Title	**TRIANGLE**: autologous **T**ransplantation after a **R**ituximab/**Ibrutinib**/**A**ra-c containing i**N**duction in **G**eneralized mantle cell **L**ymphoma – a randomized **E**uropean MCL Network trial
Short title	**TRIANGLE**
EudraCT-no.	**2014-001363-12**
Trial design	Randomized, three-arm, parallel-group, open label, international phase III trial comparing six alternating courses of R-CHOP/R-DHAP (one cycle every 21 days) followed by ASCT versus the combination with ibrutinib in induction and maintenance (2 years) or the experimental arm without ASCT **Study Overview (Figure 1 and 2)**
Number of subjects	Up to 870 patients
Number of sites	Up to 250 sites internationally
Target population	Untreated patients (≥ 18 and ≤ 65 years) with mantle-cell lymphoma (MCL)
Study Duration	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.
Trial participation duration for individual patient	The maximal trial participation duration per patient will be up to 10 years (18 weeks induction therapy, 6 weeks ASCT, 2 years Ibrutinib-Maintenance, observation until progression, and follow-up until the end of the trial)
Investigational medicinal product (IMP)	Trade Name: Imbruvica Substance: Ibrutinib Manufacturer: Janssen Research & Development, LLC (JRD) and Pharmacyclics LLC.
Inclusion criteria	All patients must meet the following criteria: • 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 • Written informed consent form according to ICH/EU GCP and national regulations • Sexually active men and women of child-bearing potential must agree to use highly effective contraceptives (eg, condoms, implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence, or sterilized partner) while on study; this should be maintained for 90 days after the last dose of study drug.
Exclusion criteria	Any potential subject who meets any of the following criteria will be excluded from participating in the study. • Major surgery within 4 weeks prior to randomization. • Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg 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 (eg, 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 protein • Previous lymphoma therapy with radiation, cytostatic drugs, anti-CD20 antibody or interferon except prephase therapy according to trial protocol • 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 • Pregnancy or lactation • Any psychological, familiar, sociological, or geographical condition potentially hampering compliance with the study protocol and follow up schedule • Subjects not able to give consent • Subjects without legal capacity who are unable to understand the nature, scope, significance and consequences of this clinical trial • Therapy in another clinical trial within 30 days before randomization in this study.
Scientific rationale	According to current European guidelines (Dreyling, Ann Oncol 2014), the standard of care in younger patients with mantle cell lymphoma (MCL) is a dose-intensified approach with a cytarabine containing immunochemotherapy induction followed

	by autologous transplantation (ASCT; Hermine, ICML 2013). Ibrutinib has recently shown impressive efficacy data in relapsed MCL while tolerability was rather favorable (Wang, NEJM 2013). Based on these prerequisites, our study proposal challenges the current standard of care and questions, whether the addition of ibrutinib (arm A+I) to the standard (control arm A) results in a superior clinical outcome. In addition, we investigate whether ASCT which sometimes is hampered by short and long term toxicity is still superior to a (hopefully much better tolerated) conventional treatment without ASCT and with the addition of ibrutinib in induction and maintenance (duration 2 years, arm I). As so far combination data are only available with the R-CHOP regimen, ibrutinib is only applied in combination with R-CHOP. There will be an initial safety run-in phase of 50 patients which will be closely monitored for the observed toxicities during induction. Analysis of minimal residual disease (MRD) will play a critical role in identifying specific patient subpopulations which may be especially prone to one of the three therapeutical strategies. According to the recently completely recruited LyMa trial rituximab maintenance may be added to all 3 study arms depending on national guidelines.
Objectives and Endpoints	***Primary Objective:*** To establish one of three study arms, R-CHOP/R-DHAP followed by ASCT (control arm A), R-CHOP+ibrutinib /R-DHAP followed by ASCT and ibrutinib maintenance (experimental arm A+I), and R-CHOP+ibrutinib /R-DHAP followed by ibrutinib maintenance (experimental arm I) 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, 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

Secondary Toxicity Endpoints:

- Rates of AEs, SAEs, and SUSARs by CTC grade (Version 4.03) during induction immuno-chemotherapy and during periods of follow-up after response to immune-chemotherapy
- Cumulative incidence rates of SPMs

Exploratory Objectives:

- To compare feasibility of ASCT in arm A+I vs. arm A
- To compare minimal residual disease status between the three treatment groups
- To determine the impact of ibrutinib during induction immuno-chemotherapy and during maintenance therapy on the minimal residual disease status
- To determine the prognostic value of minimal residual disease status
- To determine the prognostic value of positron emission tomography with fluorine 18-fluorodeoxyglucose
- To determine clinical and biological prognostic and predictive factors
- To determine the role of total body irradiation (TBI) in ASCT conditioning

Exploratory Endpoints:

- Rate of successful stem cell mobilisations (success: separation of at least $2x2x10^6$ CD34-positive cells, including a back-up)
- Rate of molecular remissions (MRD-negative patients) at

	midterm, at end of induction immuno-chemotherapy, and at staging time-points during follow-up in patients with remission after end of induction immuno-chemotherapy • Time to molecular remission from start of therapy • Time to molecular relapse for patients in clinical and molecular remission after end of induction immuno-chemotherapy • RD in FDG-PET negative or positive patients after induction and ASCT ***Exploratory objectives may be evaluated only in a subset of patients according to local standards and resources.***

Regimen, Frequency, Dose and Route of Administration

ARM A: Standard of Care
Alternating 3 cycles R-CHOP / 3 cycles R-DHAP induction followed by ASCT (THAM or BEAM)

Induction: Alternating 3 x R-CHOP / 3 x R-DHAP, every 21 days,

R-CHOP (cycle 1,3,5):		R-DHAP (cycle 2,4,6):	
Rituximab 375 mg/m^2	D0 or 1 I.V.	Dexamethasone 40 mg	D 1-4 oral or I.V.
Cyclophosphamide 750 mg/m^2	D 1 I.V.	Rituximab 375 mg/m^2	D 1 I.V.
Doxorubicine 50 mg/m^2	D 1 I.V.	Ara-C 2x 2 g/m^2 q12h	D 2 I.V. 3 h
Vincristine 1,4 mg/m^2(max 2mg)	D 1 I.V.	Cisplatine 100 mg/m^2	D1 I.V. 24h
Predniso(lo)ne 100 mg	D 1-5 oral	(alternatively 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 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 1h

or

BEAM:

BCNU 300 mg/m^2	D –7,IV 1h
Etoposide 2x 100 mg/m^2 q12h	D –6 to –3 IV 1 h
Cytarabine 2x 200 mg/m^2 q12h	D –6 to –3 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 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[1]

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

Experimental 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

Induction: Alternating 3x R-CHOP / 3x R-DHAP, every 21 days plus oral Ibrutinib in cycles 1, 3, 5, days 1-19

Due to lack of published data Ibrutinib is applied only in cyles 1, 3, 5 (R-CHOP) and not in combination with R-DHAP.

R-CHOP (cycle 1,3,5):		R-DHAP (cycle 2,4,6):	
Rituximab 375 mg/m^2	D 0 or 1I.V.	Dexamethasone 40 mg	D 1-4 oral or I.V.
Cyclophosphamide 750 mg/ m^2	D 1 I.V.	Rituximab 375 mg/m^2	D 1 I.V.
Doxorubicine 50 mg/ m^2	D 1 I.V.	Ara-C 2x 2 g/m^2 q12h	D 2 I.V. 3 h
Vincristine 1,4 mg/m^2(max 2mg)	D 1 I.V.	Cisplatine 100 mg/ m^2	D1 I.V. 24h
Predniso(lo)ne 100 mg	D 1-5 oral	(alternatively Oxaliplatin130mg/m^2	D1 I.V.)
Ibrutinib 560mg	D1-19 oral	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 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 1h

or

BEAM:

BCNU 300 mg/m^2	D –7,IV 1h
Etoposide 2x 100 mg/m^2 q12h	D –6 to –3 IV 1 h
Cytarabine 2x 200 mg/m^2 q12h	D –6 to –3 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 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[1]

Ibrutinib-Maintenance: Ibrutinib 560 mg (daily, oral), for 2 years, see above

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

Experimental Arm I
Alternating 3 cycles R-CHOP+Ibrutinib / 3 cycles R-DHAP induction, followed by 2 years Ibrutinib-Maintenance

Induction: Alternating 3x R-CHOP / 3x R-DHAP, every 21 days plus oral Ibrutinib in cycles 1, 3, 5, days 1-19

Due to lack of published data Ibrutinib is applied only in cyles 1, 3, 5 (R-CHOP) and not in combination with R-DHAP.

R-CHOP (cycle 1,3,5):		R-DHAP (cycle 2,4,6):	
Rituximab 375 mg/m^2	D 0 or I.V.	Dexamethasone 40 mg	D 1-4 oral or I.V.
Cyclophosphamide 750 mg/ m^2	D 1 I.V.	Rituximab 375 mg/m^2	D 1 I.V.
Doxorubicine 50 mg/ m^2	D 1 I.V.	Ara-C 2x 2 g/m^2 q12h	D 2 I.V. 3 h
Vincristine 1,4 mg/m^2(max 2mg)	D 1 I.V.	Cisplatine 100 mg/m^2	D1 I.V. 24h
Predniso(lo)ne 100 mg	D 1-5oral	(alternatively Oxaliplatin 130mg/m^2	D1 I.V.)
Ibrutinib 560mg	D1-19oral	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

Since no ASCT is applied in this arm, stem cell apheresis is not planned but may be performed due to local standards.

Ibrutinib-Maintenance: Ibrutinib 560 mg (daily, oral), 2 years

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

Data management	All data will be included in an e-CRF via a safe internet access. The data will be entered by the local study team.
Assessments of :	
– **Efficacy**	Response assessment at midterm (after 4 cycles), at end of induction, 6 weeks after end of induction response assessment, and thereafter half-yearly for 2 years and thereafter yearly until progression.
– **Safety**	During a safety run-in phase, 50 patients will be fully monitored. If no unexpected toxicity has been observed, subsequent patients will be monitored only for patient informed consent, grade III/IV toxicities and SAEs as well as remission status.
Statistical methods	
– **Statistical tests**	Three pairwise one-sided statistical hypothesis tests will be performed using the log-rank statistic for FFS. The evaluation will be performed based on the intention to treat. The hypotheses are as follows: **FFS comparison** / **Null Hypothesis** / **Alternative Hypothesis** **A vs. I** / A not superior to I / A superior to I **A+I vs. A** / A+I not superior to A / A+I superior to A **A+I vs. I** / A+I not superior to I / A+I superior to I For each pairwise test, the local significance level will be 0.05/3, such that a global significance level of 5% is maintained (Bonferroni-correction for multiple testing). The trial is planned to be powered to detect a superiority of A compared to I of 16% in FFS at 5 years (64.8% vs. 48.5%, hazard ratio 0.60) with a probability of 95%. These differences are based on the clinical assumption that only a major benefit (>15% difference of FFS at 5 years) justifies the application of a myeloablative consolidation with potential late toxicities. It is also planned to detect a superiority of A+I vs. A and of A+I vs. I of 12% at 5 years (77.1% vs. 64.8% failure free, hazard ratio 0.60) with a probability of 90% each.
– **Interim analyses and early stopping rules**	Regular pre-planned interim analyses will be performed for each pairwise comparison half-yearly. The multiple testing correction for interim analyses will be performed using truncated sequential probability ratio tests (Whitehead, 1985). If the statistical monitoring decides for superiority of A compared to I, allocation to arm I will be closed prematurely, and the comparison of A+I vs. A will be continued until its decision. If the true hazard ratio of A vs. I is 0.60, 0.53, or 0.46, the median duration until the decision for superiority of A vs. I will be 5, 4, or 3.25 years, respectively. If the statistical monitoring for A vs. I decides for the null hypothesis,

allocation to arm A will be closed prematurely, and the comparison of A+I vs. I will be continued until its decision. If the true hazard ratioof A vs. I is 1.0, 1.29, or 1.67, the median time until a decision for of A vs. I will be 4.75, 3.75, or 3.5 years, respectively. If the true hazard ratios are 1.0 for A vs. I and 0.6 for A+I vs. A, the median trial duration will be 6.5 years. The maximal trial duration will be 10 years (5 years of recruitment and 5 years additional follow-up).

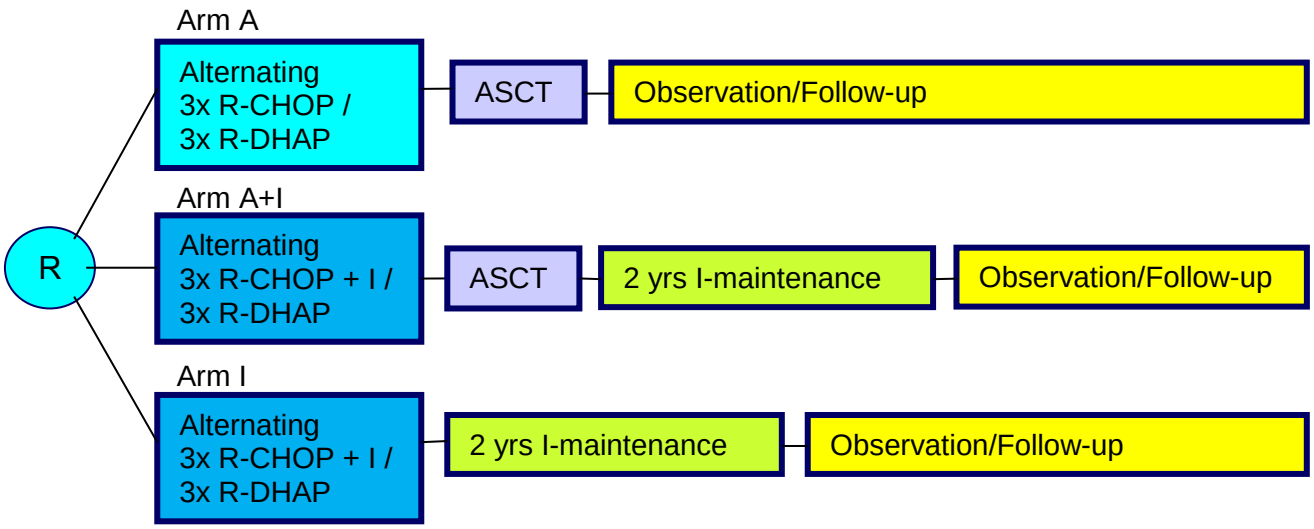
– **Decision for new standard**

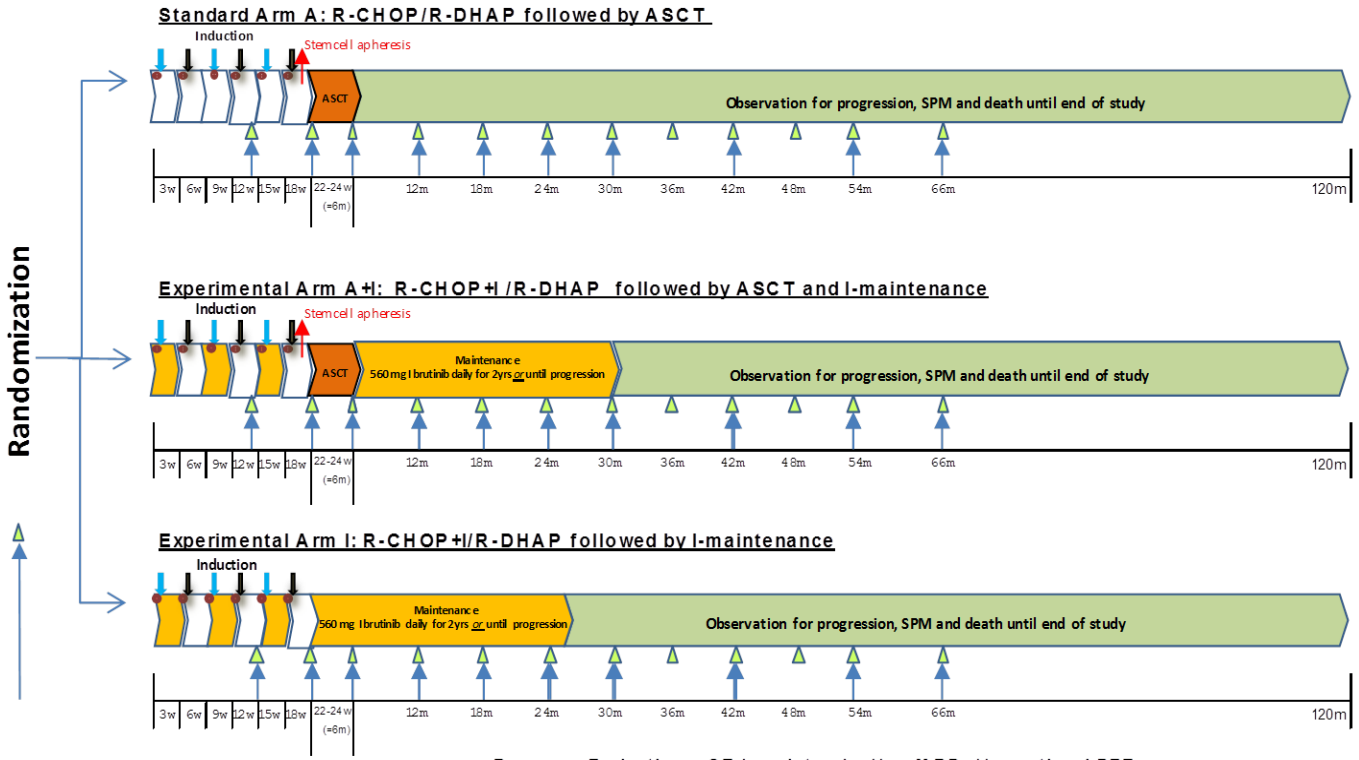
Based on the results for the three pairwise statistical tests, the formal decision for the new standard will be taken according to the following procedure:

Test FFS A vs. I	**Test FFS A+I vs. A**	**Test FFS A+I vs. I**	**Future Standard**
A not significantly superior to I	A+I not significantly superior to A	A+I not significantly superior to I	**I**
A not significantly superior to I	A+I significantly superior to A	A+I not significantly superior to I	**I**
A not significantly superior to I	A+I not significantly superior to A	A+I significantly superior to I	**A+I**
A not significantly superior to I	A+I significantly superior to A	A+I significantly superior to I	**A+I**
A significantly superior to I	A+I not significantly superior to A	A+I not significantly superior to I	**A**
A significantly superior to I	A+I significantly superior to A	A+I not significantly superior to I	**A+I**
A significantly superior to I	A+I not significantly superior to A	A+I significantly superior to I	**A**
A significantly superior to I	A+I significantly superior to A	A+I significantly superior to I	**A+I**

The final decision for a new standard will be based on this formal strategy taking into account all available clinical information at that time point.

Fig. 1+2 Study flow charts





Response Evaluation: CT (mandatory) // MRD // optional PET

Initial	CT and MRD	Before randomization
Midterm	CT and MRD	After completing cycle 4; before starting cycle 5 // appr. week 11
End of Induction	CT and MRD	After completing 6 cycles induction treatment // appr. week 18
pASCT	CT and MRD	Arm A and A+I: 3-5 weeks after ASCT // Arm I: 4-6 weeks after completing
Maintenance / Observation	CT	Every 6 months for 2 years after "p-ASCT"-Evaluation, then yearly observation until 5 years. Thereafter according to clinical routine on suspicion
	MRD	Every 6 months for 4 years and once 5 years after "pASCT"-Evaluation time

SD or PD: No study specific treatment, only follow-up for survival