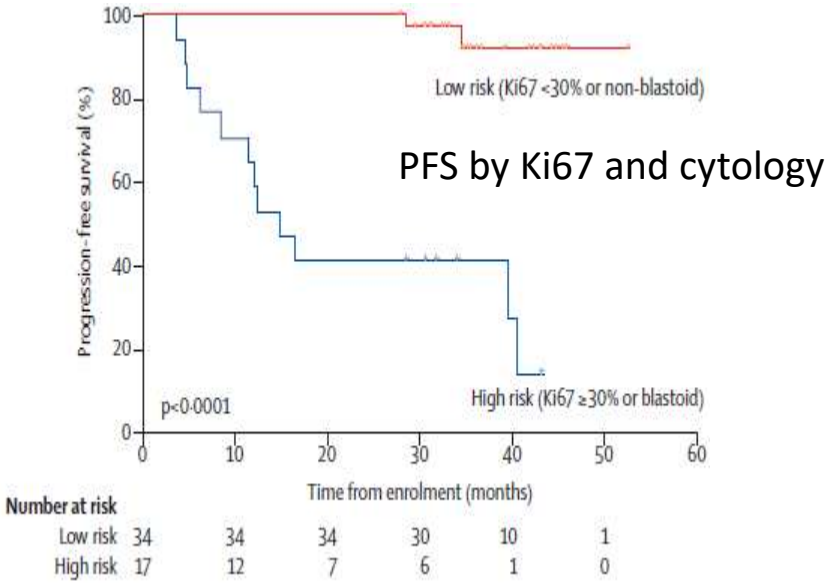
Rituximab, Bendamustine and Cytarabine (RBAC500) As Induction Therapy in Elderly Patients with MCL: Final Results of a Phase 2 Study from the FIL

Evaluable patients	57
ORR	52 (91%)
CR	52 (91%)



Overall PFS



PFS by Ki67 and cytology

Visco C et al, Lancet Haematol 2017

V-RBAC: inclusion criteria

- Previously untreated patients with MCL aged ≥65 years if they are FIT according to the geriatric CGA assessment.
- age ≤64 years not eligible to high-dose chemotherapy plus transplantation, FIT or UNFIT according to the geriatric CGA assessment.
- No indolent MCL (disease confined to the bone marrow/peripheral blood/spleen, without any other nodal or extranodal involvement).
- No chronic treatment with strong CYP3A inhibitors (e.g. ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole)

V-RBAC: endpoints and study design

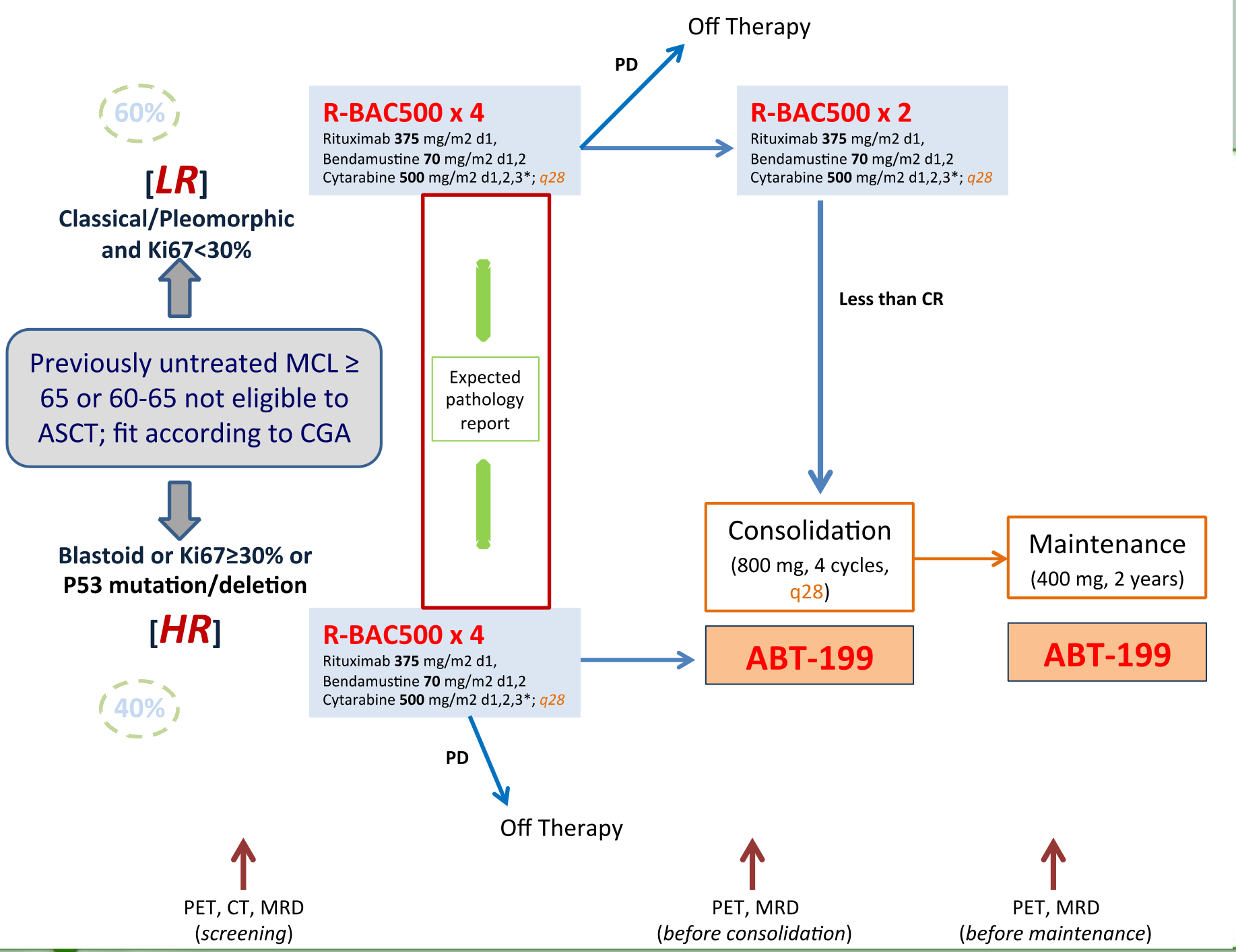
Primary Endpoint: 2-years PFS from date of diagnosis

- 35 FIL Centers
- Time of enrollment: 2.5 years
- Minimum follow-up: 2 years
- Study duration: 7 years
- Statistical Tool: one arm non parametric survival (SWOG)
- Alpha-error (one tail): 0.05

2-years PFS RBAC500 (H0)	2-years PFS RBAC500+V(H1)	Power	Patients number (**High Risk**)	Patients to be enrolled
40%	60%	90%	52	130

Secondary Endpoints

The rate of molecular response (analyzed in the labs of the FIL-MRD Network) of *HR* patients
The progression-free survival (PFS) of *LR* patients, of all enrolled patients, and of P53 mutated patients
The overall survival (OS)
The duration of responses (DoR)
The rate of complete remission (CR) before and after Venetoclax in the HR group
The rate of patients that complete the expected treatment schedule
The rate of patients that are subject to dose reductions or delays
The safety of Venetoclax when administered as consolidation or maintenance after R-BAC


Off Therapy
PD
60%
R-BAC500 x 4
Rituximab 375 mg/m2 d1,
Bendamustine 70 mg/m2 d1,2
Cytarabine 500 mg/m2 d1,2,3*; q28
R-BAC500 x 2
Rituximab 375 mg/m2 d1,
Bendamustine 70 mg/m2 d1,2
Cytarabine 500 mg/m2 d1,2,3*; q28
[LR]
Classical/Pleomorphic
and Ki67<30%
Less than CR
Previously untreated MCL ≥ 65 or 60-65 not eligible to ASCT; fit according to CGA
Expected pathology report
Consolidation
(800 mg, 4 cycles, q28)
Maintenance
(400 mg, 2 years)
Blastoid or Ki67≥30% or
P53 mutation/deletion
[HR]
R-BAC500 x 4
Rituximab 375 mg/m2 d1,
Bendamustine 70 mg/m2 d1,2
Cytarabine 500 mg/m2 d1,2,3*; q28
ABT-199
ABT-199
40%
PD
Off Therapy
PET, CT, MRD
(screening)
PET, MRD
(before consolidation)
PET, MRD
(before maintenance)

V-RBAC: MRD analysis

All enrolled patients

Only HR

MRD Baseline

Follow-up

1) nPCR and qPCR (*Affiliated Lab*)

PB and BM

PB and BM x 5

2) Flow cytometry^ (*Vicenza Lab*)

*PB only**

Only if+
at baseline

PB x 5

^Two 8-colour combinations on PB

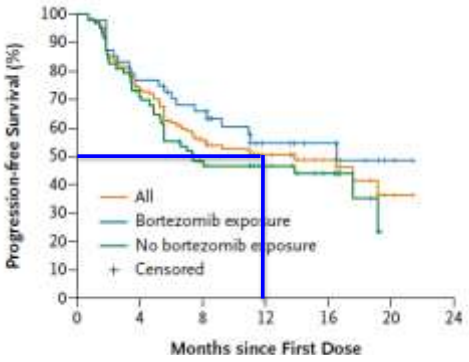
a) CD20/CD23/CD5/CD19/CD200/CD62L/CD3/CD45

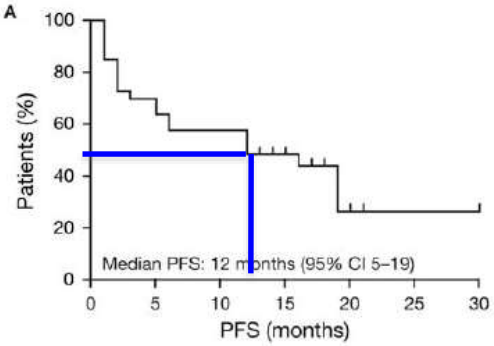
b) lambda/kappa/CD5/CD19/CD305/CD11a/CD3/CD45

*TransFix/EDTA
Storage 2-8°C

KRD for BTKi R/R MCL: a phase 2 study

- Investigator Sponsor Study
- Sponsor: FIL
- Phase 2, single arm, multicenter study
- Involves centers participating FIL and the MCL network





- Lenalidomide is approved for the treatment of MCL
- Bortezomib received FDA approval for R/R MCL
- KRD in MM: ASPIRE Study (Stewart 2015)

Salvage treatment with lenalidomide and dexamethasone in relapsed/refractory mantle cell lymphoma: clinical results and effects on microenvironment and neo-angiogenic biomarkers

Francesco Zaja,[1] Stefano De Luca,[1] Umberto Vitolo,[2] Lorella Orsucci,[2] Alessandro Levis,[3] Flavia Salvi,[3] Chiara Rusconi,[4] Erika Ravelli,[4] Alessandra Tucci,[5] Chiara Bottelli,[5] Monica Balzarotti,[6] Ercole Brusamolino,[7] Maurizio Bonfichi,[7] Stefano A. Pileri,[8] Elena Sabattini,[8] Stefano Volpetti,[1] Chiara Monagheddu,[9] Angelo Vacca,[10] Roberto Ria,[10] and Renato Fanin[1]

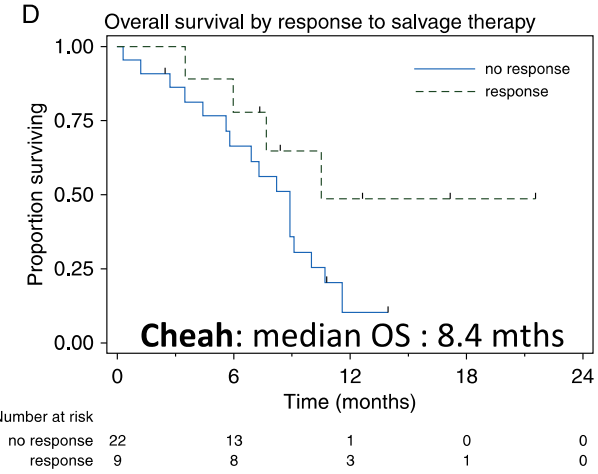
haematologica | 2012; 97(3)

KLIMT: backgrounds

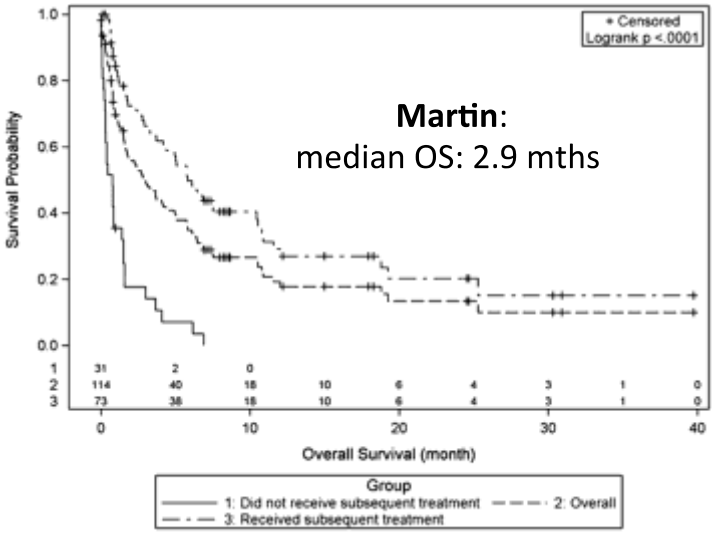
Table 2. Treatment regimens and response rates among patients treated for disease progression following discontinuation of ibrutinib

Regimen	*N*	ORR	CRR	mOS (months)
Hyper-CVAD	8	3 (37%)	2 (25%)	7.3
Bendamustine based	6	2 (33%)	2 (33%)	10.0
Investigational agent	3	2 (66%)	1 (33%)	NR
Lenalidomide based	3	1 (33%)	0 (0%)	10.5
Bortezomib based	3	0 (0%)	0 (0%)	6.9
Platinum based	2	1 (50%)	1 (50%)	8.2
Radiation	4	1 (25%)	0 (0%)	5.6
Fludarabine based	2	0 (0%)	0 (0%)	2.7
Overall	31	10 (32%)	6 (19%)	8.4

All salvage chemotherapy regimens contained rituximab.
hyper-CVAD, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; ORR, objective response rate; CRR, complete response rate; mOS, median overall survival.



Subsequent treatment		
Rituximab	39	53%
Lenalidomide	19	26%
Cytarabine	13	18%
Bendamustine	12	16%
Bortezomib	7	10%
Anthracycline	5	7%
PI3K inhibitor	4	5%



Cheah C.Y. et al. Annals of Oncology 2015;
Martin P et al. Blood 2016

KLIMT: population, objectives

Target population: BTKi R/R MCL

Primary objective: 12-months OS

Secondary enpoints: ORR, CR, PR, SD, PFS, TTR, DoT, Safety

- Age </= 80 years
- PS </= 2
- At least one previous line of therapy
- Previous treatment with Ibrutinib monotherapy or in combination
- Previous treatment with Lenalidomide is accepted if patient resulted responsive and interrupted Lenalidomide at least 12 months before enrollment to this study
- No CNS
- Adequate hepatic, hematologic, and renal function
- Excluded patients with cardiac disorders

KLIMT: treatments

Lenalidomide (maximum period of treatment= *24 cycles*)

•Lenalidomide: 25* mg/daily on day 1 to 21 of a 28 days course

* For patients with creatinine clearance ≥ 30 mL/min but < 50 mL/min the dosage of R will be 10 mg/daily on day 1 to 21 of a 28 days course;

Carfilzomib (maximum period of treatment= *24 cycles*)

•*Cycles 1-12*: Carfilzomib: on days 1, 2, 8, 9, 15, 16

The dosage of Carfilzomib will be 20 mg/m^2 on days 1 and 2 during cycle 1 and then Carfilzomib 27 mg/m^2 thereafter;

•*Cycles 13-24*: Carfilzomib: on days 1, 2, 15, 16

The dosage of Carfilzomib will be 27 mg/m^2

Dexamethasone (maximum period of treatment= *24 cycles*)

•Dexamethasone 20 mg on days 1-2, 8-9, 15-16, 22-23

•Dexamethasone 10 mg on days 1-2, 8-9, 15-16, 22-23 (age > 75)

KLIMT: statistics

Hypothesis:
in this setting of patients, the addition of Carfilzomib to Lenalidomide + Dexa may produce a **15% increase of the expected 12-months OS** with available treatments (from 30% to 45%).

Sample size:
- Fleming's Single Stage Phase II Design
- alpha error (one sided), equal to 0.05, a beta error equal to 0.20
- 2 years of accrual
- 1 year of follow up
- required sample size is **59 patients** who start treatment after screening phase

The lower limit of the 90% confidence interval (according to 1-sided alpha error of 0.05) of the 1-year OS must be higher than the null hypothesis of 0.30 to conclude that the new treatment is promising.

KLIMT: timing, centers

Participating centers:

- Italy: 20
- UK: 5
- Spain: 4
- Poland: 3
- The Netherlands : 2

The anticipated study dates (start/end) are:

- 1st patient enrolled (FPFV): January 2018 (?)
- Last patient enrolled (LPLV): December 2019 (?)

Patients will be evaluated at 12 cycles after the start of treatment of the last patient

Responsive patients (CR, PR, SD) may continue to receive KL until to 24 cycles.

Grazie per l'attenzione