HARMONY

#BigDataforBloodCancer

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Public-Private Partnership for Big Data in Hematology
Accelerating better treatment of blood cancer patients

Community of approx. 400 professionals

Over 100 organizations from 18 countries

14 key targeted blood cancers

Big Data analytic services

Big Data Platform with >70,000 anonymized patient records identified

Research, Delphi and Multi-stakeholder projects

Funded by Innovative Medicines Initiative
Support from European Union’s Horizon 2020 Research and Innovation Programme
Part of European Federation of Pharmaceutical Industries and Associations

IMI Big Data for Better Outcomes (BD4BO)
About HARMONY

The first and largest Public-Private Partnership in Hematology

Focus on **Big Data** in:

- Acute Lymphoblastic Leukemia
- Acute Myeloid Leukemia
- Childhood Hematologic Malignancies
- Chronic Lymphocytic Leukemia
- Multiple Myeloma
- Non-Hodgkin Lymphoma
- Myelodysplastic Syndromes

Community of multi-stakeholder organizations representing **18 European countries**

- **53 Partners**
- **7 European Patient Organizations**
- **43 Associated Members**

Budget **40 million Euro**

5-year project from January 2017 until Dec 2021
About HARMONY PLUS

Part of the largest Public-Private Partnership in Hematology

Focus on Big Data in
- MPN
- CML
- PV
- ET
- HL
- WM
- Myelofibrosis
- Polycythaemia Vera
- Essential Thrombocythaemia
- Hodgkin's Lymphoma
- Waldenström Macroglobulinaemia
- and other rare blood cancers

Community of
- 39 Partners
- 8 Associated Partners

Budget
- 11.8 million Euro

3-year project
- from October 2020 until Oct 2023

Will create the availability of a historical control arm as a new model of supporting HMs’ CT design

Will build additional modules that will enable data driven decisions for payers and regulators, based on Artificial Intelligence techniques

Will pursue more collaborations with other big data projects worldwide
HARMONY – Uniting the European hematological community

- Building a high-quality Big Data platform on hematologic malignancies
- Harmonization of outcome measures and endpoint definitions for HMs at European level
- Speed up drug development, access pathways, and bench-to-bedside process
- Increase the application of omics data in clinical practice
## Data barometer HARMONY Big Data Platform

by number of data sets identified per country

<table>
<thead>
<tr>
<th>Country</th>
<th>Data Sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czechia</td>
<td>1.375</td>
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<tr>
<td>Greece</td>
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<tr>
<td>Switzerland</td>
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<td>Denmark</td>
<td>2.814</td>
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<td>Italy</td>
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<td>The Netherlands</td>
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<tr>
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<td>Germany</td>
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<tr>
<td>Sweden</td>
<td>1.423</td>
</tr>
<tr>
<td>Other</td>
<td>1.661</td>
</tr>
</tbody>
</table>
Data barometer HARMONY Big Data Platform
by number of data sets identified per blood cancer

- June 2021: 73,682 data sets
- March 2020: 52,000 data sets
- March 2019: 45,000 data sets
- January 2017: 0 data sets

MDS: 12,523 data sets
ALL: 13,523 data sets
AML: 20,278 data sets
MM: 16,026 data sets
NHL: 3,324 data sets
APL: 3,588 data sets
CLL: 4,220 data sets
Core elements of the HARMONY Architecture
HARMONY Case: Acute Myeloid Leukemia (AML)
AML Pilot Study: Gene–gene interactions influence treatment outcomes

Transferred: 7,221 cases

=> proof-of-concept study to establish the legal and ethical framework

~10,000 cases signed and being prepared for transfer

- MRC (~3000)
- Karolinska Institute (~550)
- GPOH (~3700)
- Queens Univ. Belfast (~300)
- ALFA (~1500)
- GIMEMA (~500)
- CETLAM (~400)
— Data Dictionary has to be completed in order to finalise and sign the legal agreements.

— Data Dictionary is assessed by the Data Quality Supervision Committee.

— **Data granularity**
  - Demographic data
  - Diagnostic information
  - Omics data (NGS)
  - Treatment information (treatments received, response to the therapy, OS, DFS, follow-up including MRD data, etc.)
  - Quality of Life (QoL) data

— Data sets include treatment with new agents (e.g. midostaurin)
Model of clonal evolution

- Bradley-Terry analysis of the variant allele frequency (VAF)

- Epigenetic driver mutations in genes affecting DNA methylation are very early events (e.g. DNMT3A, TET2, IDH1/IDH2)

- Mutations in histone modifying enzymes occur later (e.g. KMT2D, EZH2, ASXL1, EP300)
Gene–gene interactions

- gene-gene interaction analysis confirmed known patterns of co-occurrence and mutual exclusivity

- provided e.g. additional evidence for the co-occurrence of EZH2 mutations with RUNX1

- co-occurrence of RUNX1 with “aberrant splicing” (SRSF2, SF3B1, and STAG2)

Only relationships with a p-value ≤ 0.05 are presented:
- blue color: co-occurrence
- red color: mutual exclusivity
Clinical impact of gene-gene interactions
Gene-gene interactions – clinical implications

⇒ Interactive tools to explore gene-gene interactions
Classification based on gene interactions

The age cutpoints are defined for the minimum p value of a $\chi^2$ test on gene mutation cooccurrences for the split populations. The p values are corrected according to the asymptotic formula of Miller and Siegmund (see, e.g., Lausen and Schumacher 1994). Shown: only significant gene pairs.
Summary – Overall Components

Genetic Drivers
NPM1, RUNX1/ASLX1, IDH2, CEPBAbi, TP53-CK

Gene Fusion Drivers
inv3, inv16, t821, t69-FLT3, rearq23, t1517

New Drivers Emerging from Bayesian Network Analysis:

CBL
PHF6
20 ongoing projects

- 2 projects recently approved in CLL and CML
- 2 projects under review in AML and MDS
Thank you

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HARMONY Alliance | Public-Private Partnership for Big Data in Hematology