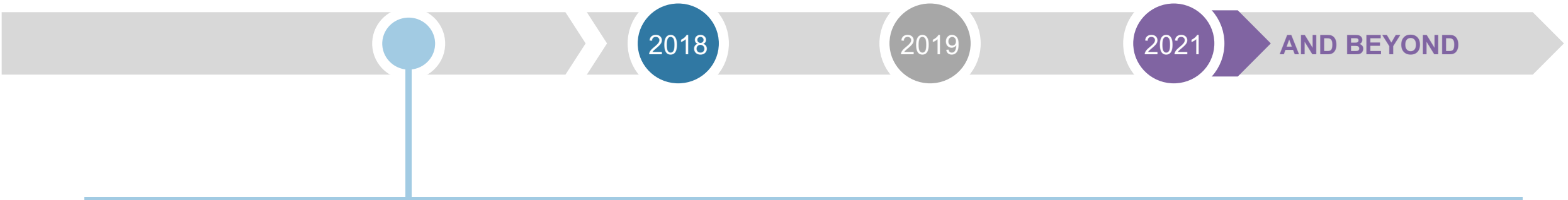
BPCDN: lo stato dell'arte: passato, presente e futuro

F. Ferrara (Napoli)

Historical Treatment of BPDCN



Historically, standard frontline therapy was not established for patients with advanced-stage BPDCN[1]

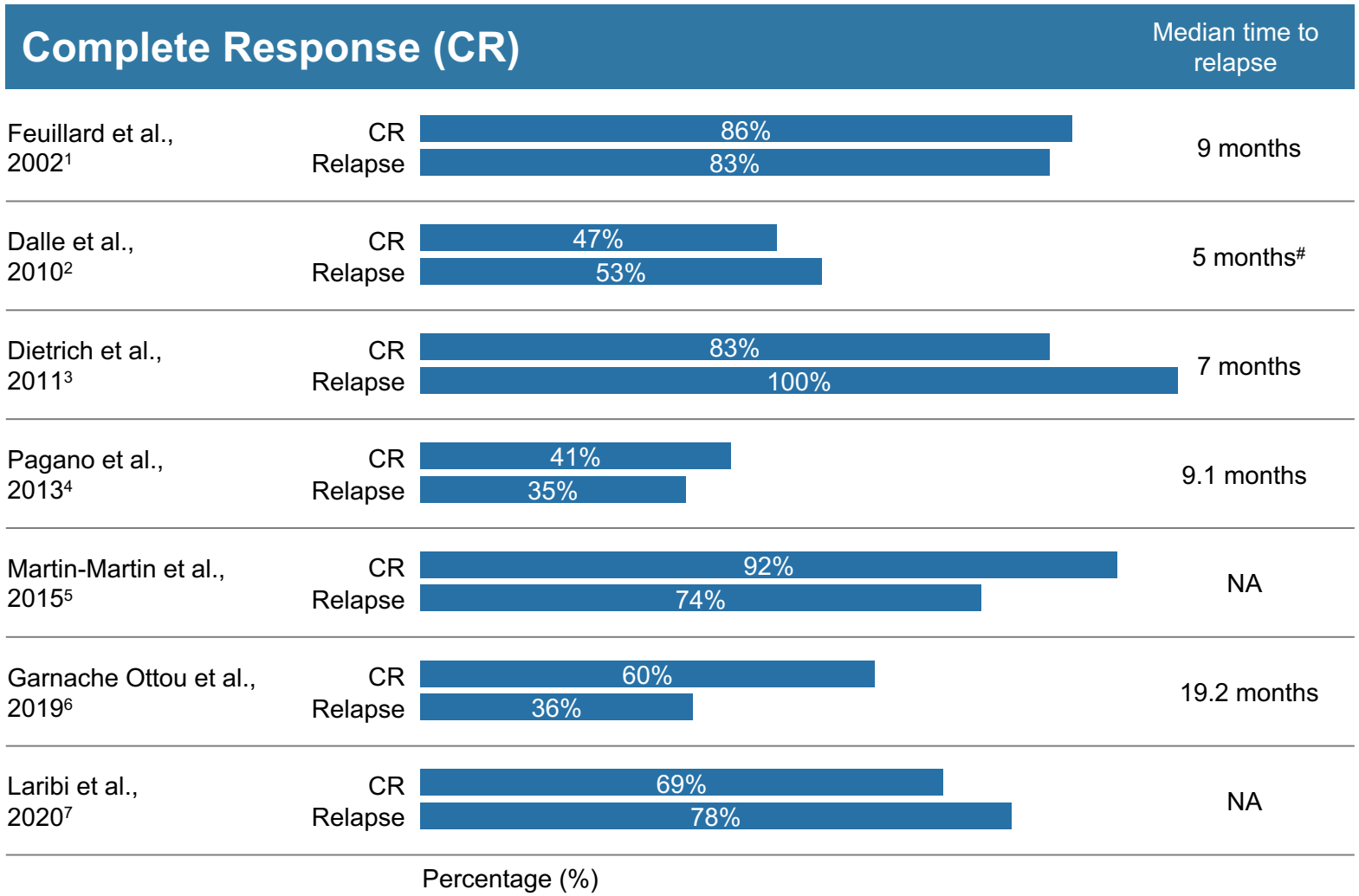
- Participation in a clinical trial was encouraged[1]
- Multi-agent chemotherapy regimens inspired by AML, ALL or NHL
- Although patients initially respond to chemotherapy, they almost universally relapse soon thereafter and progress rapidly[1,2]

BPDCN = blastic plasmacytoid dendritic cell neoplasm.

References: 1. Riaz W, et al. Cancer Control. 2014;21(4):279-289. 2. Pemmaraju N. Curr Hematol Malig Rep. 2017;12(6):510-512.

Historically, chemotherapy has been used to treat BPDCN

- It is well established that chemotherapies have a high CR with a very fast relapse, thus not translating into overall survival (OS)



* Combined rate of complete response (CR/CRC); # Mean relapse free survival.

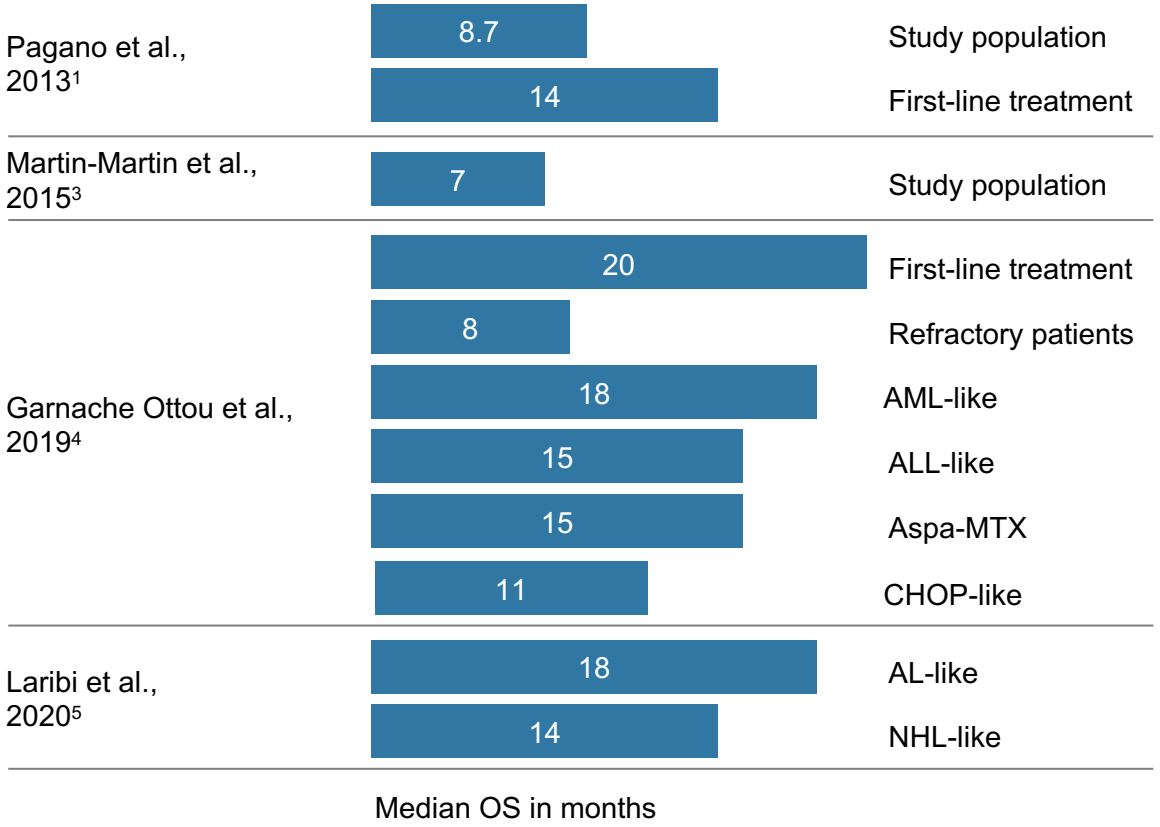
BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete response; NA = not assessed; OS = overall survival.

References: 1. Feuillard J, et al. Blood. 2002 Mar 1999(5):1556-1563. 2. Dalle S, et al. Br J Dermatol. 2010 Jan;162(1):74-79. 3. Dietrich S, et al. Biol Blood Marrow Transplant. 2011 Aug;17(8):1250-1254. 4. Pagano L, et al. Haematologica. 2013;98(2):239-246. 5. Martín-Martín L, et al. Oncotarget. 2015 Aug 7;6(22):19204-19216. 6. Garnache-Ottou F, et al. Blood Adv. 2019 Dec 23;3(24):4238-4251. 7. Laribi K, et al. Blood Adv. 2020 Oct 13;4(19):4838-4848.

Historically, chemotherapy has been used to treat BPDCN

- No prospective studies investigating chemotherapy regimen in the treatment of BPDCN have been performed
- A variety of retrospective analyses provide some insights into the effectiveness of chemotherapies for the treatment of BPDCN
- Studies have reported a 24-months overall survival of 7-25% for patients with BPDCN treated with chemotherapy[1,2]

Median Overall Survival (mOS)



AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; AL = acute lymphoblastic leukemia ; Aspa-MTX = asparaginase-methotrexate; BPDCN = blastic plasmacytoid dendritic cell neoplasm; mOS = median overall survival; NA = not assessed; NHL = non-Hodgkin lymphoma.

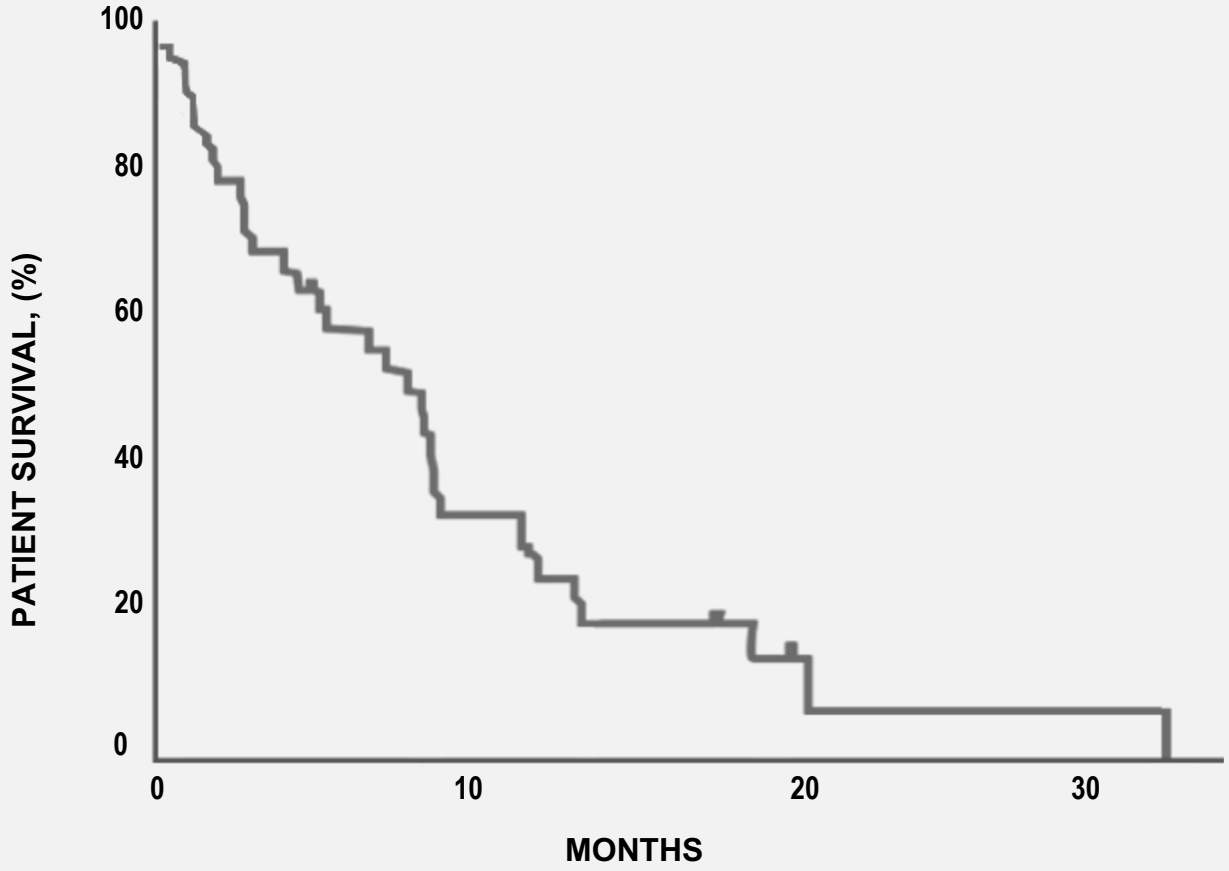
References: 1. Pagano L, et al. Haematologica. 2013;98(2):239-246. 2. Feuillard J, et al. Blood. 2002 Mar 1999(5):1556-1563. 3. Martín-Martín L, et al. Oncotarget. 2015 Aug 7;6(22):19204-19216. 4. Garnache-Ottou F, et al. Blood Adv. 2019 Dec 23;3(24):4238-4251. 5. Laribi K, et al. Blood Adv. 2020 Oct 13;4(19):4838-4848.

Historically, Clinical Outcomes for BPDCN Have Been Poor

BPDCN rapidly progresses to behave like acute leukemia with high risk factors[1,2]

Median overall survival for BPDCN is approximately **8 to 14 months after diagnosis**[2,3]

Historical Overall Survival[2]



BPDCN = blastic plasmacytoid dendritic cell neoplasm.

References: 1. Riaz W, et al. Cancer Control. 2014;21(4):279-289. 2. Pagano L, et al. Haematologica. 2013;98(2):239-246. 3. Pemmaraju N. Curr Hematol Malig Rep. 2017;12(6):510-512.

Chemotherapy regimens for the treatment of BPDCN

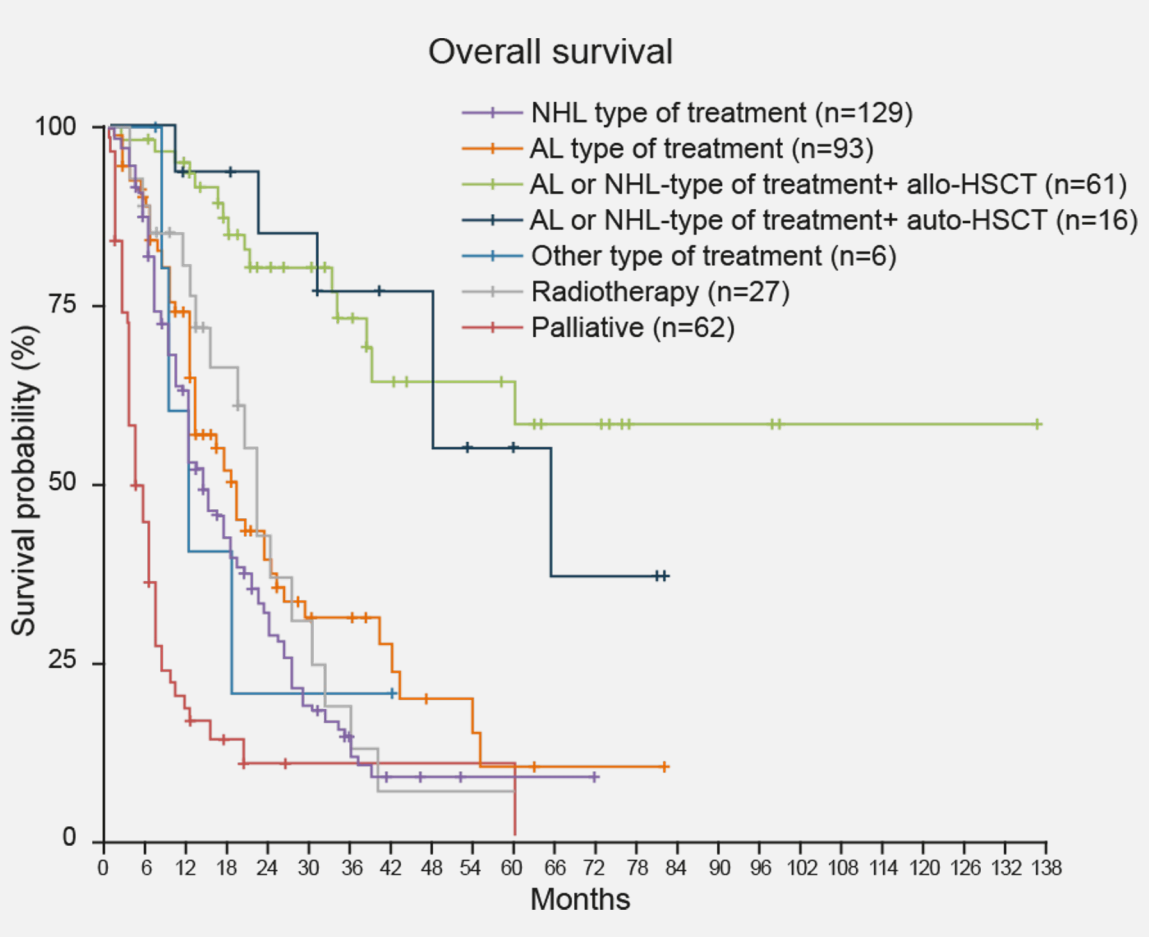
Results of an international survey on 398 adult patients

- A total of 398 patients from 75 centers were included in the study.
- Treatment consisted of
  - non-Hodgkin lymphoma (NHL)–like regimens [129 (32.8%) patients]
  - acute leukemia (AL)–like regimens [113 (23.5%) patients]
  - Allogeneic hematopoietic stem cell transplantation (HSCT) [61 (15.5%)]
  - Autologous HSCT [16 (4.1%)]
  - Radiotherapy [27 (6.9%) patients]
  - New agents* [6 (1.5%)]
  - Palliative care [62 (15.7%)].

NHL- or AL-type therapy, followed by consolidation transplantation strategies, showed the best outcomes for patients with BPDCN.

Any stem cell transplantation should be a goal for the treatment of BPDCN

OS according to each type of treatment



*Tagraxofusp, bortezomib, 5-azacitidine, venetoclax

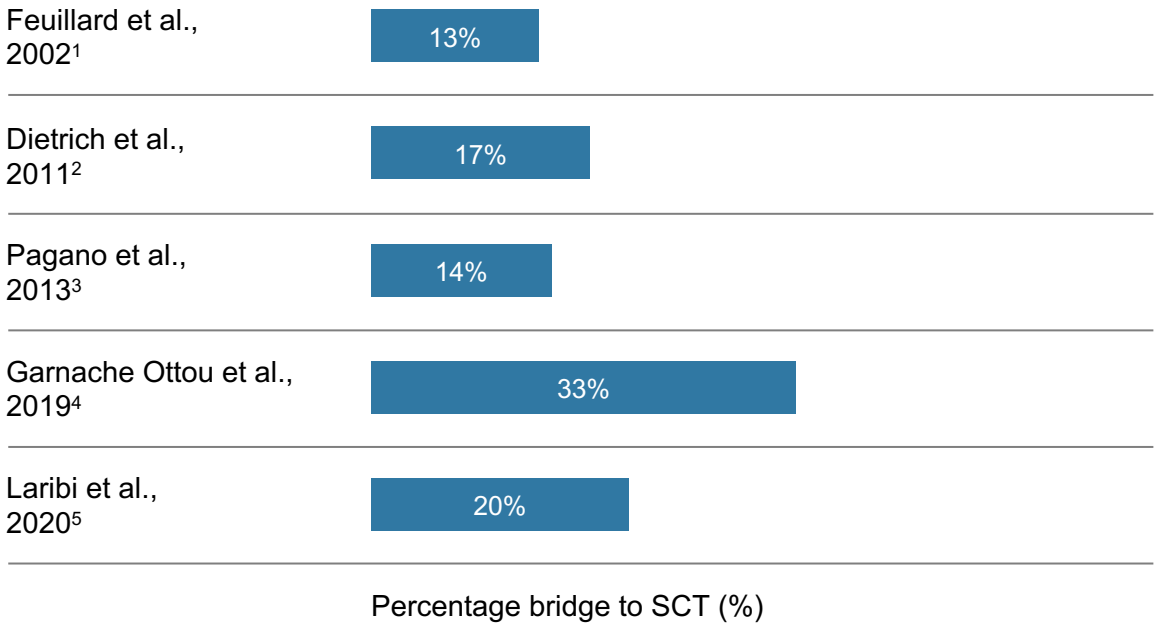
AL = acute leukemia; BPDCN = blastic plasmacytoid dendritic cell neoplasm; HSCT = hematopoietic stem cell transplantation; NHL = non-Hodgkin lymphoma.

References: 1. Laribi K, et al. Blood Adv. 2020 Oct 13;4(19):4838-4848.

Historically, chemotherapy has been used to treat BPDCN

- Intensive chemotherapies used to achieve a CR that is durable enough to enable a subsequent SCT come with significant toxicities.
- Toxicity of chemotherapies can turn down potential candidates for SCT
- Intensive chemotherapy-induced remission leading to bridge to transplant is a limited option in a largely middle-aged to elderly patient population who often have comorbid conditions

Bridge to Stem Cell Transplantation



BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete response; SCT = stem cell transplantation.

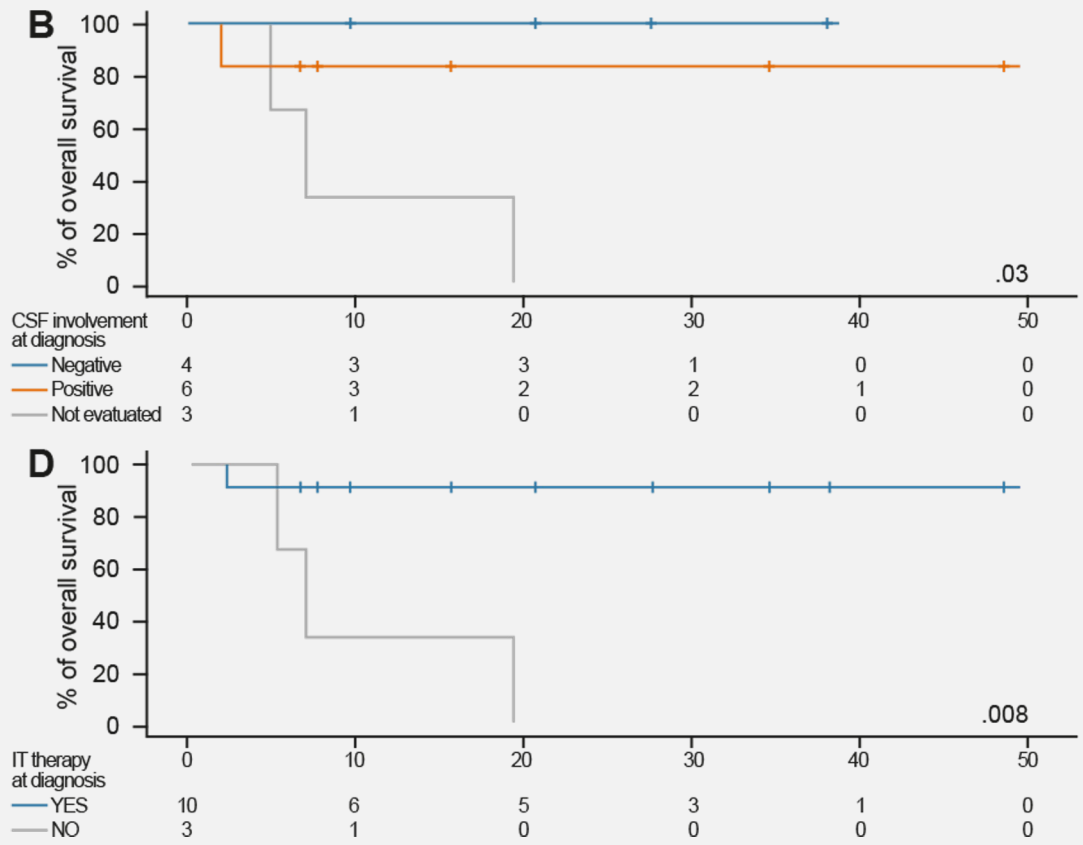
References: 1. Feuillard J, et al. Blood. 2002 Mar 1999(5):1556-1563. 2. Dietrich S, et al. Biol Blood Marrow Transplant. 2011 Aug;17(8):1250-1254. 3. Pagano L, et al. Haematologica. 2013;98(2):239-246. 4. Garnache-Ottou F, et al. Blood Adv. 2019 Dec 23;3(24):4238-4251. 5. Laribi K, et al. Blood Adv. 2020 Oct 13;4(19):4838-4848.

CNS involvement in BPDCN

Central nervous system (CNS) is involved in up to 30% of BPDCN cases[1]

- **Guidelines recommend LP** to rule out CNS disease at diagnosis and disease relapse[2]
- In addition to intensive chemotherapy, **intrathecal chemotherapy** may be indicated in the treatment of disease[2-5]
  - Treatment with intrathecal therapy at diagnosis seems to strongly impacts the overall survival of patients with BPDCN[3]

PROGNOSTIC IMPACT OF OCCULT CSF INVOLVEMENT and administration of IT therapy AT DIAGNOSIS OF BPDCN[3]



CSF = cerebrospinal fluid; IT = intrathecal; LP = lumbar puncture.

References: 1. Deconinck E, et al. Hematol Oncol Clin North Am. 2020;34(3):491-500. 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.3.2020. Accessed July 2020. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1411. 3. Martín-Martín L, et al. Oncotarget. 2016;7(9):10174-10181. 4. Pagano L, et al. Haematologica. 2013;98(2):239-246; 5. Pemmaraju N, et al. Blood. 2021 Jun 7:blood.2021011817.

Goals of Treatment

- Stem cell transplantation (SCT) may offer the best chance of remission in select cases, where the patient is in a durable complete remission **and** is a candidate for SCT[1,2]
  - Most patients with BPDCN are older, have multiple comorbidities, or are unfit for SCT[2]

BPDCN = blastic plasmacytoid dendritic cell neoplasm; SCT = stem cell transplantation.

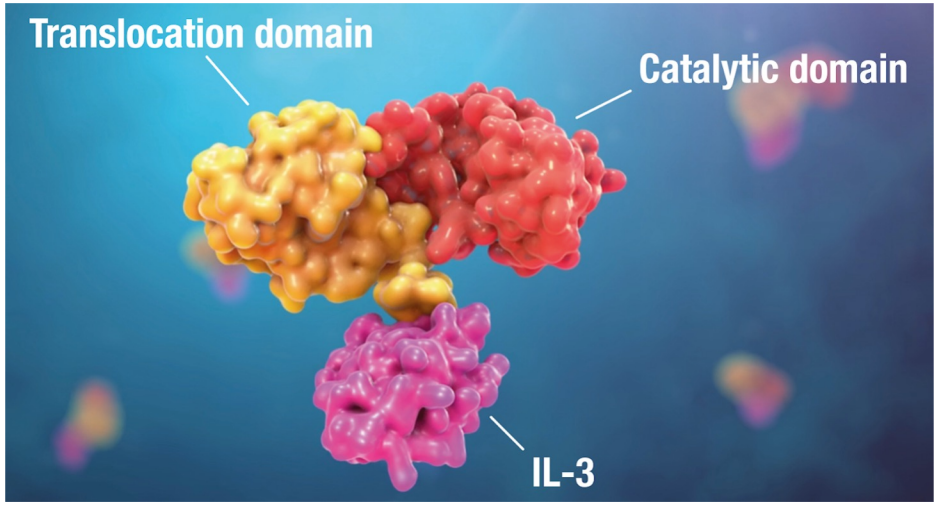
References: 1. Riaz W, et al. Cancer Control. 2014;21(4):279-289. 2. Pemmaraju N. Curr Hematol Malig Rep. 2017;12(6):510-512.

Tagraxofusp in BPDCN

Please see full Summary of Product Characteristics (SmPC).
The SmPC is available on the website of the European Medicines Agency http://www.ema.europa.eu

Structure of Tagraxofusp

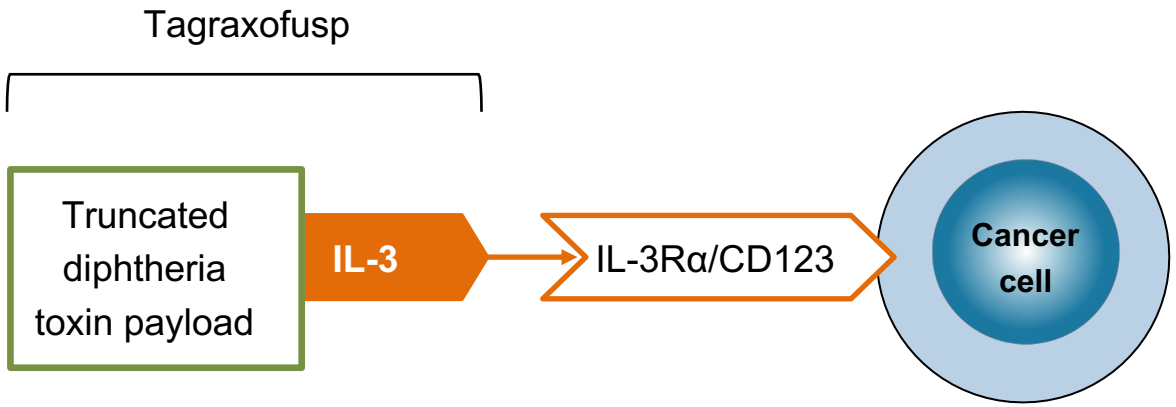
- The active substance, tagraxofusp, is a 524-amino acid, recombinant non-glycosylated fusion protein expressed in an *Escherichia coli* cell line.[1]
- Tagraxofusp is composed of human IL-3 and truncated diphtheria toxin that inhibits protein synthesis and induces apoptosis in cells expressing the IL-3 receptor. [1]
- The finished product is a concentrate for solution for infusion presented as a single use, sterile aqueous solution at a concentration of 1mg/mL in a 2mL vial.[1]



BPDCN = blastic plasmacytoid dendritic cell neoplasm; CD = cluster of differentiation; DT = diphtheria toxin; His-Met IL-3 = interleukin-3.

References: 1. EMA assessment report, Procedure No. EMEA/H/C/005031/0000. 2. Alkharabsheh O, Frankel AE. Biomedicines. 2019 Jan 5;7(1):6.

Tagraxofusp: Targeted Therapy Directed to the IL-3 Receptor (IL-3Rα / CD123)



- Interleukin receptor (IL)-3Rα/CD123 is expressed in BPDCN and in many other hematologic cancers[1-5]
- Tagraxofusp (SL-401) is a targeted therapy directed to CD123[1]
- Tagraxofusp has shown activity against BPDCN cells *in vitro* and *in vivo*[1,7]

BPDCN = blastic plasmacytoid dentritic cell neoplasm; CD = Cluster of Differentiation; IL = interleukin; CR = complete response; PR = partial response.

References: 1. Frankel AE, et al. Blood. 2014;124(3):385-392. 2. Laribi K, et al. Biol Blood Marrow Transplant. 2016;22(8):1357-1367. 3. Facchetti F, et al. Mod Pathol. 2016;29(2):98-111. 4. Pagano L, et al. Haematologica. 2013;98(2):239-246. 5. Pemmaraju N. Curr Hematol Malig Rep. 2017;12(6):510-512. 6. Patnaik MM, et al. Leuk Lymphoma. 2021 Nov;62(11):2568-2586. 7. Frankel AE, et al. Leukemia (2000) 14, 576–585.

Regulatory History of Tagraxofusp

11 November 2015

Tagraxofusp **designated orphan medicine** for the treatment of BPDCN

Tagraxofusp **submitted to the EMA** for approval as treatment for adult patients with BPDCN

7 January 2019

23 July 2020

Marketing authorization for the treatment of all BPDCN-patients regardless of previous treatments denied by CHMP

Request of re-examination of tagraxofusp

5 August 2020

12 November 2020

EMA **recommended granting marketing authorization** for tagraxofusp under exceptional circumstances

Approval by MHRA **in the UK** under exceptional circumstances with orphan drug designation

15 October 2021

Tagraxofusp has been indicated as monotherapy for the first-line treatment of adult patients with BPDCN in the EU and should be administered under the supervision of a physician experienced in the use of anti-cancer agents.

BPDCN = blastic plasmacytoid dendritic cell neoplasm; CHMP = Committee on Human Medicinal Products; EMA = European Medicines Agency; MHRA = Medicines and Healthcare products Regulatory Agency.

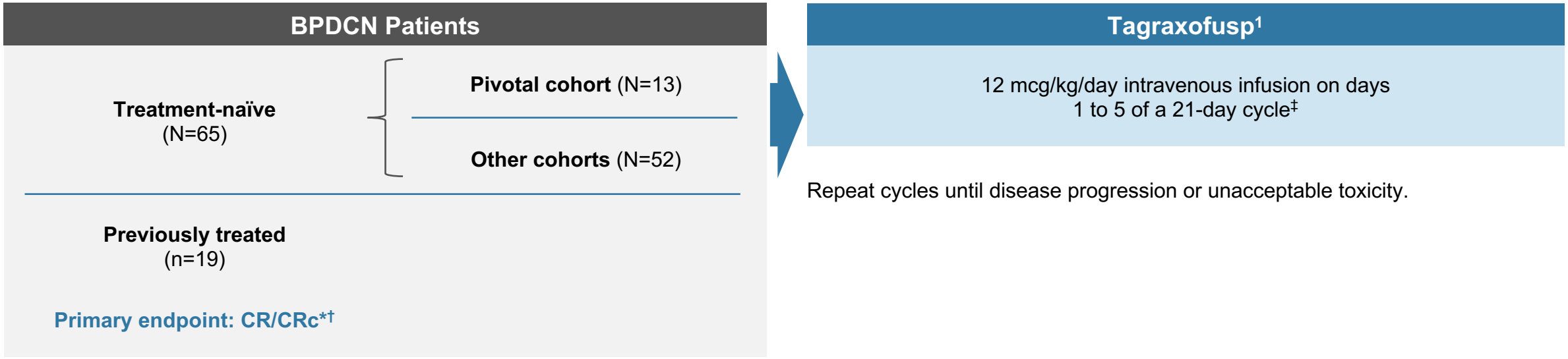
References: 1. EMA assessment report, Procedure No. EMEA/H/C/005031/0000.

Tagraxofusp – study design

Study design for STML-401-0114 clinical trial[1,2]

Phase I/II, non-randomized, **open-label, single-arm**, multicentre study

The most extensive prospective trial ever designed to test the effect of tagraxofusp in BPDCN patients



* Complete response (CR) criteria: normalization of blast percentage (≤ 5 %) in the bone marrow; normalization of neutrophil count (≥ 1,000/µL) and platelet count (≥ 100,000/µL) in the peripheral blood; absence of leukemic blasts in the peripheral blood; 100 % clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline; regression of nodal masses to normal size on CT; no palpable nodules on the spleen or liver.[1,2]

† Clinical complete response with minimal residual skin abnormality (CRc) criteria: marked clearance of all skin lesions from baseline; residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed).[1,2]

‡ Dosing period may be extended for dose delays up to day 10 of the cycle.[1,2]

BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete response; CRc = clinical complete response.

References: 1. Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034. Epub ahead of print. 2. ELZONRIS® (tagraxofusp). Summary of Product Characteristics https://www.ema.europa.eu/en/documents/product-information/elzonris-epar-product-information_en.pdf

Information on this slide may not be consistent with the approved SmPC. Please consult the full SmPC on the EMA website. A summary is available in this slide deck.

Overview of Study 0114

- Divided into **four stages** which had their own specific goals with the overarching purpose of generating clinical experience with multiple cycles of tagraxofusp
- TAG was administered at 12 mcg/kg/day IV on days 1–5 of each 21-day cycle
  - A 10-day treatment window was allowed to accommodate dose interruptions, if needed
- The primary efficacy endpoint was CR + CRc; CRc† was defined as residual skin abnormality not indicative of active disease

Overall BPDCN population enrolled: 89 BPDCN patients (69 treatment naïve and 20 R/R)*

STAGE 1: **Dose escalation**	STAGE 2: **Expansion at the selected dose**	PIVOTAL COHORT STAGE 3: **Confirmatory of efficacy**	STAGE 4: **Continued access**
OBJECTIVE: Determine the maximum tolerated dose or maximum tested dose (7 and 12 mcg/kg/day doses)	**OBJECTIVE:** Further evaluate efficacy and safety profile of multi-cycle therapy at the recommended dose (12 mcg/kg/day)	**OBJECTIVE:** Provide confirmatory evidence of efficacy in treatment-naïve patients at the recommended dose of 12 mcg/kg/day	**OBJECTIVE:** Provide continued access in a clinical study setting, to further characterize efficacy & safety, and evaluate a lyophilized formulation in a subset of pts

*All patients were treated with 12mcg/kg, except three patients in stage 1 who received 7mcg/kg.

Complete response (CR) criteria: normalization of blast percentage (≤ 5 %) in the bone marrow; normalization of neutrophil count (≥ 1,000/μL) and platelet count (≥ 100,000/μL) in the peripheral blood; absence of leukemic blasts in the peripheral blood; 100 % clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline; regression of nodal masses to normal size on CT; no palpable nodules on the spleen or liver.[1,2]

† Clinical complete response with minimal residual skin abnormality (CRc) criteria: marked clearance of all skin lesions from baseline; residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed).[1,2]

BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete response; CRc = clinical complete response.

References: 1. Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034. Epub ahead of print

Selected Inclusion and Exclusion Criteria

Selected Inclusion Criteria

- Patient population: BPDCN
  - Treatment-naïve or
  - previously-treated
- Age ≥18
- ECOG PS 0-2
  Adequate organ function including:
  LVEF ≥ lower limit of normal,
  creatinine ≤1.5 mg/dL, albumin ≥3.2 g/dL,
  bilirubin ≤1.5 mg/dL, AST/ALT ≤2.5×ULN

Selected Exclusion Criteria

- Persistent clinically significant toxicities from prior chemotherapy
- Received chemotherapy or other investigational therapy within the prior 14 days
- Clinically significant cardiopulmonary disease
- Active or suspected central nervous system (CNS) leukemia
- Receiving immunosuppressive therapy

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; LVEF = left ventricular ejection fraction; ULN = upper limit of normal.

References: 1. Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034. Epub ahead of print

Baseline Demographics of Patients Treated Once Daily With Tagraxofusp 12 mcg/kg (N=84)[1]

PARAMETER	TREATMENT-NAÏVE BPDCN N = 65	PREVIOUSLY TREATED BPDCN N=19
Gender, N (%)		
Male	52 (80)	16 (84)
Race, N (%)		
White	57 (88)	17 (90)
Age (years)		
Median	68	72
Minimum, Maximum	22, 84	44, 87
ECOG, N (%)		
0	31 (48)	7 (37)
1	31 (48)	12 (63)
BPDCN at Baseline, N (%)		
Skin	60 (92)	15 (79)
Bone Marrow	32 (49)	12 (63)
Peripheral Blood	17 (26)	1 (5)
Lymph Nodes	33 (51)	9 (47)
Visceral	9 (14)	4 (21)
Previous lines of therapy – no. (%)**		
1	-	11 (58)
2	-	3 (16)
≥3	-	4 (21)

** not reported for one patient.

BPDCN = blastic plasmacytoid dendritic cell neoplasm; ECOG = eastern cooperative oncology group.

References: 1. Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034. Epub ahead of print

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Tumor Response Criteria for Patients With BPDCN

Location	Complete Response (CR) Criteria	CR (clinical) With Minimal Residual Skin Abnormality (CRc) Criteria
Marrow	Normalization of blast percentage (≤5%)	
Peripheral blood	Normalization of neutrophil count (≥1,000/μL) and platelet count (≥100,000/μL)	
	Absence of leukemic blasts	
Skin*	100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline	Marked clearance of all skin lesions from baseline; residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed)
Nodal masses	Regression to normal size on CT	
Spleen, liver	Not palpable, nodules disappeared	

*The percentage of clearance or increase in skin disease is calculated using the Modified Severity Weighted Assessment Tool (mSWAT).
CRc defined as complete response with minimal residual skin abnormalities not indicative of active disease.
BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete response; CRc = clinical CR; CT = computer tomography.

References: 1. Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034. Epub ahead of print. 2. Cheson BD, et al. J Clin Oncol. 2007 Feb 10;25(5):579-86.

Efficacy

EFFICACY MEASURES FOR TREATMENT-NAÏVE PATIENTS (12 µG/KG BODYWEIGHT)[1]		
PARAMETER	**CONFIRMATORY COHORT (N=13)**	**TREATMENT-NAÏVE BPDCN (N=65)**
CR/CRc* rate, % (n)	54% (7)	57% (37)
Median duration of CR/CRc, months (min, max)	NR 7.3, NR	24.9 3.8, NR
ORR, % (n)	77% (10)	75% (49)
Bridged to stem cell transplantation, % (n)	46% (6)	32% (21)
Bridged to stem cell transplantation after CR+CRc, n (%)	46% (6)	51% (19*)

*Two patients, who achieved a CR/CRc in all disease sites except skin, where a partial response (PR) was confirmed, were offered SCT by the treating physicians

- **The median time to CR/CRc** in treatment-naïve patients was 39 days (range, 14-131 days)[1]**

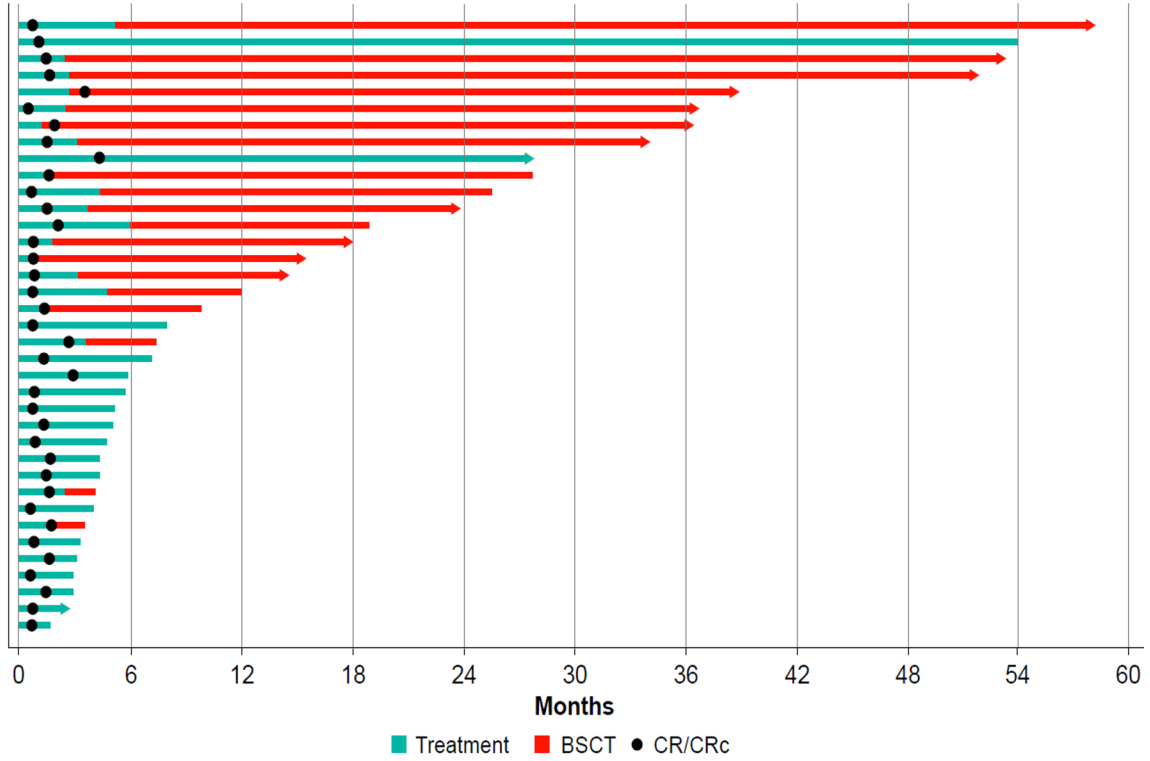
**CRc = clinical complete response; defined as complete response with residual skin abnormality not indicative of active disease.
CR = complete response; CRc = clinical complete response; NR = not reached; ORR = overall response rate.

References: 1. Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034. Epub ahead of print

Best response and treatment duration in treatment naïve patients with BPDCN who achieved CR/CRc[1]

- Overall, 51% of patients (N=19) who achieved CR + CRc were bridged to SCT
  - Autologous SCT, n = 6
  - Allogeneic SCT, n = 13
- Median number of cycles prior to SCT was 4 (range: 2–8)
- **Of patients who achieved CR + CRc and underwent transplant, median OS was 38.4 months (range: 3.4–58.1)**
- Median follow-up post-SCT was 34 months (range: 19–47)
- **72% remaining in remission for ≥12 months post-SCT**
- **The survival probability at 24 months was 66% (95% CI: 43, 88)**

Swimmer Plot-Best Response & Treatment Duration in Treatment-Naïve Patients who Achieved CR/CRc



Each horizontal line represents 1 patient. Color of the bar represents first response and bridge to stem cell transplantation, if applicable. Length of bar represents follow-up through last assessment. Arrow represents patients in remission

CR = complete response; SCT = stem cell transplantation.

References: 1. Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034. Epub ahead of print

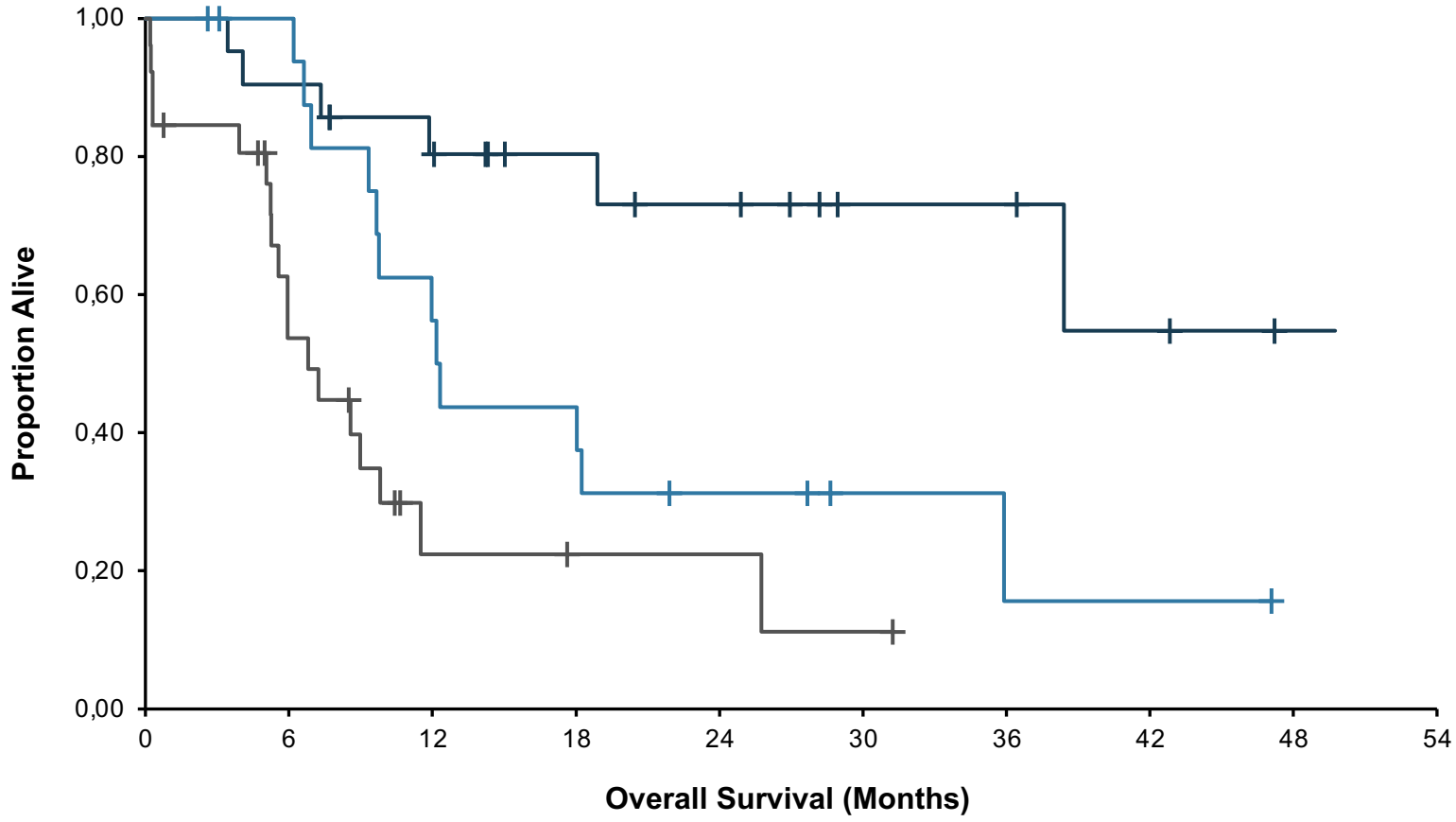
Demographic and Baseline Disease Characteristics (N=65) by Stem Cell Transplant Status

	Bridged to HSCT	Not Bridged to HSCT
	First-Line N= 21	First-Line N= 44
Age (years)		
Median	63	70
Range (min, max)	(22,78)	(23,84)
Race, N (%)		
White	21 (100)	36 (82)
Gender, N (%)		
Male	15 (71)	37 (84)
ECOG Performance Status, N (%)		
0	14 (67)	17 (39)
1	7 (33)	24 (55)
2	0	2 (5)
BPDCN at Baseline, N (%)		
Skin Disease	21 (100)	39 (89)
Bone Marrow Disease	7 (33)	25 (57)
Peripheral Blood Disease	5 (24)	12 (27)
Lymph Node Disease	11 (52)	22 (50)
Visceral Disease	2 (10)	7 (16)
≥ 2 Disease Sites	13 (62)	32 (73)

BPDCN = blastic plasmacytoid dendritic cell neoplasm; ECOG = Eastern Cooperative Oncology Group; HSCT = hematopoietic stem cell transplantation.

References: 1. Pemmaraju N, et al. TCT 2021; Poster 150.

Overall Survival: First-Line Patients by Response & Bridged to HSCT



Bridged to SCT (n=21) CR/CRc and Not Bridged to SCT (n=18) Non-CR/CRc and Not Bridged to SCT (n= 26)

CR/CRc = complete response (clinical); SCT = stem cell transplantation.

References: 1. Pemmaraju N, et al. TCT 2021; Poster 150.

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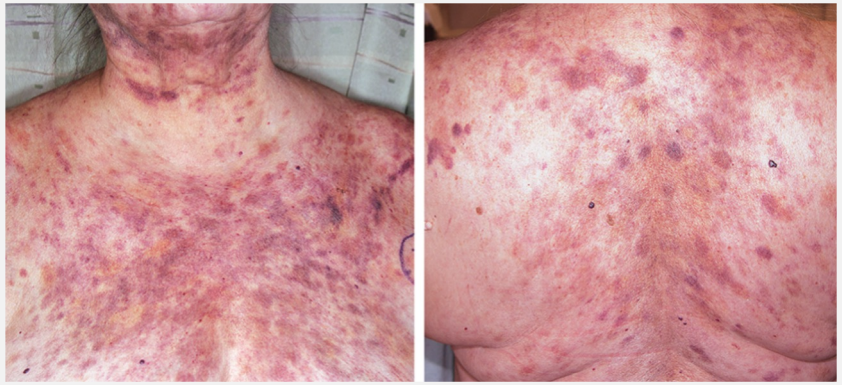
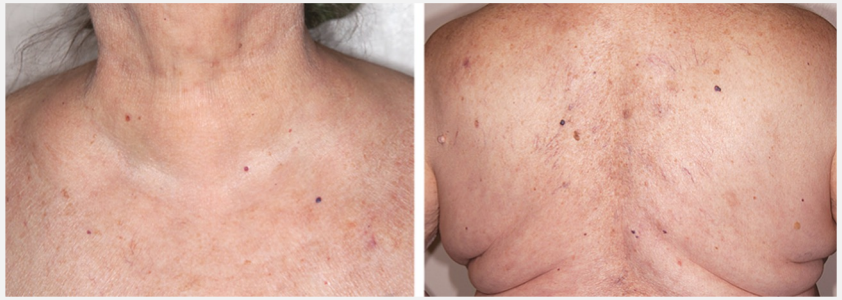
Example of a Dermatologic Response to Tagraxofusp[1]

- Photographs of chest and back of a 71 year old female patient participating in clinical trial
- Treatment naïve patient with extensive skin and bone marrow (BM) involvement
- Received six cycles of tagraxofusp at 12 mcg/kg
- Panel A (baseline): Extensive skin and BM involvement
  - BM blasts – 14%
  - mSWAT – 11.3%
- Panel B (day 21): Skin and BM responses
  - BM blasts – 3%
  - mSWAT – 0%
- Bridged to stem-cell transplantation after achieving CR and 6 cycles of tagraxofusp
- This example portrays a response which can be qualified as good, individual results may vary

A Before Treatment



B Day 21 after Treatment Initiation



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BM = bone marrow; CR = complete response; mSWAT = Modified Severity Weighted Assessment Tool

References: 1. Pemmaraju N, et al. N Engl J Med. 2019;380(17):1628-1637.

Safety of Tagraxofusp[1]

Safety of tagraxofusp was assessed in 176 patients with hematologic malignancies including 89 patients with BPDCN*

TABULATED LIST OF VERY COMMON AND COMMON ADVERSE REACTIONS ≥ GRADE 3		
MEDORA SYSTEM ORGAN CLASS	**FREQUENCY OF ADVERSE REACTIONS ≥ GRADE 3**	
	VERY COMMON (≥1/10)	**COMMON** (≥1/100 to < 1/10)
Blood and lymphatic system disorders	Thrombocytopenia	Febrile neutropenia Anaemia Neutropenia Leukopenia Lymphopenia
Metabolism and nutrition disorders		Tumor lysis syndrome Hyperglycemia Hypoalbuminemia Hyponatremia
Nervous system disorders		Syncope
Vascular disorders		Capillary leak syndrome Hypo tension[a]
Respiratory, thoracic and mediastinal disorders		Hypoxia Pulmonary edema
General disorders and administration site conditions		Fatigue[b]
Investigations	Transaminases increased[c]	

a: Includes procedural hypotension, orthostatic hypotension; b: Includes asthenia, lethargy; c: Includes ALT / AST increased, liver function test increased, hepatic enzyme increased.
* 4 clinical studies, with 88 % of patients receiving 12 mcg / kg bodyweight of tagraxofusp as monotherapy.
BPDCN = blastic plasmacytoid dendritic cell neoplasm; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

References: 1. ELZONRIS® (tagraxofusp). Summary of Product Characteristics. 11/2021.

Safety and Tolerability[1]

- Most common adverse events (AEs; in >40% of patients [N=89, all enrolled patients]) were increased alanine aminotransferase (64%), increased aspartate aminotransferase (60%), hypoalbuminemia (51%), fatigue (44%), pyrexia (43%), thrombocytopenia (43%), nausea (42%), & peripheral oedema (42%)

- **The most common grade 3+ adverse events were thrombocytopenia (29 [33%]), increased alanine aminotransferase (28 [32%]), and increased aspartate aminotransferase (27 [30%])**

- **The median time (range) to capillary leak syndrome (CLS) onset from therapy start was 6 days (range: 3–51) with all but 1 patient experiencing CLS in cycle 1. Median duration of CLS was 6 days (range: 3–69). CLS was managed by dose interruption, albumin supplementation, diuretics, and steroids, per recommended CLS Risk Minimization Guidelines**

Adverse Events Summary	Total BPDCN (N=89)* N (%)
Adverse events of any grade that occurred in at least 20% of the patients	
Alanine aminotransferase increased	57 (64)
Aspartate aminotransferase increased	53 (60)
Hypoalbuminemia	45 (51)
Fatigue	39 (44)
Pyrexia	38 (43)
Thrombocytopenia	38 (43)
Nausea	37 (42)
Edema peripheral	37 (42)
Weight increased	31 (35)
Hyperglycemia	27 (30)
Chills	25 (28)
Headache	23 (26)
Constipation	22 (25)
Anemia	21 (24)
Hypotension	21 (24)
Capillary leak syndrome	19 (21)

Summary of CLS Events	Total BPDCN (N=86)*
Total CLS, n (%)	18 (21%)
Grade 3, n (%)	2 (2%)
Grade 4, n (%)	2 (2%)
Grade 5, n (%)**	2 (2%)
Time to any CLS days (range)	6 (3, 51)
Time to ≥ grade 3, days (range)	8 (4, 12)
Any Recurring CLS, n (%)	0 (0%)
Time to Resolution, days (range)	6 (3, 69)
Time to Resolution ≥grade 3, days (range)	9 (5, 69)

* Patients treated at 12 mcg/kg.

AE = adverse event; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CLS = capillary leak syndrome.

References: 1. Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034. Epub ahead of print

Capillary Leak Syndrome (CLS)

- **18/86 patients (21%) had CLS**
  - **Most cases were non-severe (grade 2, 67%) and resolved**
  - **All but one event occurred in cycle 1**
- Median time to CLS onset: 6 days (range: 3–51)
- Median duration of CLS: 6 days (range: 3–69)
- 9 patients (56%) who experienced CLS **continued TAG after CLS resolved**
  - **No patients experienced a recurrence**
- CLS was managed by TAG dose interruption, intravenous albumin supplementation, steroids, and managing volume status
  - n = 18 received concurrent albumin
  - n = 8 received steroids

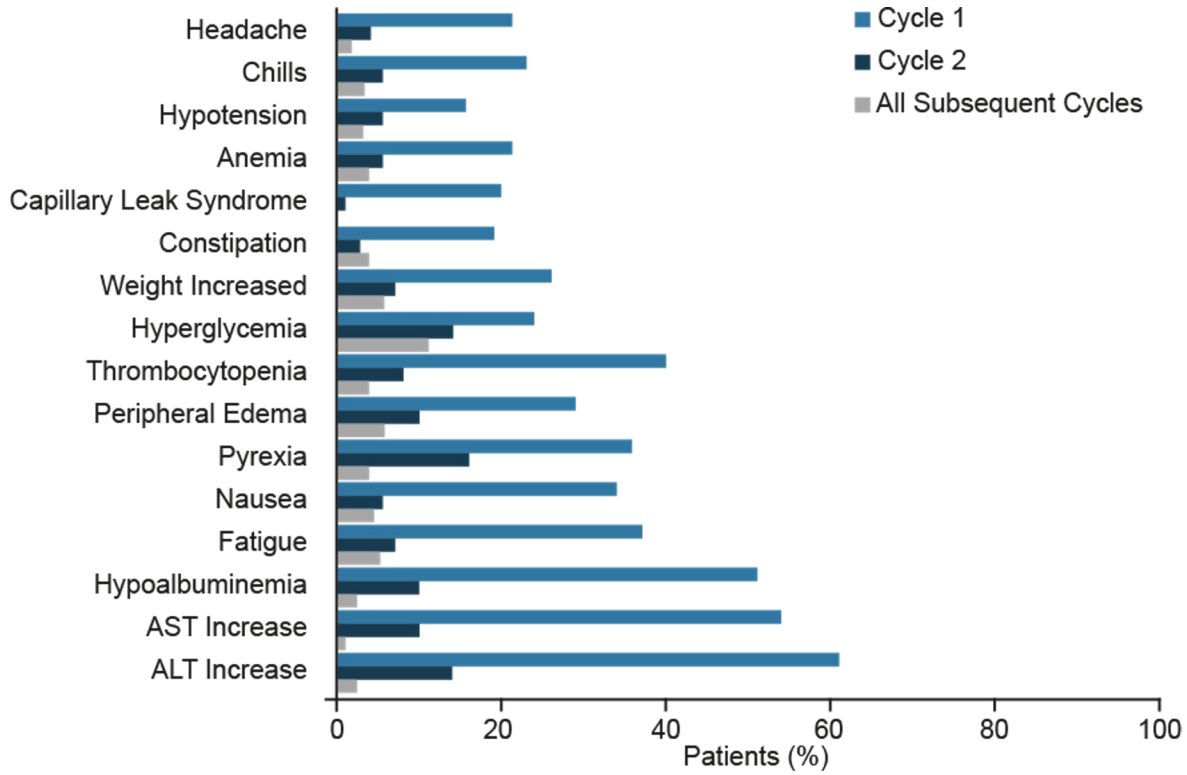
Summary of Capillary Leak Syndrome (CLS) Events in Patients Treated With Tagraxofusp 12 mcg/kg

	1L BPDCN n = 66	R/R BPDCN n = 20	Total BPDCN N = 86
Total CLS, n (%)	12 (18)	6 (30)	18 (21)
Grade 3 CLS, n (%)	2 (3)	0	2 (2)
Grade 4 CLS, n (%)	1 (2)	1 (5)	2 (2)
Grade 5 CLS, n (%)	2 (3)	0	2 (2)
Time to any CLS, days (range)	6 (3–12)	6 (3–51)	6 (3–51)
Time to grade ≥3, days (range)	8 (4–12)	8 (8–8)	8 (4–12)
Any recurring CLS, n (%)	0	0	0
Time to resolution, days (range)	5 (3–69)	9 (4–19)	6 (3–69)
Time to resolution grade ≥3, days (range)	37 (5–69)	9 (9–9)	9 (5–69)

Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034.

Adverse Events by Cycle[1]

- Most Treatment Emergent Adverse Events (TEAEs) occurred in cycle 1, with notably lower rates in cycles 2-4



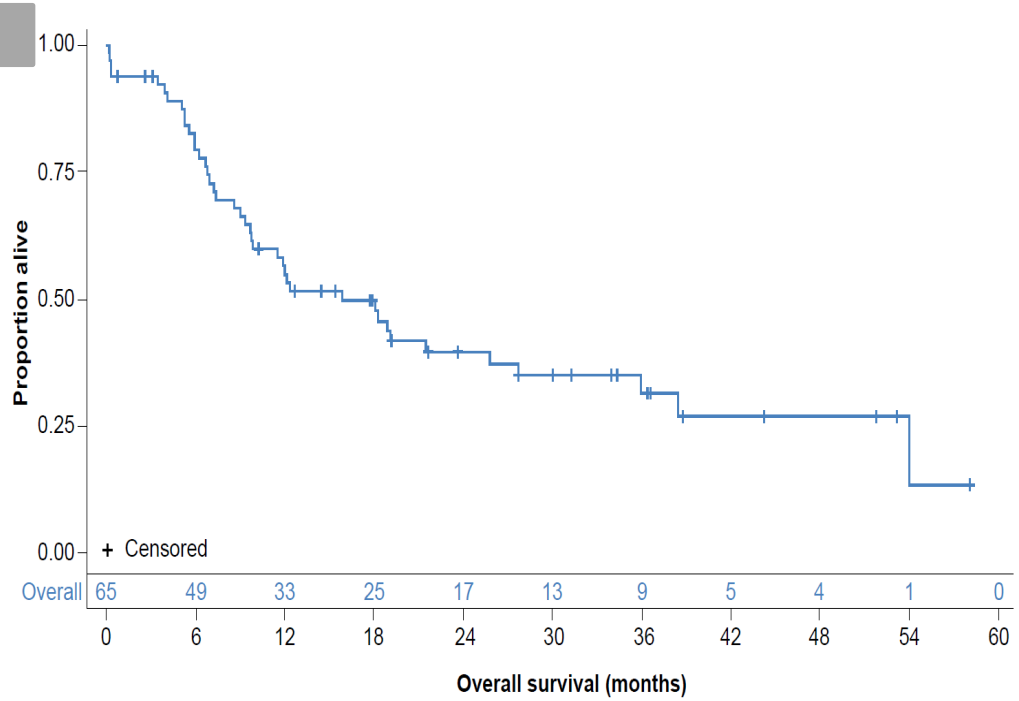
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SCT = stem cell transplantation.

References: 1. Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034. Epub ahead of print

Efficacy Outcomes: Overall Survival

First Line Patients with BPDCN

Kaplan-Meier Curve of Overall Survival in 1L Patients (N=65)



	Stages 1–3 n = 29	Stage 3 n=13	Stage 4 n = 36	Overall N = 65
Median OS, months (95% CI)	25.8 (9.7, 53.9)	18.9 (5.2, NE)	11.5 (6.8, 19.1)	15.8 (9.7, 25.8)
Survival probability at 12 months	62%	54%	49%	55%
Survival probability at 18 months	59%	54%	41%	50%
Survival probability at 24 months	52%	46%	25%	40%

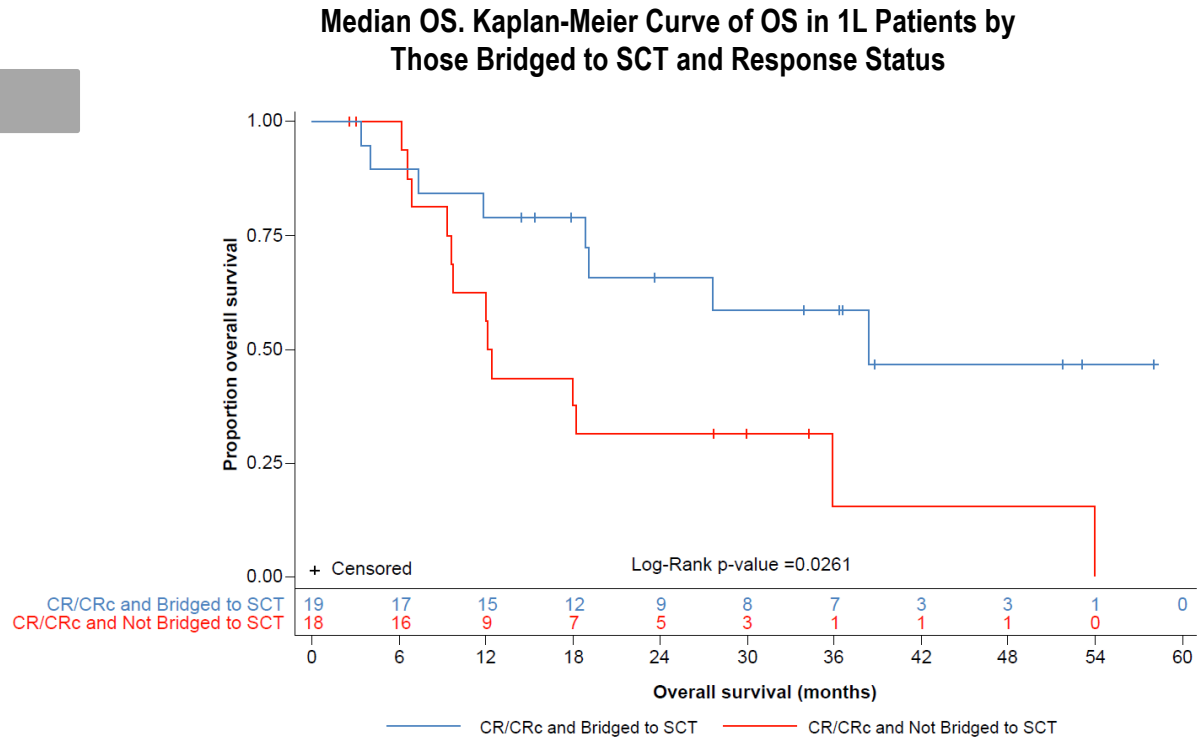
CI, confidence interval; OS, overall survival.

Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034.

Efficacy Outcomes: SCT (II)

First Line Patients with BPDCN

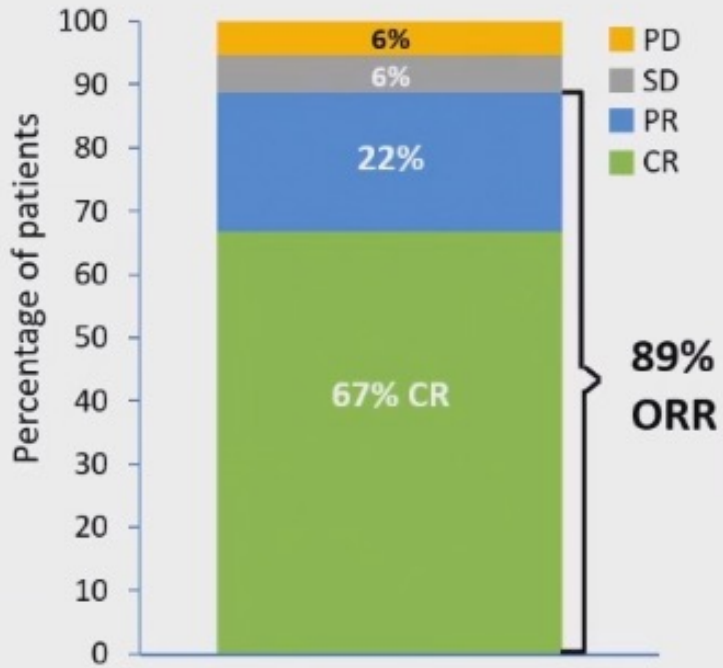
- Of patients who achieved CR + CRc and underwent transplant, median OS was 38.4 months (range: 3.4–58.1)
  - Median follow-up post-SCT was 34 months (range: 19–47)
- 72% remaining in remission for ≥12 months post-SCT
- The survival probability at 24 months was 66% (95% CI: 43, 88)
- 4/18 patients who achieved CR + CRc and were not transplanted had prolonged duration of responses (>6 months)
  - 2 patients had responses lasting 27 and 52 months, respectively



Pemmaraju N, et al: J Clin Oncol. 2022 July 12:JCO2200034. doi.org: 10.1200/JCO.22.00034.

Treatment-Naïve Patients with BPDCN Achieved Durable Outcomes with TAG Treatment

Best Overall Response (n=18)[a]



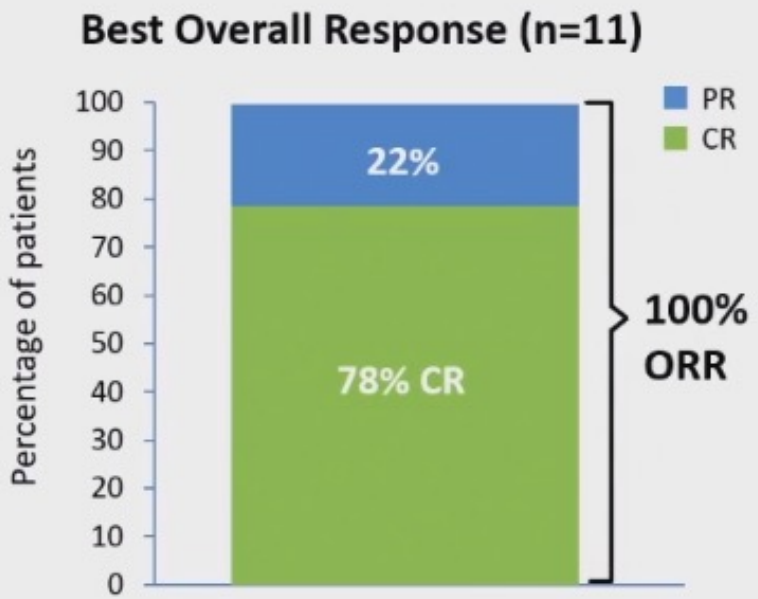
At a median follow-up of 10 months (range, 0.2 – 25),

- **Rapid time to onset of response:**
  - Median onset at 21 days (range, 11 – 74)
  - Median time to CR: 29 days (range, 11 – 58)
- **High overall and complete response rates:**
  - ORR of 89% including 67% CR and 22% PR
- **Durable responses with median DOR 8.9 months** (95% CI, 3.2 – NE):
  - 40% (95% CI, 20% – 70%) probability of continued response at 12-months
  - Median PFS 10.2 months (95% CI, 7.5 – NE)

NE, not estimable; ORR, overall response rate.
[a]Patients with ≥1 tumor assessment (n=18)

Angelucci et al. TAG 1L NPP, ASH 2023

Half of Patients were Bridged to Transplant

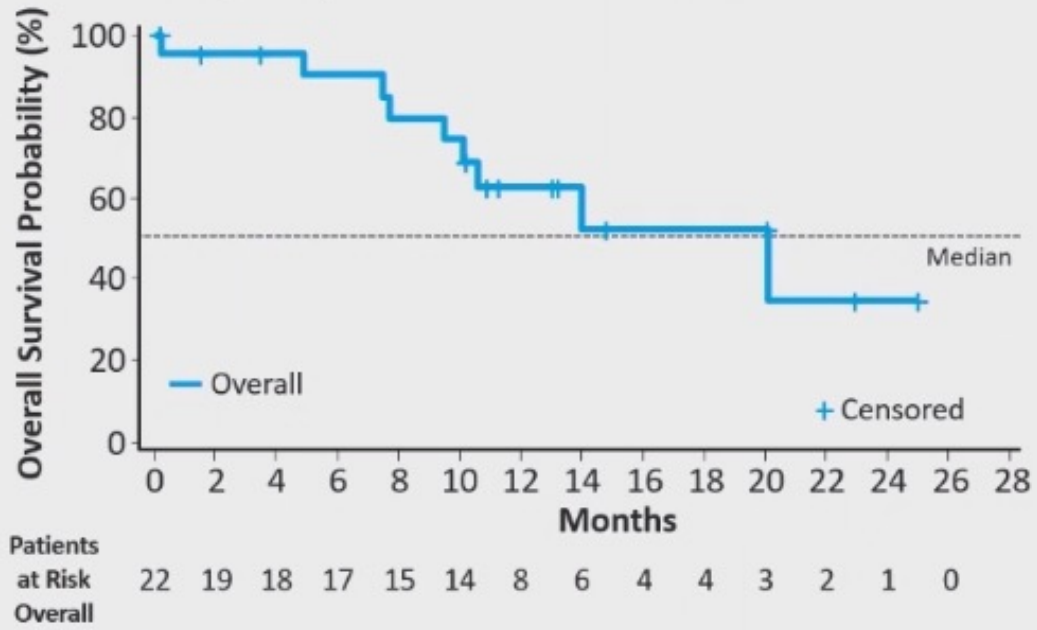


- 50% of patients (11 of 22) and 69% of responders (11 of 16) were bridged to HSCT
- Transplanted patients were younger
  - Transplanted: median age 64 yrs
  - Non-transplanted: median age 71 yrs
- At a median 13 months (range, 4 – 25) follow-up for transplanted patients,
  - **Responses were highly durable with median DOR not reached**
  - 60% (95% CI, 20-80%) probability of continued response at 12-months

Angelucci et al. TAG 1L NPP, ASH 2023

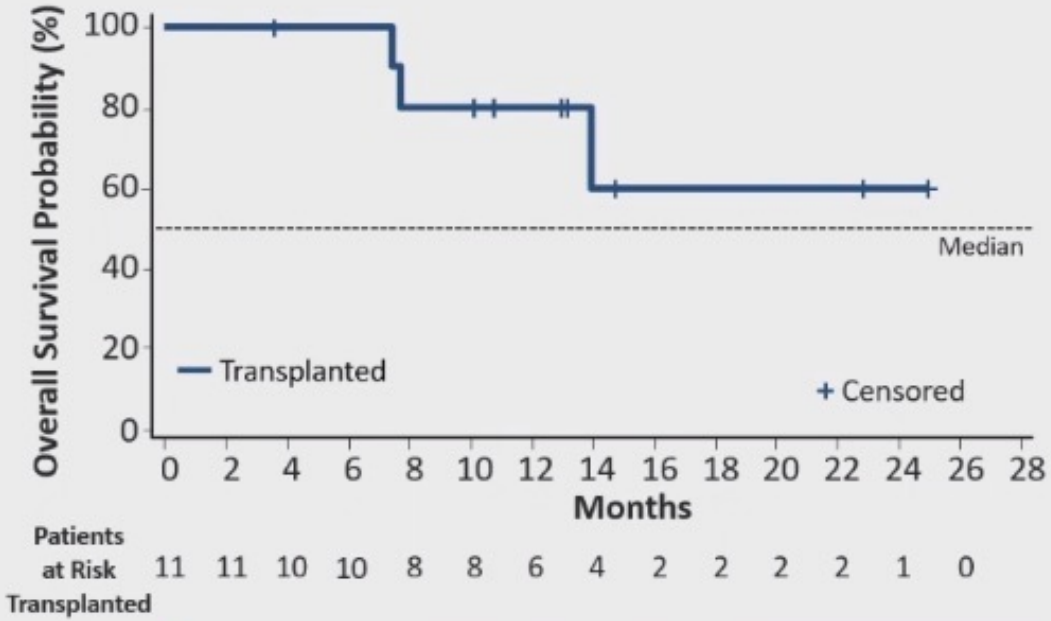
Real World TAG Treatment for Treatment-Naïve Patients with BPDCN Led to Prolonged Survival

All Patients (n=22)



- Median OS for all patients was 20 months (95% CI, 10 – not estimable)

Transplanted Patients (n=11)



- Median OS was not reached in transplanted patients

OS is the time from TAG start date to date of death from any cause.

Angelucci et al. TAG 1L NPP, ASH 2023

TAG was Safely Combined with IT Chemotherapy and Results in Favorable Outcomes for Patients with CNS Involvement

Parameter	Patient 1: 47-year-old man	Patient 2: 68-year-old woman
Time to TAG	1.1 months	2.1 months
TAG treatment[a]	2 cycles	7 cycles
IT treatment[a]	2 cycles	1 cycle
BPCDN best response	CR	CR
CNS response (IT therapy response)	NA[b]	CR

- Two patients with baseline CNS involvement received both IT treatment and TAG treatment

Outcomes

- Both patients achieved a CR and both proceeded to HSCT
- Survival from time of diagnosis
  - 9.8 months for patient 1
  - 14.8 months and alive without documented disease for patient 2
- Only one patient had an AE[c]

IT, intrathecal; NA, not available.
[a]Time from diagnosis to treatment. [b]Given as prophylaxis (no response collected). [c]Hypertransaminasemia (1 event on cycle 1 and 1 on cycle 2) .

Angelucci et al. TAG 1L NPP, ASH 2023

Conclusions

- With up to 2 years of follow-up, patients with BPDCN who received TAG as first-line treatment achieved fast and durable responses, regardless of CNS involvement, and prolonged survival beyond that of chemotherapy
  - Median DOR 8.9 months; ORR of 89% (CR 67%)
  - Median OS 20 months which exceeds chemotherapy's historically shorter median OS (~8 to 14 months)
- For the 50% of patients who were bridged to transplant
  - Median DOR and Median OS not reached
- No new safety issues were observed with TAG therapy
  - With proper patient selection, monitoring for early recognition and directed intervention, CLS is manageable and in most cases mild, limited to the first cycle and does not recur

These real-world results confirm TAG is a treatment of choice in first line BPDCN, with better OS results than historical chemotherapy data and manageable safety profile

Angelucci et al. TAG 1L NPP, ASH 2023

Recommended in the NCCN Guidelines®

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

Tagraxofusp

The only EMA and FDA-approved treatment for BPDCN **recommended by the NCCN Clinical Practice Guidelines in Oncology** (NCCN Guidelines®)

BPDCN = blastic plasmacytoid dendritic cell neoplasm; EMA = European Medicines Agency; FDA = Food and Drug Administration; NCCN = National Comprehensive Cancer Network.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.3.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed December 23, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Current guidelines

Europe

- German Onkopedia guidelines on “Blastische plasmazytoide dendritische Zellneoplasie (BPDCN)” were published on Jan 2022 with solitary focus on BPDCN[5]
- Generally considered a specific form of acute leukemia and included in leukemia working programs[1]
- Eligible patients are offered an allogeneic HCT, which remains the best consolidation treatment[1]
  - e.g. Guideline by the German Working Group for Hematopoietic Stem Cell Transplantation and Cellular Therapy recommends allogenic HCT for patients with BPDCN in CR12
  - **AWMF Guideline (Germany): Tagraxofusp is indicated as monotherapy for the first-line treatment of adult patients with BPDCN.[3]**

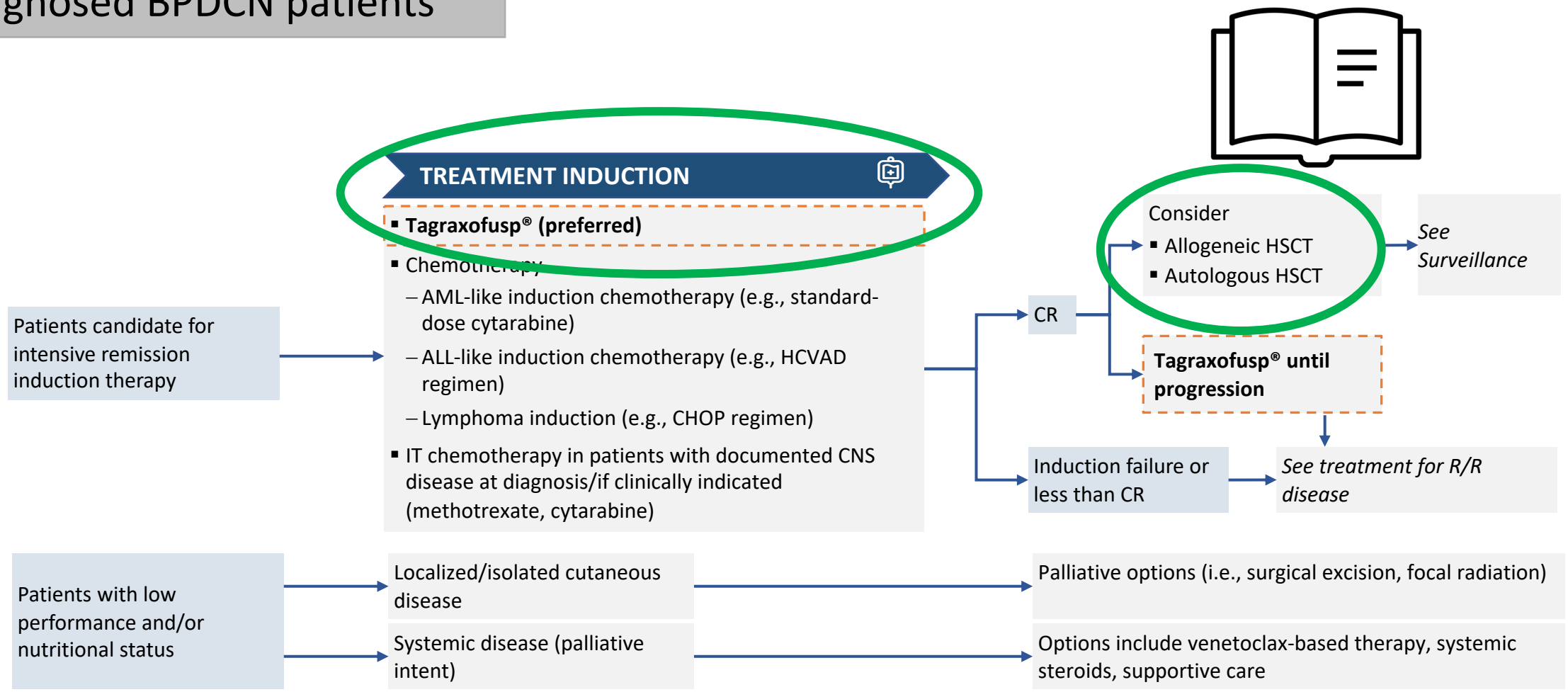
US[4]

- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend a multidisciplinary approach for the treatment of BPDCN
- **Tagraxofusp as a preferred therapy option as the only EMA- and FDA-approved treatment for BPDCN**
- Alternatively, high-dose chemotherapies usually used for other hematologic malignancies[3]
- The goal of both treatment options is CR, after which either the therapy with tagraxofusp can be continued or HCT can be considered.

AWMF = Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CR = complete response; EMA = European Medicines Agency; FDA = Food and Drug Administration; HCT = Hematopoietic stem-cell transplantation; NCCN = National Comprehensive Cancer Network.

References: 1. Deconinck E, et al. Hematol Oncol Clin North Am. 2020;34(3):613-620. 2. Beelen W, et al. Leitlinien zur allogenen Stammzelltransplantation von der Deutschen Arbeitsgemeinschaft für Knochenmark- und Blutstammzelltransplantation (DAG-KBT) 2016:1-5. 3. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)-Ständige Kommission Leitlinien. S2k - Leitlinie - Kutane Lymphome (ICD10 C82 - C86). Update 2021 Verfügbar: https://www.awmf.org/leitlinien/detail/ll/032-027.html (Accessed 03.12.2021). 4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.3.2021. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed August 31 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 5. Onkopedia guidelines on “Blastische plasmazytoide dendritische Zellneoplasie (BPDCN)” available at https://www.onkopedia.com/de/onkopedia/guidelines/blastische-plasmazytoide-dendritische-zellneoplasie-bpdcn/@@guideline/html/index.html. Accessed February 8 2022.

NCCN Guidelines for newly diagnosed BPDCN patients

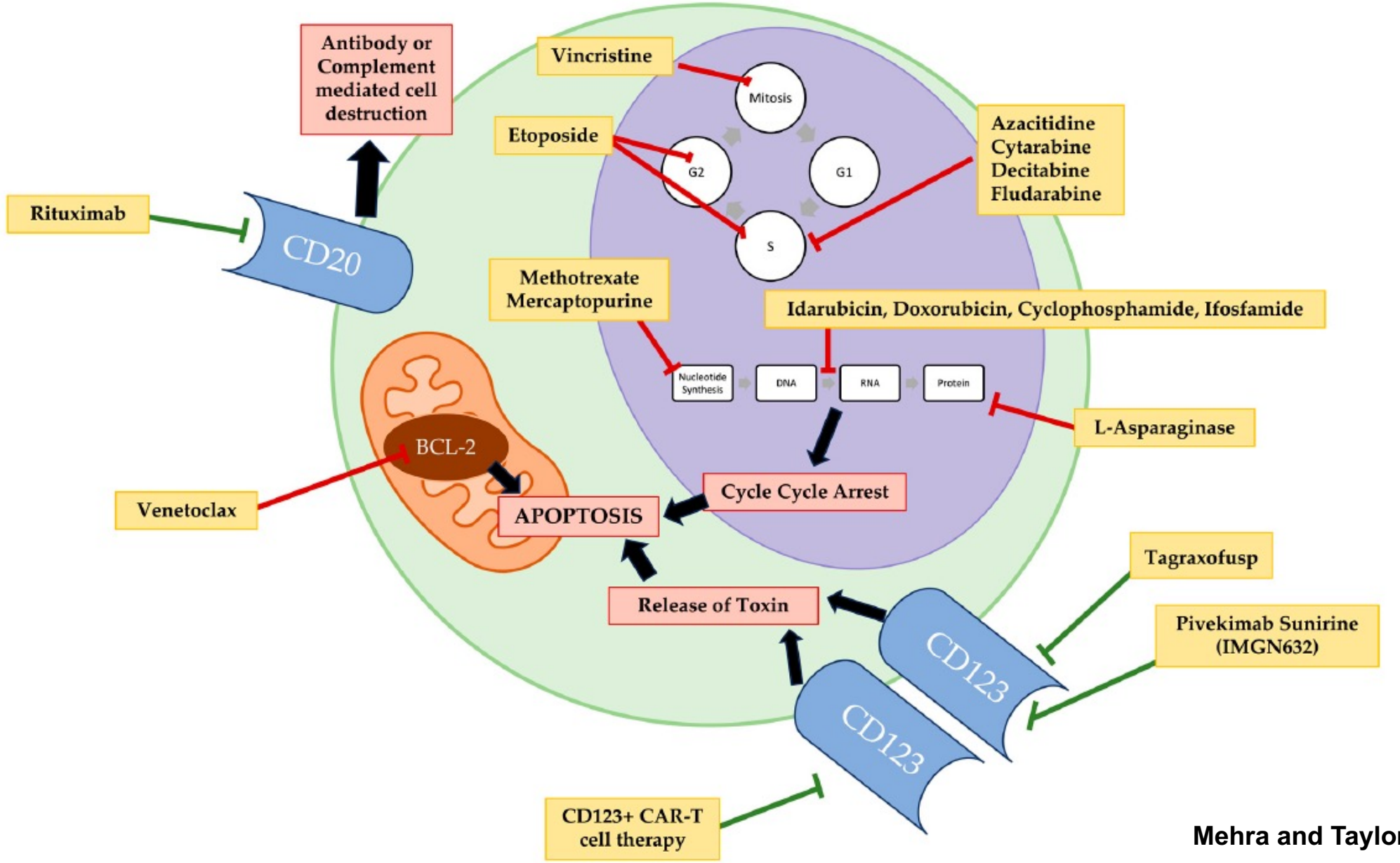


Tagraxofusp is the only EMA and FDA-approved treatment for BPDCN recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[1]

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

Potential targets for the treatment of BPCDN



Mehra and Taylor, Cells, 2024

Table 1. A list of current clinical trials, disease status of patients being enrolled, and central nervous system exclusion criteria for patients diagnosed with blastic plasmacytoid dendritic cell neoplasm.

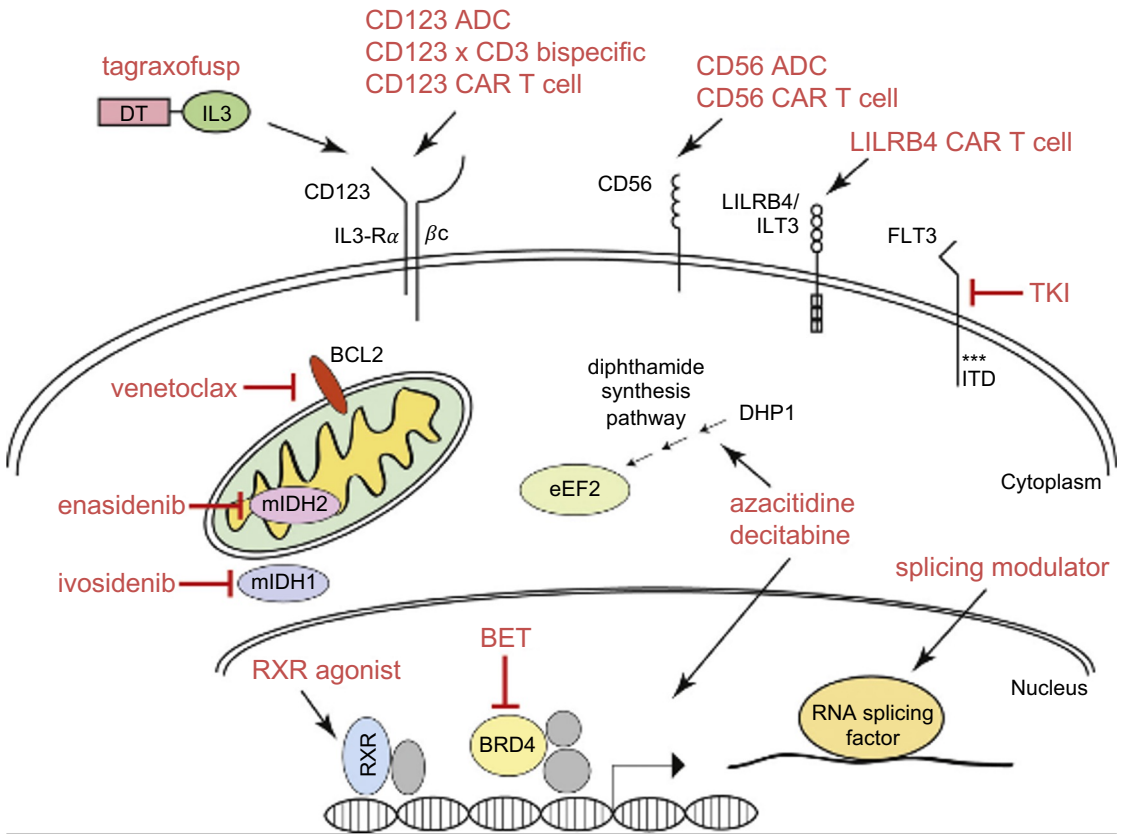
Trial Identifier	Agents	Eligible Patients	Exclusion CNS Criteria
NCT03485547	Venetoclax	BPDCN	None
NCT03113643	TAG + Azacitidine/Azacitidine and Venetoclax	Relapsed/refractory BPDCN	Yes
NCT02159495	Autologous/Allogeneic CD123CAR-CD28-CD3zeta-EGFRt-expressing T Lymphocytes	Relapsed/refractory BPDCN after first-line therapy	None—Lymphodepletion for IT
NCT04230265	UniCAR02-T Cells	BPDCN	Yes
NCT03386513	IMGN632	BPDCN	Yes
NCT04109482	MB-102	Relapsed/Refractory BPDCN	Yes
NCT04317781	TAG	BPDCN post-HSCT	Yes
NCT04216524	Venetoclax + TAG + Cyclophosphamide + Cytarabine + Doxorubicin + Mercaptopurine + Methotrexate + Rituximab + Vincristine	BPDCN	Yes
NCT03599960	Idarubicin + Methotrexate + L-asparaginase + Dexamethasone followed by allo- or auto-SCT or Methotrexate + L-asparaginase + Dexamethasone	BPDCN	None
NCT03404193	Venetoclax + Decitabine	BPDCN	Partial

Mehra and Taylor, Cells, 2024

Targeted Research to Novel Therapeutic Strategies

- Development of novel targeted therapies for patients with BPDCN is ongoing
- Among the targets are transcription factors such as BCL-2 or TCF-4 specific for pDCs or protooncogene transcription factors such as MYC
- Treatments already in use for other cancers such as Bortezomib (which amongst others targets the NF-kB pathway) might also be useful for BPDCN, since BPDCN has signatures of constitutive NF-kB activation and BPDCN cells are sensitive to an NF-kB p65 inhibitor.

Novel targets and agents in BPDCN



ADC = antibody-drug conjugate; BCL-2 = B-cell lymphoma 2; BETi = bromodomain and extraterminal motif inhibitor; BPDCN = blastic plasmacytoid dendritic cell neoplasm; CAR = chimeric antigen receptor; CD = cluster of differentiation; DT = diphtheria toxin; eEF2 = eukaryotic elongation factor 2; IL3 = interleukin 3; mIDH1/mIDH2 = mutant isocitrate dehydrogenase 1/2; NFκB = nuclear factor kappa-light-chain-enhancer of activated B cells; pDC: plasmacytoid dendritic cell; RXR = retinoid X receptor; TKI = tyrosine kinase inhibitor.

References: 1. Lane AA. Hematol Oncol Clin North Am. 2020;34(3):589-600.