XIX CONGRESSO NAZIONALE SIES 2026

CLINICAL IMPACT OF UNTARGETED BASELINE PLASMA METABOLOMICS IN NEWLY DIAGNOSED DIFFUSE LARGE B CELL LYMPHOMA

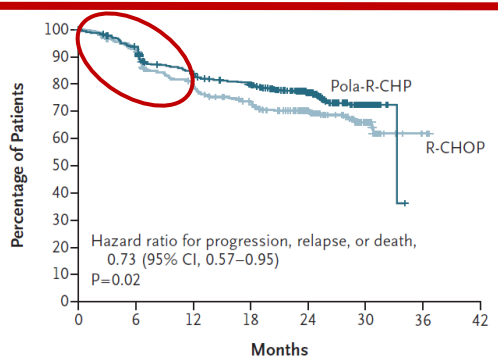
Mohammad Almasri
Università del Piemonte Orientale
Novara-Italy

Firenze | 4-6 marzo 2026
Palazzo degli Affari

Disclosures of Mohammad Almasri

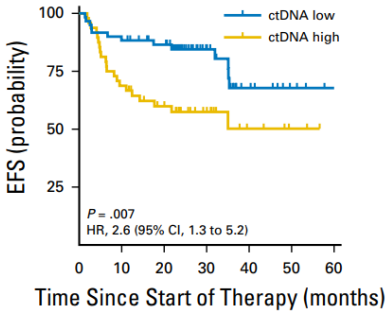
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NONE							

Combining different biomarkers may help identifying early R/R DLBCL

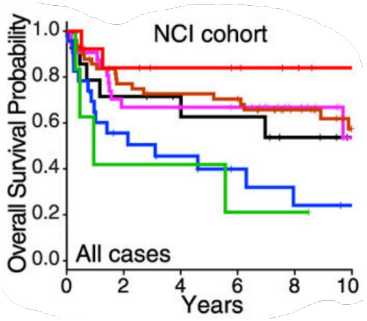


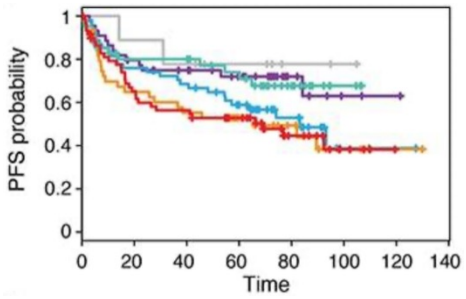
Even with the latest improvements in frontline therapy,
R/R DLBCL remains an unmet clinical need
and its identification *a priori* may improve treatment tailoring

Baseline ctDNA levels

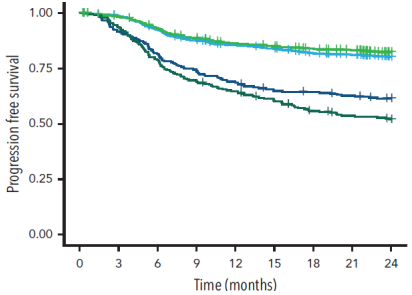


Molecular clusters





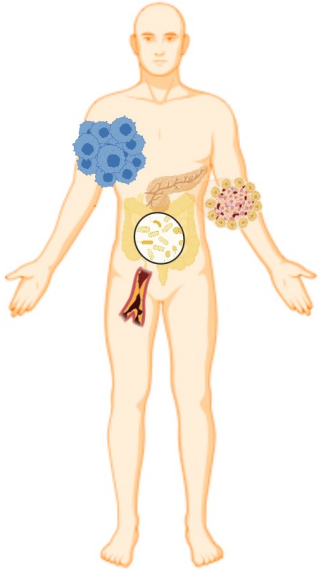
PET/CT radiomics



ctDNA: Circulating tumor DNA

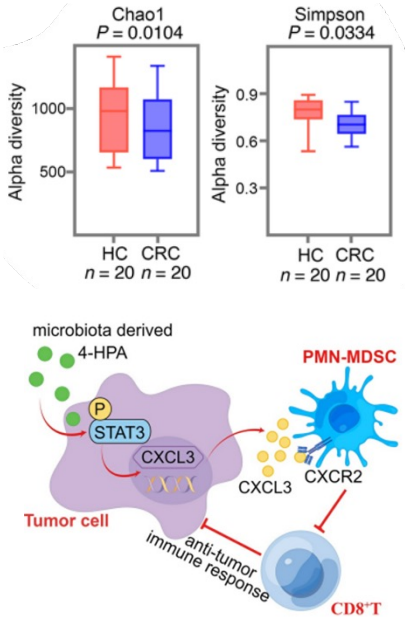
Kurtz *et al., JCO*. 2018; Chapuy *et al., Nat Med*. 2018; Schmitz *et al., NEJM*. 2018; Wright *et al., Cancer Cell*. 2020; Tilly *et al., NEJM*. 2022; Eertink *et al., Blood*. 2023; Chapuy *et al., Blood 2025;* Ceriani *et al., Br J Haematol*. 2025

Metabolomics as a promising prognostic tool in oncohematology

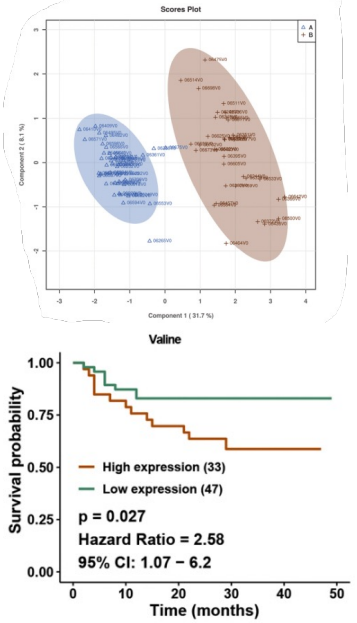


Lymphoma-related
- ctDNA
- PET/CT scans
- Metabolomics

Patient-related
- Metabolomics



Gut microbial 4-hydroxybenzeneacetic acid is upregulated in colorectal cancer



Initial reports identified some plasma metabolites with potential prognostic value in DLBCL

Stenson *et al., Leuk Lymphoma*. 2016; Mi *et al., Leuk Res*. 2021; Fei *et al., Front Oncol*. 2022; Liao *et al., J Clin Invest*. 2025

Aims of the study

To investigate the potential clinical impact of baseline plasma metabolomics in newly diagnosed DLBCL and its relationship with ctDNA levels and PET/CT radiomics features

Experimental workflow

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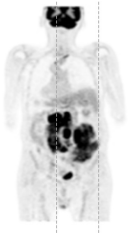
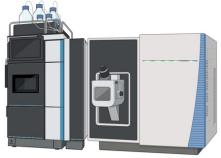
Discovery cohort

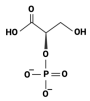
96 newly diagnosed DLBCL

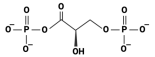


PET/CT Scans
tMTV
(N=87 patients)

Plasma samples
(N=96 patients)

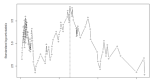




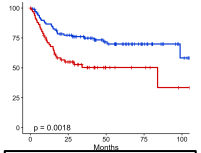


Untargeted metabolomics
High-resolution mass spectrometer coupled/bidimensional gas chromatography

Maxstat Test

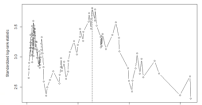


CAPP-Seq panel
of genes recurrently mutated in DLBCL



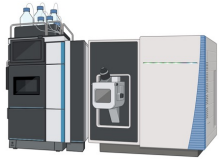
ctDNA level

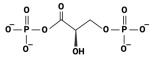
Maxstat Test



Validation cohort

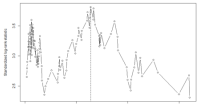
42 newly diagnosed DLBCL





Deuterated internal standards and external calibration curves
High-resolution mass spectrometer coupled/bidimensional gas chromatography

Maxstat Test



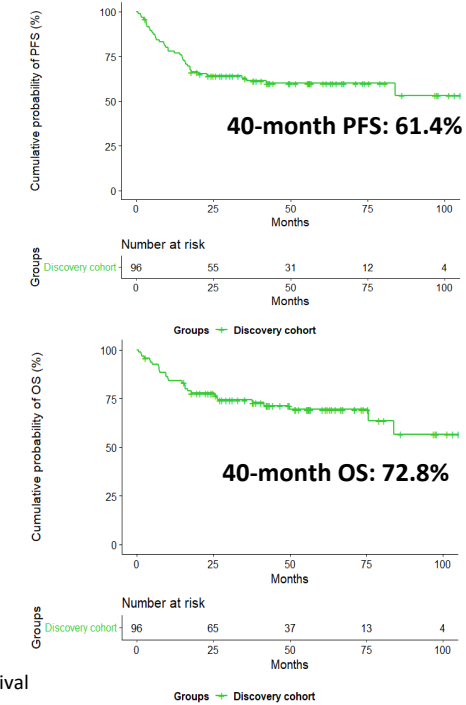
Patient characteristics

Discovery cohort (N=96 DLBCL)

Characteristics	Values
Median Age	68 (IQR 54-76)
Stage	
I-II	25 (26.0%)
III-IV	71 (74.0%)
IPI	
0-1	21 (21.9%)
2	19 (19.8%)
3	23 (24.0%)
4-5	33 (34.3%)
COO	
GC	30 (31.3%)
Non-GC	56 (58.3%)
Not available	10 (10.4%)
LDH above ULN	
Yes	59 (61.5%)
No	37 (38.5%)
Extranodal sites	
Yes	60 (62.5%)
No	36 (37.5%)

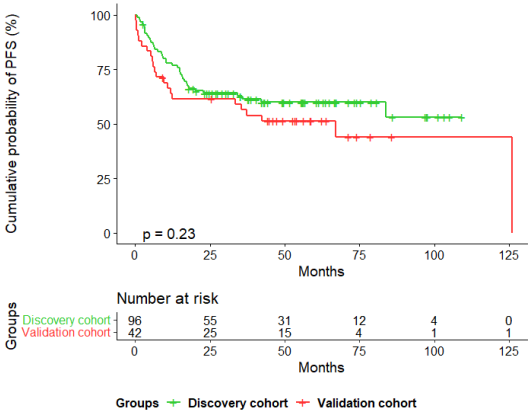
IPI: International Prognostic score**; PFS:** Progression-free survival ;**OS:** Overall survival

Median follow-up: 55.6 months



Validation cohort (N=42 DLBCL)

Median follow-up: 58.8 months



Training cohort: 40-month PFS: 61.4%

Validation cohort: 40-month PFS: 53.9%

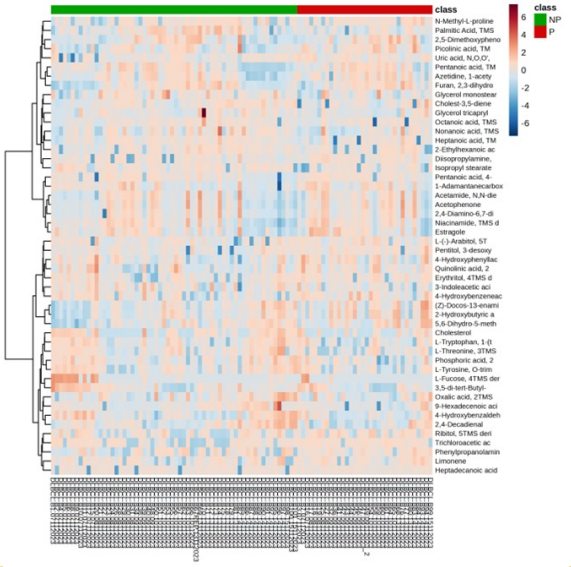
Metabolomics profile is different according to progression status

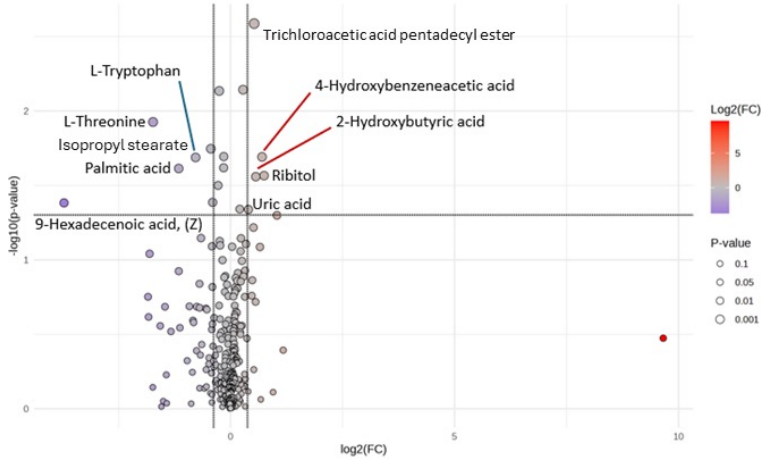
96 DLBCL patients → Classification based on PFS at 24 months from diagnosis

- **62 non-progressive** patients
- **34 progressive** patients

→ **5 upregulated** and **5 downregulated** metabolites in progressive patients

Modulated metabolite	FC	p-value
Trichloroacetic acid, pentadecyl ester	1.4406	0.002587
L-Threonine	0.30129	0.011853
Isopropyl stearate	0.73707	0.017925
4-Hydroxybenzeneacetic acid	1.6272	0.020335
L-Tryptophan	0.58224	0.020506
Palmitic Acid	0.44858	0.024333
Ribitol	1.6796	0.027174
2-Hydroxybutyric acid	1.4773	0.027604
9-Hexadecenoic acid, (Z)	0.076041	0.041421
Uric acid	1.3184	0.04588





High 4-Hydroxybenzeneacetic acid (4-HPA) levels associate with poor outcome

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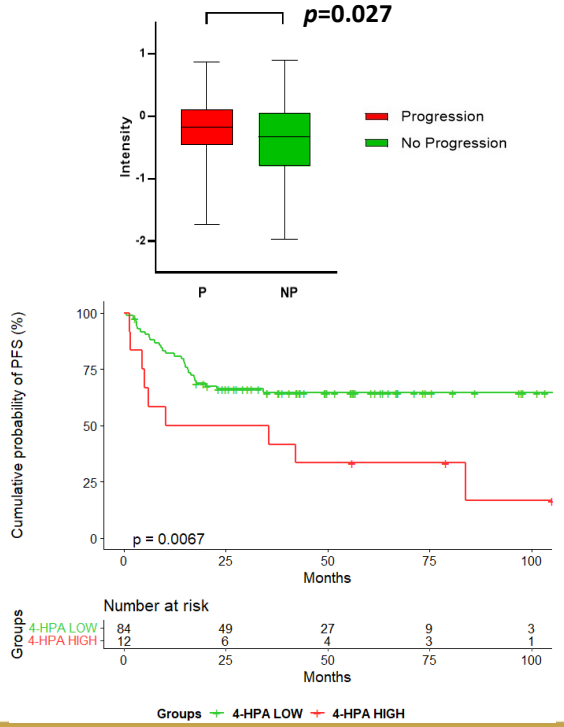
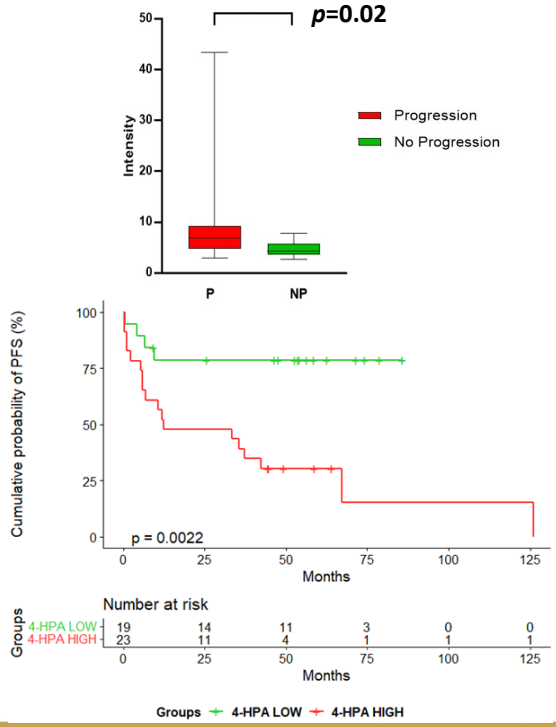
Discovery cohort (N=96)

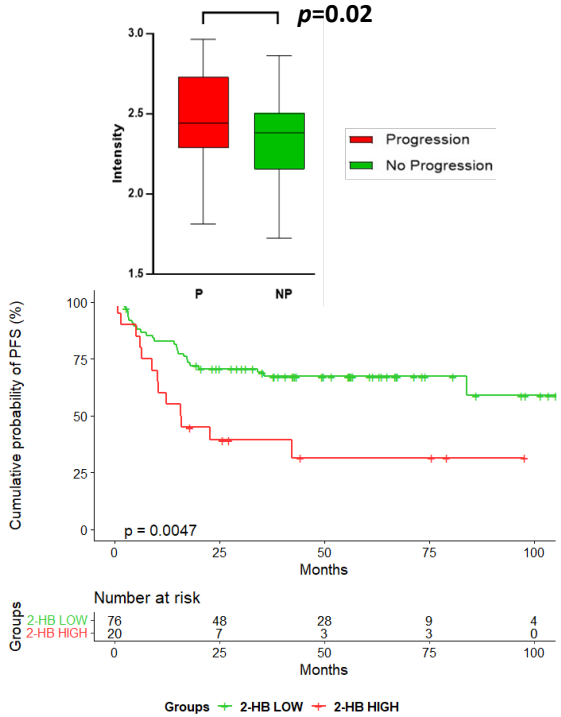


Validation cohort (N=42)

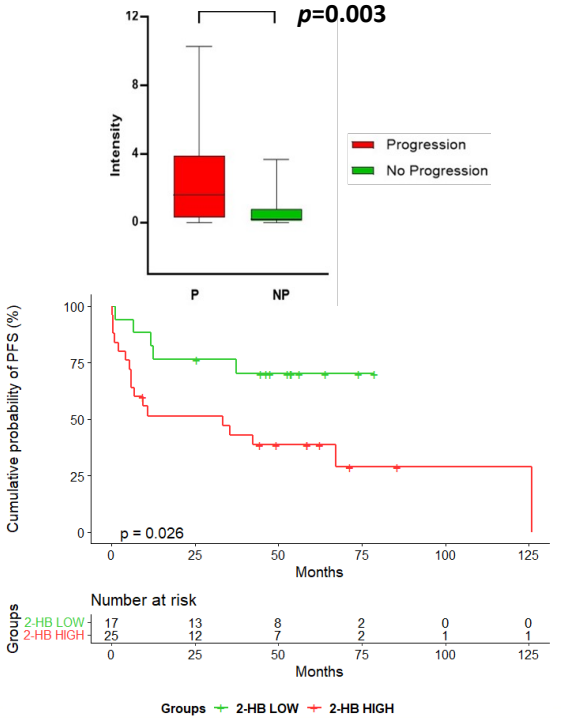


High 2-Hydroxybutyric acid (2-HB) levels associates with poor outcome

Discovery cohort (N=96)



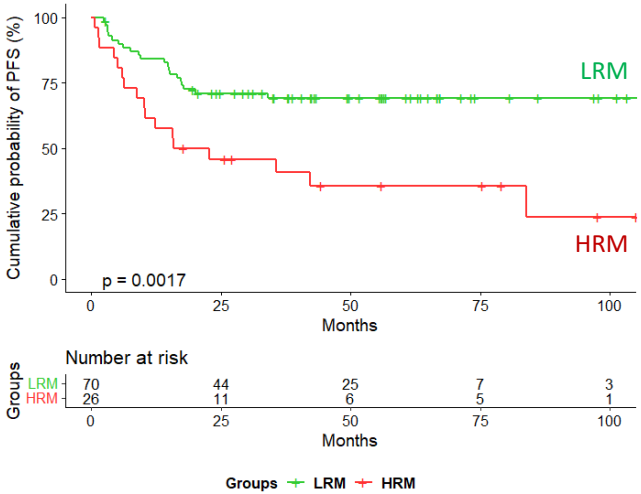
Validation cohort (N=42)



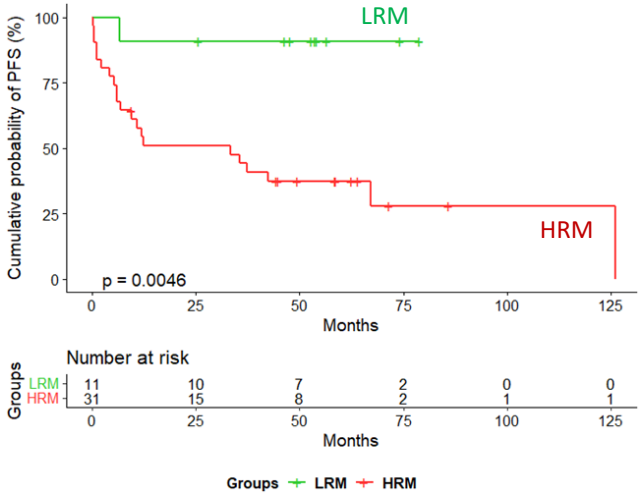
Metabolomic profile classification

- HRM class: patients with high level of 4-HPA/2-HB
- LRM class: patients with low levels of 4-HPA/2-HB

Discovery cohort (N=96)



Validation cohort (N=42)



HRM: high-risk metabolomics; **LRM:** low-risk metabolomics

Metabolomic profile further refines outcome of low-risk patients according to ctDNA level and PET/CT tMTV

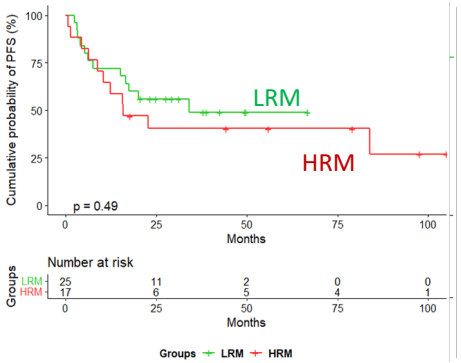
ctDNA level cutoff = 2.5 Log10hGE

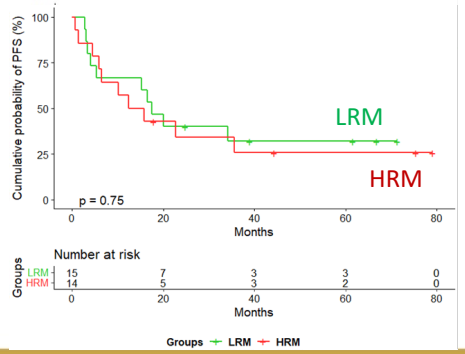
ctDNA High

tMTV cutoff = 640 cm³

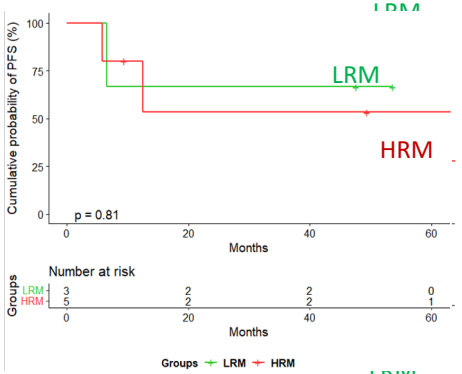
tMTV High

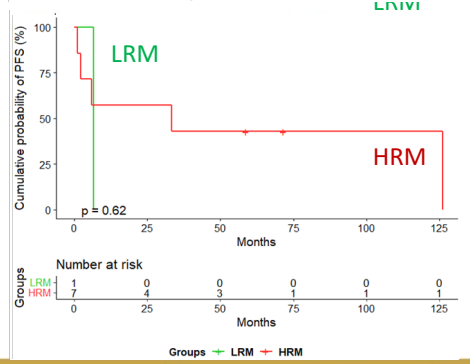
Discovery cohort





Validation cohort





HRM: high-risk metabolomics; **LRM:** low-risk metabolomics

Conclusions

- **Baseline plasma metabolites** differs between progressive and non-progressive DLBCL patients and **harbor promising prognostic value.**

- Baseline **4-Hydroxybenzeneacetic acid** and **2-Hydroxybutyric acid** levels are **associated with shorter PFS** in newly diagnosed R-CHOP-treated DLBCL and further **refine the prognosis of low-risk patients** according to ctDNA levels and tMTV
  - **4-Hydroxybenzeneacetic acid** levels reflect the potential contribution of **microbiome** changes to disease course and response to therapy
  - **2-Hydroxybutyric acid** levels may capture the prognostic relevance of **oxidative stress** and **metabolic dysregulation** in DLBCL patients

- Since its potential ability to **capture both lymphoma- and patient-related prognostic determinants**, metabolomics should be integrated in multilayer prognostic models for early identification of high-risk DLBCL patients to allow timely disease evaluation and treatment tailoring

Hematology department:
Riccardo Moia
Riccardo Dondolin
Chiara Cosentino
Jana Nabki
Bashar Al Deeban
Luca Cividini
Samir Mouhssine
Matteo Bellia
Francesca Maiellaro
Eleonora Secomandi
Sreekar Kogila
Monia Lunghi
Joseph Ghanej
Nawar Maher
Gloria Margiotta Casaluci
Abdurraouf Mahmoud
Clara Deambrogi
Silvia Rasi
Nursing staff

Marco Ladetto

Gianluca Gaidano

BiologicalMass Spectrometry Lab:
Denise Marradi
Elettra Barberis
Marcello Manfredi

Nuclear Medicine Department:
Federico Garrou
Gian Mauro Sacchetti

Patology Department:
Annalisa Andorono
Fracesca Mercalli
Renzo Luciano Boldorini

Monica Leutner
Angela Lorenzi

Giovanni Assanto
Ilaria Del Giudice
Alice Di Rocco

Maurizio Martelli
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Valter Gattei

Ilaria Romano
Matin Salehi
Lodovico Terzi di Bergamo
Gabriela Forestieri

Davide Rossi

Enrica Antonia Martino
Massimo Gentile

Grant support:

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Ministero della Salute
AIL Novara VCO
ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE - LINFOMI E MIELOMI
MINISTERO DELL'ISTRUZIONE, DELL'UNIVERSITÀ E DELLA RICERCA
UPO AGING PROJECT