High-Grade B-cell Lymphoma Double Hit or Double Expressing

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MYC-R confer inferior pronostic

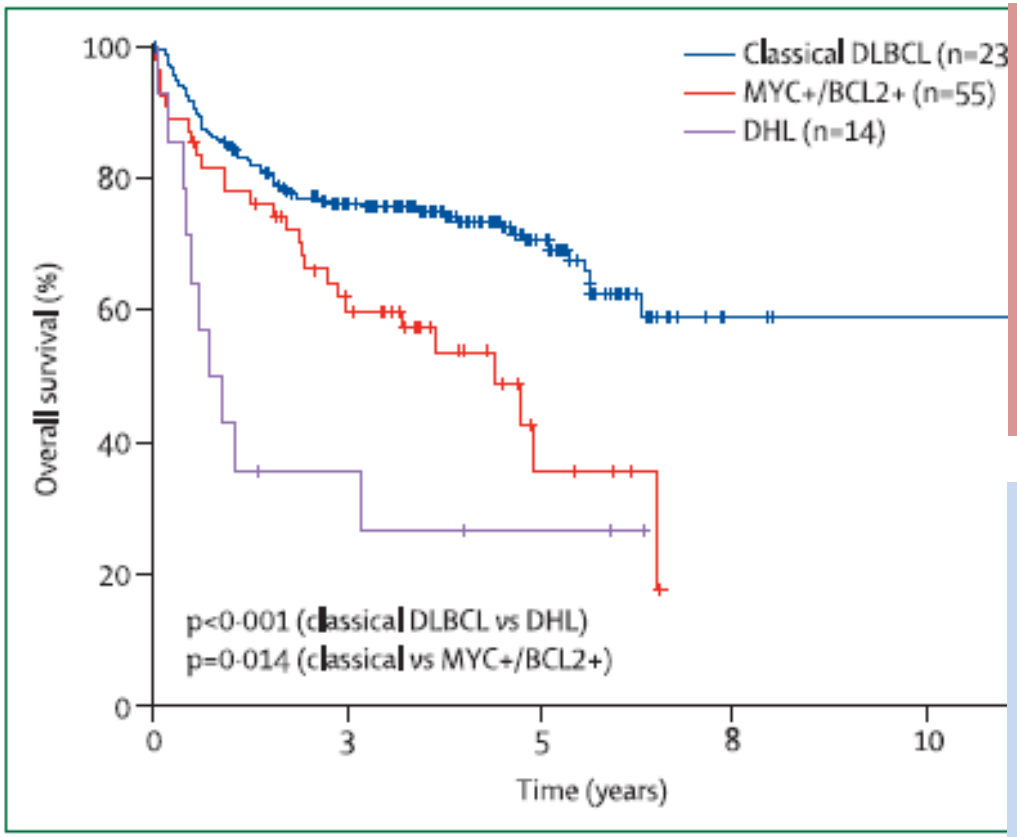


Figure 2: Double-protein-expression lymphoma has an intermediate outcome between DHL and classical DLBCL
DHL=double-hit lymphoma. DLBCL=diffuse large B-cell lymphoma. Reproduced with permission from Johnson and colleagues [28]

DOUBLE/TRIPLE HIT LYMPHOMA
Separate provisionnal entity
WHO 2016
HIGH GRADE B LYMPHOMA

- **2/3 MYC-R=**
  - **BCL2 and/or BCL6-R**
- **HGBL-DH :**
  - **80% MYC-R/ BCL2-R**
  - **20% MYC –R/ BCL6-R/BCL2-E not having a BCL2-R**

Sarkozy C, Traverse-Glehen A, Coiffier B
Lancet Oncol 2016

Coexpression of MYC and BCL2 confer inferior pronostic

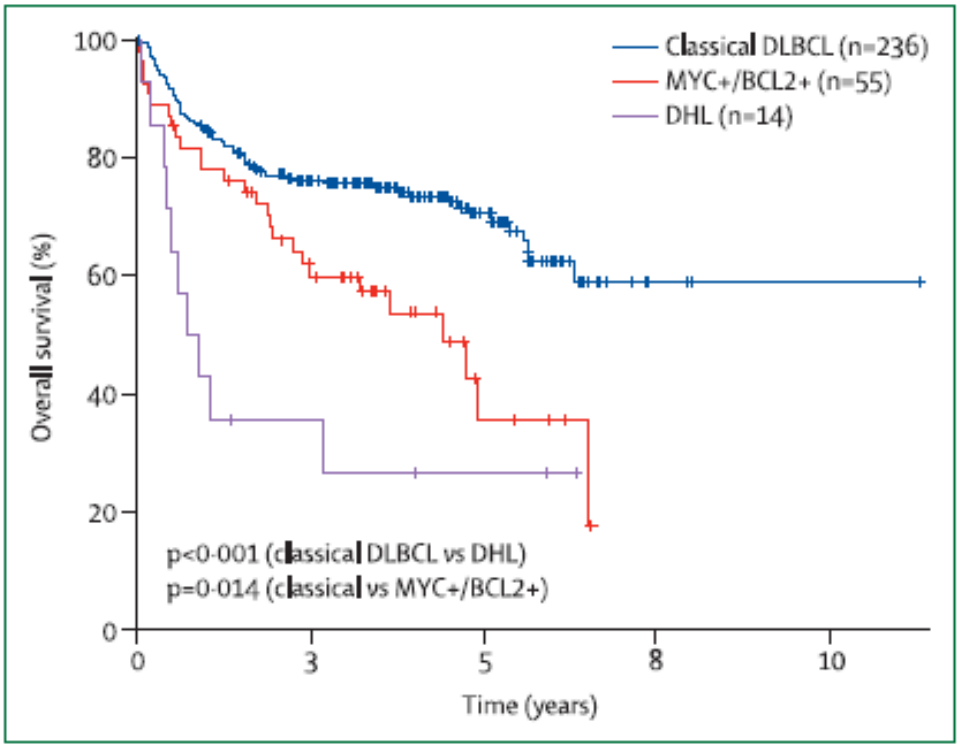


Figure 2: Double-protein-expression lymphoma has an intermediate

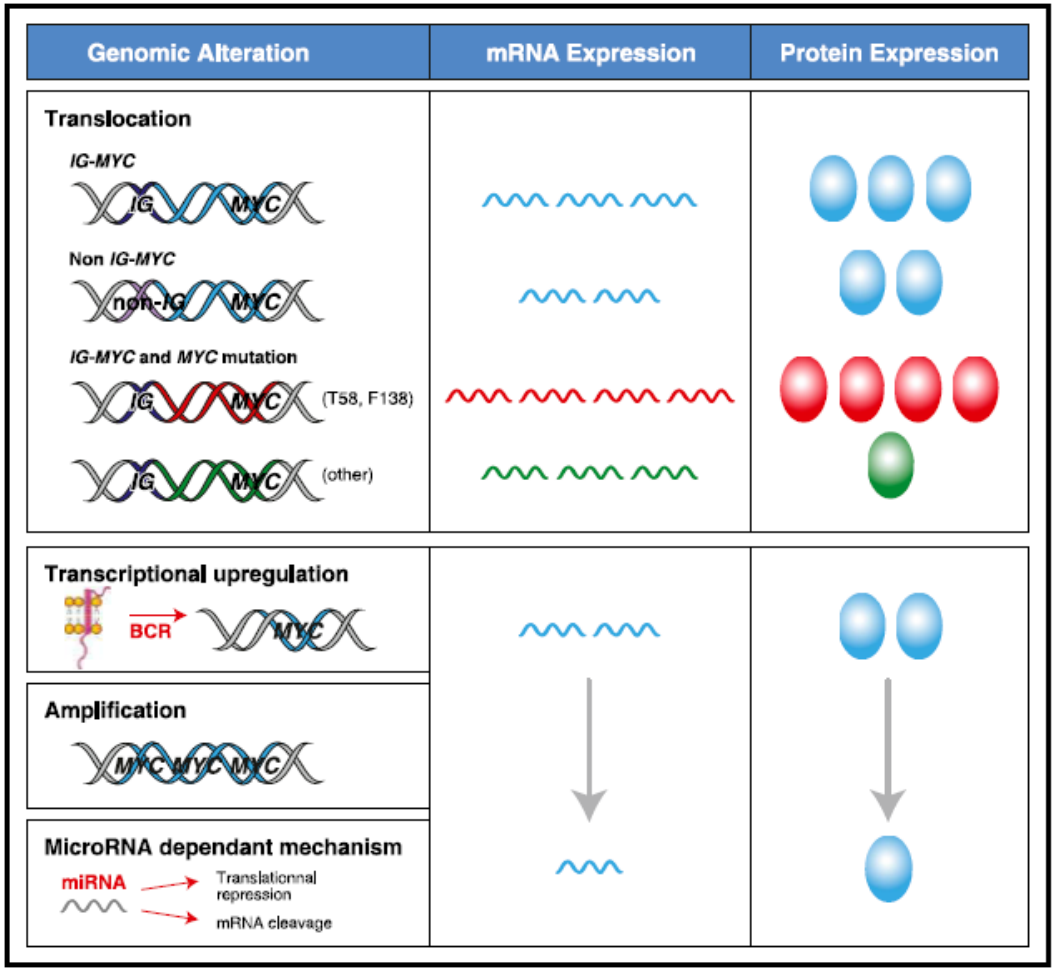
Sarkozy C, Traverse-Glehen A, Coiffier B
Lancet Oncol 2016

DUAL EXPRESSOR DLBCL

Outcome superior to that of HGBL-DH

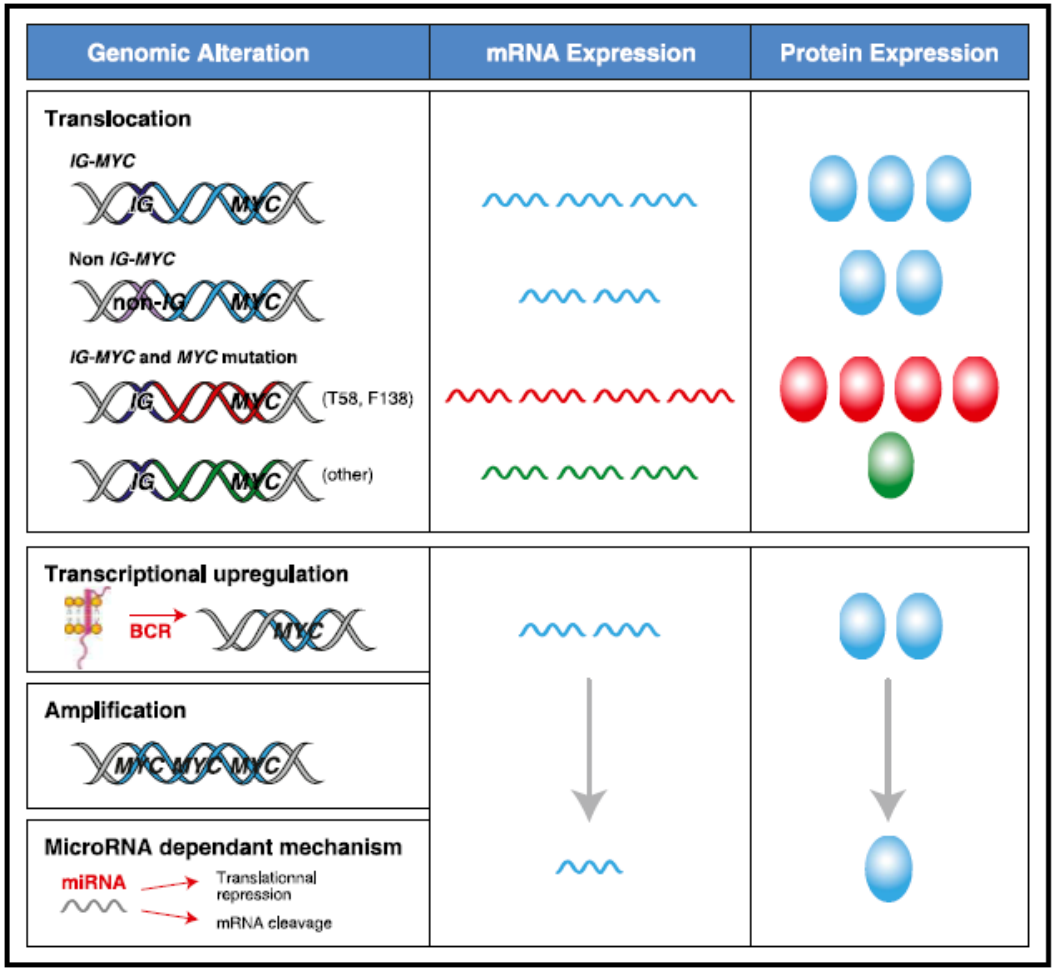
DLBCL, NOS (WHO 2016)

Mechanism of MYC upregulation

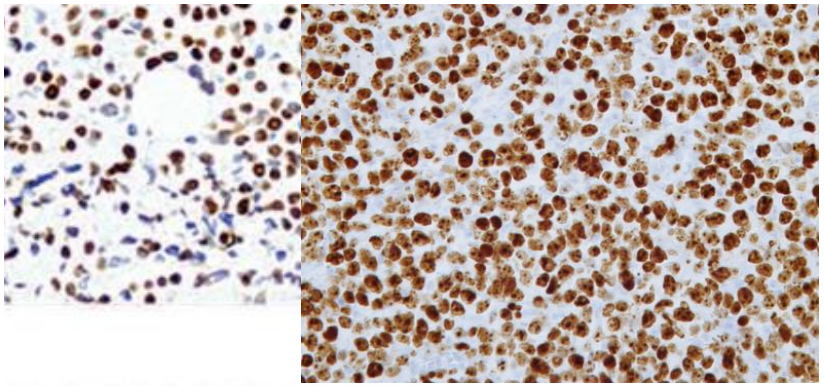


Sesques P, Blood 2017

Mechanism of MYC upregulation



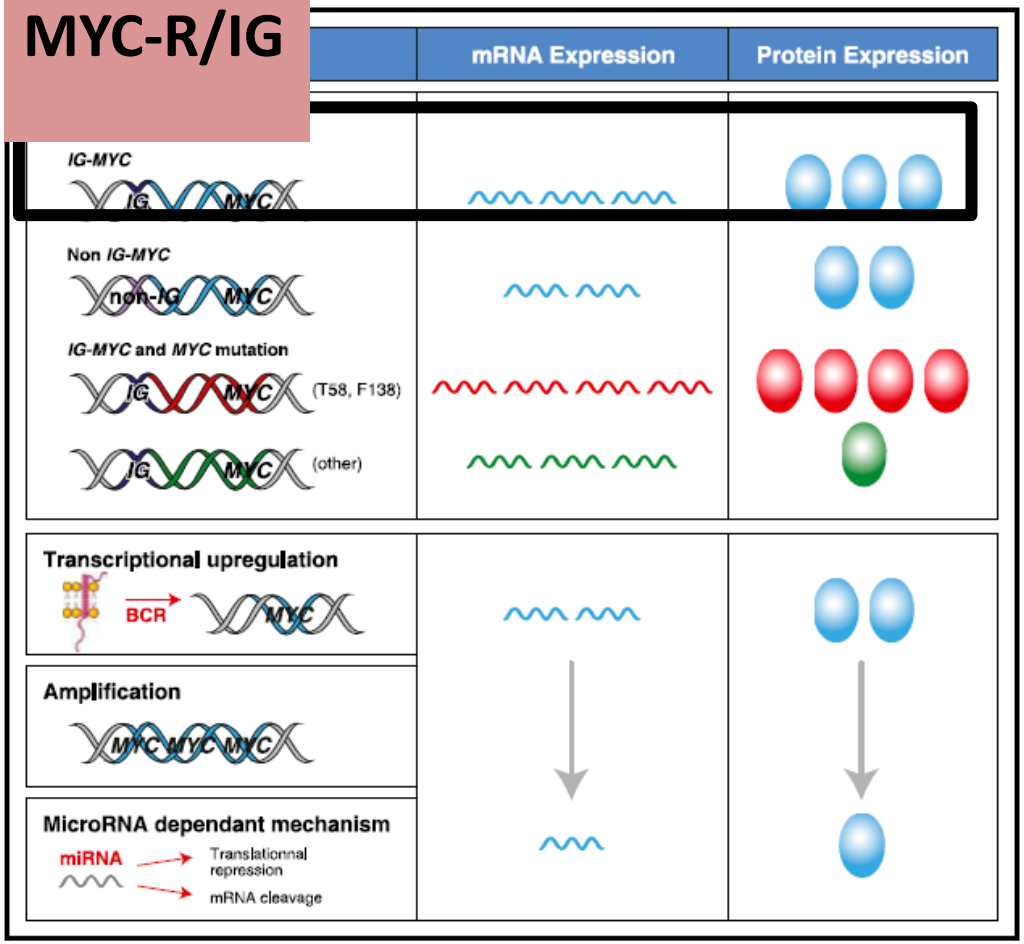
impact on the level of protein expression

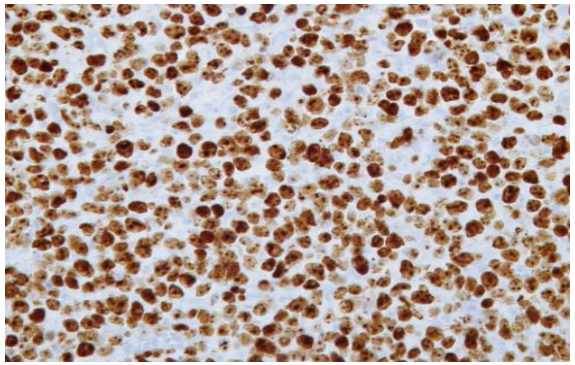


- **30 to 40 % DLBCL,**
- **60% HGBL,**
- **70 to 100% of BL,**
- **5% of normal GC B cells**

Mechanism of MYC upregulation

MYC-R/IG



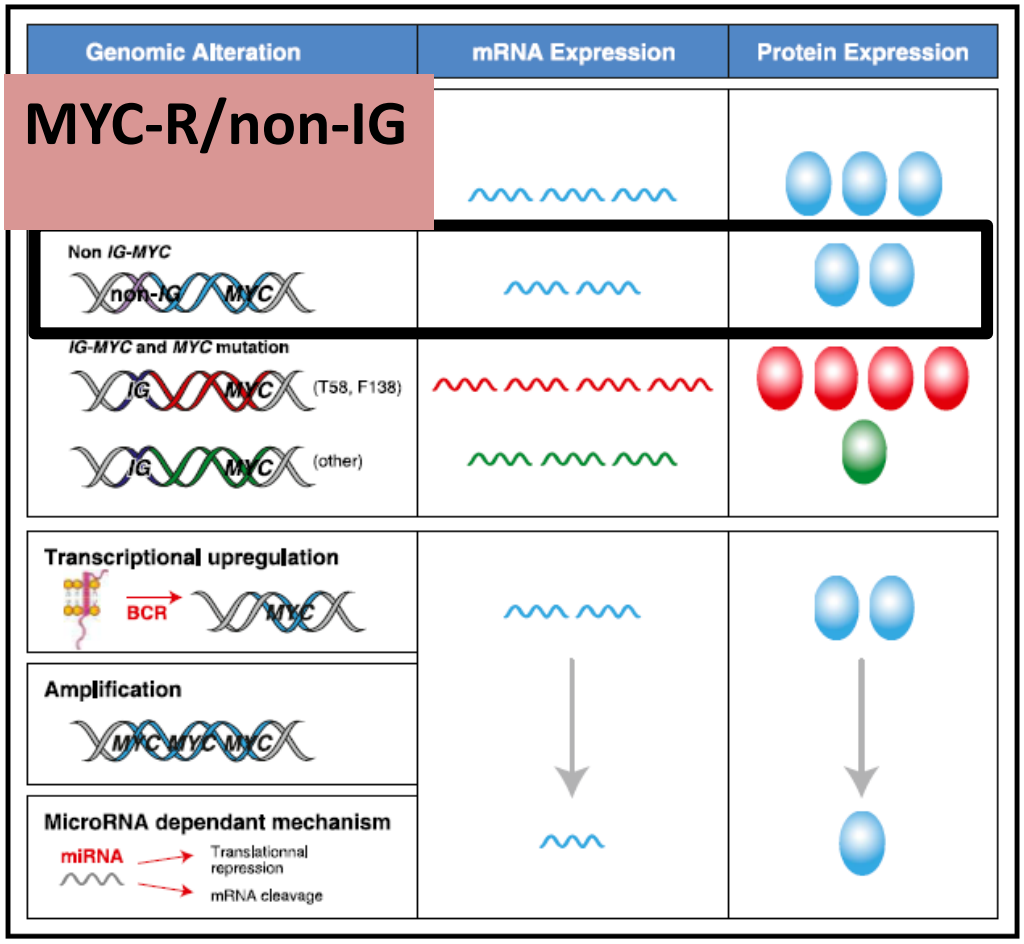


Highest levels of MYC mRNA/protein

Constitutively active transcription driven by the IG promoter

100% BL, 60% HGBL
5% DLBCL

Mechanism of MYC upregulation

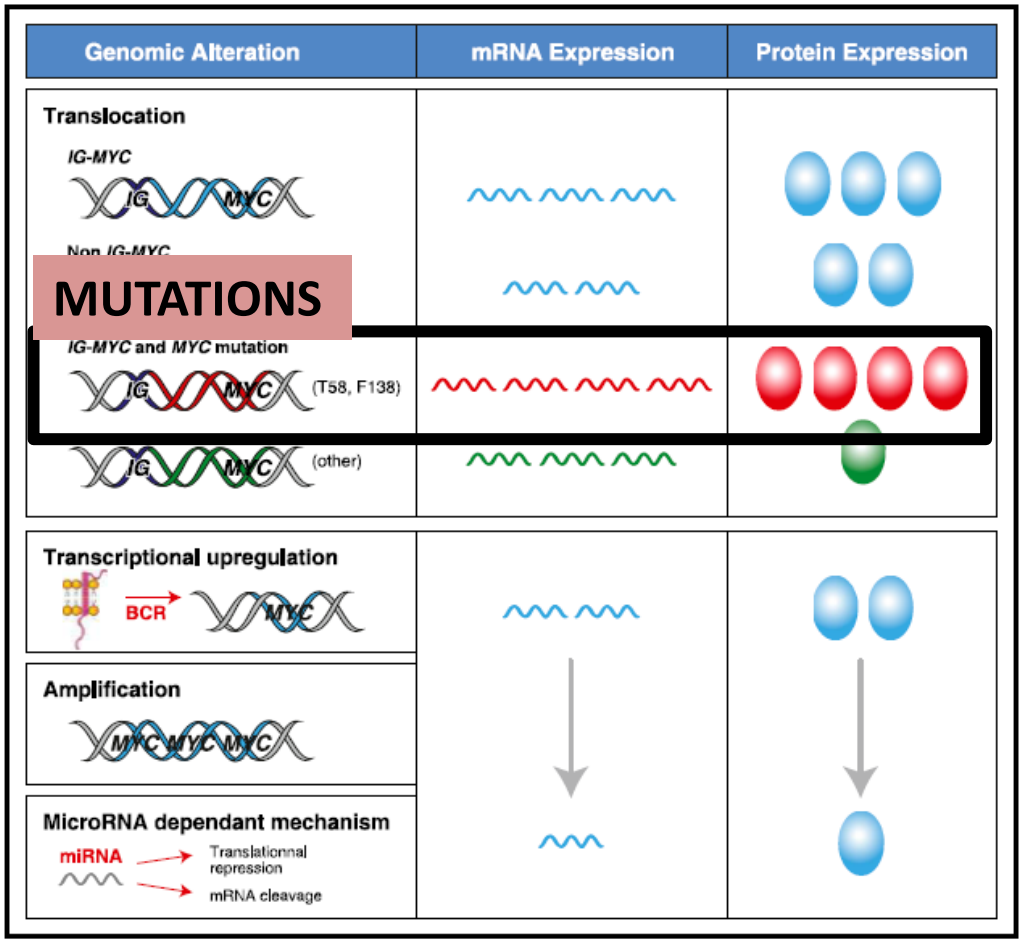


5% DLBCL

Mechanism unclear

Quantity of mRNA and protein lower than in IG/MYC

Mechanism of MYC upregulation



SomaticHM

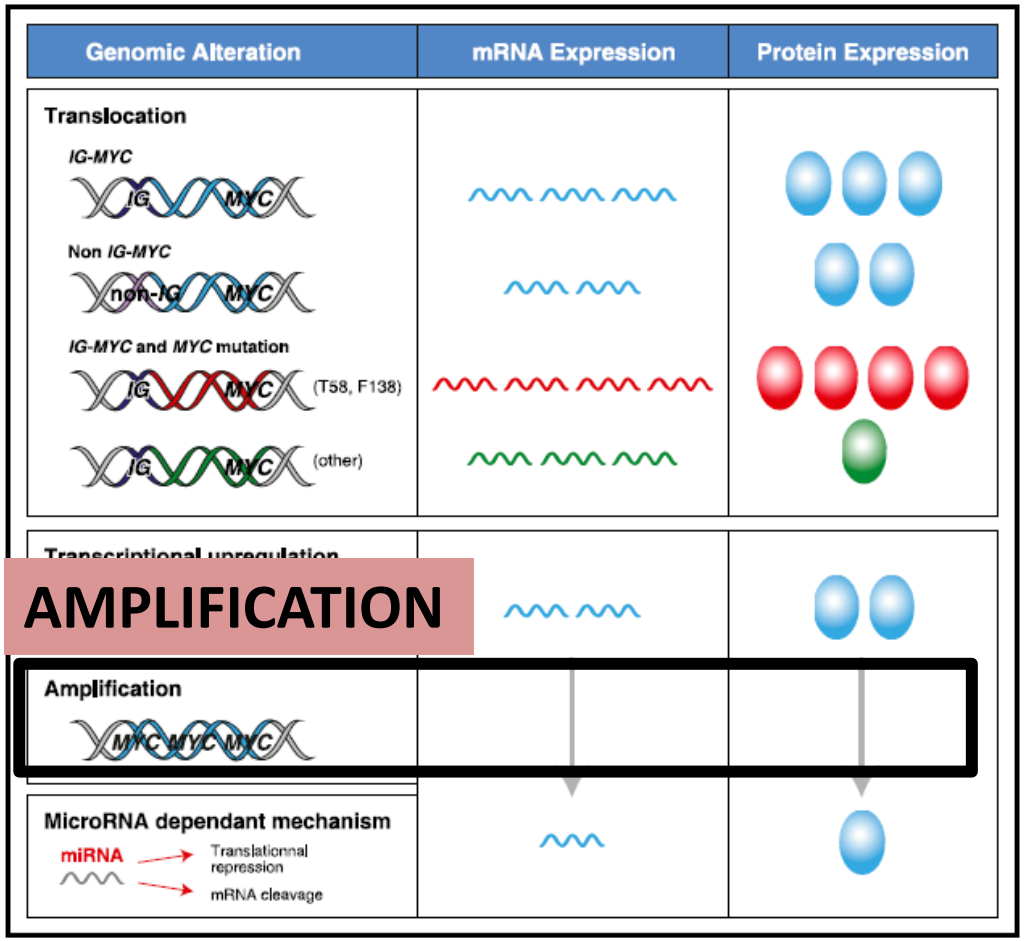
In the presence or absence of translocations

Prevalence and pattern of mutation distinct between BL and DLBCL

Upregulation of MYC by SHM

- Prevalence: BL>DLBCL
- Gain of function MYC mutants (T58 and F138) common in BL, <1% DLBCL
- In BL: T58 mutants
  - protect MYC RNA degradation leading to higher protein level
  - accelerate cellular proliferation
  - inhibit apoptosis
- In contrast, in DLBCL,
  - non T58 or F138 variants decrease MYC expression

Mechanism of MYC upregulation



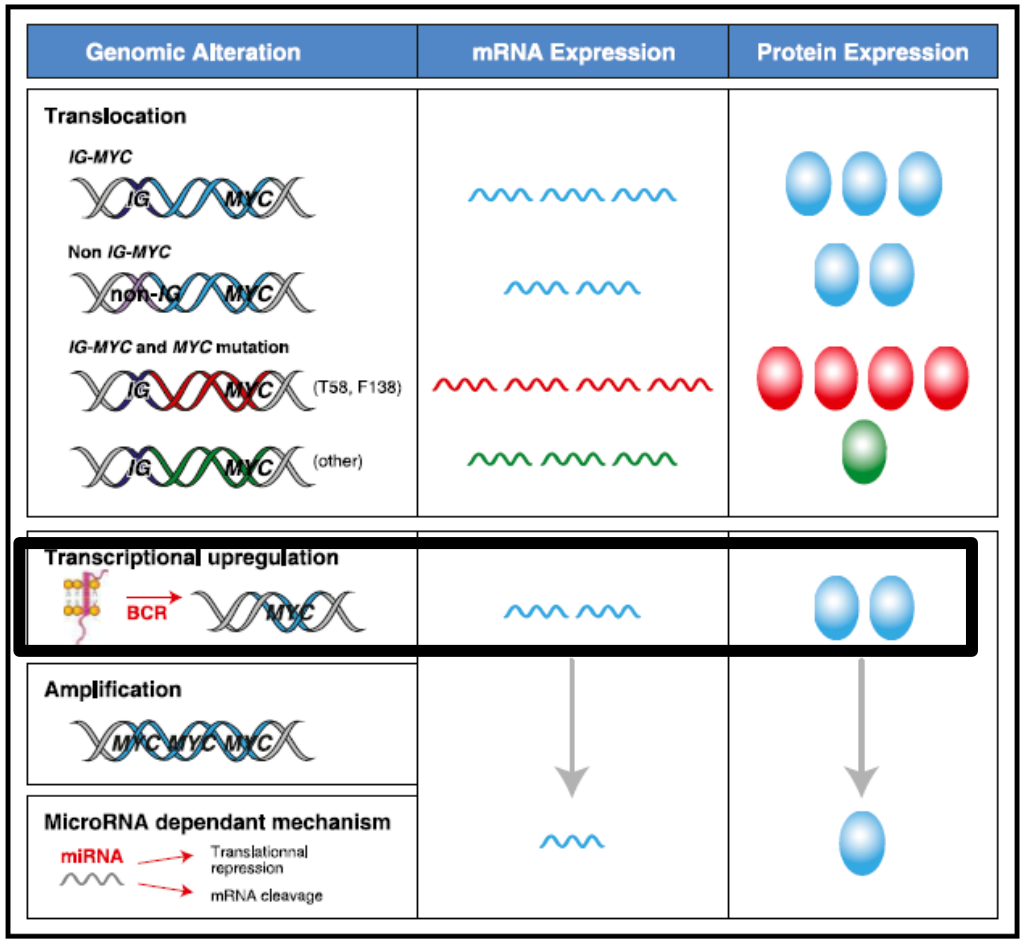
AMPLIFICATION

8 to 20% DLBCL

Not associated with increased MYC protein expression

Not associated with inferior survival

Mechanism of MYC upregulation



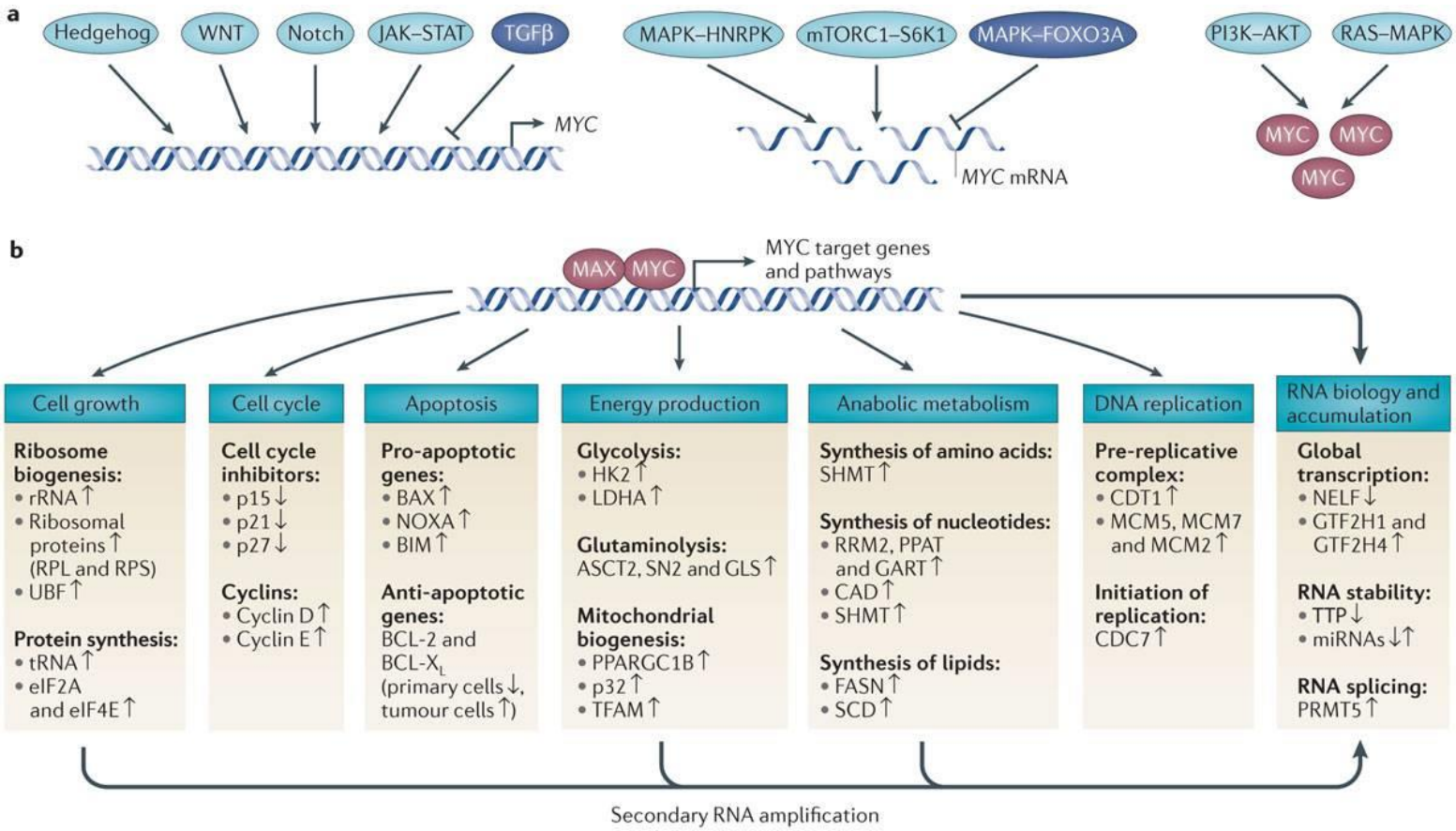
Other factors can affect MYC level without altering the integrity or location of the MYC locus

BCR and NFKB signaling pathway: increase transcription of MYC through direct or indirect interaction at the promoter

BCL2 deregulation

- BCL2 translocations usually early events
- Result of aberrant VDJ recombination in IG gene in the BM
- BCL2 mutated
  - in 68% GCB-DLBCL and 6% of ABC-DLBCL
  - Associated with BCL2 –R and protein expression
  - Consistently spare the BH3 domain, necessary for its antiapoptotic function
  - Binding site for BH3 mimetics such as venetoclax

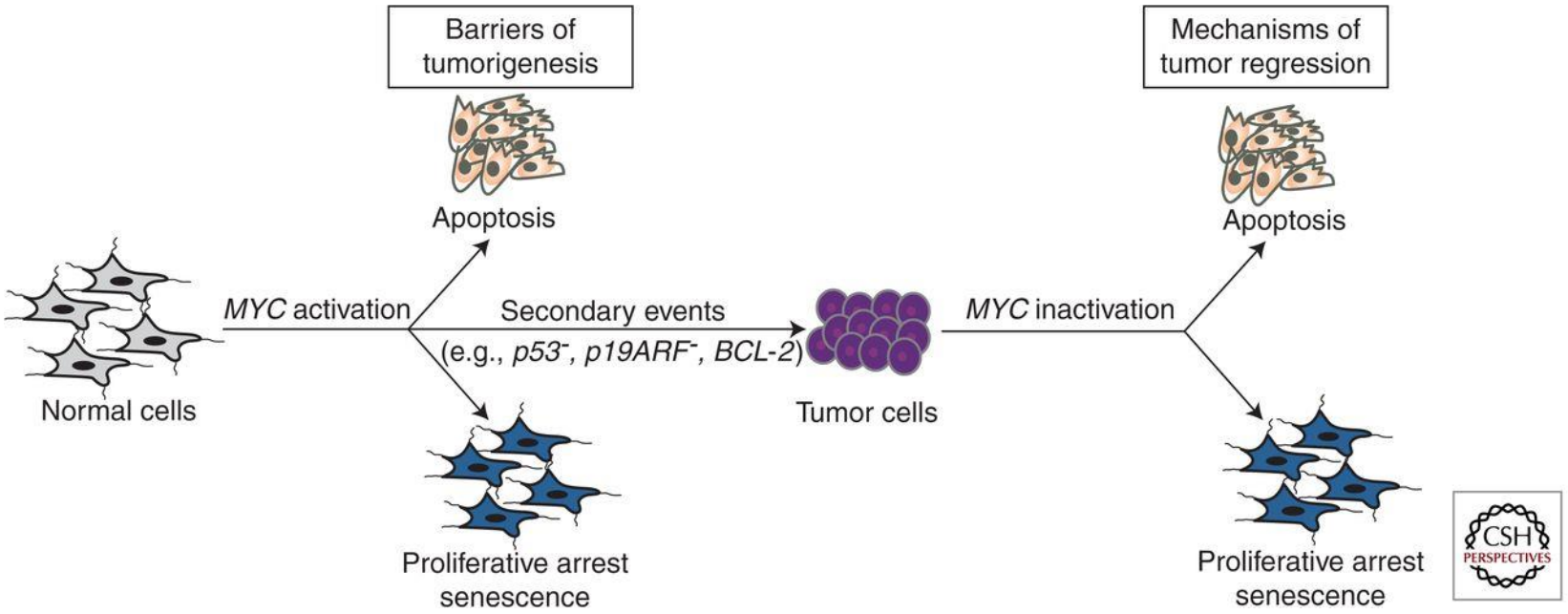
MYC: 8q24



gene-activating and gene repessing functions dependent on its binding partners and the cellular context

Nature Reviews | Cancer

MYC-induced cancer initiation and maintenance.



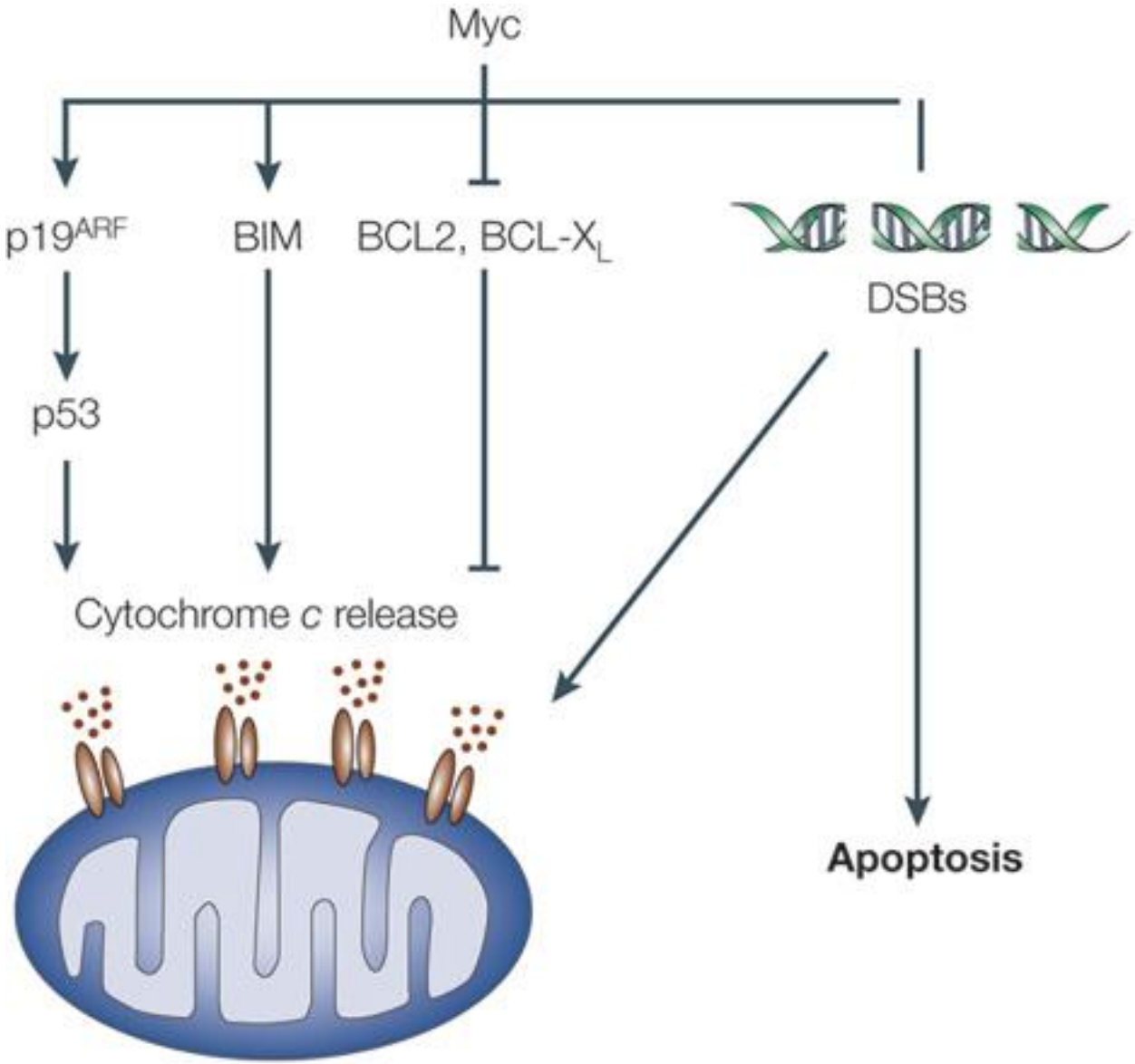
Meital Gabay et al. Cold Spring Harb Perspect Med 2014;4:a014241

MYC= transcriptional amplifier

- Increases the transcription of genes that are already poised to be expressed
- Rather than inititiating the transcription of new target genes
- In agressive lymphoma:
  - Myc expression promotes cell proliferation, induces genomic instability and amplifies the transcriptional programm already in places

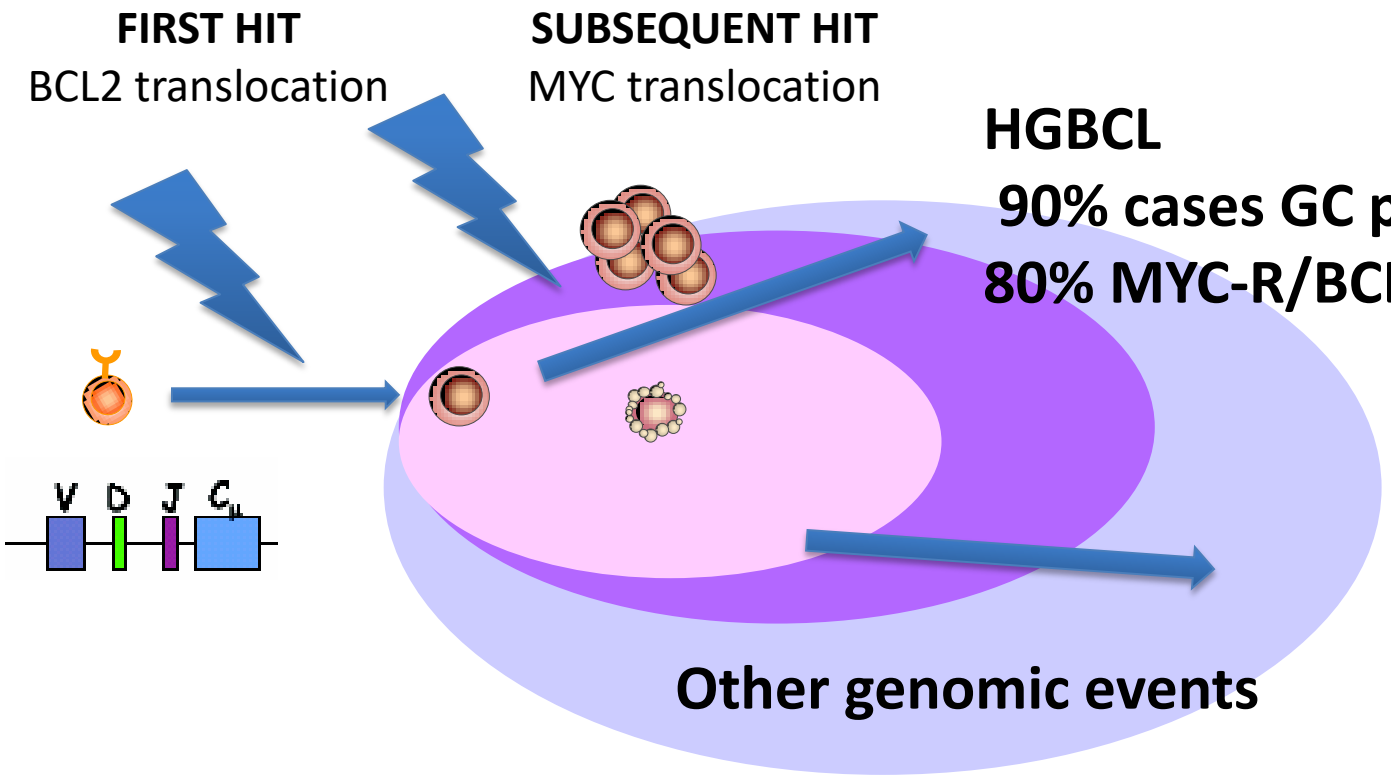
BCL2= 18q21

- Originally describe in FL
- BCL2 protein expression in >50% DLBCL, 80% of HGBL, not observed in BL or normal GC cell
- Oncogene,
  - but lymphocytes overexpressing BCL2 require additional genomic alterations before developing overt lymphoma
- Primary function:
  - to promote cell survival by inhibiting apoptosis



Nature Reviews | Molecular Cell Biology

Pathogenesis HGBL-DH : MYC/BCL2



Other HGBCL
20% MYC-R/BCL6-R
ABC cases
20% do not exp MYC and BCL2

Double expressor DLBCL

- **Not define a specific tumor biology**
- A **pronostic biomarker** of poor outcome at diagnosis and relapse
- Reproducible despite using different AB clones and threshold
- Functional readout of the cumulative genomic alterations that ultimately lead to their overexpression, mainly BCR and NFKB signaling in ABC patients and translocations in GCB patients
- May be clinically relevant: targeting BCR and BCL2 in ABC but not GCB DE DLBCL

MYC translocation alone?

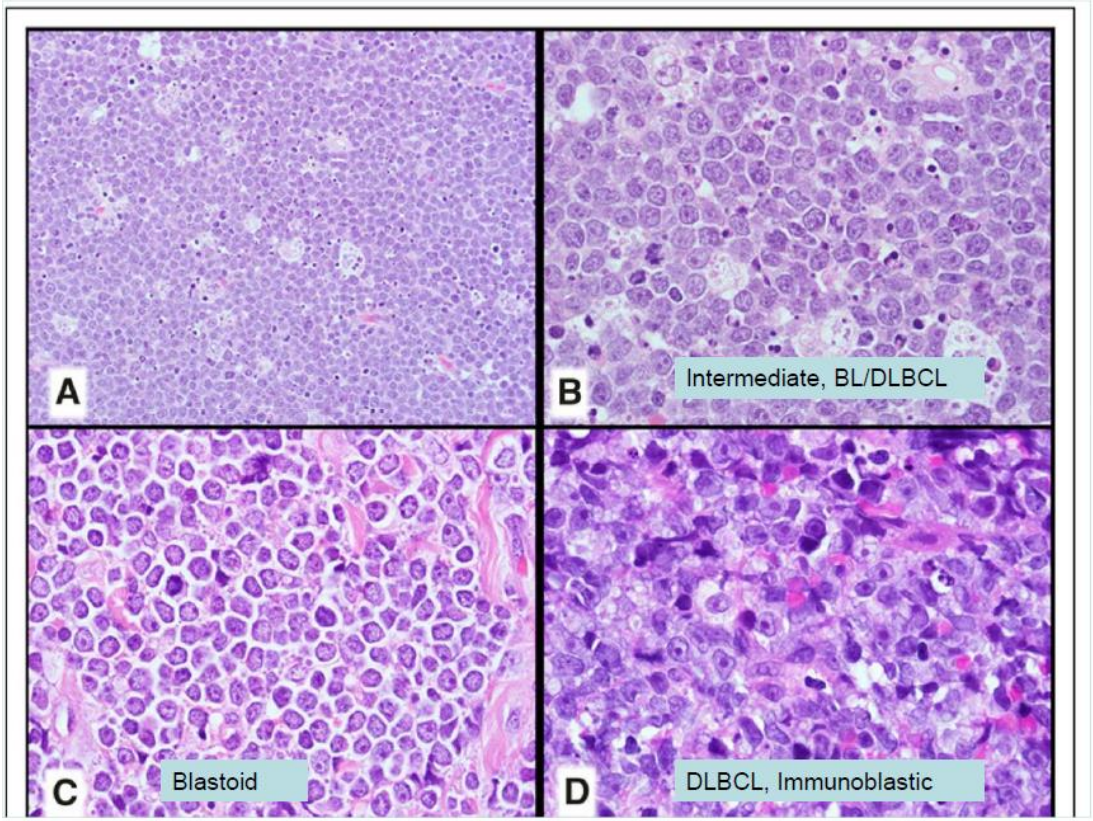
- Pronostic significance ?
- 60 to 80% of those patients still exp BCL2 protein
- In a large cohort of DLBCL the outcome of MYC rearrangement without BCL2 expxression was excellent

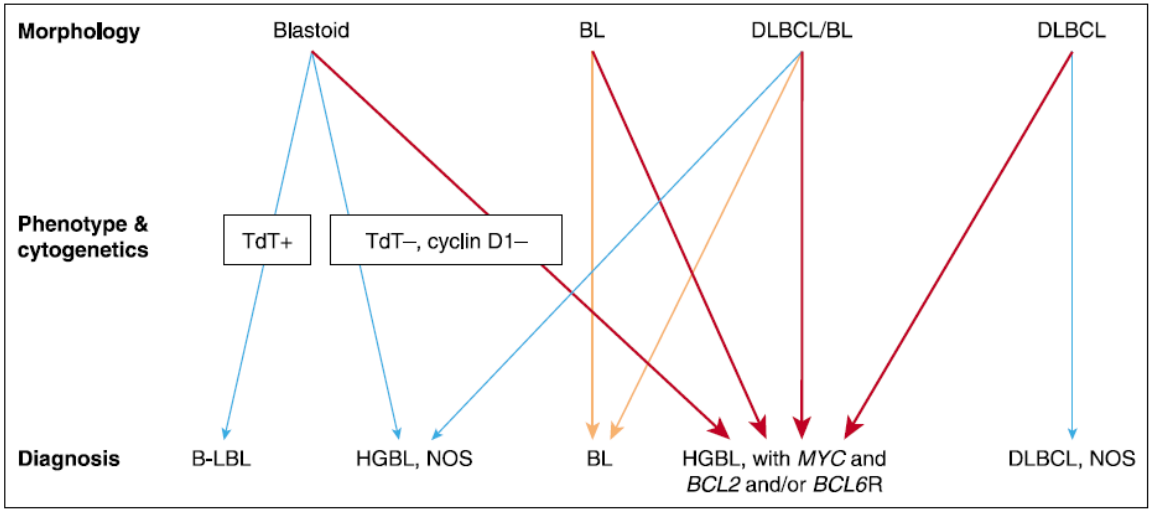
Jonhson NA JCO 2012

Key questions in 2017

- Identification HGBCL
- MYC detection
- Therapeutic impact

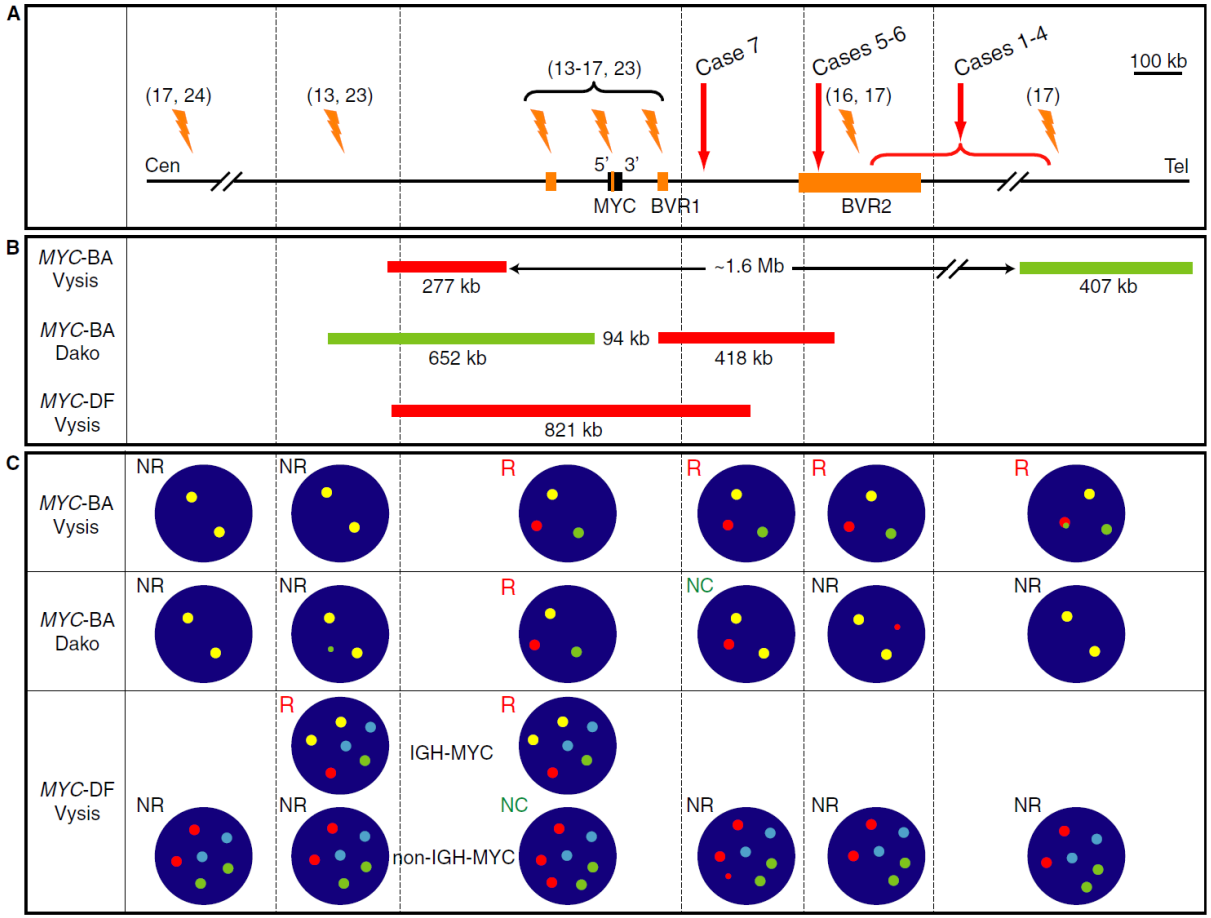
Morphology HGBL-DH





Interphase FISH

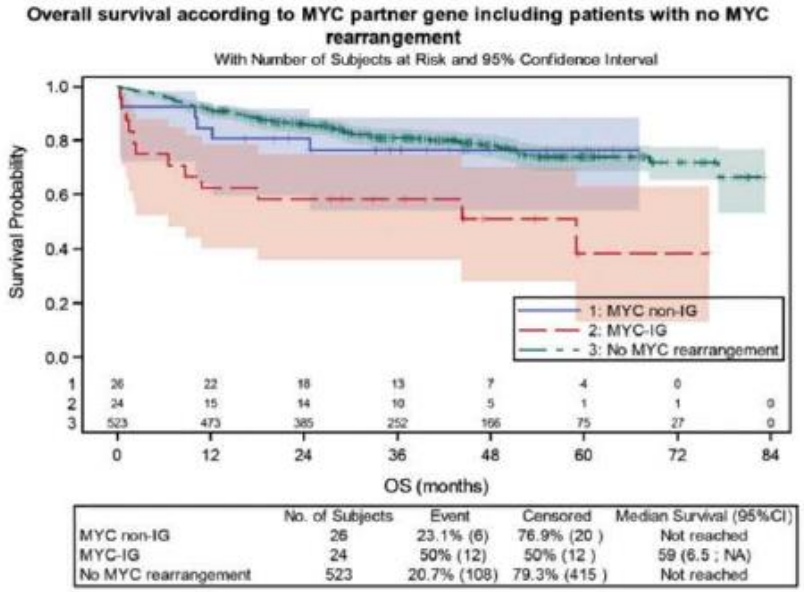
Break apart probes



MYC-IG rearrangements are negative predictors of survival in DLBCL patients treated with immunochemotherapy: a GELA/LYSA study

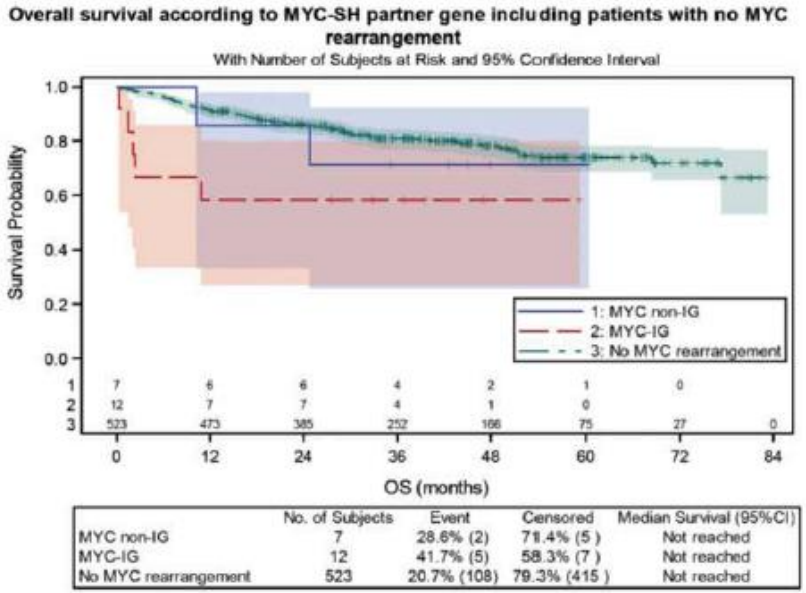
Christiane Copie-Bergman,[1-3] Peggy Cuillière-Dartigues,[4] Maryse Baia,[3] Josette Briere,[5] Richard Delarue,[6] Danielle Canioni,[7] Gilles Salles,[8] Marie Parrens,[9] Karim Belhadj,[10] Bettina Fabiani,[11] Christian Recher,[12] Tony Petrella,[13] Nicolas Ketterer,[14] Frederic Peyrade,[15] Corinne Haioun,[10] Inga Nagel,[16] Reiner Siebert,[16] Fabrice Jardin,[17] Karen Leroy,[1-3] Jean-Philippe Jais,[18] Herve Tilly,[17] Thierry Jo Molina,[19,*] and Philippe Gaulard[1-3,*]

MYC-IG



	No. of Subjects	Event	Censored	Median Survival (95%CI)
MYC non-IG	26	23.1% (6)	76.9% (20)	Not reached
MYC-IG	24	50% (12)	50% (12)	59 (6.5 ; NA)
No MYC rearrangement	523	20.7% (108)	79.3% (415)	Not reached

MYC-SH-IG



	No. of Subjects	Event	Censored	Median Survival (95%CI)
MYC non-IG	7	28.6% (2)	71.4% (5)	Not reached
MYC-IG	12	41.7% (5)	58.3% (7)	Not reached
No MYC rearrangement	523	20.7% (108)	79.3% (415)	Not reached

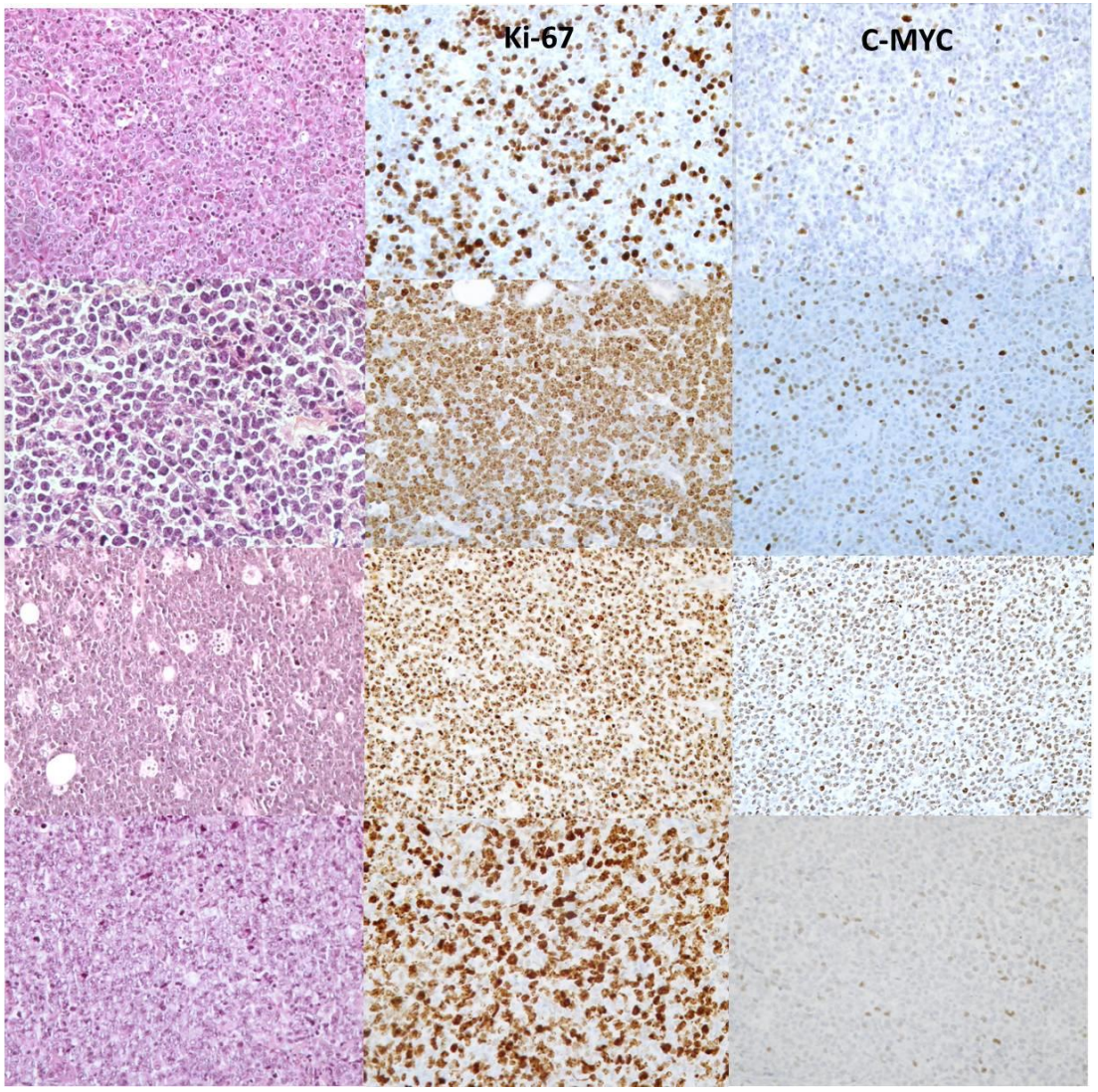
Immunohistochemistry
useful for screening patients who require FISH

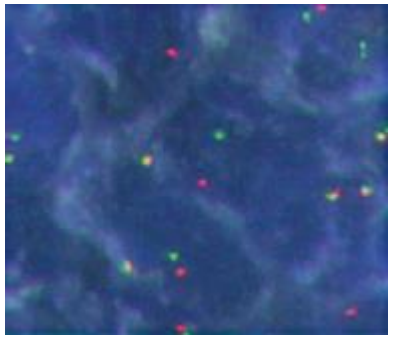
KI67 variable

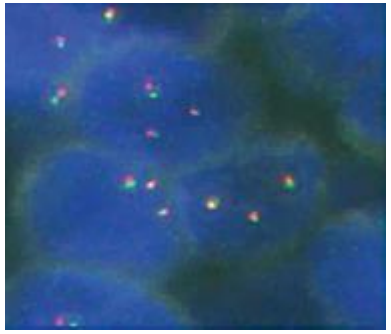
Not a reliable marker for screening

MYC AB clone Y69
Good Reproducibility

Useful for the detection of MYC-R
Threshold of 40%







283 cases agressive B cell lymphomas

Diagnosed in pathology Dept Lyon Sud Hospital, France from 2010 to 2015

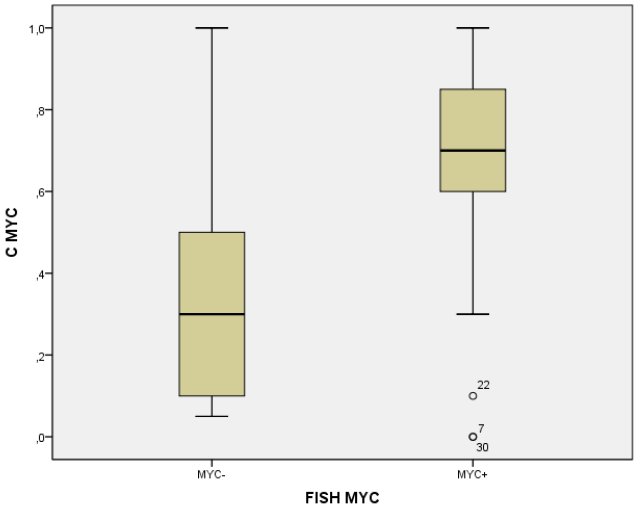
45 FISH MYC+

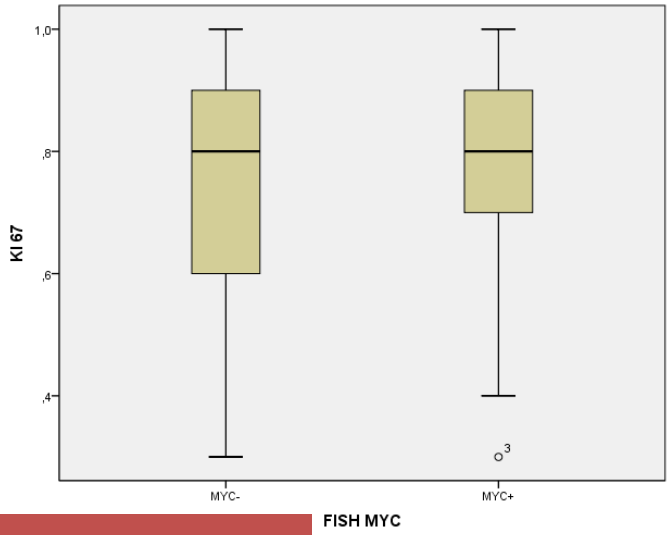
IHC MYC+/MYC- p<0,05

BCL-U AND IMMUNOBLASTIQUE

GC>ABC

No differences KI67/BCL2

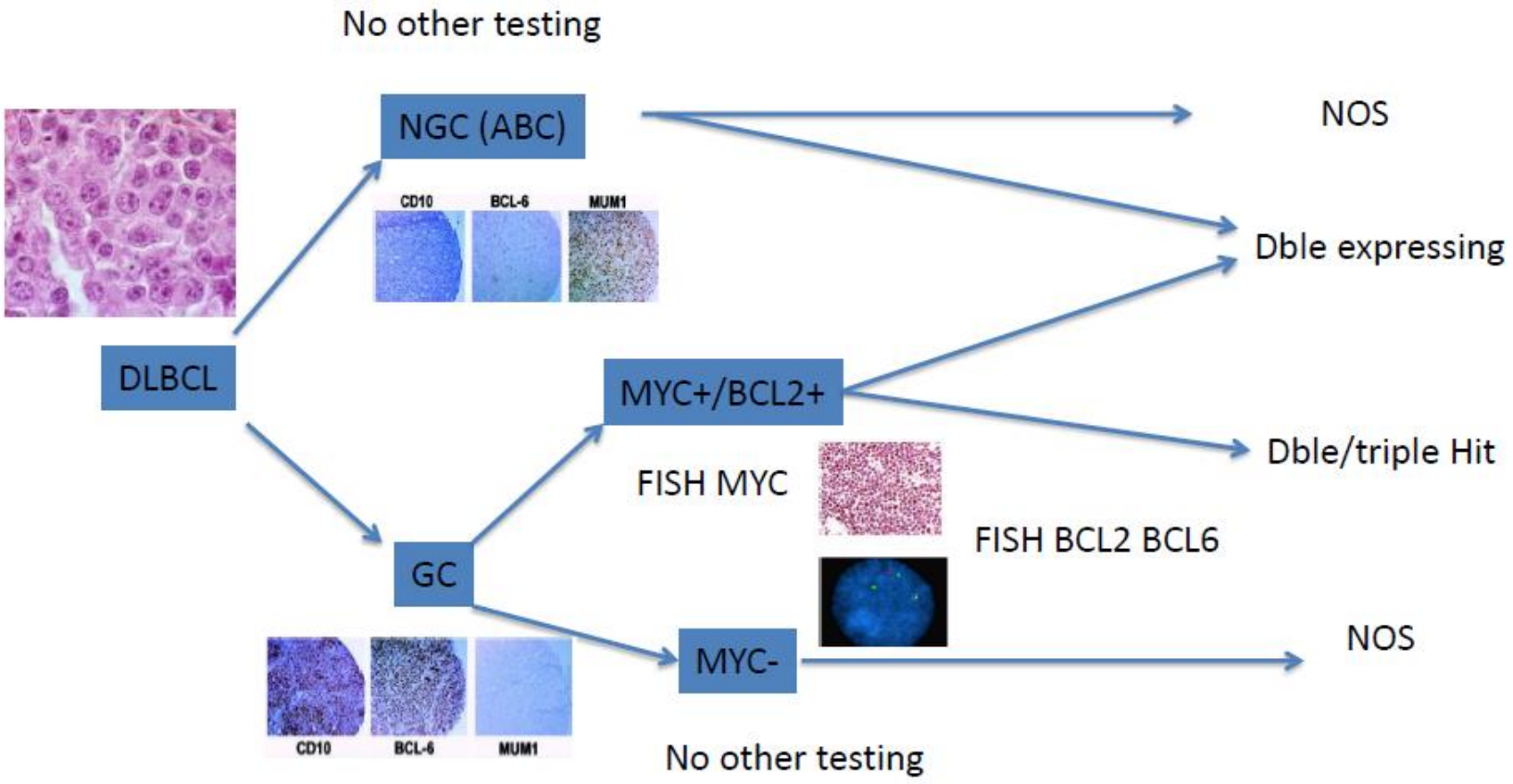




Negative predictive value of <40% MYC expression = absence of MYC R

Unpublished data

Recommendations for FISH screening strategy



Therapeutic impact

- Active BCR signalisation pathway
- BCL2
- PI3K
- P53
- ……

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