Development of array-based diagnostics for leukemia
Executive Summary

Biochip aimed to develop *in vitro* diagnostic (IVD) genetic assays for acute myeloid leukemia (AML), multiple myeloma (MM) and Acute Lymphatic Leukemia (ALL) to provide clinical utility for faster and improved treatment outcome while saving healthcare cost in these life-threatening types of blood cancer.

One of the challenges was to identify correlations between known and novel genetic alterations with specific cancer subtype outcomes and to develop these into all-in-one assays to support individualized treatment. Additionally, in the time where tests in which the whole genome will be assessed in a single assay are emerging, like microarrays or next generation sequencing, and will ultimately be used to guide patient management decisions like companion diagnostics, a large demand for fast and reliable interpretation of large amounts of data exists.

As a result of the biochip project, large well characterized patient cohorts and datasets have been generated by the biochip participant. It is has become clear that beyond traditional cytogenetic aberrations, novel genetic aberrations were discovered to have prognostic value in AML. Additionally, a fully validated, centralized, GMP compliant IT infrastructure was developed for complex data analysis for use in these strongly regulated health care applications. Consequently, the AMLprofiler IVD assay was CE registered in March 2011.

In MM, biochip has produced and validated a novel prognostic 92-gene signature to predict overall survival which has been validated in 5 independent clinical cohorts. Additionally, several other prognostic gene signatures have been developed of which some are indicative of treatment effectiveness and are now available as the MMprofiler assay as a clinical research tool (RUO kit).

To support reimbursement of the assays, an independent cost effectiveness evaluation Medical Technology Assessment (MTA) looking at both cost and quality of life are have been performed for the AMLprofiler and MMprofiler and demonstrated a health as well as cost benefit over existing practice.
A major challenge for future treatment development of hematological malignancies is to develop tests that distinguish various subtypes of disease and to provide treatment that is tailor-made to the type of leukemia. This will allow for appropriate therapy selection which will include targeted therapy for genetically comparable groups of patients that are known to respond successfully for certain treatments and preclude unnecessary exposure of patients to ineffective and usually toxic therapies. This will enhance the cost-benefit ratio of treatment and furnish the development of rationalized therapy aimed at increased survival. Microarray-based technologies offer realistic opportunities for developing such tests.

**Clinical Need**
- Distinguish various subtypes of disease to provide tailor-made treatment to the type of leukemia
- Increase effectiveness of treatment
- Decrease side effects
- Decrease health-care cost
- Improve Quality of Life and patient survival

**Tools**
Development of all-in-one genomic and proteomic based assays that are capable to identify prognostic subtypes that are additionally (non) responding for specific treatment requires the following tools:
- Whole genome based assays like Gene Expression arrays
- Well characterized clinical datasets
- Validated IT infrastructure for complex data analysis
- Clinical, scientific, bioinformatics, laboratory, quality, regulatory and health economic infrastructure and expertise
Diagnostic Tests for Acute Myeloid Leukemia (AML) and Multiple Myeloma (MM) to stratify patients for better treatment options.
Organization and Partners

Advisory board
ISAC CTMM

SteeringCie
Partner Representatives
CTMM

Project Team
PI: Prof. B Löwenberg (EMC)/Prof. P. Sonneveld (EMC)
All WP leaders
Industrial partners
Dr. T. Dijkmans (Skyline)
Dr. E. Caldenhoven (CTMM)

Workpackage leaders
WP1: Dr. H. Vietor (Skyline Diagnostics)
Msc L. de Best (SkylineDx)
WP2: Dr.Ir. J.M.L.M. van Helvoort (FlexGen)
WP4: Dr. R. Nanninga (Crosslinks)
WP5: Prof. Dr. C.A. Uyl – de Groot (EUR)

University of Edinburgh (UK)
Atos
FlexGen
UMCU
CTMM
SkylineDx
Skyline Diagnostics
Crosslinks
EMC
EUR

CTMM
Partners
Coordination
Finance
Publications
Budget: CTMM manages the flow of funds

Funding:
- 25% Academia
- 25% Industrial
- 50% Government Subsidy

Project costs:
- Personnel
- Materials
- Use of existing equipment
- Investments
- Third parties
- Management (5%)
Facts & Figures

Distribution of the BioCHIP consortium budgets to perform the R&D activities

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<th>Budget</th>
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### CASH COSTS

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## Facts & Figures

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<td>Awards</td>
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- **Papers**: 51 papers in submission - mean impact factor all published BIOCHIP papers: **9.2**
- **Theses**: 8, 1 planned for 2016
- **Personal grants**: 1, Vici for Mrs. Den Boer (EUMC)
- **Patent Applications**: 0
- **Spin-off Companies**: 0
- **Raising Capital (> 1 M€)**: 0
- **Awards**: 2,
  - 2011, Prof. Löwenberg: Jean Bernard Life Time Achievement of “Europese vereniging van hematologen” 2010, ISPOR Best New Investigator Podium Presentations Award. P. Sonneveld juni 2015, Robert A. Kyle Lifetime Achievement Award for Multiple Myeloma.

### Budget

- **Budget**: 20.5 M €
- **Start**: 2008
- **End**: 2014
- **Partners**: 8
- **Charity**: 0
- **Persons**: 73
- **FTE**: 128 (5 years period)
SCIENTIFIC VALUE CREATION – BREAKTHROUGHS

- CD34 expression as important factor to determine prognosis in AML
- CEBPA double mutants as important favorable prognostic marker in AML
- 2012: The EMC-92-gene signature is better or comparable to previously published signatures. This signature contributes to risk assessment in clinical trials and could provide a tool for treatment choices in high-risk multiple myeloma patients.
- 2012: DNMT3A mutation has been shown as an independent poor prognostic marker with a prevalence of 23% and its hazard has been found to be most significant in those cases without FLT3-ITD but with NPM1 mutations
- 2013: A new tool has been developed for the discovery of regions of interest (ROI) in microarray and sequencing data that can also identify significant cellular pathways (EUMC)
- 2013: Identification of a BCR-ABL1-like group in adult ALL with high relapse rate and non-response to treatment
- 2013: Comparison of the DCOG/Erasmus MC and COG/St. Jude BCR-ABL1-like signatures in pediatric BCP-ALL shows that these signatures are partially complementary and that both should be used to identify patients at high risk of relapse
- 2013: New classifiers trained on pediatric ALL cases predict the recurrent subtypes in pediatric and adult ALL with sensitivities above 90% with the exception of BCR-ABL1, which has a more heterogeneous expression signature

HIGHEST IMPACT PAPERS – MEAN 27,0


MEAN IMPACT FACTOR

INTERNATIONAL - ONCOLOGY

CTMM - ONCOLOGY

0 2 4 6 8 10

2 - Mean impact factor based on 200 papers from the CTMM oncology first call projects.
### Scientific Value Creation - Theses

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A company and laboratory infrastructure was successfully developed to allow for:

- Manufacturing of in-vitro diagnostic (IVD) products according to EU and US IVD directives with a quality management system compliant with ISO-13485 and 21CFR820.
- Performing molecular diagnostic assays on e.g. Acute Myeloid Leukemia (AML) and Multiple Myeloma (MM) patient material (bone marrow) under a quality management system compliant with ISO-15189 standard (CCKL and CLIA compliant)

Proof of concept:
- AMLprofiler Diagnostic Services (registered Dec 2009)
- AMLprofiler CE IVD assay (registered March 2011)
- AMLprofiler IUO assay applied in a prospective clinical trial (200 patients analyzed) in 5 prestigious hematological centers in US and EU (Ulm-DE Cardiff-UK, Rotterdam-NL, OHIO-US, New York-US) for FDA pre-market approval (PMA).  

A fully validated, centralized, FDA compliant IT infrastructure was developed for complex data analysis for use in strongly regulated health care applications.

Gene expression data is automatically transferred from the Affymetrix DX2 system to the central servers, subsequently data quality is assessed and the gene expression levels are interpreted by the proprietary algorithms. Within 15 minutes a report with the presence or absence of the molecular markers of interest is returned to the user in a secure manner.

Proof of concept:
- AMLprofiler CE IVD assay (March 2011)
- 2nd application: MMprofiler RUO assay (IT in development)
- 9 Affymetrix DX2 systems have been successfully connected to the infrastructure so-far

Future applications:
- IVD assays or companion diagnostics based on any “big data” technology

Health economic evaluations for risk stratified treatment for MM and AML were performed,

- Better risk stratification results in better QoL for AML patients. Favorable risk patients are not exposed to side-effects of unnecessary intensive treatments and unfavorable risk patients will receive more intensive treatment with a higher chance of being cured. Health care cost are slightly increased by applying the AMLprofiler.

- Both health gains and cost-savings were demonstrated for MM patients bearing adverse prognostic markers in a study evaluating bortezomib vs thalidomide treatment.

Two comprehensive assays have been developed and are currently commercialized:
- AMLprofiler CE IVD assay (March 2011)
- MMprofiler RUO assay (September 2013)
- MMprofiler CE IVD diagnostic service assay (July 2015)

Gene expression signatures in Acute lymphatic Leukemia (ALL) have been developed for potential future diagnostic applications.

Novel clinically relevant biomarkers in AML have been discovered.

General infrastructure output on NGS and the Huvariome database.

Future perspectives:
- have an additional IVD marker (#8, CD34) added to AMLprofiler CE IVD for significant improvement of intermediate risk group stratification.
- Develop and validate the MMprofiler as Diagnostic Service and an IVD kit to allow for use for clinical decision making, extend health economic investigations and ensure reimbursement.
- Apply the assays in clinical trials to identify drug (non-) responder sub-populations for Companion Diagnostic development.
Clinical and Economic Value Creation of BIOCHIP

New ‘products’ for clinical care
Development of the AML profiler:

Acute myeloid leukemia (AML, 3.7/100,000/year) is a heterogeneous group of hematologic malignancies, as illustrated by various genetic alterations, showing variable response to therapy. Skyline Diagnostics has developed the AMLprofiler microarray based gene expression assay by the translation of the scientific findings at Erasmus University hematology department into a fully validated, commercially available CE IVD registered kit. The AMLprofiler measures 7 clinically relevant biomarkers. With this product, an improved risk stratification is possible especially for patients that traditionally could not be further stratified than “intermediate cytogenetic risk”. The product therefore may aid in AML therapeutic decision making.

More recently, new recurrent mutations have been identified in AML by next generation sequencing. The clinical relevance of these novel biomarkers is currently unknown. These novel biomarkers for AML may be included on an AML biochip in the future.

Device: AMLprofiler CE IVD assay

Leading Company
SkylineDx B.V.

Current Diagnostics
Based on traditional cytogenetic risk stratification (WHO 2008) ~16%, 62% and 22% AML patients are respectively favorable, intermediate and unfavorable cytogenetic risk. With the AMLprofiler, these 62% intermediate risk cases can now be further stratified in a small very unfavorable group (5%) and a large new favorable group (57%). Leaving only 38% of the original intermediate cases unclassified.

Future Outlook:
- Addition of new clinically relevant biomarkers
- Find the companion therapeutic for the AMLprofiler subgroups

Main results in CTMM

Biomarker discovery:
Initially, many novel biomarkers have been discovered and evaluated for further development however many could, and were not further developed due to lack of sufficient reference data as a result of very low prevalence or did not show consistent accuracy or prognostic value across independent datasets.

Demonstrator development:
Ultimately, 7 markers were analytically and clinically validated successfully; gene aberration markers inv(16), t(8;21), t(15;17), mutation markers for NPM1 and CEBPA double mutations and EVI1 and BAALC expression markers.

Next development:
Based on new insights, a new and very potent prognostic biomarker was discovered. Fortunately it has been part of the initial design of the array although not of the software. In the near future, implementation of this novel 8th marker in the AMLprofiler assay data analysis software may be pursued and after full validation it may be released as the next “CE IVD” marker. The addition of the new marker is expected to only leave approximately 10% of the original intermediate cases unclassified.

Number patients per year: 200
Avg. costs per treatment €150,000

1 Only patients aged 18-60 years

Quality of Life (QoL):
Better risk stratification results in better QoL. Favorable risk patients are not exposed to side-effects of unnecessary intensive treatments and unfavorable risk patients will receive more intensive treatment with a higher chance of being cured.

Accessibility:
All patients can have access to the AMLprofiler if the hospital has purchased the technology.

Affordability:
The total treatment costs for AML are on average €2,800 more expensive if the AMLprofiler is used. This is accompanied with a gain of 0.2 QALYs per patient.
Development of the MM profiler:

Multiple Myeloma Profiler
(MM) is a heterogeneous, incurable plasma cell cancer with an age adjusted yearly incidence of 5.9 / 100,000 persons and rising. Multiple Myeloma treatment improvements have nearly doubled the survival of MM patients in the last decade but cases with very short survival (high risk disease) remained. Erasmus Medical Center has identified the EMC92 gene expression based classifier that detects cases with substantial shorter survival and are thus classified as “High Risk MM” and that outperforms all other existing classifiers as well as FISH risk biomarkers. Skyline Diagnostics has developed and used this signature as an CE IVD diagnostic service in trials and in datasets of several international collaborations recapitulating its clinical utility.

This new unique tool classifies approximately 20% of newly diagnosed MM patients that have an unmet medical need, represents a separate biological class of MM disease and should be studied with alternative treatments including novel experimental agents, combinations of existing and novel agents or considered for (allo)geneic bone marrow transplantation.

Device: MMprofiler RUO assay
Diagnostic service: MMprofiler assay (CE IVD)

Leading Company
SkylineDX B.V.

Current Diagnostics
Current and only molecular patient stratification tool (i.e. based on iFISH) has proven inconsistent prognostic value. Gene expression profiling is not part of diagnostic practices (i.e. patient stratification for treatment practices) in Europe yet due to lack of validated and registered tests, but has the potential to become a leading prognostic and potentially a predictive (companion) stratification tool.

Progress obtained in translational pipeline

Main results in CTMM

- **Biomarker discovery:**
  In addition to SKY92, on the same gene expression assay, Skyline Diagnostics has developed cytogenetic detection algorithms (markers) for the detection of t(4;14), t(11;14), t(14;16)/t(14;20), add1q, del13, del17p, hyperdiploid MM as well as MS and MF cluster type MM.

- **Demonstrator development:**
  The SKY92 marker has consistently shown to be prognostic in at least 5 independent clinical trial cohorts. The marker identifies a group of MM patients of approximately 20% who have at least a two times higher chance to die from the disease than other MM patients.

Analytical validation was successfully executed of the SKY92 and other markers of the MMprofiler CE IVD assay for diagnostic service through the SkylineDx laboratories in Rotterdam, The Netherlands (for clinical use i.e. patient management decisions).

- **Next development:**

Future Outlook:
Find the companion therapeutic for the MMprofiler patient subgroups and contribute to improved survival

Quality of Life:
The quality of life for transplant eligible patients identified by the MMprofiler to have high risk prognosis is improved due to longer time spent in remission when stratified toward treatment with bortezomib.

Accessibility:
All patients have access to the MMprofiler if the hospital has purchased the technology.

Affordability:
The total average treatment costs per patient are reduced by €2,068 or €1,842 when risk-stratified treatment is applied using the MMprofiler alone or in combination with conventional cytogenetics. The corresponding health gains equal 0.04 or 0.034 QALYs for the MMprofiler alone or in combination with conventional cytogenetics.
Construction of a validated IT infrastructure:

Valued Data Analysis Platform
Skyline Diagnostics and Crosslinks have developed a unique validated IT infrastructure for fully automated centralized diagnostic analysis and (complex) data management using proprietary software in a fully secured "virtual private GxP-compliant Cloud" (CE and FDA compliant).

Such an infrastructure was essential for this product as it facilitates the treatment decision process for patients with Acute Myeloid Leukemia. The test uses microarrays in order to provide a detailed risk profile of individual patients based on a complex analysis of the activity of hundreds of genes simultaneously.

The infrastructure is very flexible and can now be implemented for other applications. This is of particular interest to the rapidly evolving diagnostic landscape. Technology has shifted from simple tests, with limited numbers of parameters towards complex tests with numerous parameters enabling the development of personalized medicine.

SkylineDx offers this unique platform to other companies in order to fully exploit the potential of this technology in the ever evolving complexity of diagnostics.

Device: Validate Data Analysis Platform

Leading Company
Crosslinks, SkylineDx

Current Diagnostics
Backbone of the data analysis for AMLprofiler CE IVD assay

Main results in CTMM

- **Design and development**
  - Design, development, and validation of the infrastructure according to all applicable regulatory requirements and the preparation of the applicable registration files thereof.

- **Demonstrator development:**
  - Successful full process validation of the infrastructure as being part of the AMLprofiler assay in a world-wide clinical trial (NL 3*, UK, DE, USA 2*) and clinical evaluation studies (DE, SA) with at least 9 Affymetrix DX2 systems connected simultaneously for automated data analysis.

- **Next development:**
  - Application of the IT infrastructure for the MMprofiler development and future products of SkylineDx. And potentially products for other diagnostic assay development companies.

Future Outlook: Application for other diagnostics

Benefits for patients:
- Secured data transfer, processing and storage.
- Privacy of the patient is guaranteed.
- Standardized and reliable results.

Benefits for diagnostic laboratories / manufacturers:
- Enables more reliable, faster and more cost-efficient diagnosis for laboratories.
- Faster future diagnostic product development and validation.
- Allows world-wide comparison of assay results.

Benefits for insurance companies / society:
- Assay development costs much lower; i.e. validation of only one IVD assay according to ISO-13485 instead of validation at many labs according to ISO-15189.
- More reliable and comparable results for the patients.

Number of Patients: 200
Yearly Costs: xx M€
**Kinome Profiler:**

**Kinome profiling:** A comprehensive tool for diagnosis and treatment prediction of human leukemia is being developed, based upon combined kinome and phosphoproteome profiling. Protein phosphorylation by serine/threonine and tyrosine kinases is estimated to affect up to one third of all proteins and has been widely studied. However only a small subset of in vivo targets/sites has been identified. The kinome profiler assay was developed for purified proteins and has to be extended for in vitro and ex vivo cell-based application. It is based on phosphorylation of a PNA-barcode peptide library and the use of microarray technology platforms as a read-out. Phospho-proteome profiling is mass-spectrometry based. The combination of both methods will provide a comprehensive and robust monitor of kinase activity in leukemia.

**Tool:**
Kinome Profiler

**Leading Company:**
FlexGen BV.

**Current Diagnostics:**
Currently no approved diagnostic tools are available for monitoring substrate specificity of kinases in combination with a disease indication. Current research options for analysis of kinase activity are limited to a maximum of 200 substrates in a single assay. The kinome profiler extends this to 10,000 substrates making the data analysis more robust and suitable for profiling approaches and diagnostics.

**Main results in CTMM**

- **Biomarker Development:**
The kinome assay has been optimized by the UMC Utrecht based on a proof-of-concept by the University of Edinburgh. The assay can clearly distinguish between distinct kinase activities in vitro. However, there have been difficulties in applying this technology to a cell-based assay that is required to distinguish human leucocyte samples. The most successful adaptation of the protocol has been modification of the library enabling it to be (i) cell permeable, and (ii) that it can be purified before applying it on array avoiding any constituents of the cell lysate to give rise to background signals.

- **Next development:**
The kinome profiling assay has been optimized for studies of kinase activity of purified proteins. As the major hurdles have been taken to make the assay work with cell lysates, the next step is to apply the assay to patient samples.

**Future Outlook:**
- Define the kinome profile for leukemia patients: AML and ALL

**Number patients per year:**

**Quality of Life (QoL):**
Better risk stratification through profiling results in better QoL. Successful application of kinase profiling will mean prevention of unnecessary intensive treatments or more intensive treatment with a higher change of being cured.

**Accessibility:**
The goal is to make access to the kinome profiler available through hospitals.

**Affordability:**
The pricing of the kinome profiler has not yet been set, but similar to the AML profiler and the MM profiler the kinome is based on microarray platform technologies. Therefore the pricing is expected to be in the similar range.
Early HTA: Key Elements and Findings

Key elements of early HTA

Health economic modeling
For acute myeloid leukemia (AML), a decision-analytic model has been developed which has been validated by clinical experts and with the data used to develop the decision-analytic model. The model is an individual patient-level simulation to take into account the large patient heterogeneity. This model can be used to evaluate both new diagnostic tests and treatments for patients with AML.

For multiple myeloma (MM), a first model has been developed to assess the potential value of personalized medicine in MM. This is a basic model that distinguishes between uniform treatment and risk-stratified treatment. Patients with standard risk will no longer receive a bortezomib-based regimen. Within both treatment arm, a Markov-model was used with three different health states (progression-free, progressive disease and death). The cycle length was one month and the total time horizon was 15 years.

Cost-effectiveness analysis
The cost-effectiveness analysis for both AML and MM focus on an evaluation of risk-stratified treatment. For AML, two different risk-stratified treatment approaches were evaluated: 1) reclassification of newly favorable patients within the intermediate cytogenetic risk group and 2) reclassification of newly unfavorable patients within the intermediate cytogenetic risk group. For MM, three different scenarios of risk-stratified treatment were evaluated: 1) identification of high-risk group based upon prognostic factors in standard practice (golden standard), 2) identification of high-risk based upon newly developed gene-signature and 3) identification of high-risk group based upon both golden standard and the gene-signature.

Key findings BioCHIP

Within the BioChip project, genetic tests are used to further classify patients and guide treatment.

For AML, the genetic tests were able to identify subgroups with a good prognosis and another subgroup with a poor prognosis. These subgroups could be treated differently. In general, an allogeneic hematopoietic stem cell transplantation (HSCT) is the most effective treatment for AML, but it is also associated with severe complications (GVHD). For good prognosis patients, the benefits of an allogeneic HSCT compared do not outweigh the disadvantages of the GVHD. Contrary, poor prognosis patients can only be cured with an allogeneic HSCT.

For MM, the risk-stratified treatment includes a restriction of the bortezomib-based regimen to the subgroup of patients who cannot be cured otherwise. Bortezomib is associated with high cost and a relatively large proportion of peripheral neuropathy. Furthermore, it has been shown that bortezomib has no benefit over other agents in patients without high-risk factors. Therefore, bortezomib treatment is restricted to MM patients with high-risk treatment.
Early HTA: Potential Impact of New Technologies

Cost-effectiveness analyses: Patient stratification

**AML**
The treatment change for the newly favorable patients results in a reduction of the total treatment costs (€152,536 versus €158,514) since high-dose chemotherapy is less expensive than an allogeneic or autologous HSCT. Furthermore, the resulted quality-adjusted life years (QALYs) increases (18.30 versus 17.29) as patients live longer and have fewer comorbidities. The treatment change for the newly unfavorable patients results in an increase of the total treatment costs (€246,838 versus €168,898). The number of life years also increases with 0.925 years, but these years are spent in a worse quality of life resulting in a QALY gain of 0.599. If the costs of testing are attributed to all patients, it is shown that the reclassification of the newly favorable patients is likely to be cost-effective given a threshold of €80,000, while the reclassification of the newly unfavorable patients is not cost-effective. For this subgroup, more effective or less expensive treatment is required in order to have a cost-effective treatment strategy.

**MM**
All three risk-stratified treatment scenarios resulted in lower treatment costs than a uniform treatment as the standard-risk group was no longer treated with the expensive bortezomib-regimen. The reduction in costs ranges between €1,842 and €4,924. All three scenarios resulted in more QALYs as the standard risk group was no longer exposed to bortezomib-induced peripheral-neuropathy. The increase in QALYs ranges between 0.009 and 0.034.

Health economic model

**Model structure**
The model for AML is an individual patient level simulation to include patient heterogeneity. With the following events: complete remission (CR), relapse, second complete remission and death. The probability of (second) complete remission and the time to relapse or death depends upon individual patient or disease characteristics like gender, white blood cell count (WBC), number of cycles needed to achieve CR and risk group. The complete model structure is shown in the figure below. The estimation of the probabilities and the time to relapse or death are derived from a selection of 427 patients who previously participated in Hovon trials with stored blood samples available. Cost were derived from Dutch daily practice and quality of life was measured in 89 patients who previously participated in clinical trials.

The model for MM is a combination of a decision-tree and a Markov model. The decision-tree identifies the two different treatment options (uniform and risk-stratified treatment. While the Markov model identified the disease process with three health states: progression free, progressive disease and death. The transition probabilities were derived from the overall survival and progression-free survival of 815 patients who participated in the HOVON65/GMMG-HD4 trial. Costs were derived from Dutch daily practice and and quality of life was derived from the literature.
Partners

Erasmus University Medical Center (EUMC)  Rotterdam
Erasmus University Rotterdam (EUR)  Rotterdam
University of Edinburgh  Edinburgh (UK)
University Medical Center Utrecht (UMCU)  Utrecht
Atos Nederland BV  Amsterdam
Crosslinks BV  Rotterdam
FlexGen BV  Rotterdam
Skyline Diagnostics BV  Rotterdam
SkylineDx  Rotterdam


List of Publications


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<tr>
<td>Abbreviation</td>
<td>Description</td>
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</tr>
<tr>
<td>ALL</td>
<td>Acute Lymphoblastic Leukemia</td>
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<tr>
<td>AML</td>
<td>Acute Myeloid Leukemia</td>
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<tr>
<td>BCR-ABL</td>
<td>Break Point Cluster and Abelson</td>
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<tr>
<td>CE</td>
<td>Conformité Européenne</td>
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<tr>
<td>CCKL</td>
<td>Coördinerende Commissie voor Kwaliteitsverbetering van Laboratoriumonderzoek</td>
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<tr>
<td>CEBP</td>
<td>Caat Enhancing Binding Protein</td>
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<tr>
<td>CLIA</td>
<td>Clinical Laboratory Improvement Amendments</td>
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<tr>
<td>DNMT3A</td>
<td>DNA methyltransferase 3A</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administartion</td>
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<tr>
<td>FISH</td>
<td>Fluorescent in situ hybridisation</td>
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<tr>
<td>FLT3</td>
<td>Fms-like tyrosine kinase 3</td>
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<tr>
<td>IVD</td>
<td>In Vitro Diagnostic</td>
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<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
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<tr>
<td>MM</td>
<td>Multiple Myeloma</td>
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<tr>
<td>MTA</td>
<td>Medical Technology Assessment</td>
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<tr>
<td>PMA</td>
<td>Pre-Market Approval</td>
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<tr>
<td>PNA</td>
<td>Peptide Nucleic Acid</td>
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<tr>
<td>ROI</td>
<td>Regions of Interest</td>
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<tr>
<td>RUO</td>
<td>Research Use Only</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
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