
**Giovanni Martinelli**
**Universita' di Bologna Istituto Seragnoli**
**IRCCS della Romagna - Meldola**

# Conflict: no direct conflict

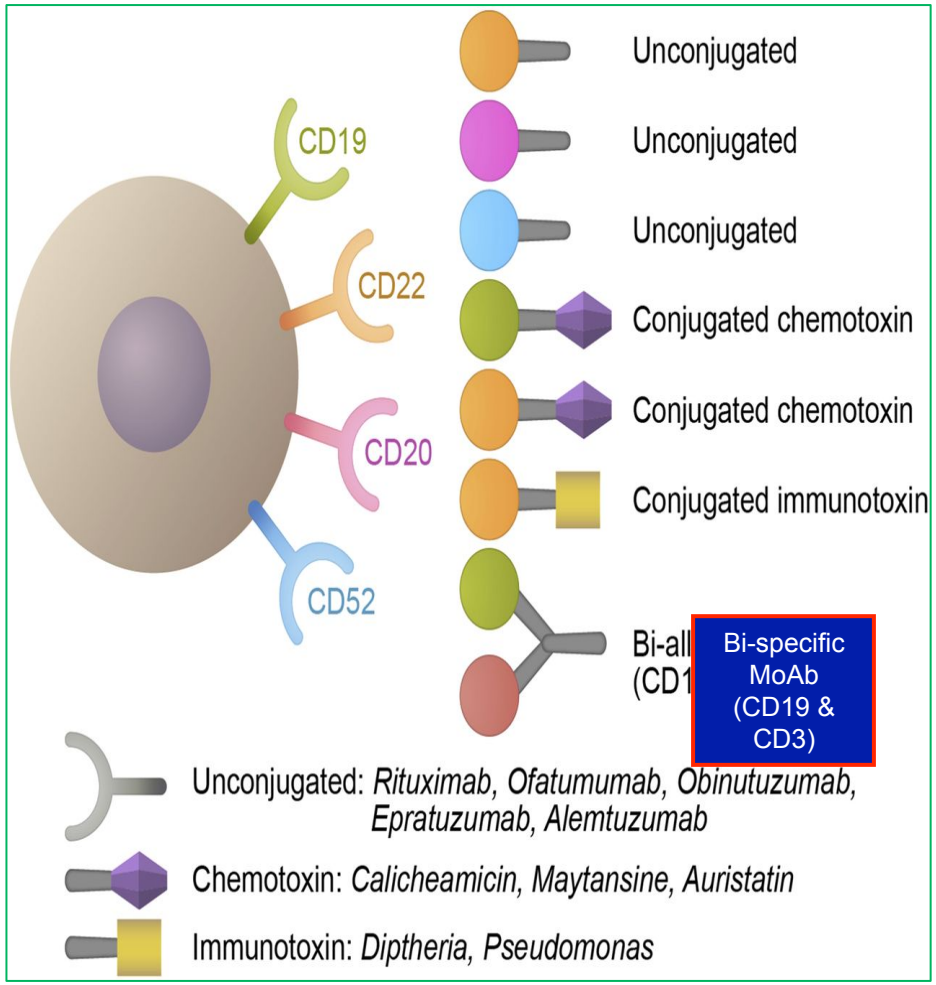

**Giovanni Martinelli**
**University of Bologna**
**and**
**IRCCs Romagna**

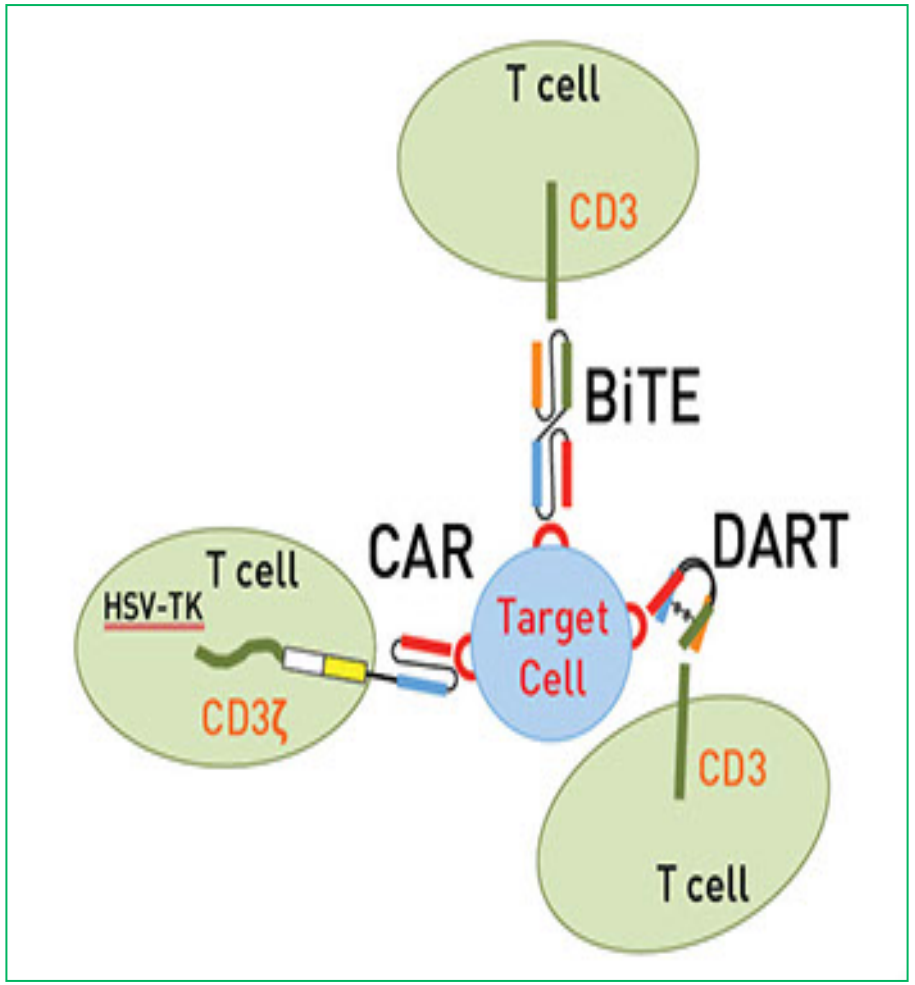
ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI


REFERENCE:
1. Vardiman J, Thiele J, Arber D et al. The 2008 revision of the world health organization (WHO) classification of myeloid neoplasms and acute leukemias: rationale and important changes. *Blood*. 2009;114(5):937-951.

# Immuno-oncology

## Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR-T cells




Jabbour E, *et al. Blood* 2015;125(26):4010-4016.

# Expression of surface antigens in ALL

| | | Expression on >20% of LBC | | |
|---|---|---|---|---|
| **Surface antigen** | **ALL subtype** | **Thiel,*** | **Raponi,** | **Martinelli **** |
| CD19 | B-precursor<br>Mature B-ALL | 95%<br>94% | 100%<br>100% | |
| CD20 | B-precursor<br>Mature B-ALL | 41%<br>86% | 22–30%<br>100% | |
| CD22 | B-precursor<br>Mature B-ALL | 60–85%<br>69% | 93–96%<br>100% | |
| CD200 | B-precursor<br>CRLF2 Hi<br>T-precursor<br>Ph+ ALL | | | 95%** |
| CD52 | B-precursor<br>T-precursor | 79%<br>77% | | |
| CD123 | B-precursor<br>T-precursor<br>Ph+ ALL | | | 93% ** |

*Data from the GMALL central immunophenotyping (E.Thiel and S.Schwartz, Berlin, Germany, personal communication). LBC, lymphoblastic cells
Hoelzer D. *Hematology* 2011:243–249
Martinelli et Al. personal comunication

# CD123+ hematological malignancies

## CD123= Interleukin-3 receptor

IL-3 is a pleiotropic cytokine, mainly produced by activated T-lymphocytes, regulating the function and production of hematopoietic and immune cell

CD123 is expressed in a variety of hematological neoplasms including:

- **Blastic plasmacytoid dendritic cell neoplasm** (BPDCN),
- **Acute myeloid leukemia** (AML**),**
- **Acute lymphoblastic leukemia** (ALL),
- **Chronic myeloid leukemia** (CML),
- **Hodgkin's lymphoma**
- **Hairy cell leukemia**

# CD123+ and hematological malignancies

| Diagnosis | % CD123 positive pts (n=pts number) | References |
|---|---|---|
| AML | >95 (n>500) | *Jordan et al, 2000; Munoz et al, 2001; DeSmet et al, 2012; Ehninger et al. 2014; Adelini et al, 2015* |
| CML | >70 (n=42)<br>~ 100% for CML in blast crisis | *Florian et al, 2006; Nievergall et al., 2014* |
| Myelodysplastic syndrome | 54 (n=84) | *Orazi et al, 2006; Florian et al, 2006; Yue et al, 2010; Xie et al, 2010; DeSmet et al, 2012; Zhang et al, 2015* |
| Blastic Plasmacytoid DC neoplasm (BPDCN), leukemia | 100 (n>160) | *Garnache-Ottou et al, 2009; Kharfan-Dabaja et al, 2013; Fanny et al, 2014; Pemmaraju et al, 2015 ASH; Poret et al, 2015 ASH* |
| B-ALL | 92 (n>300)<br>Very high levels in hyperdiploid B-ALL | *Munoz et al, 2001; Djokic et al., 2009; Hassanein et al., 2009; Coustan-Smith et al., 2011* |

| Diagnosis | % CD123 positive pts (n=pts number) | References |
|---|---|---|
| T-ALL | 42 (n=72)<br>83% in early T-precursor ALL | *Due et al, 2015; Hellman et al 2016* |
| Hairy cell leukemia | 100 (n=140) | *Munoz et al, 2001; Del Giudice et al, 2004; Venkataraman et al, 2011* |
| Hodgkin Lymphoma | 60 (n=59) | *Fromm, 2011* |
| Systemic Mastocytosis | 64 (n=69) for all subtypes<br>100% (n=10) for ASM subtype | *Pardanani et al., 2015; Pardanani et al., 2016* |

# Plasmacytoid dendritic cell (PDC) neoplasm as model to study CD123+ hematologic malignancies and to study the metastatic process

# Plasmacytoid dendritic cells (PDC)

Two distinct forms of neoplasms derived from plasmacytoid dendritic cells (PDC) exist:

1) Mature PDC proliferations associated with myeloid neoplasms

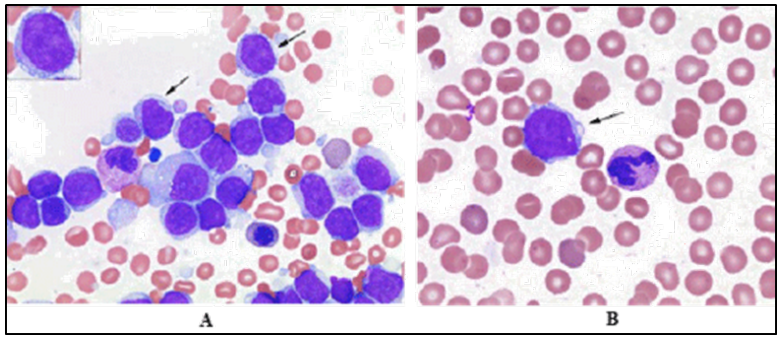
2) Blastic PDC neoplasms (BPDCN)

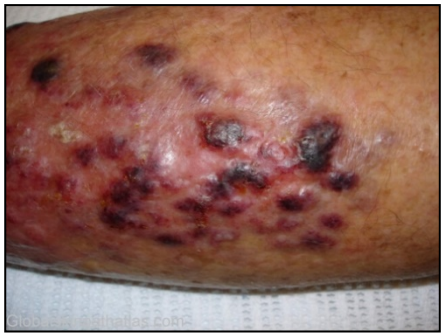
# Blastic plasmacytoid dendritic cell neoplasm as a model

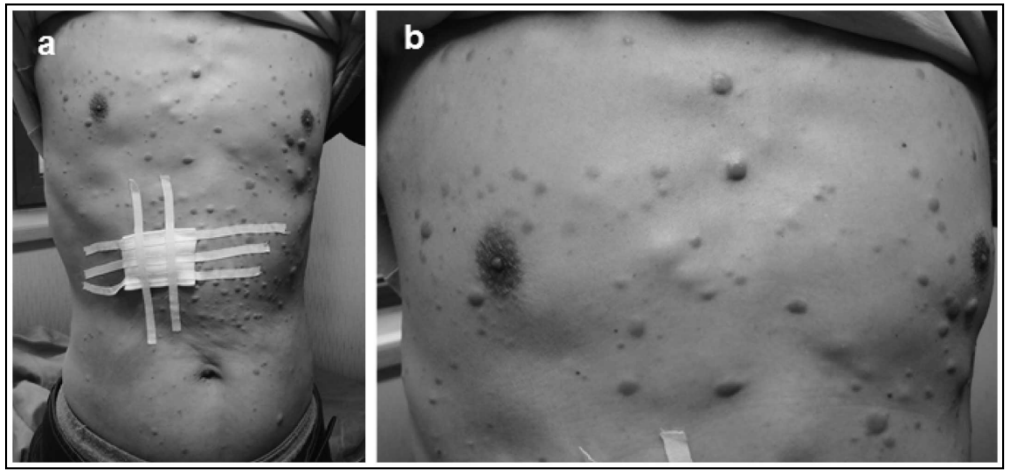
Blastic plasmacytoid dendritic cell neoplasm consists of **clonal proliferation of plasmacytoid dendritic cells precursors.**

The **striking cutaneous tropism** of blastic plasmacytoid dendritic cell neoplasm and localization in the bone marrow

Frequent evolution in AML





# Genetic and molecular findings in PDCs

No specific karyotypic abnormalities are found in PDCs neoplasm, but complex chromosomal aberrations often occur, with six major recurrent chromosomal targets, represented by 5q (72%), 12p (64%), 13q (64%), 6q (50%), 15q (43%), and 9 (28%)

Frequent **genomic loss** involving tumor suppressor genes or **genes related to the G1/S transition** have been reported the most recurrent being represented by deletions of **CDKN2A** (27% of cases).

**TET2 is the most common mutated gene** (36 to 80% of cases) in blastic plasmacytoid dendritic cell neoplasm

Targeted sequencing identified deleterious mutations of **IKZF3** and **ZEB2** genes (12–16%), previously unreported in human leukemia.

# SL-401

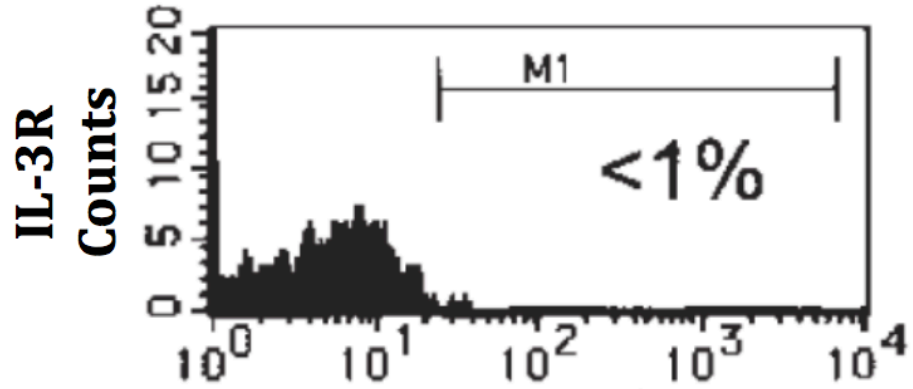
# Stemline

## SL-401
## Investigator's Brochure

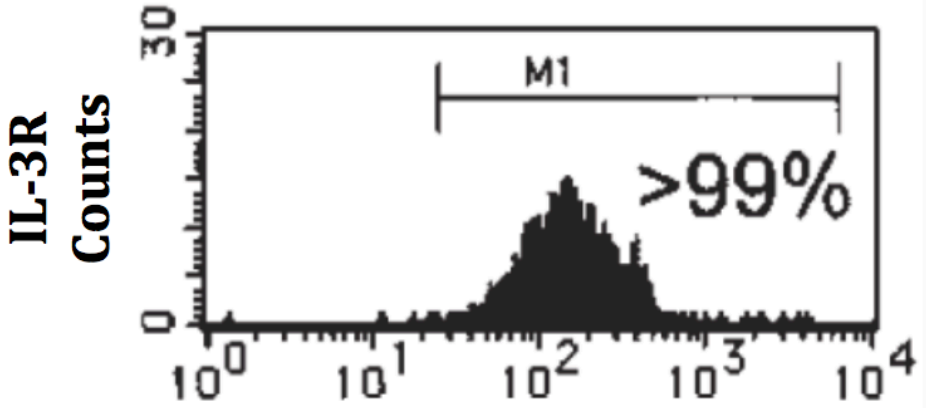
Sponsor: Stemline Therapeutics, Inc.
750 Lexington Avenue
11th Floor
New York, NY 10022

**Figure 2-2: IL-3R Overexpression on AML CSCs vs. Normal Hematopoietic Stem Cells**

**≤1% normal hematopoietic stem cells express IL-3R**



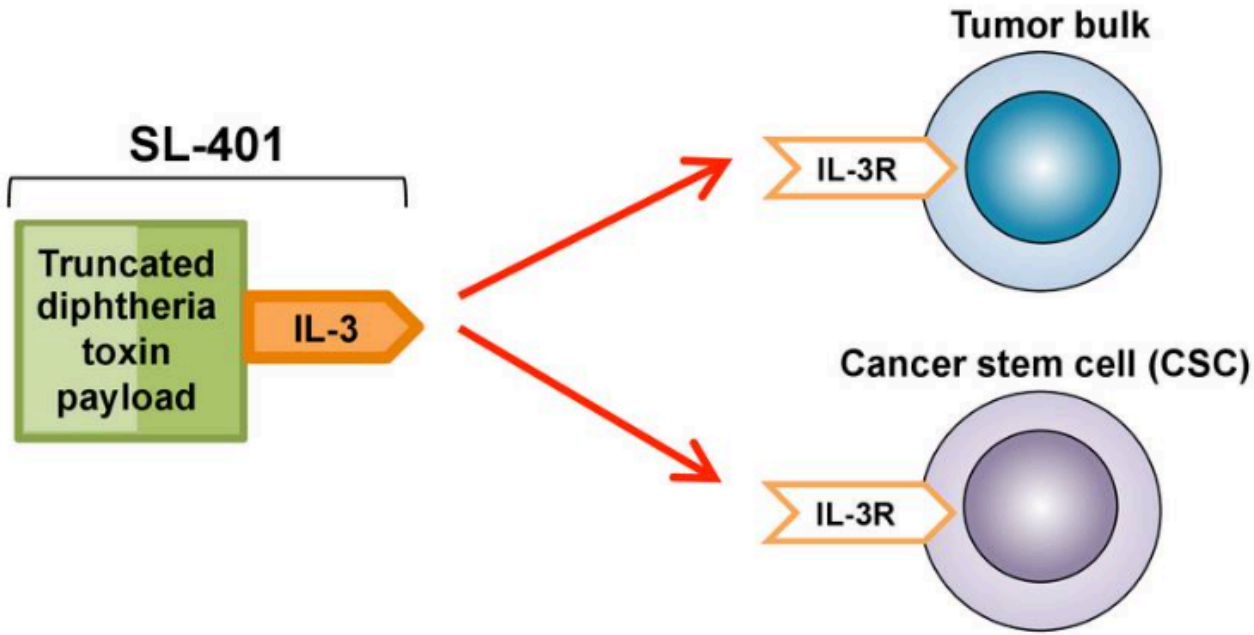

**>99% of AML CSCs express IL-3R**



# Pipeline

| Program | Target | IND | Lead-in/dose escalation | Phase 2 |
|---|---|---|---|---|
| SL-401 | IL-3R | BPDCN | | Enrolling |
| | | AML (r/r) | | Enrolling |
| | | AML (in CR, MRD+) | | Enrolling |
| | | MPN | | Enrolling |
| | | Myeloma | | Enrollment targeted mid-16 |

# SL-401 Targeted Therapy




**IL-3R (CD123) is expressed on many hematologic cancers**

- Leukemias
  - AML, MDS, CML, ALL, et al
- Lymphomas
  - Hodgkin's lymphoma, certain Non-Hodgkin's lymphoma (NHL)
- Additional hematologic malignancies
  - BPDCN
  - Myeloproliferative neoplasms (MPN)
  - Myeloma



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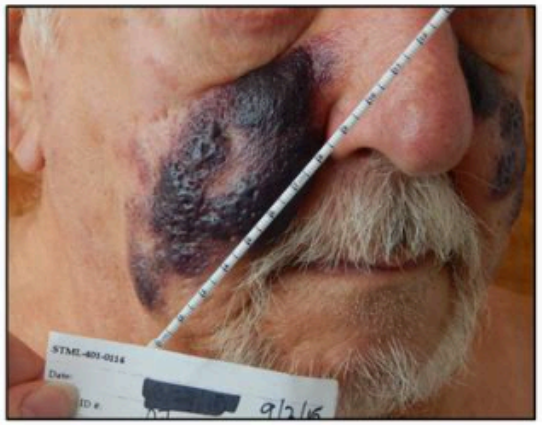
# BPDCN Disease and Rationale for SL-401

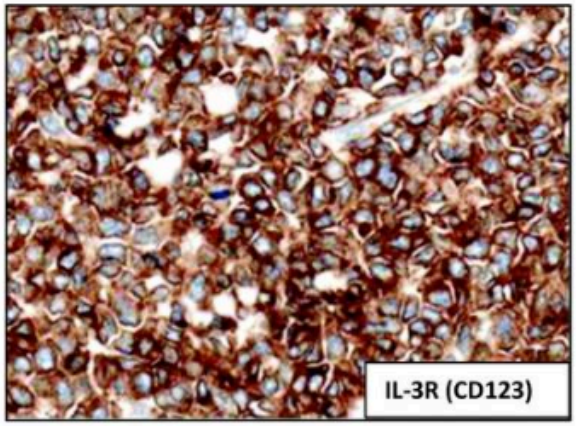
**BPDCN is a highly aggressive malignancy of unmet medical need**

- Multi-organ involvement: skin, bone marrow, lymph nodes, spleen, other
- Very poor prognosis with no accepted standard of care

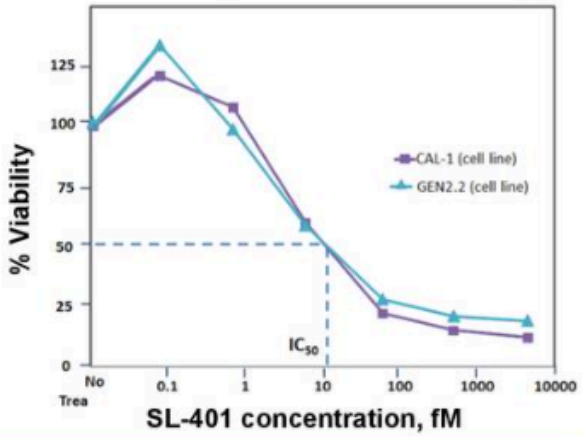
**BPDCN skin lesions**



**Elevated IL-3R is expression**
**(IHC of BPDCN skin lesion)**




**SL-401 highly potent against BPDCN (femtomolar $IC_{50}$)**




**SL-401 demonstrated robust single agent activity in previous Phase 1/2 trial**

- Single cycle SL-401 had major responses, including CRs, in BPDCN and AML
  - Published in *Blood* 124: 385–392, 2014
- ***2 BPDCN pts remission >2 yrs***



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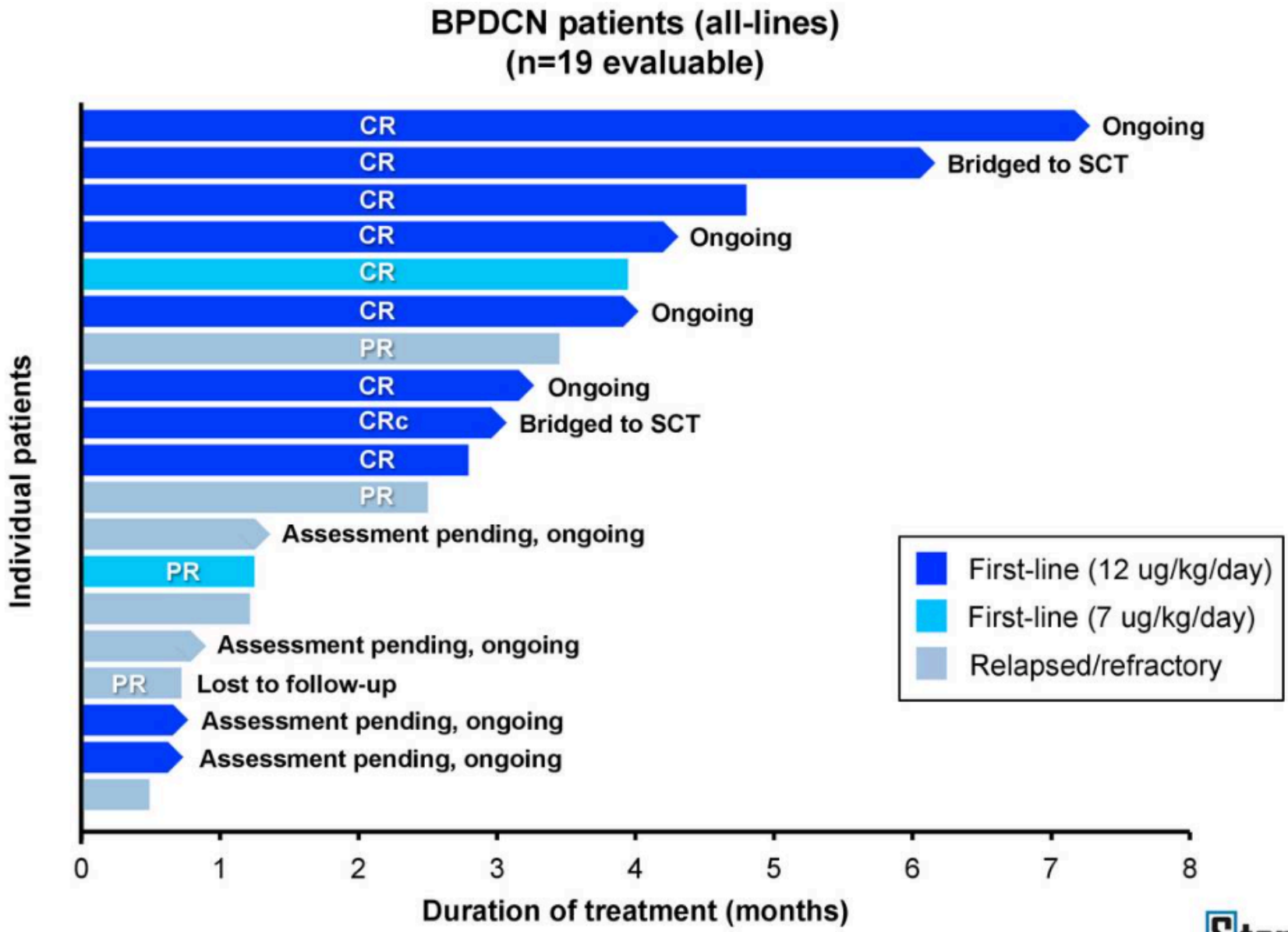
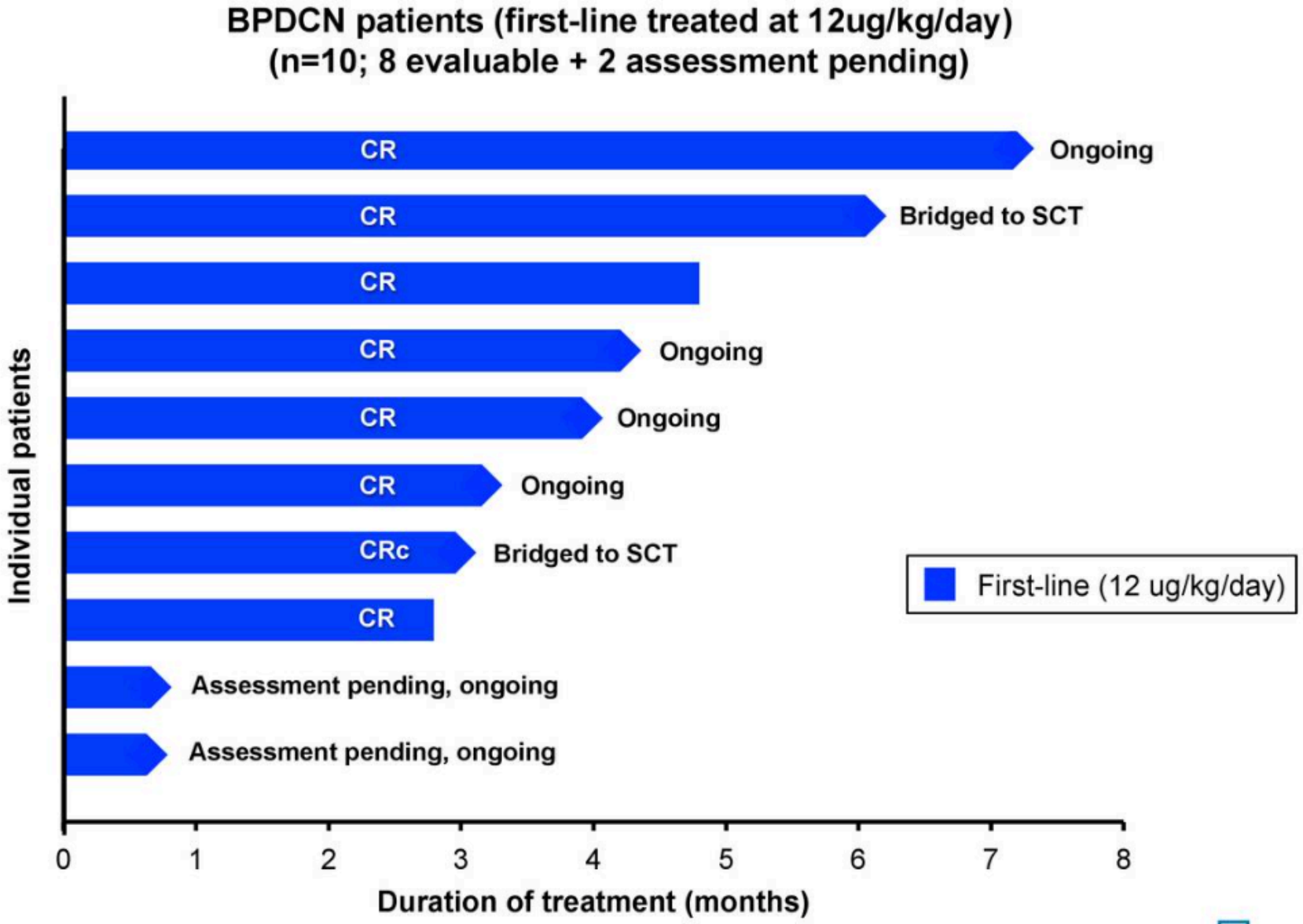
# Duration of Treatment and Responses



# Duration of Treatment and Responses



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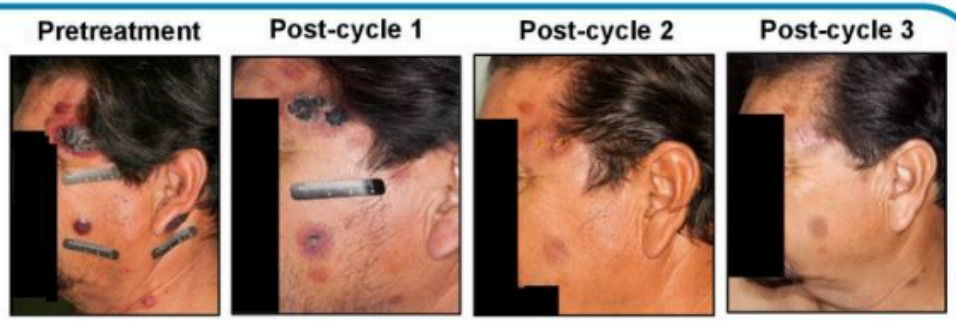
# Skin and Visceral Responses

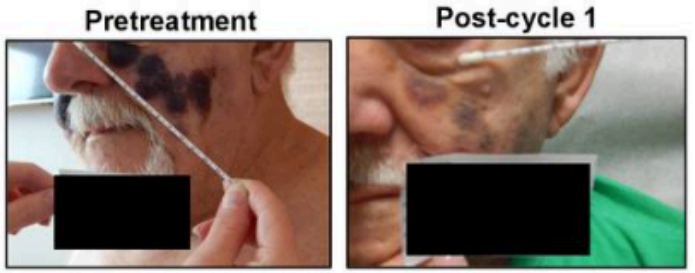
## Representative skin response #1

- 63 year old male with extensive BPDCN involving skin, bone marrow and lymph nodes
- Received 6 cycles of SL-401 and achieved a CRc which included a CR in the bone marrow and lymph nodes, with resolution of gross skin lesions and positive residual microscopic skin biopsy




## Representative skin response #2

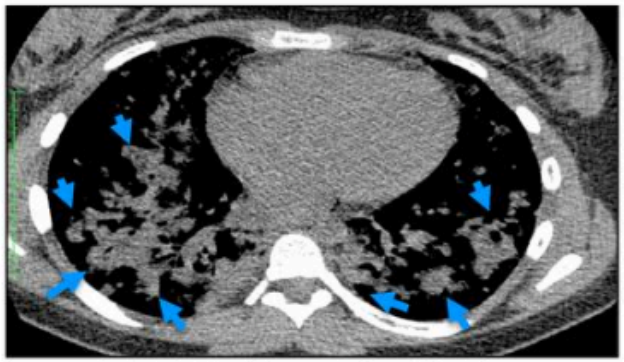
- 75 year old male with r/r BPDCN involving skin
- Received 1 cycle of SL-401 and achieved a PR with >75% reduction of gross skin lesions by mSWAT analysis



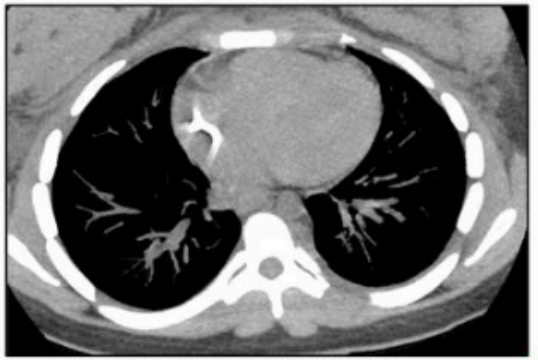

## Representative visceral (organ) response: lung involvement

- 15 year old female with r/r BPDCN involving skin and bone marrow and requiring supplemental oxygen for extensive pulmonary involvement
- Received 2 cycles of SL-401 and achieved a PR with improvement of pulmonary lesions

**Pretreatment**
**(bulky disease indicated with blue arrows)**



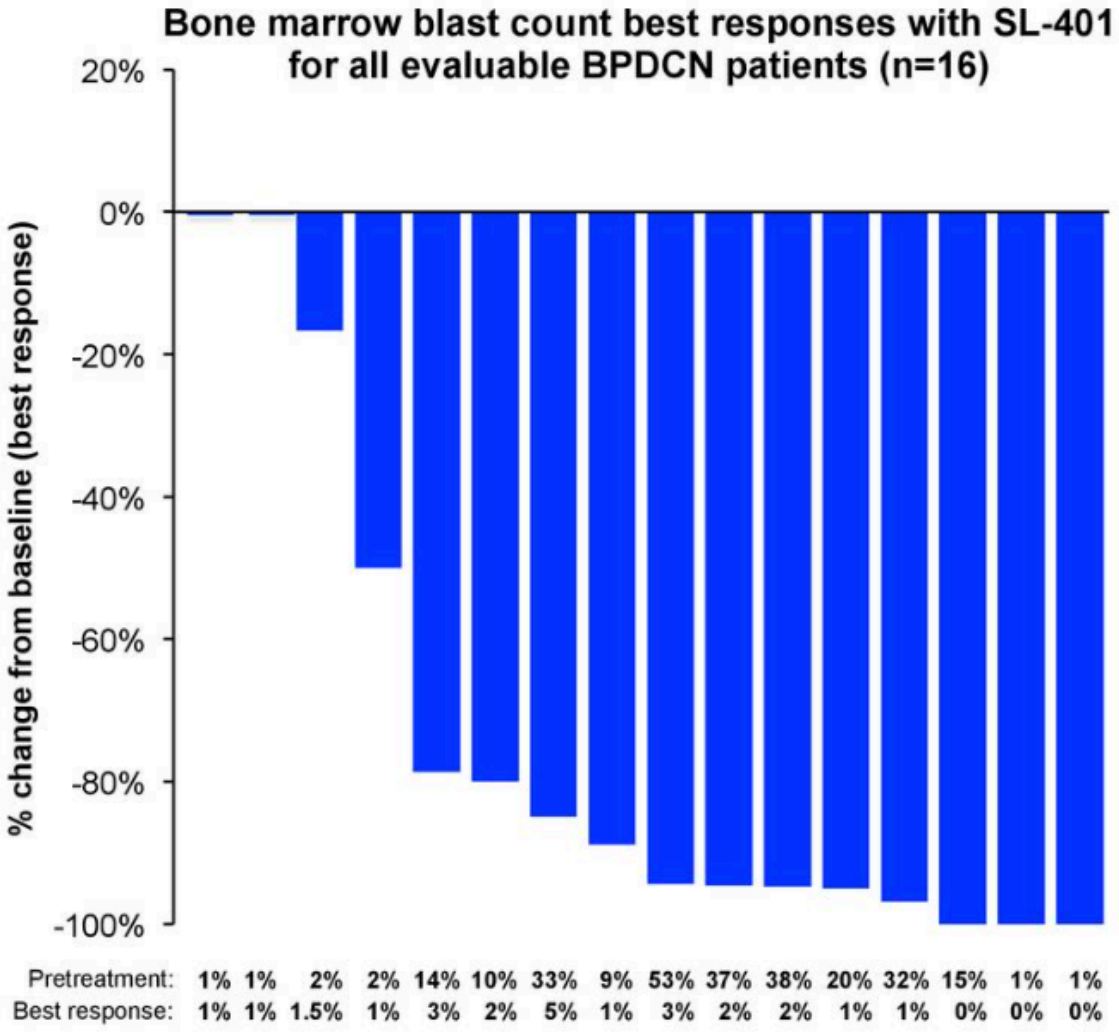
**Post-cycle 2**
**(normal-appearing bronchial structures)**



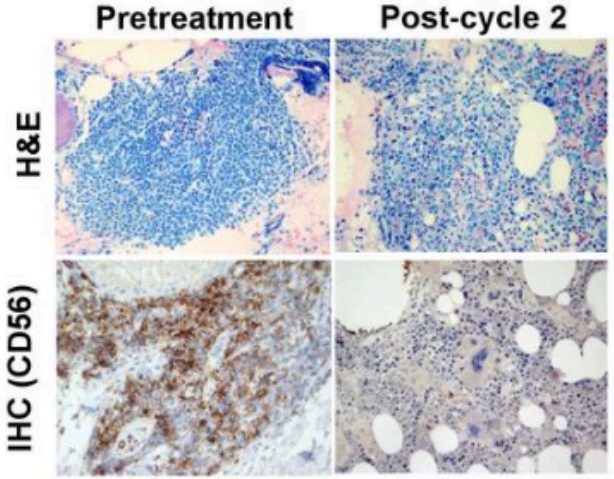


Stemline

# Bone Marrow Responses




**Representative bone marrow response**




- 62 year old female with extensive BPDCN involving skin, bone marrow, lymph nodes, viscera (spleen, eyelids, gums)
- Received 4 cycles of SL-401 and achieved a CR
- Bone marrow biopsy (pretreatment and end of cycle 2) shows clearance of CD56+ BPDCN cells



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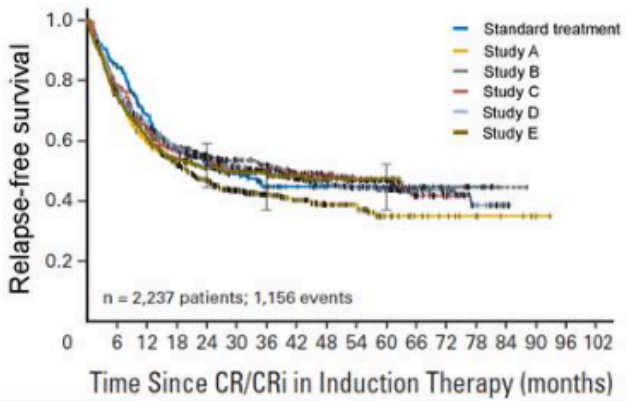
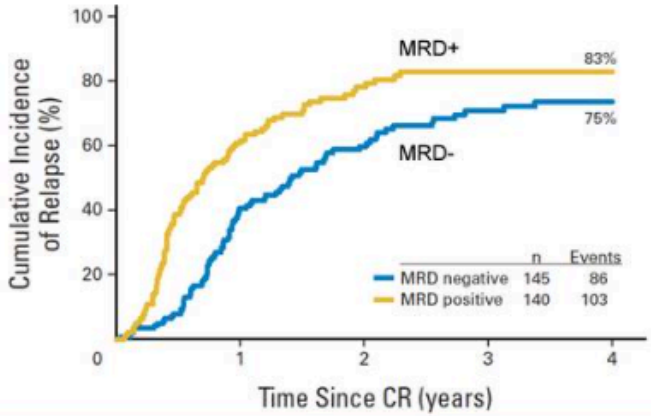
# Rationale for SL-401 in AML in CR, MRD+

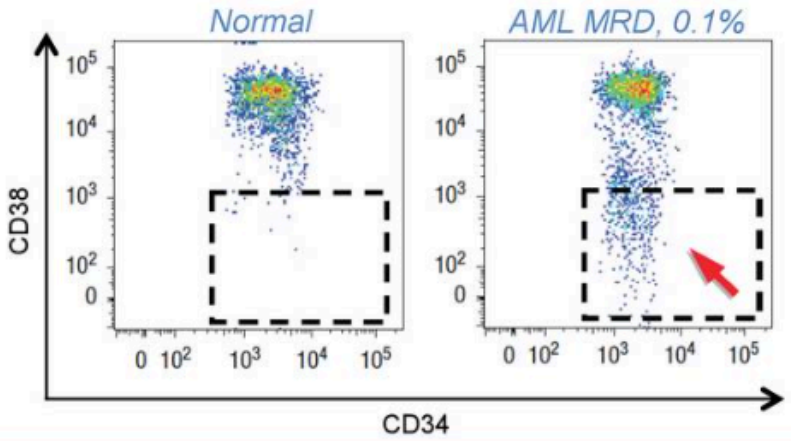
## Majority of AML patients in 1st CR will relapse



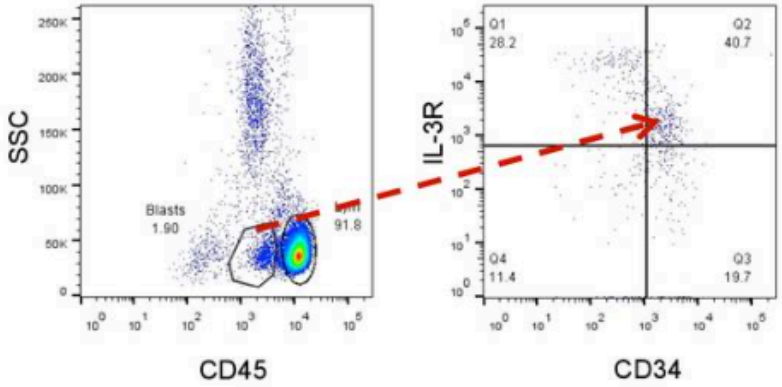

## MRD is a predictor of 1st relapse




## MRD is CSC-rich




## MRD is IL-3R+




*Buchner, T. JCO, 2012; Freeman, S. D. JCO, 2013; Jorgensen, J. L. Clin Lymphoma Myeloma Leuk, 2011; Konopleva, M. (unpublished)*



Stemline

Opening and Enroling
CMS -IRCCS Meldola approved

# A phase 2, open-label, BASKET study of SL-401 in combination with standard of care for relapsed/ refractory CD123 highly positive neoplasms.

NEXT in Leukemia trial

( Non Company trial

(Support STEMLINE approved)

# Madrid, Spain

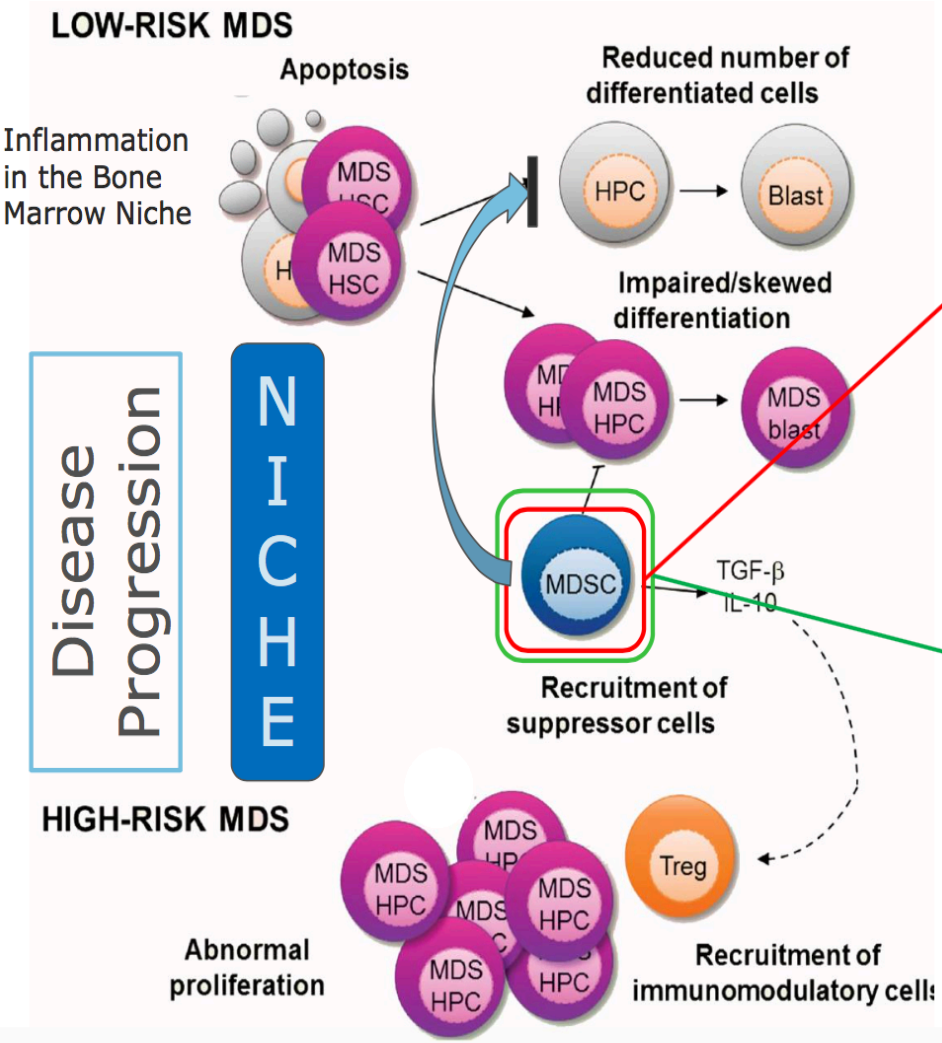
janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

# Talacotuzumab and Daratumumab in Low-Risk MDS

**Jeffrey R. Harris, PhD**

*Translational Research Lead - Talacotuzumab*

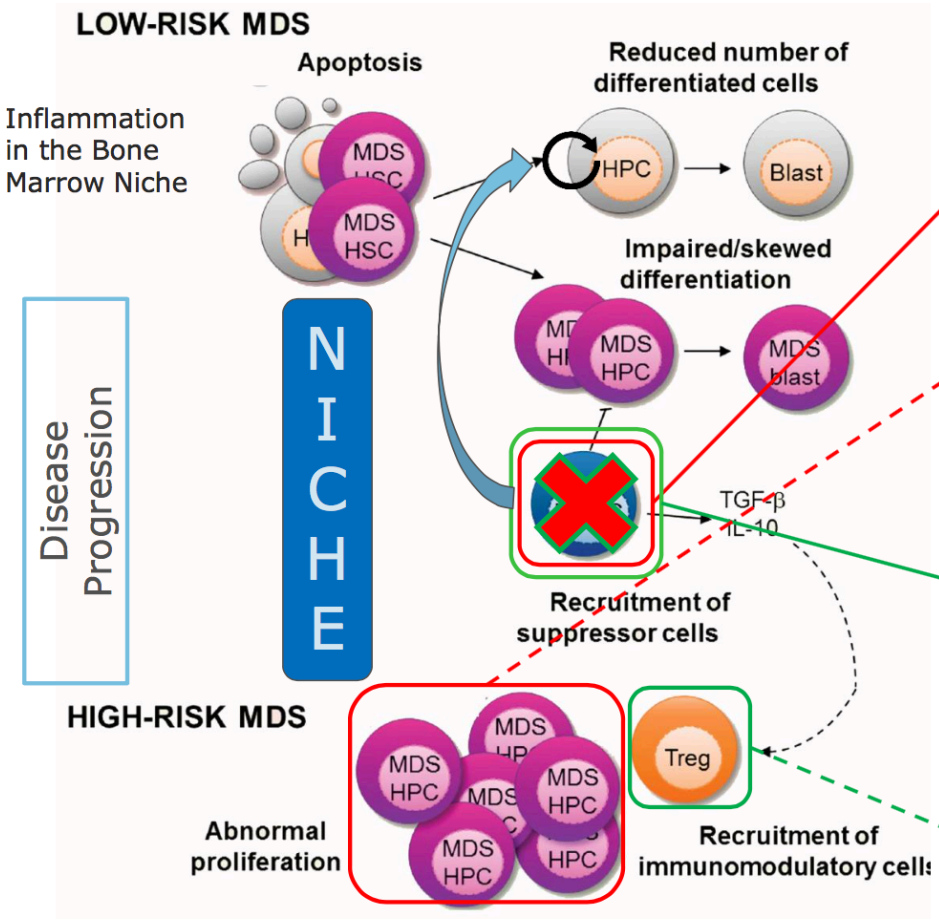
# MDSCs in the Context of MDS Disease Progression and Therapeutic Intervention




Talacotuzumab may target CD123+ MDSC reduce immune suppression and improve clinical outcomes in LR-MDS.

Daratumumab may target CD38+ MDSC to reduce immune suppression and improve clinical outcomes in LR-MDS.

# Summary for MDS Treatment with Talacotuzumab or Daratumumab




**Talacotuzumab may target CD123⁺ MDSC reduce immune suppression and improve clinical outcomes in LR-MDS.**

Talacotuzumab may target CD123⁺ MDS blasts and synergize with depletion of CD123⁺ MDSCs.

**Daratumumab may target CD38⁺ MDSC to reduce immune suppression and improve clinical outcomes in LR-MDS.**

Daratumumab targeting CD38⁺ Tregs may inhibit disease progression and synergize with depletion of CD38⁺ MDSCs.

Adapted from Ganan-Gomez, et al. Leukemia 2015

# Translational Research Strategy Summary

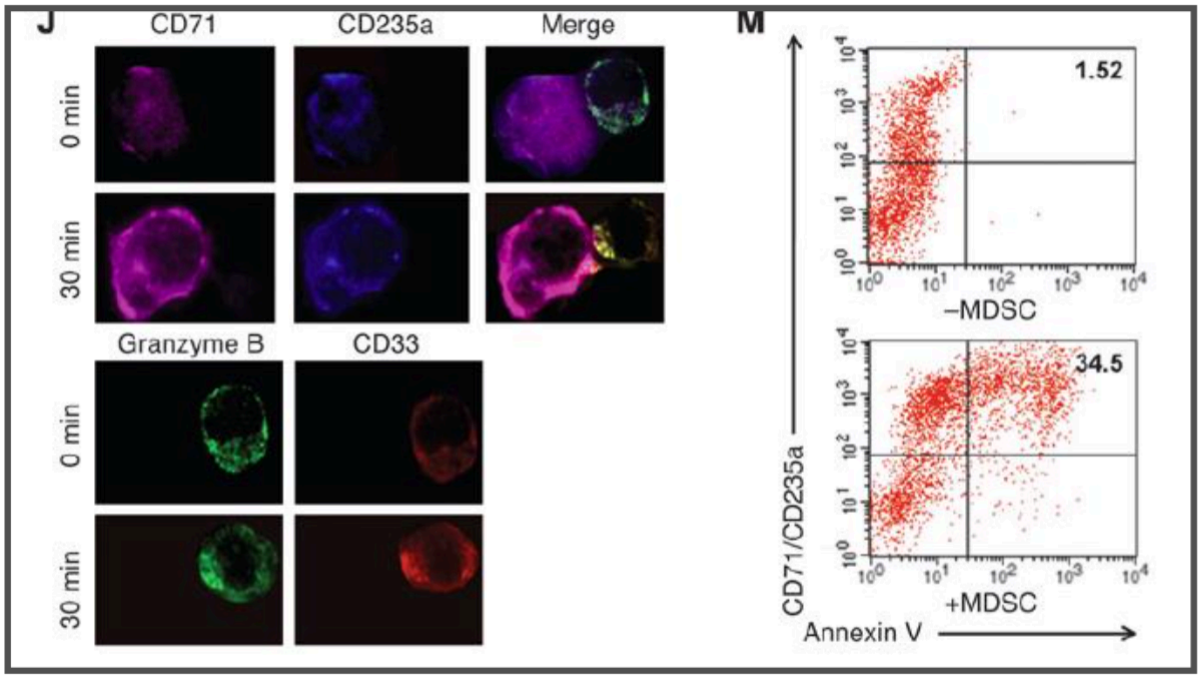
## Hypotheses:

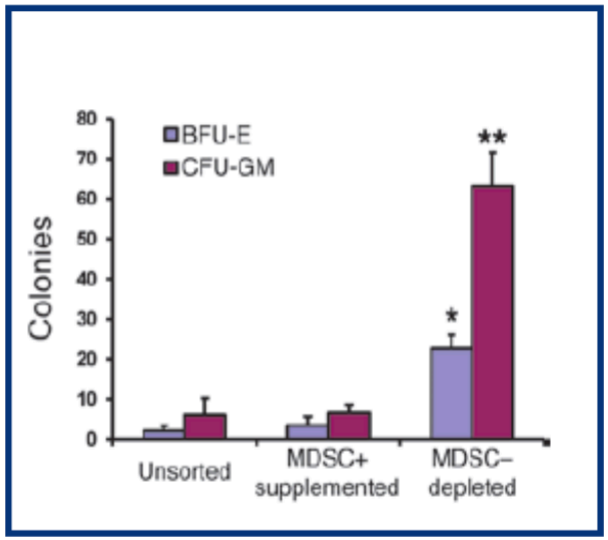
- Talacotuzumab will deplete CD123$^+$ MDSCs to reduce immune suppression, and deplete CD123$^+$ blasts to improve clinical outcomes.
- Daratumumab will deplete CD38$^+$ MDSC and CD38$^+$ Tregs to reduce immune suppression, and improve clinical outcomes.

## Biomarker Objectives:

- To assess reduction of CD123$^+$ and CD38$^+$ MDSCs, CD123$^+$ Blasts, and CD38$^+$ Tregs following treatment, and explore association with clinical outcomes.
- Explore associations between potential predictive biomarkers and clinical outcomes:
  - Frequency of MDSCs, blasts, the level of CD123 expression on MDSCs or MDS blasts, and CD38 expression on MDSCs or Tregs.
  - Frequency and absolute numbers of effector cells (NK and T cells).

# MDSCs Directly Inhibit Hematopoietic Progenitor Cells in MDS



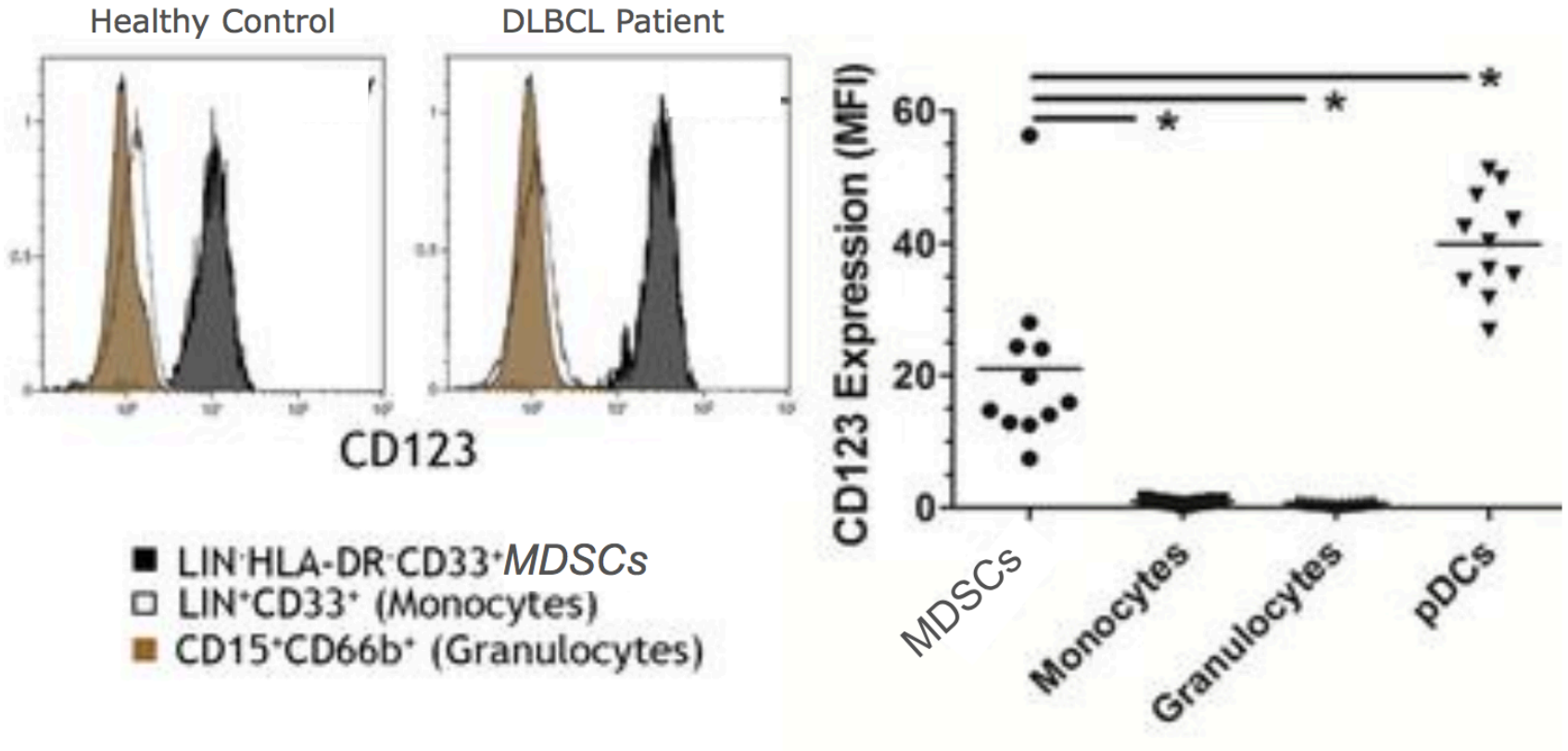




MDSC interacts directly with erythroid progenitors (CD235a/CD71), causing increased granzymeB and increased cell death of EPC

MDSC inhibits HPC colony formation in CFU assays

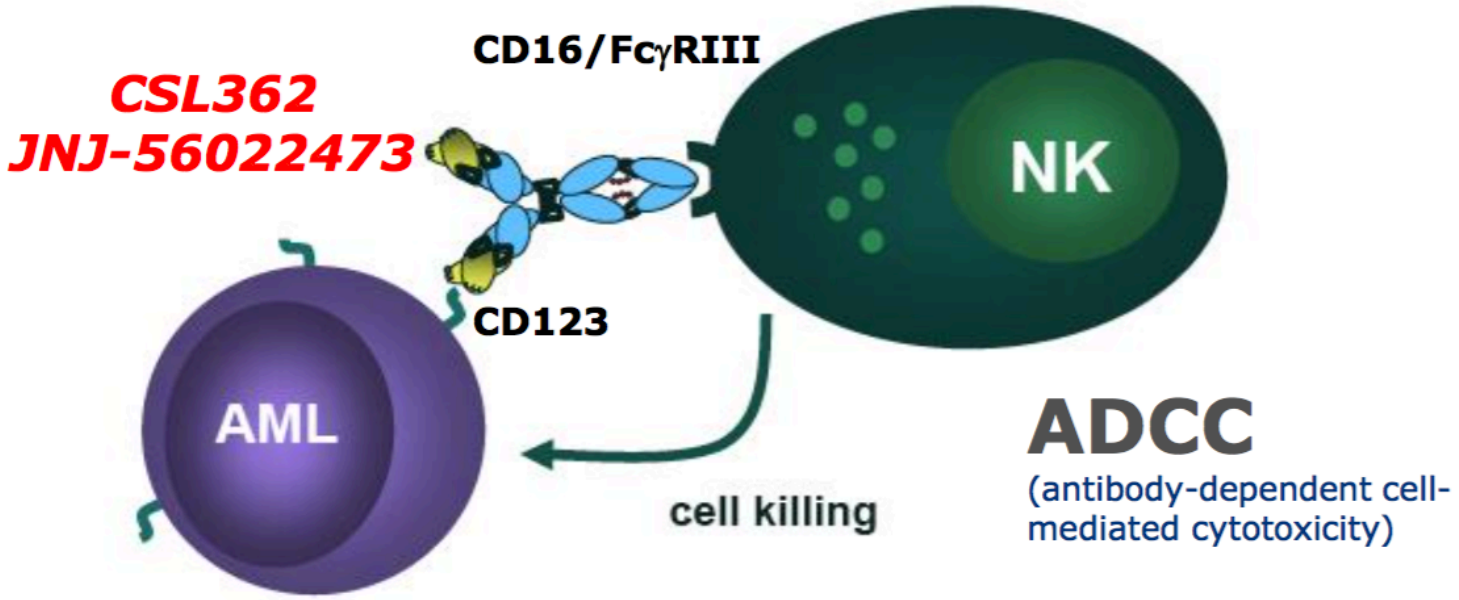
*Chen et al. JCI. 2013*

# CD123 is Expressed on MDSCs




*Gustafson, et al. PLOS One, 2015.*

# Talacotuzumab: Second Generation CD123 Antibody




Humanized from murine antiCD123 monoclonal antibody

Modifications in Fc improved binding to enhance NK binding

Leads to redirection of NK cells and induction of ADCC against CD123 overexpressing quiescent LSCs and leukemic blasts

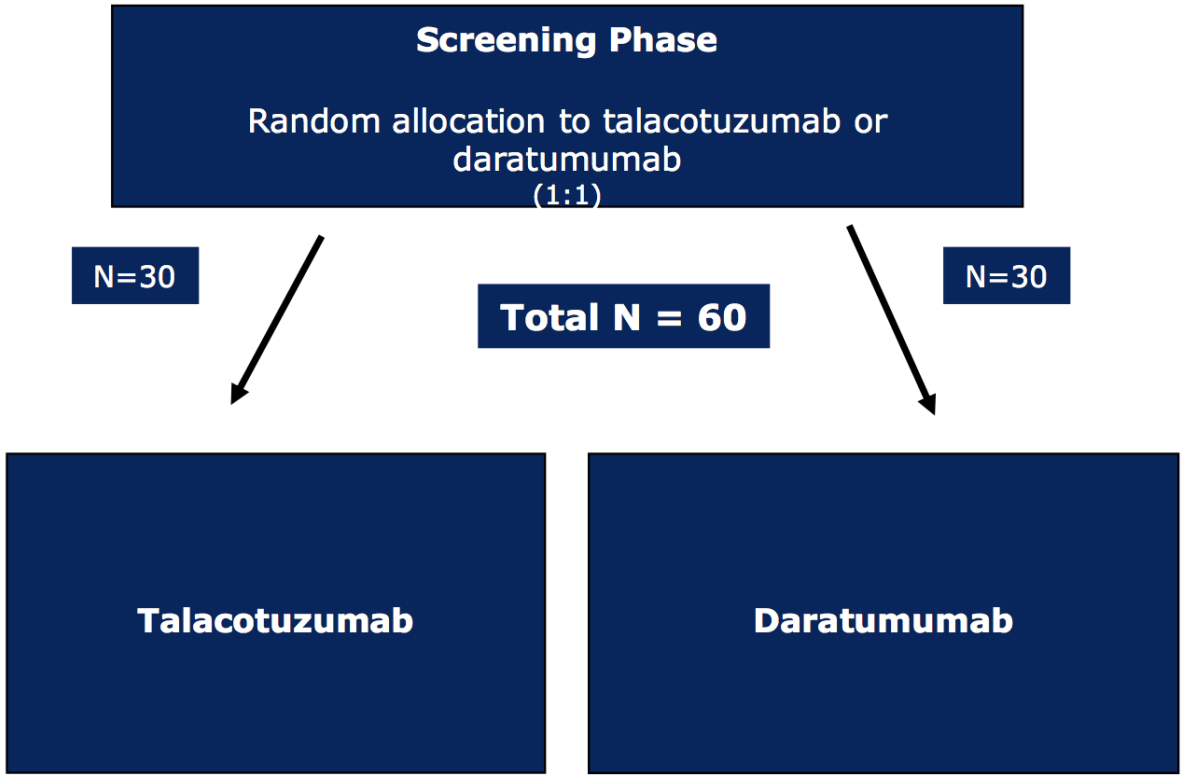
Talacotuzumab produced in different cell line with a different process compared with CSL362

**Patient Population:**

IPSS = Low or Intermediate-1 Risk

Transfusion Dependent

Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment



Next In Leukemia

| | |
|---|---|
| **PROTOCOL TITLE:** | A SAFETY RUN-IN AND PHASE 2, OPEN-LABEL, MULTICENTRE, STUDY INVESTIGATING SAFETY, TOLERABILITY AND EFFECTIVNESS OF TALACOTUZUMAB (JNJ-56022473) ADD IN COMBINATION AT CYRATABINE AND IDARUBICINE IN ELN LOW AND INTERMEDIATE-1 RISK NON-M3 ACUTE MYELOID LEUKEMIA WITH POSITIVE MINIMAL RESIDUAL DISEASE AFTER INDUCTION |
| **SHORT NAME:** | TAI |
| **PROTOCOL NUMBER:** | |
| **VERSION NUMBER:** | |
| **EUDRACT NUMBER:** | |
| **IND NUMBER:** | |
| **TEST PRODUCT:** | Talacotuzumab (JNJ-56022473) |
| **SPONSOR:** | |
| **DATE FINAL:** | |

# Flotetuzumab

MACROGENICS

**Clinical Trial Protocol: CP-MGD006-01**
**Study Site Feasibility Questionnaire**

**Study Title:** A Phase 1, First-in-Human, Dose Escalation Study of MGD006, a CD123 x CD3 Dual Affinity Re-Targeting (DART) Bi-Specific Antibody-Based Molecule in Patients With Relapsed or Refractory Acute Myeloid Leukemia or Intermediate-2/High Risk Myelodysplastic Syndrome

# Interim Results from a Phase 1 First-in-Human Study of Flotetuzumab, a CD123 x CD3 Bispecific DART® Molecule, in AML/MDS

Norbert Vey, Jan K. Davidson-Moncada, Geoffrey L. Uy, David Rizzieri, H. Jean Khoury, Matthew C. Foster, John Godwin, Max S. Topp, Giovanni Martinelli, Fabio Ciceri, Matteo G. Carrabba, Geert Abraham Huls, Antje Wegener, Kathy Tran, Michele Shannon, Jichao Sun, Jon M. Wigginton, John F. DiPersio

MADRID 2017 ESMO congress

September 10, 2017



SERVIER MACROGENICS

# IL-3 Receptor α (IL-3Rα): CD123

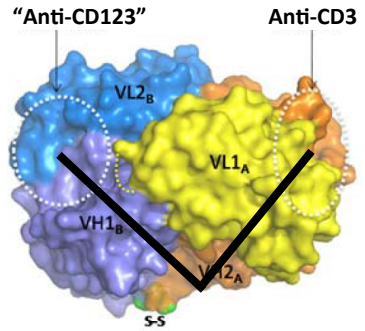
- Low affinity ligand binding subunit of IL-3R
- Binds IL-3 and heterodimerizes with common β subunit of GM-IL-5-IL-3 receptor complex to induce proliferative and anti-apoptotic signaling
- Differentially overexpressed in 93% of AML patients
- CD123 is expressed on AML LSC
- Correlation between CD123+ cells frequency and prognosis

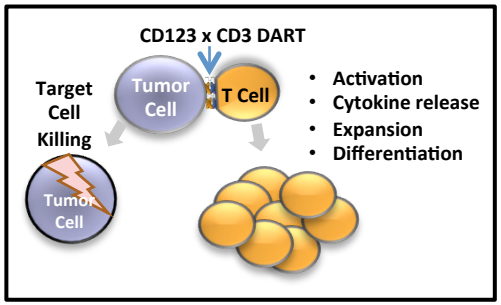
| Disease | CD123 Positivity |
|---|---|
| **AML** | 93% |
| **MDS** | >50% |
| **CML** | >50 - 77.5% |
| **B-cell ALL** | 80 - 99% |
| **Classical Hodgkin's Lymphoma** | 50 - 60 % |
| **Hairy Cell Leukemia** | 100% |
| **CLL** | 10% |
| **Systemic Mastocytosis** | >50 - 100% |
| **pDC Leukemia** | 100% |

*Jordan, et al. Leukemia. 2000 Oct; 14(10):1777-84; Jin, et al. Cell Stem Cell 2009 Jul 2;5(1):31-42; Munoz, et al. Haematologica 2001 Dec;86(12):1261-9; O'Brien and Rizzieri Cancer Invest 2013 May;31(4):215-20; Testa, et al. Blood. 2002 Oct 15; 100(8):2980-8; Tettamanti, et al. Br J Haematol 2013 May; 161(3):398-401; Vergez, et al. Haematologica 2011 Dec;96(12):1792-8*

# Flotetuzumab: CD123 x CD3 Bispecific DART® Protein

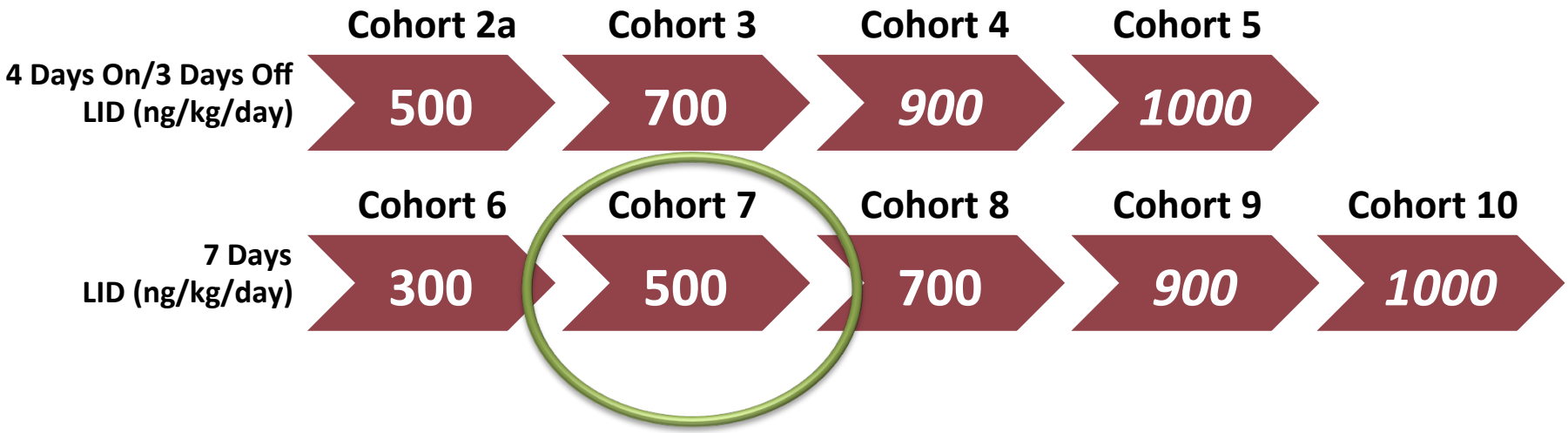
- DART bispecific platform
  - Multiple applications across different diseases
  - Predictable manufacturability
  - Long-term stability
  - 'Plug and Play' flexibility
  - Ability to tailor half-life and valency
- Multiple DART molecules in clinical testing
- Flotetuzumab (MGD006/S80880) mode of action:
  redirected T-cell killing of CD123+ Cells
- Flotetuzumab has short half-life, requiring continuous infusion



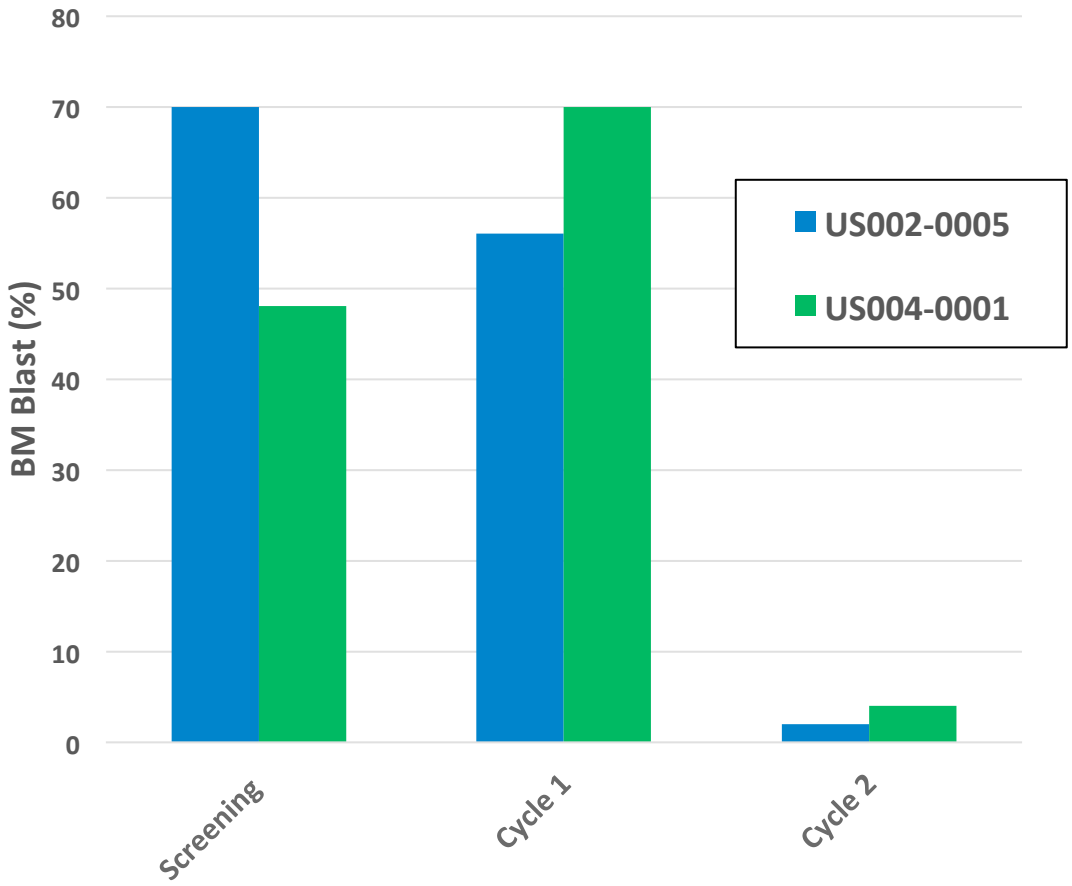

*Root, et al. Antibodies 2016, 5, 6*
*Chichili, et al. Sci Transl Med. 2015 May 27;7(289)*

# Current Dosing Scheme in Multi-Patient Dose Escalation

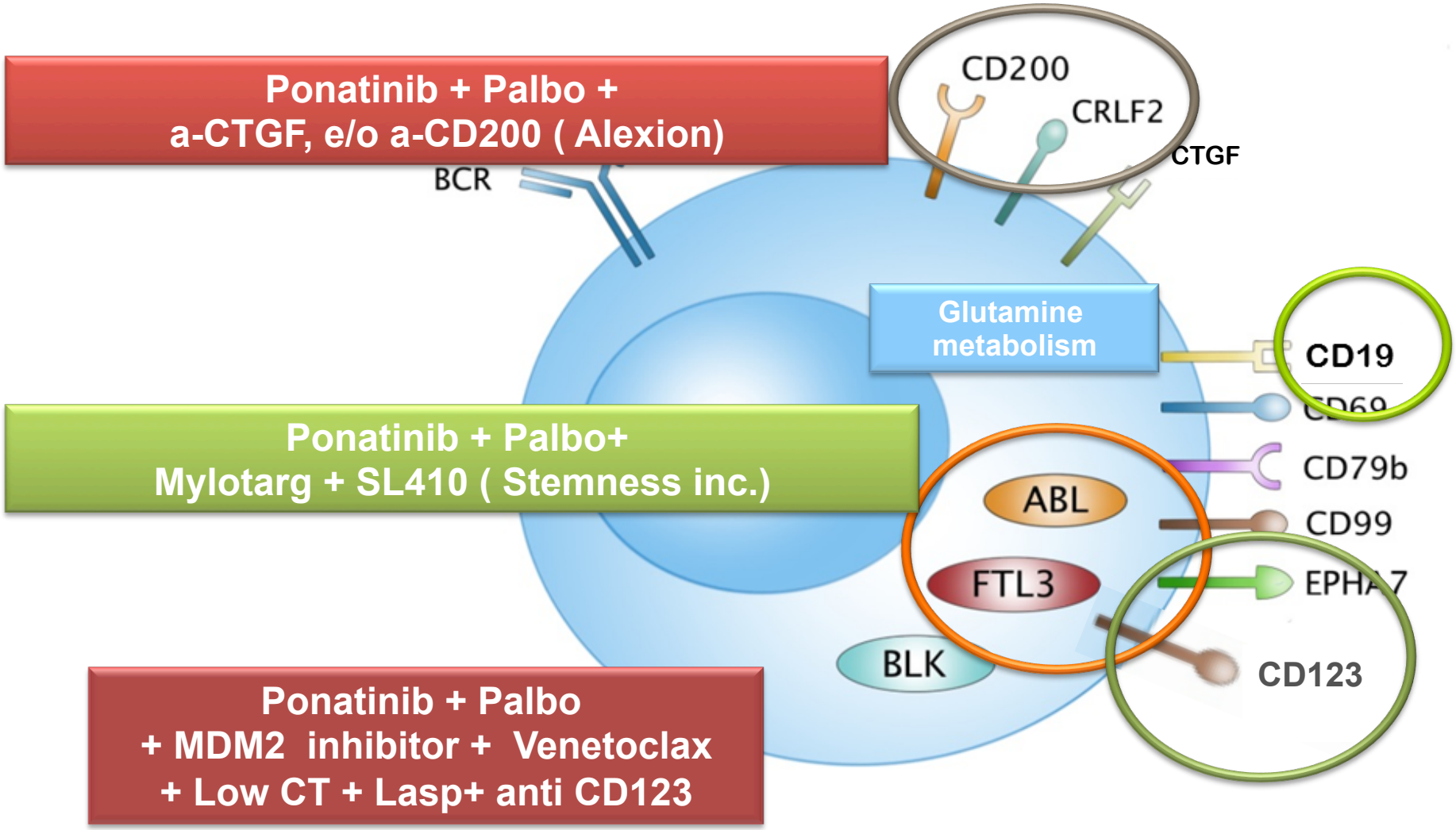



| | |
|---|---|
| **Lead-in Dose** | • LID: Week 1 30 ng/kg/day x 3 days, 100 ng/kg/day x 4 days |
| **Cycle 1 Weeks 2-4** | • Arm A: (Cohorts 2-5): 4-on 3-off schedule<br>• Arm B: (Cohorts 6-10): 21 days continuous infusion |
| **Cycle 2 and Beyond** | • 4-on 3-off schedule |

# “Response Beyond Progression”

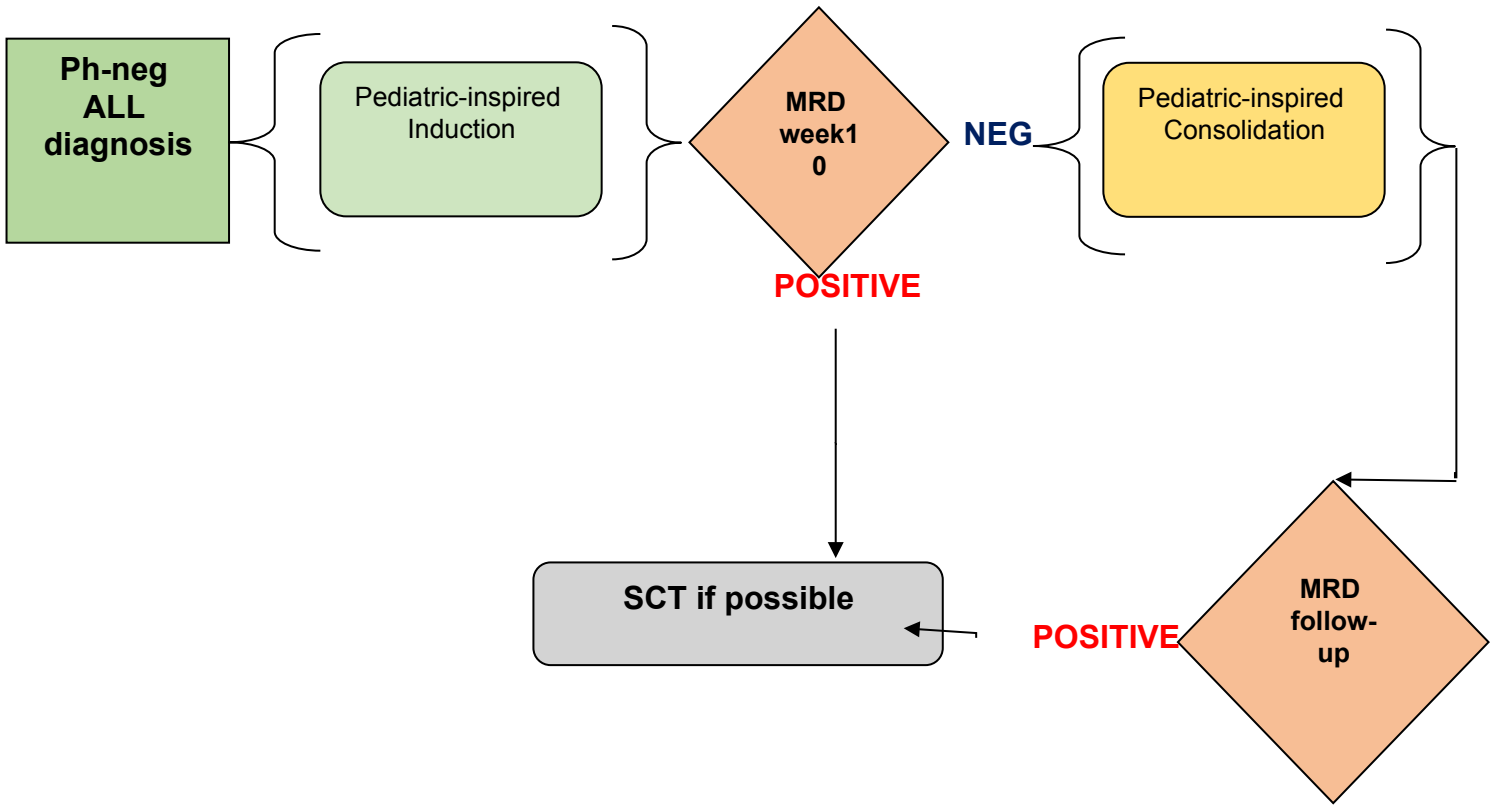


# Basket Trial with Anti CD123 ( SL-401)
# In Triple negative ALL (Ph-/-/-)
# and AML/ MF/ MDS7 CMML



# Lite

## Reduce intensity regiment in adult patient with ph- ALL



**Project (supported by JeJ) : molecular, metabolic and profile and immunomodulatory actyvity of CD123 Acute leukemia**

# Clinical and molecular characterization of Acute Myeloid Leukemia and Myelodysplastic syndrome patients treated according to Italian clinical practice

Bone marrow

- SNPs array

SCHOOL OF NGS

FOCUS ON myeloid solutions

Buccal swab

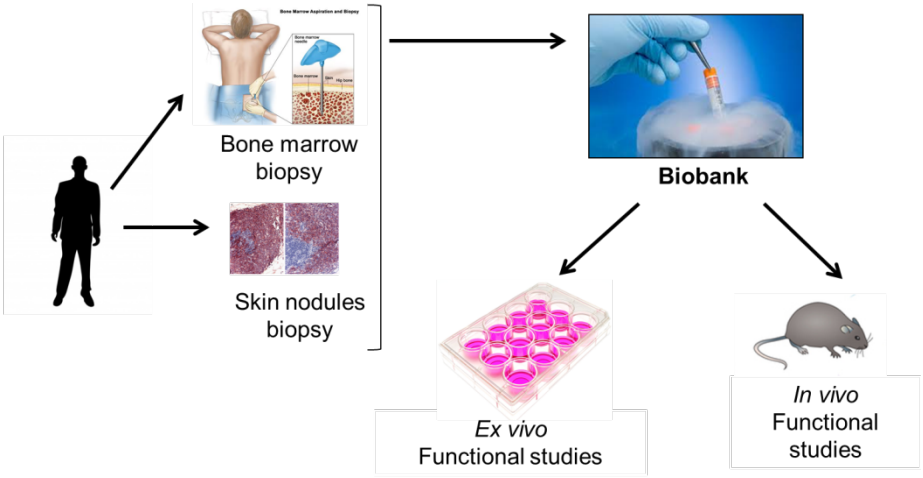
Project under approval for JeJ

# AIM 2 Functional analyses

- To highlight the potential mechanisms of localization of **CD123+ neoplasms** on the peripheral tissue and to elucidate **the role of hypoxia** in the tumor dissemination using **mouse model** (xenograft using primary leukemic cells).

- To evaluate the effect of novel therapeutic options for the treatment of **CD123+ neoplasms** , CD123 inhibitors (**SL-401 and Talacotuzumab**) and/or BCL-2 inhibitor ( **venetoclax**) in single agent and in combination in ex vivo/ in vivo analyses

- To evaluate the efficacy of **exosomes-based therapies (anti-CD123) and of functionalized optic fibers** for the treatment of **CD123+ neoplasms**

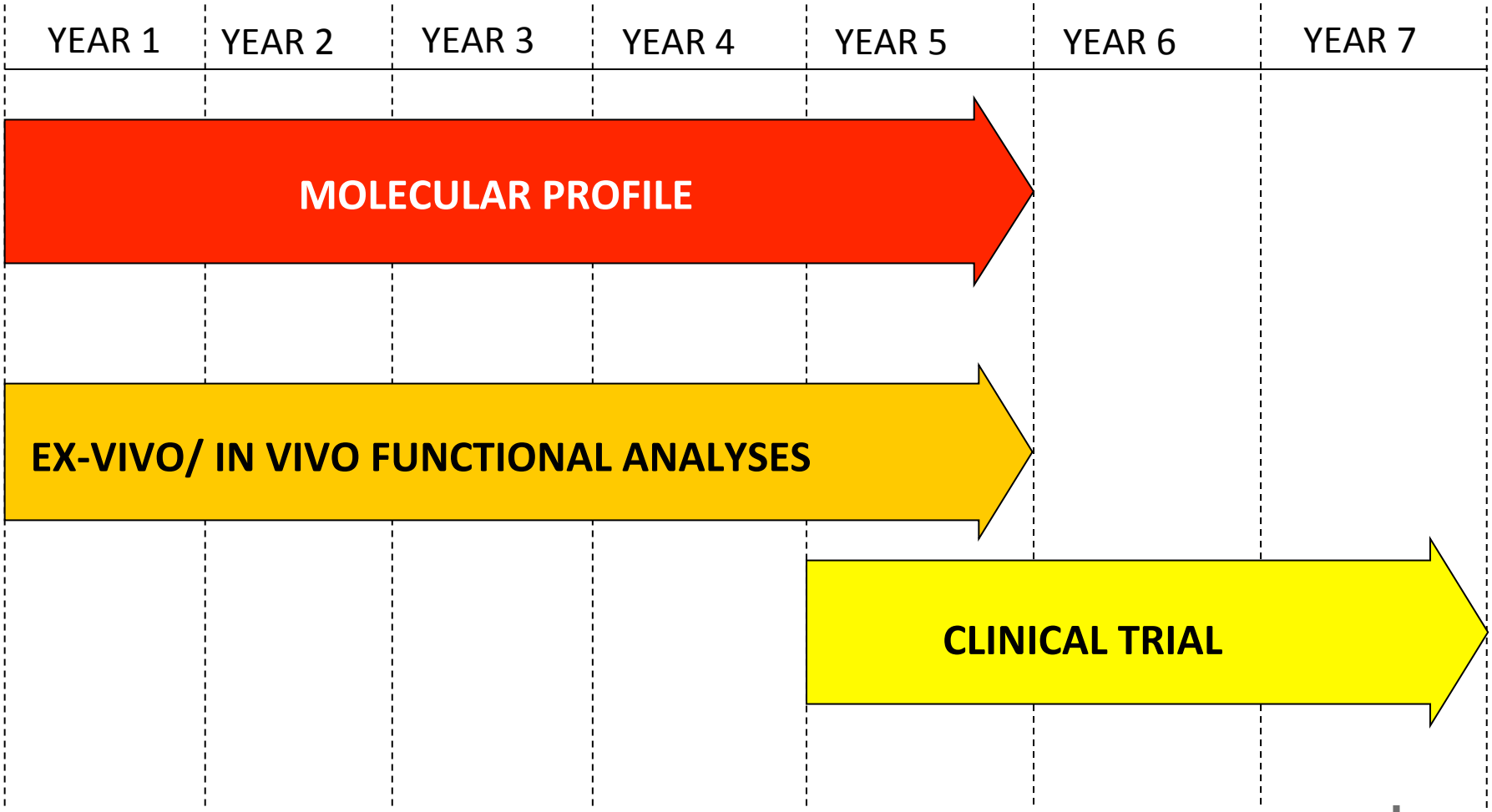



NEXT in Leukemia

# AIM 3 Clinical trial

Clinical trial on CD123+ neoplasms

NEXT in Leukemia


YEAR 1
YEAR 2
YEAR 3
YEAR 4
YEAR 5
YEAR 6
YEAR 7
MOLECULAR PROFILE
EX-VIVO/ IN VIVO FUNCTIONAL ANALYSES
CLINICAL TRIAL

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