SIXTH FRAMEWORK PROGRAMME
LSH-2002-2.2.0-3
Life Sciences, genomics and biotechnology for health
(LifeSciHealth)

Proposal/Contract no.: 503216

Project acronym: European LeukemiaNet

Project full title: Strengthen and develop scientific and technological excellence in research and therapy of leukemia (CML, AML, ALL, CLL, MDS, CMPD) by integration of the leading national leukemia networks and their interdisciplinary partner groups in Europe

Network of Excellence

Second Annual Activity Report

Period covered: from 01/01/2005 to 31/12/2005 Date of preparation:

Start date of project: 01/01/2004 Duration: 60 months

Project coordinator: Prof. Rüdiger Hehlmann

Project coordinator organization name: Universität Heidelberg Revision: 1. Draft

Section 2: Workpackage progress of the period

Objectives and starting point of work at beginning of reporting period

The general objective of WP9 investigators during this second period of activity was to establish:

a) protocols for collaborative clinical studies of novel therapies in CMPDs and
b) multicenter registries of rare clinical aspects of these disorders.

Starting points of work were the objectives achieved during the first period, including:

a) creation of WP management and communication structure and regular WP meetings
b) written reports on test standardization and state-of-art regarding new drugs for CMPD
c) definition of priorities for future collaborative initiatives.

Specific objectives are listed as deliverables and a substantial progress has been achieved in most of them.

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

9.5. Regular WP meetings

WP participants met regularly at least every 4 months and written minutes of these meetings are available.

9.6. LP reports to NMC regarding structure, trial activities and integration of national leukemia trial group (1 page, bullet point style)

LP reports to NMC have been produced and are available

9.7 First proposal of diagnostic, prognostic and staging definitions of CMPD to be used in clinical trials

Response criteria for idiopathic myelofibrosis to be used in clinical trials have been established and publicated. A core set of 5 clinicohematologic criteria was selected out of 9 candidates on the basis of their sensitivity to change measured in 196 patients treated either during clinical trials or routine clinical practice. A consensus panel of 16 international experts was convened and asked to score the level of response in 104 patient profiles as major, moderate, minor, or no response according to changes of the clinicohematologic criteria. Using the experts' consensus as the gold standard, the performance of 100 possible definitions of response was evaluated. Criteria for major or moderate clinicohematologic response were determined to be changes in hemoglobin (Hb) and spleen size and the presence of constitutional symptoms, while changes in platelet count and white blood cell (WBC) count served as complementary criteria and were of value for defining minor responses. A histologic

response was defined by changes in bone marrow fibrosis and cellularity grades. The combined use of these response definitions should help standardize the design and reporting of future clinical studies in MMM.

9.15 Protocol for phase II clinical study of Imatinib therapy in PV patients

A protocol for a phase II clinical study of Imatinib therapy in PV patients was prepared. This study is currently ongoing in Germany and 20 patients have been included so far. The extension of this trial in other European countries will be a future goal of the WP (see new list of deliverables 2006/2007)

9.16 Improvement of web-based information- and communication services on CMPD

A number of protocols regarding ongoing clinical trials (n=8), documents regarding ongoing research activities (n=8) and the minutes of the work package meetings (n=4) have been uploaded.

9.17 Implementation of a Registry of rare MPD variants in MPDs

A registry of patients with "Essential Thrombocythemia with Ringed Sideroblasts" has been set up and it is ongoing in Germany. Future plans in this setting will include a collaborative project of biological characterization of these rare variant (see new deliverable list).

9.18 Implementation of a Registry of pregnancies in ET

A web-based, on-line registry of pregnancies in ET has been set up (Document 4 attached) and 25 patients have been enrolled so far in Germany. The European extension of this Registry is included in the programme of activities for the future period.

9.22 Protocol for phase II clinical study of Velcade in MPDs

A protocol for a phase II clinical study of Velcade in patients with MMM was prepared (title: A phase II Study of Bortezomib (VelcadeÒ), a Proteasome Inhibitor, in Treating Patients with Idiopathic Myelofibrosis (IM) Randomized to Receive New Investigational Drugs, chair: Giovanni Barosi). The funding for the study is currently under negotiation with the company. Advancement in this project is foreseen in the deliverable list for the next period.

9.23 Protocol for pilot randomized clinical trial of 2 phlebotomy regimens in low-risk PV

A protocol for a randomized clinical trial of 2 phlebotomy regimens in patients with PV was prepared (title: A randomised trial to assess efficacy and tolerability of two levels of hematocrit reduction in patients with Polycythemia Vera, chair: Tiziano Barbui and Guido Finazzi). An application for funding the study is currently submitted to the Italian Drug Agency (AIFA). Advancement in this project is foreseen in the deliverable list for the next period.

9.24 Protocol for registration of MPDs patients treated with Anagrelide

A protocol for an European observational study of high-risk patients with ET treated with Anagrelide has been prepared (EXELS study). The study is supported by Shire and the company requires a signed confidentiality agreement for the protocol. A copy of the protocol to be used as a confidential reference tool within the network is available. The study has recruited 229 patients so far, 122 with anagrelide, the rest with other cytostatic treatment for comparison. Recruiting countries are Denmark, Sweden, France, Germany, UK and several other centers are initiated and will start recruiting soon. Future plans include expansion of enrolment according to protocol until 1000 patients of anagrelide have been reached. The first published report is foreseen after 5 years of follow-up.

9.25 Identification of new molecular targets in bcr-abl negative CMPDs

Identification of new molecular targets in bcr-abl negative CMPDs. Three original manuscripts have been published in 2005 in which the ELN was reported as funding authority in the acknowledgement (see references below). It should be pointed out that all three manuscripts had authors from different European countries which are active members of the ELN. In addition, a European Eosinophilia Study Group has been established. Main interests of this group are the identification of molecular targets and treatment of hypereosinophilic syndrome, chronic eosinophilic leukemia and related disorders, e.g. eosinophilia-associated myeloproliferative disorders and systemic mastocytotis with eosinophilia. This group is initially based in WP12 (MRD) but there is an obvious overlap with WP9.

Deviations from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

9.14 Proposal on harmonization of CMPD transplant protocols and procedures

A proposal on harmonization of CMPD trasplant protocols in Europe is still pending since a similar project has been submitted by some European groups to the National Institute of Healh (USA). The lead contractor for this deliverable, Dr. Rambaldi, recommended to wait for an answer of NIH (foreseen for the end of this year) to better harmonize tranplant procedures both in Europe and USA.

9.19 Implementation of a Registry of leukemic complications in MPDs

A registry of leukemic complications in MPDs was not set up yet. This deliverable will be further discussed with the lead contractor Dr Gisslinger.

9.20. “Model” protocols for phase I/II clinical trials in CMPD with quality of life assessment instruments and response criteria

“Model” protocols are almost ready and will be delivered by Drs. Birgegard and Hasselbalch soon.

9.21 Protocol for phase II clinical study of Revlimid in MPDs

A protocol for phase II clinical study of Revlimid in MPDs is still pending and will be further discussed with the lead contractor Dr. Gisslinger

List of deliverables WP 9

Deliv. No.	Deliverable Name	Date due	Actual/Forecast delivery date	Estimated indicative person months*)	Used indicative person months*)	Lead contractor
WP 9	**CMPD**					
9.5	Regular WP meetings	18,24,30	18,24	6	6	Barbui, Barosi, Finazzi
9.6	LP reports to NMC regarding structure, trial activities and integration of national leukemia trial group (1 page, bullet point style)	15,18,21, 24,27,30	18,24	4	4	Finazzi
9.7	**First proposal of diagnostic, prognostic and staging definitions of CMPD to be used in clinical trials**	**18**	**18**	**(3)**	**3**	**Barosi**
9.14	**Proposal on harmonization of CMPD transplant protocols and procedures**	**18**	**36**	**(4)**	**0**	**Rambaldi**
9.15	Protocol for phase II clinical study of Imatinib therapy in PV patients	18,30	24	6	6	Hasselbalch, Lengferlder
9.16	**Improvement of web-based information- and communication services on CMPD**	**18**	**18**	**4**	**4**	**Reiter**
9.17	**Implementation of a Registry of rare MPD variants in MPDs**	**24,30**	**24**	**6**	**6**	**Schmitt-Graff**
9.18	**Implementation of a Registry of pregnancies in ET**	**24,30**	**24**	**6**	**6**	**Griesshammer**
9.19	**Implementation of a Registry of leukemic complications in MPDs**	**24,30**	**36**	**6**	**0**	**Gisslinger**
9.20	"Model" protocols for phase I/II clinical trials in CMPD with quality of life assessment instruments and response criteria	18	36	6	0	Birgegard, Hasselbalch
9.21	Protocol for phase II clinical study of Revlimid in MPDs	18,30	36	6	0	Gisslinger
9.22	Protocol for phase II clinical study of Velcade in MPDs	18,30	24	6	6	Barosi
9.23	Protocol for pilot randomized clinical trial of 2 phlebotomy regimens in low-risk PV	18,30	24	6	6	Barbui, Finazzi
9.24	Protocol for registration of MPDs patients treated with Anagrelide	18,30	24	6	6	Birgegard
9.25	**Identification of new molecular targets in bcr-abl negative CMPDs**	**18**	**18**	**4**	**4**	**Reiter**

*) if available

List of milestones WP 9

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
WP 9	**CMPD**			
9.7	**First proposal of diagnostic, prognostic and staging definitions of CMPD to be used in clinical trials**	**18**	**18**	**Barosi**
9.14	**Proposal on harmonization of CMPD transplant protocols and procedures**	**18**	**36**	**Rambaldi**
9.16	**Improvement of web-based information- and communication services on CMPD**	**18**	**18**	**Reiter**
9.17	**Implementation of a Registry of rare MPD variants in MPDs**	**24,30**	**24**	**Schmitt-Graff**
9.18	**Implementation of a Registry of pregnancies in ET**	**24,30**	**24**	**Griesshammer**

Milestone No.	Milestone Name	Date due	Actual/Forecast delivery date	Lead contractor
9.19	**Implementation of a Registry of leukemic complications in MPDs**	**24,30**	**36**	**Gisslinger**
9.25	**Identification of new molecular targets in bcr-abl negative CMPDs**	**18**	**18**	**Reiter**

Section 3: Consortium management

Section 4: Other Issues

Ethical issues - none

Competitive calls - none

Annex - Plan for using and disseminating the knowledge

Section 1: Exploitable knowledge and its Use

Not relevant

Section 2: Dissemination of knowledge

Table (Press release (PR), oral presentations (OP), Exhibition (E), Project (P), Poster (PO), Flyer (F), email (E), Website (www), Video (V), Workshop (WS))

Planned/actual Dates	Type	Type of audience	Countries addressed	Size of audience	Partner(s) responsible/involved
3.6.2005	Specialist meeting	Research	Europe	100	
20.9.2005	Specialist meeting	Research	Italy	32	
18.11.2005	Specialist meeting	Research	Europe	300	

A scientific session of the European Working Group on MPDs has been organized in Stockholm, 3.6.2005, during the 10th congress of the European Hematology Association. About 100 investigators attended the meeting which lasted about 1 hour anf half and covered the most recent issues in the field.
A meeting of the Italian network of investigators in MPDs has been organized in Bergamo, 20.9.2005, to explain and disseminate the ELN WP9 projects. The Italian MPD group, under the heading of GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto), agreed to participate in the multicenter studies proposed by the WP 9.
A scientific meeting devoted to the recently discovered JAK-2 mutation in MPDs has been organized in Paris, 18.11.2005 by dr.J.J.Kiladjian. About 300 investigators attended this one-day meeting which covered all the biological, diagnostic and, potentially, therapeutic aspects of this new advancement.

WP meetings

A separate meeting of the WP9 investigators was carried out in Heidelberg during the general ELN Congress, 1 February 2005.

The following investigators attended the Meeting: Guido Finazzi (Bergamo), Tiziano Barbui (Bergamo), Gunnar Birgegard (Uppsala), Annette Schmitt-Graff (Freiburg), Hans Hasselbalch (Denmark), Martin Griesshammer (Ulm), Andreas Reiter (Heidelberg), Jean-Jacques Kiladjian (Paris), Eva Lengfelder (Heidelberg), S. Zweegman (NL) and some other unidentified attendants.

An informal meeting of the WP9 investigators was organized in Stockholm during the EHA 10 Congress, 3 June 2005.

The following investigators attended the Meeting: Guido Finazzi (Bergamo), Tiziano Barbui (Bergamo), Giovanni Barosi (Pavia) Gunnar Birgegard (Uppsala), Hans Hasselbalch (Denmark), Martin Griesshammer (Ulm), Andreas Reiter (Heidelberg), Jean-Jacques Kiladjian (Paris), Holger Cario (Ulm), John Reilly (Sheffield), Juergen Thiele (Koln), J.J. Michiels (Rotterdam), Pinhas Stark (Israel).

A meeting of the WP9 investigators was organized in Paris in the occasion of the one-day Symposium devoted to JAK-2 mutation in MPDs, 18 November 2005.

The following investigators attended the Meeting: Guido Finazzi (Bergamo), Tiziano Barbui (Bergamo), Giovanni Barosi (Pavia), Jean-Jacques Kiladjian (Paris), Tony Green (Cambridge), Hans Hasselbalch (Denmark), J.J. Michiels (Rotterdam), Heike Pahl (Freiburg), Annette Schmitt-Graff (Freiburg).

A separate meeting of the WP9 investigators was organized in Atlanta during the ASH Congress, 11 December 2005

The following investigators attended the Meeting: Tiziano Barbui (Bergamo), Giovanni Barosi (Pavia) Gunnar Birgegard (Uppsala), Hans Hasselbalch (Denmark), Martin Griesshammer (Ulm), Tony Green (Cambridge), J.J. Michiels (Rotterdam), Heike Pahl (Freiburg), Annette Schmitt-Graff (Freiburg) Eva Lengfelder (Heidelberg), Andreas Reiter (Heidelberg), and some other unidentified attendants..

Section 3: Publishable results

Jones, A.V., Kreil, S., Zoi, K., Waghorn, K., Curtis, C., Zhang, L., Score, J., Seear, R., Chase, A.J., Grand, F.H., White, H., Zoi, C., Loukopoulos, D., Terpos, E., Vervessou, E.-C., Schultheis, B., Emig, M., Ernst, T., Lengfelder, E., Hehlmann, R., Hochhaus, A., Oscier, D., Silver, R.T., Reiter, A., Cross, N.C.P. Widespread occurrence of the JAK2 V617F mutation in chronic myeloproliferative disorders. Blood 106, 2162-2168, 2005

Reiter, A. , Walz, C., Watmore, N., Schoch, C., Blau, I.,Schlegelberger, B., Berger, U., Telford, N., Aruliah, S., Yin, J.A., Vanstraelen, D., Barker, H.F., Taylor, P.C., O'Driscoll, A., Benedetti, F., Rudolph, C., Kolb, H.-J., Hochhaus, A., Hehlmann, R., Chase, A., Cross, N.C.P. The t(8;9)(p22;p24) is a recurrent abnormality in chronic and acute leukemia that fuses PCM1 to JAK2. Cancer Research 65, 2662-2667, 2005.

Walz, C., Chase, A., Weisser, A., Hochhaus, A., Schoch, C., Schlegel, F., Fuchs, R., Schmitt-Gräff, A., Hehlmann, R., Cross, N.C.P. Reiter, A. The t(8;17)(p11;q23) in the 8p11 myeloproliferative syndrome fuses TIAF1 to FGFR1. Leukemia 19, 1005-1009, 2005.

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Barbui T, Finazzi G. When and how to treat essential thrombocythemia. N Engl J Med 2005; 353: 85-6.

Finazzi G, Harrison C. Essential Thrombocythemia. Semin Hematol 2005; 42: 230-8

Barosi G, Hoffman R. Idiopathic myelofibrosis. Semin Hematol 2005; 42: 248-58.

Marchioli R, Finazzi G, Marfisi RM, Tognoni G, Barbui T. Clinical trials in myeloproliferative disorders: looking forward. Semin Hematol 2005; 42: 259-65

Finazzi G, Barbui T. Risk-adapted therapy in essential thrombocythemia and polycythemia vera. Blood Rev. 2005; 19: 243-52

Marchioli R, Finazzi G, Landolfi R, Kutti J, Gisslinger H, Patrono C, Marilus R, Villegas A, Tognoni G, Barbui T. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. J Clin Oncol 2005; 23: 2224-32

Finazzi G, Caruso V, Marchioli R, Capnist G, Chisesi T, Finelli C, Gugliotta L, Landolfi R, Kutti J, Gisslinger H, Marilus R, Patrono C, Pogliani EM, Randi ML, Villegas A, Tognoni G, Barbui T. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. Blood 2005; 105: 2664-70.

Jones AV, Silver RT, Waghorn K, Curtis C, Kreil S, Zoi K, Hochhaus A, Oscier D, Metzgeroth G, Lengfelder E, Reiter A, Chase AJ, Cross NCP. Minimal molecular response in polycythemia vera patients treated with imatinib or interpheron alpha. Blood, prepublished online December 13, 2005; DOI 10.1182/blood-2005-09-3917