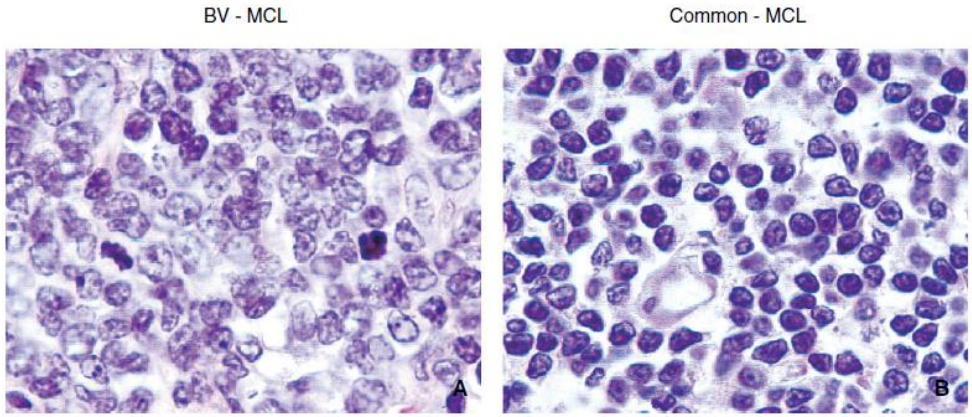
Linfomi Mantellari: focus sulle varianti istologiche e sulle aberrazioni genetiche

Carlo Visco, Verona



Disclosures of NAME SURNAME

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen	V				V	V	
Gentili						V	V
Roche						V	
AbbVie	V				V	V	

Sommario

Breve inquadramento della patogenesi

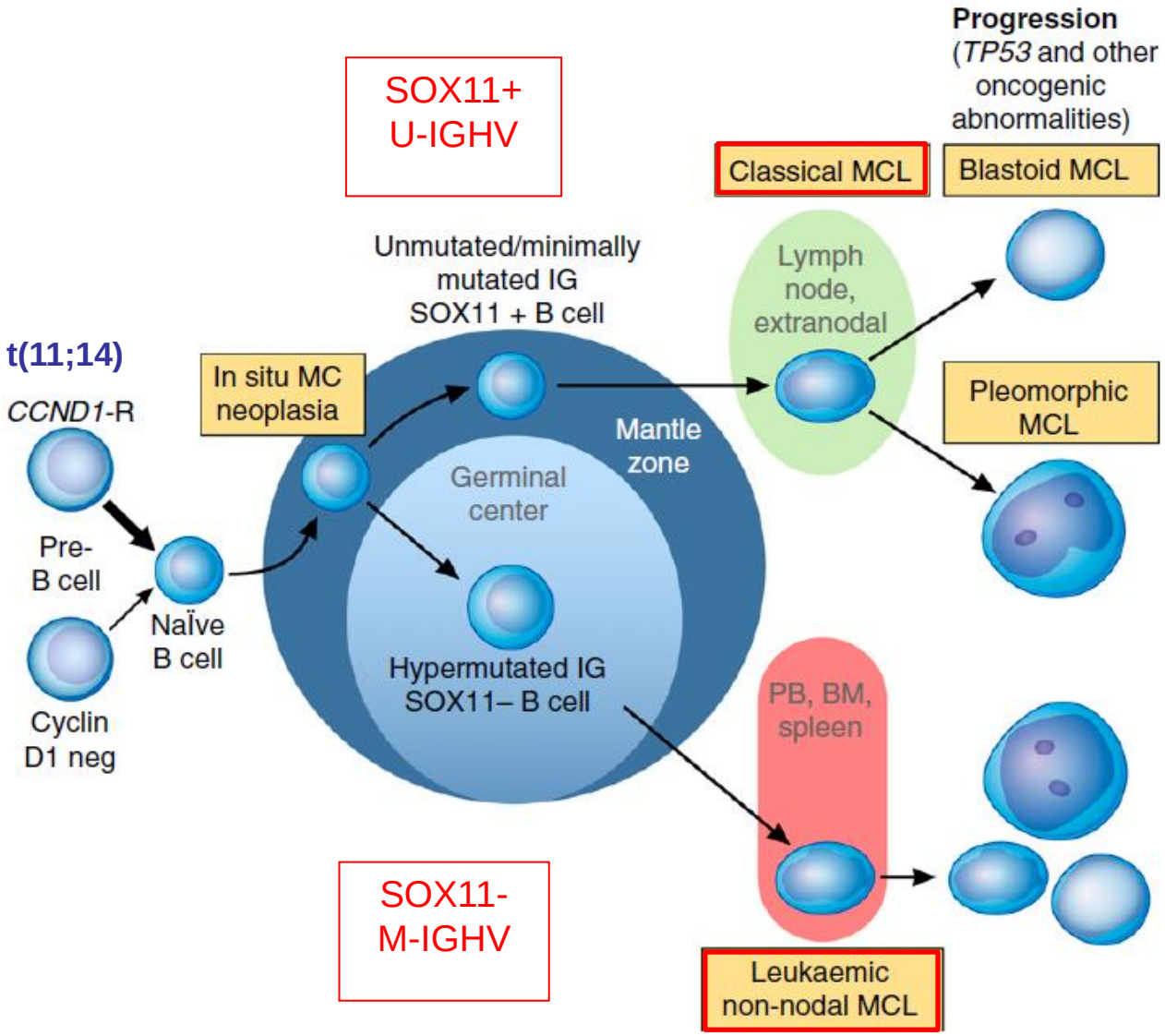
Varianti citologiche e morfologiche
Impatto clinico

Alterazioni genetiche e molecolari
Impatto clinico

Mantle cell lymphoma (MCL)

- About 6% of non Hodgkin's lymphomas
- Predominantly elderly (>60), male patients
- Advanced Ann Arbor stage
- Extranodal involvement (bone marrow, gastrointestinal tract, liver, spleen)

Model Of Molecular Pathogenesis of MCL

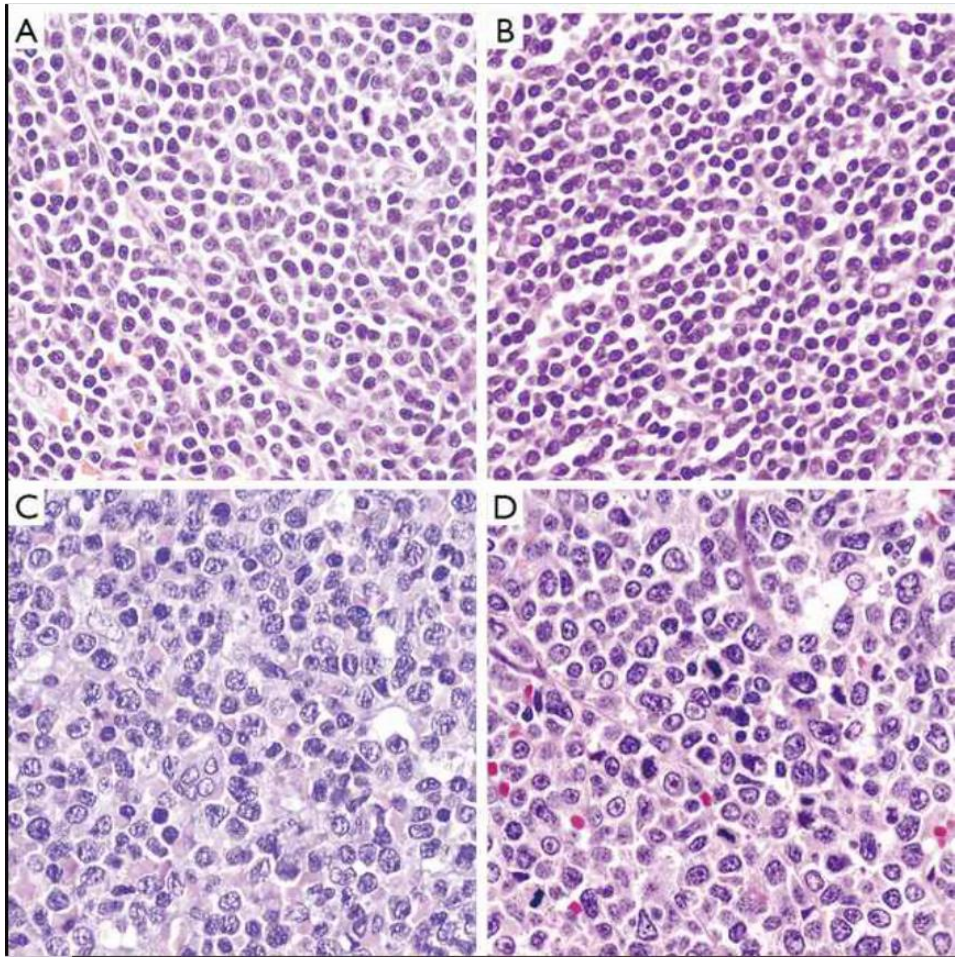


Jares et al, JCI 2012
Swerdlow SH et al, Blood 2016

MCL, *cytological variants*

classic

small cell

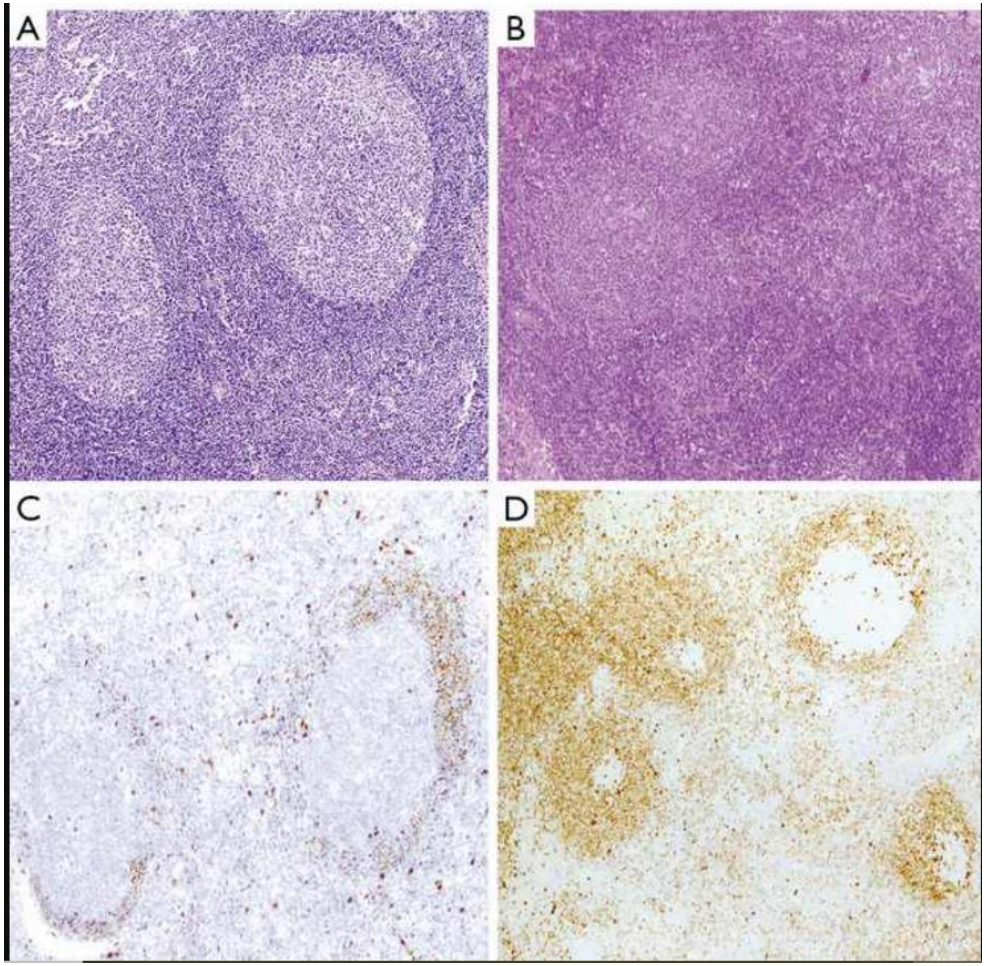


blastoid

pleomorphic

MCL, *WHO 2016, «in-situ MCL»*

in situ

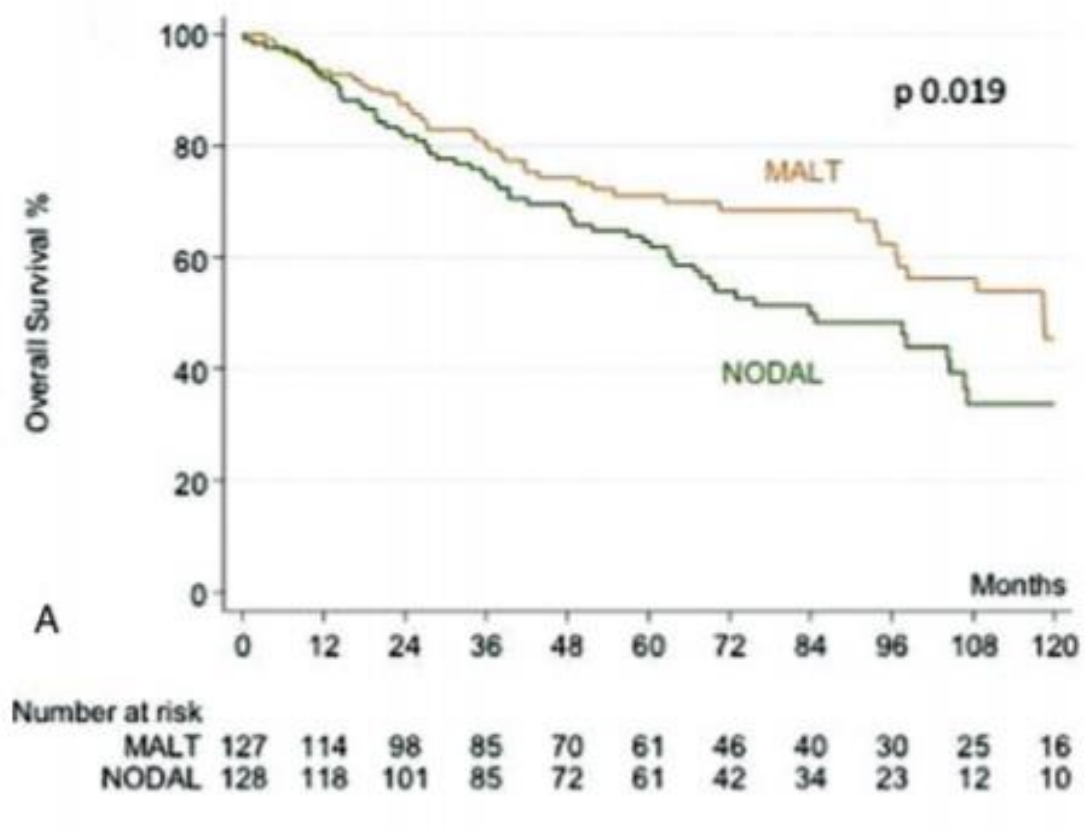


mantle zone growth pattern

Mantle Cell Lymphoma of Mucosa-Associated Lymphoid Tissue: A European Mantle Cell Lymphoma Network Study

Hemasphere, 2020

Lucia Morello[1], Sara Rattotti[2], Laura Giordano[3], Mats Jerkeman[4], Tom van Meerten[5], Katarzyna Krawczyk[6], Filipa Moita[7], Dario Marino[8], Simone Ferrero[9], Michał Szymczyk[10], Igor Aurer[11], Tarec Christoffer El-Galaly[12], Alice Di Rocco[13], Carlo Visco[14], Giuseppe Carli[15], Irene Defrancesco[2], Carmelo Carlo-Stella[1,16], Martin Dreyling[17], Armando Santoro[1,16], Luca Arcaini[2,18]



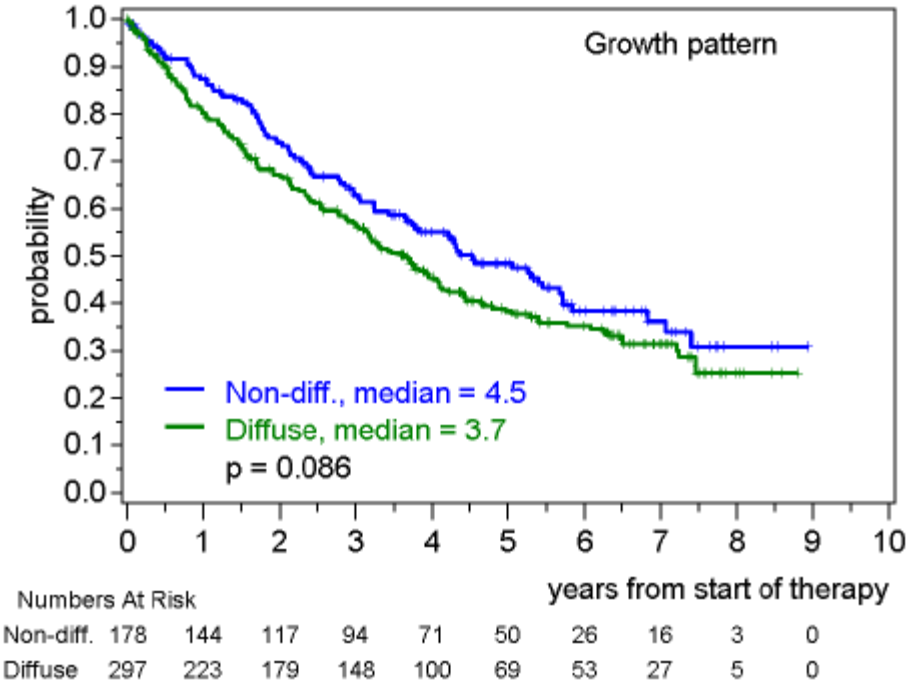
FONDAZIONE ITALIANA LINFOMI

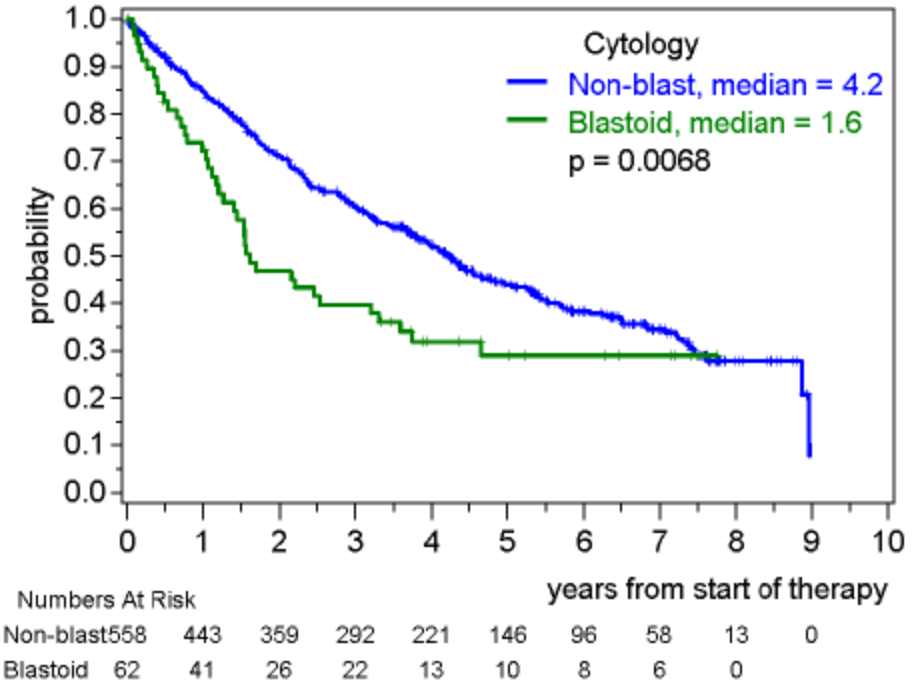
European MCL Network

Blastoid variant

- Blastoid variant (BV) predominantly involves men in their sixth decade, has frequent extranodal involvement (40–60%), stage IV disease and central nervous system (CNS) involvement.
- Diagnosis relies on **morphological features** and is challenging.
- Immunophenotyping may display CD23 and CD10 positivity and CD5 negativity in a subset.
- Mitotic index is frequently high and TP53 often mutated
- BV responds poorly to conventional chemotherapy and has a short duration of response.

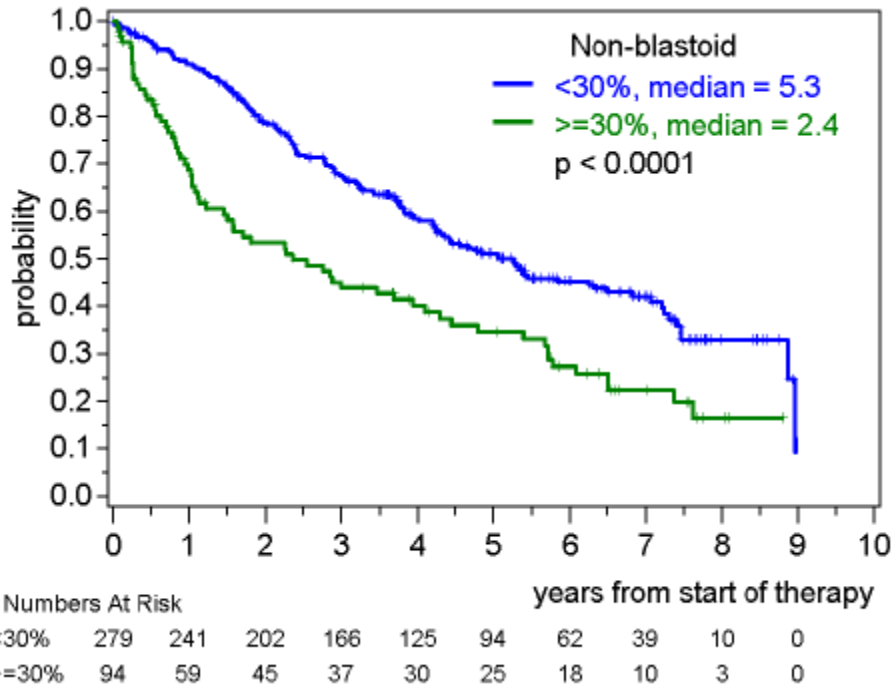
PFS according to blastoid vs. nonblastoid cytology, and diffuse vs. nondiffuse growth pattern.

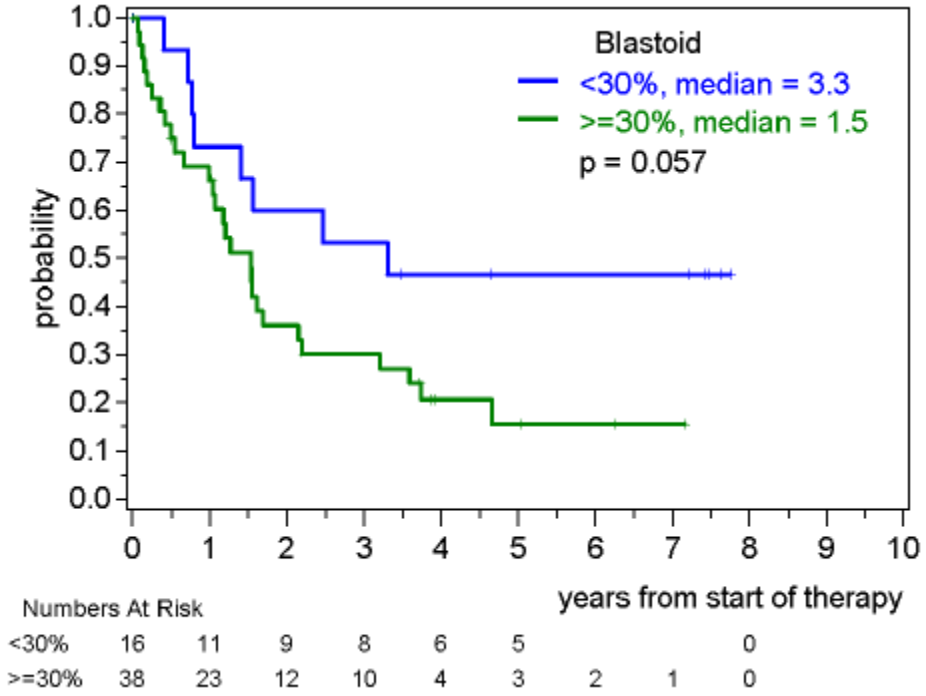




Hoster E et al, JCO 2016

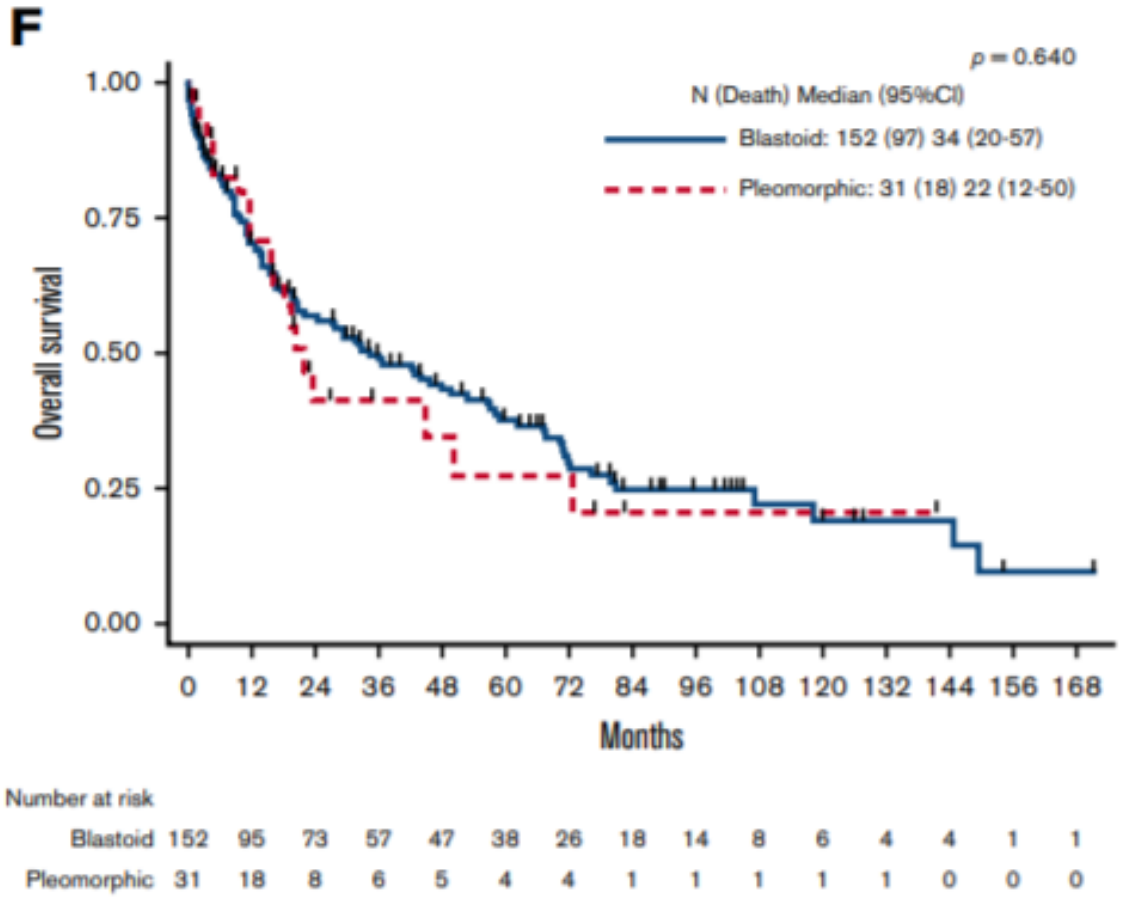
PFS according to Ki-67 index (<30% vs. ≥30%) among patients with nonblastoid and blastoid MCL.





Hoster E et al, JCO 2016

Pleo versus Blastoid

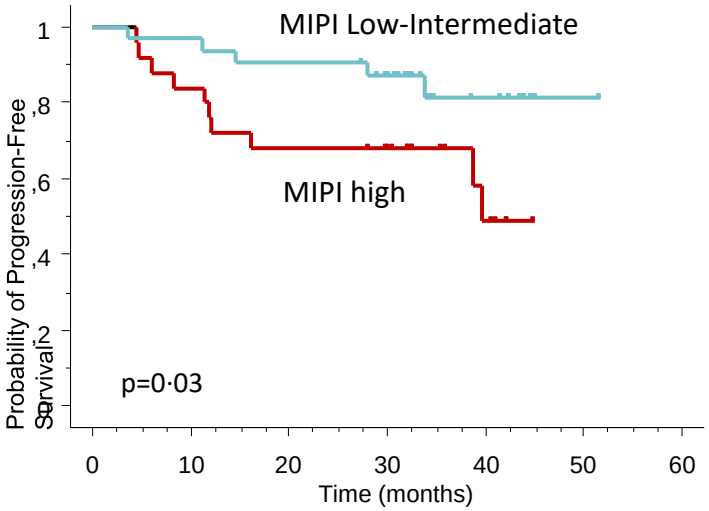


Jain P et al, Blood Advances 2020

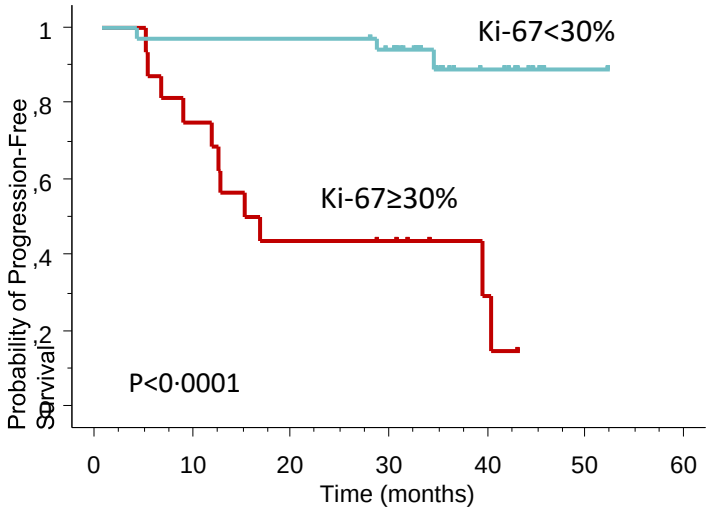
Survival curves

Univariate analysis for PFS

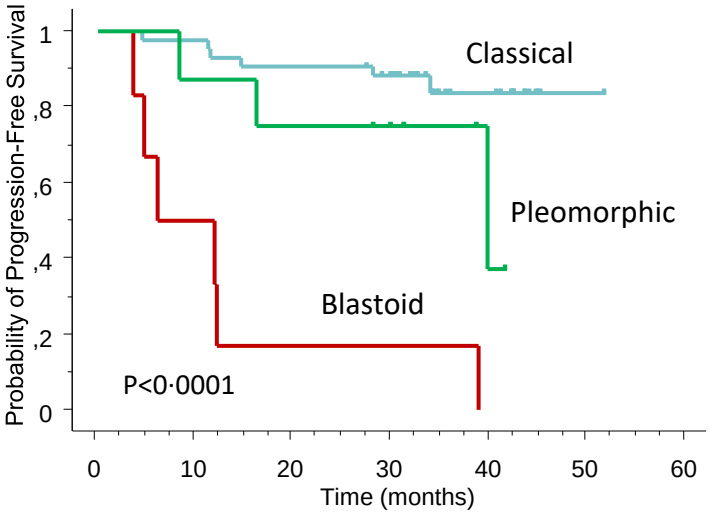
Grouping Variable: **MIPI**

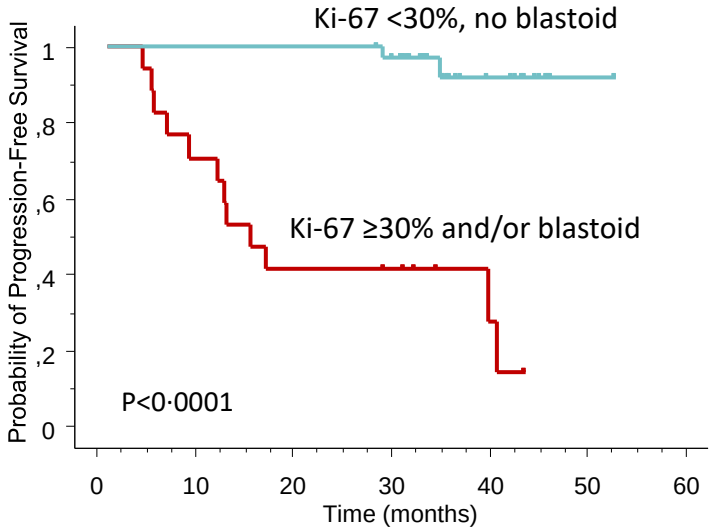


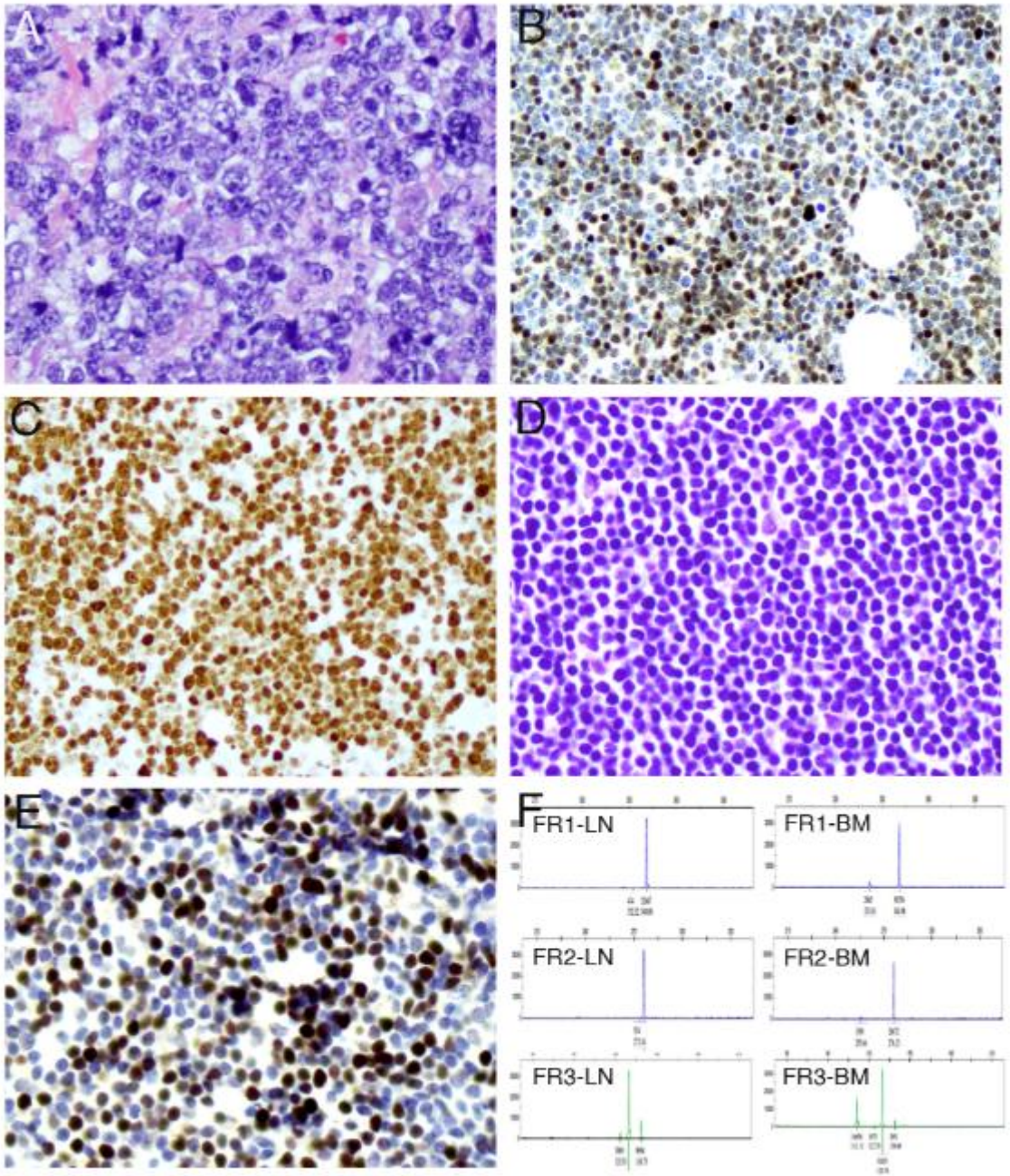
Grouping Variable: **Ki-67**



Grouping Variable: **Morphology**







Pleomorphic and small cell can coexist in the same patient

Blood Work, 2019

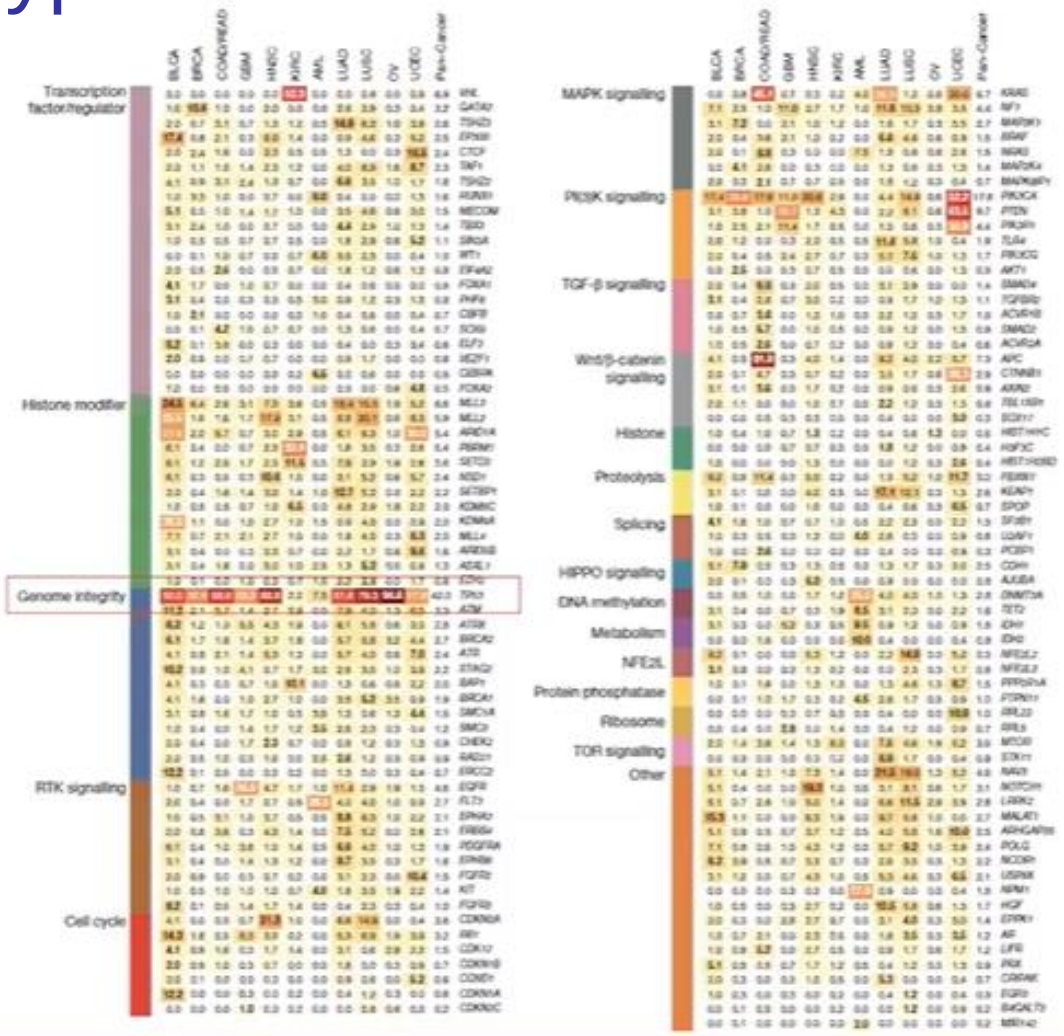
Mutational landscape and significance across 12 major cancer types

127 SMGs identified in 12 cancer types
The Cancer Genome Atlas (TCGA)
3281 tumors

Kandoth et al., Nature 502, 333-9, 2013

TP53 is the most frequently mutated gene in these 12 cancer types: 42%

PIK3CA: 17.8%
PTEN: 9.7%
APC: 7.3%



Kandoth C et al, Nature 2013

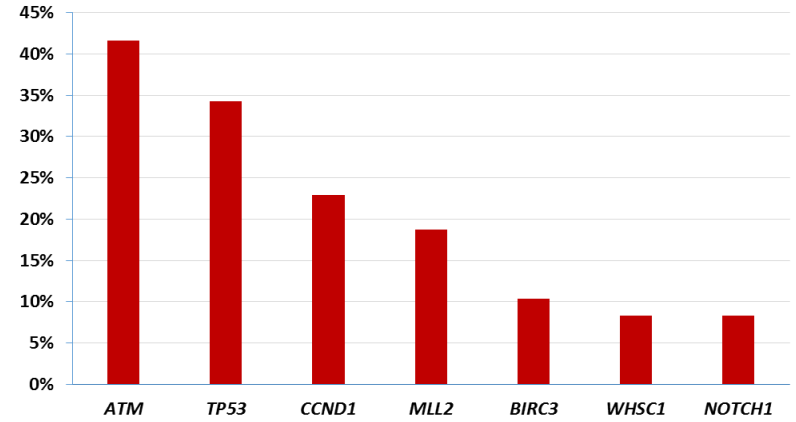
TP53 mutations in hematological malignancies

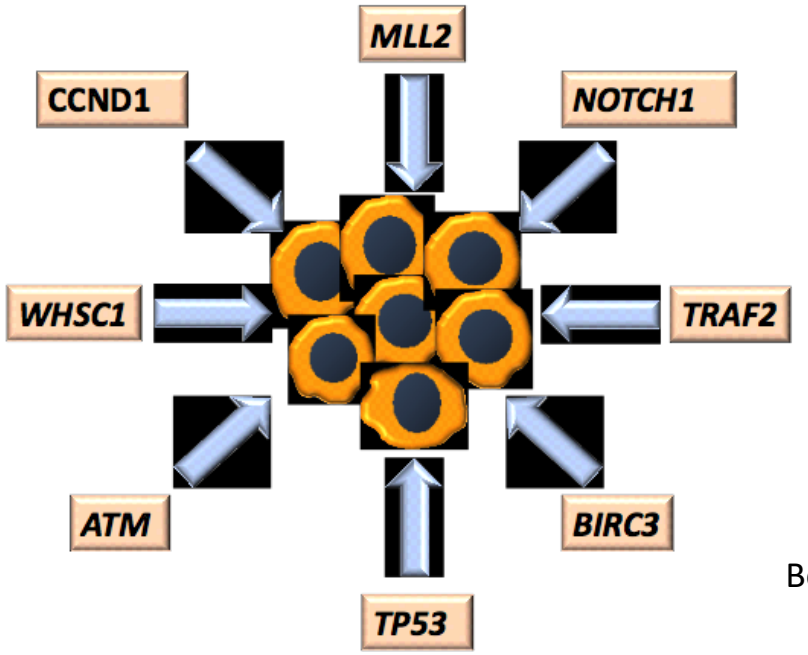
• AML	13%
• MDS	19%
• ALL	19%
• CLL	8%
• B cell lymphoma	20-25%
• Myeloma	13%

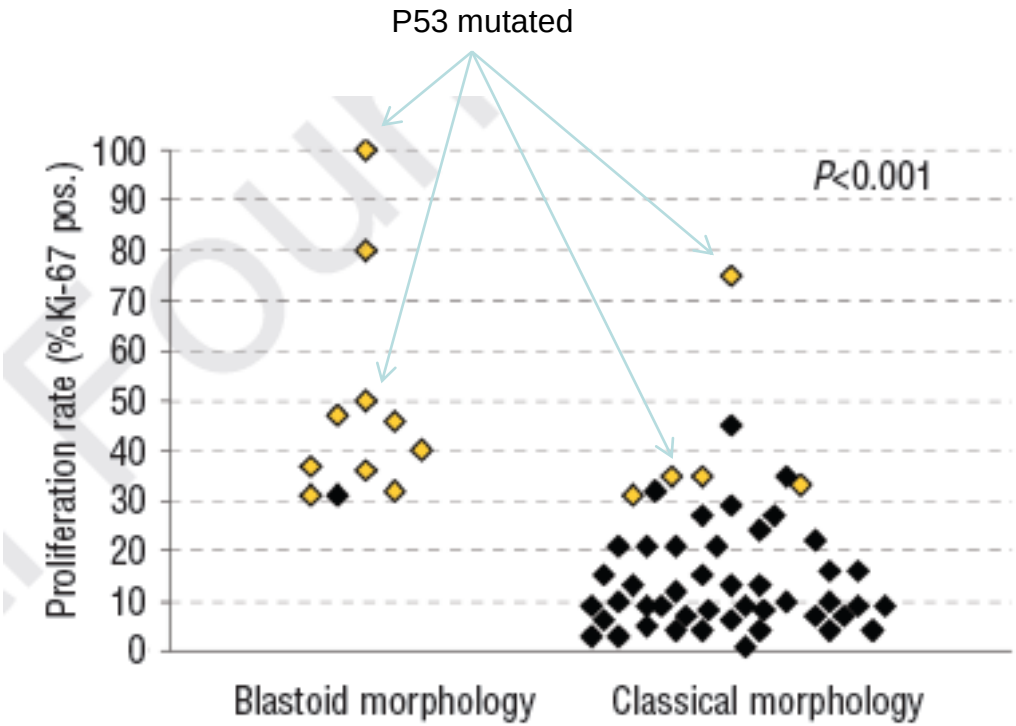
TP53 mutation is associated with poor prognosis

Stengel et al., Leukemia 2017; Lindsley et al., New Engl J Med 2017;
Zenz et al., Int. J Cancer 2017; Chng et al., Leukemia 2007

TP53 and genes recurrently mutated in MCL



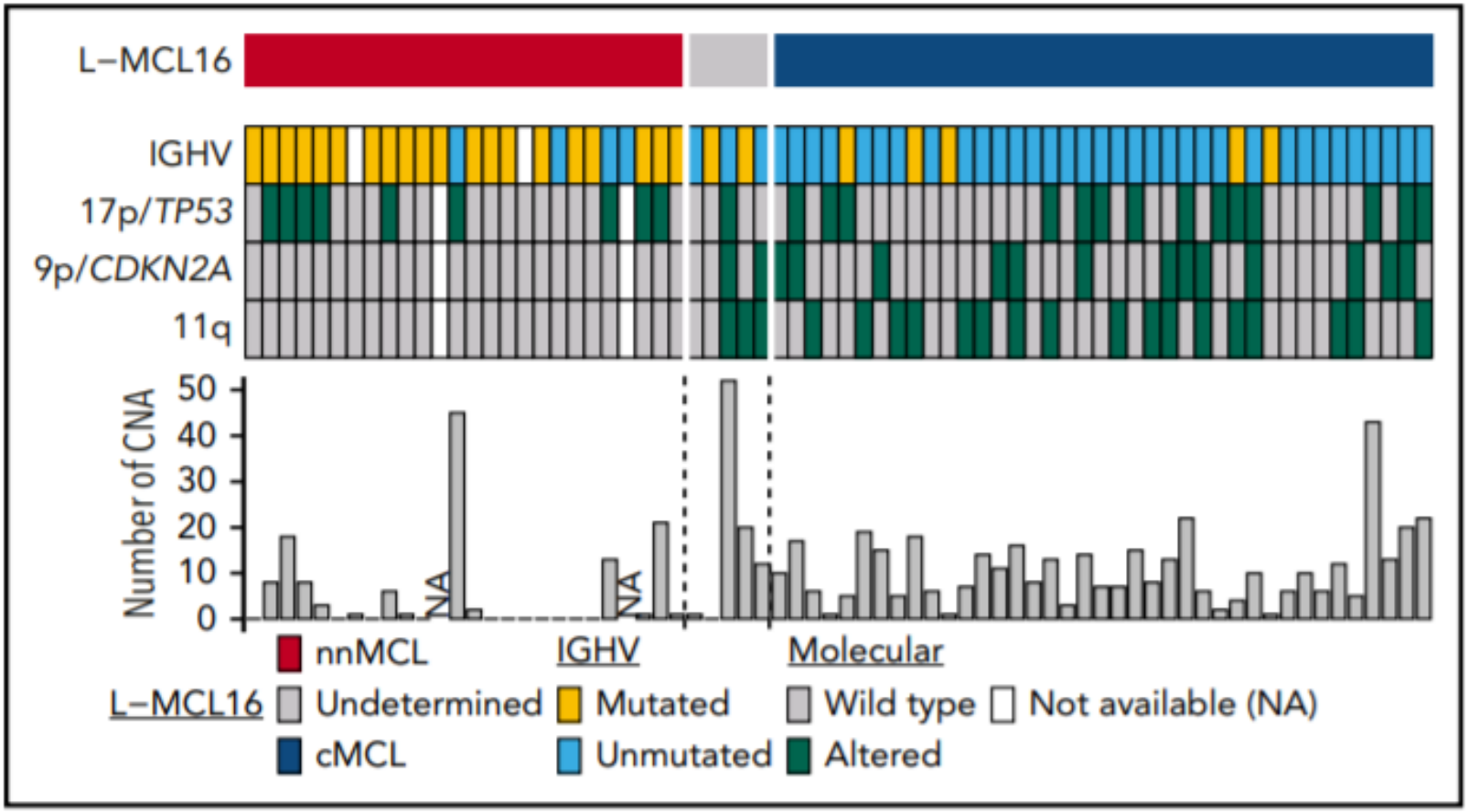




Slotta-Huspenina J et al, Haematologica 2012

Beà et al. *Proc Natl Acad Sci U S A*. 2013
Zhang et al. *Blood* 2014

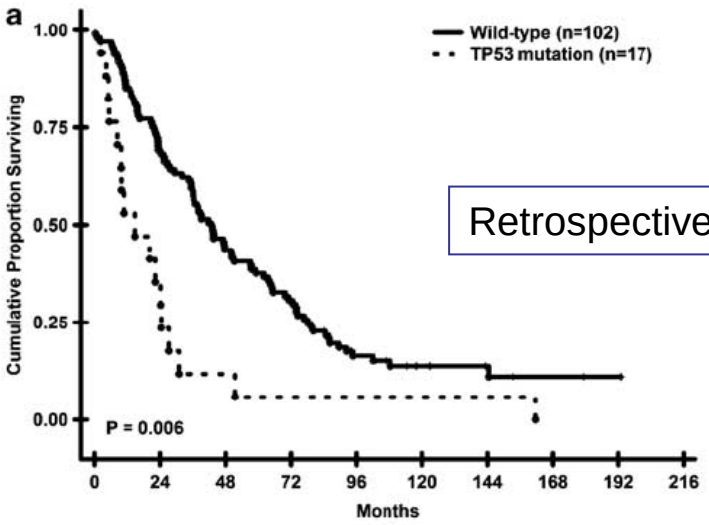
Classic and nn-MCL have similar TP53 mutation frequency



Clot G et al, Blood 2018

P53 disruption and survival

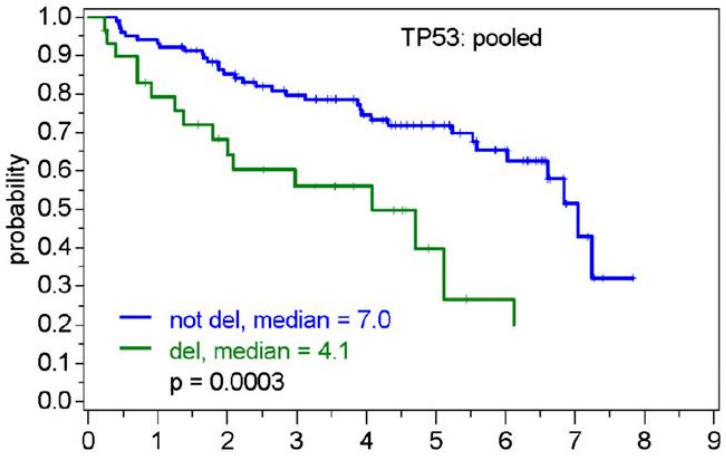
P53 mutations 7-22%
P53 deletions 20-32%

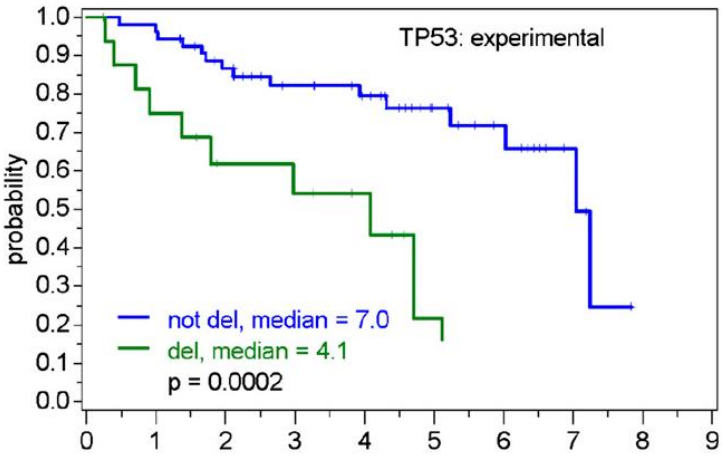


Retrospective series

Haldosdottir et al, Leukemia 2011

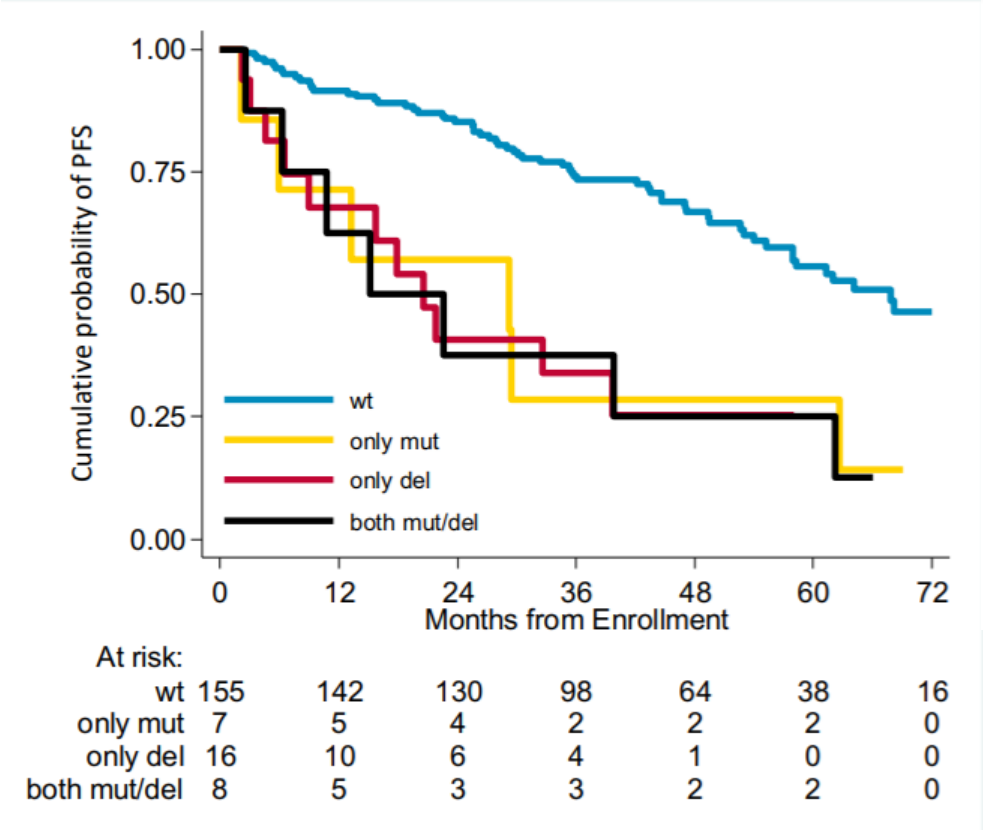
Prospective series

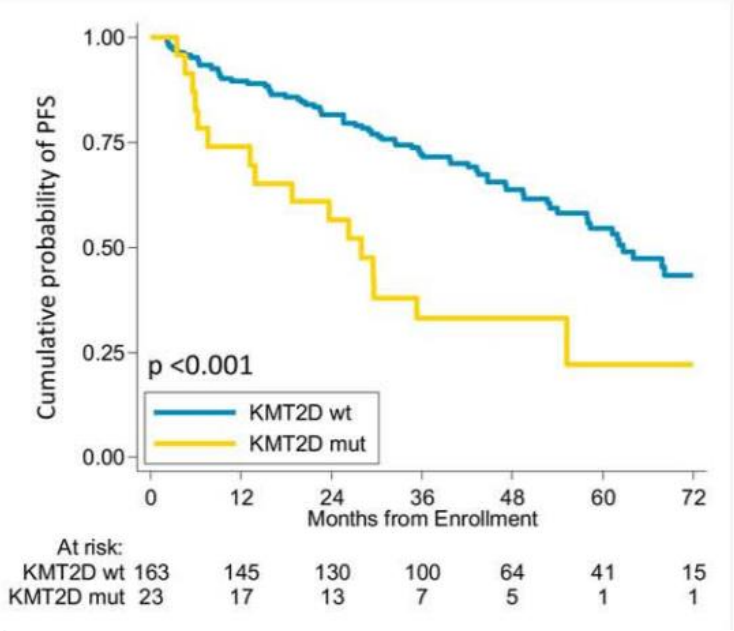




Delfau-Larue, Blood 2015

KMT2D mutations and TP53 disruptions are poor prognostic biomarkers





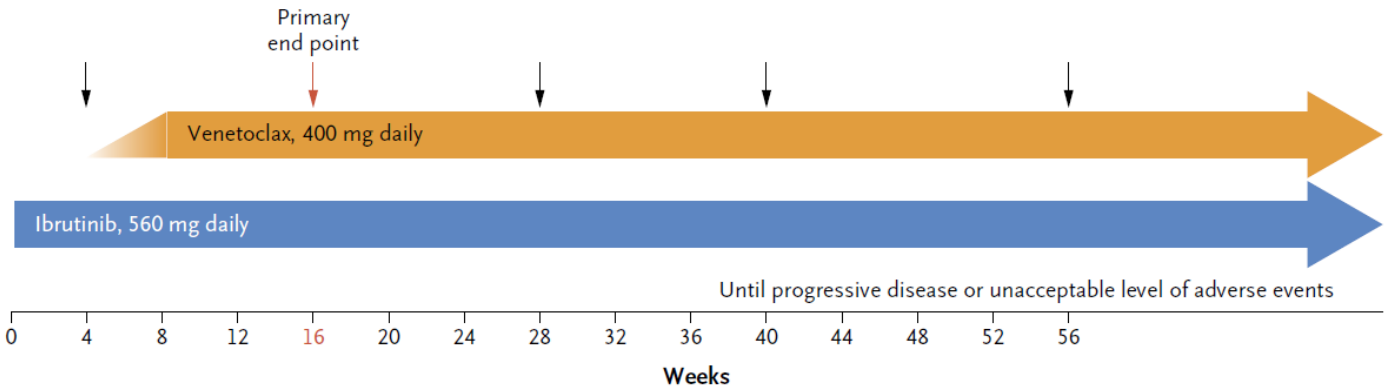
P53 mutations 8%
P53 deletions 13%
KMT2D mut/del 14%

Ferrero S et al, Haematologica 2019

The NEW ENGLAND JOURNAL of MEDICINE

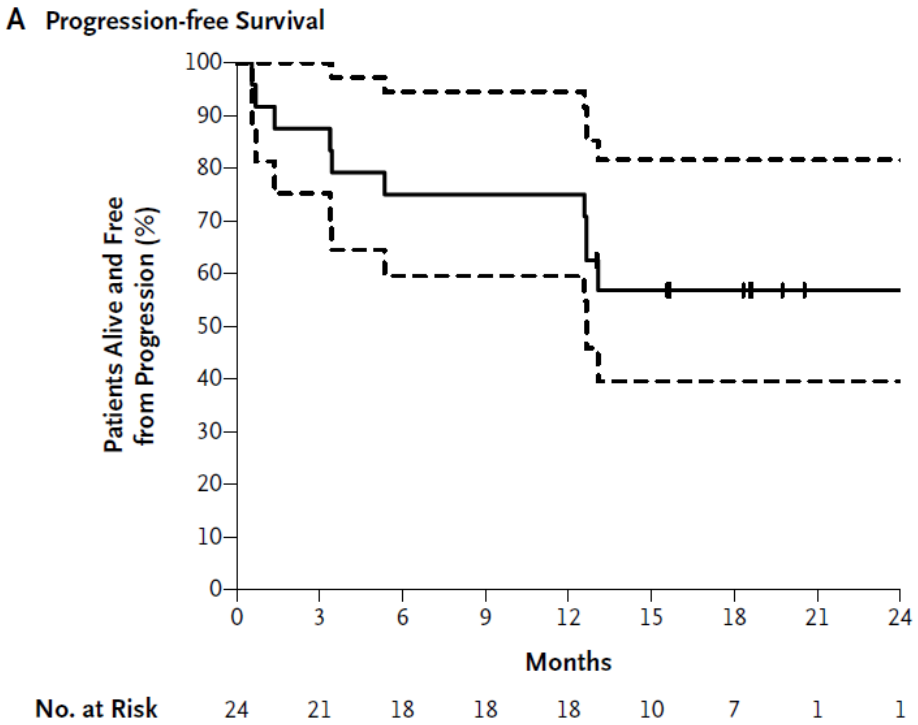
ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma



Tam CS et al, NEJM 2018

Response, PFS with Ibrutinib-Venetoclax



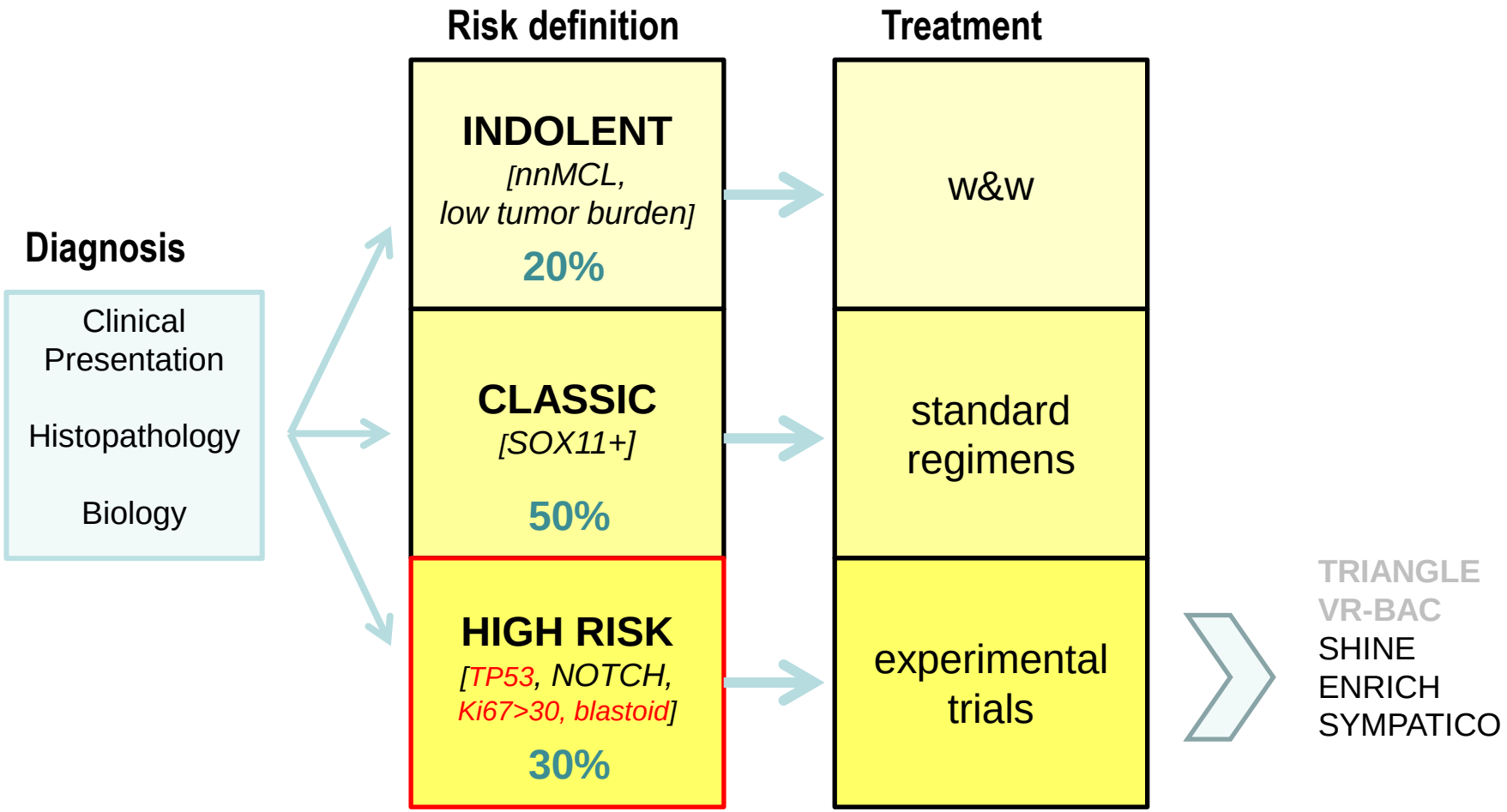
Median follow-up 15,9 months

Response at wk 16	CT-scan	PET
CR	10 (42)	15 (62)
PR	4 (17)	2 (8)
PD	3 (12)	4 (17)

12 patients *TP53* mut/del
6 (50%) had CR
5 (42%) progression free for 13-20 m

Tam CS et al, NEJM 2018

Flow Chart: standard treatment has to be individual



Grazie per l’attenzione