Present
de Witte, Hellström-Lindberg, Ganser, Bowen, Lübbert, Jansen, Huber, Padua, Germing, Krieger, Malcovati, Della Porta, Giagounidis, Steider, Büsche, Haase, Watters, Grote-Netke, Ossenkoppele, Radulescu, Bratu, Heim, Mecucci, Sambani, Hiuhe, Niemeijer, Cermak, Stadler, Royer-Polora, Junghanss, Fonatsch, Serve, Kneber, Raff, Zheng, Ganz, Lahaye, Seifried, Stuhlmenn, Dvorakova, K-H Lee, Tobal, Faber, Gratwohl, Hussein, Krahl, P. Bernasconi, Hagemeijer, Fischer, Mohr, Schäfer-Echan,

Next meetings
-MDS and joint MDS/AML WP meetings at EHA, Amsterdam, Wednesday, June 14, 2006, from 17:15 - 20:15.
-Joint MDS/AML session „Novel targets, novel drugs" during the Int. conference on differentiation therapy, Paris, Nov., 2006?

Joint session together with AML work package

Treatment decision-making for older patients with AML/MDS M. Lübbert, Deliverable 8.24
Results were presented of a comprehensive literature search of AML, high-risk MDS clinical studies published between 1989 and 2005 (34 studies):
What are the therapeutic options and what is the outcome in AML/MDS >60 years?

Prognostic system for induction chemotherapy M. Lübbert, Deliverable 8.34
Results of the following study were summarized: Results of Intensive Chemotherapy in 998 Patients Aged 65 Years or Older with Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome – Predictive Prognostic Models for Outcome (E. Jabbour et al., ASH 2005)
Predictive Prognostic Models for outcome are being developed using patient-specific clinical data. No validated tools to support decision-making process using patient-, and age-specific evaluation of psycho-social and self-assessed functioning.

Quantification of age-related factors (geriatric assessment) M. Lübbert, Deliverable 8.24
Background: Geriatric Assessment expected to benefit therapeutic decision-making processes (Balducci et al., 2000). Need for validated Instruments for the age-specific assessment within clinical trials apparent (Friedrich et al, 2004, Bokemeyer et al., 2003).
Results of an observational study on AML/MDS pts. treated with low-dose Decitabine were presented. Statistical significance of separate variables not possible yet (n=37). Geriatric Assessment appears to be a valuable tool in detecting "severely compromised" patients prior to study initiation. Validation in larger numbers of patients necessary and warranted to reveal possible prognostic relevance (cytogenetics).
This study should be included in the frailty index for AML/MDS which will be developed by A. Burnett (see Minutes Atlanta, Dec. 11, 2005 on http://www.leukemia-net.org section MDS WP8/meetings).

RAEB-t/AML double classification and impact M. Lübbert, Deliverable 8.33
Listing of European AML trials recruiting patients with 30 % blasts or less (MDS according to the FAB classification) (13 trials). The majority of AML trials is including patients with RAEB-t according to FAB/AML according to WHO. A portion of AML trials also includes patients with MDS according to FAB and WHO (>10<20% blasts).
RAEB-t (FAB) and AML with 20-30% blasts (WHO): is there a need to double-classify?
Investigate outcome for patients with RAEB-t, and MDS <20% blasts, in AML/MDS trials receiving either induction chemotherapy or non-intensive therapy, according to morphology (no. of dysplastic lineages) and according to cytogenetics.
(see also Minutes Atlanta, Dec. 11, 2005 on http://www.leukemia-net.org section MDS WP8/meetings).

The role of RIC for allografting AML/MDS R Martino/ T. de Witte, Deliverable 8.36, 8.37
•Retrospective analysis (Martino within EBMT). A data set needs to be determined. Starting point: patient HLA typing or intention-to-treat? A letter to ask centers to participate (EORTC, Spain have agreed).
•Incorporation of frailty index?
•Ultimate goal prospective randomized study in elderly patients and/or patients with co-morbidity (should include QoL study): to be discussed in SCT-WP?
•Lead participants of each WP will request the statisticians to develop a joint protocol/draft agreement (new deliverable).

Integration of diagnostic guidelines in MDS and AML E. Hellström-Lindberg, Deliverable 8.26
The current co-existing FAB and WHO classification leads to the situation that patients with FAB RAEB-t can be classified as either MDS or AML. WP 5 and 8 recommend that all patients with MDS, and all AML patients with marrow blast counts <50% are classified according to both FAB and WHO. Motivation for this procedure was presented.
If we apply a detailed classification, including exact blast%, MDS and AML patients can be resorted according to future classifications based on biological / genetic features. Potential examples for future MDS / AML classifications were presented.
Reproducibility of blast % and value of morphological parameters (complementary to biological parameters, required for future comparison with old studies) were discussed.
Probably we can develop guidelines for "myeloid diseases'' (MDS and AML included, CML excluded).

Integration of WP16 „New targets, new drugs" into MDS and AML WP H. Serve and R-A. Padua
Proposal for a joint session „Novel targets, novel drugs" during the Int. conference on differentiation therapy, Molecular Target-based Treatment of Human Cancer, Paris, Nov., 2006.
Animal models of MDS/AML for molecularly targeted therapies.

MDS WP session

Introduction T. de Witte
New deliverables for month 25-42 and the MDS section on the LeukemiaNet website were presented.

Evidence- and consensus-based guidelines for the therapy of primary myelodysplastic syndromes
L. Malcovati, Deliverables 8.27, 8.28, 8.29

Methods:
1. Selection of an Expert Panel (fulfilled);
2. Systematic review of the literature and synthesis of evidence (fulfilled);
3. Key questions and list of indications were presented;
4. Scenario analysis was explained;
5. Formulation of recommendations.

Proposal to ask several MDS groups from outside of Europe to comment on the guidelines.
New drugs/ treatment in clinical trials will be linked to the guidelines.

Possible time schedule:
- formulation of the final list of key questions and preparation of the website : 2 weeks;
- time for key questions assessment by the expert panel: 4 weeks;
- evaluation of statements from the expert panel and definition of simulated clinical cases for scenario analysis: 3 weeks;
- rating of scenarios by the expert panel and appropriateness analysis: 3 weeks;
- possible final consensus conference and formulation of recommendations: second half of May;

See http://www.leukemia-net.org/MDS_guidelines_methods_2006.pdf

The guidelines will be presented on the LeukemiaNet website and will be published in Haematologica. Continuous updates will be developed within LeukemiaNet.

In addition, a web-based training program will be developed using virtual patients to excercise the therapeutic guidelines and supervised by experts and European clinicians. A physician can enter clinical data, the program delivers recommended treatment (possibly the Hematology/Haematologica website can be used).

Additional funding is crucial, but should be independent from pharmaceutical companies.

Coordination of ongoing and new trials within framework of LeukemiaNet T. de Witte, Deliverable 8.19
Aims:
1.List MDS trial groups that have been active up to now: achieved on website and regularly updated.
2. Proposal for definition of responsibilities of study coordinators within LeukemiaNet.
3. Formalize interactions between trials.
4. Compare outcome of different trials.
5. List pharmaceutical companies active in MDS and willing to cooperate with LeukemiaNet: achieved on website and regularly updated: Pharma consortium (Hannover).
6. Common control arm for different trials, analogous to german AML studies.

LeukemiaNet is not a trial group: it is a platform to develop trials.

Ad 2:
Responsibilities directed towards achievement of aims 3/5 (6?)
Present outline of study including study design, objectives, selection criteria on the LeukemiaNet website as soon as possible: interaction on trials before start of trial! (discuss with pharm. company whether information on the study can be made publically available).
Promote use of developed study formats.
Promote use of developed core data sets to promote exchange of data between trials.

Ad 4: LeukemiaNet should define Data access. David Bowen will present a (general) contract proposal to Hehlmann (coordinator LeukemiaNet).

Group from Mainz has developed an internet based tool for pseudonomization using unique patient identification numbers. This will allow anominous exchange of data between different data files. Use of this system by study groups could be promoted by LeukemiaNet. Hasford (WP17 Biometrics) has access to this system.
Study files can be transferred to Hasford in their present form of the various study groups. He will transform the data into a general common format in Mannheim (ILEC). Group can perform analyses with his support.

Progress clinical trial list website T de Witte, Deliverable 8.31
•Olga Huber has updated list on the website on basis of previous list, recently reported new trials, list MDS Foundation.
•Olga Huber has put format study protocol on website, please comment; more versions needed?

Czech MDS Study Goup: new member of WP8 presented by J. Cermak
Head: Radana Neuwirtova
Scientific secretary: Jaroslav Cermak
25 centers in Czech Republic (+3 in Slovak Republic).
8 centers with intensive care units for hematologic patients.
6 centers performing allogeneic SCT.
Database: 2101 patients (1980 - 2004).
Distribution of patients according to hematological centers and according to diagnoses was presented.
New MDS Registry since 2005: Core data/ Extended data. Annual increment of patients:132.
DNA bank : 200 patients.
Therapeutic studies: EORTC, Pharmion, MGI, local.

Proposal for a protocol for treatment of high-risk del 5q myeloid disease with Lenalidomide
E. Hellström-Lindberg
•Participants: –ELN WP 5 and 8
–European Study Groups for MDS / AML
•Since there most likely are competing studies ongoing, the different study groups could choose from the different eligibility groups.
•Overall platform, support and trial registry: ELN.
•Local management (ethics, MPA, etc) by study group.
(see http://www.leukemia-net.org section MDS WP8/Study proposals)
If interested to join, please contact: eva.hellstrom-lindberg@ki.se

European MDS registry D. Bowen, Deliverable 8.21
Bowen has moved to Leeds/University of York (contracted as LN participant).
Plans to merge database from dep. of Epidemiology, University of York with database diagnostic lab. Leeds. Probably, the programmer who has setup the database for the diagnostic lab. in Leeds, will be involved in setting up the Eur. MDS registry.

Translational Studies Myelodysplastic Syndromes J. Jansen

I: Genetic Aberrations in MDS measured by array-based comparative genome hybridization
Deliverable 8.43
Separate myeloid and lymphoid cells. Isolate DNA. Perform high-resolution Array CGH (42.000 loci).
Current Status: arrays have been made, first patients have been hybridized.
=> Goal: analyze more than 100 patients.

II: Expression pattern of apoptosis and cell cycle-related genes in MDS Deliverable 8.44
Microfluidic Card-Quantitative PCR, 8 x 48 genes for simultaneous analysis.
Erythroid differentiation markers are comparable in MDS and normal sorted CD71+ bm-cells.
WT-1 in MDS bone marrow subfractions: overexpression & misexpression.
TRAFs: differences between CD34+ and CD71+ cells; no differences between normal and MDS.
Results sofar:
CARD has been designed, system has been tested.
CD34, CD71 and CD33/CD13 sub-fractions have been isolated by FACS-sorting.
CD34 and CD71 subfractions of 15 MDS patients (various subtypes) and 3 normal controls have been analysed on CARD, ongoing.
Several genes show a MDS-specific gene expression pattern: some are CD34 specific, others CD71, some both.
=> Confirm in larger panel, test the CD33/CD13 fraction.
=> Add more patients of all subtypes.
Test 384 genes in: Normal, MDS and sAML.
CD34+, the CD71+ and in the CD33+/CD13+ fractions.
Response to therapy (Revlimid-Bortezomib etc): in vitro/ in vivo.

III: Development of software for Integrated PCR & micro-array analysis Deliverable 8.46
-PCR and micro-array data can be analyzed using similar algorithms.
-For analysis of micro-array data: software available (e.g. Gene-Spring).
-Automated conversion of PCR data for integrated analysis of CARD and micro-array data.
Contribution of samples: FAB / WHO
Cytopenias and dysplasia
Cytogenetics
Clinical data
Expression profiling: 40 x 10E6 viable bone marrow cells.
Array-CGH: 5 x 10E6 cells / 5-10 ug high quality DNA.

If interested to join, please contact: j.jansen@chl.umcn.nl

Finally, details of sample banking have been discussed.

Action items not (yet) listed as a deliverable
Define shared criteria of response for AML and MDS, including the Cheson criteria?

Common core data set in AML and MDS E. Hellstöm-Lindberg/ M. Lübbert
A letter will be sent to study groups.

Frailty index: to be developed/adapted A. Burnett

MDS-WP: new activity? European consensus on immunophenotyping in MDS in cooperation with M.C. Bene, coordinator WP diagnostics. Discuss with Frank Preijers (Dutch imput), Anna Porwit-Mc Donald (Nordic MDS group).

MDS registry: Check legal issues of European registry, ownership, data access and informed consent.

Harmonize diagnostic guidelines with the existing guidelines from the MDS Foundation.