Webinars

Cutaneous Lymphoma

EuroBloodNet Topic on Focus

Primary cutaneous Diffuse Large B-cell Lymphoma, Leg Type

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INSERM U 1053 UMR BaRITON; Cutaneous lymphoma oncogenesis team;
ERN-EuroBloodNet subnetwork cutaneous lymphoma
Bordeaux– France, November 2020

Co-funded by
the Health Programme
of the European Union

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Investigator : Celgene, Roche, BMS, MSD

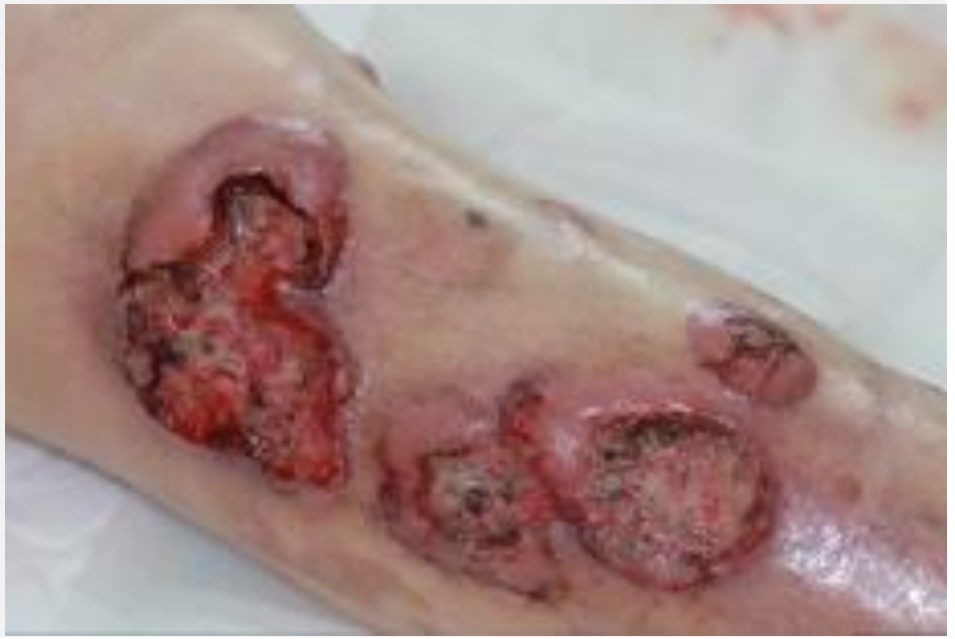
Travel, Accomodation, Expenses: BMS, MSD.

Therapeutic recommendations

First line therapy = Rituximab + polychemotherapy

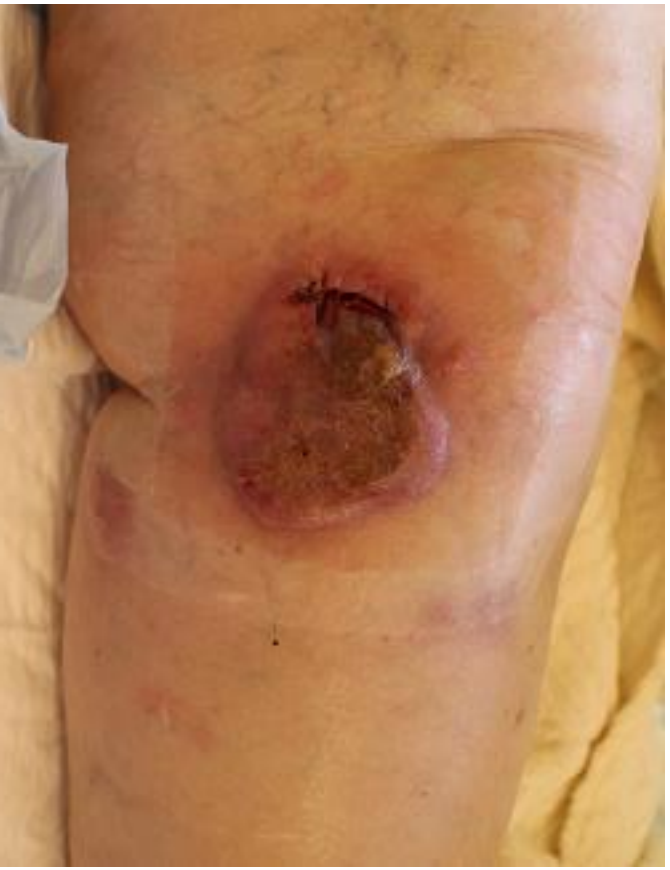
In refractory / relapsing cases ... Which therapy?

- Radiation ?
- Second line chemotherapy?
- Lenalidomide?
- Other targeted therapies ?

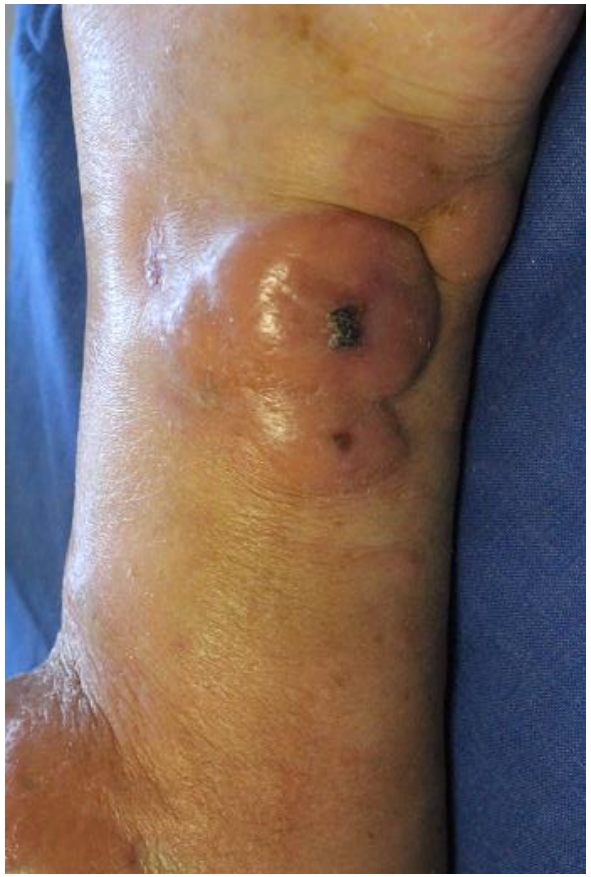


Clinical case : chemoresistance with second line therapy

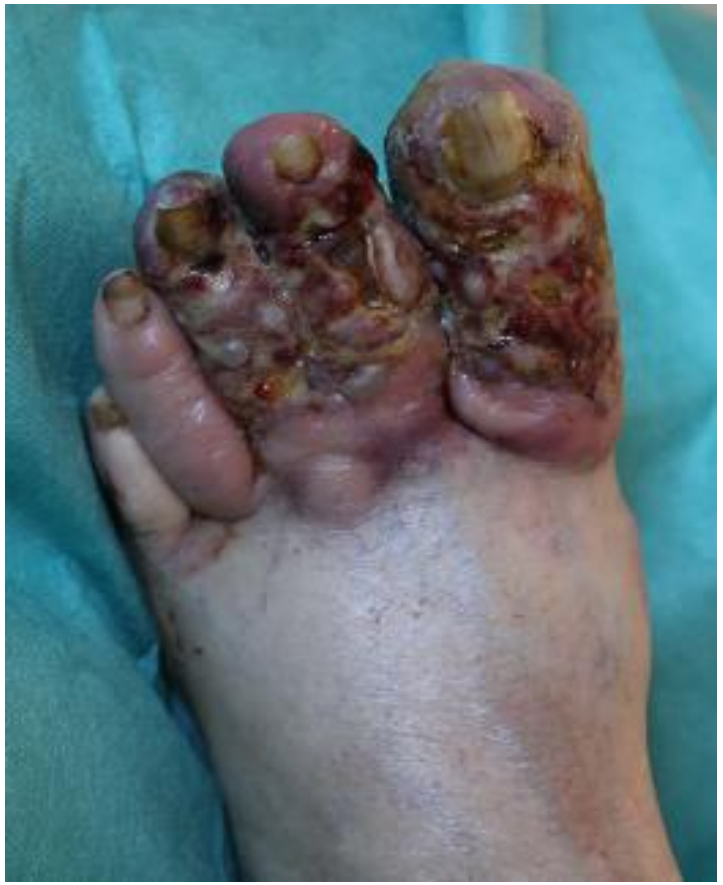
82 years old women
PCDLBCL Leg type (knee)



Cutaneous relapse (leg)
3 months later



Diffuse finger tumor infiltration
while receiving chemo



R-CHOPx6 → CR

Rituximab + Gemcitabine + Oxaliplatine

→ Poor response
→ Impaired quality of life, chemo side effects in elderly

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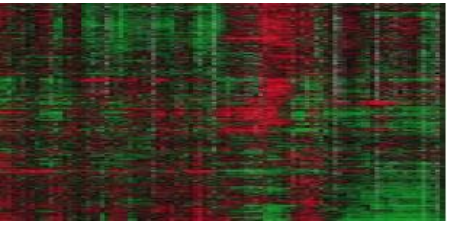
Why to study PCDLBCL Leg type biology?

It is mandatory to :

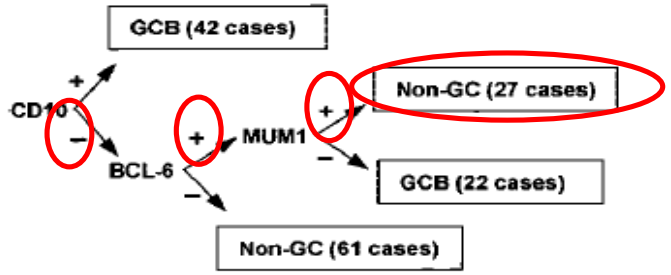
Understang genomic landscape
Oncogenesis mechanisms

→ **To develop new therapies**

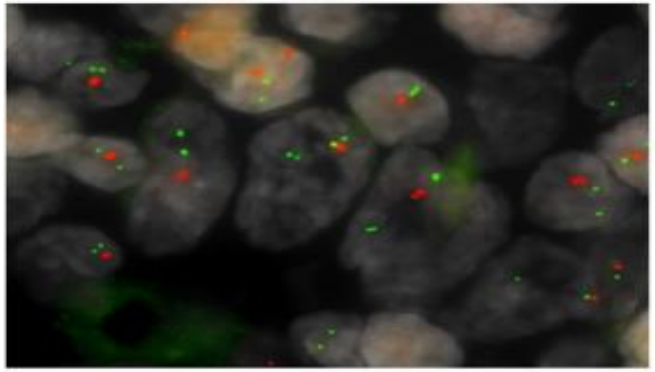
Leg type Lymphoma exhibit same features as ABC DLBCL



Transcriptomic profile

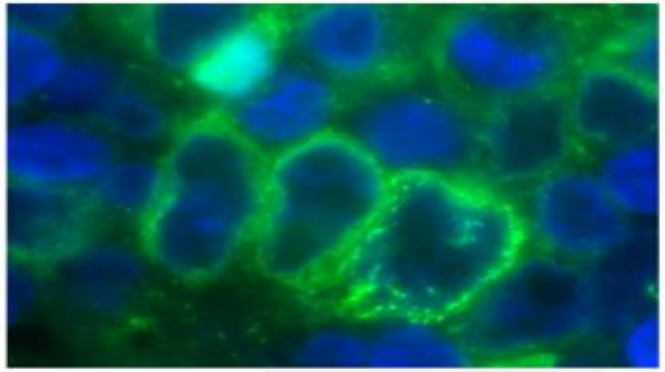


Han's algorythm, immunophenotype



Cmu deletion (switch)

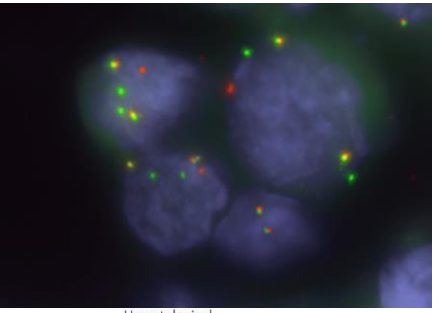
D



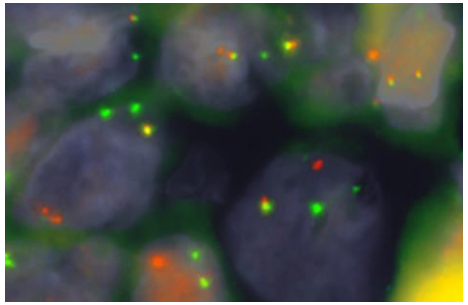
IgM expression

E

Pham-Ledard et al, J Derm Sci, 2017,



FISH *BCL6*



FISH *MYC*

- Transcriptomic and phenotypic profile consistent with ABC DLBCL

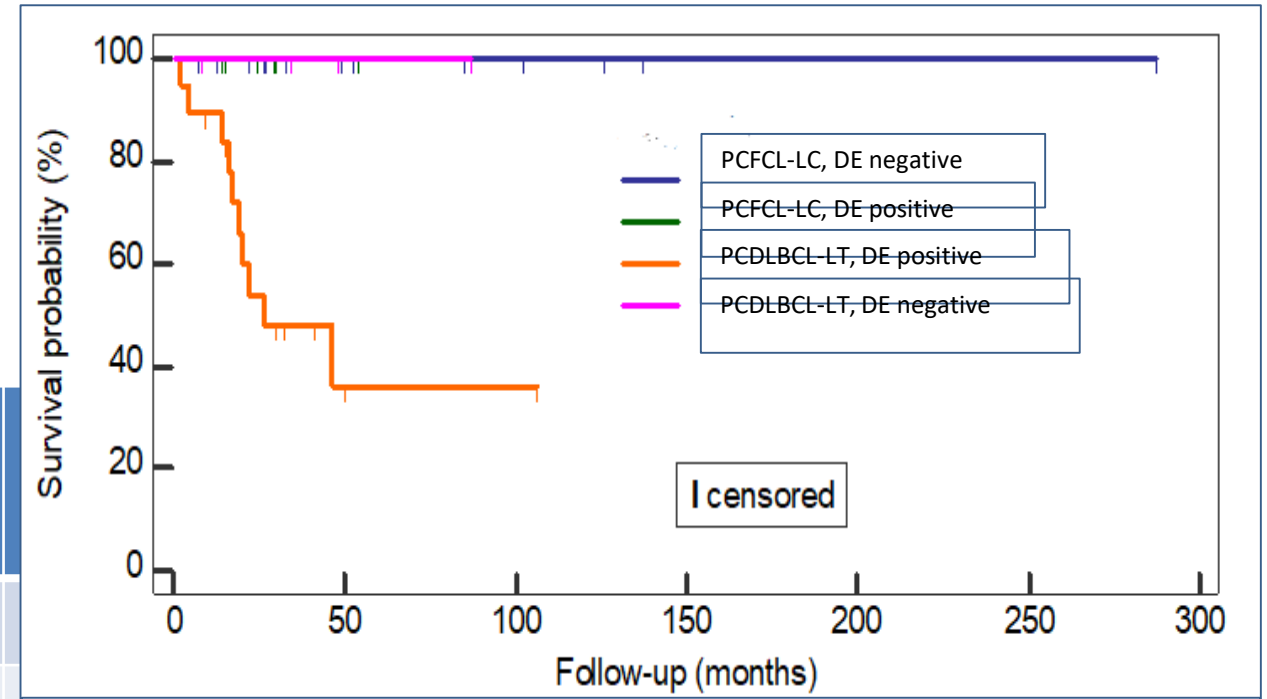
Hoefnagel et al, Blood, 2005
Menguyet al, Histopathology 2019

- IgH Gene analysis: post germinal-center profile

- Oncogene alterations
  - **CDKN2A/ p16 deletion**
  - **MYC (10-30%),** BCL6 (25%)
  - No BCL2 (0%)
- = as DLBCL, ABC (non GC) subtype

Controversies about MYC/BCL2 Hit / Dual Expression

	BCL2 split				
Pham-Ledard et al., 2013	1/23 (4%)				
Lucioni et al., 2016	1/20 (5%)				
Menguy et al., 2018	0/23				
Schrader et al., 2018			14/44 (32%)	2/44 (4%)	28/43 (65%)



Poor Specific survival in PCDLBCL leg type with BCL2-MYC expression

MYC split (in this study)
Associated with **reduced specific survival and disease free survival** but not for overall survival

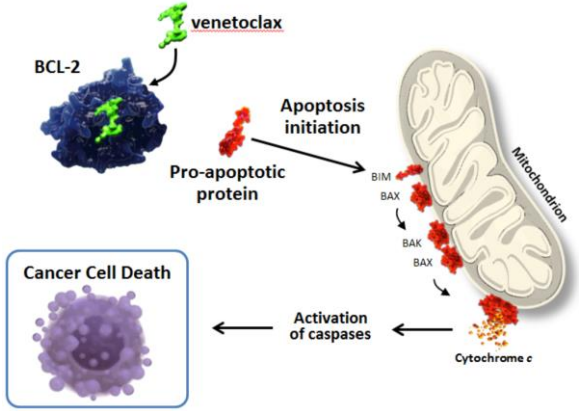
DH = Very rare event

DE=Frequent Prognosis impact?

Successful Treatment of Primary Cutaneous Diffuse Large B-Cell Lymphoma Leg Type With Single-Agent Venetoclax

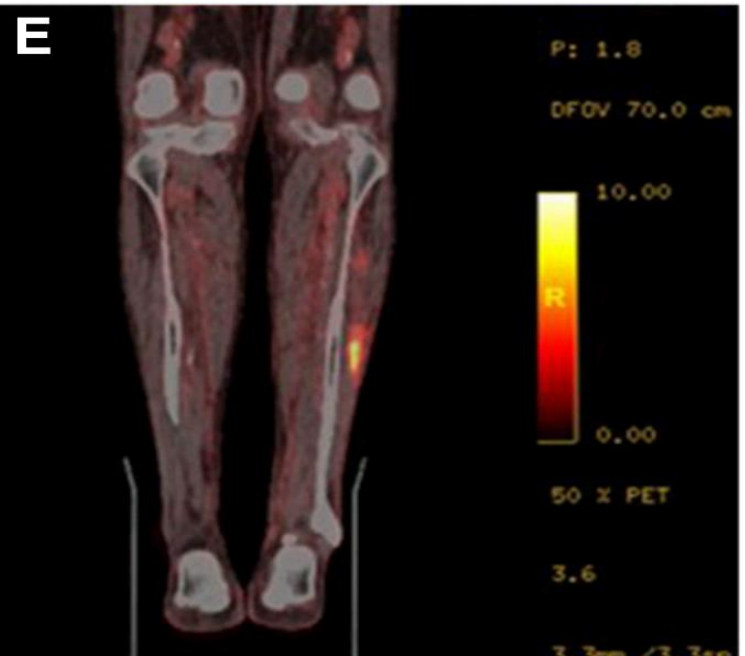
Harriet S. Walter, MBChB, PhD[1,2]; Christopher S. Trethewey, MSc[1]; Matthew J. Ahearne, MBChB, MD[1,2]; Ross Jackson[1]; Sandrine Jayne, PhD[1]; Simon D. Wagner, MD, PhD[1,2]; Gerald Saldanha, MBChB[1,2]; and Martin J.S. Dyer, MD, DPhil[1,2]

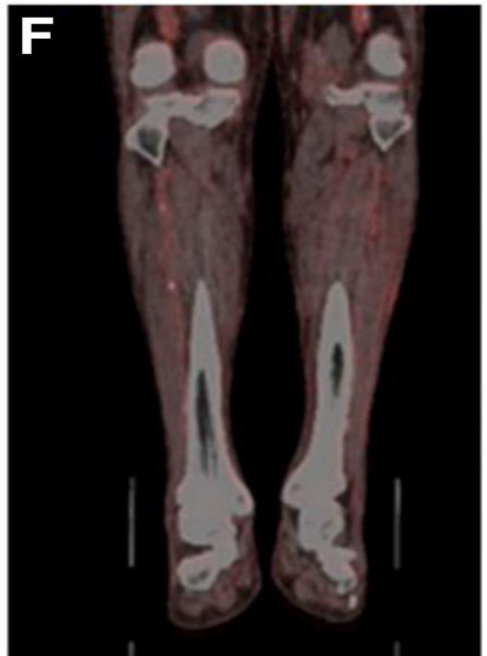
BCL2 Inhibitor Venetoclax

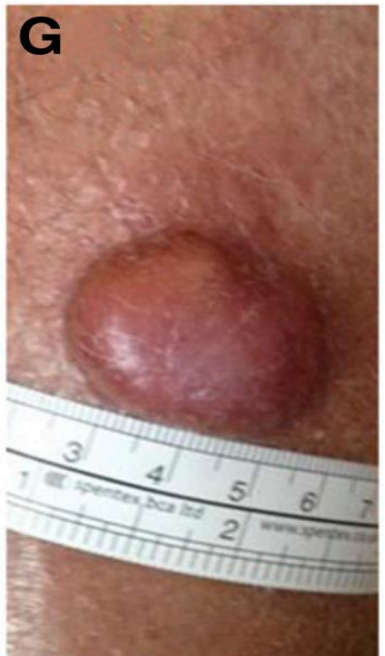


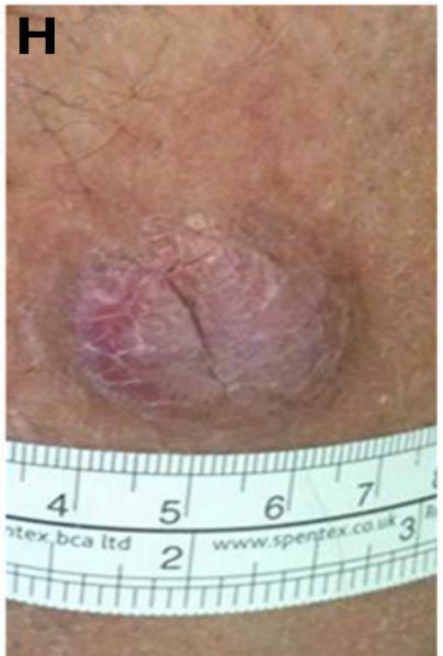
- Active in DLBCL with BCL2 alterations (ampli/DH)
- In PCDLBCL leg type: no *BCL2* mutation/ampli/hit
- **BCL2 strong expression**

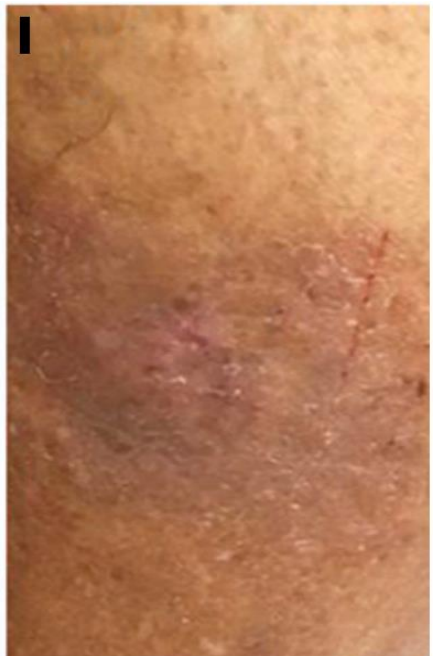
75 years old man, Refractory to poly chemo
***MYD88* WT, *BCL2* WT**











Next generation sequencing in Leg type Lymphoma

ORIGINAL ARTICLE

See related commentary on pg 1831

Identification of Somatic Mutations in Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type by Massive Parallel Sequencing

Sylvain Mareschal[1], Anne Pham-Ledard[2,3], Pierre Julien Viailly[1], Sydney Dubois[1], Philippe Bertrand[1], Catherine Maingonnat[1], Maxime Fontanilles[1], Elodie Bohers[1], Philippe Ruminy[1], Isabelle Tournier[4], Philippe Courville[5], Bernard Lenormand[5], Anne Bénédicte Duval[5], Emilie Andrieu[5], Laurence Verneuil[6], Beatrice Vergier[2,3], Hervé Tilly[1], Pascal Joly[4], Thierry Frebourg[4], Marie Beylot-Barry[2,3], Jean-Philippe Merlio[2,3] and Fabrice Jardin[1]

Journal of Investigative Dermatology (2018) **138**, 2365–2376; doi:10.1016/j.jid.2018.04.038

ORIGINAL ARTICLE

Genomic Analyses Identify Recurrent Alterations in Immune Evasion Genes in Diffuse Large B-Cell Lymphoma, Leg Type

Xiaolong Alan Zhou[1,12], Abner Louissaint Jr.[2,3,12], Alexander Wenzel[4], Jingyi Yang[4,5], Maria Estela Martinez-Escala[1], Andrea P. Moy[2,3], Elizabeth A. Morgan[6], Christian N. Paxton[7], Bo Hong[8], Erica F. Andersen[8], Joan Guitart[1], Amir Behdad[9], Lorenzo Cerroni[10], David M. Weinstock[3,11] and Jaehyuk Choi[1,4,5]

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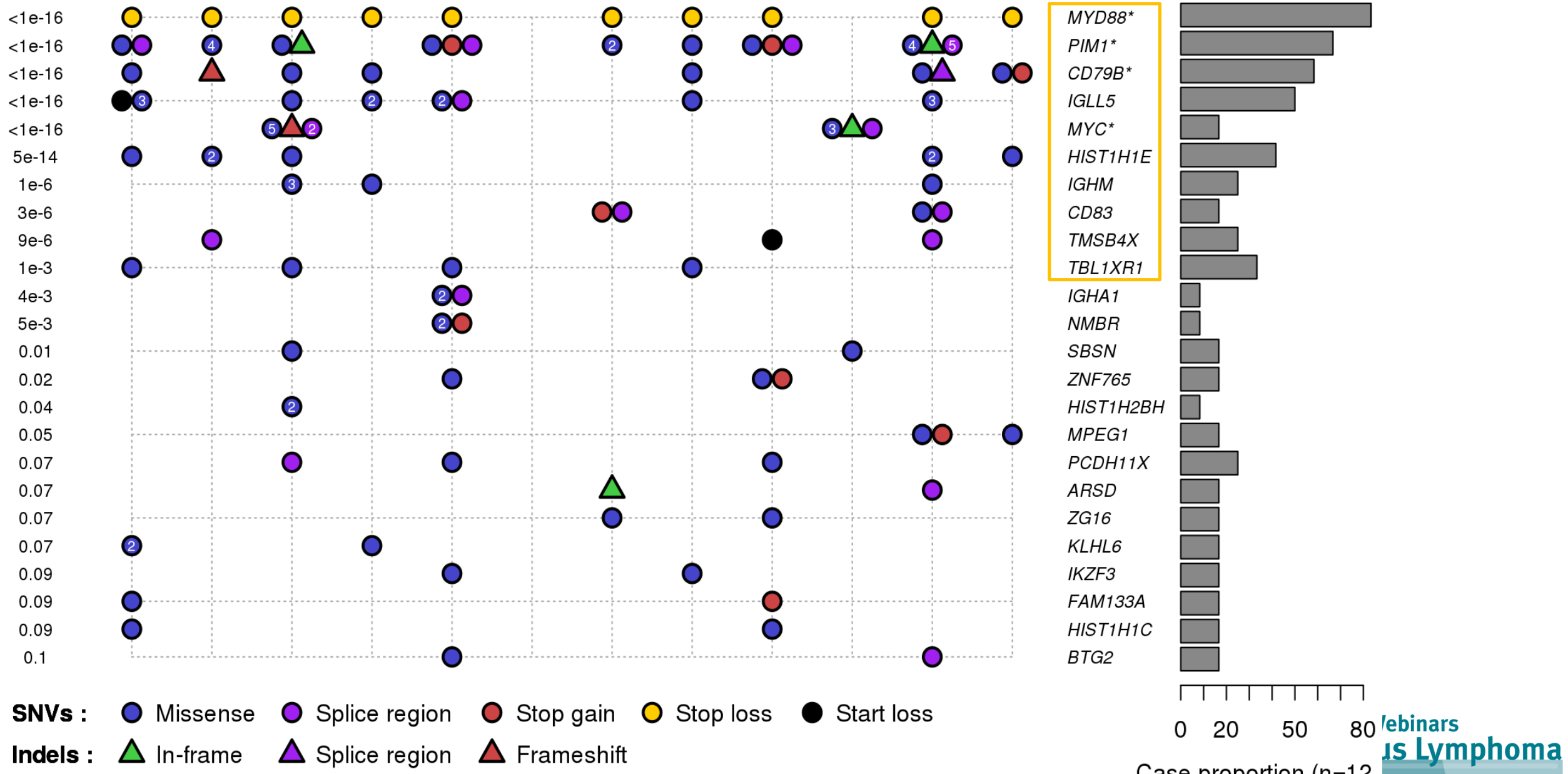
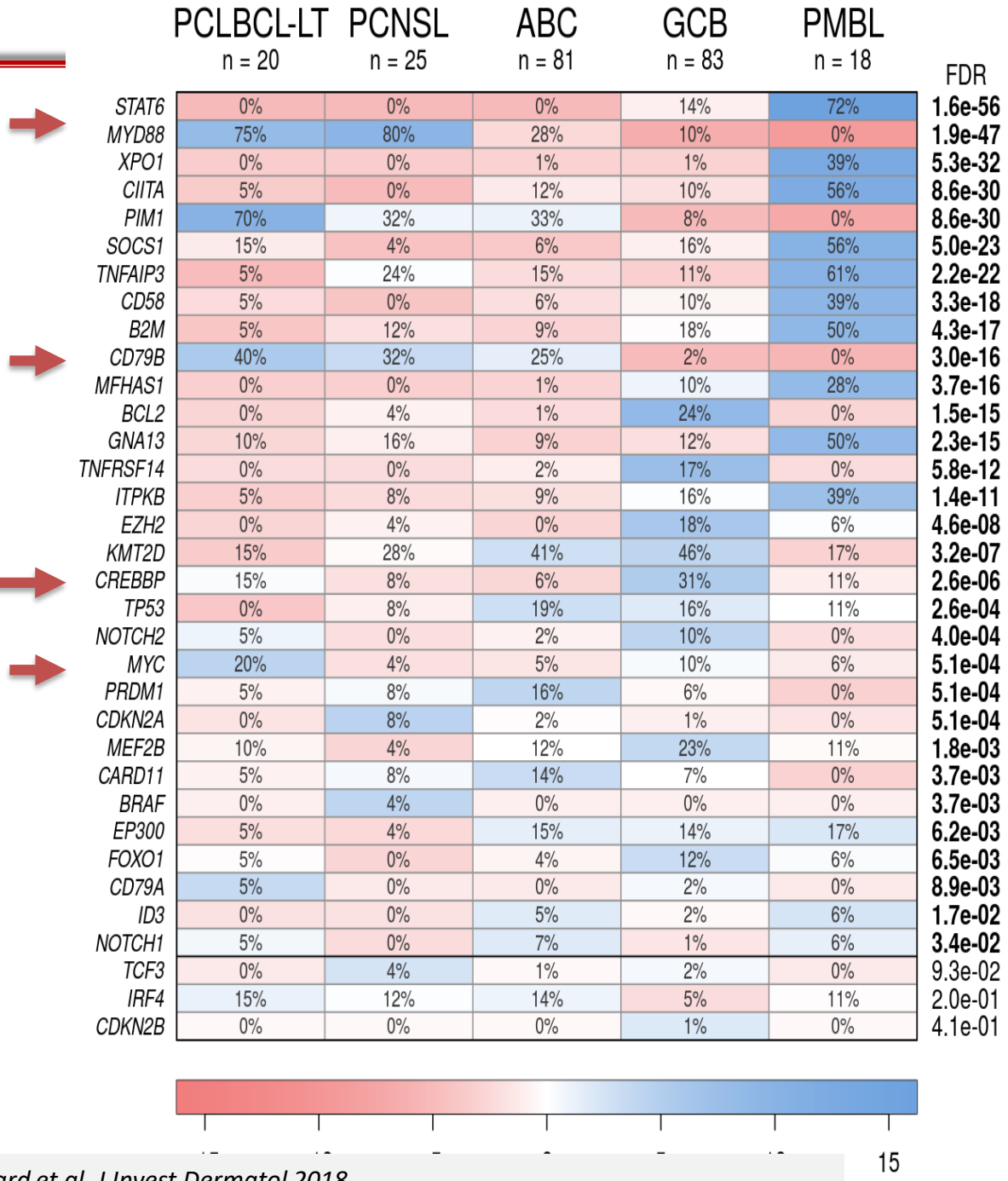
NGS profile: confirms MYD88 frequency and shows recurrent genes mutations



Mareschal, Pham-Ledard et al, J Invest Dermatol 2018



Mutations in PCDLBCL-leg type: closer pattern to CNS (Central Nervous System) than other DLBCL

- High *MYD88*
- *PIM1*
- *CD79B*
- *TBL1XR1*: 30%

- *CREBBP*
- *MYC*
- *IRF4*

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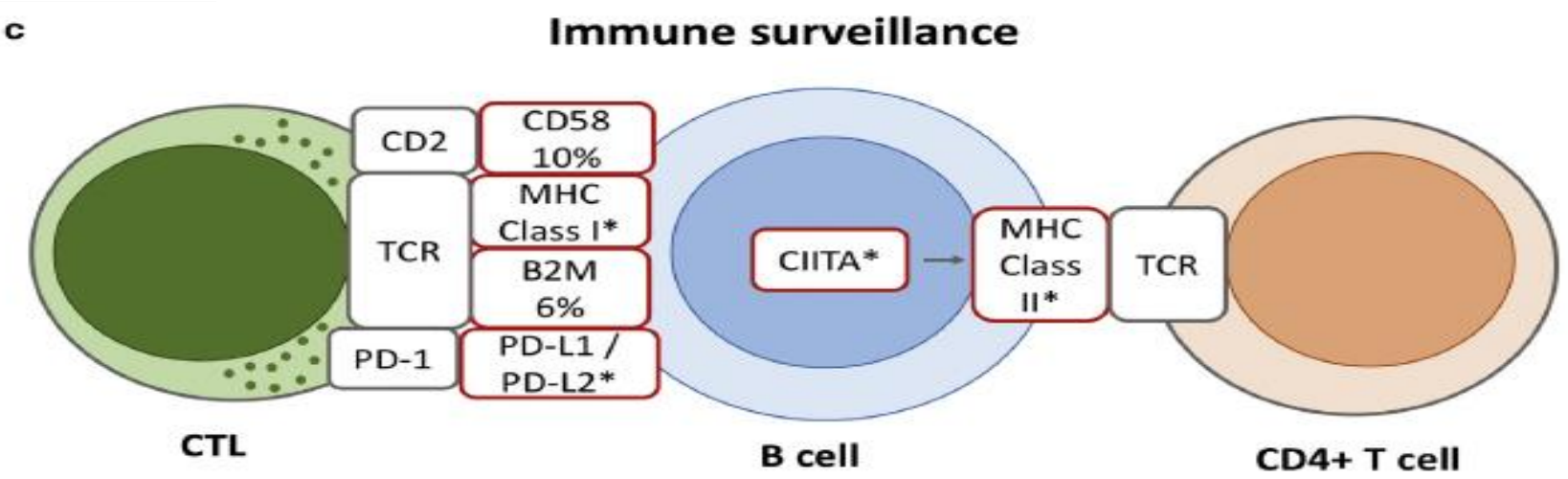
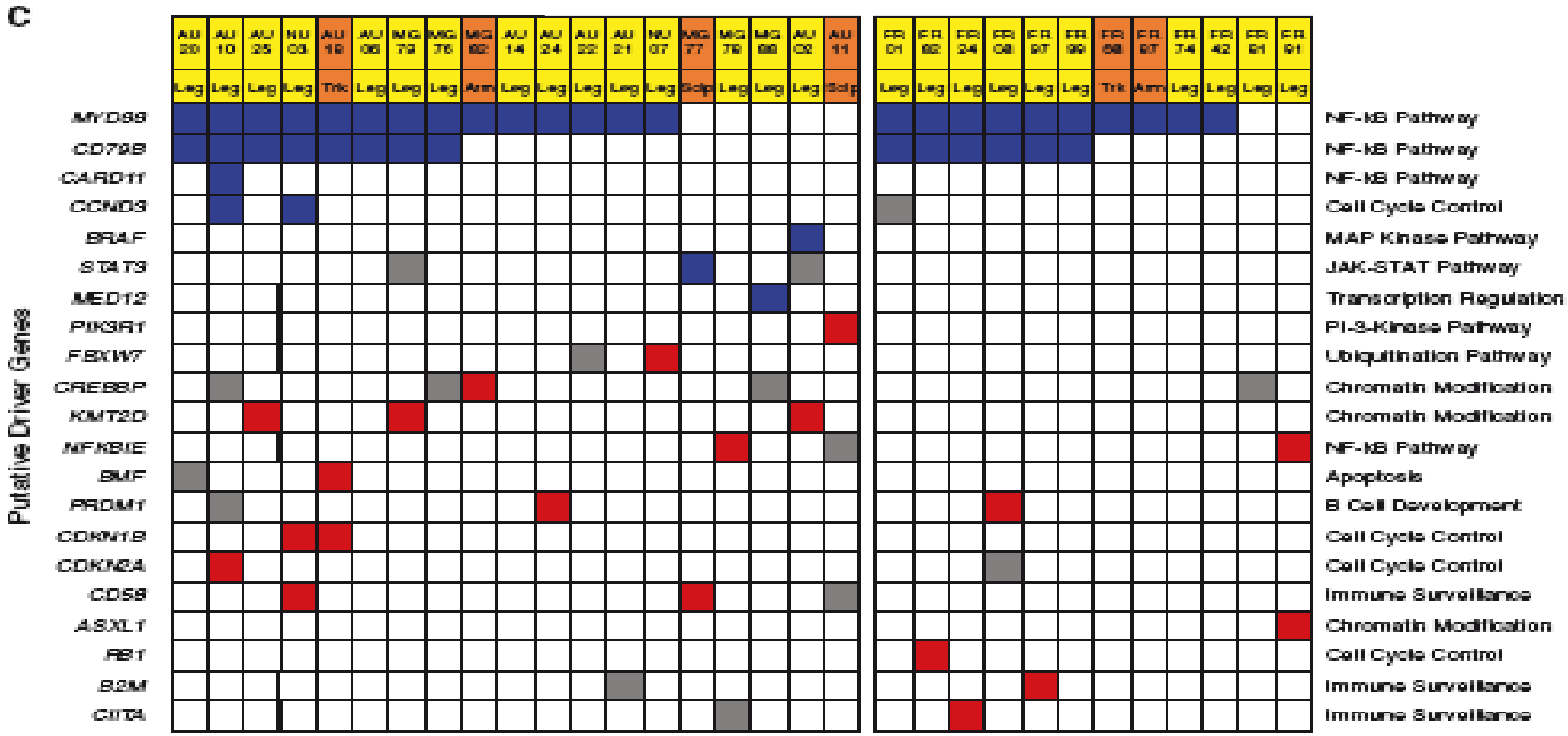
Mareschal, Pham-Ledard et al, J Invest Dermatol 2018

Mutations activating NFkB pathway / Immune Surveillance

Zhou et al, J Invest Dermatol, 2018





Genes involved in

- **antigen presentation**
- **T-cell co-stimulation**

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Genetic landscape of PCDLBCL Leg -Type

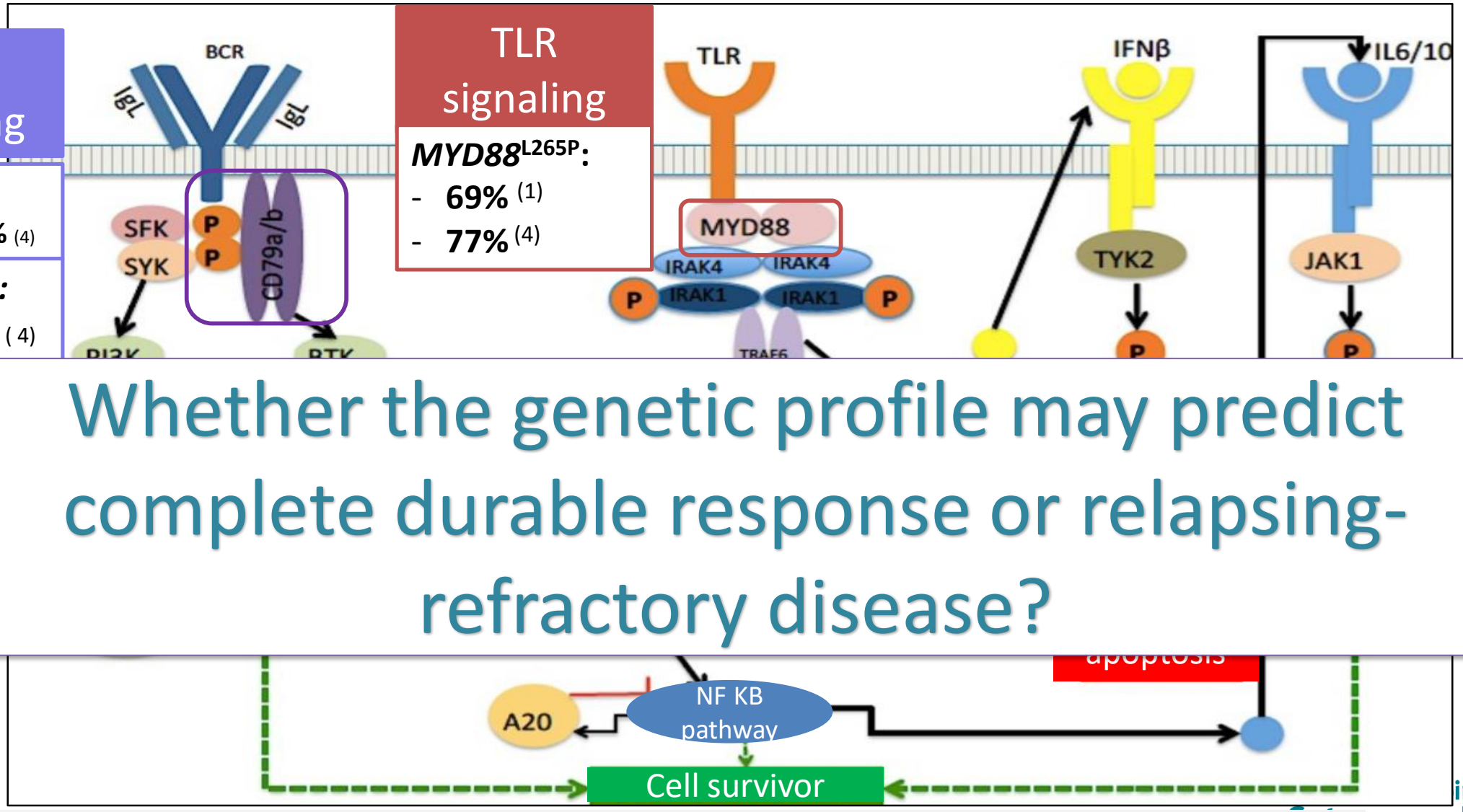
BCR signaling

***CD79B*:**
40 % (3)/ **45%** (4)

CARD11:
10% (2), **3%** (4)

TLR signaling

***MYD88*^{L265P}:**
- **69%** (1)
- **77%** (4)



Whether the genetic profile may predict complete durable response or relapsing-refractory disease?

European Reference Network

(1) *Pham-Ledard et al. J Invest Dermatol. 2012; (2) Koens L et al. J Invest Dermatol. 2014 ;*
(2) *(3) Mareschal J et al. J Invest Dermatol. 2012 (4) Zhou et al. J Invest Dermatol. 2019*

Targeted NGS of PCDLBCL leg type : RR versus good response

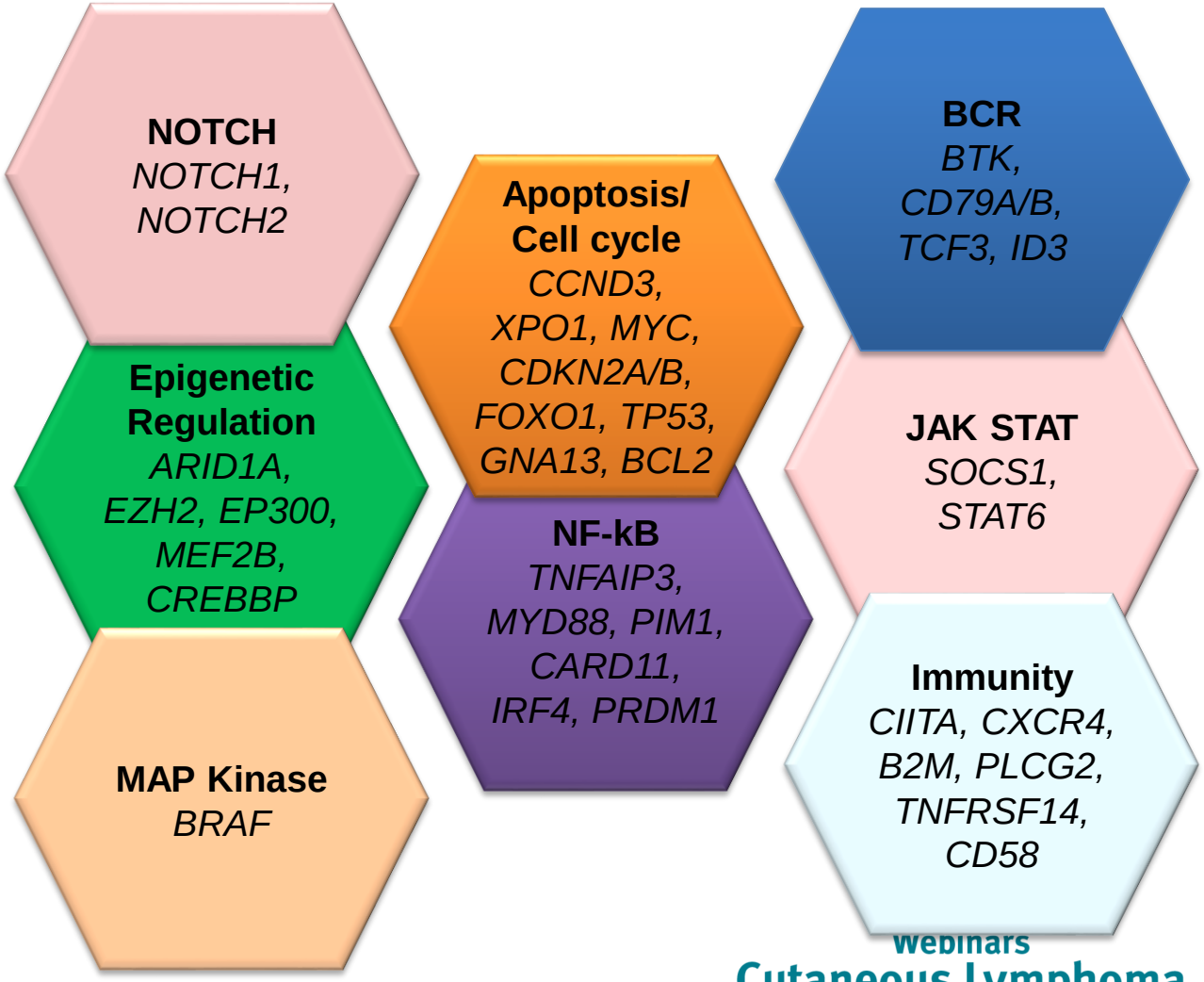
Biopsy at diagnosis
n=32

Refractory/ Relapse n= 18

Responders n= 14

Targeted NGS

Lymphopanel designed for DLBCL targeting 36 genes



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Ducharme O et al, J Invest Dermatol. 2019

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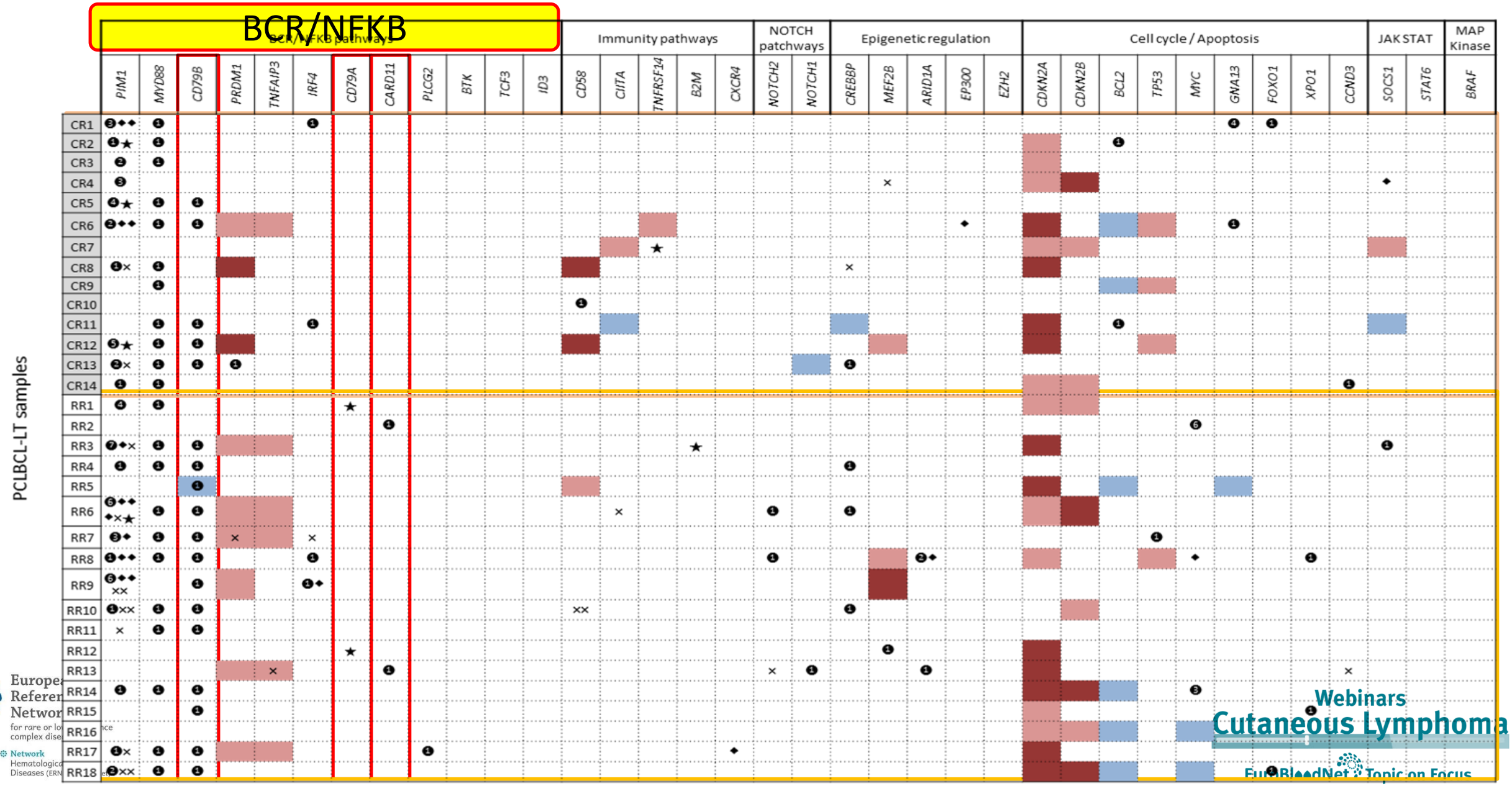
More BCR signaling mutations (CD79A/B / CARD11) in the RR subgroup



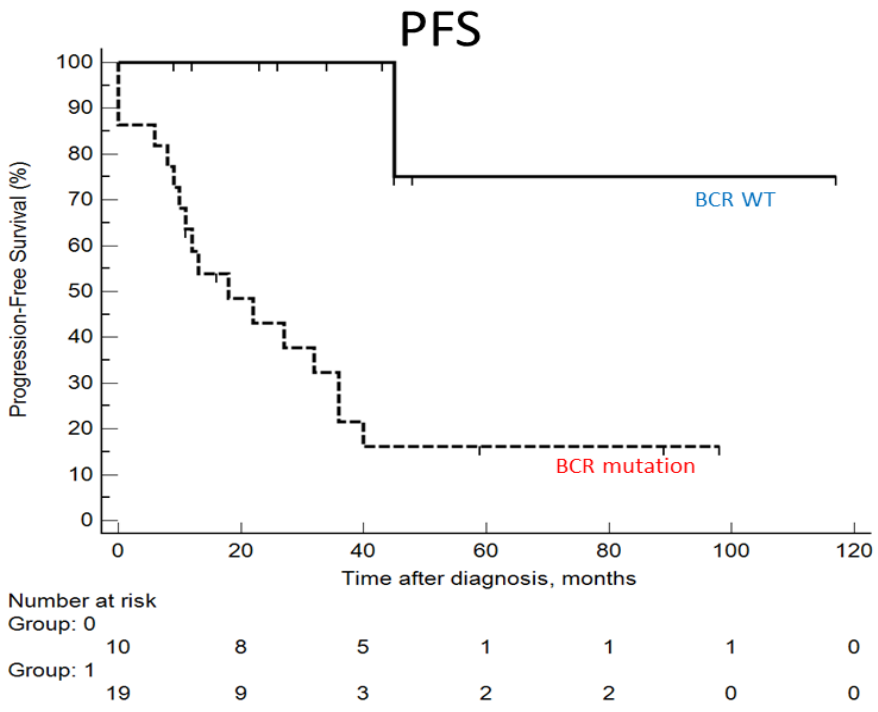
Ducharme O et al, J Invest Dermatol. 2019

ORIGINAL ARTICLE

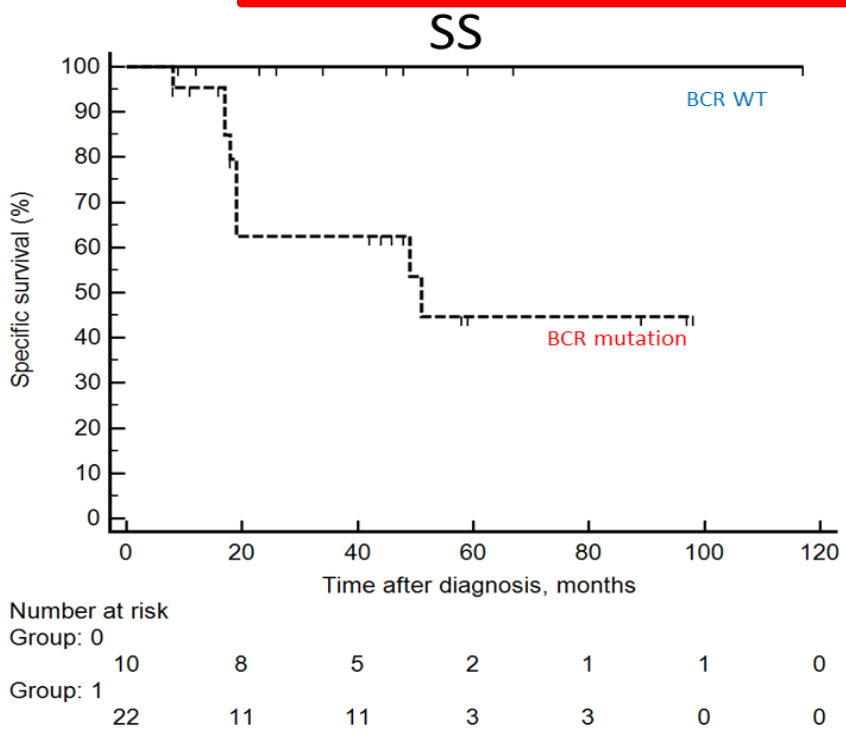
Mutations of the B-Cell Receptor Pathway Confer Chemoresistance in Primary Cutaneous Diffuse Large B-Cell Lymphoma Leg Type

Océane Ducharme[1,2], Marie Beylot-Barry[1,2], Anne Pham-Ledard[1,2], Elodie Bohers[3], Pierre-Julien Viailly[3], Thomas Bandres[4], Nicolas Faur[4], Eric Frison[5], Béatrice Vergier[2,6], Fabrice Jardin[3], Jean-Philippe Merlio[2,4] and Audrey Gros[2,4]

Patients with BCR mutation displayed a reduced PFS and specific survival

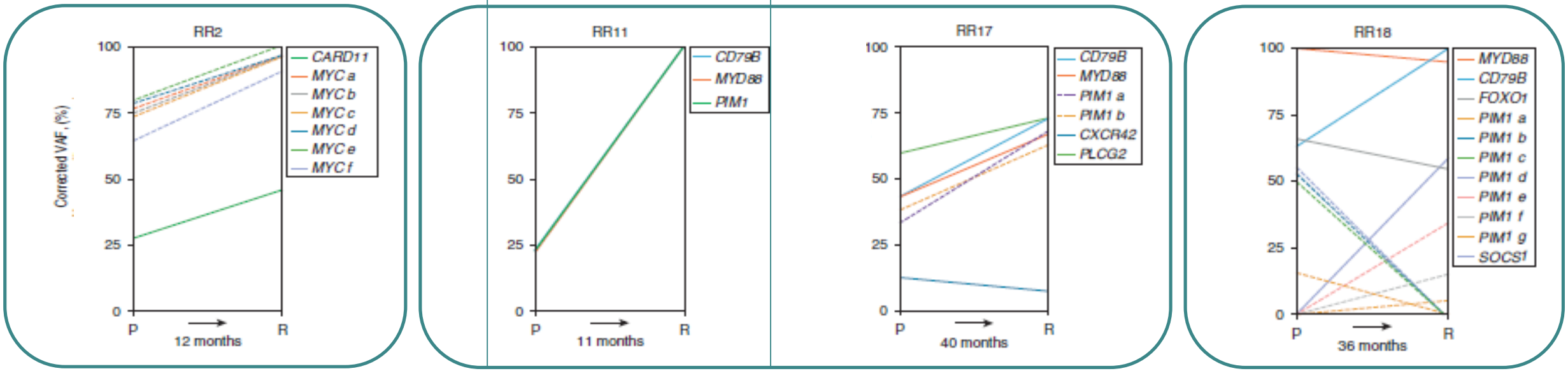


Median 18 months, Log-rank, *P=0.002*
not reached in the wild-type group



Median 51 months, Log-rank, *P=0.03*
not reached in the wild-type group

Clonal selection between diagnosis and relapse: BCR and *MYD88* mutations



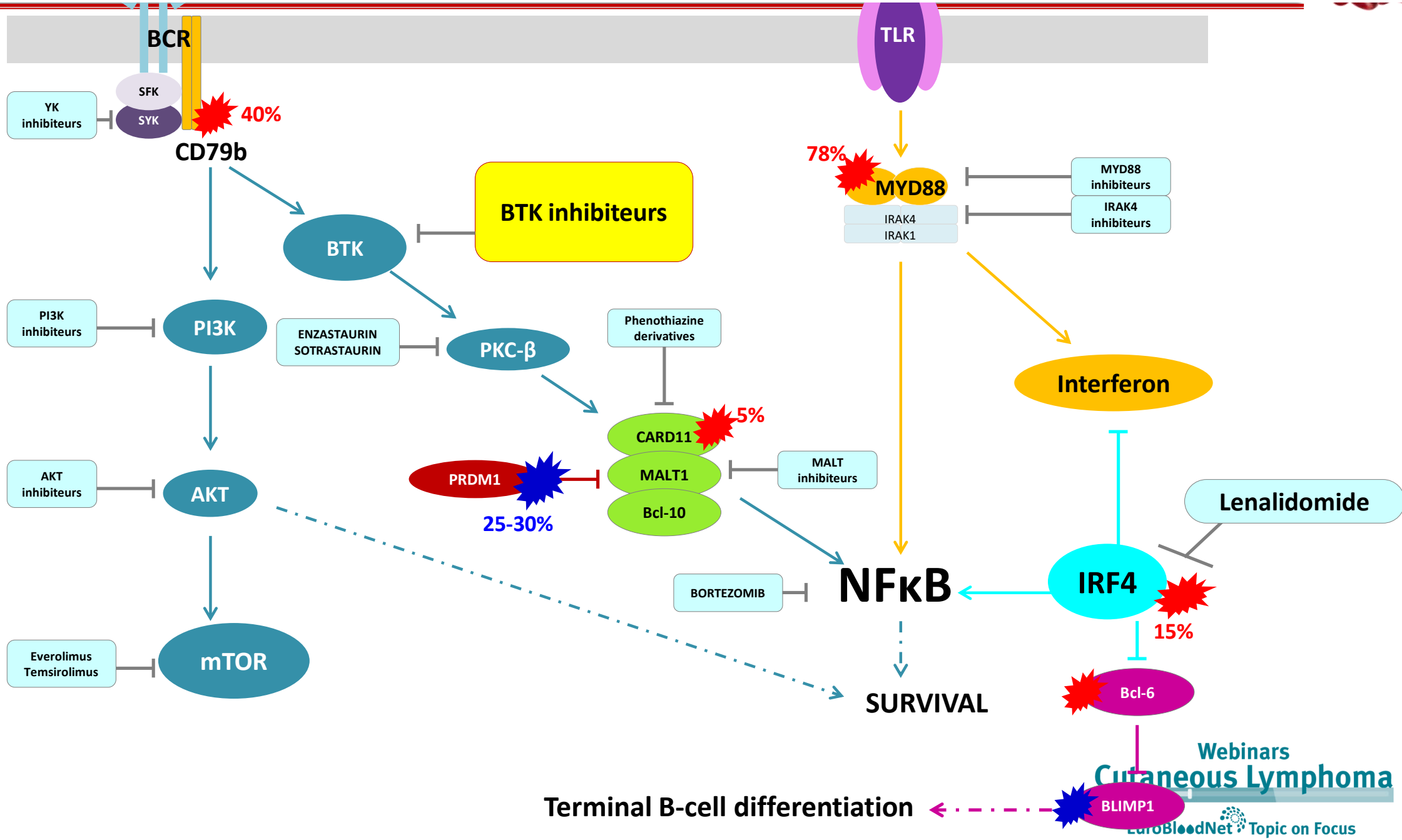
VAF enrichment of primary mutations affecting

- *CD79B*
- *CARD11*
- *MYD88*

→ **pivotal role in disease oncogenesis**

Ducharme O et al, J Invest Dermatol. 2019

BCR targeting in these patients?



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BCR inhibitor IBRUTINIB in PCDLBCL Leg type

Rare Tumors 2015

Excellent outcome of immunomodulation or Bruton's tyrosine kinase inhibition in highly refractory primary cutaneous diffuse large B-cell lymphoma, leg type

Eva Gupta,[1] Joseph Accurso,[2] Jason Sluzevich,[3] David M. Menke,[4] Han W. Tun[1]

[1]Division of Hematology and Oncology, [2]Department of Diagnostic Radiology, [3]Department of Dermatology, [4]Department of Pathology, Mayo Clinic, Jacksonville, FL, USA

Addictive response of primary cutaneous diffuse large B cell lymphoma leg type to low-dose ibrutinib. Pang A, Au-Yeung R, Leung RYY, Kwong YL. Ann Hematol. 2019

complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Case Report

Molecular Mechanisms of Disease Progression in Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type during Ibrutinib Therapy

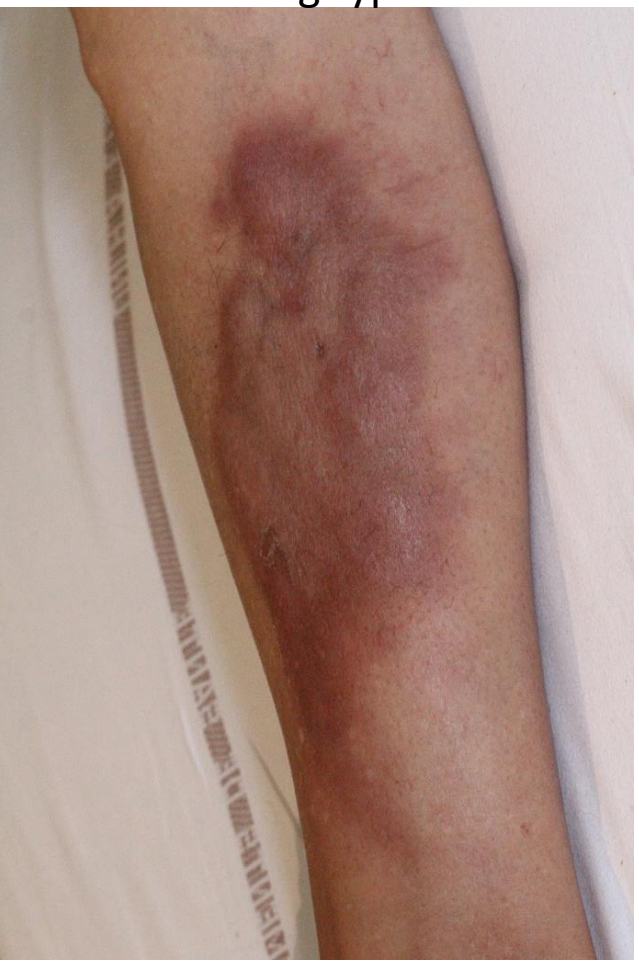
Lucy C. Fox, Costas K. Yannakou, Georgina Ryland, Stephen Lade, Michael Dickinson, Belinda A. Campbell and Henry Miles Prince *

Genomic Alteration	Pre-Ibrutinib (Skin)	Post-Ibrutinib (Node)
Variants	*MYD88* c.794T > C;p.L265P *CD79B* c.586T > C;p.Y196H	*MYD88* c.794T > C;p.L265P *CD79B* c.586T > C;p.Y196H ***CARD11* c.367G > T;p.G123C** ***CARD11* c.644A > T;p.K215M** ***NFKBIE* c.1379G > C;p.G460A**
Copy-number changes	Gain **chr7, chr8,** chr9, **chr10**, 11q, chr12, **19q**, **chrX** Amplification 18q (*BCL2/TNFRSF11A*) Del 4q Homozygous deletion 9p containing *CDKN2A* Second homozygous deletion 9p containing *PTRPD*	Gain 8q, chr9, 11q, chr12, 16p Amplification 18q (*BCL2/TNFRSF11A*) **Del 2q, 4p, 4q, 6p, 7q, 8p, 8q, 16p, 16q, 17p, 17q, 19p,** Homozygous deletion 9p containing *CDKN2A* Second homozygous deletion 9p containing *PTRPD*
Translocation	Not detected	**t(14;16)(q32.33;q24.1) IgH-IRF8**

BTK Inhibitor

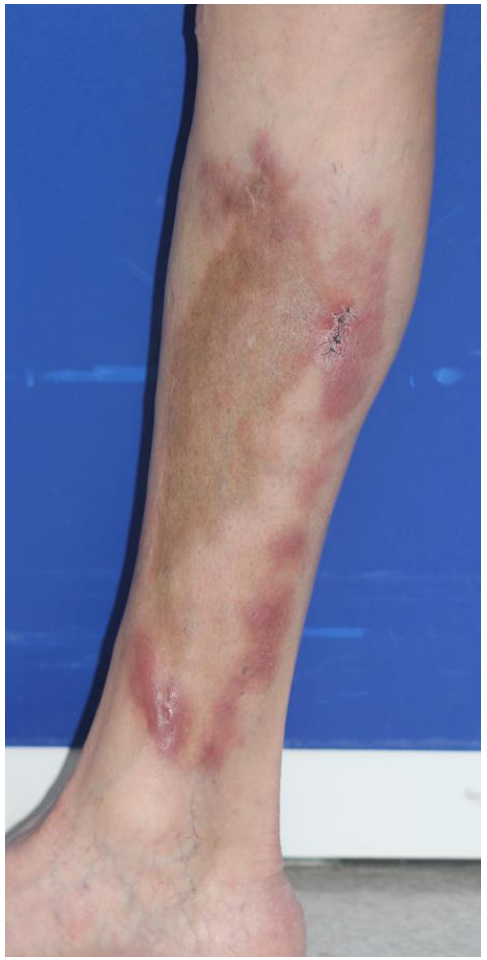
Clinical case with ibrutinib efficacy

July 2019
65 years woman
PCDLBCL Leg type



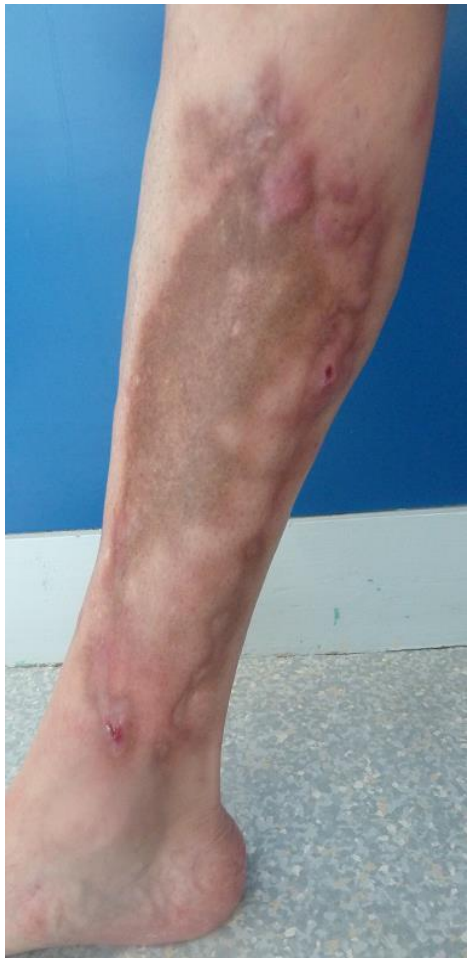
R-CHOPx6→ CR

Feb 2020
3 months later
Cutaneous Relapse



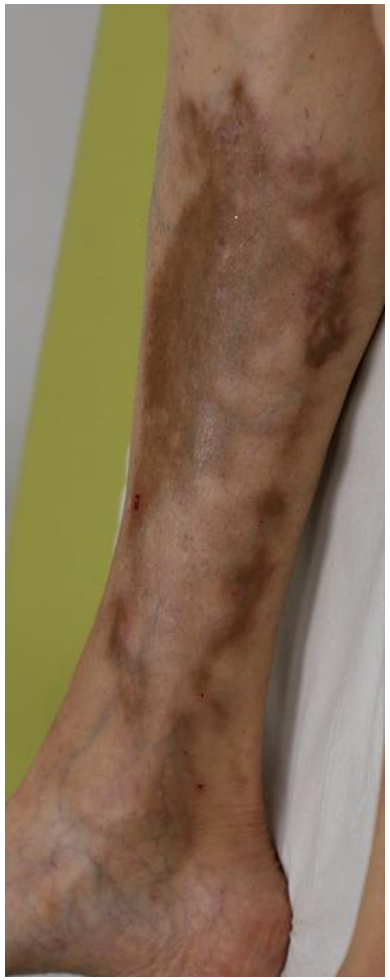
LENALIDOMIDE + Rituximab

June 2020
Lenalidomide refractory



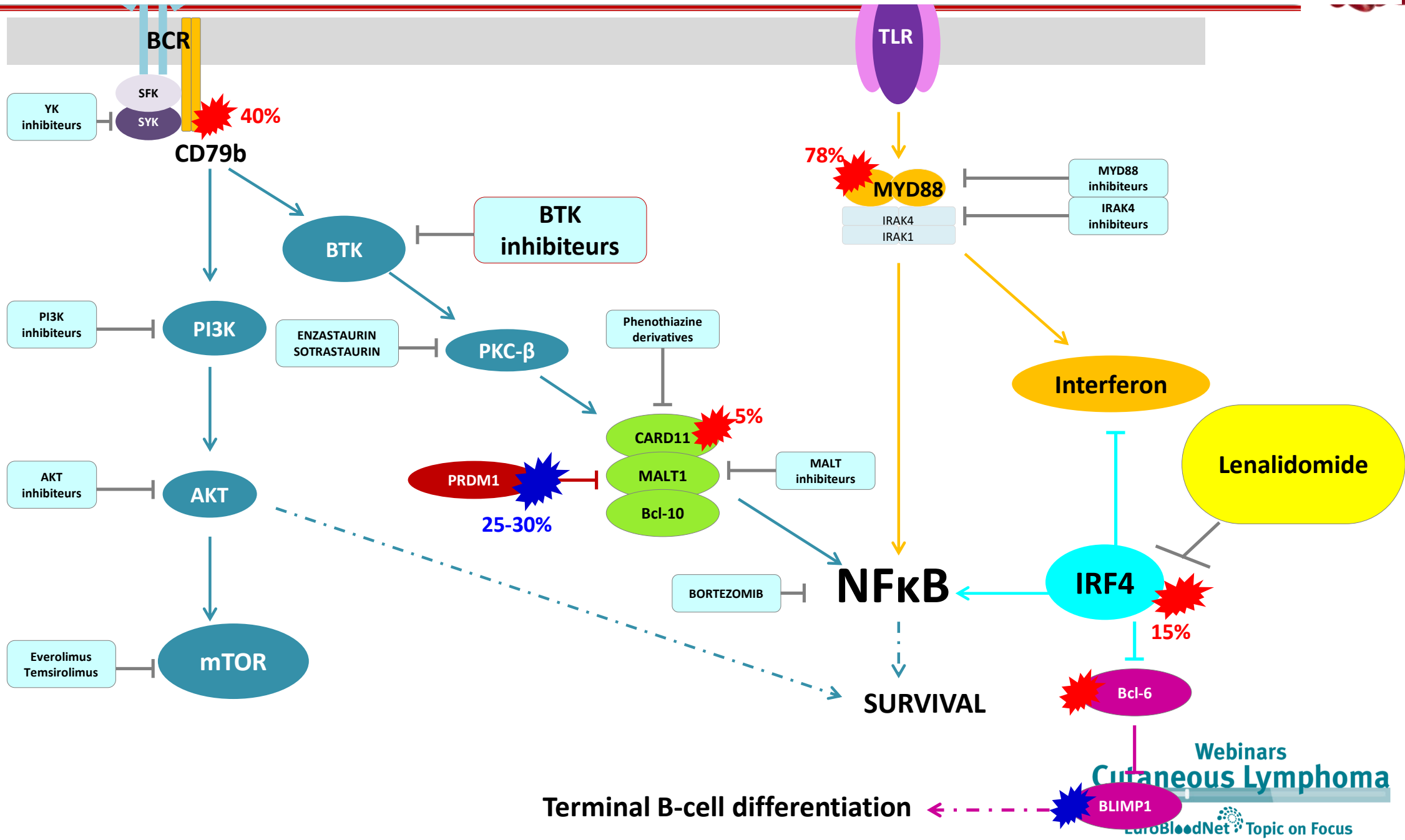
IBRUTINIB

Oct 2020
Complete Remission



Mutations: MYD88, CD79B, PIM1

Lenalidomide in PCDLBCL Leg type?



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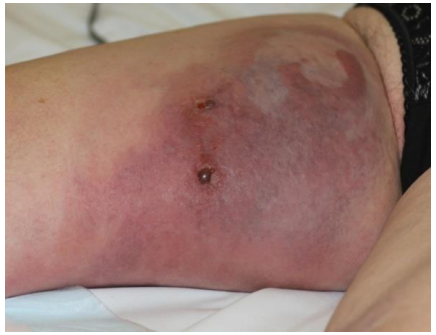
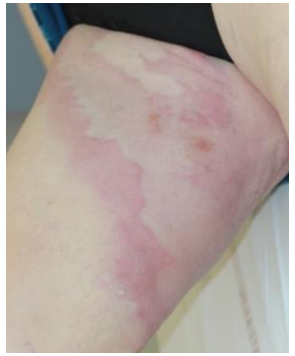
A Single-Arm Phase II Trial of Lenalidomide in Relapsing or Refractory Primary Cutaneous Large B-Cell Lymphoma, Leg Type

Marie Beylot-Barry[1,2,19], Diane Mermin[1,19], Aline Maillard[3], Reda Bouabdallah[4], Nathalie Bonnet[5], Anne-Bénédicte Duval-Modeste[6], Laurent Mortier[7], Saskia Ingen-Housz-Oro[8], Caroline Ram-Wolff[9], Stéphane Barete[10], Stéphane Dalle[11], Eve Maubec[12,20], Gaelle Quereux[13], Isabelle Templier[14], Martine Bagot[9], Florent Grange[15], Pascal Joly[6], Béatrice Vergier[2,16], Pierre-Julien Vially[17], Audrey Gros[2,18], Anne Pham-Ledard[1,2], Eric Frison[3] and Jean-Philippe Merlio[2,18]

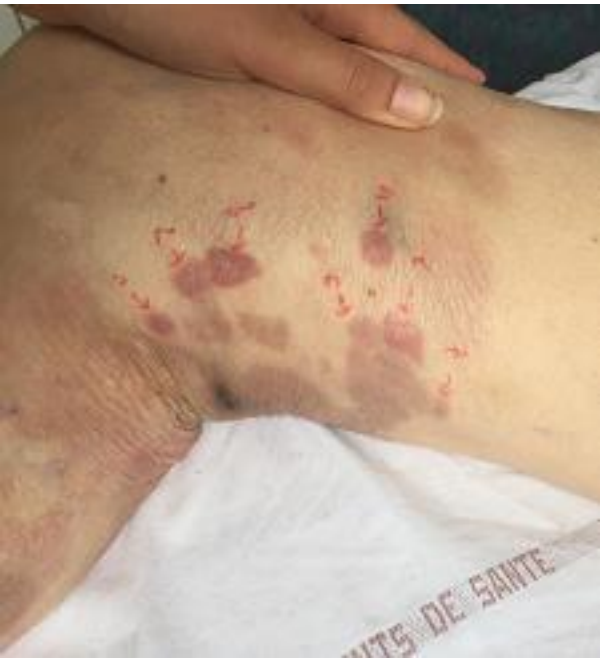




Lenalidomide

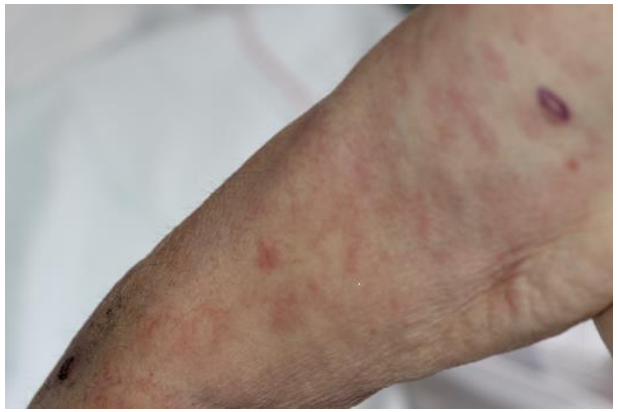
Clinical case

Aug 2018
85 years man
PCDLBCL Leg type

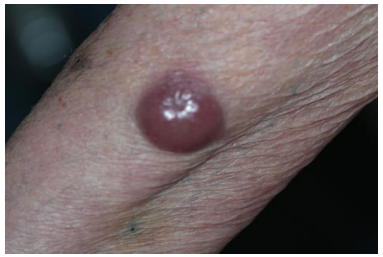


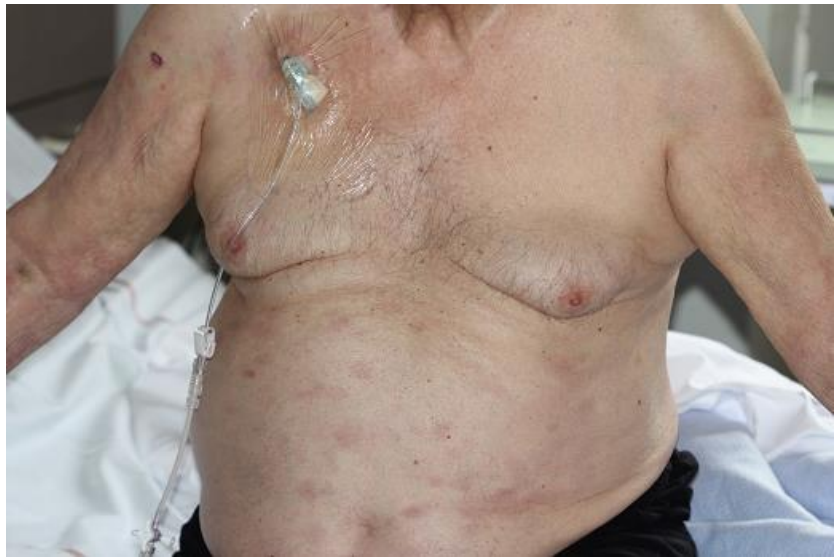
R-CHOPx6→ CR

Feb 2019



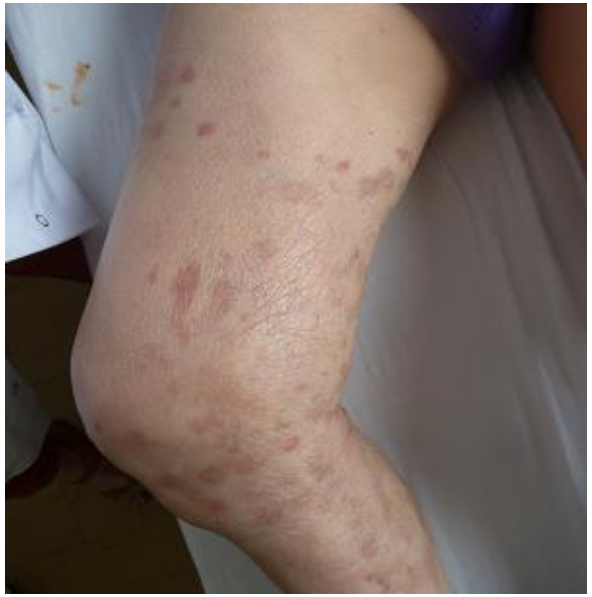
Diffuse cutaneous relapse

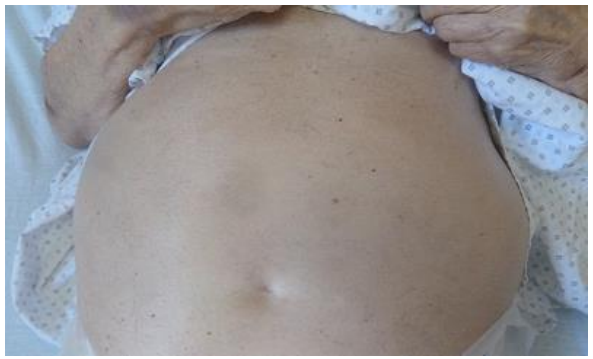




Low dose
Lenalidomide
10 mg/day
10 days / month

October 2020: minimal disease



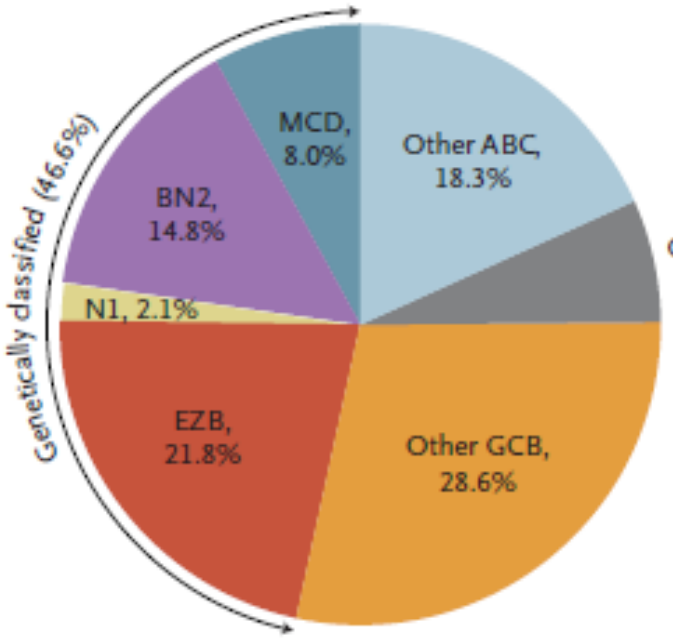


NGS: mutation **MYD88**
PIM1
GNA13

LENALIDOMIDE + Rituximab

Molecular classification of DLBCL: Leg type are « MCD »

240 DLBCL at diagnosis, prior to R-CHOP therapy



Schmitz et al, NEJM 2018

ABC

GC

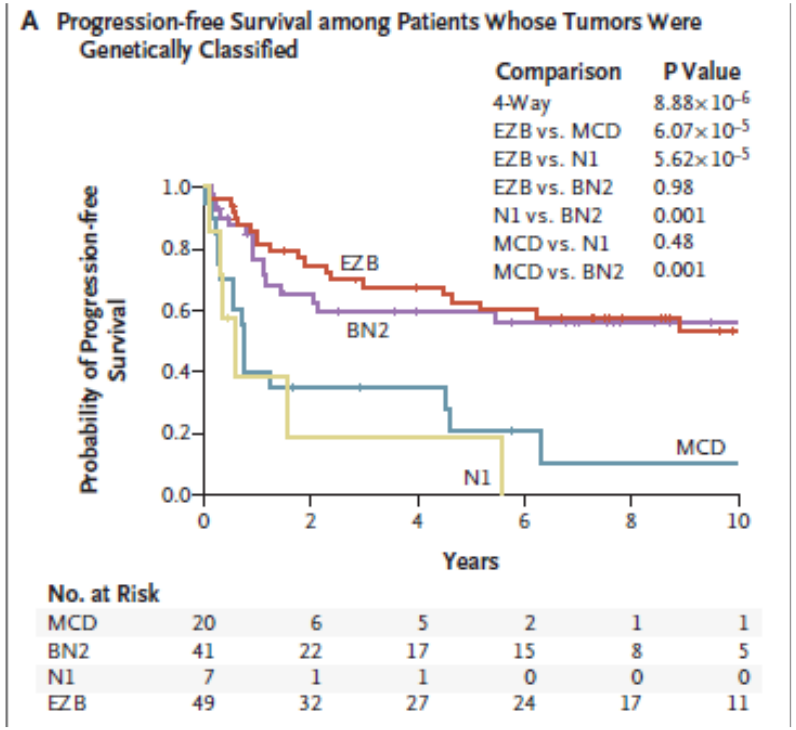
Exome and RNAseq classification

MCD: *MYD88*^{L265P} and *CD79B* mutated

N1: *NOTCH1* mutation

BN2: BCL6 fusion and *NOTCH2* mutation

EZB: *EZH2* mutation and BCL2 rearrangement



As primary CNS DLBCL PCDLBCL leg type belong to « **MCD** » subtype

MYD88 + CD79b

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

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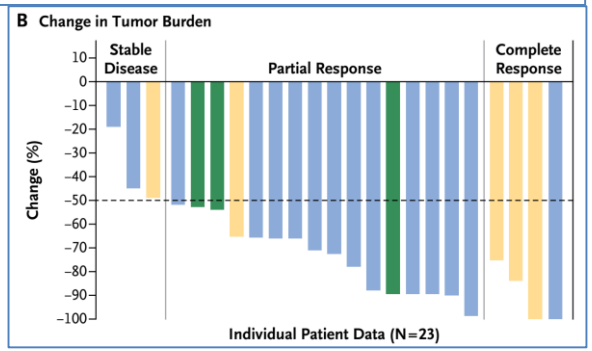
9p24.1 locus (PDL1/PDL2) in PCDLBCL leg type?

• **Hodgkin lymphoma :**

Amplification of 9p24.1 locus encoding for *PD-L1* and *PD-L2* associated with protein expression → Efficacy of PD-1 inhibitors.[4]

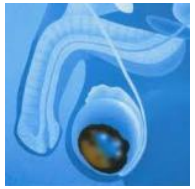
PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

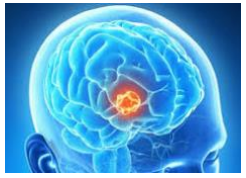


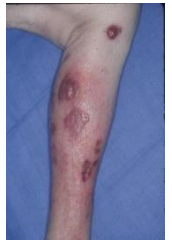
• **Primary testicular and primary central nervous system DLBCLs :**

Common features :
-Phenotypic (ABC)
-Genetic (**MCD**)
MYD88 + CD79b

- Primary testicular DLBCL
- Primary central nervous system DLBCL
- PCDLBCL-LT





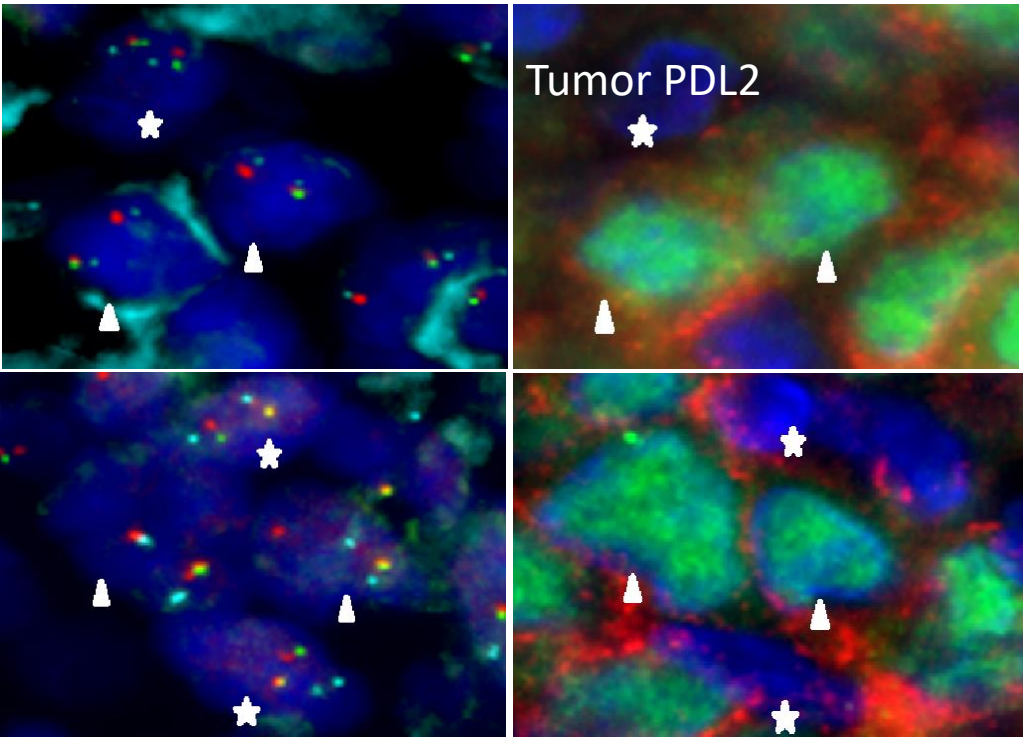


Locus 9p24.1 [5] :
- Copy number gains
- Amplifications
- Translocations

→ Expression of proteins PD-L1 and PD-L2

4. Ansell, S. M. *et al.* PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma. *N. Engl. J. Med.* **372** (2015)
5. Chapuy, B. *et al.* Targetable genetic features of primary testicular and primary central nervous system lymphomas. *Blood* **127**(2016).

Rares PDL1/PDL2 rearrangements but PDL1 expression by TAM

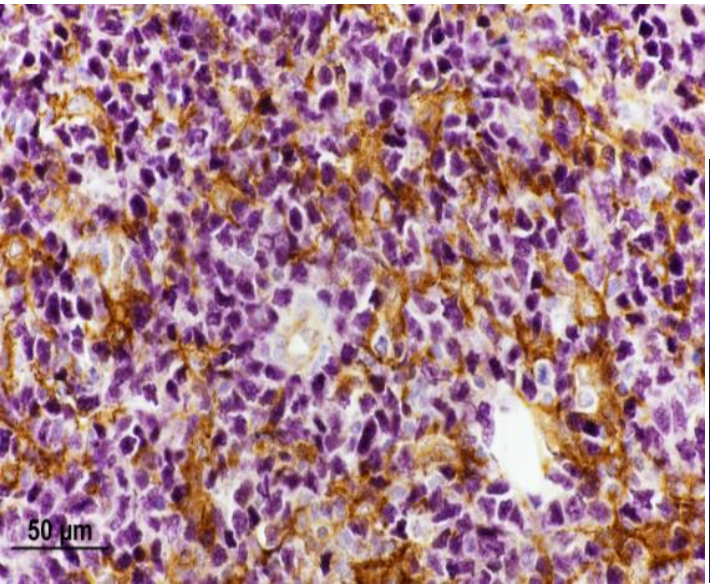


PD-L1 and PD-L2 are Differentially Expressed by Macrophages or Tumor Cells in Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

Sarah Menguy, MD,† Martina Prochazkova-Carlotti, PhD,* Marie Beylot-Barry, MD, PhD,*‡ Fréderic Saltel, PhD,§ Béatrice Vergier, MD, PhD,*† Jean-Philippe Merlio, MD, PhD,*‖ and Anne Pham-Ledard, MD, PhD*‡*

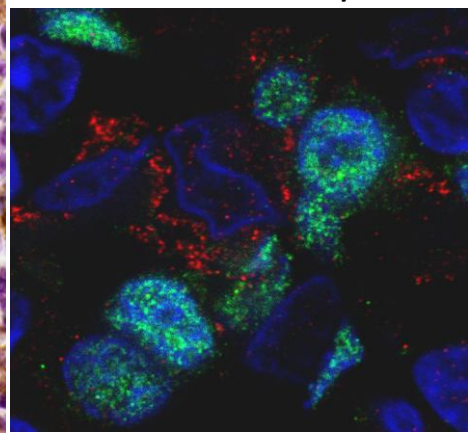
Am J Surg Pathol 2018

- **PDL1/2 rearrangements: 2/27 (7,4%)**
- → expression of PDL2 in these 2 only cases (tumor)
- **Microenvironnement expression of PDL1: 27/27** (TAM tumor associated macrophages)

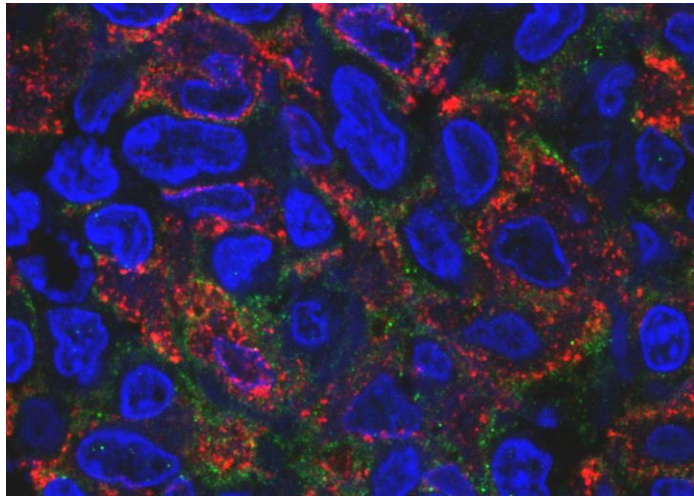


PDL2/PAX5

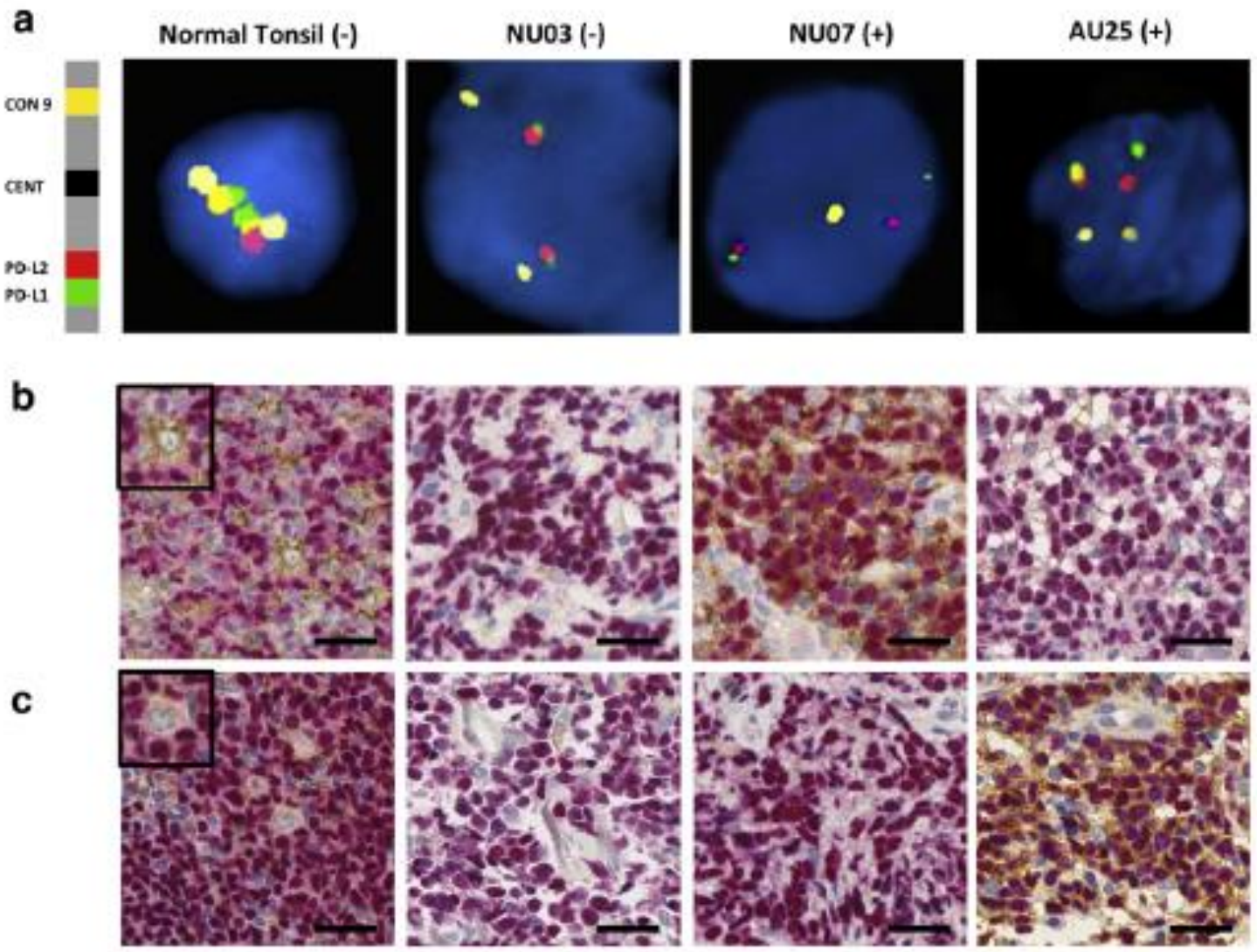
PDL1/PAX5



PDL1/CD163



Some *PDL1/PDL2* rearrangements in this paper



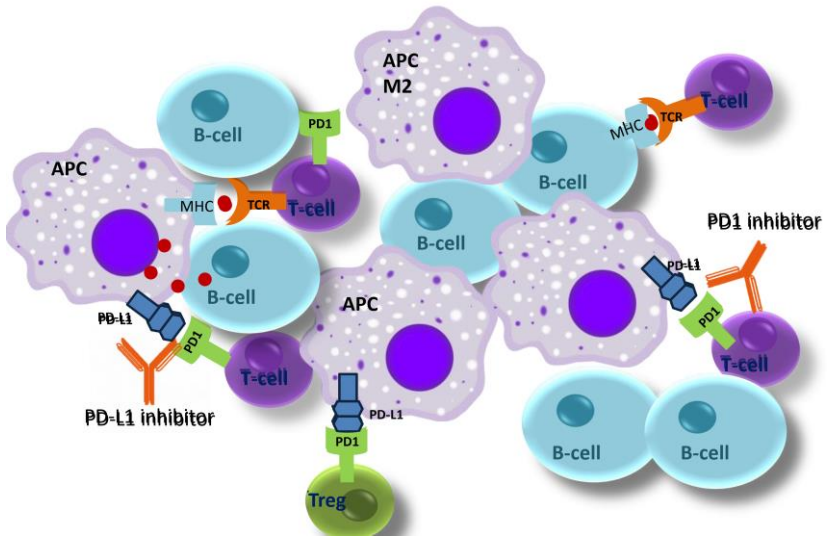
Genomic Analyses Identify Recurrent Alterations in Immune Evasion Genes in Diffuse Large B-Cell Lymphoma, Leg Type

Xiaolong Alan Zhou[1,12], Abner Louissaint Jr.[2,3,12], Alexander Wenzel[4], Jingyi Yang[4,5], Maria Estela Martinez-Escala[1], Andrea P. Moy[2,3], Elizabeth A. Morgan[6], Christian N. Paxton[7], Bo Hong[8], Erica F. Andersen[8], Joan Guitart[1], Amir Behdad[9], Lorenzo Cerroni[10], David M. Weinstock[3,11] and Jaehyuk Choi[1,4,5]

Zhou XA et al, J Invest Dermatol 2019

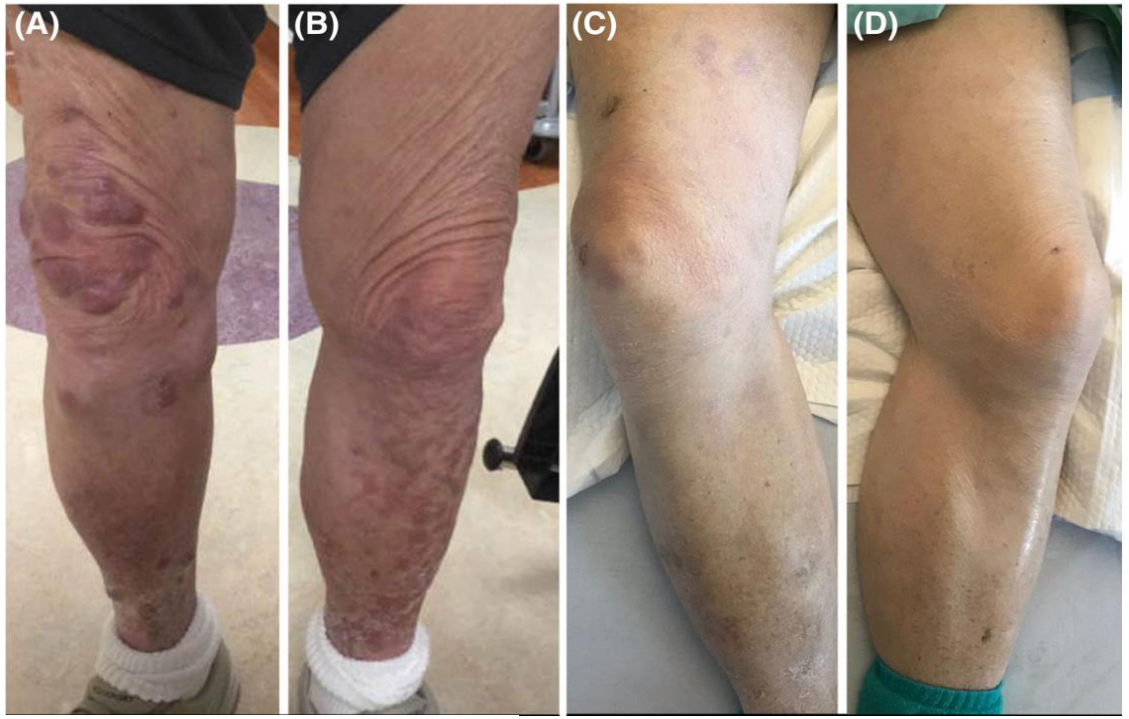
- 4/10 cases with *PDL1/ PDL2* break
- 50% with tumor (n=2) expression of PDL1/2

Checkpoint inhibitors in PCDLBCL Leg Type?



Rituximab, lenalidomide and pembrolizumab in refractory primary cutaneous diffuse large B-cell lymphoma, leg type

Di Ramondo et al,
Br J Haematol, 2019

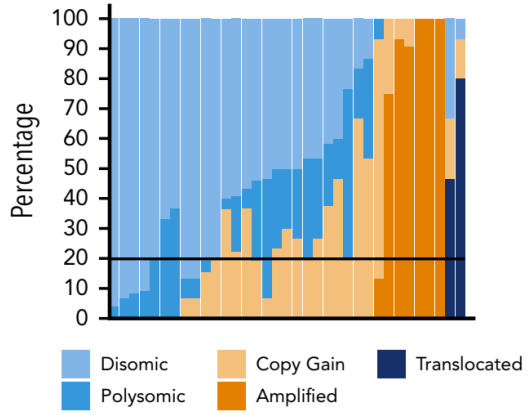


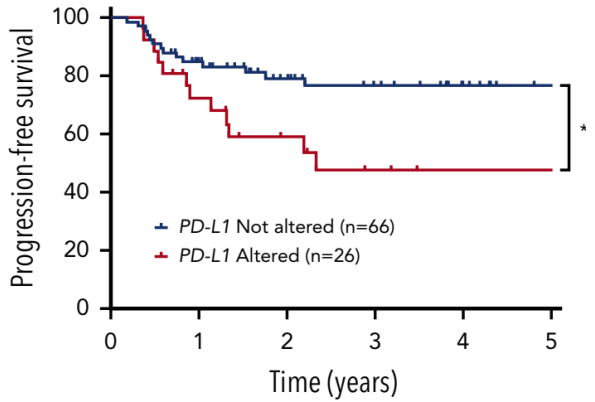
PD-L1 gene alterations identify a subset of diffuse large B-cell lymphoma harboring a T-cell–inflamed phenotype

Godfrey J et al, Blood, 2019

Checkpoint inhibitors:
Modest objective RR in DLBCL
(10-30%)

→ Select patients among PDL1/2 gene status?





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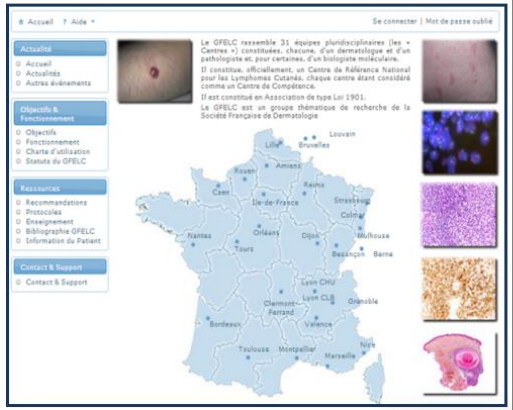
Take Home Messages

1. PCDLBCL Leg type display typical clinical behavior and may be identified with **BCL2 +/ MUM1+ (> 50%) / CD10-/ FOXP1 + phenotype**
2. Advances in oncogenesis knowlegge **: *MYD88* (70%), NFkB alterations and BCR pathway, Immune genes** are involved
3. Therapeutic perspectives have to be investigated: for who, when and how? **Lenalidomide, BTK inhibitors, NFkB targets, checkpoint inhibitors**

Pascal JOLY Rouen

Fabrice JARDIN - Rouen



Florent Grange, Reims,

INSERM U1053 UMR BaRITON; Team 3 : Oncogenesis of cutaneous lymphoma

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Edith Chevret

Sandrine Poglio

Audrey Gros

Laurence Bresson-Bepoldin

Martina Carlotti

Sarah Menguy

Élodie Laharanne

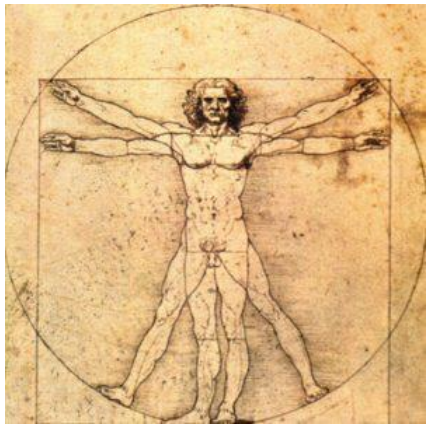
Yamina Idrissi

Alexandra Prévot

Alban Giese

Lamia Azzi-Martin

Jacky Ferrer



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