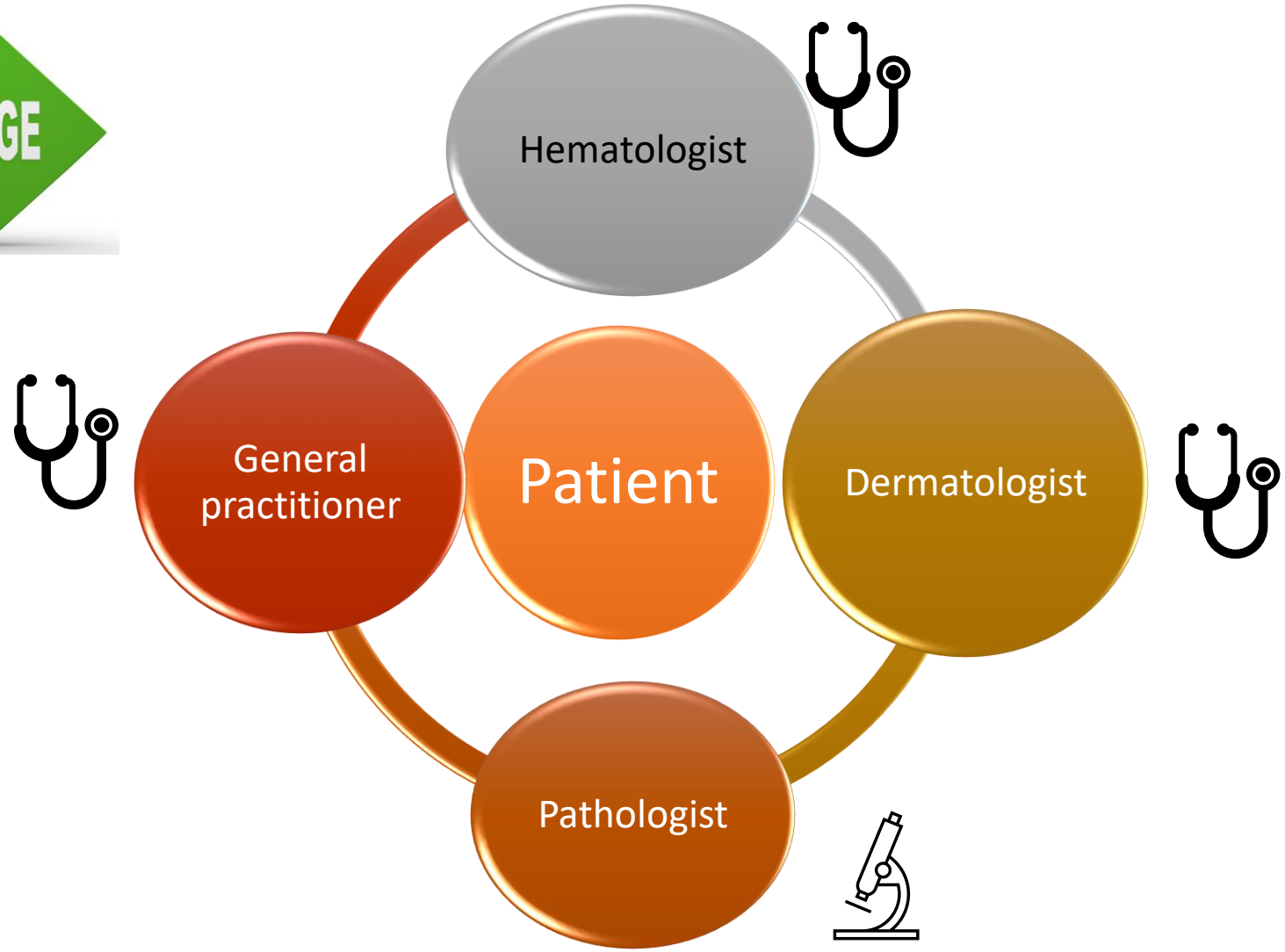
L’esperienza «real life» di Bologna

Cristina Papayannidis
Antonio Curti

A multidisciplinary approach is required to diagnose and treat BPDCN patients



Speaker's opinion

Path to diagnosis: 1st scenario

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

Path to diagnosis: 1st 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

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

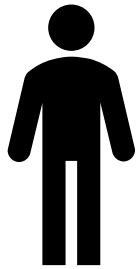
Expertise is required:
Differential diagnosis

Speaker's opinion

Tagraxofusp experience at Bologna Hematology Institute

	Sex	Age at diagnosis	Sites of disease at diagnosis	Lines before Tag	Sites of disease before Tag	Number of Tag courses	alloSCT	Status
Pt 1	M	76	Skin	2	Skin, BM, Lymph nodes	1 dose (course 1)	No	Died (cerebral hemorrhage)
Pt 2	M	72	Skin, BM, Lymph nodes	1	Skin, BM, Lymph nodes nasopharynx, CNS	3 doses (course 1)	No	Died (COVID19 pneumonia)
Pt 3	M	67	Bone marrow	1	Bone marrow MRD+	1	YES	Alive (+30 mths SCT)
Pt 4	M	47	Bone marrow	0	Bone marrow	2	YES	Alive (+2 years SCT)
Pt 5	F	53	Skin, Bone marrow MRD+	0	Skin, Bone marrow MRD+	7	NO	Alive (+ 8 months dg)

Pt 1, 76 years



Skin lesion

March 2019

Skin biopsy August 2019:

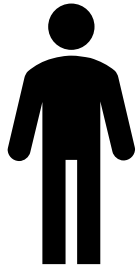
BPDCN

Referred to Hematology Unit

October 2019

7 months

Staging



- At clinical examination: no splenomegaly, no hepatomegaly, no further skin lesions
- Peripheral counts: WBC 6300/mmc, PMN 65%, Hb 13 g/dl, PLTs 257000/mmc. Liver and kidney functions in range, as well as coagulation
- **Bone marrow biopsy**: cellularity 30%, not involvement by BPDCN
- **PET-CT**: hyperuptake of the right pectoral skin lesion (SUV max 6.1)
- **Lumbar puncture**: **no pathological cells at liquor examination**
- Echocardiogram: EF 60%

Treatment (I)

Tagraxofusp requested for compassionate use in October 2019
Waiting for the drug, chemo was started:

CVP 1 course: stable disease

IMG-632:
2 courses
(at another site)

DISEASE PROGRESSION:
Skin, lymphnodes, BM

WBC 257000/mmc, LDH 1852 U/L
Cytogenetics:
47,XY, t(6;8)(p21;q24), +8,
-12,del(13)(q12q14),-18,
+2mar in 20/20 metaphases

Treatment (II)

Tagraxofusp available

Vinblastine 10 mg → Dysarthria and cognitive/motor slowing → Brain CT: right frontal hemorrhagic suffusion

WBC 215000/mmc, PLTs 38000/mmc
LDH 2100 U/L
Tagraxofusp 1st dose was administerd
Worsening of neurological conditions, the patient died after 48 hours

Path to diagnosis: 2nd scenario

- 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 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

Path to diagnosis: 2nd 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????

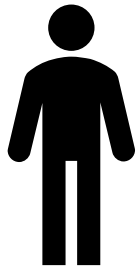
Expertise is required:
Differential diagnosis

Speaker's opinion

Tagraxofusp experience at Bologna Hematology Institute

	Sex	Age at diagnosis	Sites of disease at diagnosis	Lines before Tag	Sites of disease before Tag	Number of Tag courses	alloSCT	Status
Pt 1	M	76	Skin	2	Skin, BM, Lymph nodes	1 dose (course 1)	No	Died (cerebral hemorrhage)
Pt 2	M	72	Skin, BM, Lymph nodes	1	Skin, BM, Lymph nodes nasopharynx, CNS	3 doses (course 1)	No	Died (COVID19 pneumonia)
Pt 3	M	67	Bone marrow	1	Bone marrow MRD+	1	YES	Alive (+30 mths SCT)
Pt 4	M	47	Bone marrow	0	Bone marrow	2	YES	Alive (+2 years SCT)
Pt 5	F	53	Skin, Bone marrow MRD+	0	Skin, Bone marrow MRD+	7	NO	Alive (+ 8 months dg)

Pt 3, 67 years



Fever unresponsive to antibacterial therapy

September 2019

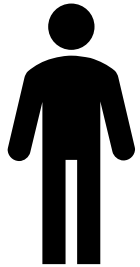
Blood tests:

Pancytopenia

WBC 1890/mmc (BC 17%) , Hb 9.1 g/dl, PLTs 43000/mmc

Referred to Hematology Unit

Diagnostic work-up (I)

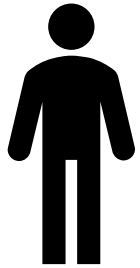


- Past medical history: **acute myocardial infarction in 2007** treated with PTCA and stent and subsequently double aorto-coronary bypass
- Moderate hepatic steatosis and hyperlipidemia

- At clinical examination: no splenomegaly, no hepatomegaly, **no skin lesions**
- Peripheral counts: WBC 1400/mmc (BC 22%) , Hb 8.6 g/dl, PLTs 41000/mmc
- BM aspirate: **punctio sicca**
- Bone biopsy: cellularity 80%. Diffuse nodular proliferation, consisting of small-medium size blast cells, CD34-, CD3-, CD117-, MPO-, TCL1+, CD56+, CD123+, CD4-. **Bone marrow involvement by BPDCN**

- **PET-CT**: **no hyperuptakes**
- **Lumbar puncture**: **no pathological cells** at liquor examination

Diagnostic work-up (II)



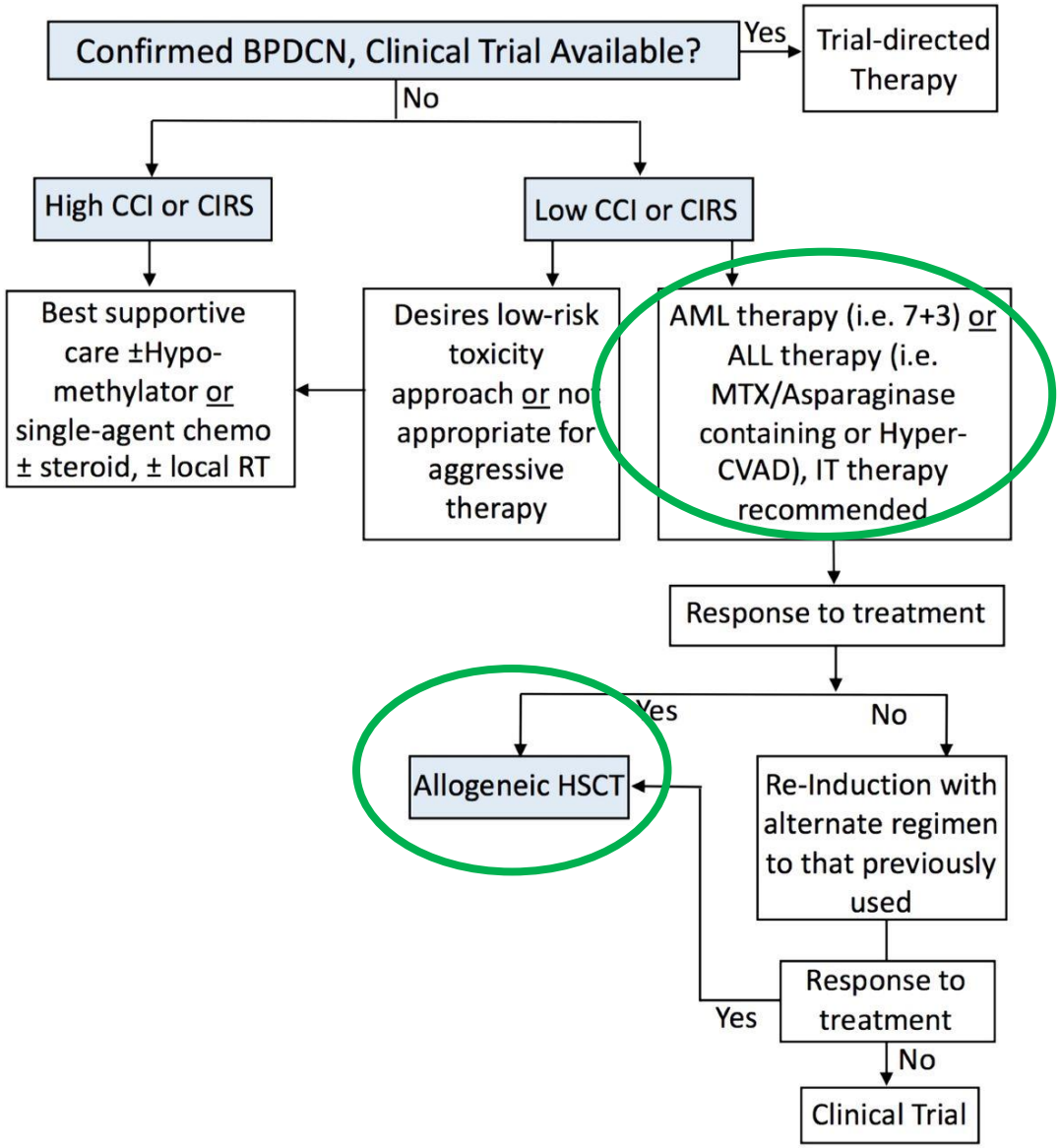
- Cytogenetics: **46, XY in 8/8 metaphases (peripheral blood)**
- Molecular biology: NPM1, FLT3, IDH1-2: wild type
- Echocardiogram: EF 65%

Which treatment for this patient?

Therapy of BPDCN in the pre-Tagraxofusp era

- **Prior to the approval of Tagraxofusp, there were no approved therapies for the treatment of BPDCN** and no universally accepted standard of care, due to the lack of perspective trials

- Patients treated with **high-dose acute leukemia-based chemotherapy followed by allogeneic SCT** appeared to have the best outcomes



Sullivan JM et al, Hematology Am Soc Hematol Educ Program 2016

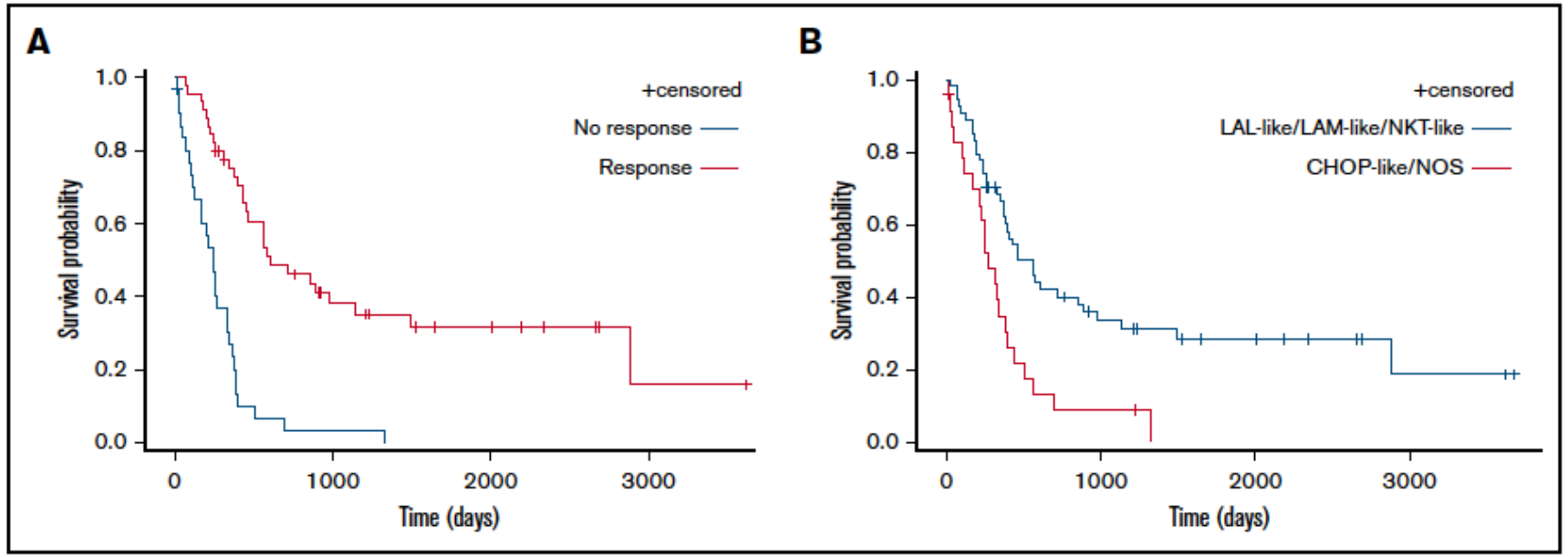
Chemotherapy in BPDCN

- High rate of response
- lack of durable response
- Low OS

Table 4. Response to first-line treatment

Treatment group	Complete remission, n (%)	Remission duration, median (range), mo	Relapse rate, n (%) of CR patients	HCT, n (%) of CR patients
AML-like (n = 19)	13 (68.4)	68 (4-399)*	4 (28.5)	7 (2 auto) (36.8-53.8)
ALL-like (n = 19)	15 (78.9)	47 (6-224)	5 (33.3)	7 (46.7)
Aspa-MTX (n = 16)	12 (75)	26 (5-166)	4 (33.3)	6 (37.5-50)
CHOP-like (n = 16)	6 (37.5)	17 (4-22)*	4 (66.7)	2 (12.5-33.3)
NOS (n = 10)	1	35	0	0

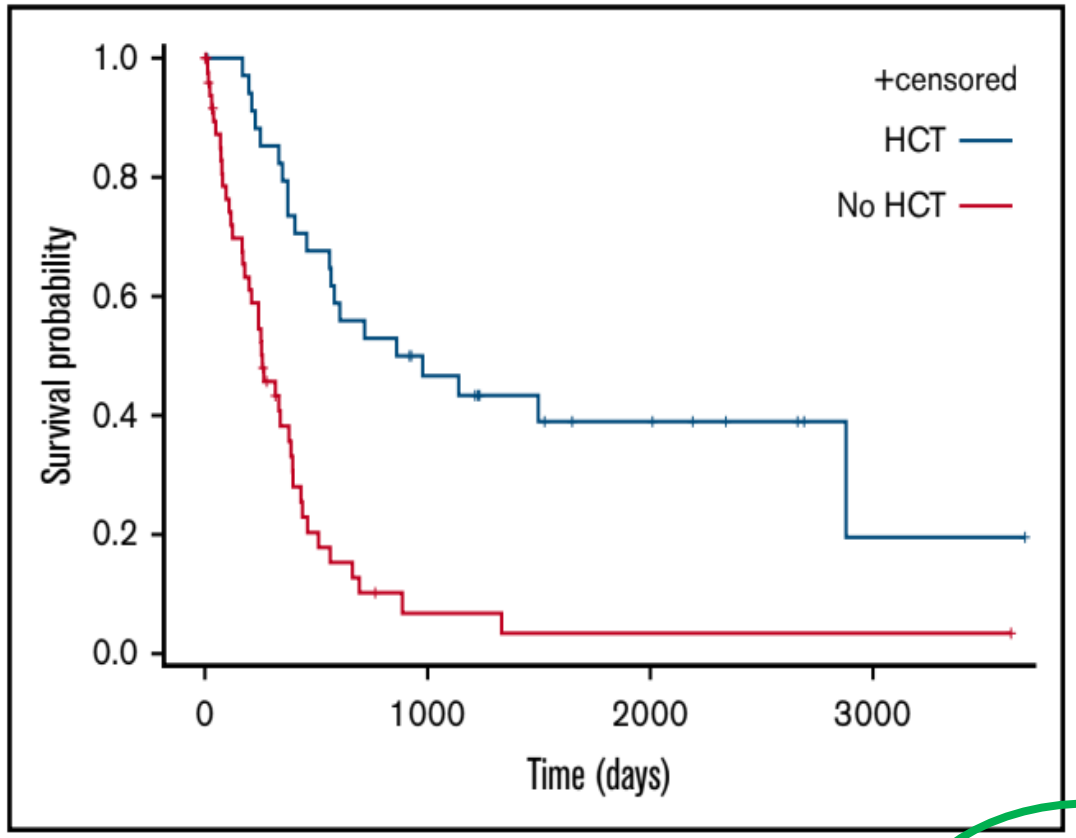
*Data



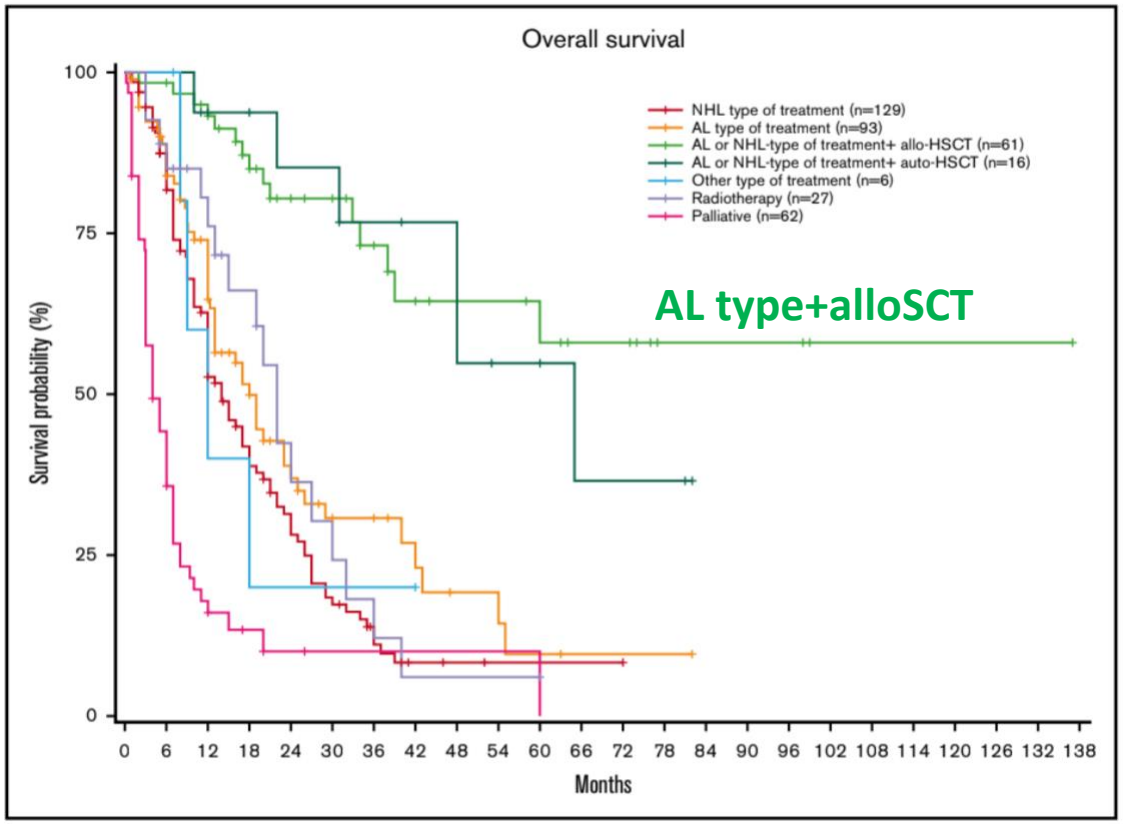
New approaches are required!

Garnache-Ottou F et al, Blood Adv 2019

AlloHSCT is mandatory in young/fit BPDCN patients



Garnache-Ottou F et al, Blood Adv 2019



Laribi K et al, Blood Adv 2020

New approaches are required!

Treatment (I)

We decided to start treatment according to **HyperCVAD** schedule (Doxorucibicin reduced by 25% due to previous myocardial infarction) and to start MUD research

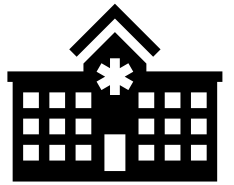
- HyperCVAD 1 st course : morphological CR
- HyperCVAD 2nd course: morphological CR, MRD IF + (0.047%)
- HyperCVAD 3rd course: morphological **CR, MRD neg** **DONOR NOT AVAILABLE YET**
- HyperCVAD 4th course: morphological CR, **MRD IF+ (0.1%)**

Lumbar punctures performed monthly: always negative for CNS involvement

No relevant adverse events occurred during the chemotherapy program

Due to the **MRD positivity** detected **after the fourth course** of chemotherapy, we asked for compassionate use of **Tagraxofusp**, in order **to «bridge» the patient to an alloHSCT avoiding further chemotherapy**

Tagraxofusp

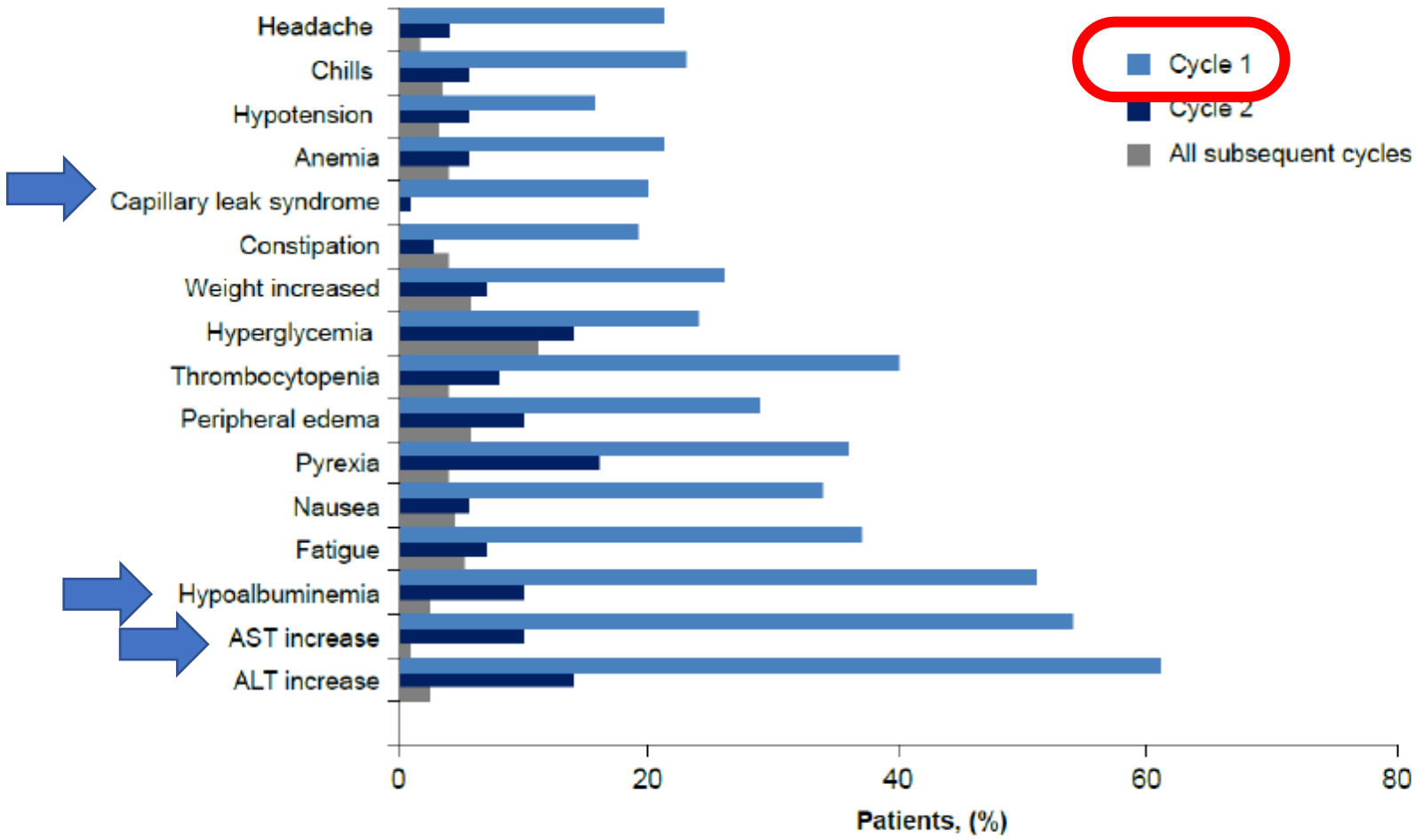


- Before Tagraxofusp administration: WBC 8100/mmc, N 69%, Hb 12 g/dl, PLTs 160000/mmc. Liver and kidney functions were in range
- CNS: negative
- Echocardiogram: EF 63%

- He received 1 course of therapy with **Tagraxofusp (5 days) at the dosage of 12 mcg/kg/die**

Which adverse events may occur with Tagraxofusp? And when?

AE	Total (N = 89), No. (%)
AE leading to discontinuations	6 (7)
AE leading to dose interruption	61 (69)
Weight increased	24 (27)
AST increased	17 (19)
ALT increased	15 (17)
Hypoalbuminemia	14 (16)
AEs of any grade that occurred in at least 20% of patients	
ALT increased	57 (64)
AST increased	53 (60)
Hypoalbuminemia	45 (51)
Fatigue	39 (44)
Pyrexia	39 (44)
Thrombocytopenia	38 (43)
Nausea	37 (42)
Edema peripheral	37 (42)
Weight increased	31 (35)
Hyperglycemia	27 (30)
Chills	24 (27)
Headache	22 (25)
Constipation	22 (25)
Anemia	21 (24)
Hypotension	21 (24)
CLS	19 (21)
Hypokalemia	18 (20)
Hypocalcemia	18 (20)
At least one grade ≥ 3 TEAE	75 (84)
Thrombocytopenia	29 (33)
ALT increased	28 (32)
AST increased	27 (30)



Pemmaraju N et al, JCO 2022

CLS prevention and management

Time of Presentation	CLS Sign/Symptom	Recommended Action	Tagraxofusp Dosing Management
Prior to first dose of tagraxofusp in cycle 1	Serum albumin <3.2 g/dL	Administer tagraxofusp when serum albumin ≥3.2 g/dL	
	Serum albumin <3.5 g/dL	Administer 25 g IV albumin (q12h or more frequently as practical) until serum albumin is ≥3.5 g/dL AND not reduced by ≥0.5 g/dL from the value measured prior to dosing initiation of the current cycle	Hold tagraxofusp dosing until the relevant CLS sign/symptom has resolved as specified by recommended action*
	Serum albumin reduced by ≥0.5 g/dL from the albumin value measured prior to tagraxofusp dosing initiation of the current cycle		
	A pre-dose body weight that is increased by ≥1.5 kg over the previous day's pre-dose weight	Administer 25 g IV albumin (q12h or more frequently as practical), and manage fluids and blood pressure, as clinically indicated, until body weight increase has resolved (i.e., the increase is no longer ≥1.5 kg from the previous day's pre-dose weight)	
During tagraxofusp dosing	Edema, fluid overload, and/or hypotension	Administer 25 g IV albumin (q12h, or more frequently as practical) until serum albumin is ≥3.5 g/dL.	
		Administer 1 mg/kg of methylprednisolone (or an equivalent) per day, until resolution of CLS sign/symptom or as clinically indicated.	
		Aggressive management of fluid status, including hypotension if present, which could include IV fluids and/or diuretics or other blood pressure management, until resolution of CLS sign/symptom or as clinically indicated.	

Pemmaraju N et al, JCO 2022

Toxicity was manageable

- He received **Albumin replacement** on days 2,3,4,7,8,9,10
- He developed a **G4 Thrombocytopenia** on day 13 and a G3 Neutropenia on day 20. They both recovered in 10 and 11 days, respectively

After 1 course of Tagraxofusp:
BM: morphological CR, **MRD+ (0.7%)**

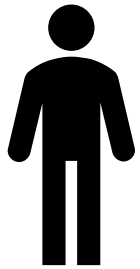
In June 2020 the patient underwent an alloSCT, from a 10/10 MUD
Conditioning regimen: Thiotepa Busulfan Fludarabine ATG
Skin G1 aGVHD

He's alive, in **CR MRD- after about 3 years** from alloSCT

Tagraxofusp experience at Bologna Hematology Institute

	Sex	Age at diagnosis	Sites of disease at diagnosis	Lines before Tag	Sites of disease before Tag	Number of Tag courses	alloSCT	Status
Pt 1	M	76	Skin	2	Skin, BM, Lymph nodes	1 dose (course 1)	No	Died (cerebral hemorrhage)
Pt 2	M	72	Skin, BM, Lymph nodes	1	Skin, BM, Lymph nodes nasopharynx, CNS	3 doses (course 1)	No	Died (COVID19 pneumonia)
Pt 3	M	67	Bone marrow	1	Bone marrow MRD+	1	YES	Alive (+30 mths SCT)
Pt 4	M	47	Bone marrow	0	Bone marrow	2	YES	Alive (+2 years SCT)
Pt 5	F	53	Skin, Bone marrow MRD+	0	Skin, Bone marrow MRD+	7	NO	Alive (+ 8 months dg)

Pt 4, 47 years



Worsening of fatigue and general conditions

August 2020

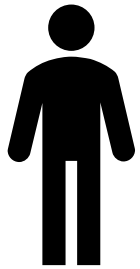
Blood tests:

Pancytopenia

WBC 2410/mmc (BC 20%) , Hb 10.9 g/dl, PLTs 73000/mmc

Referred to Hematology Unit

Diagnostic work-up (I)

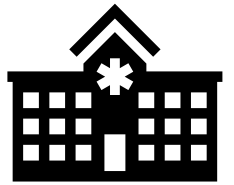


- Past medical history: autoimmune hypothyroidism

- At clinical examination: no splenomegaly, no hepatomegaly, **no skin lesions**
- Peripheral counts: WBC 2100/mmc (BC 20%) , Hb 10 g/dl, PLTs 71000/mmc
- Peripheral blood immunophenotype: blast cells 20% CD34-, HLADR+, CD7+/-, CD33low, **CD56+ bright**, **CD123+**
- Bone marrow biopsy: **blast cells 30-40%**
- Immunohistochemistry: CD2+, CD7+, CD68PGM1-, CD163-, TdT+, CD4-, **CD56+, TCL1+**, **CD123+**
- Cytogenetics: not evaluable
- Molecular biology: NPM wt, FLT3 wt, TP53 wt, ratio WT1/ABLx10.000 9.40
- PET: negative

Which treatment for this patient?

Tagraxofusp as first line



- October 1st 2020: **Tagraxofusp course 1** was started
- Day 4: AST>5xULN increase, so therapy was not administered on days 4 and 5
- Albumin was replaced on days 5,6,7,8,9,10
- Grade **III thrombocytopenia** occurred on day 14

- BM evaluation **after course 1: morphological CR, MRD+ IF (2.5 %)**
- **Monthly lumbar punctures** were performed, always negative for CNS involvement

Tagraxofusp as first line and alloSCT

- November 4th 2020 : **Tagraxofusp course 2** was started
- Peripheral counts: WBC 3400/mmc, N 76%, Hb 14 g/dl, PLTs 301000/mmc
- Liver and kidney tests were all in range (AST-ALT recovered after 15 days from the end of course 1)
- Therapy well tolerated, no adverse events occurred

- Bone marrow evaluation **after course 2: morphological CR, MRD+ IF (0.5%)**
- In December 2020 he underwent an **alloSCT** (MUD HLA 9/10, source PBSC)
- Conditioning regimen: Thiotepa Busulfan Fludarabine ATG
- No GVHD occurred

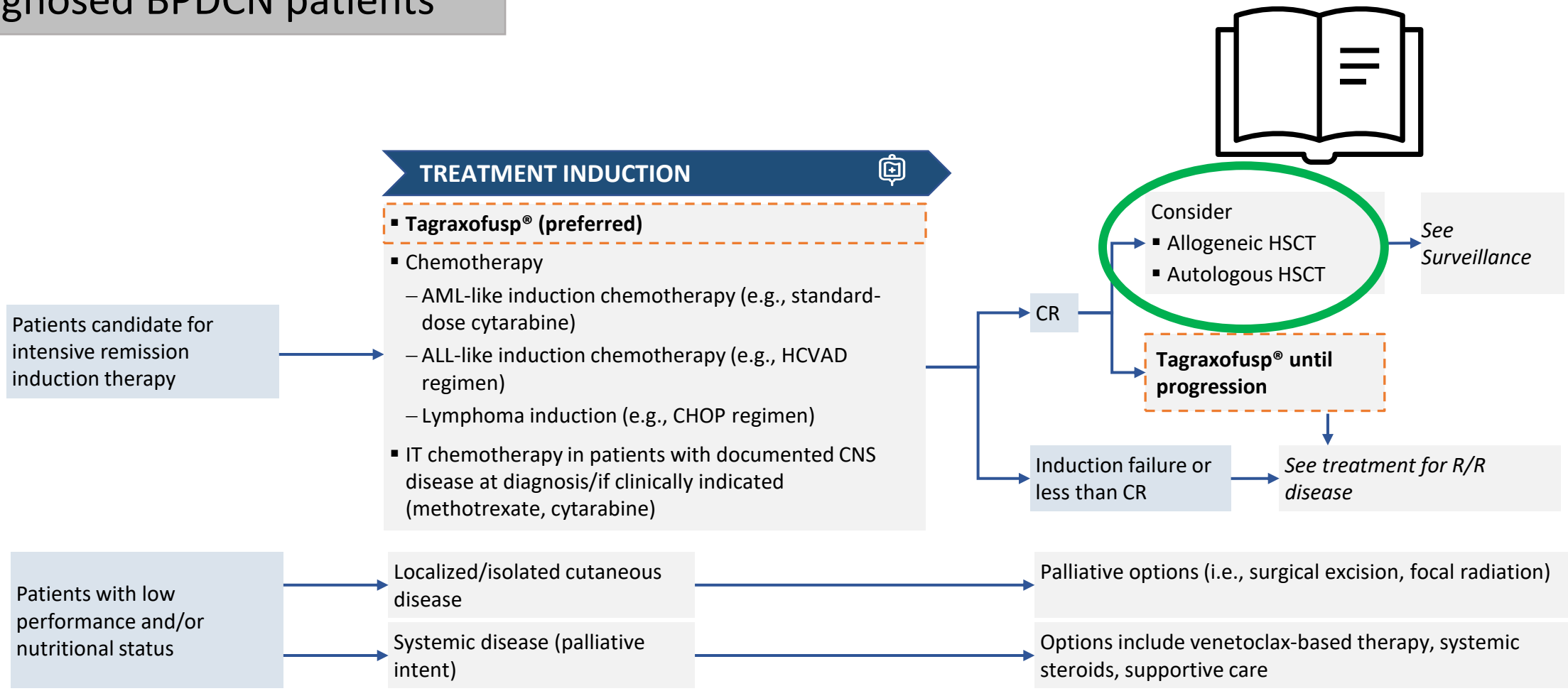
- **The patient is alive in MRD- CR after 28 months from alloSCT**

Tagraxofusp experience at Bologna Hematology Institute

	Sex	Age at diagnosis	Sites of disease at diagnosis	Lines before Tag	Sites of disease before Tag	Number of Tag courses	alloSCT	Status
Pt 1	M	76	Skin	2	Skin, BM, Lymph nodes	1 dose (course 1)	No	Died (cerebral hemorrhage)
Pt 2	M	72	Skin, BM, Lymph nodes	1	Skin, BM, Lymph nodes nasopharynx, CNS	3 doses (course 1)	No	Died (COVID19 pneumonia)
Pt 3	M	67	Bone marrow	1	Bone marrow MRD+	1	YES	Alive (+30 mths SCT)
Pt 4	M	47	Bone marrow	0	Bone marrow	2	YES	Alive (+2 years SCT)
Pt 5 ★	F	53	Skin, Bone marrow MRD+	0	Skin, Bone marrow MRD+	7	NO	Alive (+ 8 months dg)

SHE DOESN'T WANT TO PERFORM ALLOSCT

NCCN Guidelines for newly diagnosed BPDCN patients

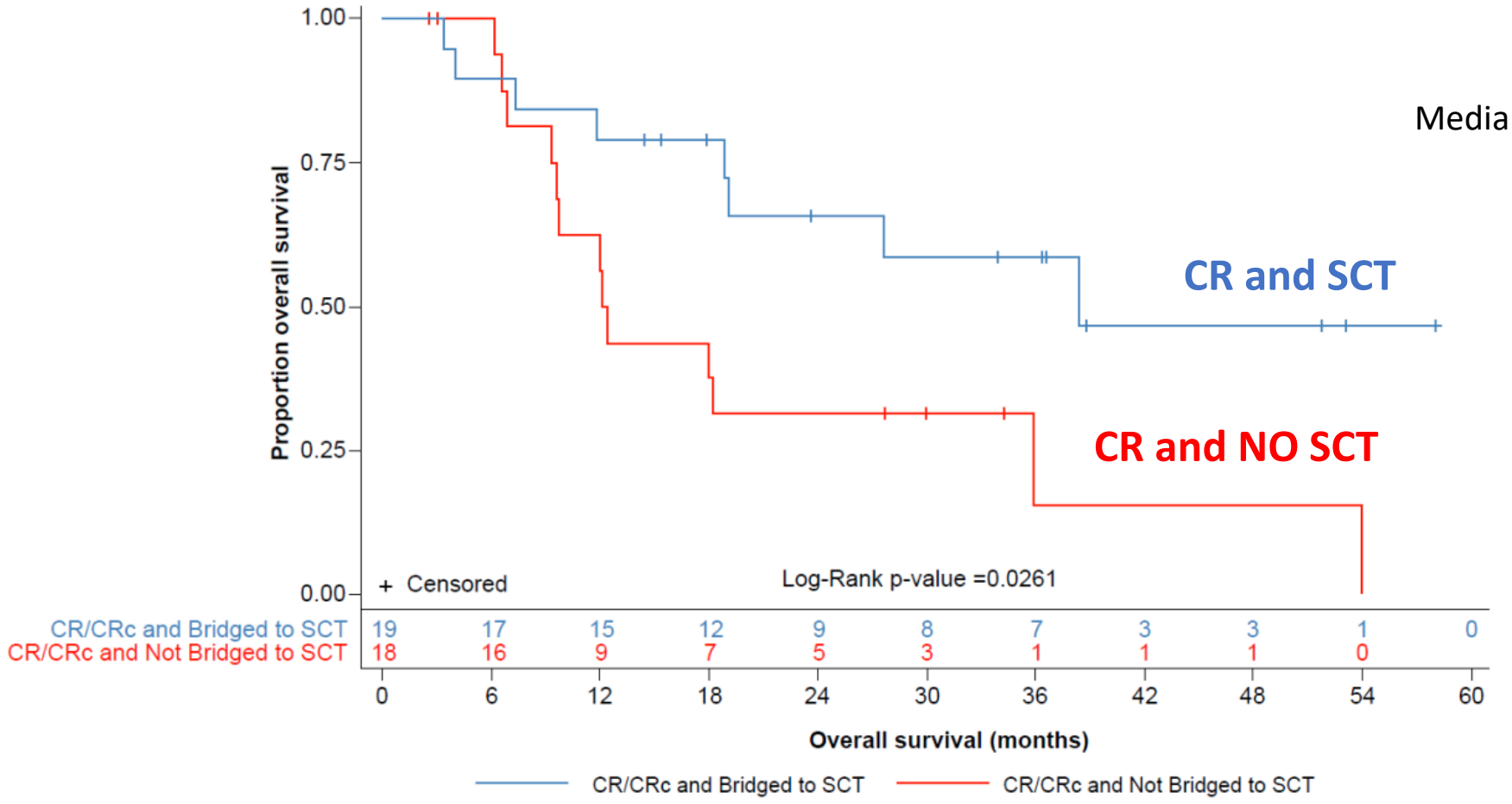


Tagraxofusp is the only EMA and FDA-approved treatment for BPDCN recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[1]

Note: ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CNS: central nervous system; CR: complete response; HCVAD: hyper fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; HSCT: hematopoietic stem cell transplantation; IT: intrathecal therapy; R/R: relapsed/refractory

Source: NCCN AML guidelines, 2022

Long term outcome with Tagraxofusp w/wo alloSCT



Median follow up: 34 months

Pemmaraju N et al, JCO 2022

Take home messages

- **Early, accurate diagnosis is essential**; any **delays** in the time before BPDCN is recognized can mean that **disease progression** may have already occurred
- Diagnosis of BPDCN requires a **multidisciplinary team**
- The use of Tagraxofusp in patients with **advanced disease**, when clinical conditions are compromised, may offer **limited results**. As a consequence, **an earlier use should be preferable**

✓ **Safety profile** in our experience was **good**, with **manageable adverse events** (liver toxicity)

✓ No **CLS** occurred

✓ **Albumin monitoring and replacement** should be administered, in particular during course 1, and guidelines remark very clearly this point

✓ The best Tagraxofusp performance is made as **«bridge» to alloSCT option**

Speaker's opinion

What's next?

IMPROVE EXPERTISE

- Creation of **multidisciplinary teams** with **expertise** in the field
- Sharing knowledges
- Discovering **biological insights for innovative combined approaches**

IMPROVE DIAGNOSIS

- Quickly **identification of BPDCN patients**, reducing delays to improve outcome

TREAT PATIENTS

- Allow more and more patients to **receive a targeted treatment**, and to improve outcome
- Development of **combination strategies**

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

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
Cinzia Bonajuto
Claudia Romano
Francesco Ingletto