XIX CONGRESSO NAZIONALE SIES 2026

GENOMIC ANALYSES OF PATIENTS WITH MANTLE CELL LYMPHOMA THAT WERE REFRACTORY OR RELAPSED AFTER INDUCTION THERAPY: RESULTS FROM THE FIL_MANTLE-FIRST BIO STUDY.

Maria Elena Carazzolo (PhD student in Biomolecular Medicine)

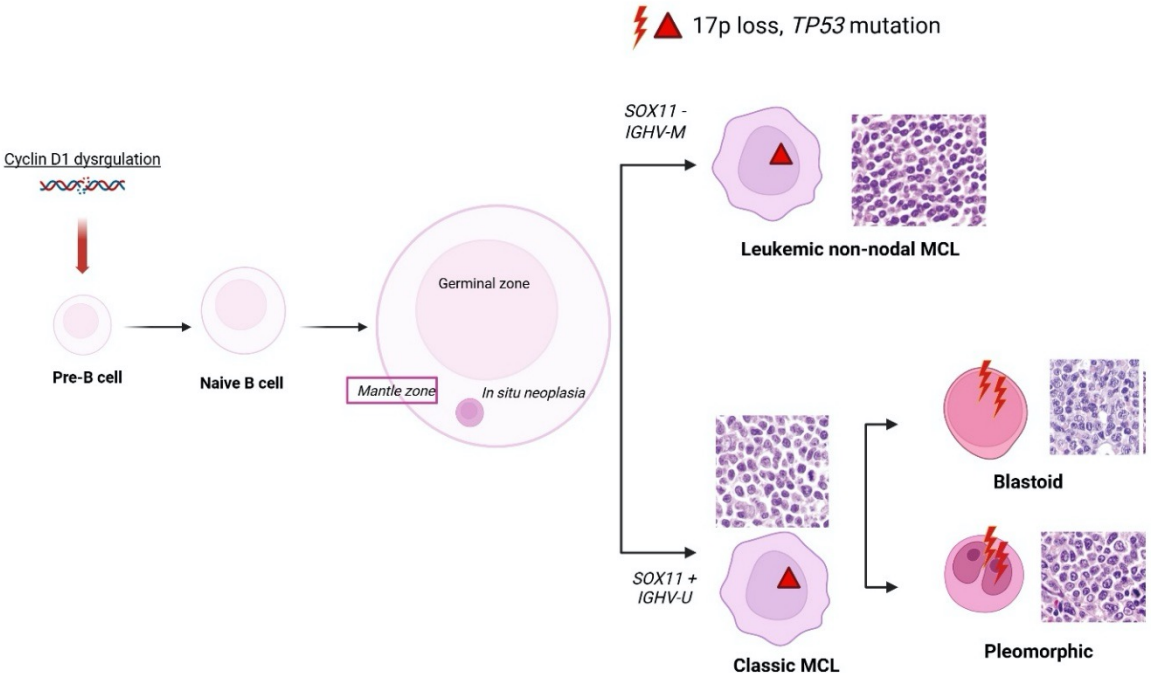
Francesca Maria Quaglia (UOC Ematologia e CTMO, AOUI Verona)

Firenze | 4-6 marzo 2026
Palazzo degli Affari

Disclosures of Francesca Maria Quaglia

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen							X
Novartis							X
Roche							X
Astra Zeneca					X		
Sandoz			X				
Kite Gilead					X		

BACKGROUND

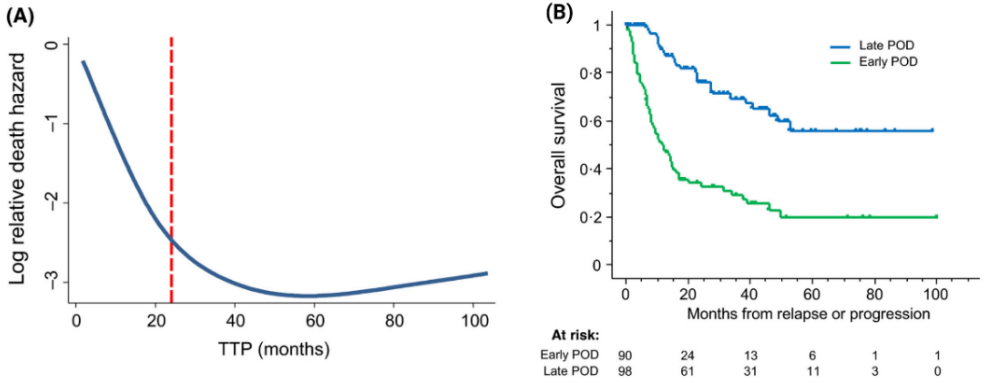


Indices of risk	High risk
Ki-67	≥30%
MIPI	≥ 6.2
Morphology	Blastoid / pleomorphic
TP53 (del or mut)	Presence

M.E Carazzolo (et.al), JCM, DOI: 10.3390/jcm14238480

PRELIMINARY REMARKS

The statistical analysis was performed associating the **previously defined threshold of 24** months since MCL diagnosis, defining: **early-POD and late-POD**, with the molecular signatures identified through Next Generation Sequencing (NGS).



A) Hazard model showing the relationship between risk of death (Log relative hazard) and time to first relapse or progression (TTP). (B) OS-2 according to POD (early POD *versus* late POD, $P < 0{\cdot}0001$).

Visco (et.al), BJHaem, 2019, https://doi.org/10.1111/bjh.15643

MANTLE-FIRST BIO

PI: FM Quaglia *NCT04882475*
PGR Ed. 2019

MANTLE-FIRST BIO STUDY

FONDAZIONE ITALIANA LINFOMI

MANTLE-FIRST BIO (NCT04882475PGR, Premio Giovani Ricercatori, Edition 2019) is a retrospective and multicentre study → 16 centers affiliated to Fondazione Italiana Linfomi (FIL).

ELIGIBILITY CRITERIA

Diagnosis	from 1st of Jan 2008 to 30th of June 2020
Treatment	**upfront therapy including rituximab**; excluded indolent or watch and wait approach patients
Relapse or refractory (R/R) event	**R/R occurrence** to induction therapy → necessary condition for enrollment.
Age	18-80 years old

MANTLE-FIRST^BIO

AIM OF THE STUDY

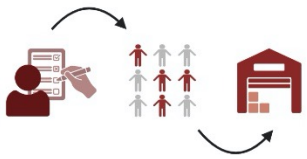
Decipher the complex molecular network predicting refractoriness to CIT/BTKi.

Activities nearing completion:

1. Histopathological characterization of R/R MCL (→ board of *pathologists by FIL*)
2. Activation status of BCR pathway (→**Gambino *et al***, Scientific Reports 2024 https://doi.org/10.1038/s41598-024-55728-9)
3. **Genomic analysis for prediction of POD** (→ subject of present study)

WORKFLOW

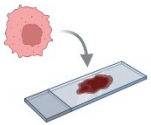
Sample centralization



Patients selection and samples **centralization** of **16 FIL** centres

Sample processing

Microtome: slides preparation



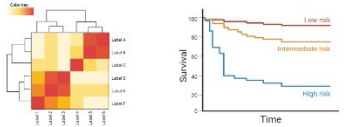
Histological evaluation:
-morphology
-SOX11
-Ki-67
-p53
-MYC

DNA extraction and **targeted sequencing** with a custom panel of 37 genes

Data analysis

Variant calling: **MuTect2 v4.1** (SNVs) and **CNVkit v.0.9.9** (CNVs)

SNVs and CNVs annotations: **public databases** and **IGV software**



Statistical analysis: clinical and genomic data integration

MANTLE-FIRST^BIO

unpublished data

RESULTS

COHORT DESCRIPTION:

The table reports the main clinical characteristics of 81 MCL R/R patients.

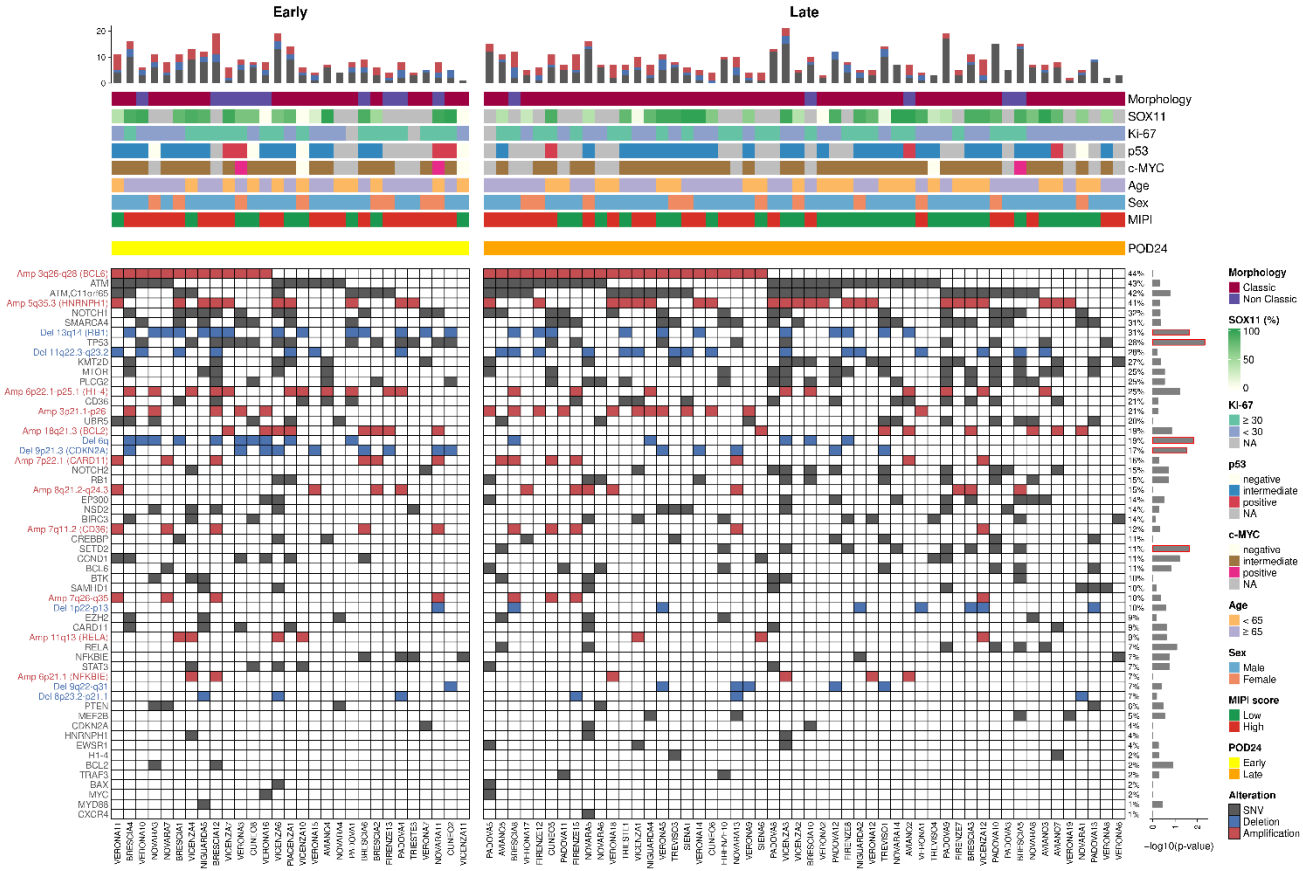
Total (n=81): Early-POD (n= 29, 36%) and Late-POD (n=52, 64%)		p- value (early vs late)
Gender		
Male	77%	p=0.6
Female	23%	
Age		
≥ 65	58%	p=0.6
< 65	42%	
MIPI		
High	53%	p=0.039*
Low	47%	
Morphology		
Classic	81%	p=0.015*
Non classic (blastoid/pleomorphic)	19%	
Ki-67 %		
<30	50%	p=0.3
≥30	50%	
Median time to POD 24	35 months (between 3 -150)	-
Median follow-up from diagnosis	70 months	
First-line treatment		
CIT-Refractory	36%	p<0.001*
CIT-Sensitive	62%	
***TP53* mut (NGS)**	28%	p=0.004*

MANTLE-FIRST BIO

unpublished data

RESULTS

	p-value
TP53	p=0.004*
SETD2	p=0.029*
Del 6q	p=0.014*
Del 13q14 (*RB1*)	p=0.021*
Del 9p21.3 (*CDKN2A*)	p=0.029*



MANTLE-FIRST BIO

unpublished data

RESULTS

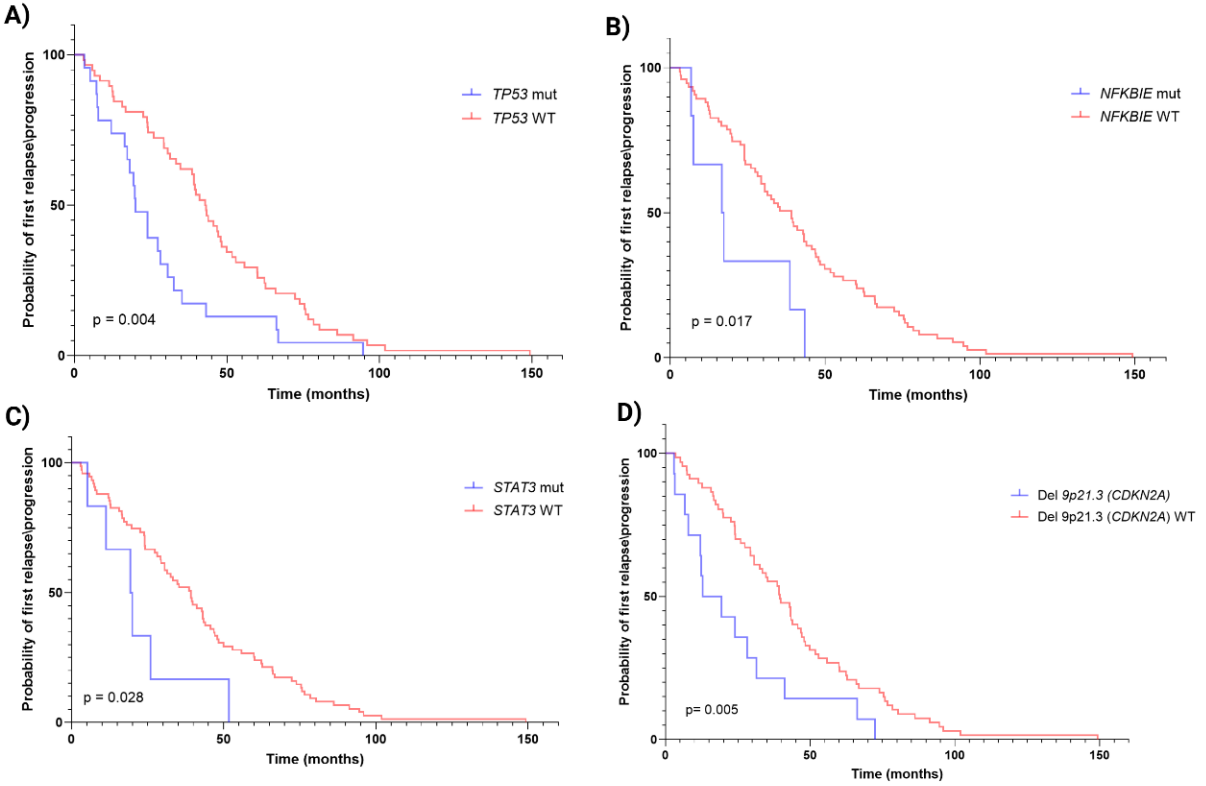
UNIVARIATE ANALYSIS: VARIABLES ASSOCIATED WITH POD

TP53 (p=0.004, HR = 1.97),

NFKBIE (p = 0.017, HR = 2.63),

STAT3 (p = 0.028, HR = 2.44),

Del 9p21.3 (***CDKN2A***, p = 0.005, HR = 2.19)

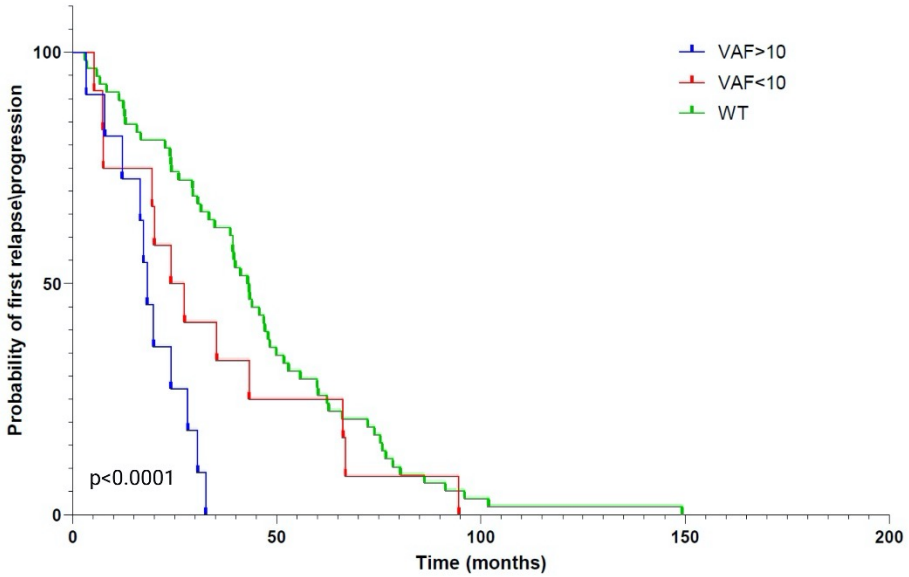


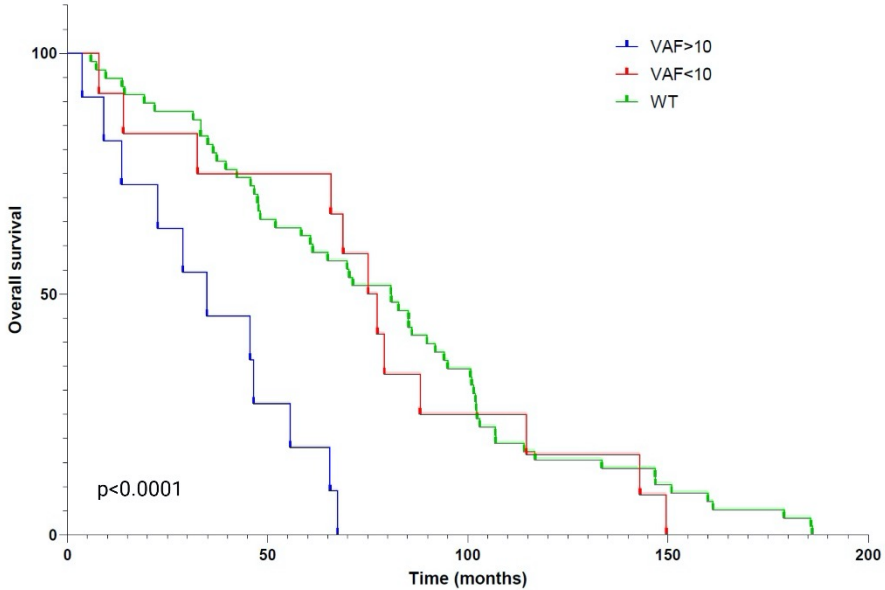
unpublished data

RESULTS

MANTLE-FIRST^BIO

VARIANT ALLELIC FREQUENCY (VAF) *TP53* ANALYSIS



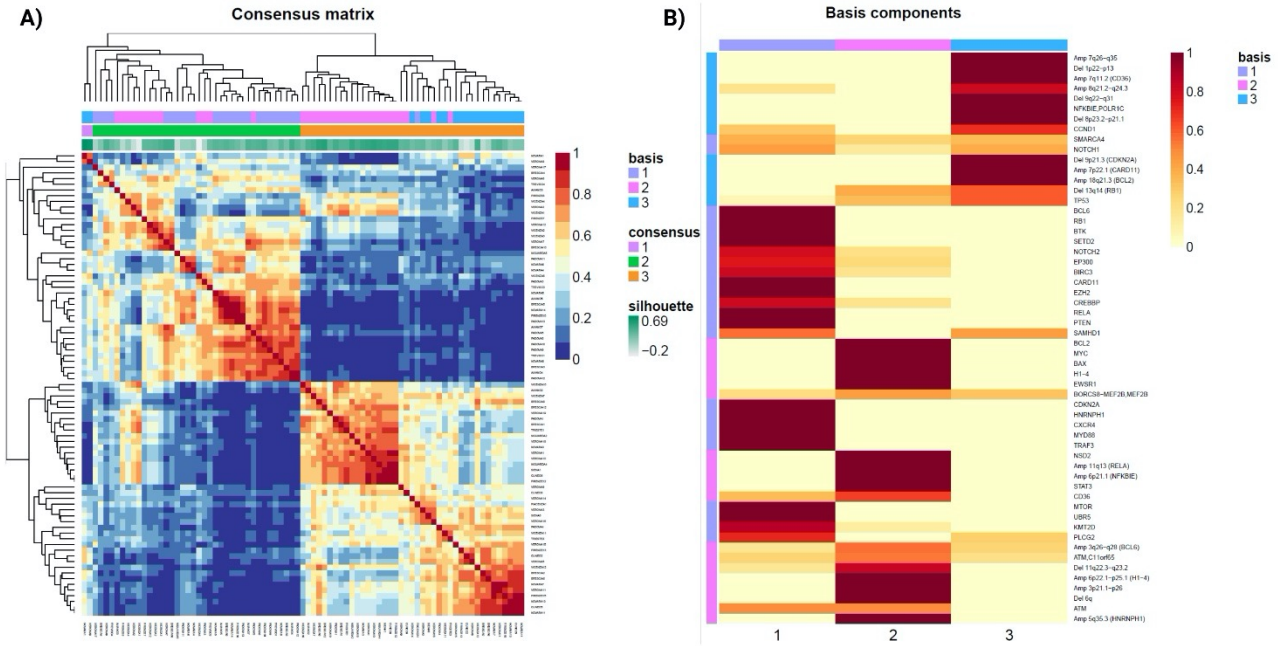


unpublished data

RESULTS

MANTLE-FIRST^BIO

Application of **UNBIASED CLUSTERIZATION:** identification of 3 well-defined molecular clusters

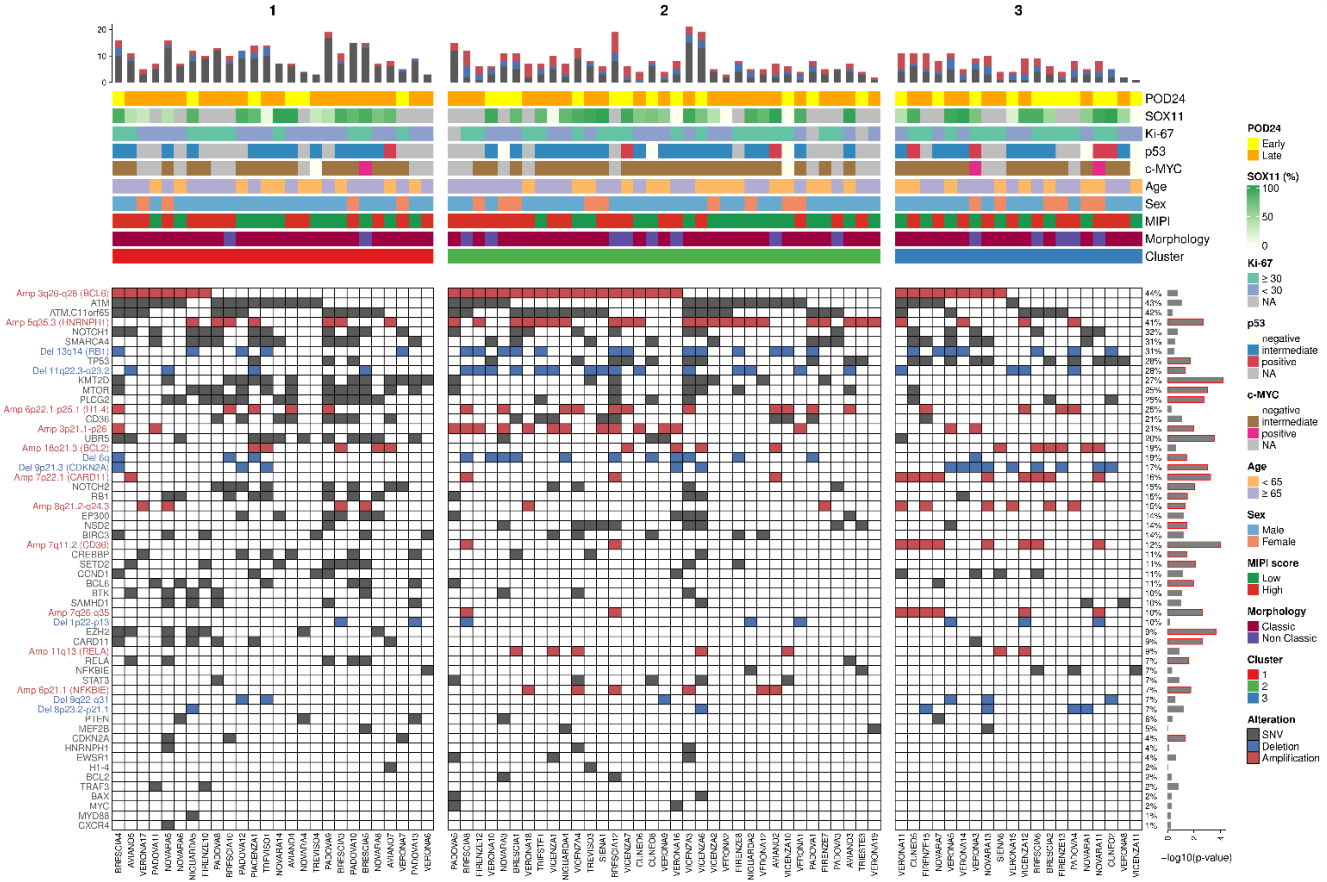


unpublished data

RESULTS

SNVs AND CNVs

DIVIDED BY CLUSTERS



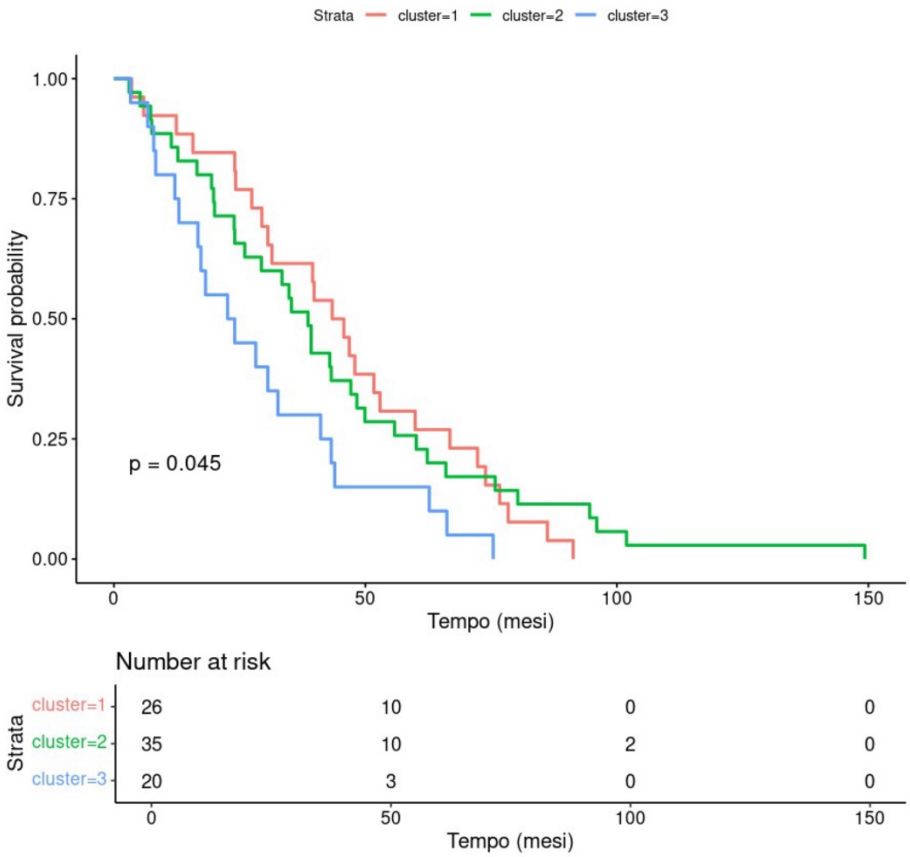
MANTLE-FIRST BIO

unpublished data

RESULTS

C3 showed the <u>shortest time to POD24</u>:

- C3 vs C1: p-value= 0.03
- C3 vs C2: p- value= 0.02



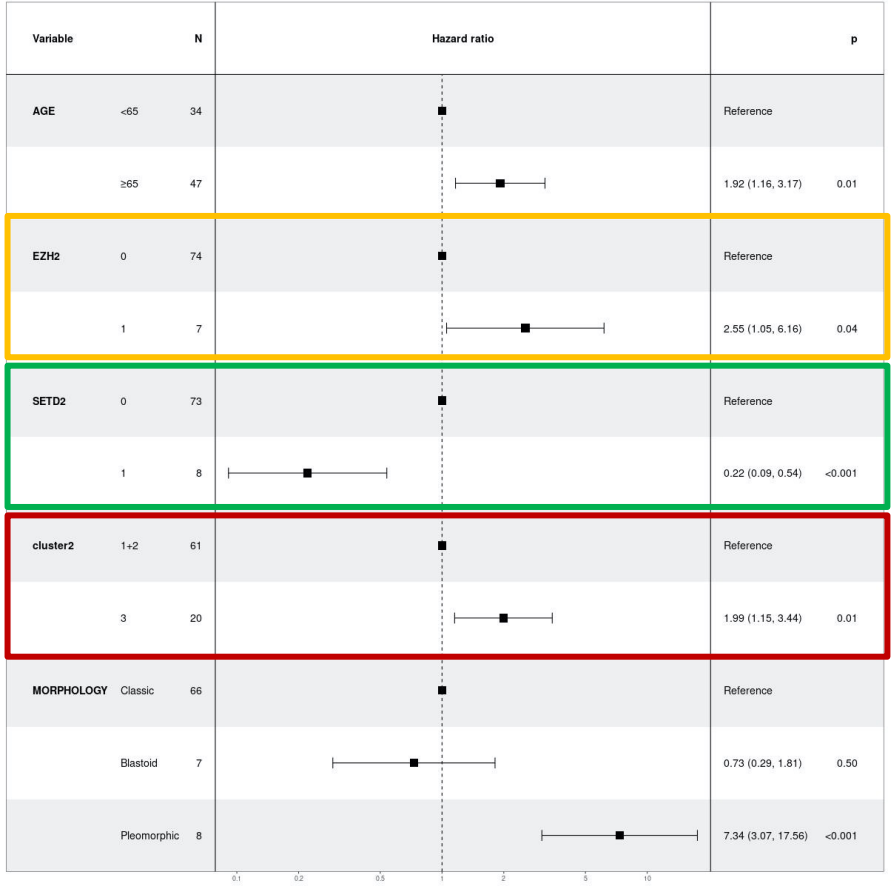
MANTLE-FIRST[BIO]

unpublished data

RESULTS

MULTIVARIATE ANALYSIS (STEP AIC METHOD):

- C3 is associated with shorter time to POD vs C1 and C2 ;
- *EZH2* SNVs are associated with shorter time to POD, whereas *SETD2* is linked to a more favorable time to POD.



TAKE HOME MESSAGE

MANTLE-FIRST^BIO

- ***TP53* mut** and **Del9p21.3 (*CDKN2A*)** were independent risk factors associated with shorter time to POD;
- The importance of **VAF** in ***TP53*** mut cases was confirmed;
- The **unbiased analysis** could effectively **recognize and stratify** the high-risk patients based on their molecular pattern.

ON GOING ANALYSIS:

- **Integration** in the multivariate analysis further molecular and clinical features;
- Integration of pathological analyses (morphology, growth pattern, histiocytic infiltration, Ki-67, SOX-11, p53, MYC, CD4/CD8 - L. Lorenzi, Commissione Patologi FIL)

MANTLE-FIRST BIO

PI: FM Quaglia *NCT04882475*
PGR Ed. 2019

FONDAZIONE ITALIANA LINFOMI

FIL_MANTLE-FIRST BIO study
https://clinicaltrials.gov/ct2/show/NCT04882475
PGR Ed. 2019. PI: FM Quaglia

The authors would like to thank all patients who have donated samples for this study

THANKS TO

Dep. of Engineering for Innovation Medicine
Marilisa Galasso
Simona Gambino
Maria Teresa Scupoli
Carlo Visco

Dep. of Medicine
Maria Elena Carazzolo
Francesca Maria Quaglia

Research Center LURM Laboratorio Universitario di Ricerca Medica
Antonino Aparo

Dep. of Pathology
Alice Parisi

Dep. of Diagnostic and Public Health, University of Verona
Vittoria Salaorni