Present
103 Registered participants.

Future meetings

- ESH/EHA MPD/MDS scientific workshop, June, Barcelona.
- EU MDS meeting, June 9, 2010, Barcelona.
- Leukemia: Insights and Challenges, Sponsored by the German Cancer Aid, September 16-18, 2010, 30 Minutes from Frankfurt airport. Sessions: Oncogenic Signaling, Transcriptional Control, Epigenetics Leukemic Stem Cells.
- Meeting on flowcytometry in MDS, November 4-6, 2010, London.
- Please, inform us about meetings.

Future of ELN MDS WP8

Feedback on MDS Work Package steering committee (S.C.) meeting, Mandelieu, France, 24 Oct, 2009. Junior members for S.C.. Proposal extension of S.C. with four new members: Uwe Platzbecker (Dresden), Lionel Ades (Avicenne), Arjan van de Loosdrecht (Amsterdam), Wolf-Karsten Hoffmann (Mannheim). Identification of expert fields of junior members S.C. It is agreed.

Extension of coordinators: (co)chairmanship of the WP. To be extended with 1-2 persons.
One of the new junior members: Uwe Platzbecker and a senior member Pierre Fenaux have both been approved as co-chairs.

Diagnostic and prognostic guidelines
T. de Witte / E. Hellström-Lindbergh

New WHO classification/WPSS: implementation in the ELN guidelines. Diagnostic and prognostic guidelines and assessment of WHO classification through ELN.
In new activities the new WHO classification will be reported. This is especially for the running MDS registries. WPSS can be applied using the core-data from the registry. So we can adapt the new guidelines. Eva Hellström-Lindbergh has produced a report on it.

Standardization of flow cytometry in MDS
A.A. van de Loosdrecht

Report from the second Workshop on flow cytometry in MDS, 30-31 Oct 2009 in Munich.
12 countries; 28 participants; in- and outside Europe.
Does flow cytometry add to diagnostics and/or prognostication?
Flow cytometry can identify abnormalities in the myelomonocytic lineage not otherwise determined by morphology in patients with 'uni-lineage' MDS (RA, RARS, MDS-U).
Flow cytometry is recognized in the diagnostic and prognostic work-up of patients with cytopenia.
An ELN consensus guideline for flow cytometry in MDS is now available (Haematologica, 2009).

Goals:

- define minimal flow cytometric criteria to analyze in MDS
- → ELN 2010 paper wp8 doc in prep
- define prospective validation studies:
  - diagnosis
  - prognostification
  - predictive value for R/ [emerging new drugs]
  - disease monitoring
  - prospective validation studies [3rd Int ELN meeting 2010]
  - adapted FSCC [3rd Int ELN meeting 2010; R. Ireland]

Question: have T cells been investigated?
Mature T cells have not been investigated using flowcytometry. Would be interesting. Future registry: one of the ideas is to perform a substudy (prospectively) using flowcytometry.

What is the proposal for quality assurance. Within Dutch working group we send fresh samples to each other. The same procedure should be performed for ELN, to verify that in different centers the same results are obtained.
Golden standard is not equal to morphology. Could flowcytometry contribute to golden standard? 600 samples collected from several countries; 4 variables will be investigated in MDS patients and controls.

Therapeutic guidelines
T. de Witte

Finalization of the guidelines for therapeutic procedures in MDS (including the place of lenalidomide in 5q- syndrome).
Lenalidomide has been approved by FDA for 5q-, but it has not yet been approved by EMA. A specific section in guidelines will address this issue. It is agreed that the physician should inform patient about potential risk. Will be published on the website.

Translational research

Novel genetic lesions in MDS/MPS: project submitted to 7th FP EU
J. Jansen

Several novel genes involved in MDS / MPN have recently been discovered, and several others will appear in the coming time.
⇒ Determination of prognostic impact requires collaboration of international groups who are active in clinical trials.
Chromosomal gain, loss and uniparental disomy in 102 MDS patients.
In Mandelieu it was decided to make a proposal for FP7.
FP7 1st stage proposal:
Genetic factors that determine prognosis and response to therapy in individuals suffering from Myelodysplastic Syndromes (MDS) or Myeloproliferative Neoplasms (MPN).
This was rejected, may be the short preparation time played a role A new proposal may be prepared together with K. Mills.
Question: were age-matched controls used?
In the Netherlands there is such a control group. This should be extended to other countries/races.

COST action project
K. Mills

A network of (nationally) funded projects (min. 5 participating countries) receive a financial contribution based on a joint work programme (4 years).
EuGESMA (European Genetics and Epi-genomics Study of MDS and AML).

- ⊡ WG1: mRNA and/or miRNA expression profiling with in AML and MDS.
  - Chairs: Lars Bullinger (De) and Margaritta Guenova (Bul)
- ⊡ WG2: Whole genome scanning applications, such as SNP or CGH.
  - Chairs: Tiziana Storlazzi (It) and Sophie Raynaud (Fr)
- ⊡ WG3: Epigenetic scanning
  - Chairs: Brigitte Schlegelberger (Ge) & Soren Lehmann (Swe)
- ⊡ WG4: Screening novel drugs in AML and MDS samples
  - Chairs: Rose Ann Padua (Fr) and Nevena Veljkovic (Ser)
- ⊡ WG5: e:Technologies for the integration of data from WG1 – 4.
  - Chairs: Martin Dugas (De) and Sakari Knuutila (Fi)

Two major FP7 applications from Action Participants

- MATRIX involving participants from WG's 1,2, 3 & 4
  - ⊡ Resistance in AML and MDS
  - ⊡ Selected from 460 Stage I applications for Stage II
- DCDVACL, a one-stage application, from WG4
  - ⊡ Innovative Therapeutic Approaches and Interventions (DNA Vaccines)
  - ⊡ One-stage application – currently in EU review

Website:

- www.qub.ac.uk/research-centres/EuGESMA
- If other countries interested in joining or you want further information contact:
- Ken Mills k.mills@qub.ac.uk

New treatments/trials

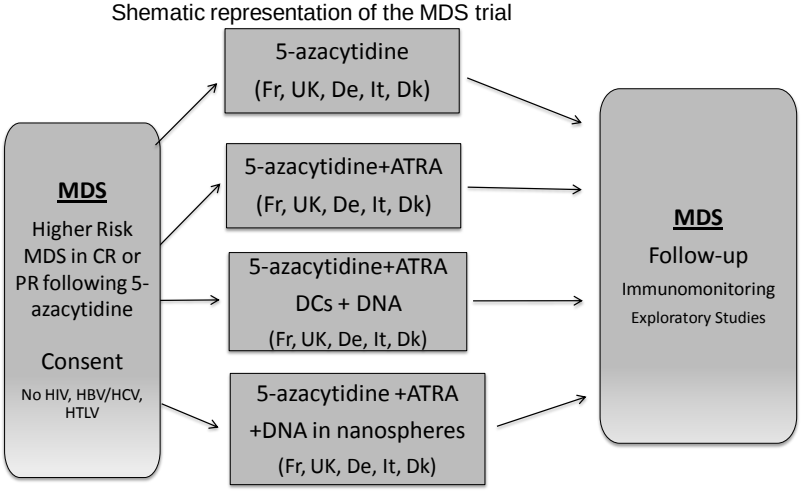
A new list of MDS studies was prepared and presented on the website of ELN:
http://www.leukemia-net.org/content/leukemias/trial_registry/trial_registry/
Please, mail LeukemiaNet@hemat.umcn.nl if you have any corrections or additions.

Dendritic Cell Delivery of a DNA Vaccine Against Leukemia
R. Padua

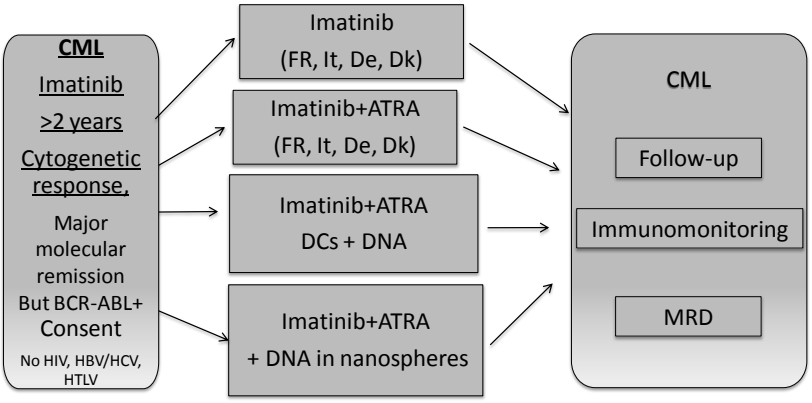
Proposal acronym: DCDVACL
Type of funding scheme: FP7 Health 2010
11 Institutes participate.

- Kaplan-Meier survival from diagnosis of mutant NRAS/BCL-2-mediated MDS transgenic mice: DNA extends life-span.
- DNA vaccination induces increased specific T-cell responses.
- DNA vaccination results in an increase of the $CD4^{+}$ $CD44^{hi}$ $CD62L^{lo}$ memory T cell population.
- ATRA+ DNA vaccination extends life span in a pre-leukemia model (MDS NRAS-BCL2).
- ATRA in vivo Downregulates Tregs.

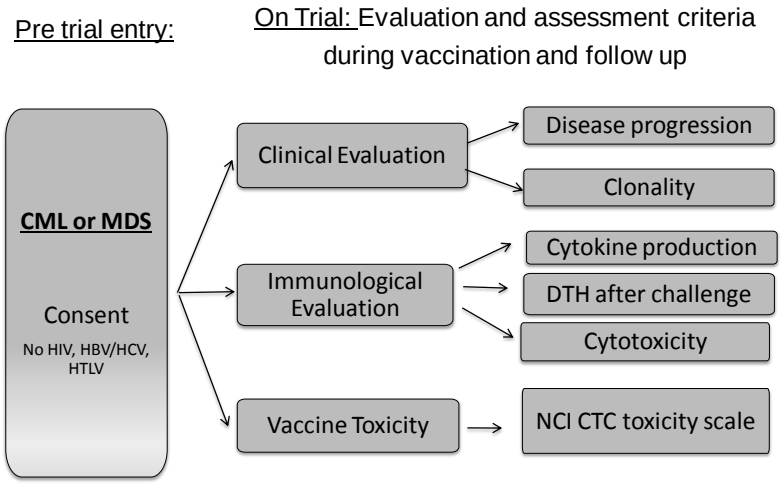
Shematic representation of the MDS trial



Schematic representation of Phase I/II trial



Vaccine strategy



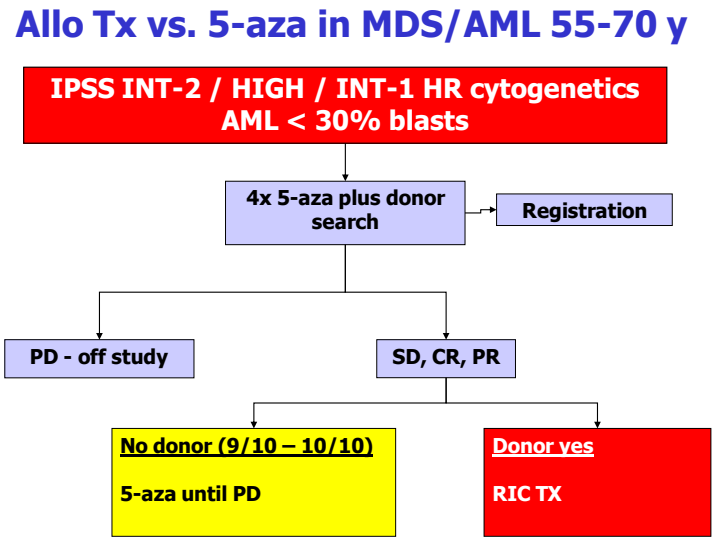
Allogeneic Tx for MDS –Who and When ?
U. Platzbecker

- Allogeneic Tx can be curative for MDS
- Question: Who and When ?

Background:

- Majority of Tx data restricted to MDS pts < 60y
- Not a reflection of the "true" elderly MDS pts
- Up to recently, not considered for allo Tx.

Comparison between 5 – aza and 5 –aza followed by allogeneic HCT in elderly patients with MDS according to donor availability.
Study will shortly be opend for inclusion in Germany.



Conclusions:

- Allo Tx feasible + can result in long-term disease control
- Advantage compared to SC

- With the availability of new agents prospective randomized studies seem to be warranted in order to define the role and time point of allogeneic Tx in the treatment algorithm of elderly patients with advanced MDS.

HOVON89 clinical trial in low-int-1-risk MDS; a phase -2 trial using lenalidomide +/- Epo/G-CSF
A.A. van de Loosdrecht

Primary objective:
Efficacy of lenalidomide [Revlimid™] in low/int-1 risk MDS with or without Epo/G-CSF in terms of Hematological Improvement.
Secondary objectives:
- Safety and tolerability according to NCI/CTC criteria
- Time-to-HI, duration-of-HI, Time-to-progression and progression-free-survival
- amount of transfusion requirements of red blood cells
- CR and PR according to Cheson
- Cytogenetic response

Experimental add on studies:
- - Flow-cytometry: mds-dysplasia score at t=0 and during treatment*/response (within the Dutch WP on flow in MDS)* (Blood 2008;111:1077-1087; Haematologica 2009;94:1124; Blood 2010;(in press)) [Van de Loosdrecht, Westers et al., VUmc]
- - SNP analysis on BM at t=0 for diagnostic/prognostication** [Jansen et al., UMCN]
- - Ultrastructural study on apoptosis/autophagy in MDS progenitors*** [Vellenga et al., UMCG]

HOVON89 open: 1-6-2009.
As per 01-02-2010:
- 19 patients included; 4 in screening
- Note: hematological toxicity:
- → follow table for dose adjustments!;
- Add-on studies!

Pierre Fenaux proposes to run this trial (using same protocol) in other countries with a different sponsor. Later on data of several studies can be merged. Theo de Witte agrees.

MDS registry

Progress of Low Risk MDS Registry, presentation of plans for the future
D. Bowen

ELN and Novartis (grant). University of Nijmegen is sponsor. 11 countries, 100 sites active, since 2008 April, >710 patients. Data are entered via Web into database (located in York). Patients: each 6 months Follow up visit.
Collecting extra urine/serum samples for substudies. Iron substudy is the first substudy.

Presentation of first interim analysis (first 400 patients)
A. Smith

Poster at ASH 2009.
Primary objectives:
- To describe the demographics and disease management of newly diagnosed patients with IPSS low and intermediate-1 MDS.

Recruitment & Visit Summary Statistics:
- N=400, diagnosed between Jan 2008 to April 2009
- Time between Date of Diagnosis to Date of Inclusion
  - Median 42 days, range (0 to 97)
- Mean number of visits = 1.7 (range 1 to 4)
- Time between 1st Visit and 2nd Visit
  - Median 163 days (60 to 359)

Outcome:

- Progression to Leukaemia
  - N=9 (2.3%)
- Progression to High Risk MDS
  - N=4 (1.0%)
- Deaths
  - N= 16 (4.0%)
    - 6 MDS related (1.5%)
    - 9 Non MDS related (2.2%)
  - Median Number of Days from Date of Diagnosis
  - 175 days (range 48 to 335)

Progress of Substudies of Low Risk MDS Registry

- *Iron pathophysiology: T. de Witte*. Impact of transfusions and disease on iron metabolism by analysis of iron parameters.
- *Cytomorphologic sub-study: T de Witte / U. Germing*. 25-30% controversion between experts on morphological diagnosis.
  10% of slides/smears will be reviewed centrally by 5 experts and 5 “non”experts. Hopefully, end of the year 100 patients.
  Second interim-analysis at ASH.
  QoL study at ASH.
  Concomitant medication/diseases at ASH.
- *Geriatric Assessment : R. Stauder*.
  - EQ-5D descriptive system was performed in 322 patients out of 400 patients analyzed so far (81%)
  - Median age 74 yrs (female 75.2; male 73.5)
  - Majority male: 203 out of 322 (63%)
  - Conclusion:
    - EQ-5D was performed in a relevant cohort of low-risk MDS patients
    - MDS impact QoL. Age- and gender effects as well as possible cross-cultural differences or differences in patient recruitment should be considered and integrated.
  - How to proceed?
    - Compare the general population and MDS patients by using EQ-5D reference data of the general population from European countries.
    - Explore gender differences. Examine the affect of age, stage of disease at presentation (IPSS score) & haemoglobin level.
    - Analyse impact of disease progression on QoL by evaluating the longitudinal data (generally performed at six monthly intervals) from participants.

  Remark: In addition, investigate whether treatment approach influences the Quality of Live.

Registry for high risk MDS
T. de Witte

High risk registry is currently planned.
One of the substudies for high risk MDS registry: Look at impact of 5-Aza and similar drugs on outcome. This substudy will run at selected sites.

Establishment of a consortium for financial support activities of WP8 of ELN
T. de Witte

Aim is to have finally one comprehensive registry. Need for financial support, finally ca. 1000 euro per patient required.
To approach a consortium of pharmaceutical and diagnostic (specially for substudies) companies.