Patients affected by Hematologic Malignancies still have unmet needs.

By sharing Big Data we can improve patient outcomes.

By applying Big Data Analytics we can enable better and faster treatments for patients with Hematologic Malignancies.
Introducing the HARMONY Alliance

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in HematologY

A pan-European project of the Innovative Medicines Initiative (IMI) uniting and aligning healthcare system stakeholders and key opinion leaders in the field of Hematologic Malignancies (blood cancers).
Involving every stakeholder group to meet patients' needs.

Focus on 7 HM diseases: AML Acute Myeloid Leukemia . ALL Acute Lymphoblastic Leukemia . CLL Chronic Lymphocytic Leukemia . MDS Myelodysplastic Syndrome . MM Multiple Myeloma . NHL Non-Hodgkin Lymphoma. Pediatric HMs.
A unique European Network of Excellence for Big Data in Hematology

First IMI project on BD4BO for Hematologic Malignancies (HMs)
Open project: EU Cooperative Groups and Hospitals welcome
Stakeholders involvement: Academia, Industry, Payers, HTA, Regulators and Patients
First and largest Public-Private partnership (PPP) in hematology
High-quality HARMONY Big Data platform to include and harmonize data on Hematological Malignancies
Increase the application of omics data in clinical practice
Speed up drug development, access pathways and bench-to-bedside process

53 Public-Private Partners from 11 European countries.
It’s all about Big Data in Hematology. Your Big Data!

HARMONY is ready to collect data and deliver outcomes.
First year achievements

Guillermo Sanz
HARMONY Co-Chair, HULAFE

Pam Bacon
HARMONY Project Co-Leader, CELGENE

23rd Congress of EHA, Stockholm, 16th June 2018
HARMONY – First 18 months

Project launch Jan 2017

2nd General Assembly Oct 2017

One year milestone Jan 2018

EHA congress Jun 2018

53 partners
+ 1 public
+ 1 private
24 associated members

51 partners
15 associated members

We have grown in number!
SOPs for the approval of bench-to-bedside research proposals

HARMONY – First 18 months

Associated Members’ Engagement Framework and Data Sharing Agreements

2nd General Assembly Oct 2017

Project launch Jan 2017

Platform ready for Data-Intake

One year milestone Jan 2018

EHA congress Jun 2018

We have achieved significant milestones

Policy Health Stakeholder Feedback Forum

Communication & Dissemination activities

Core outcome set definition for HMs started & ongoing

Green light to legal framework & de-facto anonymization process from External Law Firm
HARMONY – First 18 months

Bench-to-bedside projects ready to start!

“Bench-to-Bedside” Projects

AML (and APL)

- 2nd General Assembly Oct 2017
- Project launch Jan 2017
- One year milestone Jan 2018
- EHA congress Jun 2018

CLL

MM

First data transfer to database expected in coming weeks!
Data Management
Data Analysis

Michel van Speybroeck
HARMONY WP3 Lead, Janssen

Ana Heredia
HARMONY WP3, GMV

23rd Congress of EHA, Stockholm, 16th June 2018
Data pipeline

Source Data → 'Raw' data → Data Preparation

Data not yet anonymised

Data Preparation → Data Brokerage

Data Brokerage → 'De-facto' anonymised data

Data Anonymisation

Data upload to Harmony platform

Data Intake

Harmony Platform

Extract, Transform And Load (ETL)

BigData Storage

Data upload to Harmony platform

Data Analytics

Harmonised Data Storage

Data mapped to 'Common Data Model'

Data Analysis and Visualisation

kibana

Honest Broker / Trusted Third Party

Harmony Platform
Anonymisation “De Facto”

Data for which attributing the individual data to the relevant individual concerned requires unreasonable effort in terms of time, cost and manpower!
Keeping the data safe

Technical

- Data anonymisation
- Data encryption in transit and at rest
- Data Access Restrictions
- Backup process

Organisational

- Physical and logical data center security
- Audit trail
- Contracts and SOP’s
- Training
Privacy and security

- VPN (Virtual Private Network)
- Firewall with two levels
- Audit: WHO, WHEN, WHERE, WHAT, HOW
- Risk analysis
- Named access
- Roles segregation
- Data governance: **nobody** has access to the data

The platform is hosted on CNAF
Hosting with ISO 27001
Data journey to HARMONY

* Communication channel: harmony-data@synapse-managers.com

Data transfer SharePoint*

DATA PROVIDER

HONEST BROKER/ TRUSTED THIRD PARTY

DATA PROCESSOR

DATA PROVISION

CODE CHANGE

TRANSFER TO DB

HARMONY platform

ID1 De-identified registry
ID2 De-identified registry
ID3 De-identified registry

Eventually deleted

ID1' De-identified registry
ID2' De-identified registry
ID3' De-identified registry

Eventually deleted

Eventually deleted
**Data pipeline: summary**

- **Data Provider** reviews the contracts and prepares the data according to the AMDS and anonymisation SOP.

- **Honest Broker / Trusted Third Party** verifies the data is anonymised and replaces IDs and Data Provider’s identity.

- **DQSC** evaluates the Reports and communicates the value to the HB, who shares this information with the Coordinaton Office.

- **HARMONY Platform** performs an analysis and generates a Quality Report without knowing who the Data Provider is. Data enters the platform and gets harmonised.
Quality report

**Quality Gate:** Minimum fields a data source must contain in order to be used on the Platform.
- Minimum fields to be mapped in the CDM.
- Minimum fields are defined by the KOLs (per disease).

**Quality Report:** analysis performed on every data source to determine its quality according to the cost matrix defined by the DQSC and KOLs (per disease).
## Quality report

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DATATYPE</th>
<th>NAME</th>
<th>WEIGHT</th>
<th>VALID</th>
<th>VALUE</th>
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<tbody>
<tr>
<td>DEMOGRAPHIC DATA</td>
<td>Demographics</td>
<td>Age at onset</td>
<td>1.5</td>
<td>35</td>
<td>105</td>
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<tr>
<td>DEMOGRAPHIC DATA</td>
<td>Demographics</td>
<td>Gender</td>
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<tr>
<td>DIAGNOSIS DATA</td>
<td>M. Biology</td>
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<td>175</td>
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<td>DIAGNOSIS DATA</td>
<td>PD and BM Cytology</td>
<td>Blasts in bone marrow</td>
<td>1.2</td>
<td>34</td>
<td>804</td>
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<tr>
<td>DIAGNOSIS DATA</td>
<td>PD and BM Cytology</td>
<td>Blasts in peripheral blood</td>
<td>1.2</td>
<td>34</td>
<td>804</td>
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<tr>
<td>DIAGNOSIS DATA</td>
<td>Blood Count and Chemistry</td>
<td>Hemoglobin</td>
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<td>35</td>
<td>175</td>
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<tr>
<td>DIAGNOSIS DATA</td>
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<td>Lacasa-cytochrome a</td>
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<td>35</td>
<td>175</td>
</tr>
<tr>
<td>DIAGNOSIS DATA</td>
<td>Blood Count and Chemistry</td>
<td>Platelets</td>
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<td>35</td>
<td>175</td>
</tr>
<tr>
<td>DIAGNOSIS DATA</td>
<td>Blood Count and Chemistry</td>
<td>White blood cells count</td>
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<td>35</td>
<td>175</td>
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<tr>
<td>DIAGNOSIS DATA</td>
<td>Diagnosis data</td>
<td>Prognostic Score</td>
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<td>Karyotype</td>
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<td>35</td>
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<tr>
<td>DIAGNOSIS DATA</td>
<td>Symptoms</td>
<td>Date of diagnosis and Type AML</td>
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<td>35</td>
<td>70</td>
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<tr>
<td>TIMES DATA</td>
<td>Cases</td>
<td>Cases found</td>
<td>9</td>
<td>10</td>
<td>15</td>
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<tr>
<td>OOL DATA</td>
<td>OOL</td>
<td>Performance status (ECOG/Karnofsky)</td>
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<td>35</td>
<td>70</td>
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<tr>
<td>TREATMENT DATA</td>
<td>Response to treatment</td>
<td>Response to treatment</td>
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<td>35</td>
<td>250</td>
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<td>TREATMENT DATA</td>
<td>Treatment</td>
<td>Type of treatment</td>
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<td>250</td>
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<tr>
<td>TREATMENT DATA</td>
<td>Survival Data</td>
<td>Relapse Date</td>
<td>1</td>
<td>35</td>
<td>70</td>
</tr>
<tr>
<td>TREATMENT DATA</td>
<td>Survival Data</td>
<td>Date of last follow up</td>
<td>0.5</td>
<td>35</td>
<td>25</td>
</tr>
</tbody>
</table>
Quality report

Quality report by category and data type (HARMONY)

Quality report by all levels (HARMONY)
Outcomes demonstration

Gender distribution

- Female: 472
- Male: 521

Cases diagnosed per year

Year of Diagnosis

- 1996
- 1998
- 2000
- 2002
- 2004
- 2006
- 2008
- 2010

FAB disease classification

- M4
- M5
- M1
- M2
- Unknown
- NOS
- VC
- M7
- t(9;21)

Primary cytogenetic anomalies

- Primary Cytogenetic Code
- Total cases

- inv(16)
- t(9;21)
- Unknown
- Normal
- Other
- NUL
Outcomes demonstration
Legal aspects of Data Protection in HARMONY

Dr. John Butler (Bayer AG)
HARMONY WP8 Lead, Bayer

23rd Congress of EHA, Stockholm, 16th June 2018
A Paradigm-shift in Health Care

Our health care payment and delivery systems are shifting from volume-based to value-based care

We get sick  We seek treatment  “some one” pays

https://www.slideshare.net/athenahealth/cashing-in-on-value-based-reimbursement/4
How do we get from here to there?

By building the health information backbone necessary to deliver on the promise of Digital Medicine

We get sick

Patient centered digital medicine

Personalized medicine

Preemptive medicine

Without protocol and patient-specific outcomes data, predictive analytics is largely vendor smoke and mirrors in all but a very small number of use cases.*1
Explicit Consent

Exempt Research not considered incompatible with the original purpose. (GDPR article 5.1.b)

Anonymize Not linked to subject

article 25 & 89.1 of the GDPR require “data protection by design and by default” hence if you can you must anonymize
What is Big Data in Health Care?

• HC Providers have large amounts of patient’s data on diagnosis, treatment choice and outcomes.
• Payers (Insurance) have large amounts of patients data on prescription costs and care measures.
• Some countries and regions have large data sources pertaining social consequences of disease.

Combining this data should:

1. Improve diagnosis and patient stratification,
2. Optimize therapeutic choices,
3. Provide robust data on therapeutic value

But….

• Data Privacy is the biggest hurdle.
• Changing regulations and legal environment have generated two phenomena:
  ➢ Naïve ignorance of the current legal framework
  ➢ Paralysis by analysis: uncertainty leading to fear and inaction.
Two extreme positions lead to paralysis by analysis

- “the GDPR has only unified the fines”
- “you can be fined up to 5% of revenues!”
- “Media/NGO can get us in trouble”
- “Anonymization (with genomics) is impossible”

- “this is for the advancement of medicine”
- “no one wants to identify patients”
- “there must be valid exceptions”
- “Anonymization renders data useless”
Absolute anonymization is impossible

The infinite monkey theorem

A monkey hitting keys at random on a typewriter keyboard for an infinite amount of time will almost surely type any given text, such as the complete works of Shakespeare.

If this holds true, high performance computing can eventually break any code and identify individuals based on unique data sets.
Absolute anonymization is impossible

The infinite monkey theorem

A monkey hitting keys at random on a typewriter keyboard for an infinite amount of time will almost surely type any given text, such as the complete works of Shakespeare.

Does this sound exaggerated?

If this holds true, high performance computing can eventually break any code and identify individuals based on unique data sets.

DP-Purists argue like that!
Anonymization is not black & white

- Personal data
- Pseudonymized data
- De-identified data
- De facto anonymized data
- Fully anonymized data

Degree of anonymization:
- Pseudonymization / key-coding
- De-identification
- Anonymization methods
- Further Anonymization methods

Degree of analysis possibilities:
- Data privacy regulations apply
- Data privacy regulations do not apply
De facto anonymization assessment

Factors influencing probability of re-identification

Personal Data

Technical anonymization
- suppression
- generalization
- perturbation

Data access restrictions
- policies
- processes
- contracts

Organizational security

De facto anonymous data

Re-identification Motives
- Business value of re-identification
- Potential to sell re-identified data
- Amount of data
- Effort to collect original data

Re-identification Capabilities
- Availability of complementary data
- Access to complementary data
- Data replicability
- Data distinguishability

Legal consequences of re-identification

Risk of being uncovered when re-identifying data

Deterrence
Keeping the Data Safe in HARMONY

Technical
- Data anonymization
- Data encryption in transit and at rest
- Data Access Restrictions
- Backup process

Organisational
- Physical and logical data center security
- Audit trail
- Contracts and SOP’s
- Training
“the HARMONY Anonymization Concept can ensure that the intended import of data into the HARMONY Platform and their subsequent uses as envisaged within the HARMONY Project complies with applicable data protection laws on EU level including the General Data Protection Regulation (GDPR)”

− Osborne Clarke “Legal Assessment of the Anonymization Concept for the HARMONY Project” V 29.01.18

− HARMONY data sets qualify as anonymous and not personal data.
− a de-facto anonymization is sufficient to exclude qualification as “personal data”
− i.e. sufficient anonymity is reached if identification would require an unreasonable effort.
− “The HARMONY Anonymization Concept takes into account all necessary factors” to ensure that the “case-by-case assessments are complete and no means required by applicable data protection law is ignored”.
Data Protection is an enabler of Digital Health
We must think first, document what we intend to do and build-in safety around health data records. Anonymization, data access restriction and organizational measures do the trick.
We need to do this consciously for each Research Question
We must always question whether the means are proportional to the goal.
Then we can proceed to work...confidently!
Overview Bench-to-Bedside Pilot Projects

Lars Bullinger
HARMONY WP2 Lead, Charité

Aliki Taylor
HARMONY WP2 Co-Lead, Takeda

23rd Congress of EHA,
Stockholm, 16th June 2018
**AML pilot – time line**

**KoM Salamanca:**
Identification of lead partners

**Timeline / workplan**
- UULM – coordination
- UCAM – MRC data
- VUMC – HOVON data
- Additional CWGs

**AML project proposal outline**
⇒ Approval by WP1
⇒ Negotiation with CWGs (AMLSG)
⇒ Provide exemplary data for WP3/4

**WP2 KOL Meeting (The Hague)**
⇒ Open questions regarding pilots
⇒ Outcome definition discussion

**ELN Meeting 2017**
⇒ approach CWG
⇒ start discussion with WP6

**Data analysis strategy**
⇒ Public data sets

**Data analysis strategy discussion**
⇒ Basis for future projects
⇒ Delineation of COS

**ELN Meeting (Venice)**
⇒ “Approval”
⇒ Assembly of data sets
⇒ Feed data into data base
⇒ First results by Q3 (GA Meeting Valencia)

**WP2 KOL Meeting (The Hague)**
⇒ Open questions regarding pilots
⇒ Outcome definition discussion
Additional pilots

**MDS**
The role of hypomethylating agents (HMAs) in high-risk MDS
15+ groups
2500+ patients

**CLL**
Large-scale mutation analysis - Novel prognostic/predictive scheme for improved risk stratification aimed at personalized medicine
ERIC: 24+ groups
5000+ patients

**MM**
Revised International Staging System for Multiple Myeloma
15+ groups
6000+ patients

**Pediatrics / ALL**
Definition of a common data set in childhood malignancies for cross entity analysis comparison of pediatric and adult data

**NHL**
Future projects

What are the next steps:

• Upload pilot data sets into HARMONY and run first analyses
• Continue project on definition of “core outcome sets” (Delphi)
• Joint WP2 and WP6 efforts:
  • follow-up projects?
  • additional data sets for HARMONY (including EFPIA data)?
  • how can we involve all stakeholder groups in the generation of meaningful new projects?
AML.
Leading the way: the first results

Hartmut Döhner
Ulm University

Estella Mendelson
Novartis

23rd Congress of EHA,
Stockholm, 16th June 2018
### 2017 ELN risk stratification by genetics

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Genetic Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favorable</strong></td>
<td>t(8;21)(q22;q22.1); RUNX1-RUNXI&lt;sub&gt;T&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11</td>
</tr>
<tr>
<td></td>
<td>Mutated NPM1 without FLT3-ITD or with FLT3-ITD&lt;sub&gt;low&lt;/sub&gt; &lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Biallelic mutated CEBPA</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>Mutated NPM1 and FLT3-ITD&lt;sub&gt;high&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Wild type NPM1 without FLT3-ITD or with FLT3-ITD&lt;sub&gt;low&lt;/sub&gt; &lt;sup&gt;*&lt;/sup&gt; (w/o adverse-risk gene mutations)</td>
</tr>
<tr>
<td></td>
<td>t(9;11)(p21.3;q23.3); MLLT3-KMT2A</td>
</tr>
<tr>
<td></td>
<td>Cytogenetic abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td><strong>Adverse</strong></td>
<td>t(6;9)(p23;q34.1); DEK-NUP214</td>
</tr>
<tr>
<td></td>
<td>t(v;11q23.3); KMT2A rearranged</td>
</tr>
<tr>
<td></td>
<td>t(9;22)(q34.1;q11.2); BCR-ABL1</td>
</tr>
<tr>
<td></td>
<td>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM(EVI1)</td>
</tr>
<tr>
<td></td>
<td>-5 or del(5q); -7; -17/abn(17p)</td>
</tr>
<tr>
<td></td>
<td>Complex karyotype, monosommal karyotype</td>
</tr>
<tr>
<td></td>
<td>Wild type NPM1 and FLT3-ITD&lt;sub&gt;high&lt;/sub&gt; &lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Mutated RUNX1&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Mutated ASXL1&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Mutated TP53</td>
</tr>
</tbody>
</table>

<sup>*</sup> Low, low allelic ratio (<0.5); high, high allelic ratio (>0.5)

AML pilot – genetic landscape

Age-related frequency of selected gene mutations

Analysis based on 10,622 AML patients from the AMLSG data base
Age distribution: <45 yrs, n=2,228; 45-60 yrs, n=3,392; 61-70 yrs, 2,517; >70 yrs, n=2,485

Compilation of comprehensive AML data sets

- Identification of gene-gene interactions
- Evaluation of the clinical impact of gene-gene interactions on outcome
- Validation and further refinement of novel genomic classification
- Evaluate the impact of intensive chemotherapy on “overlap cases”, i.e., high-risk MDS cases (MDS-EB2), now commonly included in our AML protocols
- Identification of prognostic / predictive factors for novel (targeted) therapies
AML pilot – gene-gene interactions

Mutually exclusive Co-mutated

Co-mutation Mutual exclusivity

n=300

n=1,540

n=82

OR=1

82

Mutually exclusive Co−mutated

Five most important achievements in 2017

• Establishment of HARMONY platform and work flows
• Identification of major AML data sets and mapping of data sources to pilot run
• Consent on data de-identification ("De-facto anonymization": double-brokerage pseudonymization)
• Description of the technical concept (pseudonymization and "hashing" approach)
• Associated Member Engagement Framework agreements
AML data sets of Cooperative Working Groups (CWGs)

- AMLSG: ~1,500 cases (incl. mol. genetics)  
  DSA under review
- British MRC: ~1,500 cases (incl. mol. genetics)  
  DSA pending
- HOVON: ~1,000 cases (incl. mol. genetics)  
  DSA under review
- AMLCG: ~1,000 cases (incl. mol. genetics)  
  DSA under review
- Additional CWGs: PETHEMA, ALFA, GIMEMA, ...  
  contacted

AML data sets of private partners

- EFPIA data sets

Additional AML data sets from clinical centers

- Belfast, etc.  
  DSA pending
AML continued – therapy with targeted agents

Midostaurin plus chemotherapy for AML with \textit{FLT3} mutation – \textit{Targeted sequencing project}


<table>
<thead>
<tr>
<th>2017 ELN marker</th>
<th>Midostaurin-kinome</th>
<th>Discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3</td>
<td>JAK3</td>
<td>Additional 236 genes associated with myeloid neoplasms</td>
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<tr>
<td>CEBPA</td>
<td>KDR</td>
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<tr>
<td>NPM1</td>
<td>KIT</td>
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</tr>
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<td>ASXL1</td>
<td>MAP3K10</td>
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<td>RUNX1</td>
<td>MAP3K11</td>
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<td>TP53</td>
<td>MAP3K9</td>
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<td>MST1</td>
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<td>KIT</td>
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<td>NTRK3</td>
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<td>PDGFRB</td>
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<td>PRKG1</td>
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<td>RET</td>
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<tr>
<td></td>
<td>RPS6KA3</td>
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</tr>
<tr>
<td></td>
<td>TNK1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RPS6KA6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TNK2</td>
<td></td>
</tr>
</tbody>
</table>

n=496 patients; sequencing of coding region of 262 genes (1443 Mbp); target enrichment (SureSelectXT / Agilent)

N. Jahn, E. Panina, A. Dolnik, T. Blätte L. Bullinger, K. Döhner
Aims 2018

- Include >5,000 AML data sets (first data set entry: June 2018)
- Identify additional EFPIA data sets to be included
- Continue discussion on outcomes definition – Delphi survey
- Define novel projects
  \[\Rightarrow\] E.g., horizontal projects linking different disease groups (e.g., high-risk MDS/low-blast AML, childhood/adult AML)
- Refine data entry, data analysis and data interpretation in collaboration with other WPs
- Communicate first results
  \[\Rightarrow\] Publication of AML pilot results
  \[\Rightarrow\] White paper on outcomes
Partnering for a better future for people with MH

Commitment to BD4BO

Commitment to sharing data
CLL. The second successful Pilot Study

Lesley Ann Sutton
European Research Initiative on CLL

23rd Congress of EHA, Stockholm, 16th June 2018
Recurrent gene mutations in CLL: An ERIC project in HARMONY

**Rationale**

- Many recurrent gene mutations exist in CLL
- Variable and low frequency (<10% each)
- Correlate with distinct disease and clinical outcomes

Prognostic or predictive capacity of gene mutations?

Could particular gene mutation(s) aid in clinical decision-making, including therapy selection and response prediction?
1) Gene mutations:

- ATM
- BIRC3
- MYD88
- NOTCH1
- SF3B1
- TP53
- EGR2
- POT1
- NFKBIE
- XPO1

Current status

4000+ CLL cases

2) Clinical data:

- Gender
- Date of birth
- Date of diagnosis
- Date of treatment initiation
- Treatment received (first-line)
- Date of last follow-up
- Binet/Rai stage at diagnosis
- IGHV gene mutational status
- FISH aberrations (11q-, 13q-, +12, 17p-)

100%

≥90%
**Clinical Parameters**

**DIAGNOSIS (N=4011)**
- CLL/PL: 2%
- SLL: 1%
- MBL: 3%
- atypical CLL: 0%
- CLL: 94%

**TREATMENT PHASE (N=4012)**
- Pre-treatment: 80%
- Post-treatment: 9%
- Unknown: 11%

**NEED FOR TREATMENT (N=3753)**
- TREATED: 56%
- UNTREATED: 44%

**RAI STAGING**
- RAI 0
- RAI I
- RAI II
- RAI III
- RAI IV

**BINET STAGING**
- BINET A
- BINET B
- BINET C
IG GENE MUTATIONAL STATUS (N=3493)

- U-CLL: 46%
- M-CLL: 54%

GENE MUTATIONS (N=3435)

- Mutated
- Wildtype

HIERARCHICAL FISH (N=3592)

- del(17p): 232; 6.5%
- del(11q): 407; 11.3%
- trisomy 12: 454; 12.6%
- del(13q): 1476; 41.1%
- no recurrent aberrations: 1023; 28.5%

Molecular Biomarkers

- TP53
- NOTCH1
- SF3B1
- NFKBIE
- XPO1
- POT1
- BIRC3
- EGR2
- MYD88
Recurrent gene mutations in CLL: An ERIC project in HARMONY

Specific project goals

— Evaluate the **mutational status** several **recurrently mutated genes** in a large and well-annotated (both molecular parameters and clinical characteristics) series of CLL cases.

— Assess the **prognostic impact** and **clinical relevance of recurrent gene mutations**.

— Identify **distinct patterns of associations** between **recurrent mutations** with other **clinicobiological features** in CLL.

— Perform **robust validation** of recently proposed **prognostication models** that incorporate both cytogenetic and molecular lesions prognostic indices.
Update of the MM Project

Mario Boccadoro
Ospedale Molinette, Torino

Bruno Costa
CELGENE

23rd Congress of EHA, Stockholm, 16th June 2018
A unique opportunity to involve all stakeholders in the definition of a core outcomes set across and within 7 hematologic malignancies.
Diagram of the approach

**Step 1:**
23& 24 Nov. 2017

**Step 2:**
February 2018

**Step 3:**
May-June 2018

**Step 4:**
July-mid Sept. 2018

**Step 5:**
Nov. 2018

1st list of outcomes MM, AML, MDS, CLL/NHL
01/12/2017

HCP outcomes list: 7 HMs
01/03/2018

Completion of the HCP outcomes list – all HMs
31/04/2018

EHA F2F meeting
13th June 2018

Presentation
@GA 4-5 Oct. 2018

Consolidate all findings in a long list of COS

Multi-stakeholders 1st Workshop, London

Public EHA KoLs Meeting 5/02/2018, La Hague

e-consultation: list completion

Patients’ associations
Regulatory Agencies
HTA Bodies/Payers
EFPIA Companies

Delphi-survey submitted to all stakeholders

1st subset of COS

Multi-stakeholders 2nd Workshop

Core Outcomes Set by clusters

Align stakeholders on key COS?
WP2 MM – progress update

1\textsuperscript{st} Meeting of the MM WP2 in Berlin, during the general assembly (23/24 Oct 2017)
- Definition of MM-specific outcomes
- Identification of suitable data sets to be included in HARMONY
- Definition of the Work Plan/Principles and timelines

2\textsuperscript{nd} Meeting during the MSH workshop, London (23/24 Nov 2017)
- Identification of existing COS applicable to MM
- Identification of additional, MM-specific COS
- Identification of additional global outcomes

3\textsuperscript{rd} Meeting of public EHA KoLs (Den Haag, 05/02/2018)

4\textsuperscript{th} Meeting of public MM KoLs (Torino, 19/04/2018)
- Consensus on the design of the pilot study (R-ISS update)
HARMONY MM pilot project

Revised International Staging System for Multiple Myeloma: extended follow-up in the European clinical trial population and evaluation of the efficacy of different novel agents and treatment approaches in subsets of patients with standard- and high-risk features.

Mario Boccadoro, Alessandra Larocca, Mattia D’Agostino, Jesus San Miguel, Marivi Mateos, Pieter Sonneveld, Philippe Moreau, Michele Cavo
Rationale: Standard risk factors for MM

ISS

- ISS I: 62 months
- ISS II: 44 months
- ISS III: 29 months

Chromosomal abnormalities

- Good: no High Risk (HR) CA
- Intermediate: only del13
- Poor: at least one of HR-CA
  \[ t(4:14); t(14:16); del17p \]

LDH

- \( \text{LDH} \geq 300 \text{ IU/L} \): 21 months
- \( \text{LDH} < 300 \text{ IU/L} \): 54 months

Median OS:

- ISS I: 62 months
- ISS II: 44 months
- ISS III: 29 months

- Good: 50.5 months
- Poor: 24.5 months

- LDH <300: 54 months
- LDH \geq 300: 21 months

R-ISS database

11 phase II/III international trials

PAD vs VAD
N = 827

MPR vs Mel200
N = 402

VMPT-VT vs VMP
N = 511

CRD vs Mel200
N = 389

PAD-Mel100-LP-L
N = 102

VP vs CVP vs VMP
N = 152

VAD/DCEP vs VD/DCEP
N = 482

VTD vs TD
N = 474

VBMCP/VBAD vs VTD/TD
N = 386

PATIENTS INCLUDED
N = 4445

PAD: bortezomib, Adriamycin, dexamethasone; VAD: vincristine, Adriamycin, dexamethasone; MPR: melphalan, prednisone, lenalidomide; Mel200: melphalan 200 mg/m^2; VMPT-VT: bortezomib, melphalan, prednisone, thalidomide + bortezomib + thalidomide maintenance; VMP: bortezomib, melphalan, prednisone; CRD: cyclophosphamide, lenalidomide, dexamethasone; CCD: carfilzomib, cyclophosphamide, dexamethasone; RD: lenalidomide, dexamethasone, CPR: cyclophosphamide, prednisone, dexamethasone; Mel100: melphalan 100 mg/m^2; LP-L: lenalidomide prednisone + lenalidomide maintenance; VP: bortezomib, prednisone; CVP: cyclophosphamide, bortezomib, prednisone; DCEP: dexamethasone, cyclophosphamide, etoposide, cisplatin; VD: bortezomib, dexamethasone, VTD: bortezomib, thalidomide, dexamethasone; TD: thalidomide, dexamethasone; VBMCP: vincristine, BCNU, melphalan, cyclophosphamide, prednisone; VBAD: vincristine, BCNU, doxorubicin, dexamethasone

• A new risk stratification model in novel agents era

• Includes simple and widely used prognostic markers

• Allows to define three MM entities with significant different outcome

• Future personalized treatments??
HARMONY MM pilot project

- Provide an extended follow-up of the original trials included in the R-ISS project adding other relevant datasets with mature data from clinical trials enrolling NDMM patients treated with novel agents.

- Evaluation of the efficacy of different novel agents and treatment approaches in subsets of patients with standard- and high-risk features.

R-ISS: Revised International staging system, NDMM: newly diagnosed multiple myeloma
A new model for risk stratification: k-adaptive partitioning for survival data

ISS: International Staging System, HR: high risk, CA: chromosomal abnormalities LDH: lactate dehydrogenase,

Endpoints

Primary endpoint
• Validation of R-ISS comparing it with ISS, CA and LDH levels alone after an extended follow-up.

Secondary endpoints
• Outcome of patients with low and high-risk features (defined according to R-ISS, ISS alone, CA alone, LDH alone, baseline creatinine clearance, best response < VGPR vs ≥ VGPR) treated with different novel agents (i.e. thalidomide, bortezomib, lenalidomide) and different treatment approaches (i.e. ASCT vs no ASCT, FDT vs CT)

Suitable Data sets

- R-ISS database (11 clinical trials)

- Addition of other relevant data sets with mature data from clinical trials enrolling NDMM treated with novel agents (European Cooperative groups)

- Data from large completed Phase III studies from EFPIA partners will be extremely relevant (VISTA, FIRST trials….)
Data workflow: MM Pilot Study

EMN NL
EMN Spain
EMN Nordic
EMN UK
EMN Czech
EMN France
EMN Germany
EMN Turkey
EMN Greece

EMN DATA CENTER

Cooperative groups studies outside of EMN

EFPIA

HARMONY
Preliminary analysis

<table>
<thead>
<tr>
<th></th>
<th>Original R-ISS paper (N=3060)</th>
<th>Available updated data (N=1354)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow-up – median (months)</strong></td>
<td>46</td>
<td>65</td>
</tr>
<tr>
<td><strong>Age – median (months)</strong></td>
<td>61</td>
<td>68</td>
</tr>
<tr>
<td>≤ 65 years</td>
<td>68 %</td>
<td>39%</td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>32%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>54%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>ISS Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>38%</td>
<td>35%</td>
</tr>
<tr>
<td>II</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td>III</td>
<td>24%</td>
<td>26%</td>
</tr>
<tr>
<td>NA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Chromosomal Abnormalities (CA)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR: Del17 or t(4:14) or t(14:16)</td>
<td>24%</td>
<td>28%</td>
</tr>
<tr>
<td>SR: neither of HR-CA</td>
<td>76%</td>
<td>72%</td>
</tr>
<tr>
<td>NA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>LDH levels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>87%</td>
<td>89%</td>
</tr>
<tr>
<td>High</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>NA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Treatments:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCT</td>
<td>65%</td>
<td>22%</td>
</tr>
<tr>
<td>IMIDs</td>
<td>66%</td>
<td>81%</td>
</tr>
<tr>
<td>PI</td>
<td>44%</td>
<td>33%</td>
</tr>
<tr>
<td>No new drugs</td>
<td>6%</td>
<td>-</td>
</tr>
</tbody>
</table>

HR: high risk, SR: standard risk, NA: not available, ASCT: autologous stem cell transplantation, IMIDs: immunomodulatory drugs, PI: proteasome inhibitors
Next steps

1. HARMONY’s full approval of the project (already approved by steering committee)
2. EMN as an intermediate depository between cooperative working groups and Harmony for data collection
3. EMN data centre as an associated member in Harmony project
4. As soon as Harmony data platform will be ready to receive data, EMN will transfer data to Harmony.
5. Reimbursement from Harmony to cooperative groups (amount per patient will be decided by Harmony according to data quality and completeness)
6. After the pilot project big data, not only big database (Toxicity, real-life registry data, QoL, MRD, molecular data, omics)
Update of the APL Project

Francesco Lo Coco
University of Rome Tor Vergata

Laura Ciccone
University of Rome Tor Vergata

23rd Congress of EHA, Stockholm, 16th June 2018
Key achievements of these trials include:

— risk classification of APL
— adoption of risk-adapted strategies with improved survival
— demonstration that target therapy (ATO+ATRA) is superior to ATRA+Chemo, leading to ATO approval by EMA based on academic, non-sponsored studies (NCRI, Gimema-SAL-AMLSG)
➢ 5000 APL patients enrolled

➢ Heterogeneous prevention and management of complications in homogeneous treatment context
Open issues in front-line APL therapy

- **Differentiation Syndrome**: role of steroid prophylaxis in prevention (heterogeneity of approaches, e.g. NCRI vs others)
- **t-APL**: Prognosis in chemo- and ATO-based studies
- **CNS disease**: management; role of IT prophylaxis
- **Maintenance therapy**: compare maintenance vs no maintenance strategies
- **Early mortality**: compare rates in different trials and analyze predictive factors. Role of ATO vs chemo in control of the coagulopathy
- **Elderly patients**
APL proposal - Timeline

- **28 March 2018** APL study proposal (P.I. F Lo-Coco)
- **9 April 2018** Proposal accepted by Harmony Coordination Office
- **Next steps:**

1. Outline to be sent to APL cooperative group chairs to ask EOI to include pt data:
   
   M Sanz (PETHEMA), P Fenaux (French-Belgian-Swiss), U Platzbecker (SAL), H Dohner (AMLSG), G Ossenkoppele (HOVON), Niederwiser, E Lengfelder (AMLCG), Others?

2. Establishment of a Steering committee

3. Elaboration of study protocol, CRF and definition of ethical requirements in collaboration with Harmony Central Office
European Network of Excellence for Big Data in Hematology, consisting of 53 partners from 11 countries.

Future Plans

Jesus Maria Hernandez
HARMONY Coordinator, IBSAL

Mirko Vukcevic
HARMONY Project Leader, NOVARTIS

23rd Congress of EHA, Stockholm, 16th June 2018
Roadmap to the 3rd General Assembly

Incorporating the first datasets to the platform

Starting the analysis phase of the pilot studies

Access to Industry structure & data

Funded by
More achievements coming…

Data Analytics

Evidence and Value Framework

Continue defining a Standard Set of Outcomes

New project proposals

Modeling & Machine Learning
HARMONY Future Meetings

ELN Symposium
Mannheim, 12th February

24th EHA Congress
Amsterdam, 13-16th June
HARMONY is aimed at the entire haematological community!

- We are an open project
  - More than 100 European organisations have shown their interest in HARMONY: co-operative Working Groups, Hospitals, Academic Institutions...
  - 80 institutions are in the process of becoming HARMONY Associated Members
  - Apart from our 53 partners, we already count with 24 Associated Members.

- Your data are crucial!
  - All of you are invited to join the HARMONY Alliance as Associated Members!
  - Help us meet the needs of patients with HMs.
Join us in Room K11 for our Partnering Session

Feeding the HARMONY Platform: Guidelines for Data Providers

— Room K11, 16:15 - 17:15
— Q&A Roundtable Session
  • Steps in the data intake process
  • HARMONY Agreements
  • The HARMONY anonymisation concept
  • Submission of Research Proposals
  • What is the data going to be used for?
  • Data Quality Assessment
— Chairmen:
  • WP1: Jesús M Hernández, IBSAL, Spain;
  • WP2: Lars Bullinger, Charité, Germany;
  • WP3: Ana Heredia, GMV, Spain;
  • WP3&4: Michel van Speybroeck, Janssen, Belgium;
  • WP8: John Butler, Bayer, Germany.
Thank you!
Any questions?
This material is developed by the HARMONY Alliance

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Acknowledgement

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