ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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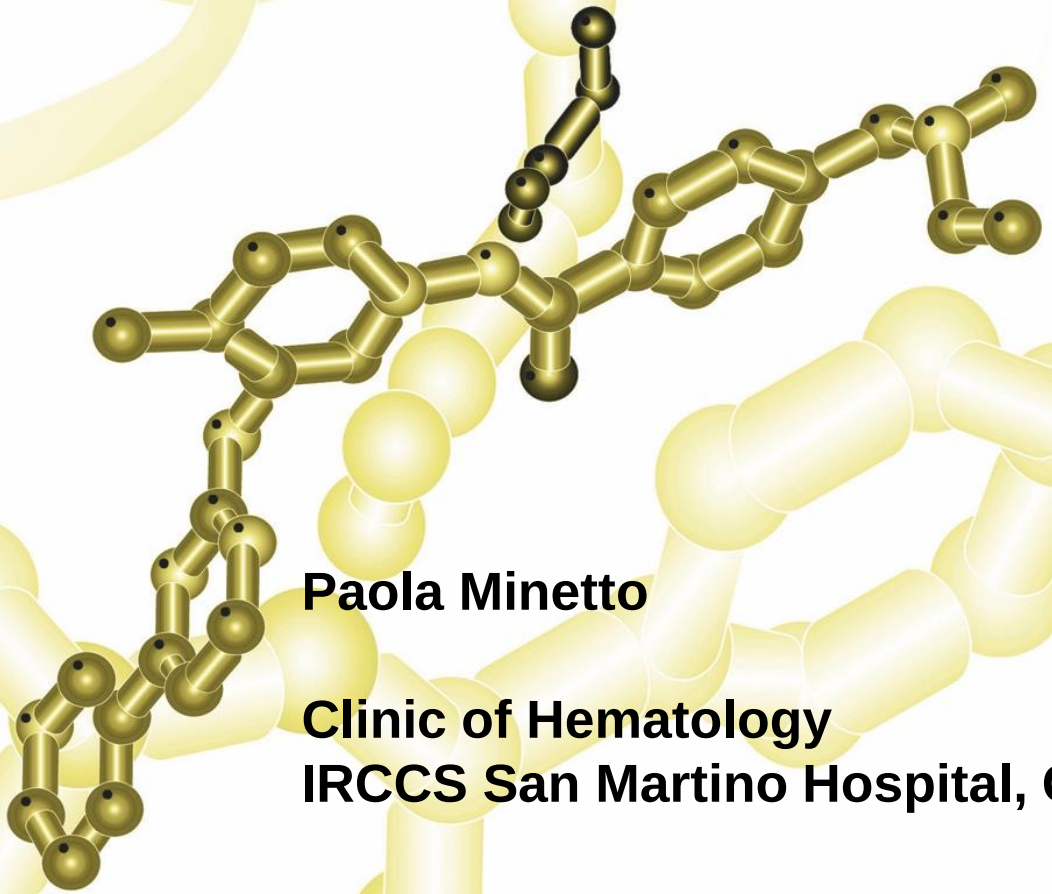
Azienda Ospedaliero - Universitaria di Bologna

Targeting CD123 in AML and BPDCN



Paola Minetto

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New Drugs in Hematology

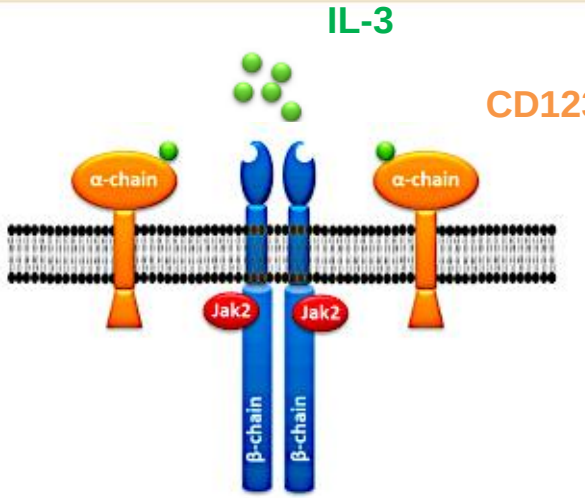
President: Pier Luigi Zinzani
Co-President: Michele Cavo

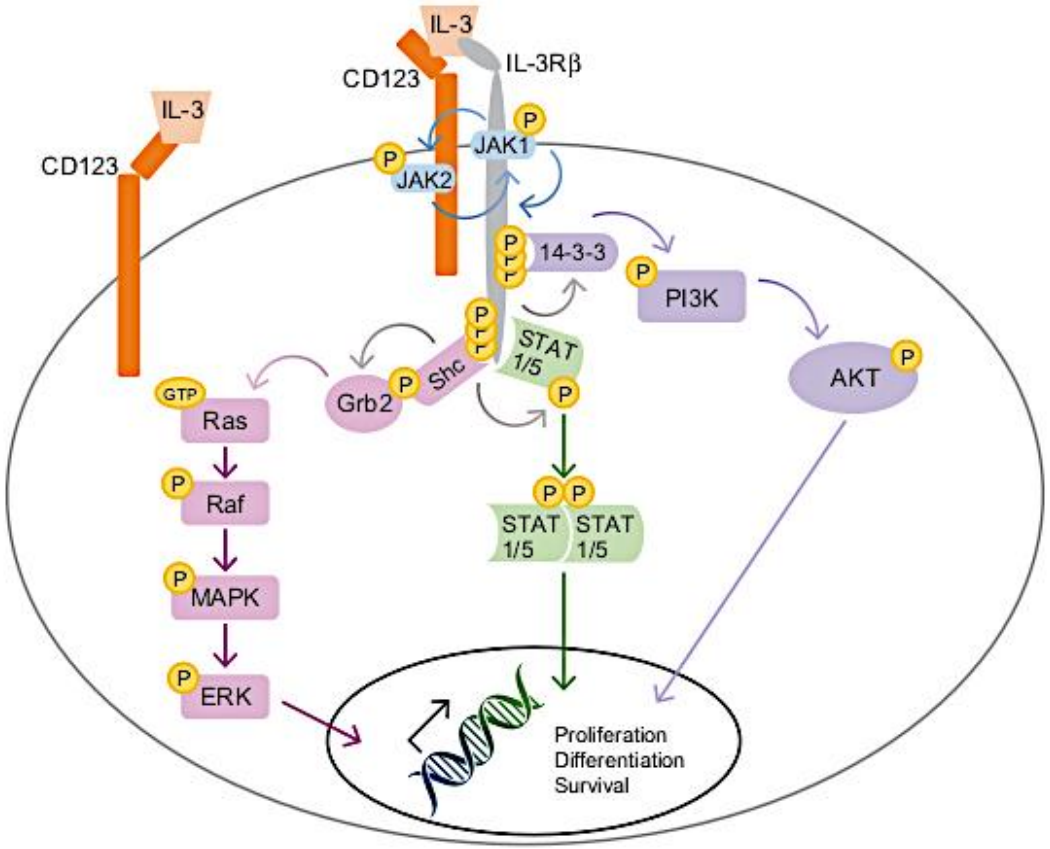
Bologna,
Royal Hotel Carlton
January 15-17, 2024

Disclosures of Paola Minetto

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						X	
Stemline Menarini							X

CD123 is the alpha chain of the interleukin 3 receptor (IL-3Rα).





- **IL-3R** is a heterodimeric receptor (α and β chains) with the β chain in common with IL-5R and GM-CSFR.
- This family of membrane receptors regulates the **growth, proliferation, survival, and differentiation of hematopoietic cells**, along with **immunity and inflammatory response**.

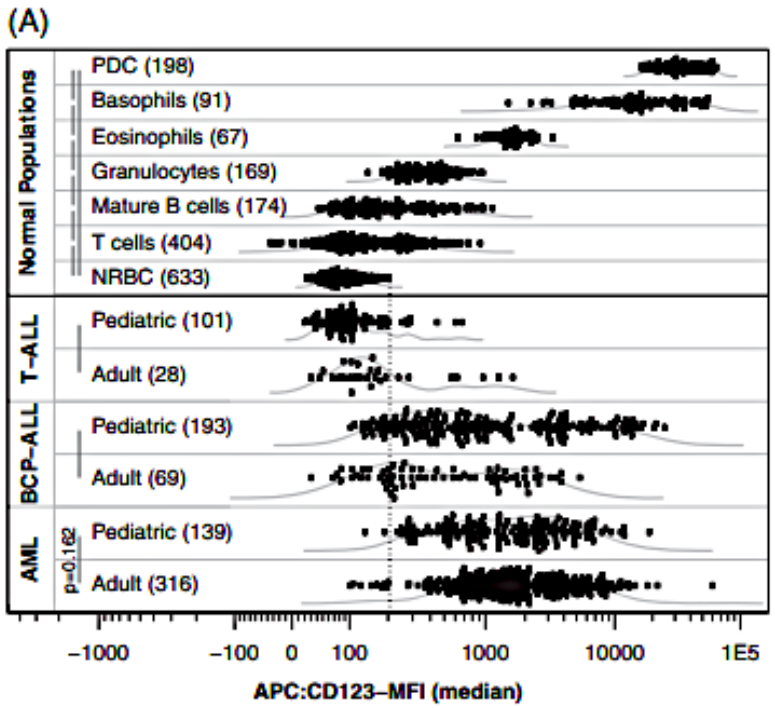
- The receptor intracellular cascades activate downstream the **JAK/STAT**, **Ras-MAPK**, and **PI3K pathways**.
- Moreover, IL-3 and GM-CSF binding modulates the levels of **SDF-1** and its receptor **CXCR4**, which play a role in the **homing and egress of bone marrow hematopoietic cells**.

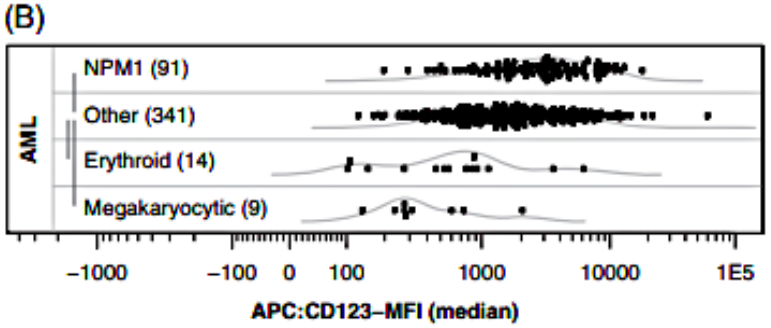
Adapted from El Achi H, et al. Cancers. 2020

CD123 Expression Levels in 846 Acute Leukemia Patients Based on Standardized Immunophenotyping

Anne E. Bras,[1] Valerie de Haas,[2] Arthur van Stigt,[3] Mojca Jongen-Lavrencic,[4] H. Berna Beverloo,[5] Jeroen G. te Marvelde,[1] C. Michel Zwaan,[6,7] Jacques J.M. van Dongen,[1] Jeanette H.W. Leusen,[3] and Vincent H.J. van der Velden[1*]

- Acute leukemia patients (n = 846) retrospectively selected based on availability of relevant flow cytometric data.
- 139 pediatric AML, 316 adult AML, 193 pediatric BCP-ALL, 69 adult BCP-ALL, 101 pediatric T-ALL and 28 adult T-ALL patients.

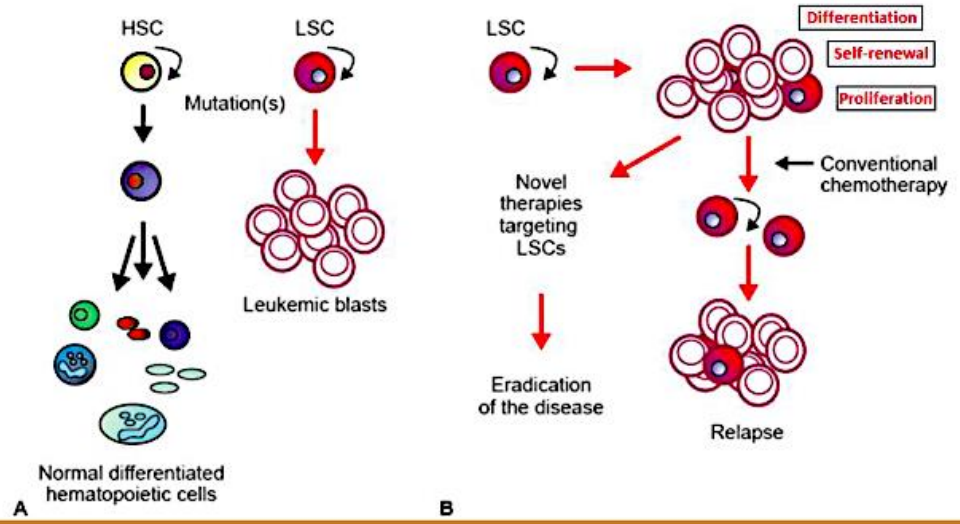




Bras AE, et al. Cytometry B Clin Cytom. 2019

CD123 is a marker of Leukemic Stem Cell (LSC)

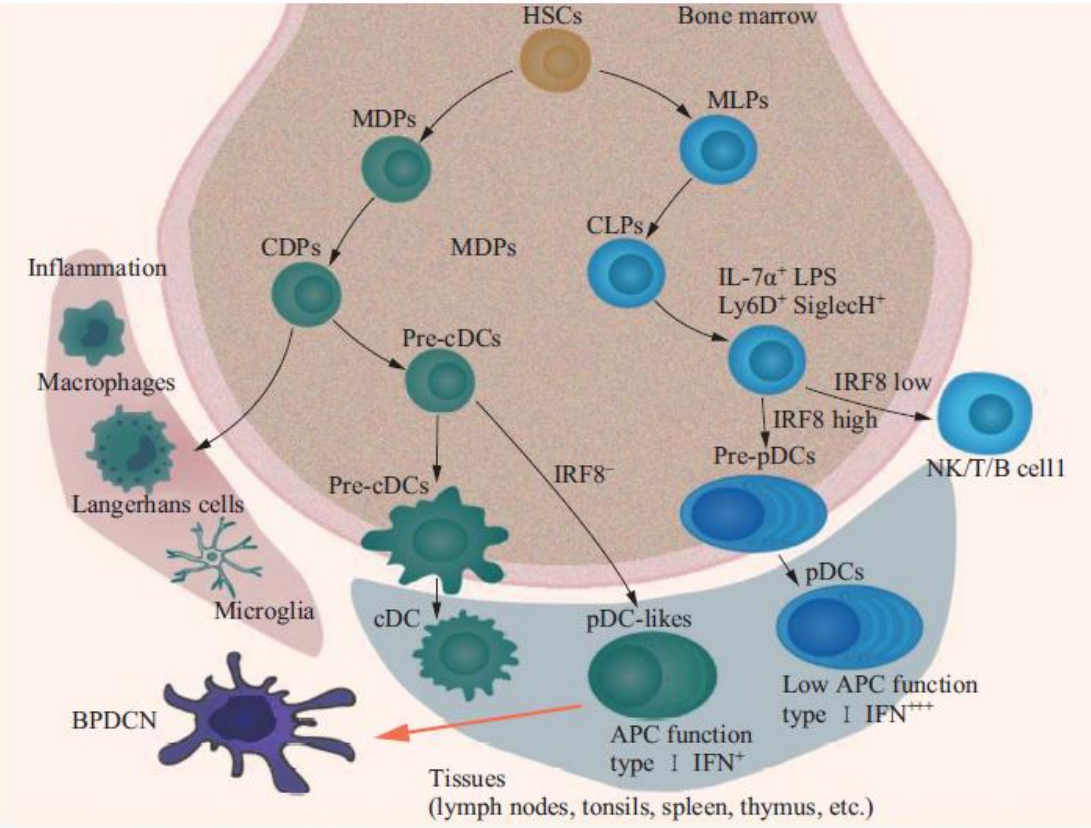
- LSCs are responsible for **initiating and maintaining leukemic cell growth following chemotherapy** and hence give rise to **relapse** of the disease
- Similar to normal hematopoietic stem cells, LSCs represent only a small fraction of cells within a given AML clone (0·2–100 cells in 106 cells)
- LSCs obtained from patients with AML are defined by their AML repopulating capacity in vivo, i.e. their ability to give rise to leukemia in immunodeficient mice
- LSCs with the CD34+CD38–CD123+ phenotype were preferentially residing in a **bone marrow endosteal region niche** in a **quiescent state** potentially resistant to chemotherapy



Al-Mawali A, et al. J Stem Cell Res Ther. 2013
Al-Mawali A, et al. Acta Haematol. 2017

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

- Blastic plasmacytoid dendritic cell neoplasm (**BPDCN**) is a rare hematologic disorder (<1 % of hematologic malignancies). Prognosis is poor, with most patients dying within one year due to **aggressive clinical behavior** and **poor responses** to conventional chemotherapies (ALL or AML-like).

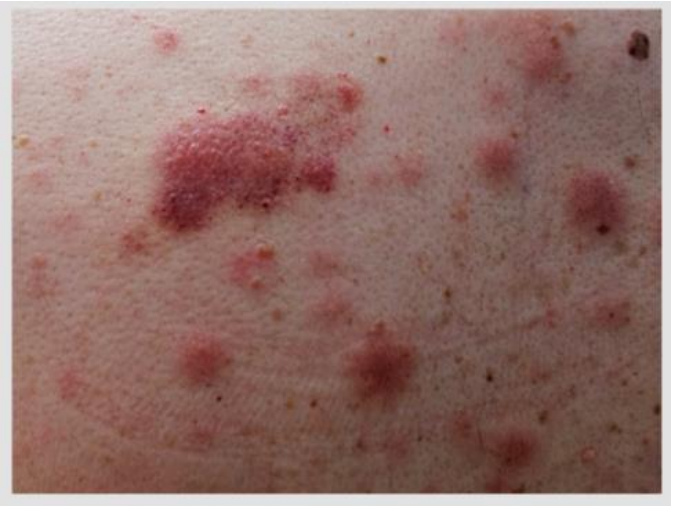


- BPDCN derives from **precursors of plasmacytoid dendritic cells** (pDCs), also known as professional type I interferon-producing APC.
- **pDC are a subpopulation of dendritic cells (DC)**
- **pDC** populations are composed of **transcriptionally** and **functionally** heterogeneous cellular subsets with distinct hematopoietic precursor origin

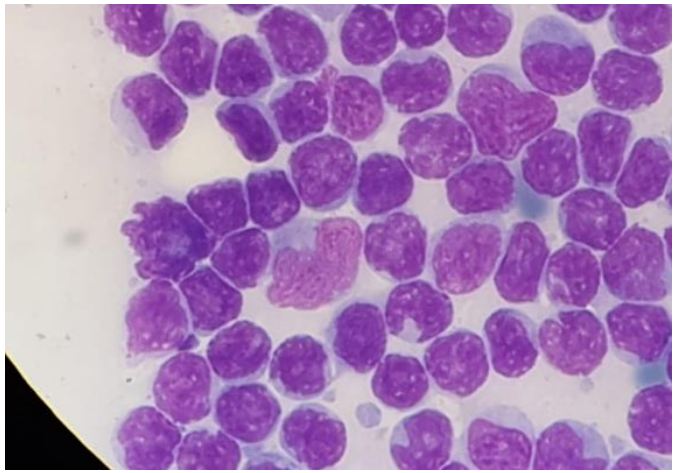
Arber DA et al. Blood 2016
Cheng W, et al. Current Medical Science 41(3):2021

BPDCN clinical presentation

- The disease involves multiple sites often affecting the **skin** (60-100% of cases), followed by **bone marrow**, **peripheral blood** (60-90%) and **lymph nodes** (40-50%). However, cases lacking cutaneous involvement are reported.



Sapienza M.R. et al. Cancers 2019



BM aspirate from local archive

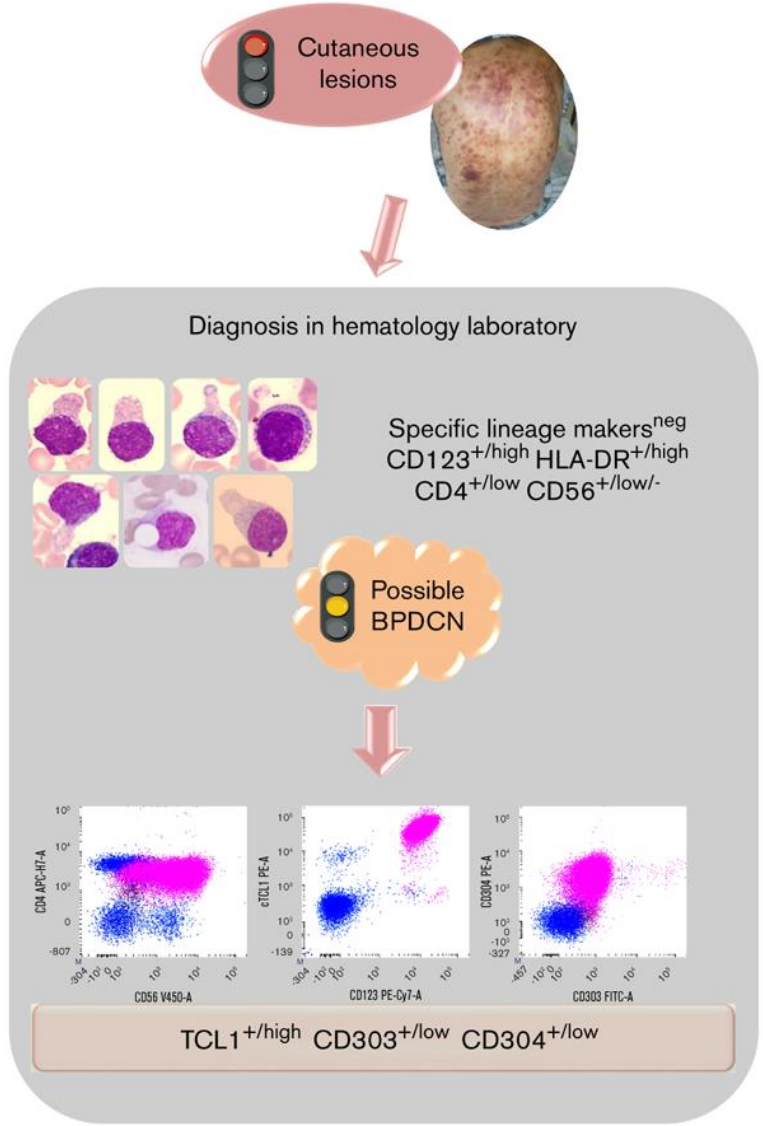
Sapienza M.R. et al. Cancers (Basel) 2019 May; 11(5): 595.
Sullivan JM and Rizzieri DA. Hematology Am Soc Hematol Educ Program. 2016 Dec; (1): 16–23.

- According to WHO classification, **BPDCN cells typically express CD4 and CD56 in addition to at least 1 of the pDC-associated antigens** (**CD123**,TCL-1, CD2AP, or CD303/BDCA2)

- Moreover, the **exclusion of other lineage-specific antigens**, such as AML markers (MPO, CD13, CD64), B-ALL markers (CD19, CD20, CD79a) and T-ALL markers (cyCD3), as well as AML-defining molecular or karyotypic lesions, is important for the diagnosis of BPDCN.

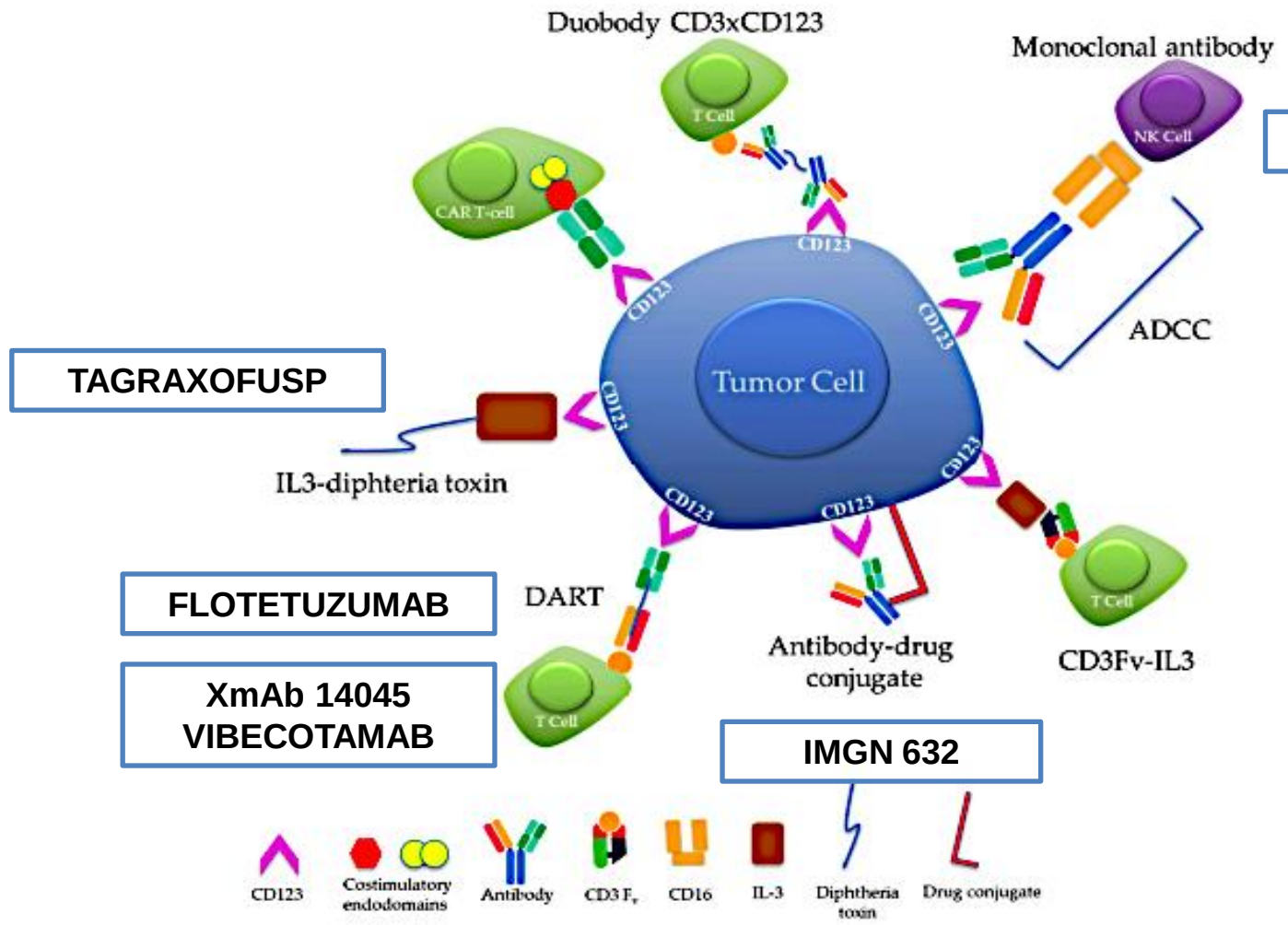
- The **overlap of shared markers** and exception of **atypical cases that lack a particular marker makes the diagnosis of BPDCN very challenging**

D		BPDCN	AML/LC/MS
SHARED	CD4	80-100 %	10-20 %
	CD56	90-100 %	5-50 %
	CD123	85-100 %	15-45 %
	TCL1	80-100 %	5-20 %
UNIQUE		CD2AP CD303/BDCA-2	MPO Lysozyme CD34 CD14 CD11c CD163



Adapted from Sullivan JM and Rizzieri DA. Hematology Am Soc Hematol Educ Program. 2016

A number of CD123-targeted therapies have been developed over the years



TALACOTUZUMAB

TAGRAXOFUSP

FLOTETUZUMAB

XmAb 14045
VIBECOTAMAB

IMGN 632

Others

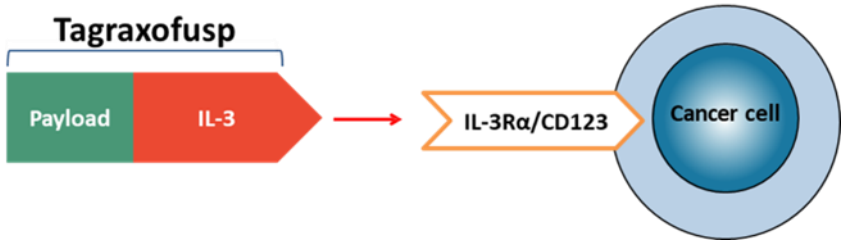
CAR-T cells

CAR-NK cells

Modified from: El Achi H, et al. Cancers. 2020

TAGRAXOFUSP

- TAGRAXOFUSP (SL-401) is a novel **CD123-directed therapy consisting of recombinant human interleukin-3 fused to truncated diphtheria alpha-toxin** (catalytic and translocation domains), **a potent inhibitor of protein synthesis.**
- Tagraxofusp internalization results from receptor-mediated binding to IL-3R and endocytosis.
- **The mechanism of killing is not cell-cycle dependent**, and thus can kill both proliferating and dormant malignant cells but spares normal marrow progenitors and is not subject to multidrug resistance mechanisms.
- **Tagraxofusp received FDA fast approval on December 2018 for the treatment of BPDCN** in adults and pediatric patients over 2 years old and it is currently being tested in many clinical trials.



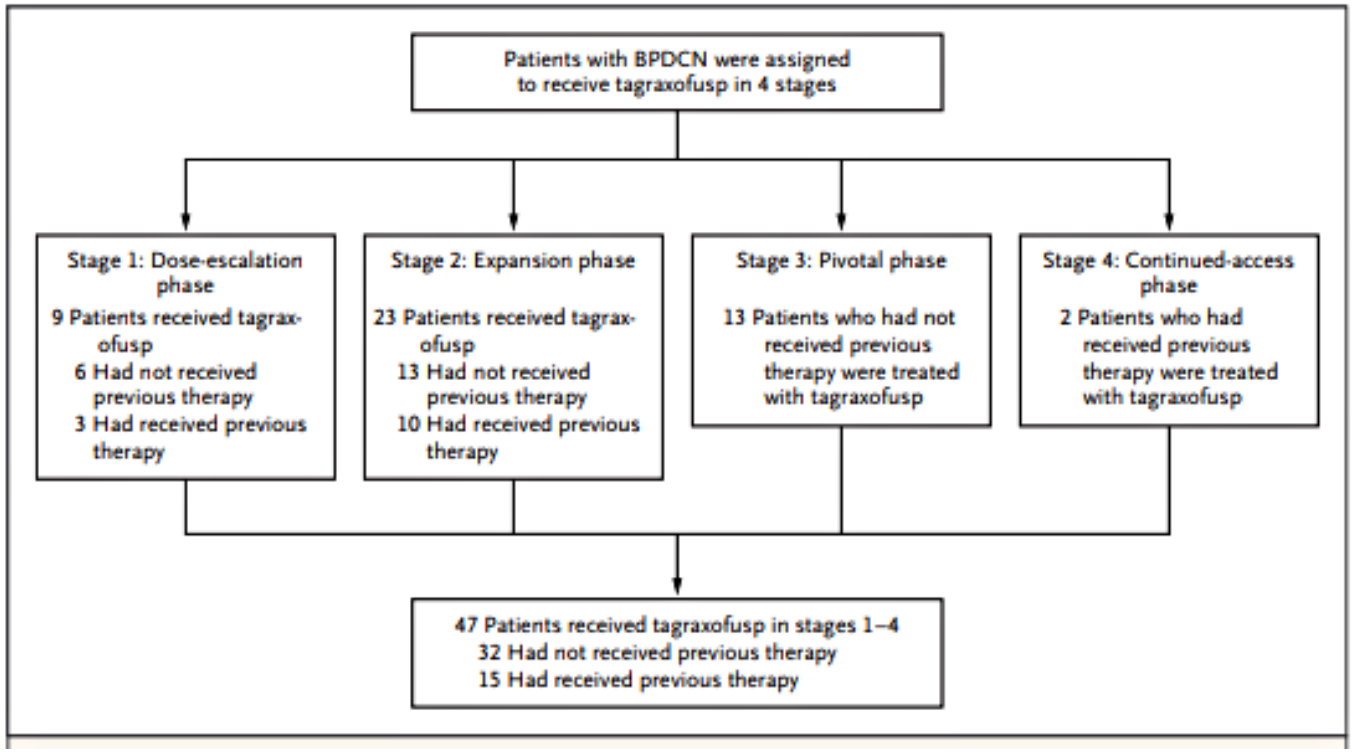
Pemmaraju N. Curr Hematol Malig Rep. 2017
Mani et al. Haematologica. 2018
Lane AA, et al. Blood (2016) 128 (22): 215. *Abstract*
Kovtun Y, et al. Blood Advances. 2018
Han L, et al. Clin Cancer Res. 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tagraxofusp in Blastic Plasmacytoid Dendritic-Cell Neoplasm

- The **Phase I/II** study was a non-randomized, open-label, single-arm prospective, multicentre study which evaluated Tagraxofusp as monotherapy in adult patients with BPDCN who were either treatment naive (1L) or relapsed/refractory (R/R)



- **Primary Objective**: CR + Clinical CR
- **Secondary Objective:** Duration of Response
- 7 o 12 µg/kg/die, days 1–5
- 21-day cycle until progression or toxicity

Pemmaraju N, et al. N Engl J Med 2019; 380: 1628–1637

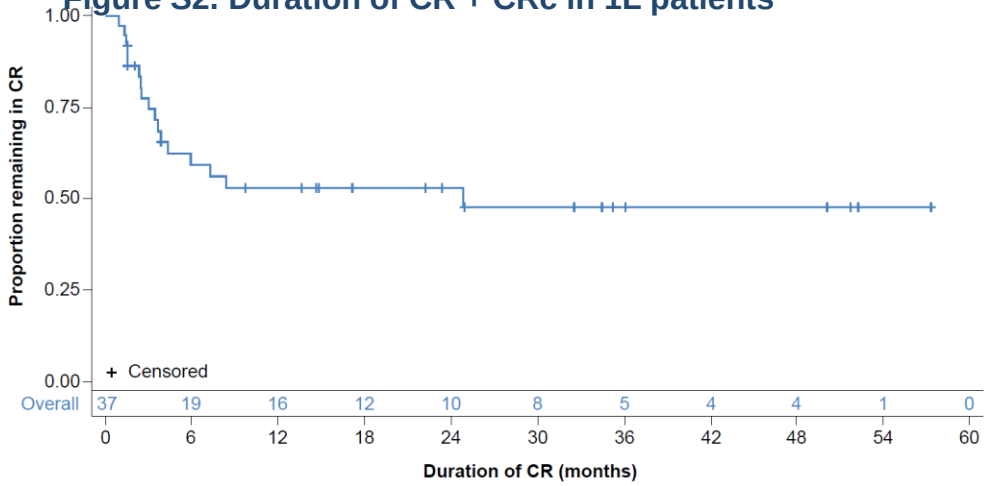
Efficacy Outcomes: First Line Patients with BPDCN (N=65)

Response Rate and Duration of CR for 1L BPDCN Patients Treated With Tagraxofusp 12 mcg/kg

	Stages 1–3 n = 29	Stage 3 n=13	Stage 4 n = 36	Overall N = 65
Response rate				
CR + CRc, n (%)	21 (72)	7 (54)	16 (44)	37 (57)
ORR, n (%)	26 (90)	10 (77)	23 (64)	49 (75)
Bridged to SCT, n (%)	13 (45)	6 (46)	8 (22)	21 (32)
Bridged to SCT after CR+CRc, n (%)	12 (57)	6 (46)	7 (44)	19 (51)
Median duration of CR + CRc, months (95% CI)	NR (5.9, NR)	NR (7.3, NR)	4.4 (2.3, NR)	24.9 (3.8, NR)
Probability at 6 months	70%	100%	44%	59%
Probability at 12 months	65%	83%	36%	53%
Probability at 18 months	65%	83%	36%	53%
Probability at 24 months	65%	83%	36%	53%
Median duration of follow-up, months	39	36	19	34

- **CR + CRc rate was 57% (95% CI: 44.0, 69.2)**
  - Median time to best response: 39 days (range: 14–131)
  - Median duration of CR/CRc: 24.9 months (95% CI: 3.8, NR)
- Median time to response was 23 days (range: 14–97)

Figure S2. Duration of CR + CRc in 1L patients

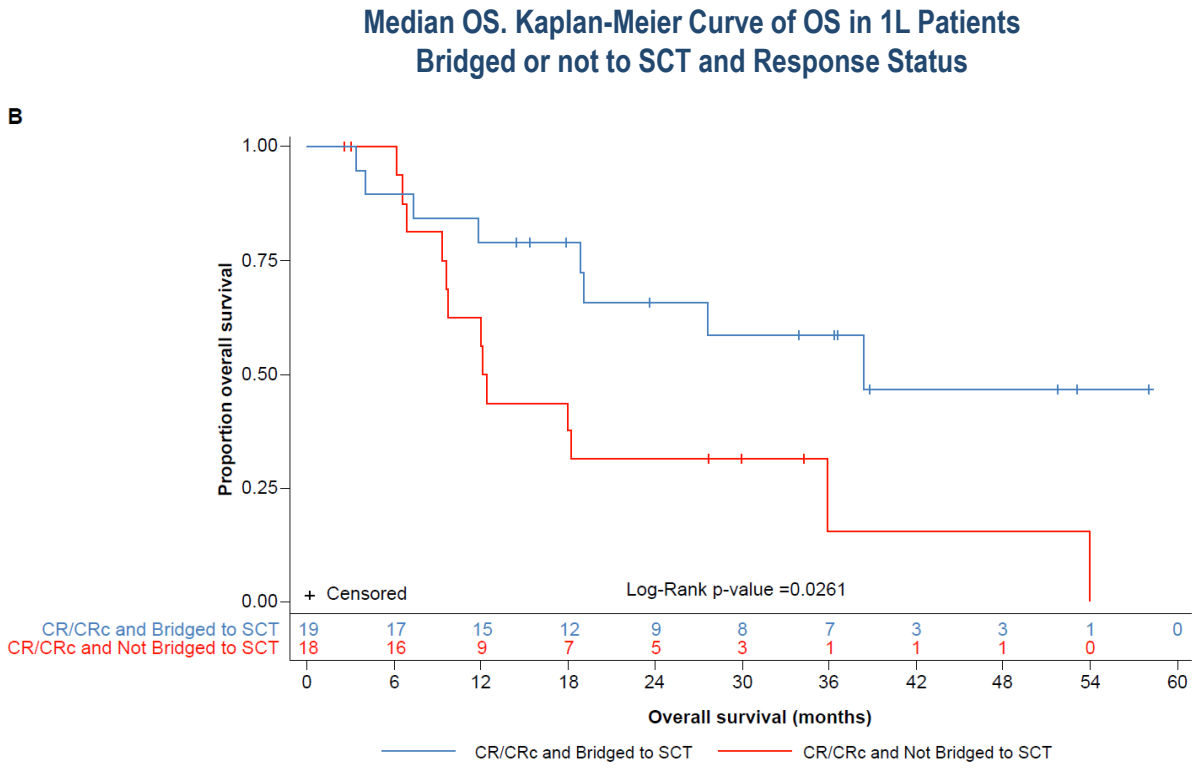


1L, first-line; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CI, confidence interval; CR, complete response; CRc, CR with residual skin abnormality not indicative of disease; NR, not reached; ORR, objective response rate; SCT, stem cell transplant.

Pemmaraju N, et al. J Clin Oncol. 2022;40:3032-3036.

Efficacy Outcomes: SCT

- 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;40:3032-3036.

Safety and Tolerability – All Patients

Tagraxofusp has a predictable and manageable safety profile

- Overall, across all study stages, TAG safety profile was consistent and predictable occurring often at cycle 1
- Most common adverse events were increased levels of AST and ALT and hypoalbuminemia
- Incidence of treatment related AEs leading to TAG discontinuation was relatively low at 7% whereas dose interruptions were more common, with an incidence of 69%
- There were grade 5 (fatal) events; four treatment-related by the investigator : Three capillary leak syndrome [CLS] and one myocardial infarction

Summary of Most Common Any-Grade and AEs in Patients With Blastic Plasmacytoid Dendritic Cell Neoplasm

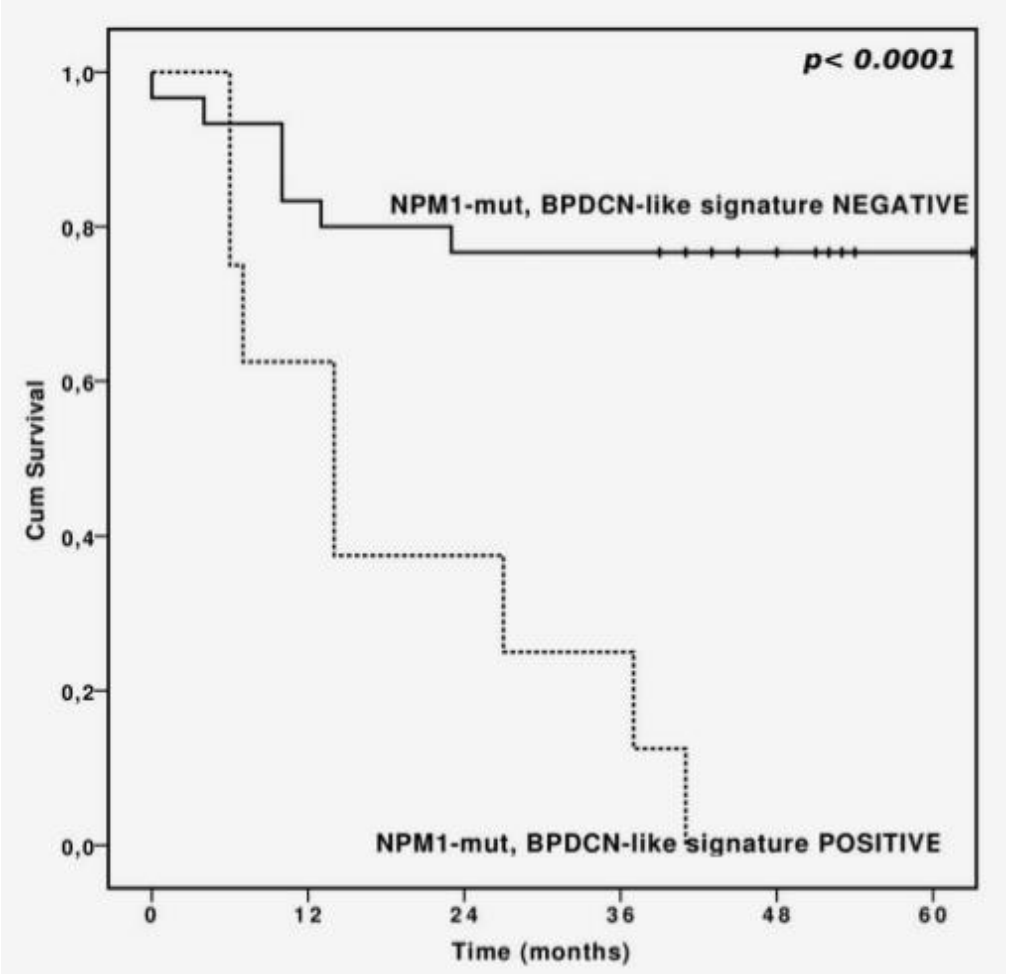
Any-grade AEs (≥20% of patients), n (%)*	Total N = 89
Increased ALT	57 (64)
Increased AST	53 (60)
Hypoalbuminemia	45 (51)
Fatigue	39 (44)
Pyrexia	39 (44)
Thrombocytopenia	38 (43)
Nausea	37 (42)
Edema peripheral	37 (42)
Weight increased	31 (35)
Hyperglycemia	27 (30)
Chills	24 (27)
Headache	22 (25)
Constipation	22 (25)
Anemia	21 (24)
Hypotension	21 (24)
Capillary leak syndrome	19 (21)
Hypokalemia	18 (20)
Hypocalcemia	18 (20)

*This analysis includes three patients treated with tagraxofusp 7 mcg/kg.

Pemmaraju N, et al. J Clin Oncol. 2022;40:3032-3036.

Prognostic relevance of BPDCN-like phenotype in AML with *NPM1* mutation

- In the subgroup of patients with *NPM1*-mut AML (n.38), the presence of **BPDCN-like signature** conferred a dismal prognosis (three-year OS 25 vs. 77% for NPM1 AML patient with or without BPDCN-like signature, respectively)
- The negative prognostic impact was confirmed irrespectively of mutational status for *FLT3*-ITD or other clinical features.
- All *NPM1*-mutated patients with BPDCN-like phenotype failed to achieve MRD-negative CR ($p < 0.05$).
- Interestingly, a trend towards an inferior OS was observed even in 7 patients presenting a partial expression (2 of three) of BPDCN markers.



Minetto P, et al. American Journal of Hematology. 2018 Feb;93(2):E33-E35.
Guolo F, et al. Leukemia and Lymphoma. 2020 Mar 18:1-7.

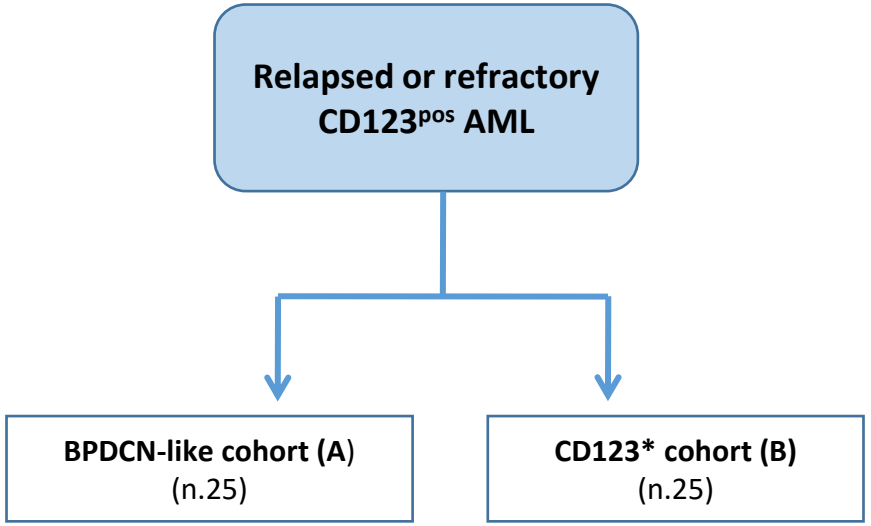
Tagraxofusp in Patients with CD123+ or with Blastic Plasmacytoid Dendritic Cell Neoplasm Immunophenotype-like Acute Myeloid Leukemia

GIMEMA AML2020

Sponsor according to European Directives	**Fondazione GIMEMA Franco Mandelli Onlus**
Study Principal Investigator	**Prof. R.M. Lemoli**
Coordinating Center	**IRCCS Ospedale Policlinico San Martino UO Clinica Ematologica – Genova**
Writing Committee	**Dott.ssa P. Minetto Dott. F. Guolo Dott. A. Curti Prof. A. Venditti Prof. L. Pagano**

- First European Study employing Tagraxofusp in AML treatment
- Primary endpoint of the study is to evaluate the **safety and activity** of 12 mcg/Kg Tagraxofusp in patients with **CD123+ or BPDCN-like phenotype Relapsed/Refractory (R/R) AML.**
- Non-randomized, open-label, multicenter phase II Study.

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI



Patient #1-3 ----------→ C1 Tagraxofusp 2 days

Patient #4-6 ----------→ C1 Tagraxofusp 2 days + 1 day optional

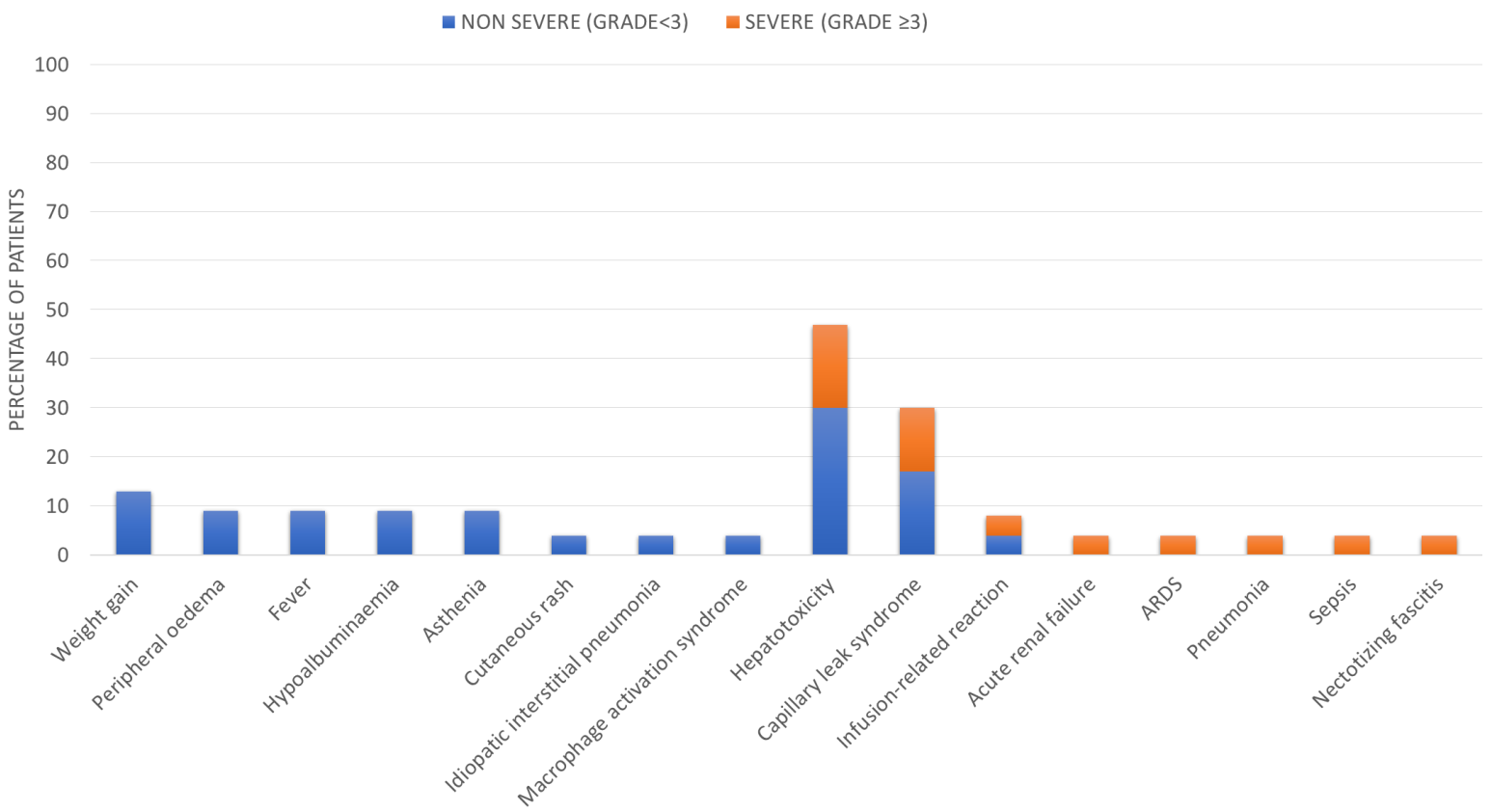
Patient #7 and beyond ----------→ C1 Tagraxofusp 3 days

RESULTS

- As of December 2023, 23 patients have been enrolled.
- Median age was 65 years (41-75).
- Eleven patients had refractory disease; 13 patients had relapsed disease.
- Ten patients were classified high risk at diagnosis according to ELN2017 classification
- Two patients, who had received allogeneic stem cell transplantation (allo-BMT) while in CR, were enrolled at first relapse post-transplant.
- **The median number of TAG cycles was 2 (range 1-10).**
- **Overall response rate (ORR) was 34.8% with 2 patients achieving MRD negative CR and 6 patients achieving partial remission (PR)**
- Early treatment discontinuation in the other cases was due to disease progression or adverse events (AEs).

Minetto P. et al. 65° ASH Annual Meeting and Exposition, #2918

ADVERSE EVENTS



- **Capillary leak syndrome (CLS) was reported in 5 patients**: 2 patient experienced grade 2 (symptomatic) CLS which resolved with mild supportive treatment; 1 patient experienced grade 3 (severe), **1 grade 4 (life-threatening) and in one case the onset of CLS triggered by infectious event resulted fatal.**

Minetto P. et al. 65° ASH Annual Meeting and Exposition, #2918

Conclusions

- **CD123** is a promising target in hematological malignancies and several new targeted agents are being developed
  - However efficacy of CD123-targeted agents varies according to their mechanism of action
- **Tagraxofusp** – the first-in-class commercialy available CD123-targeted therapy and the first approved treatment for BPDCN in both the US and EU
  - Great interest in clinical development, however, which is the ideal clinical setting out of BPDCN has to be clarified
- **GIMEMAL AML2020**: single agent TAG can exert some anti-leukemic activity in R/R CD123-positive AML, even in cases with very unfavourable prognosis
  - The safety profile require close monitoring of patients and timely supportive measures
  - Further studies are necessary to disclose predictors of response and of the risk of adverse events
  - Investigation of combinations strategies with TAG is warranted in order to optimize treatment efficacy

OSPEDALE POLICLINICO SAN MARTINO
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Thank you for your attention

UNIVERSITÀ DEGLI STUDI DI GENOVA

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