LINFOMI MANTELLARI INDOLENTI

Annalisa Chiappella

Ematologia

AOU Città della Salute e della Scienza di Torino

FONDAZIONE ITALIANA LINFOMI

DISCLOSURES, ANNALISA CHIAPPELLA

Research Support/P.I.	N/A
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Conferences/Educational Activities	Amgen, Celgene, Janssen, Nanostring, Roche, Teva
Scientific Advisory Board	Celgene, Janssen

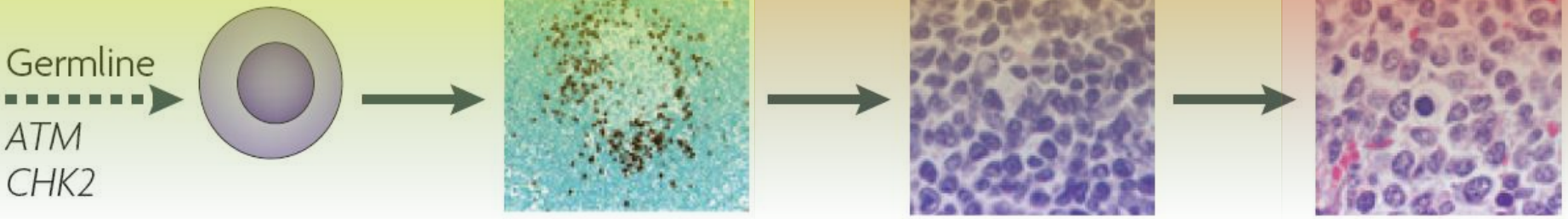
FONDAZIONE ITALIANA LINFOMI

MCL: A SPECTRUM OF DISEASE

„indolent“ MCL (15%) ***„classical“ MCL (80%)*** ***„transformed“ (5%)***

Naive B cell → Early MCL → Classical MCL → Blastoid MCL

Germline
ATM
CHK2



t(11;14)
Cyclin D1

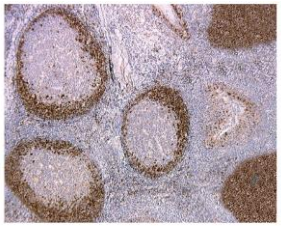


Figure 1 Tonsil: neoplastic cells are positive for cyclin D1 and located in the mantle zone of lymphoid follicles. At the upper and lower coins of the right side, primary follicles show numerous neoplastic cells (immunoperoxidase, anti-cyclin D1, ×100).

RB1 p27

ATM
CHK2

Complex karyotypes

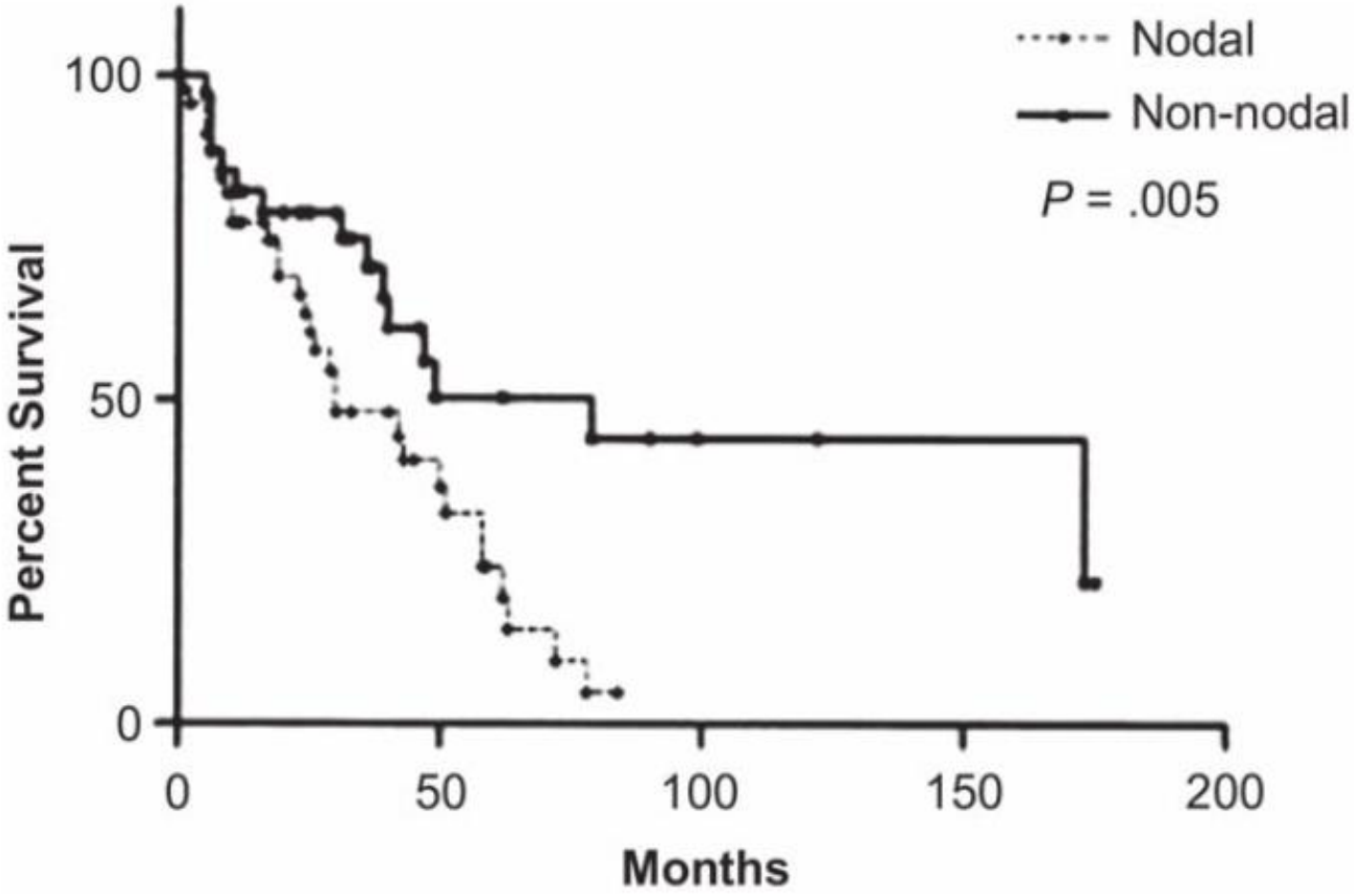
INK4A/CDK4/RB1
ARF/MDM2/p53

High proliferation

Dreyling, ASH Educational 2009

FONDAZIONE ITALIANA LINFOMI

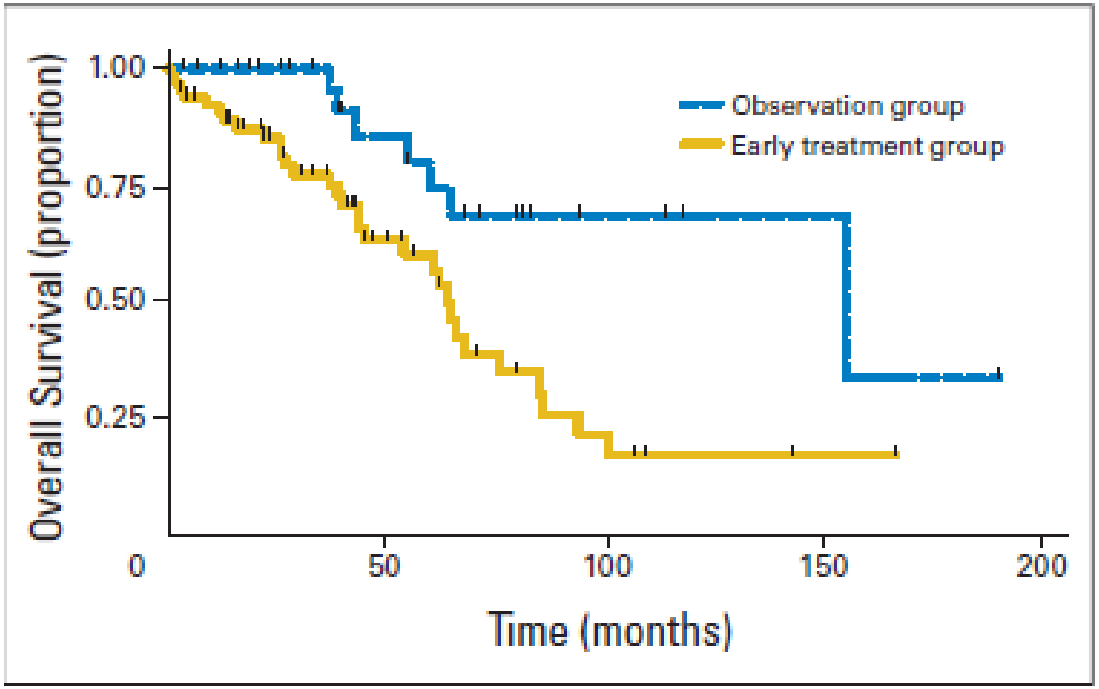
IMCL: NON-NODAL PRESENTATION



Orchard et al, Blood 2003

iMCL: LONG SURVIVAL

MCL is a heterogeneous disease, with poor prognosis, but a small subset of patients with MCL have long survival and an indolent disease course.



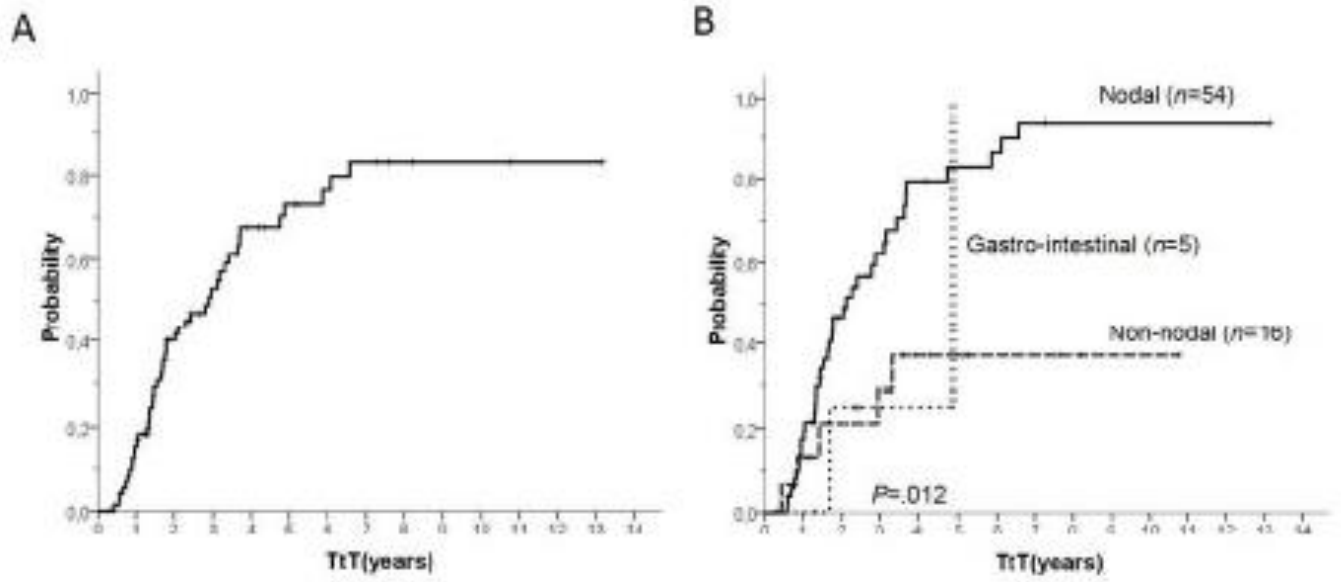
Median time to treatment in obs group:12 months (range, 4-128)
Median OS patients treated within 3 months of diagnosis vs requiring treatment: not reached vs 64 months.

Martin P, J Clin Oncol 2008

IMCL: LONG SURVIVAL

Population-based study; 440 MCL diagnosed - 1998-2014 - BCCA.
365 (83%) received early treatment and 75 (17%) were observed ≥3 months.

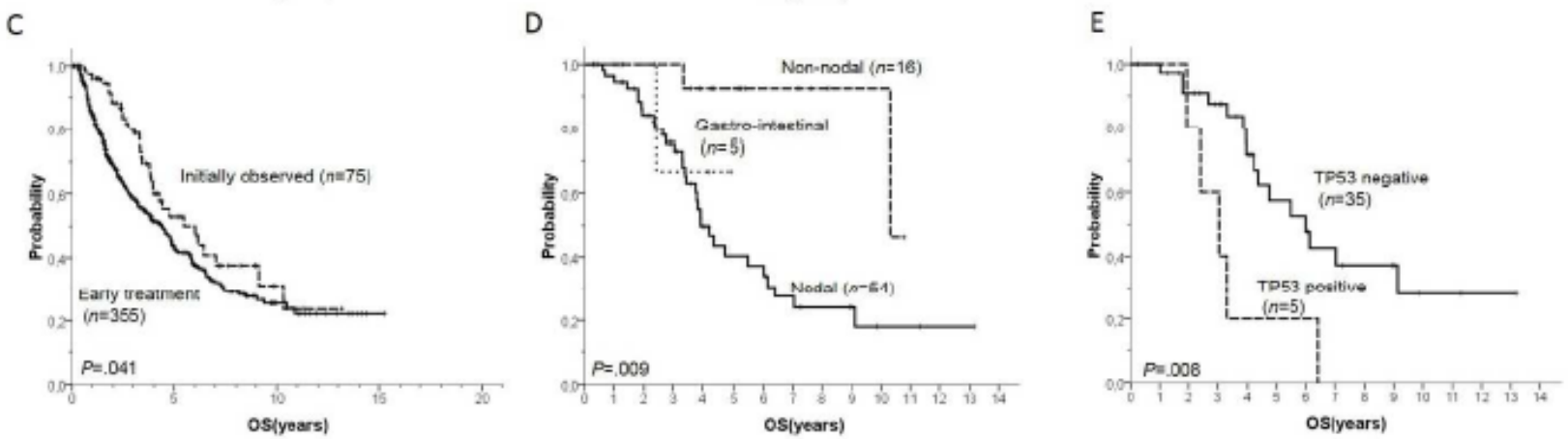
Median time to treatment: 35 months (range, 5-79).



Abrisqueta P et al et al, Ann Oncol 2017

iMCL: LONG SURVIVAL

Population-based study; 440 MCL diagnosed - 1998-2014 - BCCA.



Median OS observation group vs requiring treatment: 72 vs 52.5 months, p.041.
OS was not compromised by deferring therapy.

Factors associated with deferred treatment included:

- ✓ good performance status, no B symptoms, normal lactate dehydrogenase, non-bulky disease, non-blastoid morphology, lower Ki-67.

Abrisqueta P et al et al, Ann Oncol 2017

FONDAZIONE ITALIANA LINFOMI

iMCL: LONGER SURVIVAL

Mantle cell lymphoma—a spectrum from indolent to aggressive disease

Birgitta Sander[1] · Leticia Quintanilla-Martinez[2] · German Ott[3] · Luc Xerri[4] · Isinsu Kuzu[5] · John K. C. Chan[6] · Steven H. Swerdlow[7] · Elias Campo[8]

Longer survival was associated with:

- Limited stage disease
- Low tumor cell proliferation, mantle zone growth pattern, a high CD4/CD8 ratio
- Leukemic manifestation sometimes associated with splenomegaly
- Mutated immunoglobulin genes, low CD38 expression, interstitial rather than nodular lymphoma infiltrates in the bone marrow, and a low number of genomic aberrations
- SOX11-negative and CD200-positive; CD5-negative in 50 % of cases
- There are also examples of SOX11-positive MCL with an indolent clinical course
- No TP53 mutations

Sander B et al, Virchows Arch 2016

MCL OR EXTRANODAL PRESENTATION

- 107 consecutive patients with diagnosis of MCL (1998-2014)

✓ **CLASSIC**: 87 pts

- Prevalent nodal involvement

✓ **INDOLENT NON-NODAL**: 6 pts

- Splenomegaly
- Leukemic disease, BM involvement

✓ ***MALToma-like* MCL*:*** 14 pts

- Prevalent extranodal disease
- Absent or minimal nodal involvement
  - ❑ Waldayer's ring 7
  - ❑ Paranasal sinues 1
  - ❑ Stomach 1
  - ❑ Ocular adnexa 2
  - ❑ Multiple sites 3

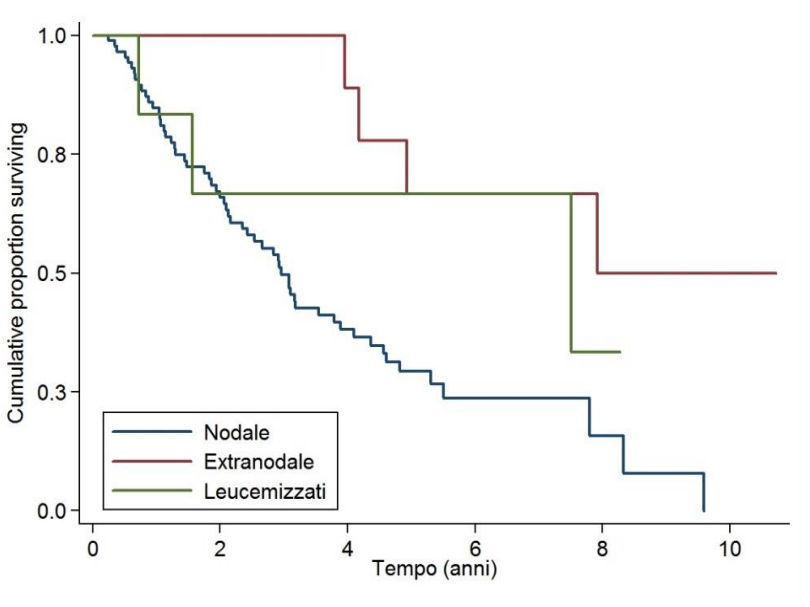
- ❖ Morphological variant
  - Classic: 12 pts
  - Blastoid/pleomorphic: 2 pts
- ❖ 2 pts **CD5**-negative
- ❖ 1 pt cyclin D1-neg. and FISH+
- ❖ SOX11: positive in 8/8 cases
- ❖ Ki67%:
  - <5%: 4 cases
  - 5-30%: 8 cases
  - >30%: 2 cases (blastoid variant)

Courtesy of Luca Arcaini

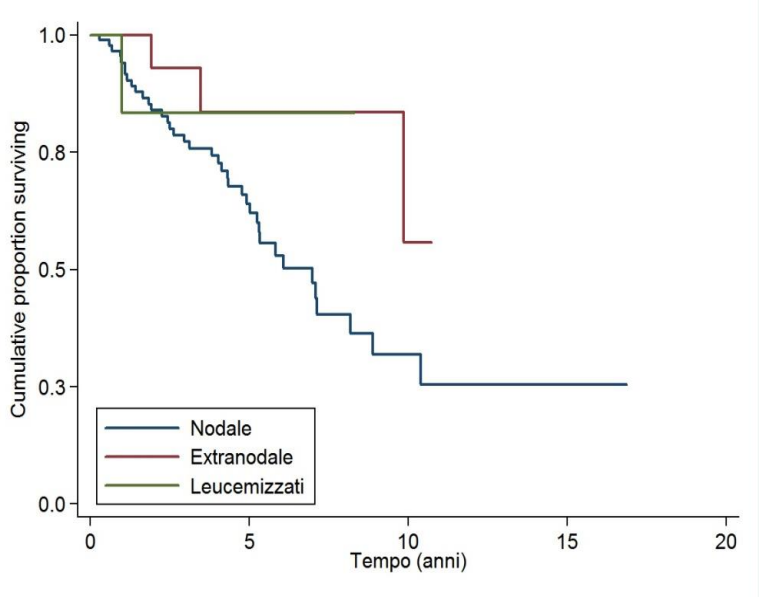
iMCL or Extranodal presentation

- 107 consecutive patients with diagnosis of MCL (1998-2014)

Progression-free survival



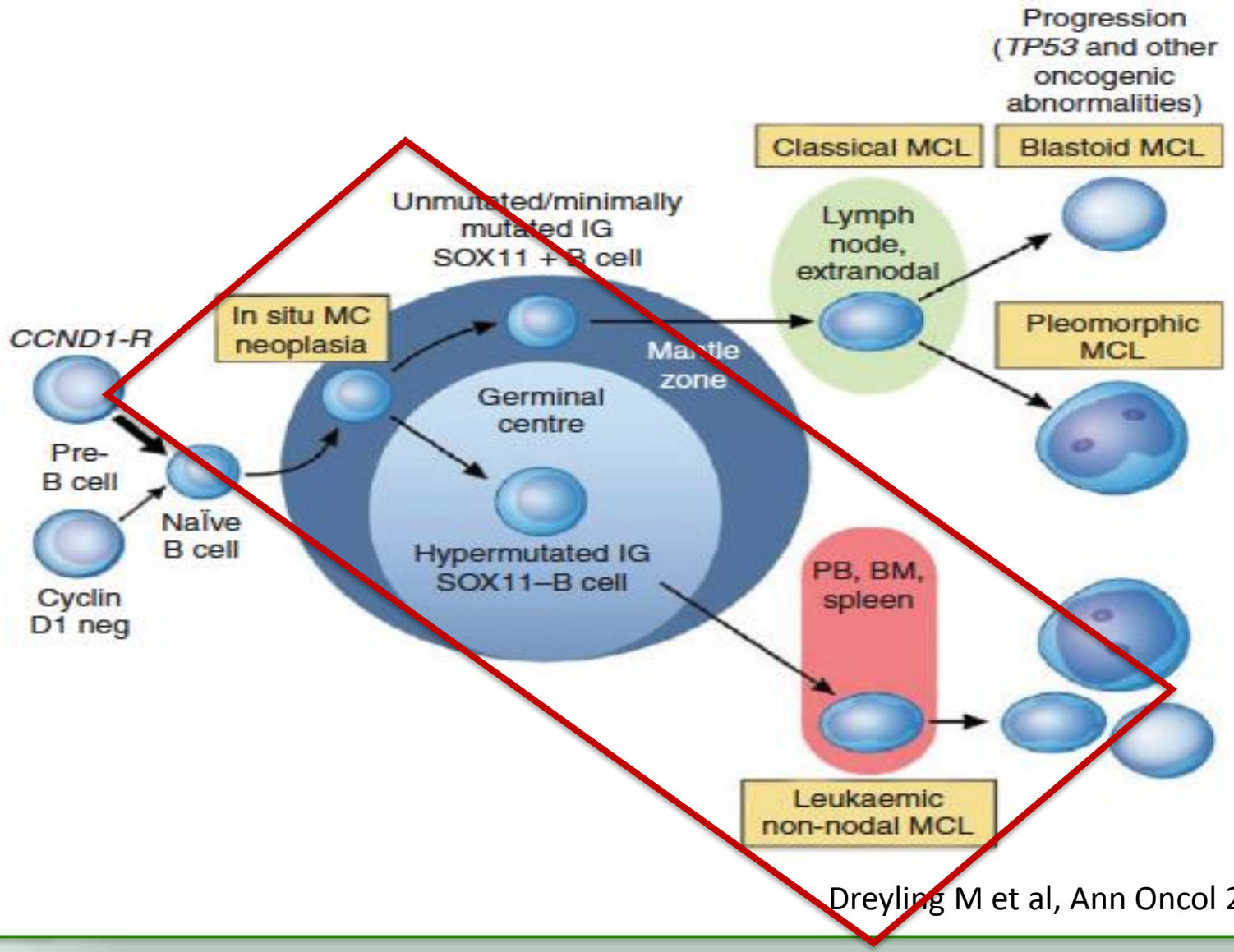
Overall survival



Courtesy of Luca Arcaini

FONDAZIONE ITALIANA LINFOMI

MCL: A SPECTRUM OF DISEASE



Dreyling M et al, Ann Oncol 2017

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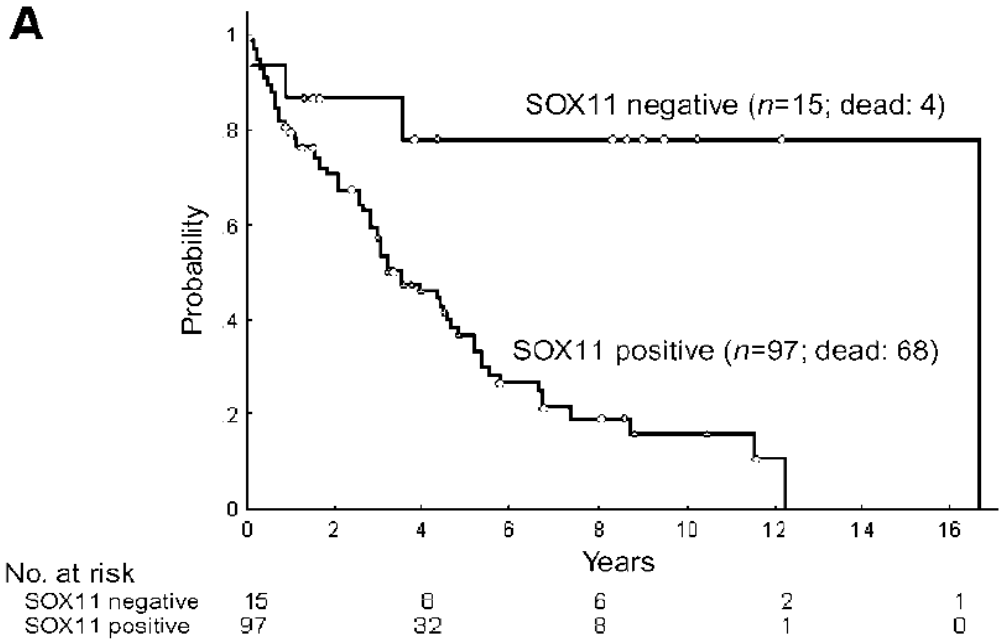
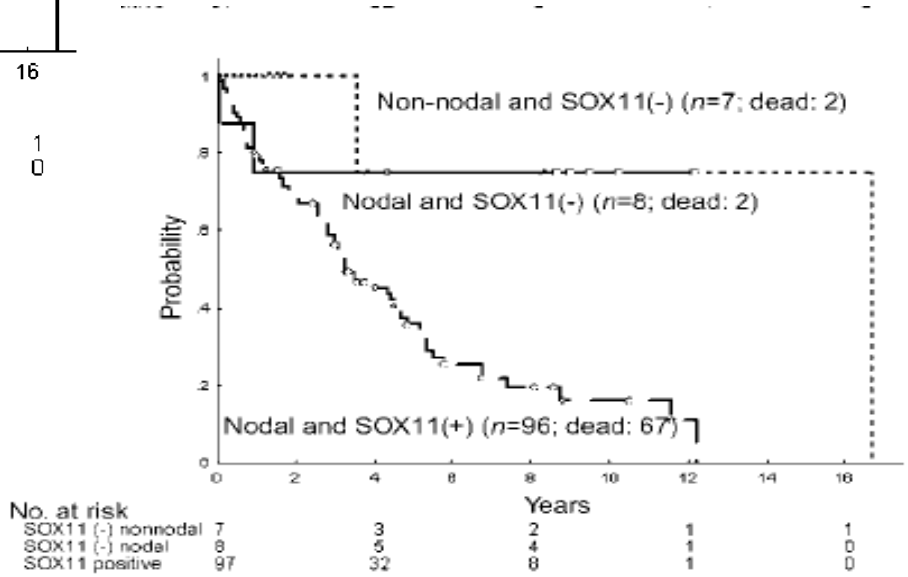
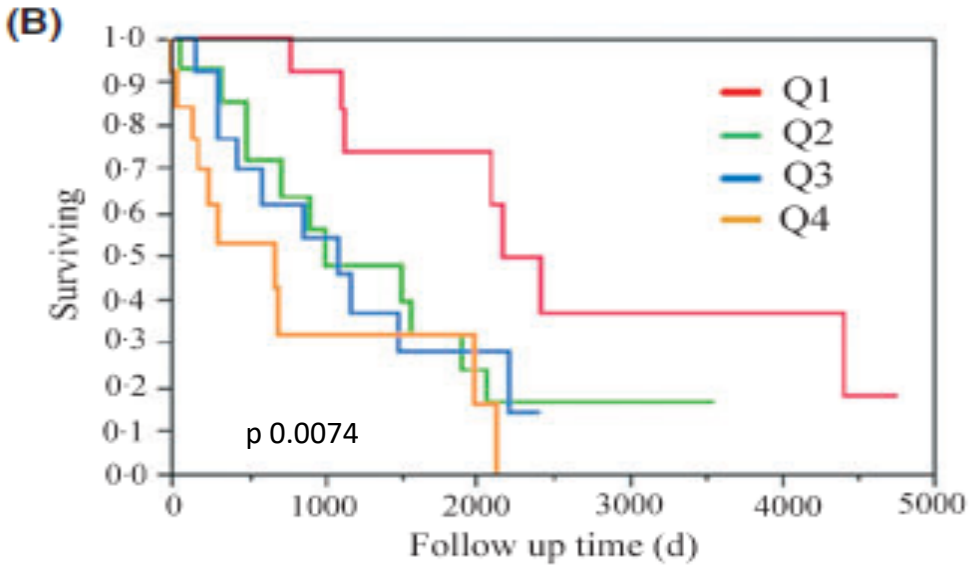
MCL: SOX11 EXPRESSION



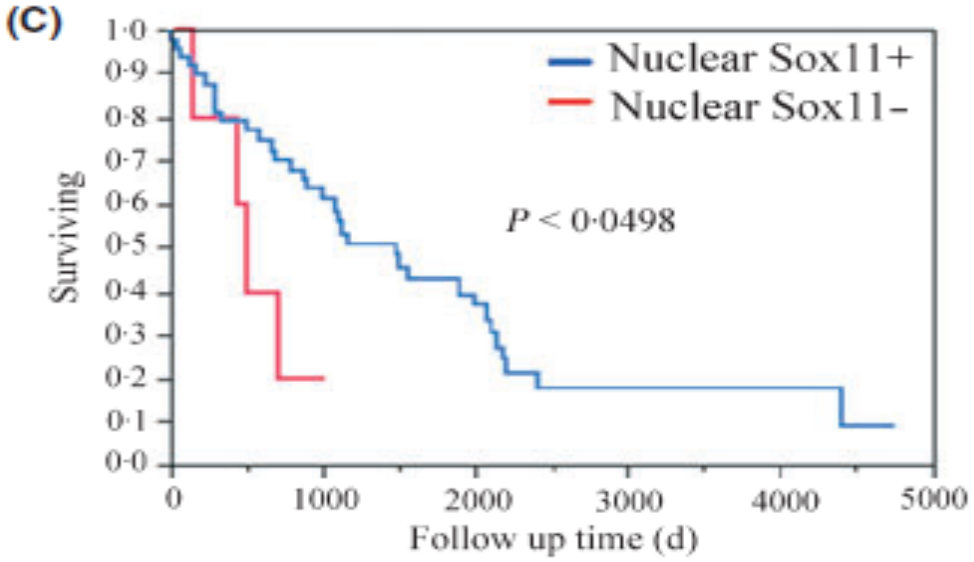


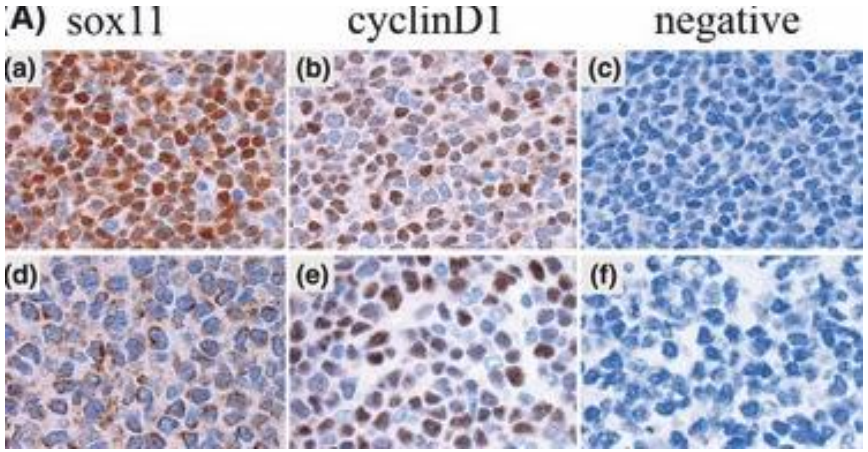
Fernandez, Cancer Research 2010

iMCL: OS correlate with SOX11 and KI67 expression



quartile 1, Q1, MIB1 7–17%, *n* = 13
Q2, MIB1 18–28%, *n* = 14
Q3, MIB1 29–40%, *n* = 13
Q4, MIB1 43–90%, *n* = 13

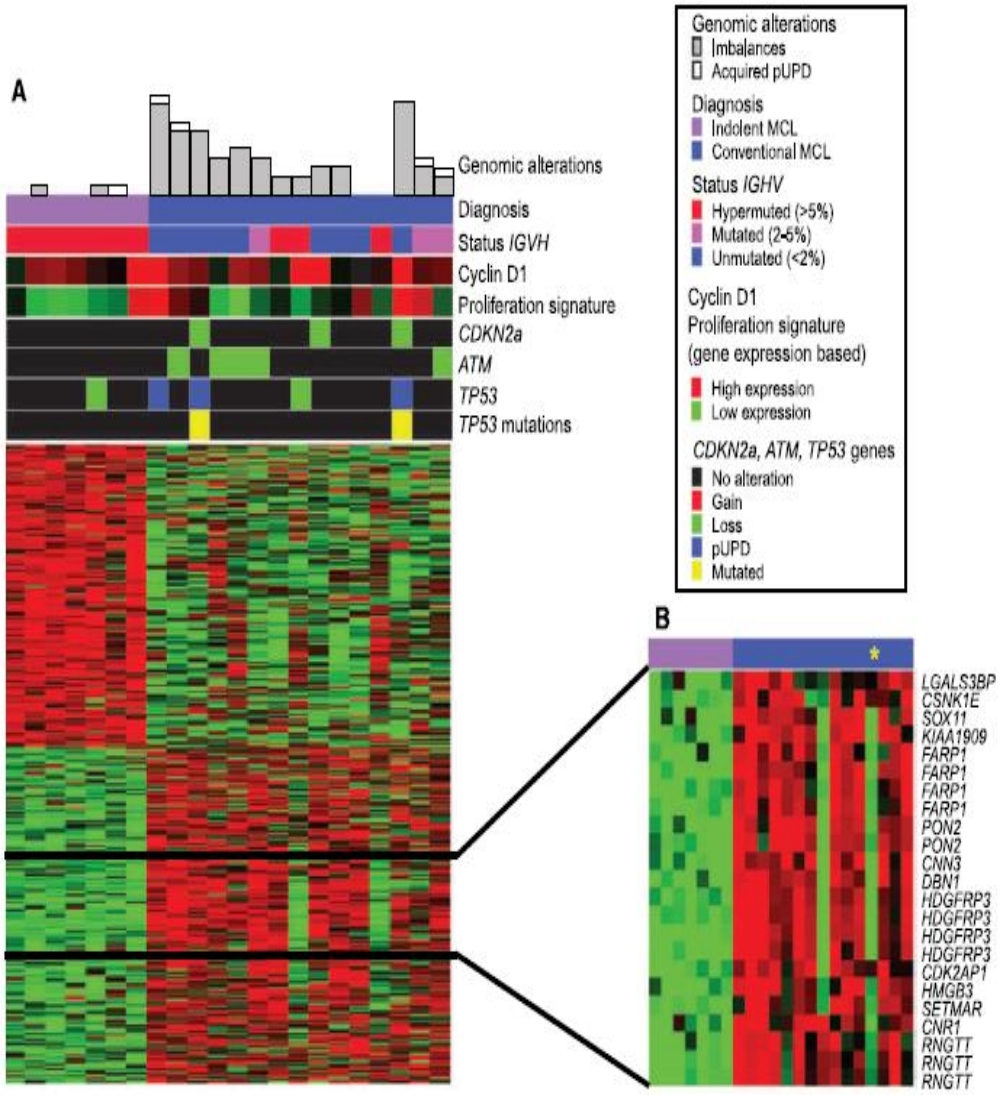


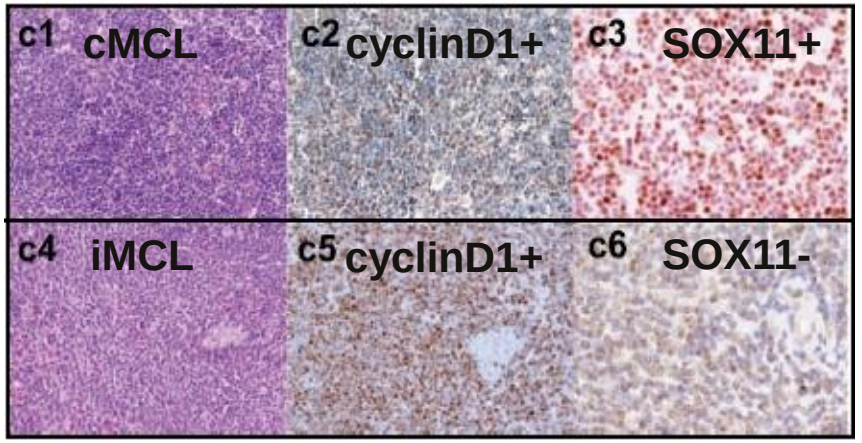


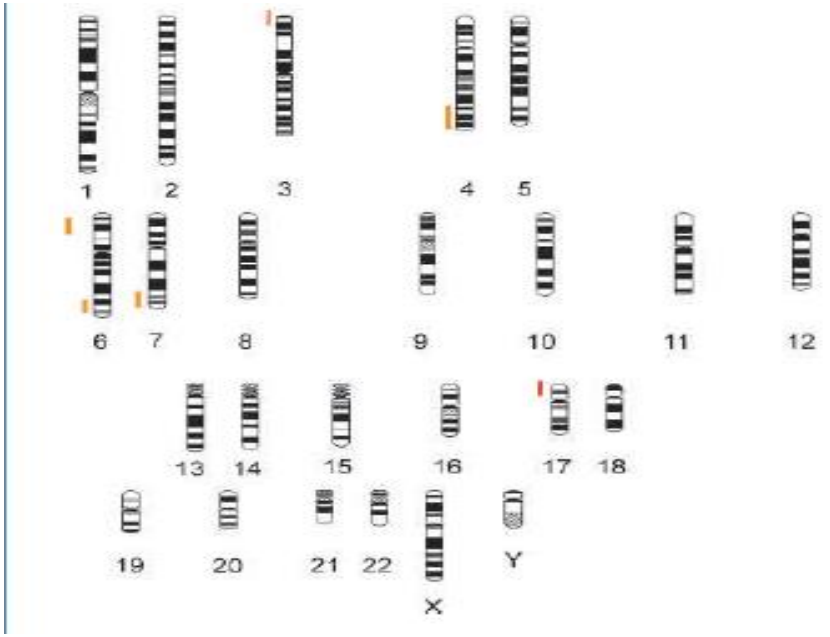
Wang et al, Br J Hematol 2008

FONDAZIONE ITALIANA LINFOMI

IMCL: SNP ARRAYS, IMMUNOHISTOCHEMISTRY, GENE EXPRESSION







Fernandez, Cancer Research 2010

LYMPHOID NEOPLASIA

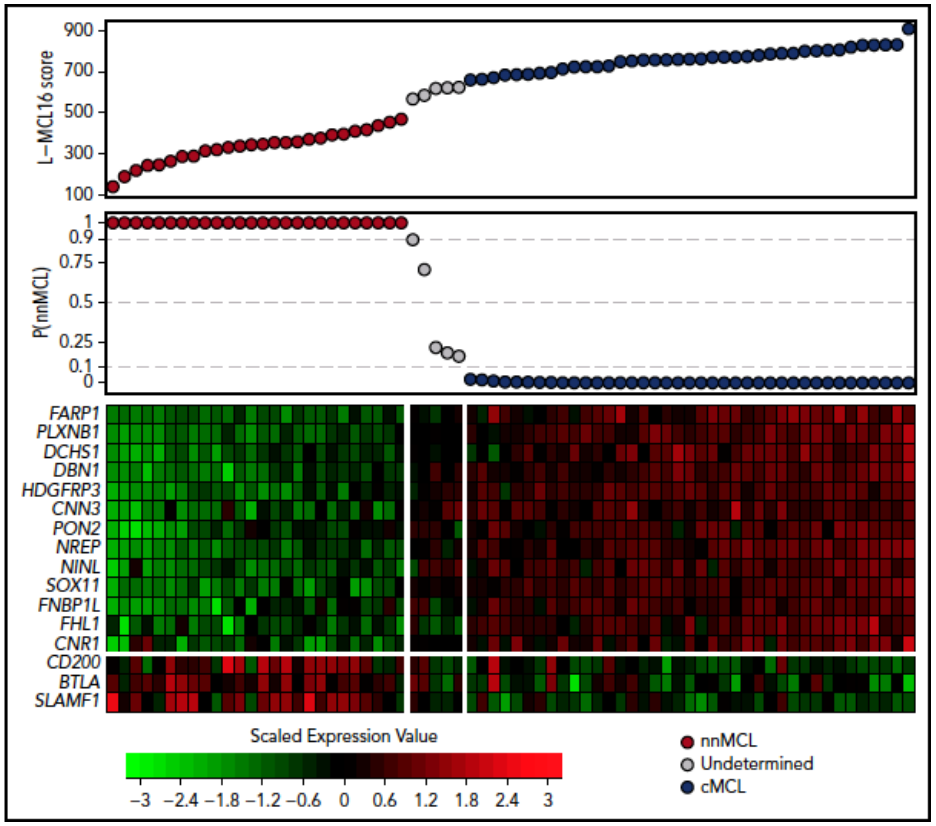
A gene signature that distinguishes conventional and leukemic nonnodal mantle cell lymphoma helps predict outcome

Guillem Clot,[1,2] Pedro Jares,[1-3] Eva Giné,[1,2,4] Alba Navarro,[1,2] Cristina Royo,[1,2] Magda Pinyol,[1,2] David Martín-Garcia,[1,2] Santiago Demajo,[1] Blanca Espinet,[5] Antonio Salar,[6] Ana Ferrer,[6] Ana Muntañola,[7] Marta Aymerich,[2,3] Hilka Rauert-Wunderlich,[8,9] Elaine S. Jaffe,[10] Joseph M. Connors,[11] Randy D. Gascoyne,[11] Jan Delabie,[12] Armando López-Guillermo,[1,2,4] German Ott,[13] George W. Wright,[9] Louis M. Staudt,[9] Andreas Rosenwald,[8,9] David W. Scott,[11] Lisa M. Rimsza,[14,*] Sílvia Beà,[1,2,*] and Elías Campo[1-3,*]

- ✓ A novel molecular assay that reliably distinguishes cMCL and nnMCL using blood samples was tested.
- ✓ 16-gene assay (L-MCL16 assay) were trained on the NanoString platform using 19 purified leukemic samples.
- ✓ The locked assay was applied to an independent cohort of 70 MCL patients with leukemic presentation.
- ✓ The assay assigned 37% of cases to nnMCL and 56% to cMCL.
- ✓ nnMCL and cMCL differed in nodal presentation, LDH, Ig heavy chain gene mutational status, management options, genomic complexity, and CDKN2A/ATM deletions, but the proportion with 17p/TP53 aberrations was similar in both subgroups.

Clot G, Blood 2018

A gene signature that distinguishes conventional and leukemic nonnodal mantle cell lymphoma helps predict outcome



Gene-expression-based L-MCL16 scores in the validation cohort.

Clot G, Blood 2018

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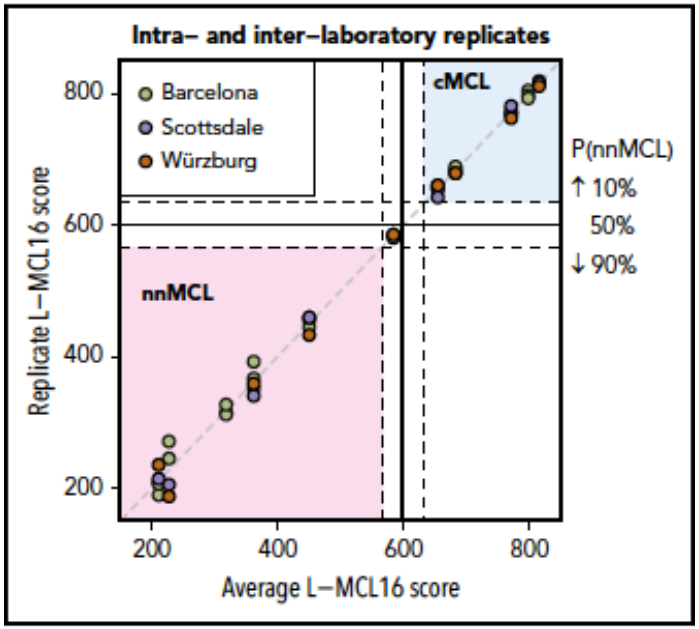
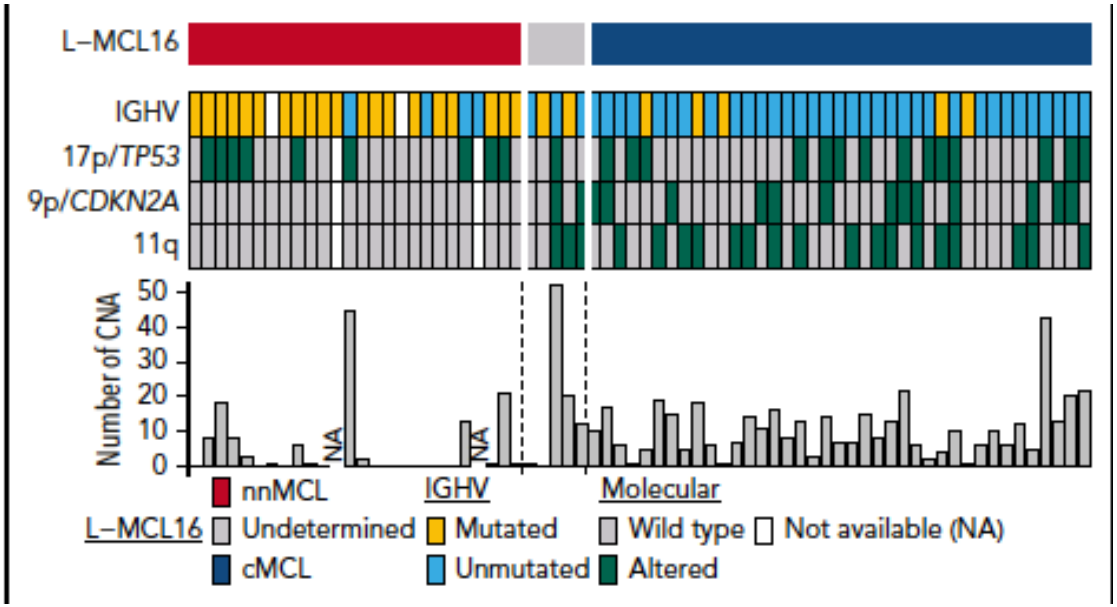


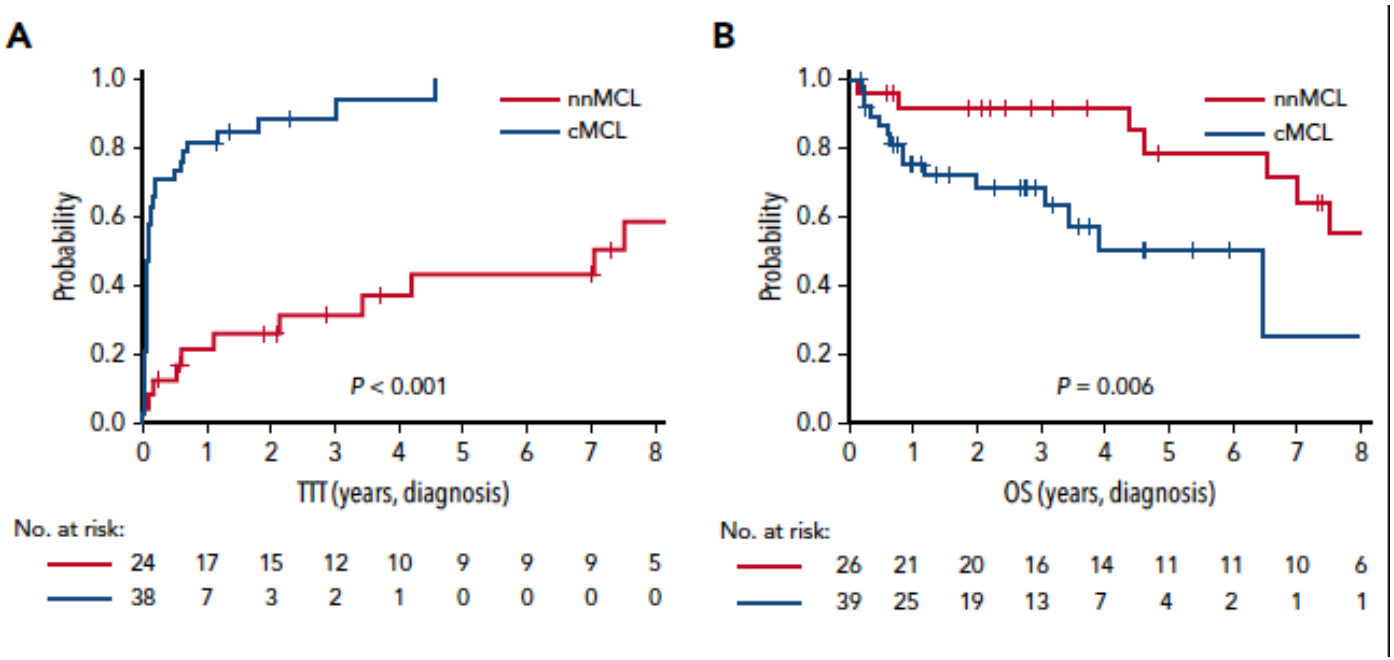
Intra and interlaboratory reproducibility of the L-MCL16 scores.



Molecular features of the 70 leukemic MCL samples in the validation cohort.

Clot G, Blood 2018

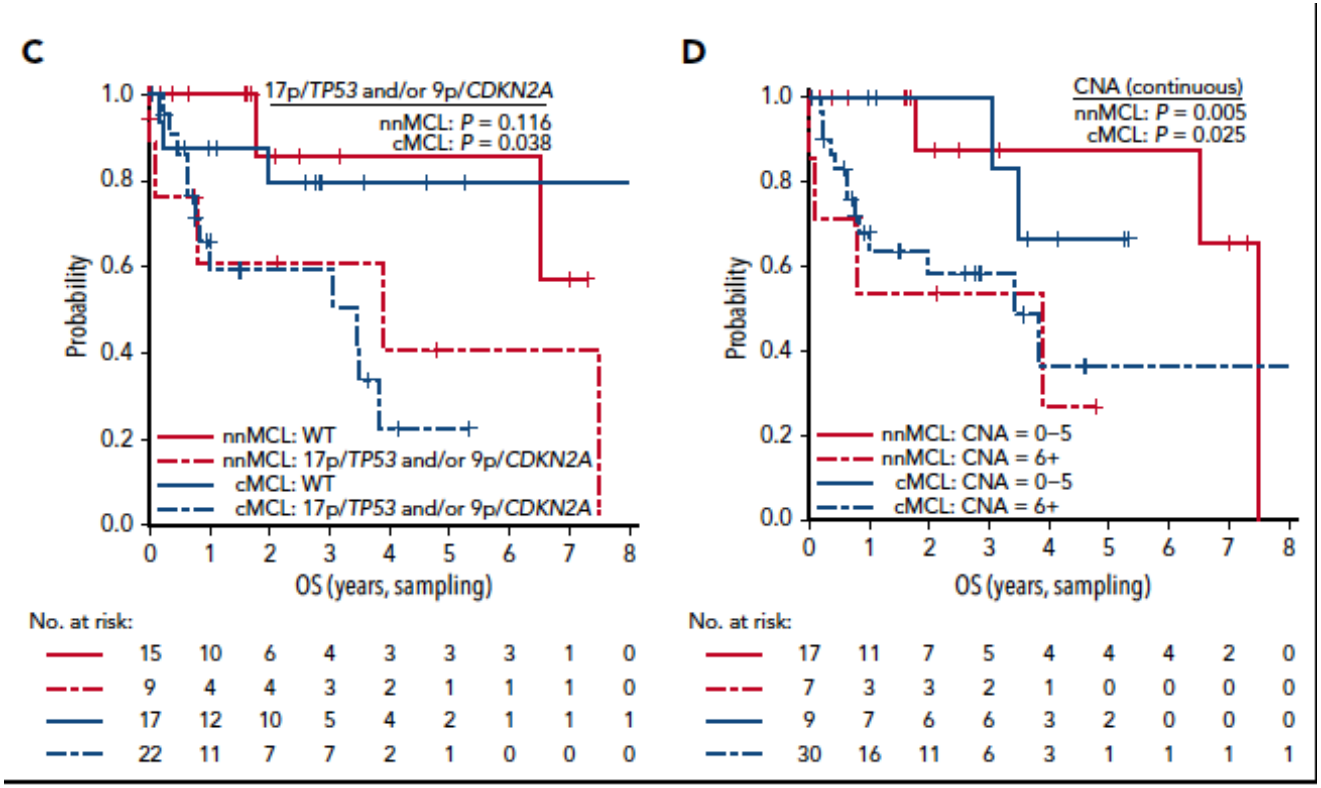
A gene signature that distinguishes conventional and leukemic nonnodal mantle cell lymphoma helps predict outcome



OS nnMCL vs cMCL: 3-year OS 92% vs 69% (p .006) from the time of diagnosis and longer time to first treatment.

Clot G, Blood 2018

A gene signature that distinguishes conventional and leukemic nonnodal mantle cell lymphoma helps predict outcome



Genomic complexity and TP53/CDKN2A aberrations predicted for shorter OS in the entire series and cMCL, whereas only genomic complexity was associated with shorter time to first treatment and OS in nnMCL.

Clot G, Blood 2018

LYMPHOID NEOPLASIA

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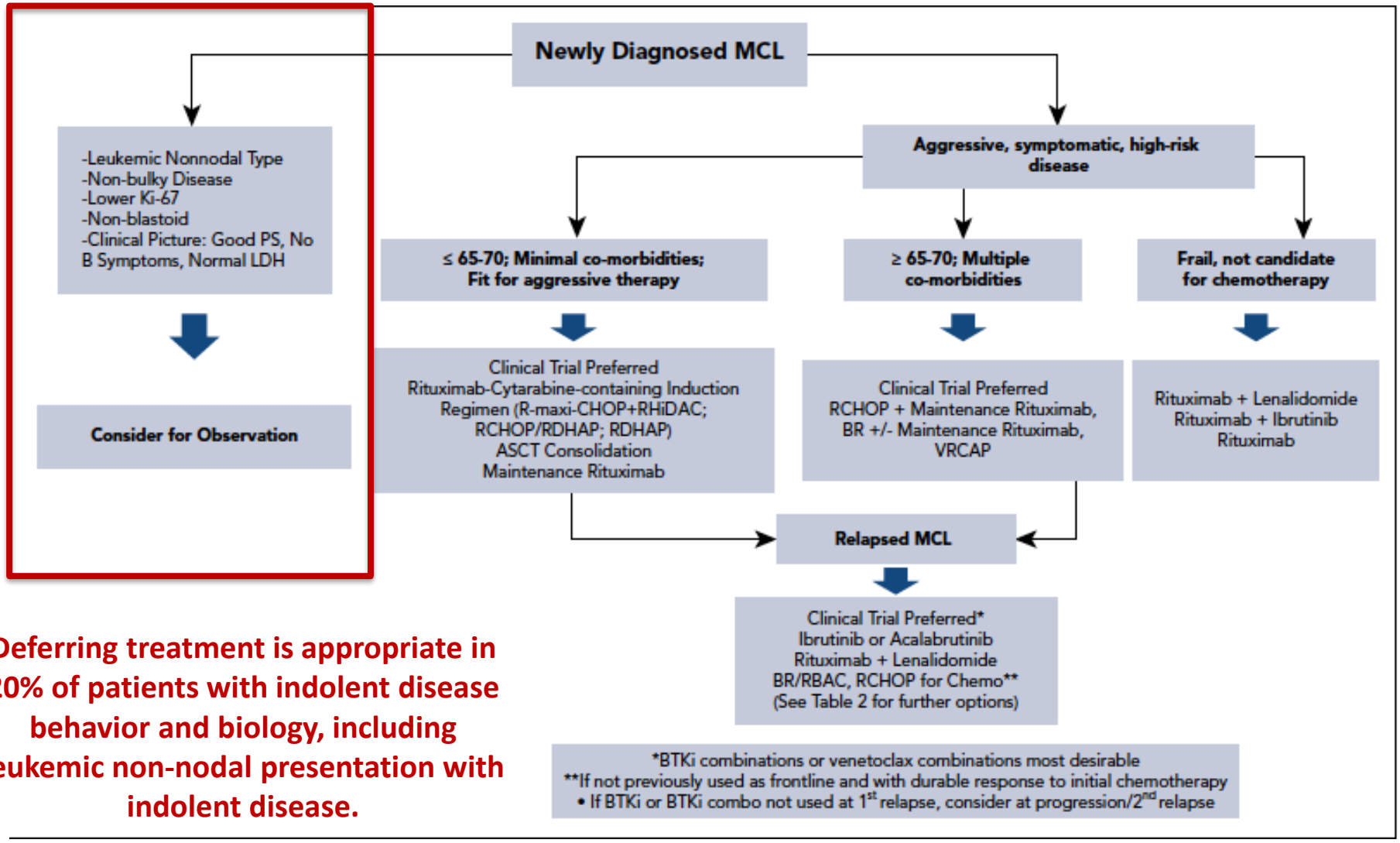
- ✓ In conclusion, the novel molecular assay developed for leukemic MCL reliably identifies the 2 cMCL and nnMCL subtypes and confirms the different clinical and biological characteristics of these patients.
- ✓ The combination of this assay with the analysis of the genomic complexity identifies subsets of patients with different outcomes.
- ✓ Therefore, **it may provide useful biological information for management decisions in these patients.**

Clot G, Blood 2018

IMCL: TREATMENT APPROACH



Deferring treatment is appropriate in 20% of patients with indolent disease behavior and biology, including leukemic non-nodal presentation with indolent disease.

Maddocks K, Blood 2018

FONDAZIONE ITALIANA LINFOMI

iMCL: Torino Experience

FP, male, 61 years old

- ✓ **2009:** WBC 10490, Neu 30%, L 40%, Hb 14.9, Plt 181.000, LDH normal
- ✓ IF: B-NHL CD20+, CD5+.
- ✓ No relevant adenopathies; no splenomegaly.
- ✓ Watch and Wait.
- ✓ **2011:** multiple adenopathies 2 cm, abdominal mass 5 cm; bone marrow involvement. Histology: MCL, cyclin D1+, Sox11 +/-.
- ✓ Treated with R-CHOP + R maintenance, obtaining CR.
- ✓ **2014:** relapse with colic involvement.
- ✓ Treated with R-BAC + ASCT.
- ✓ Persistent CR.

FONDAZIONE ITALIANA LINFOMI

iMCL REGISTRY

There are no single markers or single clinical features that can predict an indolent behavior in MCL at the time of diagnosis.

European MCL Network

FONDAZIONE ITALIANA LINFOMI

Principal investigators: **Annalisa Chiappella, Michael Mian**

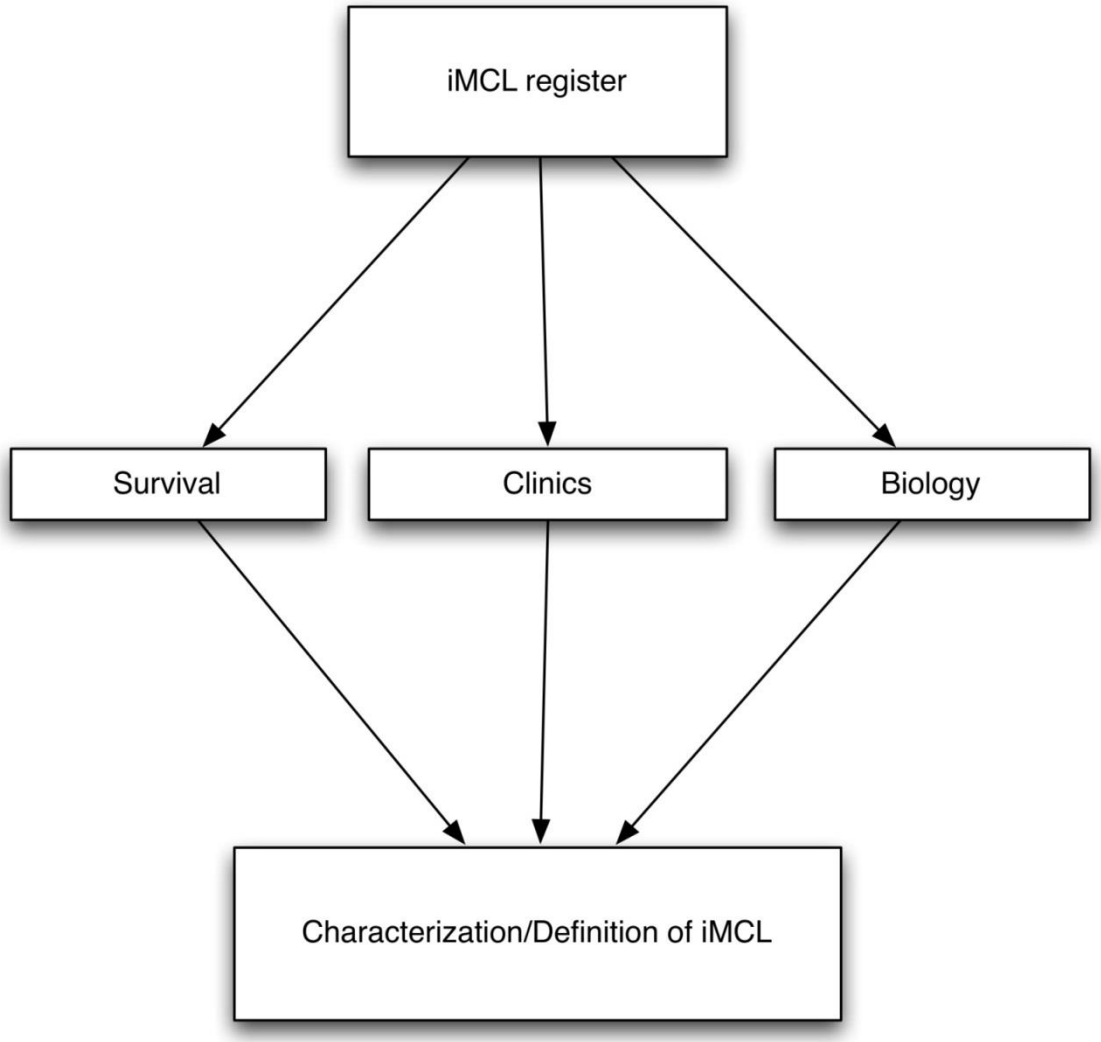
Writing committee: **Chiappella A, Mian M, Cortelazzo S, Dreyling M, Ferreri A, Visco C, Vitolo U, Zaya F**

Histopathology: **Pileri S, Klapper W**

Molecular biology: **Gaidano G, Ladetto M, Ferrero S**

FONDAZIONE ITALIANA LINFOMI

iMCL REGISTRY



FONDAZIONE ITALIANA LINFOMI

THE REGISTRY

- European coordination:
  - G. Hess – Principal Investigator and webbased data collection system
  - A. Chiappella (iMCL)
  - M. Dreyling – international coordinator

FONDAZIONE ITALIANA LINFOMI

THE REGISTRY

European MCL Network

FONDAZIONE ITALIANA LINFOMI

User: EMCL, Torino Chiappella
Pat-No: *Please choose*

Autologout in 2:00 hours

User manual

Homepage | **Overview** | **Patientlist** | **Recruitment Statistics**

Start

Welcome to the Registry of the EMCL!

Recently accessed patients

Further Links

Patientlist / Add Patient
Contact

For the sake of simplicity and easier reading, only the masculine form has been used for the individual categories of people.

FONDAZIONE ITALIANA LINFOMI

THE REGISTRY

- Webtool – browser based
  - ✓ Non interventional trial – no treatment recommendations
  - ✓ Essential information will be collected
  - ✓ Direct documentation into system, time/patient/year ~ 10-20min
  - ✓ No monitoring, **no** nominal fee will be provided
  - ✓ Once yearly reporting or at progression
  - ✓ Documentation can be offered centrally if information is provided
  - ✓ Every treating physician and national study group can obtain structured information on own patients

FONDAZIONE ITALIANA LINFOMI

THE REGISTRY

Recruitment Stats

Patients included by Quarter

Year	Quarter	Patients
2016	3	2
2016	4	20
2017	2	56
2017	3	114
2017	4	115
2018	1	207
2018	2	221
2018	3	234
2018	4	276

FONDAZIONE ITALIANA LINFOMI

iMCL Registry

FIL centers:

- January 2018: approval Ethical Committee
- Torino, Vicenza, Pavia
- iMCL cases
- please contact:

achiappella@cittadellasalute.to.it

gcuccurru@cittadellasalute.to.it

ACKNOWLEDGMENTS

Aggressive Lymphoma Committee

All FIL Centers

FIL Trial Office
FIL Biostatistics Torino