# Il quadro clinico:
# la malattia vista dall'ematologo

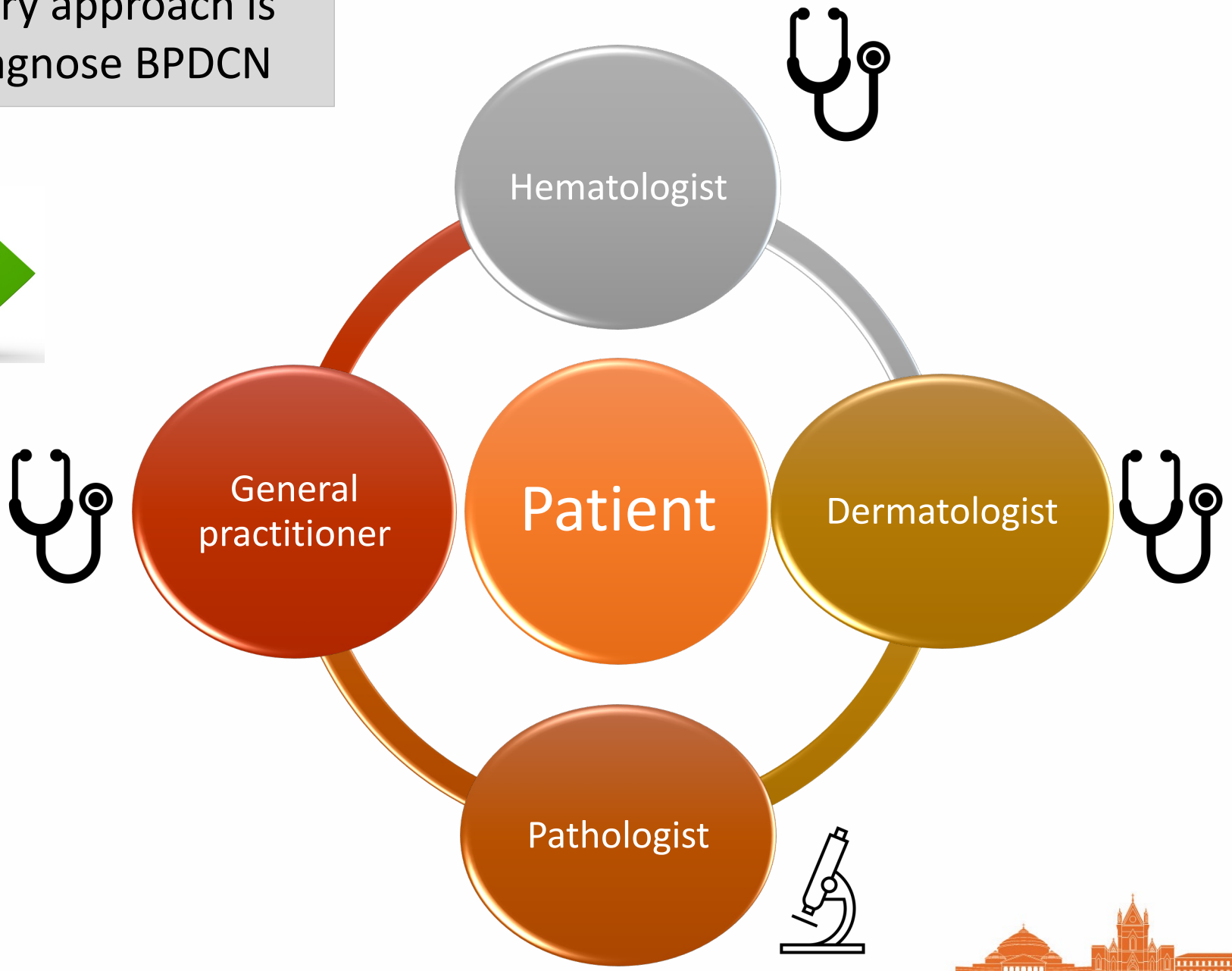
Cristina Papayannidis, MD, PhD

IRCCS Azienda Ospedaliero
Universitaria di Bologna,
Istituto di Ematologia «Seràgnoli»

# Disclosures of Cristina Papayannidis

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Abbvie | | | | | | X | X |
| Astellas | | | | | | X | X |
| Servier | | | | | | | X |
| Menarini | | | | | | | X |
| BMS | | | | | | | X |
| Pfizer | | | | | | X | X |
| Amgen | | | | | | | X |
| Janssen | | | | | | X | |
| GSK | | | | | | X | |
| Blueprint | | | | | | X | |
| Incyte | | | | | | X | X |
| Paladin Labs Inc | | | | | | | X |
| Jazz pharmaceuticals | | | | | | X | |
| Novartis | | | | | | X | |
| Delbert Laboratoires | | | | | | X | |

# Multidisciplinary approach is required to diagnose BPDCN


Speaker's opinion

# Epidemiology and background

| | |
|---|---|
| Affects all races and geographic locations, with an overall incidence of 500-1000 cases per year in the US | No documented environmental or hereditary genetic factors predispose patients to BPDCN development |
| 75% of cases occurr in men | BPDCN may be more common in men because of the gene dosage effect of a loss-of-function mutation in ZRSR2, located on chromosome X |
| Median age at diagnosis: 60-70 years | BPDCN can occur at any age; however, most often the disease occurs in elderly patients |
| May occur as a secondary malignancy | Approximately 10%-20% of patients have a history of hematologic malignancies, including MDS, CML, CMML and AML |

Guru M et al, Leuk Res 2018; Pagano L et al, Br J Haematol 2016; Pagano L et al, Haematologica 2013; Taylor J et al, Blood 2013; Julia F et al, Br J Dermatol 2013

# First scenario

GENERAL PRACTITIONER????

Often mistaken for other, more familiar hematologic malignancies (AML, leukemia cutis, NHL, ALL, CMML, MDS, cutaneous lymphoma), leading to **frequent misdiagnosis or underdiagnosis of BPDCN**

Atypical skin lesion → Dermatologist → Biopsy → Hematologist

**Mean time** between the **onset** of lesions and the pathologic **diagnosis** of BPDCN is **6.2 mos** based on a retrospective analysis

Julia F et al, Br J Dermatol 2013

**Expertise is required**:
Differential diagnosis


Speaker's opinion

# Second scenario

Often mistaken for other, more familiar hematologic malignancies (AML, leukemia cutis, NHL, ALL, CMML, MDS, cutaneous lymphoma), leading to **frequent misdiagnosis or underdiagnosis of BPDCN**

Leukemia-like symptoms+/- atypical skin lesions → Emergency Unit/Hematology → Blood tests + Biopsy

GENERAL PRACTITIONER????

**Expertise is required**:
Differential diagnosis


Speaker's opinion

# Variability of presentation of BPDCN

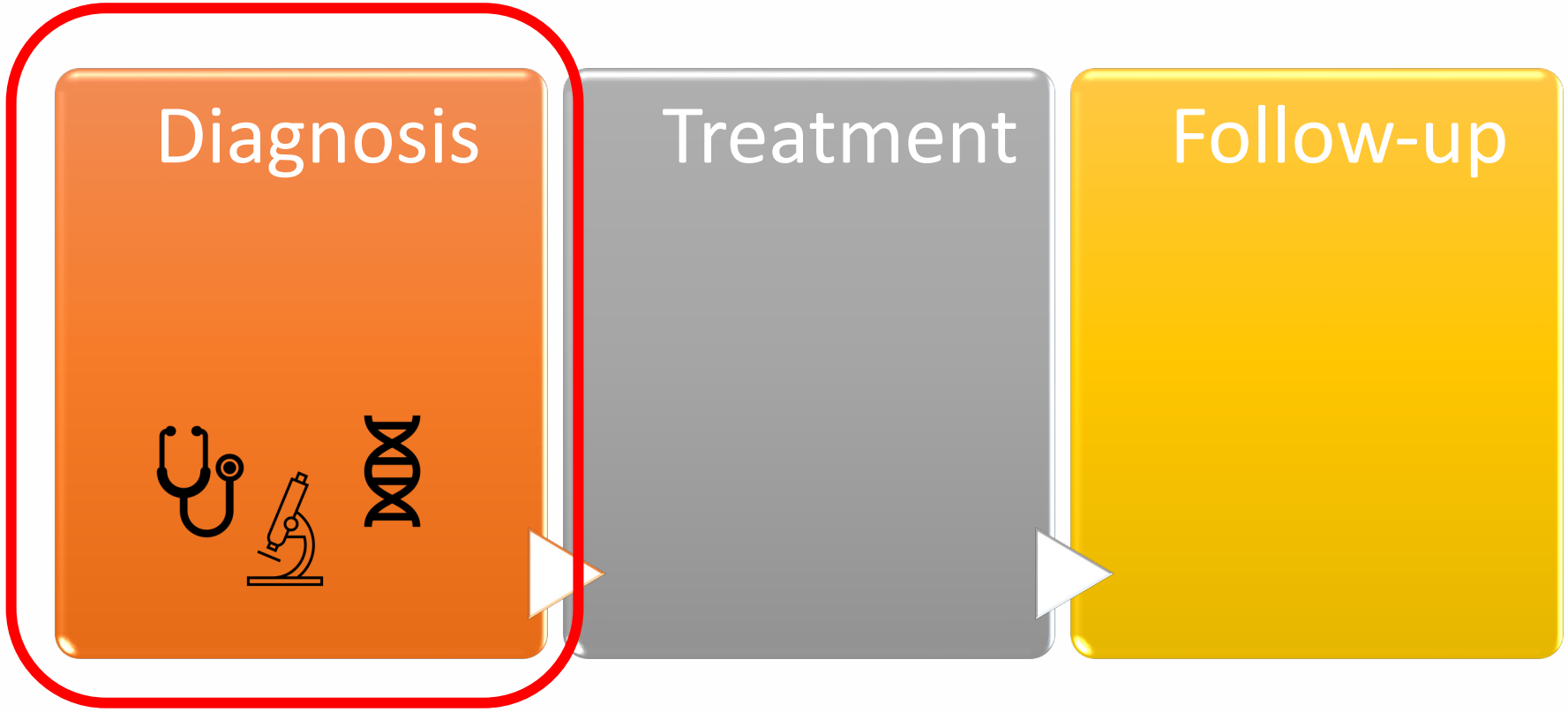
- A significant percentage **(40%-60%)** of patients initially present with involvement of the **bone marrow and lymph nodes**.
- Other extracutaneous sites may include: spleen, liver, tonsils and **CNS**
- In few cases **(11%)** BPDCN patients may present with **bone marrow disease without skin involvement**

N=398

| Characteristic | Data |
|---|---|
| Males/females | 294 (74)/104 (26) |
| ECOG score 0-1 | 207 (65) |
| Age, median (range), y | 67 (18-96) |
| **Localization** | |
| Skin | 353 (89) |
| BM | 243 (62) |
| Peripheral blood | 36 (15) |
| Lymph nodes | 152 (39) |
| **Forms** | |
| Cutaneous isolated | 121 (30) |
| Disseminated with cutaneous localization | 200 (50) |
| Disseminated with cutaneous and extranodal localization | 26 (7) |
| Disseminated noncutaneous | 43 (11) |
| Disseminated noncutaneous with extranodal localization | 8 (2) |

Laribi K et al, Blood Adv 2020

# The role of the hematologist: from diagnosis to follow-up




Speaker's opinion

# Diagnostic work-up

H&P

Skin lesions analysis

Peripheral counts

Bone marrow aspirate/biopsy and lymph node biopsy including:

.dendritic cell morphology assessment

.immunohistochemistry

.cytogenetics

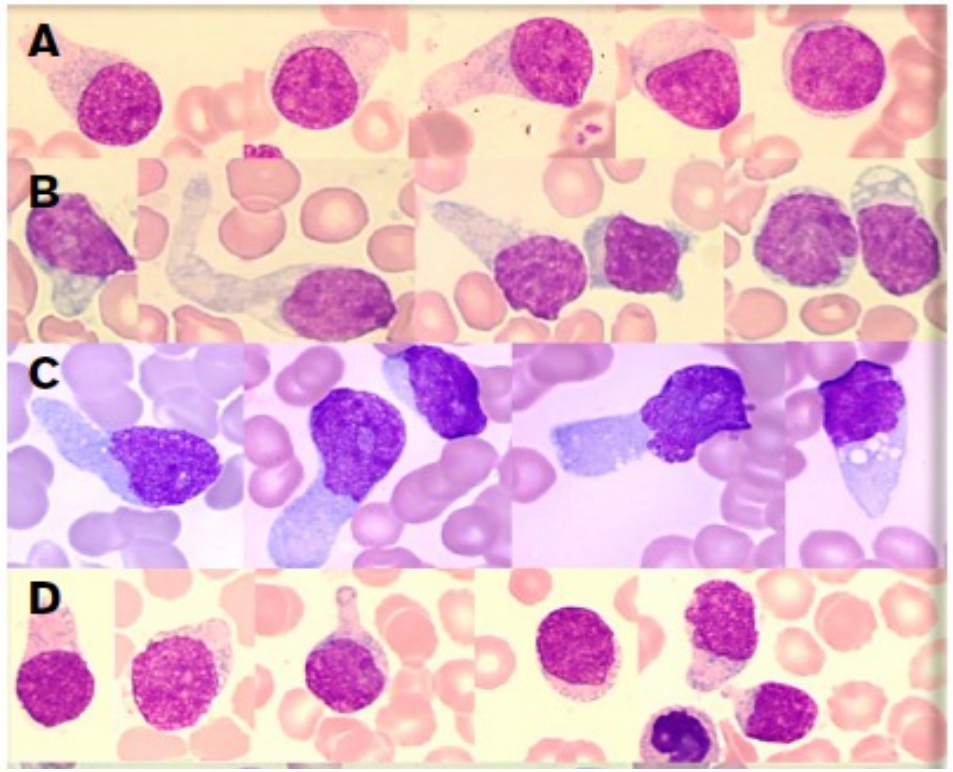
.molecular analysis

LP to rule out CNS involvement

PET/CT scan

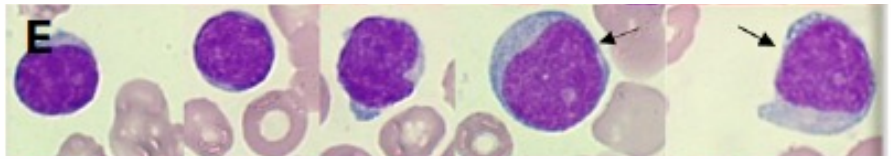
Modified from NCCN guidelines v 3.2023

# Morphology

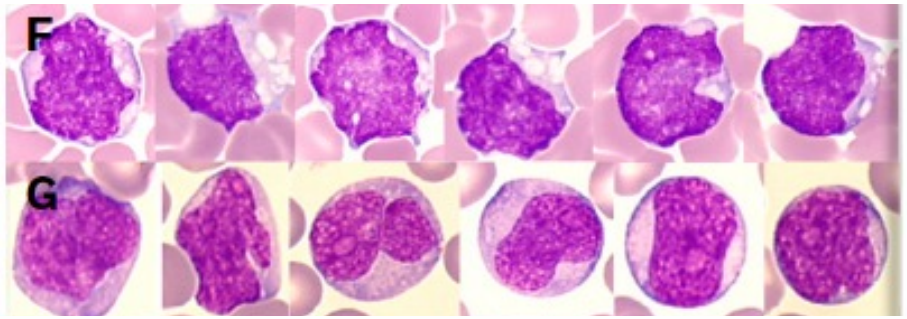



**Typical morphology** with large pseudopodia, microvacuoles, an eccentrically located nucleus, heterogeneous coloration of the cytoplasm

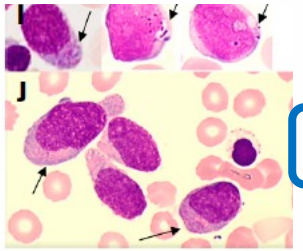
Garnache-Ottou F et al, Blood Adv 2019




**Lymphoid-like** morphology

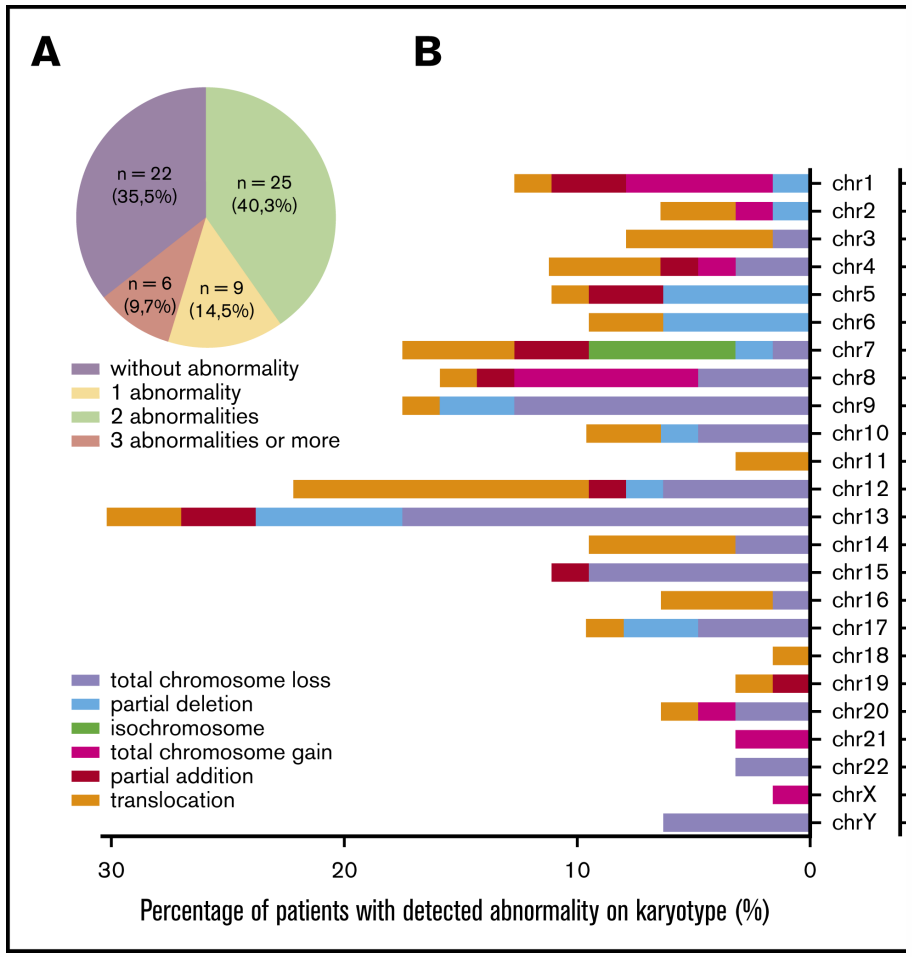



**Monoblast-like** morphology




Presence of granules in the cytoplasm

# Cytogenetics




- Cytogenetics abnormalities found in **about 60% of cases** (35% with ≥3 abnormalities.
- **Neither the number** of abnormalities **nor any particular abnormality impacted** on the **prognosis** or clinical presentation (but it's **controversial**)
- **Deletions were predominant**
- Chromosomal gains were less frequent

Garnache-Ottou F et al, Blood Adv 2019

# Molecular alterations

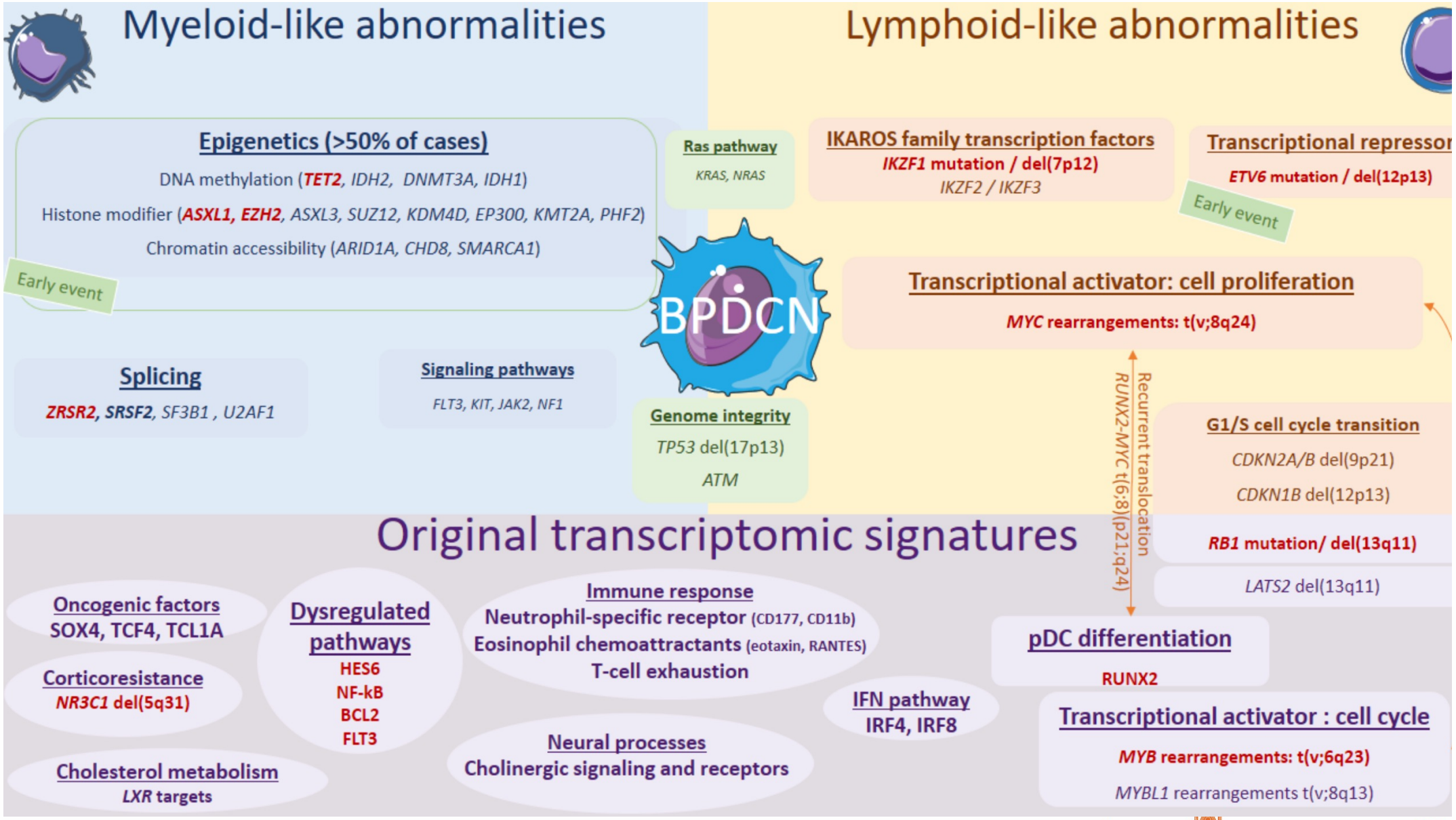
| Authors, Reference | Technique | DNA Mutated Genes |
|---|---|---|
| Jardin et al,[7] 2011 | aCGH/SNP | *TET2 TP53* |
| Alayed et al,[8] 2013 | PCR assay/TS | *TET2* |
| Taylor et al,[9] 2013 | TS | *TET2, TP53, ASXL1, IDH2, KRAS, ABL1, ARID1A, GNA13, U2AF1, SRSF2, IRF8, ZRSR2* |
| Menezes et al,[12] 2014 | WES/TS | *DNMT3A, IDH1, IDH2, TET1, TE2, ASXL1, ATRX, EZH2, KRAS, NRAS, ETV6, HOXB9, IKZF1, IKZF2, IKZF3, RUNX1, ZEB2, SF3B1, SRSF2, U2AF1, ZRSR2, NPM1, FLT3, FLT3-ID, JAK2, KIT, TP53, CBLB, CBLC, UBE2G2* |
| Stenzinger et al,[14] 2014 | TS | *NRAS, ATM, MET, KRAS, IDH2, KIT, APC, RB1, VHL,BRAF,MLH1,TP53, RET* |
| Emadali et al,[16] 2016 | TS | *ASXL1, EZH2* |
| Togami et al,[11] 2016 | WES/TS | *ZRSR2, SRSF2, SF3B1, U2AF1, SF3A2, SF3B1, TET2, ASXL1, TP53, GNB1, NRAS, IDH2, ETV6, DNMT3A, RUNX1, CRIPAK, NEFH, HNF1A, PAX3, SSC5D* |
| Sapienza et al,[17] 2019 | WES/TS | *ARID1A, CHD8, SMARCA5, SMARCAD1, SMARCD1, TET2, IDH2, ASH1L, ASXL1, ASXL3, MLL2, MLL3, MLL4, SETMAR, SUZ12, KDM4D, PHF2, EP300, EP400, MYST3, MYST4, PHC1, PHC2, EYA2, SRCAP, NRAS, KRAS, BRCA1, ATM, ATR, RAD52, ZRSR2, RET, MAPK1, BRAF, RUNX2, SYK, WNT10, WNT7B, BCL9L, WNT3.* |
| Ladikou et al,[23] 2018 | TS | *TET2, RHOA* |
| Szczepaniak et al,[24] 2019 | TS | *ASXL1, TET2, NF1* |

- ***TET2*** are the **most common** molecular mutations, followed by mutations in *ASXL1*, *RAS*, splicing factors (*ZRSR2*) and *TP53*

- The **type of *TET2*** mutation correlates with **OS** (worse outcome for nonsense and frame shift mutations vs missense)

- **CNS** positivity correlates with a higher Incidence of ***TET2*** mutations

Sapienza M.R., Pileri S.A. Hematol Oncol Clin N Am, 2020;
Pemmaraju N et al, Clin Adv in Hem and Oncology 2023




Renosi F et al, Cancers 2022

# Diagnostic work-up

H&P

Skin lesions analysis

Peripheral counts

Bone marrow aspirate/biopsy and lymph node biopsy including:

.dendritic cell morphology assessment

.immunohistochemistry

.cytogenetics

.molecular analysis

LP to rule out CNS involvement

PET/CT scan

Modified from NCCN guidelines v 3.2023

# CNS involvement in BPDCN

**Table 2**

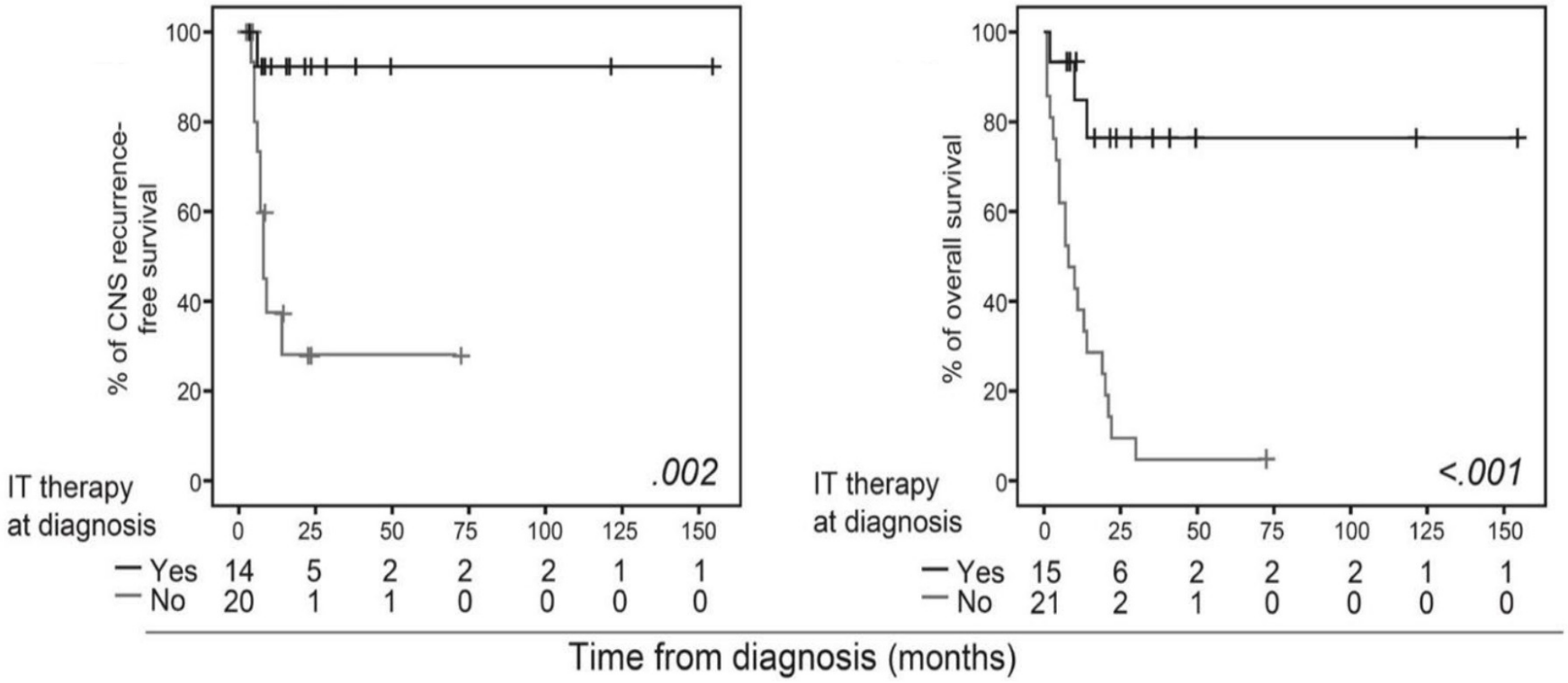
**Incidence of CNS Involvement in BPDCN Patients**

| References | BPDCN Cases | CNS Involvement | | |
|---|---|---|---|---|
| | | At Diagnosis | At Relapse | Overall |
| Pagano et al[41] | 43 | 4 (9%) | 3 (7%) | 7 (16%) |
| Julia et al[52] | 90 | nr | nr | 9 (10%) |
| Martín-Martín et al[53] | 13 | 6 (46%) | 3 (23%) | 9 (69%) |
| Yun et al[27] | 49 | 0 | 0 | 0 |
| Cernan et al[54] | 14 | 1 | 1 | 1 (7%) |
| Laribi et al[22] | 398 | NR | NR | 10 (2.5%) |
| Ozdemir et al[55] | 9 | 2 | 0 | 2 (22%) |
| Pemmaraju et al[44] | 103 | 13 (13%) | 10 (10%) | 23 (22%) |
| Valentini et al[11] | 68 | 4 | 2 | 6 (12.5%) |

- **Medicated lumbar punctures should be performed during the induction phase** (at least 6-8) by combining methotrexate, cytarabine and steroids
- A diagnostic and medicated lumbar puncture should be **mandatory** performed in patients with leukemic presentation **at diagnosis** and in all patients at relapse

Pagano L et al, Hemasphere 2023

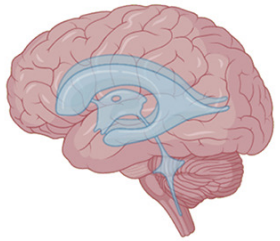
# Prognostic impact of CNS involvement and administration of IT therapy at diagnosis

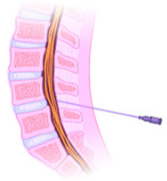



BPDCN, blastic plasmacytoid dendritic-cell neoplasm; CNS, central nervous system; IT, intrathecal.
Reproduced from: Martín-Martín L, et al. *Oncotarget*. 2016;7(9):10174-81.

## Central Nervous System (CNS) Involvement of Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

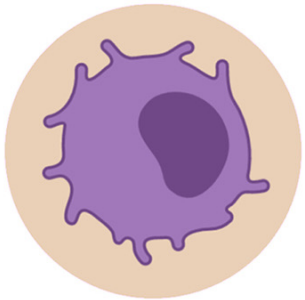
CNS incidence was 22% (n=23) out of 103 total patients with BPDCN



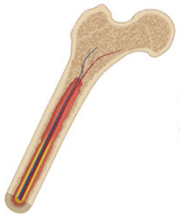


Discovery in frontline setting with routine lumbar puncture was 57%

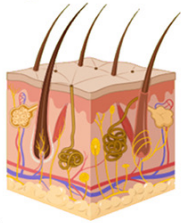
median time from diagnosis of BPDCN to discovery of CNS disease was 3.6 months (range 0-36 months)



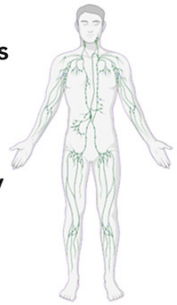
Other sites of disease involvement in patients with CNS-BPDCN:



Bone marrow (96%)



Skin (70%)



Lymph node (30%)

Outcomes:
- median duration of complete response to first-line therapy (CNS+: 20.6 months vs CNS-: 38.6 months, *p*=0.21)
- median overall survival (CNS+: 22.9 months vs CNS-: 17.8 months, *p*=0.22)

- CNS+ patients have:

- lower median baseline Hb levels
- higher frequency of TET2 mutations or variants
-bone marrow involvement in 96% of cases

Pemmaraju N et al, Blood 2021

# Diagnostic work-up

H&P

Skin lesions analysis

Peripheral counts

Bone marrow aspirate/biopsy and lymph node biopsy including:

.dendritic cell morphology assessment

.immunohistochemistry

.cytogenetics

.molecular analysis

LP to rule out CNS involvement

PET/CT scan

Modified from NCCN guidelines v 3.2023

# NCCN Guidelines Version 6.2023
# Blastic Plasmacytoid Dendritic Cell Neoplasm
# (Age ≥18 years)

National Comprehensive Cancer Network®

NCCN Guidelines Index
Table of Contents
Discussion

## EVALUATION/WORKUP FOR BPDCN[a,1]

- H&P
- CBC, platelets, differential, CMP
- Analysis of skin lesions (collaboration with dermatology is recommended),[2] peripheral blasts, BM aspirate/biopsy, and lymph node biopsy including:
  - Dendritic cell morphology assessment
  - IHC
  - Flow cytometry
  - Cytogenetic analysis (karyotype and/or FISH)
  - Molecular analysis (most common aberrations include: *ASXL1*, *IDH1–2*, *IKZF1–3*, *NPM1*, *NRAS*, *TET1–2*, *TP53*, *U2AF1*, *ZEB2*)[3]
- PET/CT scan of other sites, if clinical suspicion for extramedullary disease and/or lymphadenopathy
- All patients require a diagnostic LP at the time of initial diagnosis, at disease relapse, or any other time when there is a clinical suspicion for CNS involvement. Follow with IT chemotherapy prophylaxis as clinically indicated (see BPDCN-B).

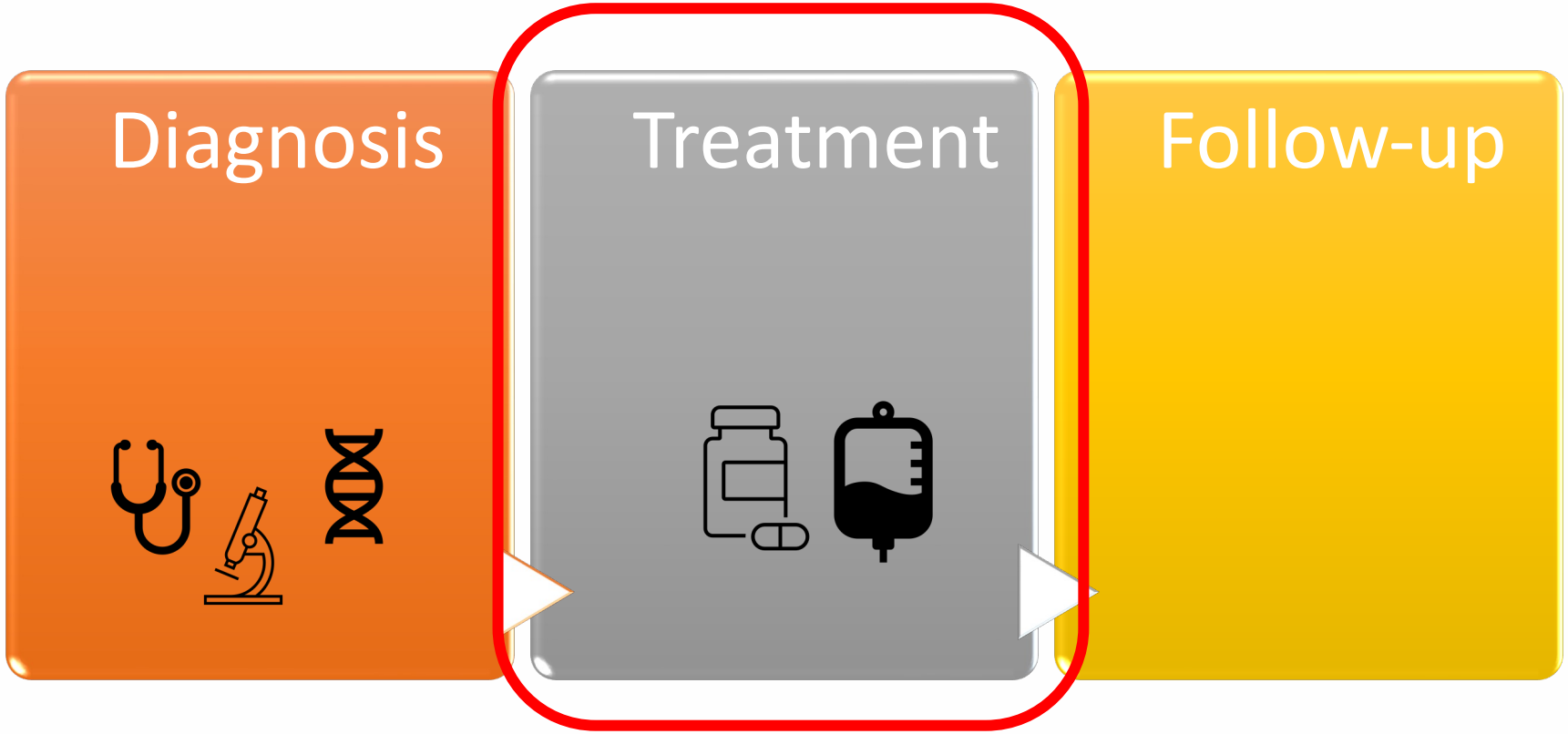
## DIAGNOSIS[3]

BPDCN diagnosis requires at least 4 of 6 BPDCN antigens:
- CD123
- CD4
- CD56
- TCL-1
- CD2AP
- CD303/BDCA-2

without myeloid,[b] T or B lineage expression markers

→ BPDCN confirmed → See Treatment Induction (BPDCN-2)

# The role of the hematologist: from diagnosis to follow-up





Speaker's opinion

# 1. Can we stratify patients?

BPDCN patients show **a dismal prognosis**, with OS of <1 year in most patients treated by **conventional therapies**

High expression of **TdT**
**Young age**
**Absence of cytogenetics abnormalities**

Better outcome

**Disseminated vs isolated skin disease**

Debated


**Multicenter studies are needed** to define prognostic/predictive factors associated with outcome and therapy response

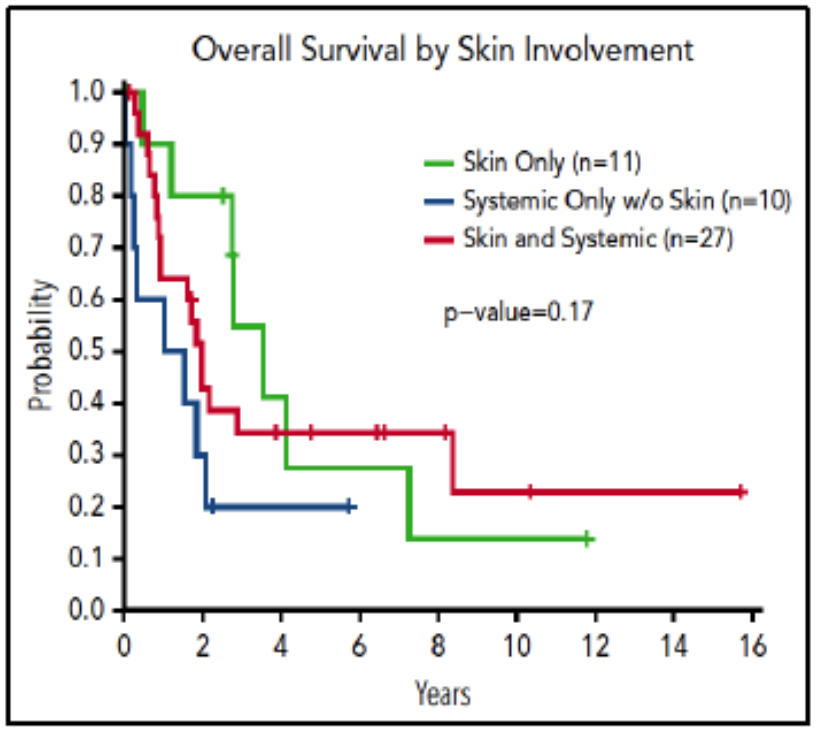
Pagano L et al, Hemasphere 2023; Laribi K et al, Blood Adv 2020

# Disseminated vs «isolated» skin disease

78 pts. French national registry, 2000- 2013:

- cutaneous lesions preceded BM / visceral involvement in 48% of pts. (by a mean of 2.5 months)
- BM **dysplasia** ≥1 lineage in **31%**
- BM blasts in 96%, with mean %-infiltration of 64%
- skin only' in 4%
- CNS involvement 4.5%

*Garnache-Ottou et al, Blood Adv. 2019 Dec 23;3(24):4238-4251*

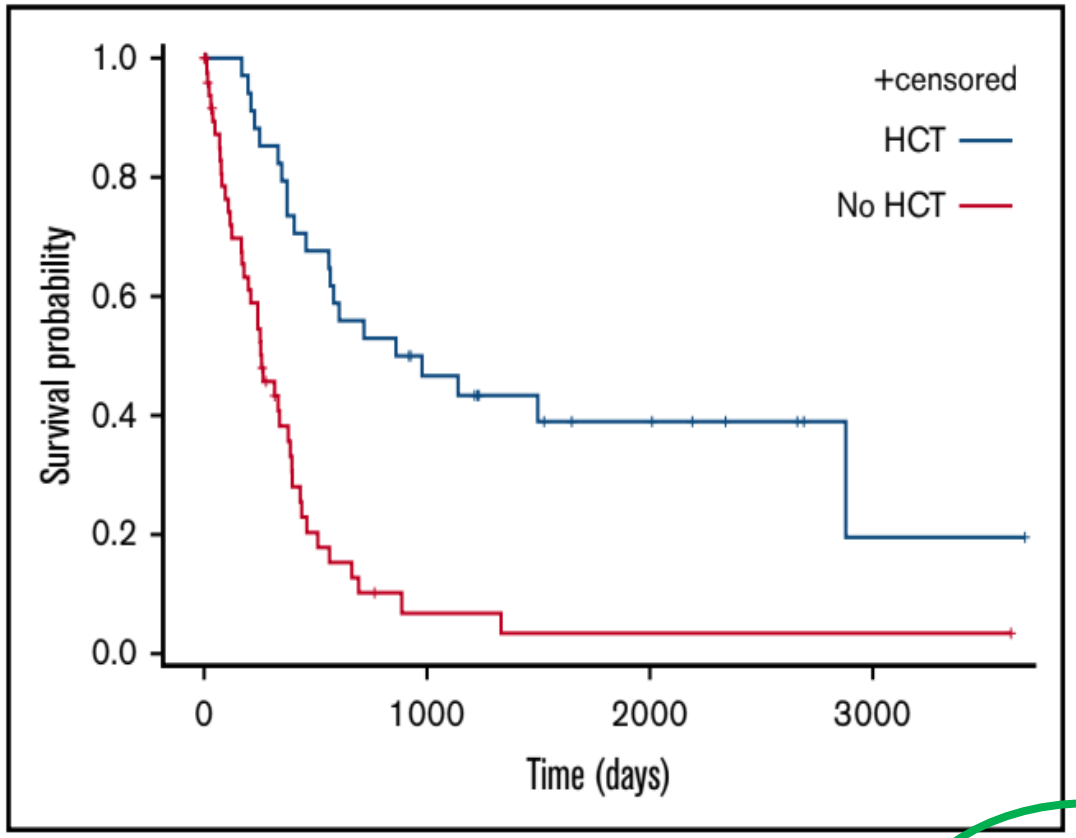



59 pts., retrospective, 3 US centers, 2000-2017

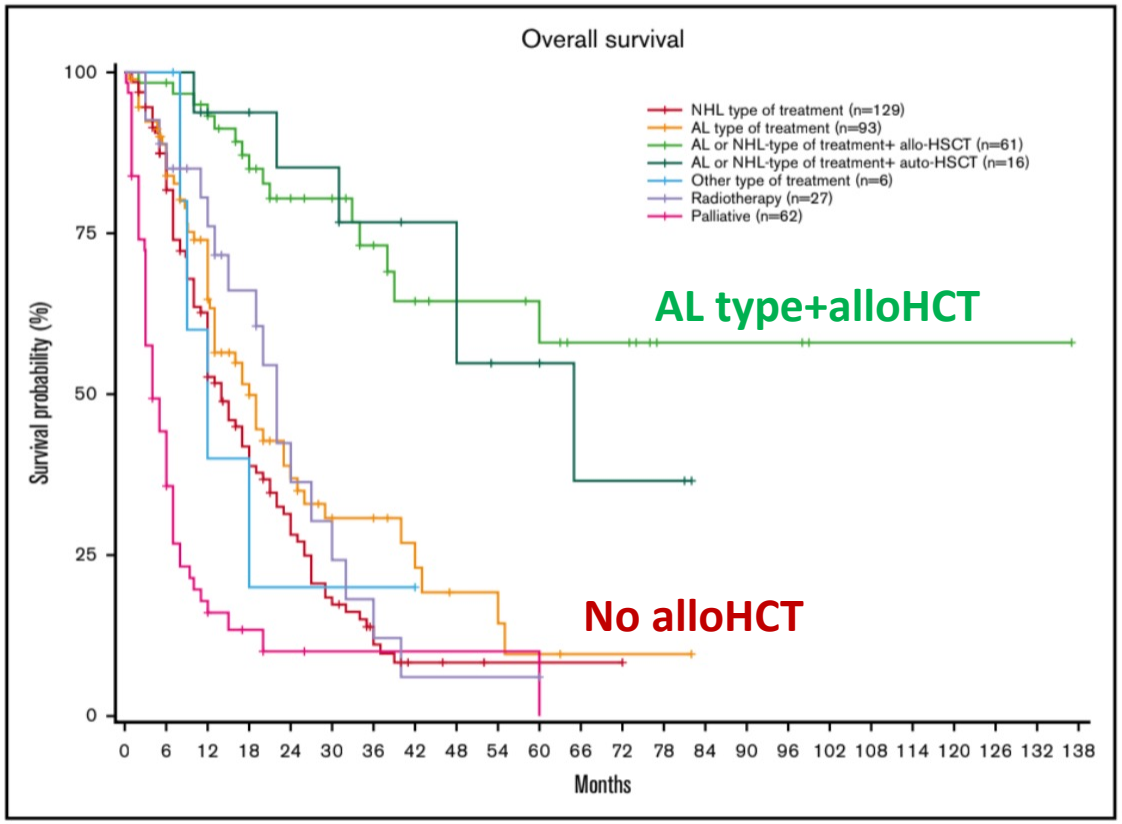
Reprinted from *Blood* (2019) 134 (8), Taylor J et al, Multicenter analysis of outcomes in blastic plasmacytoid dendritic cell neoplasm offers a pretargeted therapy benchmark, Pages No. 678–687, Copyright (2019), with permission from Elsevier.

- *Amitay-Laish et al, JAAD Case Rep 2017,3:310-15 „localized skin-limited BPDCN"*
- *Pagano L et al., Haematologica. 2013;98(2):239-246 and Zhang et al, Crit Rev Oncol Hematol. 2020 May;149:102928 „leukemic without skin"*

# 2. Is the patient fit for alloHCT?



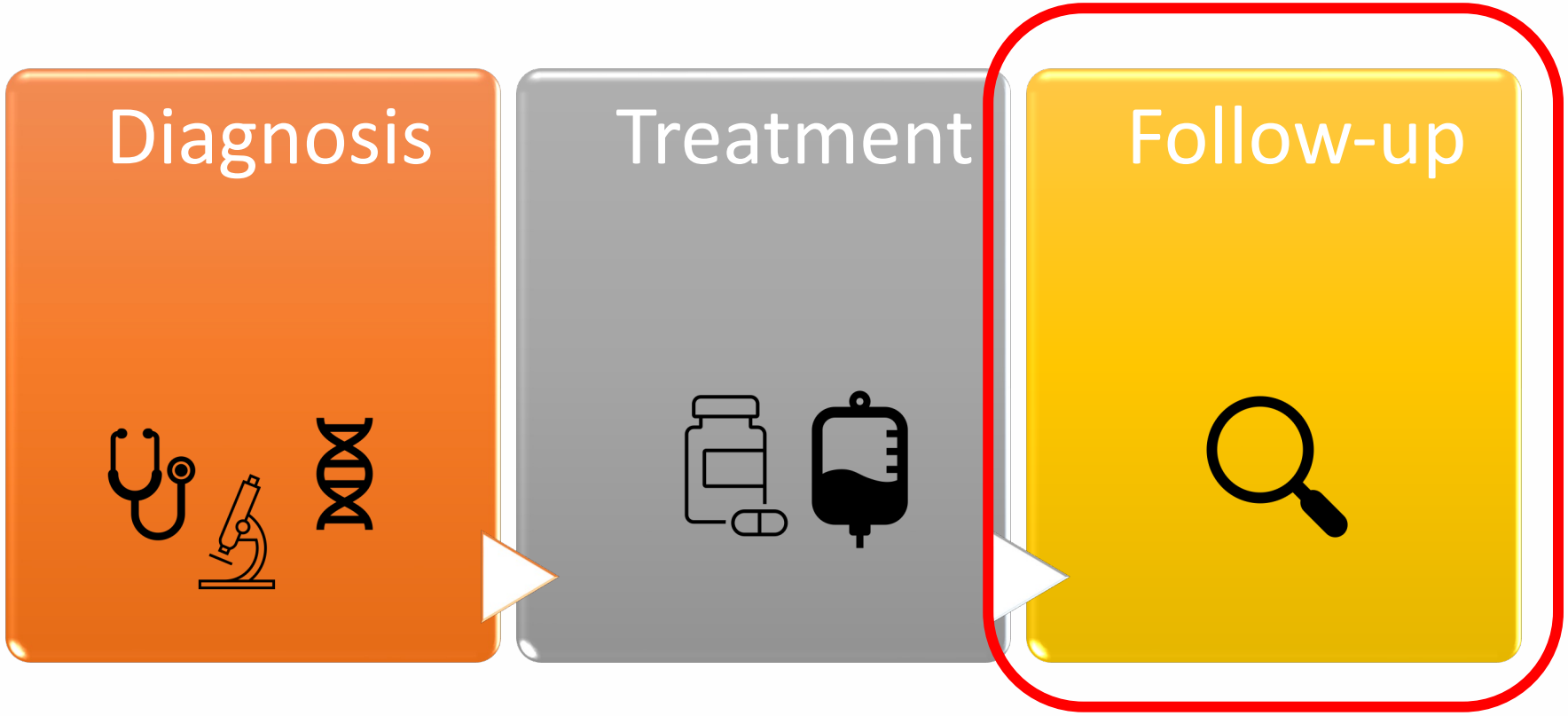

Garnache-Ottou F et al, Blood Adv 2019




Laribi K et al, Blood Adv 2020

New approaches are required!

# The role of the hematologist: from diagnosis to follow-up




Speaker's opinion

# NCCN Guidelines Version 6.2023
# Blastic Plasmacytoid Dendritic Cell Neoplasm (Age ≥18 years)



**SURVEILLANCE**

- CBC, platelets every 1–3 mo for 2 y, then every 3–6 mo up to 5 y
- BM aspirate and biopsy only if peripheral smear is abnormal or cytopenias develop
- Repeat PET/CT scan for patients with prior evidence of extramedullary disease
- Consider re-biopsy for any suspicious skin or extramedullary lesions

→ Relapsed/ refractory BPDCN →

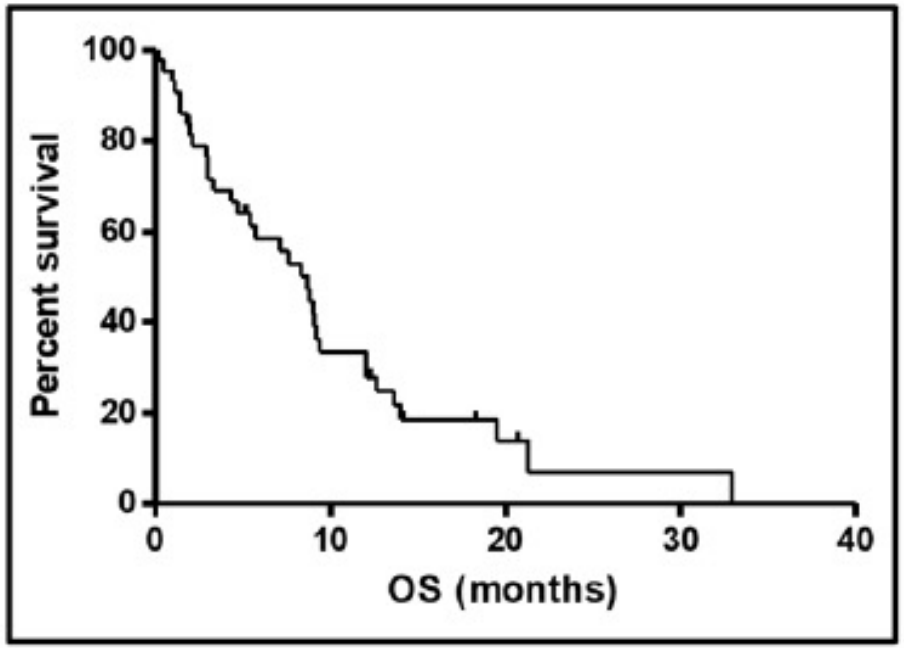
**TREATMENT FOR RELAPSED/REFRACTORY DISEASE**

- Evaluate CNS for disease/prophylaxis[14]
- Consider
  - Clinical trial (preferred)
  - Tagraxofusp-erzs[d,6] (preferred, if not already used)
    For management of adverse events, see Supportive Care (BPDCN-C)
  - Chemotherapy (if not already used), see Treatment Induction (BPDCN-2)
  - Local RT to isolated lesions/areas
  - Systemic steroids
  - Venetoclax-based therapy,[13,15,16] see AML-5
- Donor search should be initiated at first relapse in appropriate patients concomitant with institution of other therapy if no sibling donor has been identified

# Historical data showed a poor outcome…

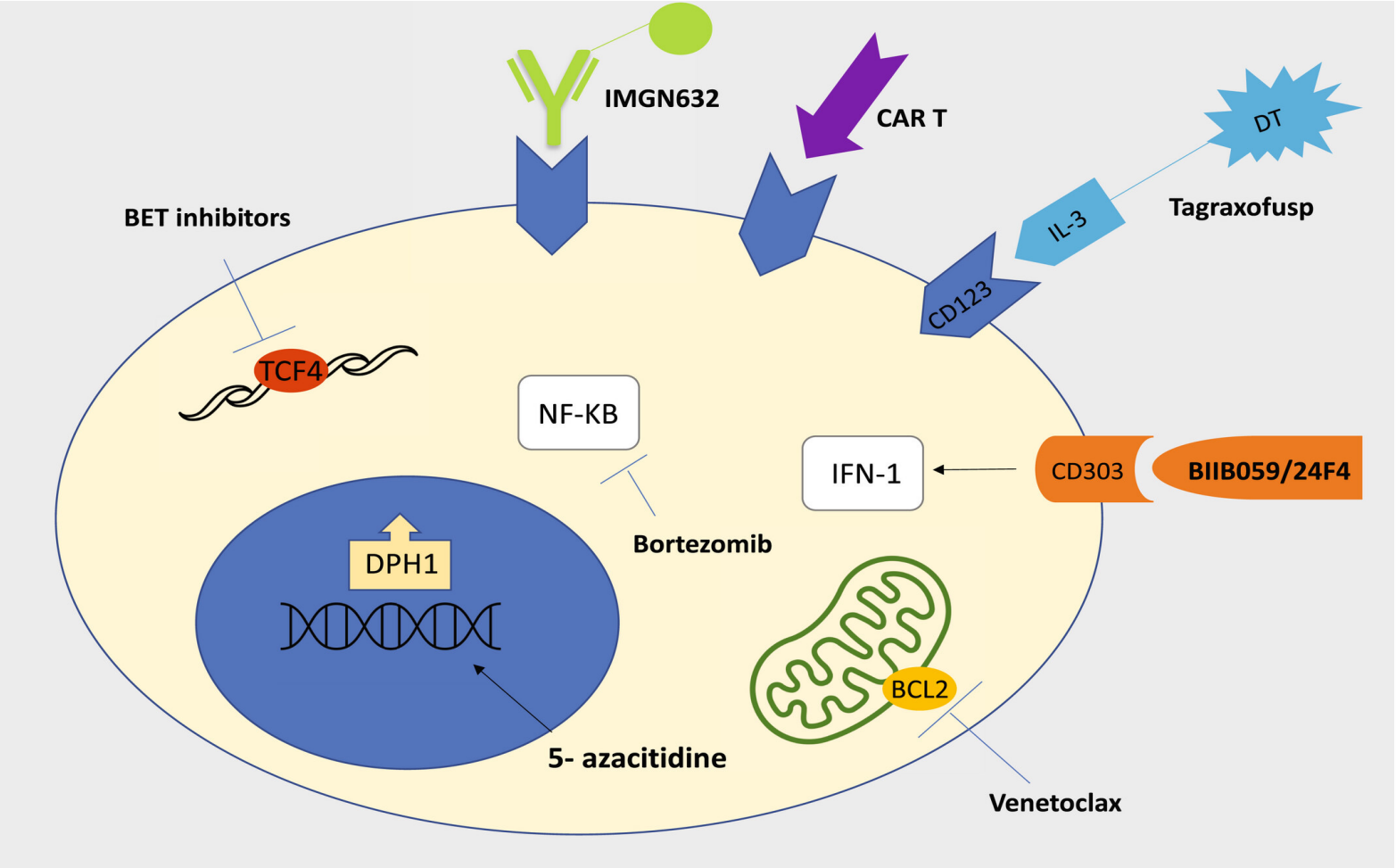
| Group | n | Response criteria used | CR rate | Early death rates |
|---|---|---|---|---|
| Poret, 2015 | 86 | Not reported | 43% | Not reported |
| Martin-Martin, 2015 | 46 | Not reported | 55% | High early death rate (26%) |
| Pagano, 2013 | 43 | AML | 41% | High death rate (17%) during induction therapy |
| Dalle, 2010 | 47 | Not reported | 47% | Not reported |

- ***For published primary series (n≥ 10 patients), the CR rate is 43-56% in first-line BPDCN***




AML, acute myeloid leukemia; CR, complete response; OS, overall survival.
Pagano L et al. *Haematologica* 2013;98:239–246.

# …but new approaches are available today




Adimora I et al, Cancer 2022

# Take home messages

| IMPROVE EXPERTISE | IMPROVE DIAGNOSIS | TREAT PATIENTS |
|---|---|---|
| • Creation of **multidisciplinary teams** with **expertise** in the field<br>• Sharing knowledges | • Quickly **identification of BPDCN patients**, reducing delays to improve outcome<br>• Optimization of **diagnostic pathway**<br>• Identification of **prognostic factors** to stratify patients | • Allow more and more patients to **receive the most appropriate treatment**<br>• Identification of **mechanisms of resistance** to new drugs<br>• **SCT unit+hematoloy unit connection** |

Speaker's opinion

# Thank you!


**cristina.papayannidis@unibo.it**

Prof M. Cavo

Antonio Curti
Stefania Paolini
Chiara Sartor
Jacopo Nanni
Sarah Parisi
Letizia Zannoni
Gianluca Cristiano
Federico Zingarelli
Andrea Davide Romagnoli
Federica Ardizzoia
Caterina Azzimondi

Francesca Bonifazi
Mario Arpinati
Enrico Maffini

Elena Sabattini
Claudio Agostinelli
Carlo Sagramoso
Alessandro Pileri

Emanuela Ottaviani
Valentina Robustelli
Carolina Terragna
Simona Soverini
Manuela Mancini
Lorenza Bandini
Nicoletta Testoni
Carmen Baldazzi
Gabriella Chirumbolo
Dorian Forte
Martina Barone
Francesco Ingletto
Ottavia Iotti
Manuel Cella
Antonella Pagano