European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

EP PerMed
European Partnership for Personalised Medicine

enrol
European Rare Blood Disorders Platform

PH like ALL:
from TAD disruption to Precise Epigenetic therapy

Bologna 2025

Giovanni Martinelli, MD
Institute Seragnoli University of Bologna

Horizon Mission Cancer Program. Grant Number: 101104421

Disclosers.

- **G.Martinelli**: Honoraria and advisory roles (AbbVie, Amgen, ARIAD Pharmaceuticals, Bristol Myers Squibb, ImmunoGen, Pfizer, Agios, Takeda, Actinium Pharmaceuticals), **etc**

- Research grants (all to institution: Pfizer, Amgen, Bristol Myers Squibb, Novartis, ARIAD Pharmaceuticals, Astex Pharmaceuticals, AbbVie, Agios, ImmunoGen, Jazz Pharmaceutical, Adaptive Biotechnologies, Incyte, Sun Pharma, Telios Pharma, Arog Pharmaceuticals, Merus, Autolus, Blueprint Medicines, GlycoMimetics, Blueprint Medicines, WUGEN, MacroGenics, Kartos Therapeutics, AstraZeneca, MEI, Sunesis…… **etc.**

IMPACT-AML project

HORIZON-MISS-2022-CANCER-01-03

Master Framework and Pragmatic Clinical Trial for Relapse or Refractory Acute Myeloid Leukemia

EACC 2025

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori
Istituto di Ricovero e Cura a Carattere Scientifico

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori
IRST-IRCCS

Le leucemie ph like

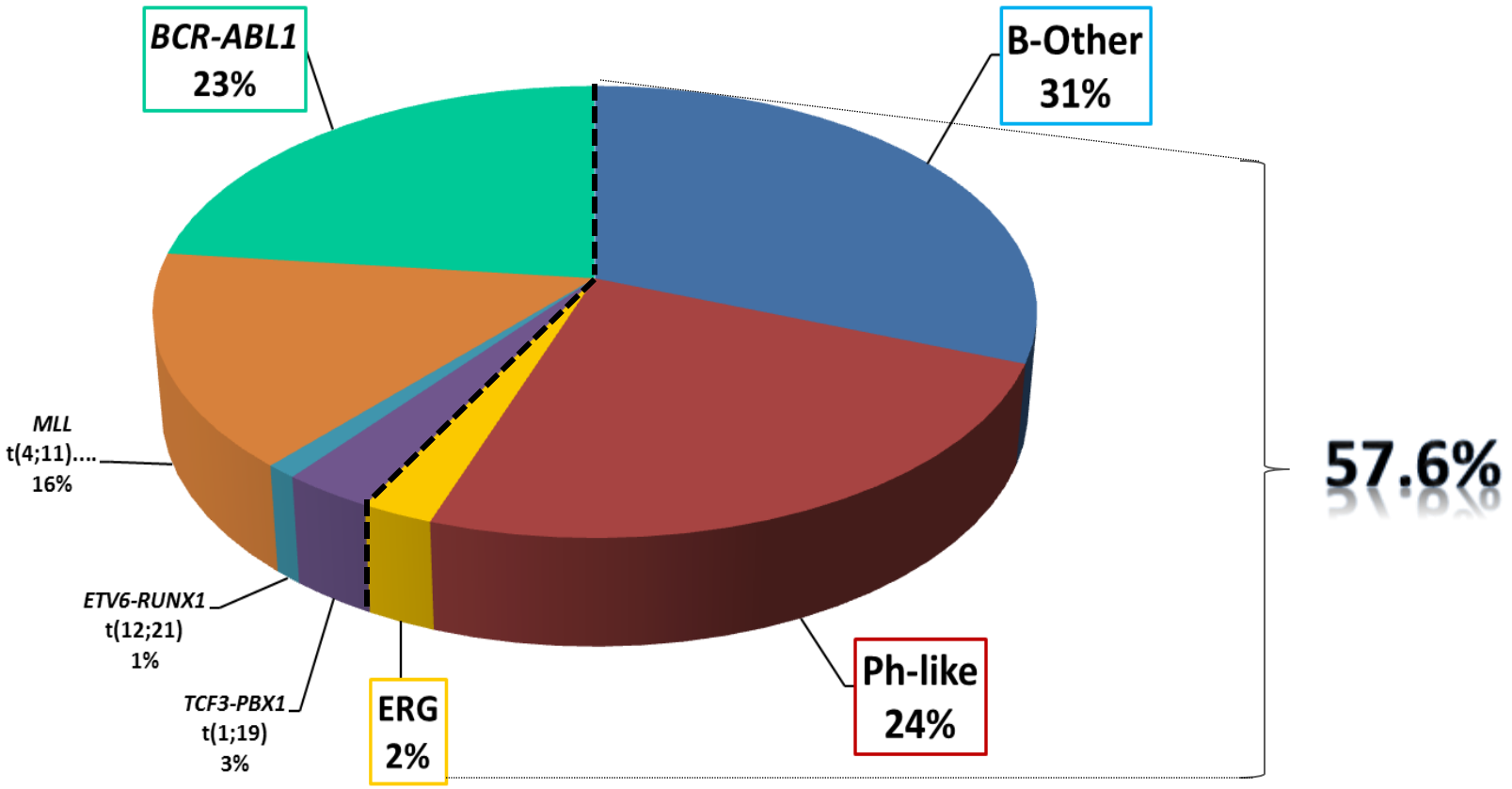
Giovanni Martinelli Scientific Director of IRST-IRCCS della Romagna
and
Institute of Hematology " Seragnoli" University of Bologna

Disclosures

Research Support/P.I.	**Novartis, BMS, AMGEN, Pfizer, AIRC, AIL, Genzyme, Celgene**
Employee	**No relevant conflict of interest to declare**
Consultant	**Novartis, BMS, AMGEN, Pfizer, AIRC, AIL, Genzyme, Celgene, Ariad Pharma, Roche….**
Major Stockholder	**No relevant conflict of interest to declare**
Speakers Bureau	**Novartis, BMS, AMGEN, Pfizer, AIRC, AIL, Genzyme, Celgene Arida Glaxo**
Honoraria	**Novartis, BMS, AMGEN, Pfizer, AIRC, AIL, Genzyme, Celgene Arida Glaxo**
Scientific Advisory Board	**No relevant conflict of interest to declare**

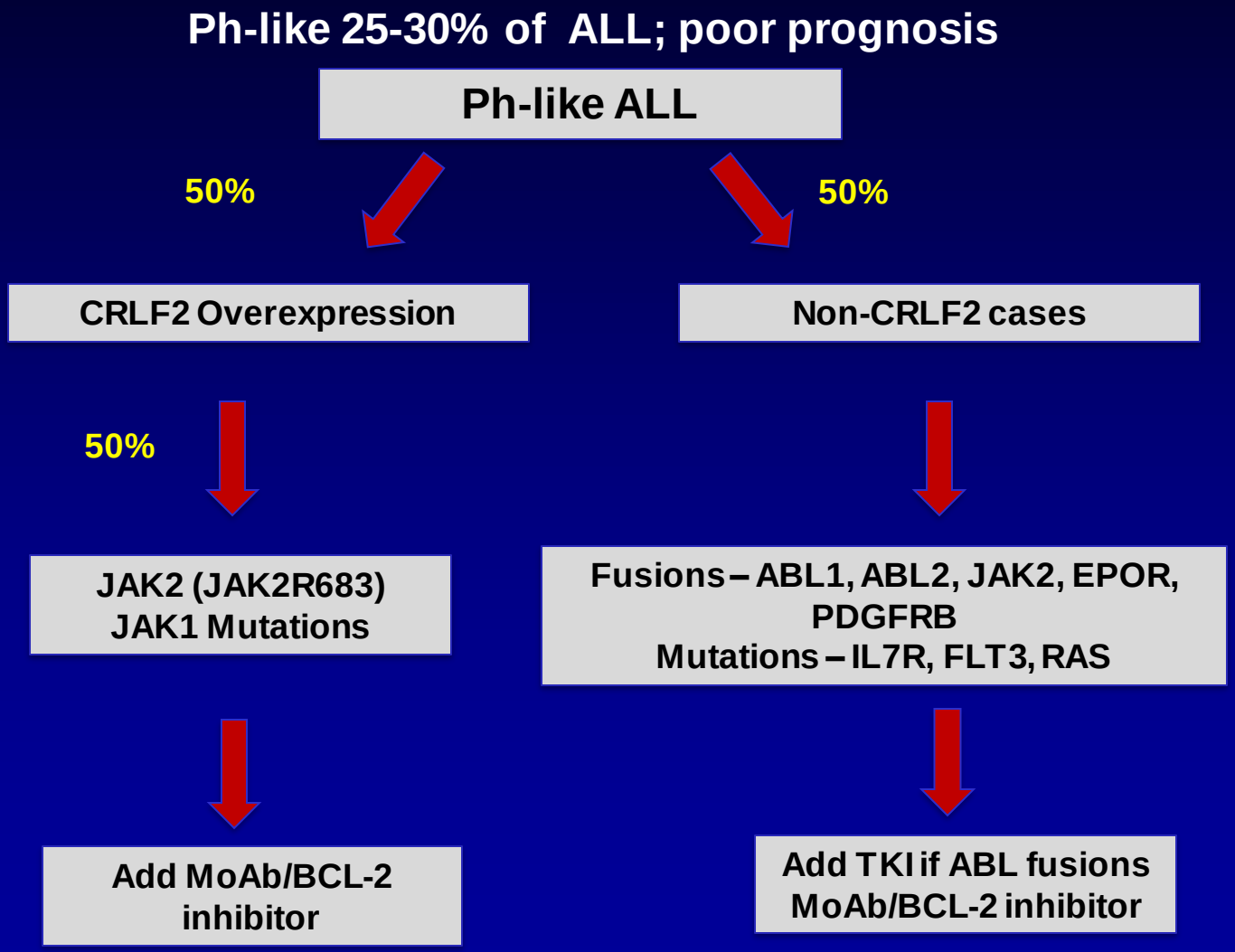
Biological characterization of Ph- ALL considering *CRLF2* overexpression event

Frequency of B-ALL subtypes in AYAOA

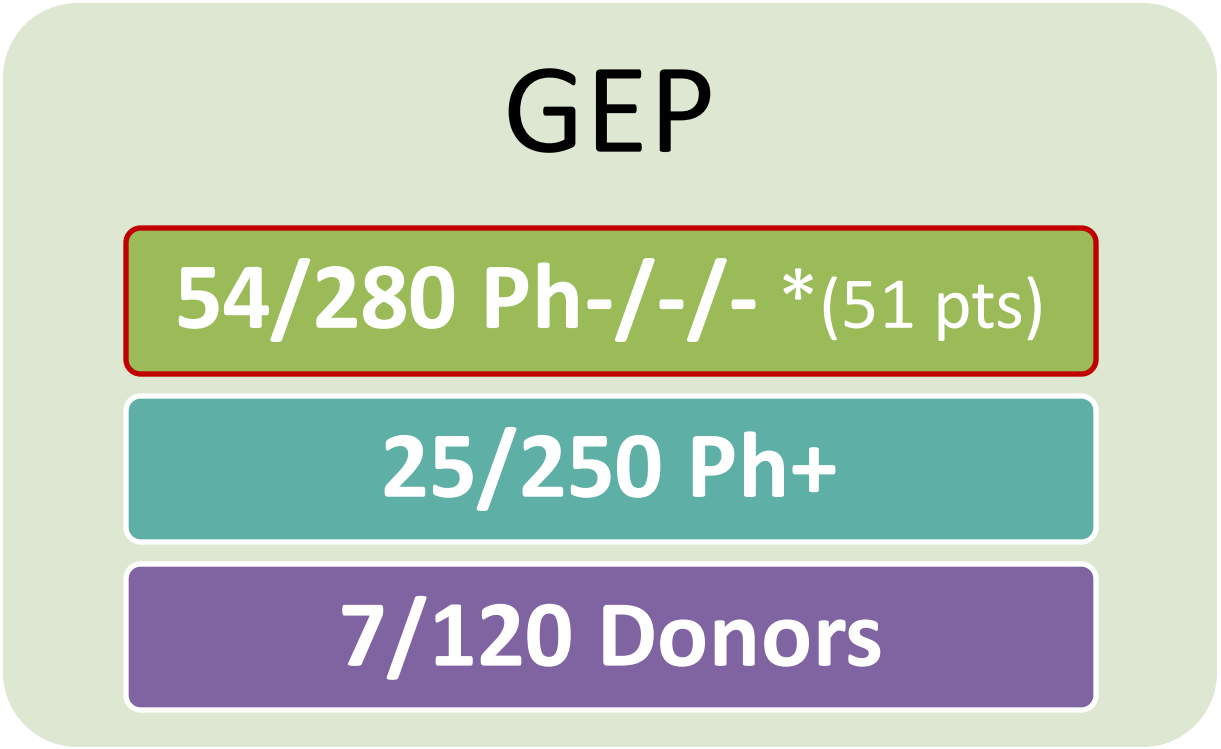


* Modified from Roberts KG et al., J Clin Oncol. 2017

How to rapidly and in a simple way identify the Ph-like ALL ? Which molecular lesions are sensitive to Inotuzumab or Blinatumumab?



Gene Expression Profile in ADULT B-ALL TRIPLE Negative

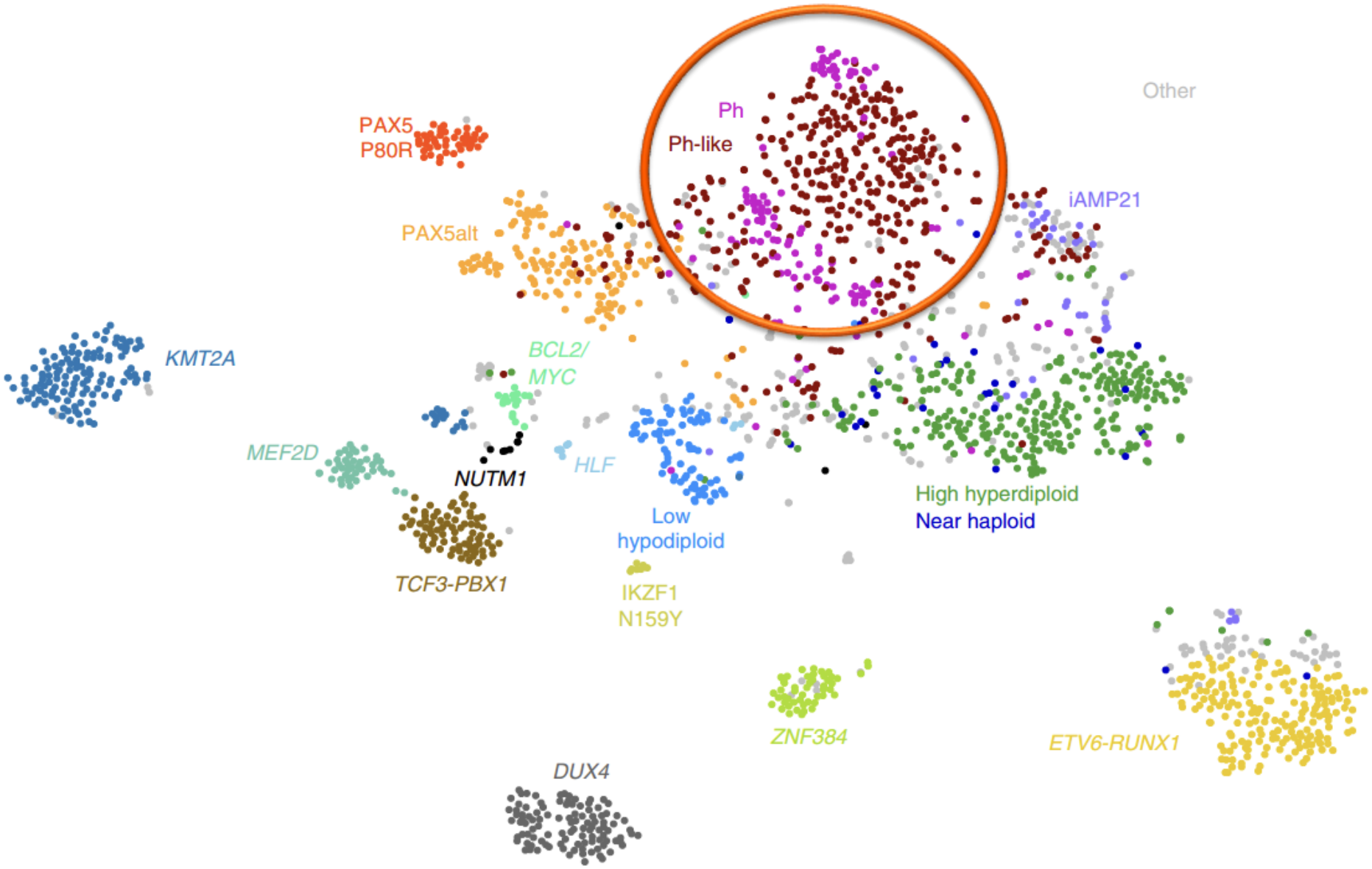


*** Negative for**
***BCR-ABL1* t(9;22)**
***TCF3-PBX1* t(1;19)**
***MLL-AF4* t(4;11)**

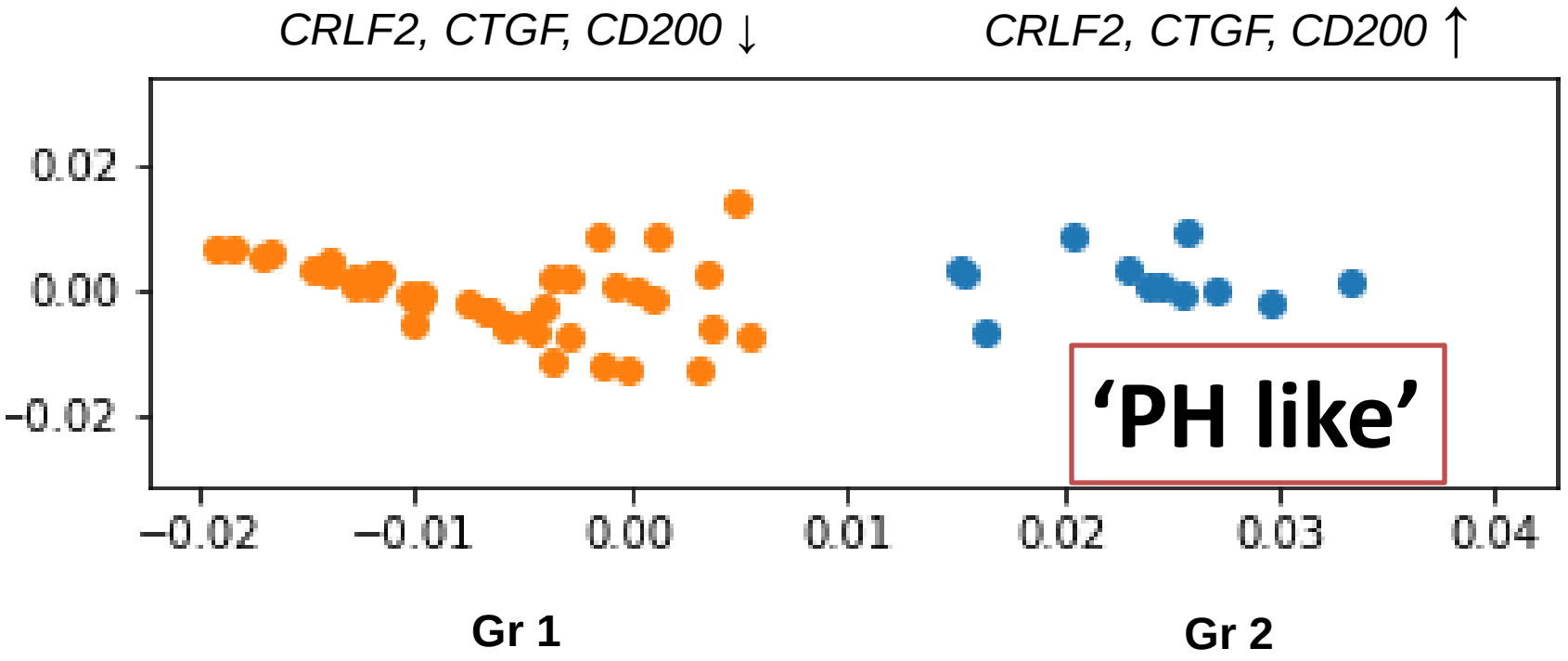
Ph-/-/- GEP clustering : Top ranked 10 genes

Gene	score gr1-/gr2-	pvalue gr1-/gr2-	pvalue gr2-/ctrl
CRLF2	-15.32	6.44E-21	4.40E-11
CRLF2	-15.32	6.44E-21	4.40E-11
CTGF	-6.04	1.65E-07	7.65E-09
CD200	-5.99	1.96E-07	1.42E-09
AMBRA1	-5.15	4.13E-06	1.98E-06

CD200 high expression is associated With Blinatumumab resistence


Other
Ph
Ph-like
PAX5
P80R
iAMP21
PAX5alt
KMT2A
BCL2/
MYC
MEF2D
NUTM1
HLF
High hyperdiploid
Near haploid
Low
hypodiploid
TCF3-PBX1
IKZF1
N159Y
ZNF384
ETV6-RUNX1
DUX4

IF of three surface markers identify triple negative ALL (Ph-/-/-) clustering with PH like ALL



…then RNA pan Cancer identified drugable fusion genes

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

Ferrari A. et Al. AACR 2018

UNEXPECTED HIGH RATE OF KNOWN AND UNKNOWN REARRANGEMENTS IN ADULT TRIPLE NEGATIVE ACUTE LYMPHOBLASTIC LEUKEMIA IDENTIFIED THANKS TO A EFFICIENT TRANSCRIPTOME FOUR TOOL PIPELINE ANALYSYS

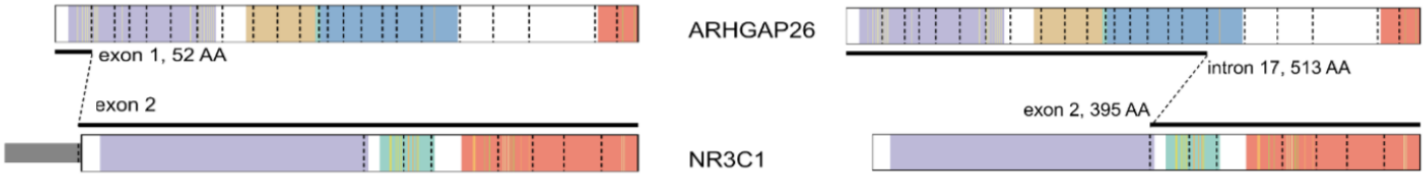
Author(s): Anna Ferrari, Silvia Vitali, Andrea Ghelli Luserna Di Rora, Carmen Baldazzi, Nicoletta Testoni, Valentina Robustelli, Eugenio Fonzi, Michela Tebaldi, Cristina Papayannidis, Mariachiara Abbenante, Giovanni Marconi, MariaChiara Fontana, Antonella Padella, Maria Teresa Bochicchio, Alessandra Santoro, JM. Hernández Rivas, Giorgia Simonetti, Gastone Castellani, Daniel Remondini, Daniele Calistri, Giovanni Martinelli

EHA Library. Ferrari A. 06/12/20; 294277; EP358

We identified **65 fusion genes**, not otherwise detected, in 41 pts with a very high fusions rate of **65.1%** (41/63).

ZNF384-TCF3/EP300/TAF15, MEF2D-BCL9, *KMT2A/MLLT1, **ABL1/RCSD1**, IGH-MYC, DUX4-IGH, **P2RY8-CRLF2*** and *PAX5/ETV6*) or in other diseases (n 10; i.e. *NONO/TFE3* B-ALL and in Renal cell carcinoma).

Furthermore we detected and validate a new CSF1R fusion: ***NUMA1-CSF1R*** .
Ph-/-/- fusion detection help to sub-classify our patients in new B-ALL subgroups. We found a) Rare MLL fusions and BCL2/MYC rearranged (r): 3.2% (2/63); b) DUX4 and MEF2D r: 1.6% (1/63); c) ZNF384 r: 11.1% (7/63); d) Ph-like fusions: 4.8% (3/63).



Pediatric blood & cancer

> Pediatr Blood Cancer. 2023 Oct;70(10):e30546. doi: 10.1002/pbc.30546. Epub 2023 Jul 6.

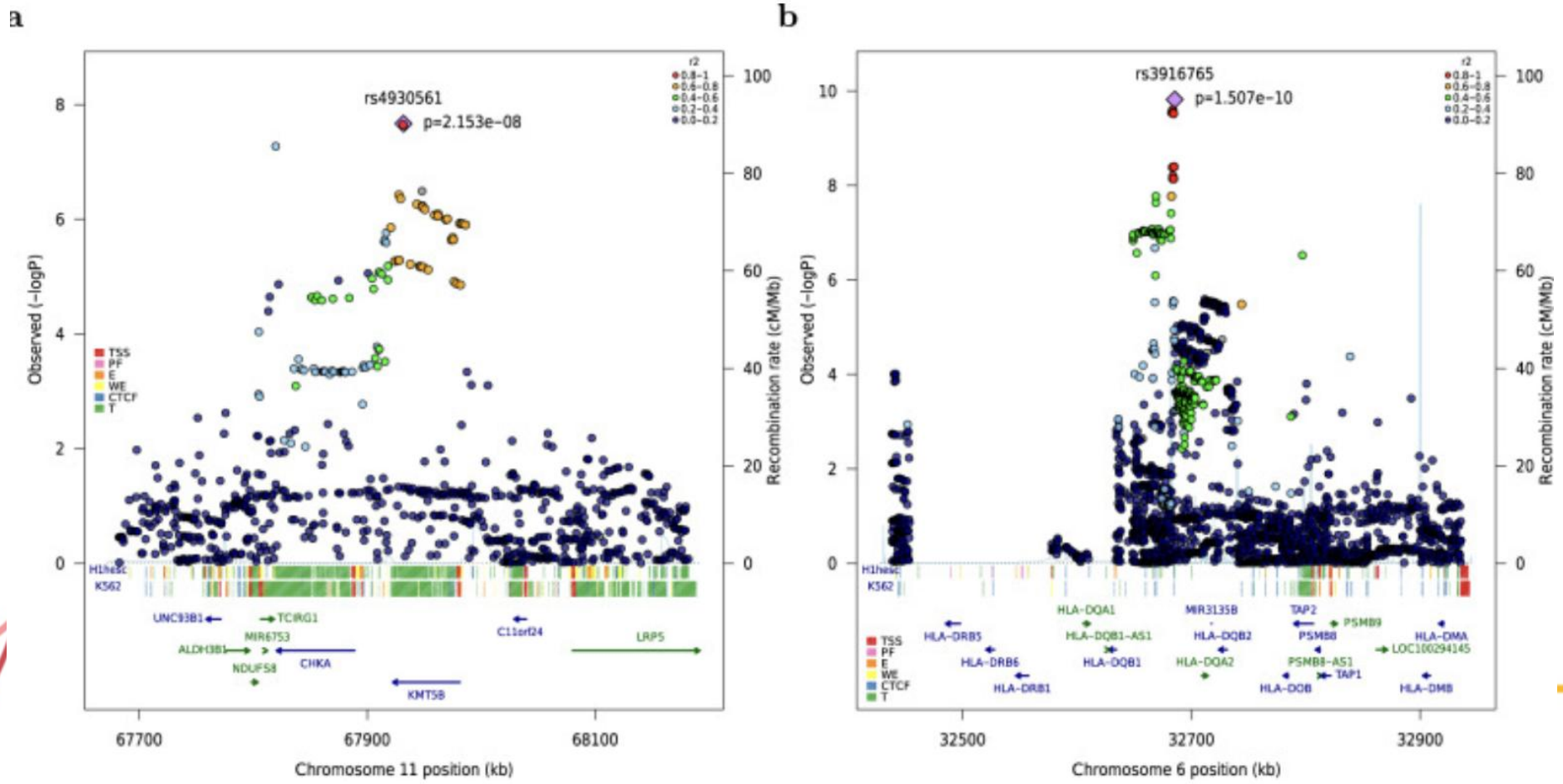
Detection of a novel SNX2 gene breakpoint in the SNX2::ABL1 fusion transcript in Ph-like B-cell acute lymphoblastic leukemia

Gadha K Leons [1], Preity Sharma [1], Sanjeev Kumar Gupta [1], Ritu Gupta [1], Lata Rani [2], Smeeta Gajendra [1], Anita Roy [3], Ranjit Kumar Sahoo [4]

Affiliations + expand

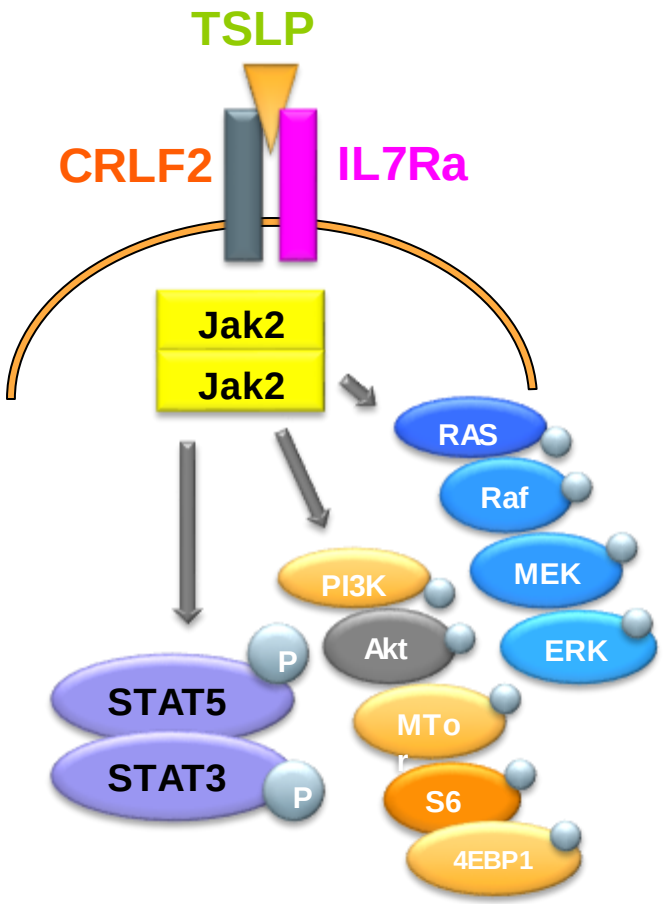
PMID: 37414723 DOI: 10.1002/pbc.30546

Fig. 3. Regional association and linkage disequilibrium plots for 4 new loci associated with acute myeloid leukemia.



Top ranked 3 genes:

CRLF2 - cytokine receptor like factor 2

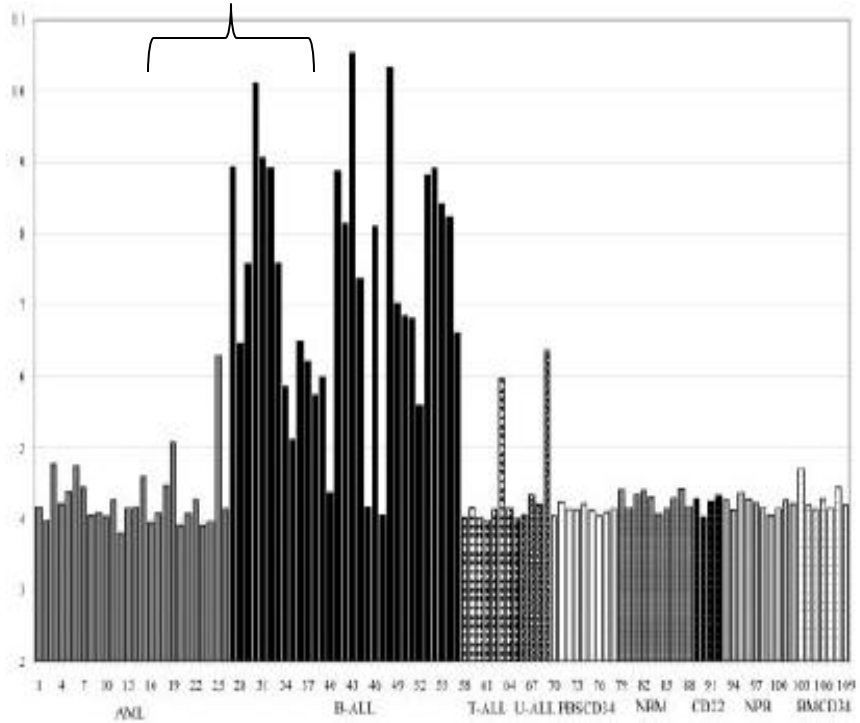


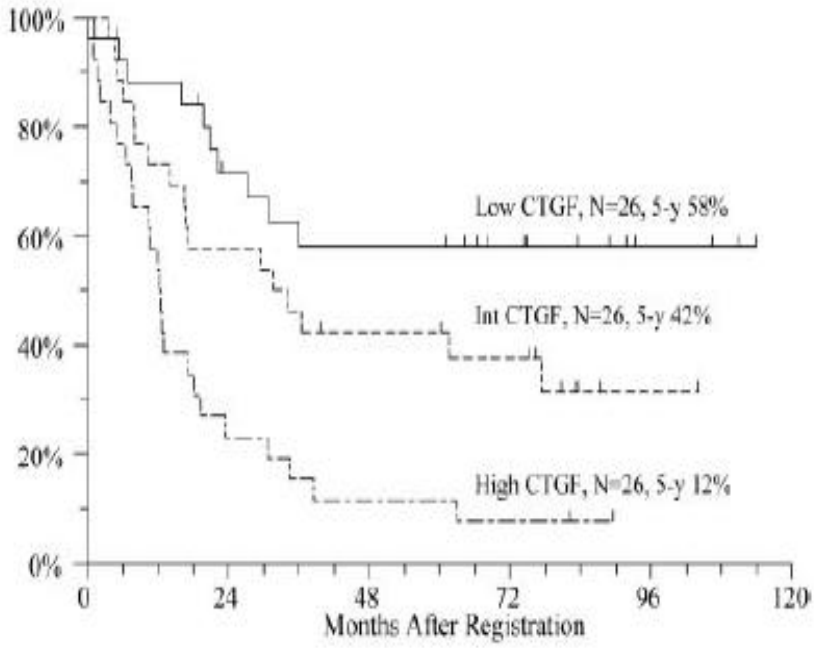
Top ranked 3 genes: *CRLF2*, *CTGF* and *CD200*

CTGF - Connective Tissue Growth Factor-

is an extracellular matrix (ECM)-associated protein

B-ALL



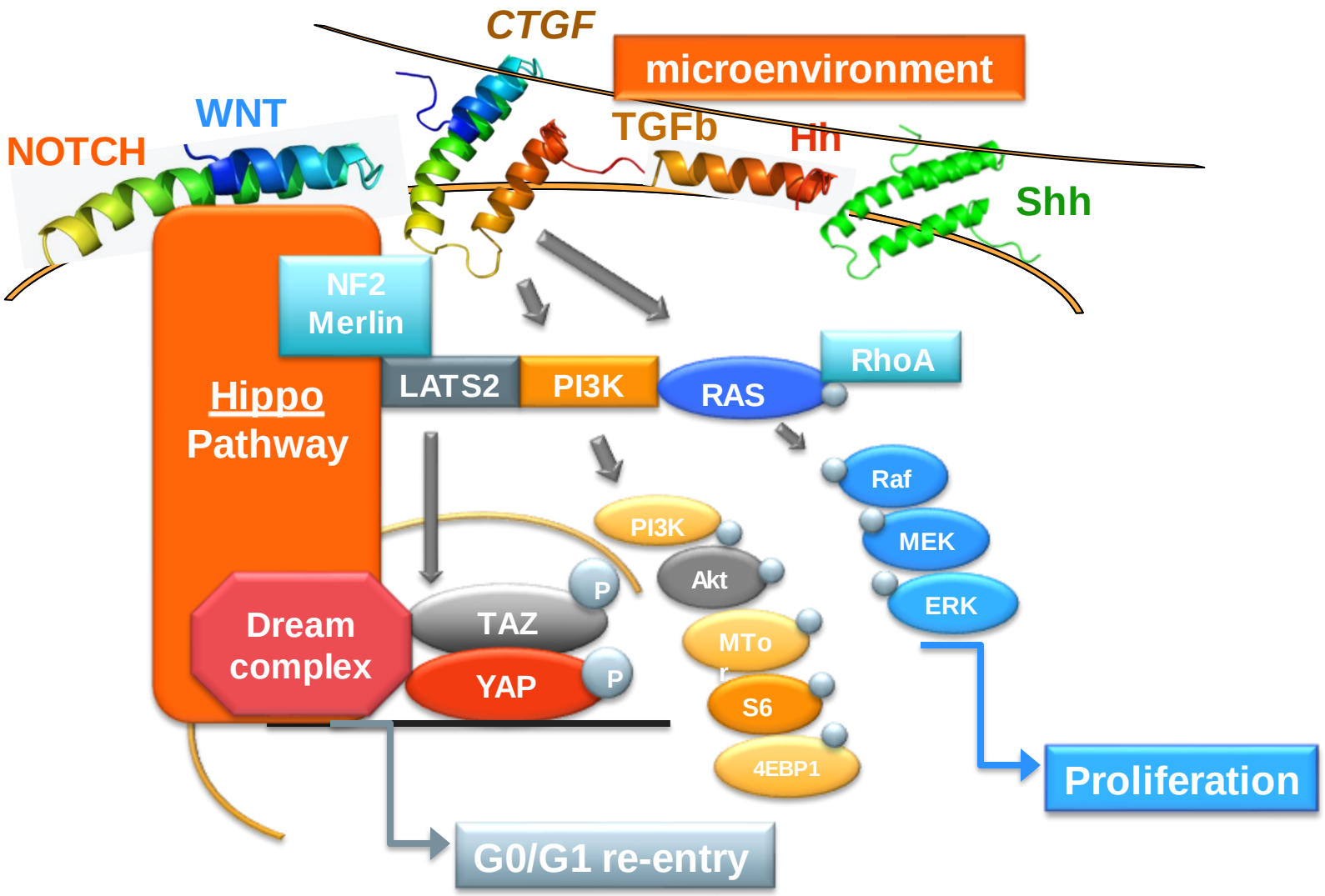


CTGF expression levels in acute leukemias and normal controls, and overall survival of a series of adult ALL patients by CTGF expression levels

Nat Cell Biol. 2002 Aug; 4(8): 599–604.

Top ranked 3 genes:

CTGF - Connective Tissue Growth Factor



Top ranked 3 genes: *CRLF2*, *CTGF* and *CD200*

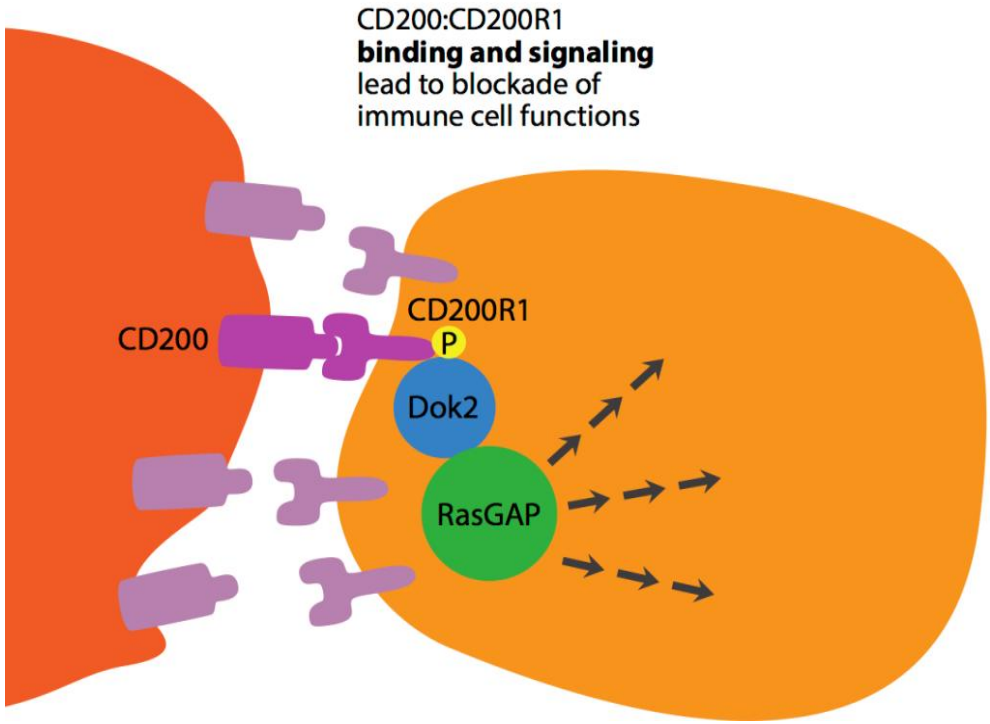
CD200 **-** encodes a type I membrane glycoprotein

Immunosuppression and regulation of anti-tumor activity

CD200 is expressed in nearly all precursor B lymphoblastic leukemias, with aberrant over- or under-expression when compared to normal B-cell progenitors in 55% of cases

CD200 is over-expressed in nearly all precursor B lymphoblastic leukemiasresistant to BLINATUMUMAB

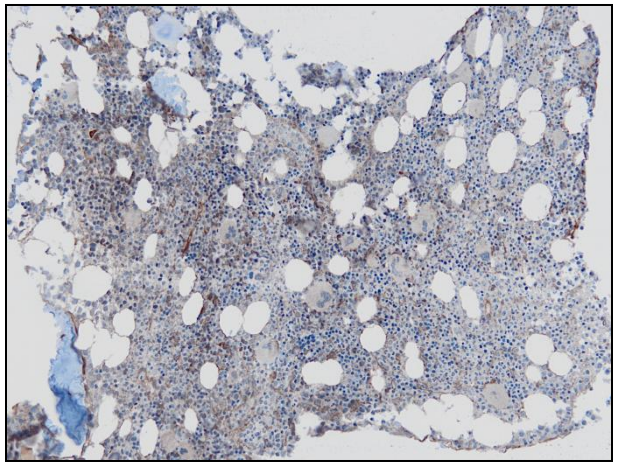
(Personal comunication)



Immunohistochemistry staining of *CD200* protein

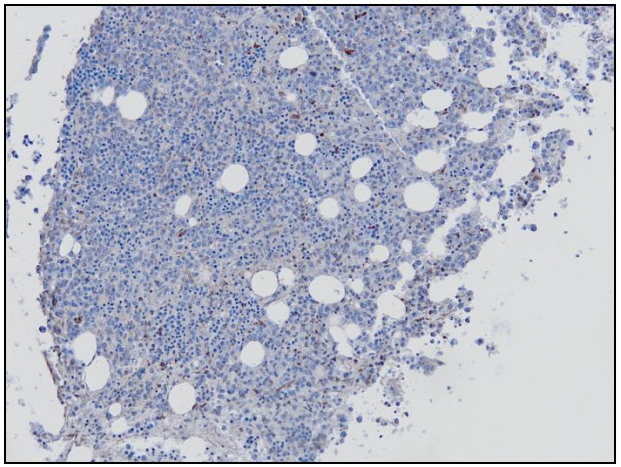
CD200 (dark brown) subcellular localization: membrane/cytoplasmatic

Ctrl*



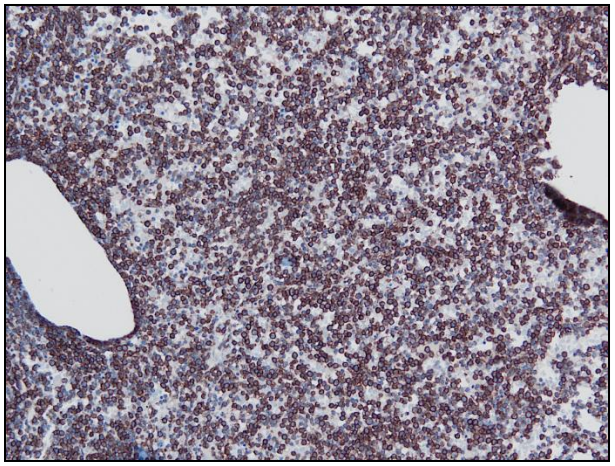
Weak-moderate

#2459 ALL



Negative-GEP 5.9

#2804 ALL



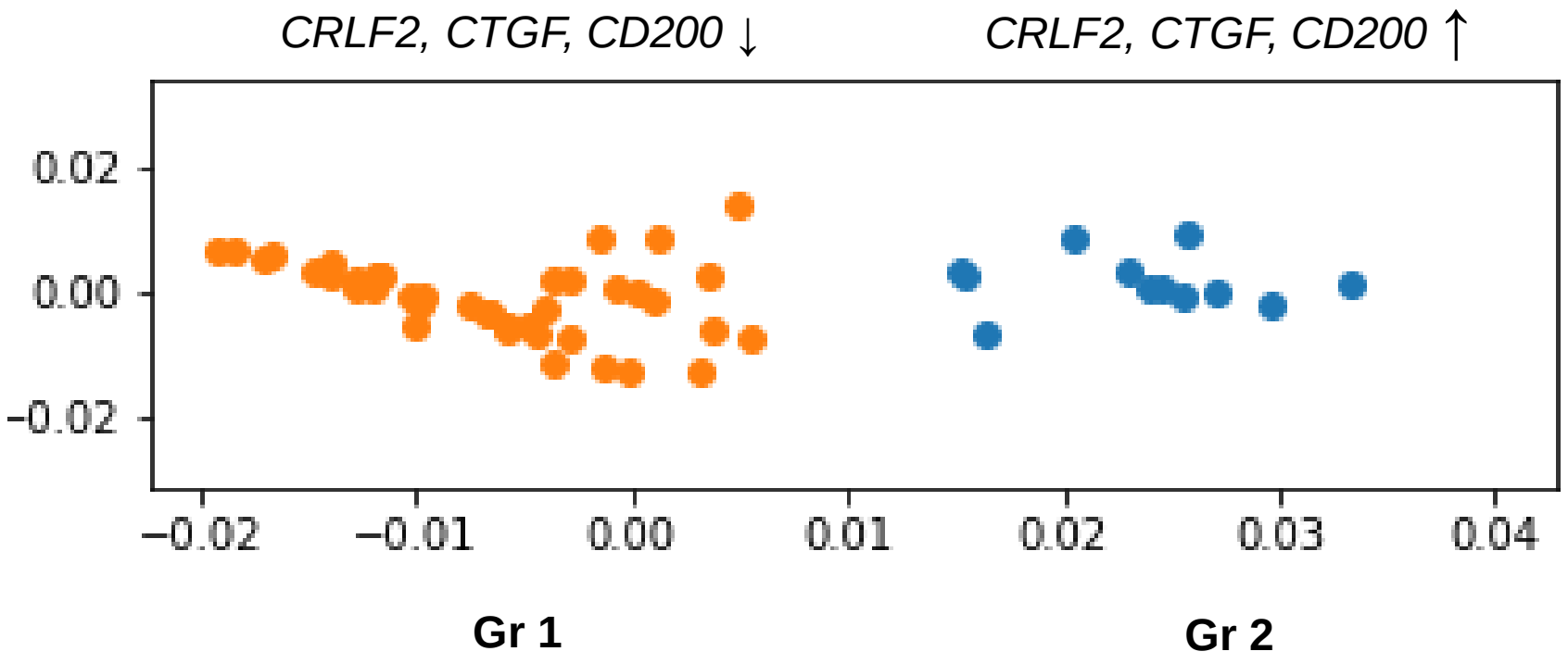
Strong Pos-GEP 12.9

Donor GEP Mean: 6.1

Courtesy to Simona Righi and Elena Sabattini

*Reactive Lymph node

Triple negative ALL (Ph-/-/-) clustering identified two well distinct subroups by GEP



K-means clustering of 2 or 3 components PCA of 10 selected genes in Ph- samples

in association with

soho

society of hematologic oncology

Under the Auspices of

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

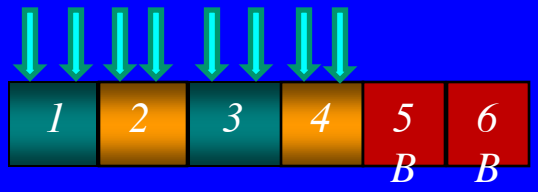
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA

2 SOHO

2ND ITALIAN CONFERENCE

How Might Future Optimal ALL Regimens Look Like?

Intensive Phase



Consolidative Phase I

Consolidative phase II

CAR-T

MiniHCVD

Mini-MTX-cytarabine

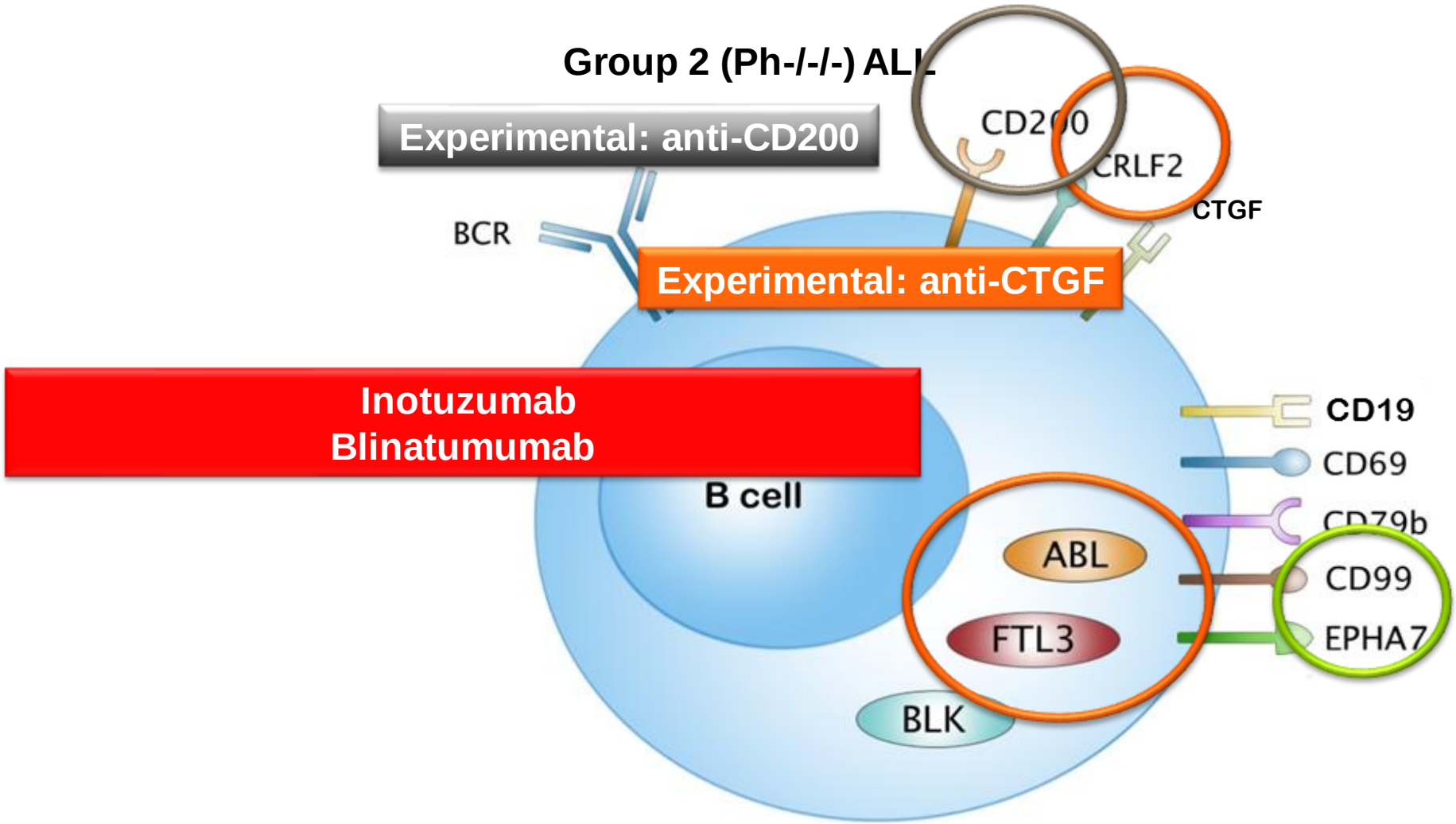
Blinatumomab

CAR-T cell Rx

Inotuzumab	Total dose	Dose per day
C 1 (mg/m^2)	0.9	0.6 D2 & 0.3 D8
C 2- 4 (mg/m^2)	0.6	0.3 D2 & D8

- Total Rx 10-11 mo; Chemo Rx minimal = 4 mo
- Possible better CD19, CD22, CD123 MoAb or bispecific Ab constructs

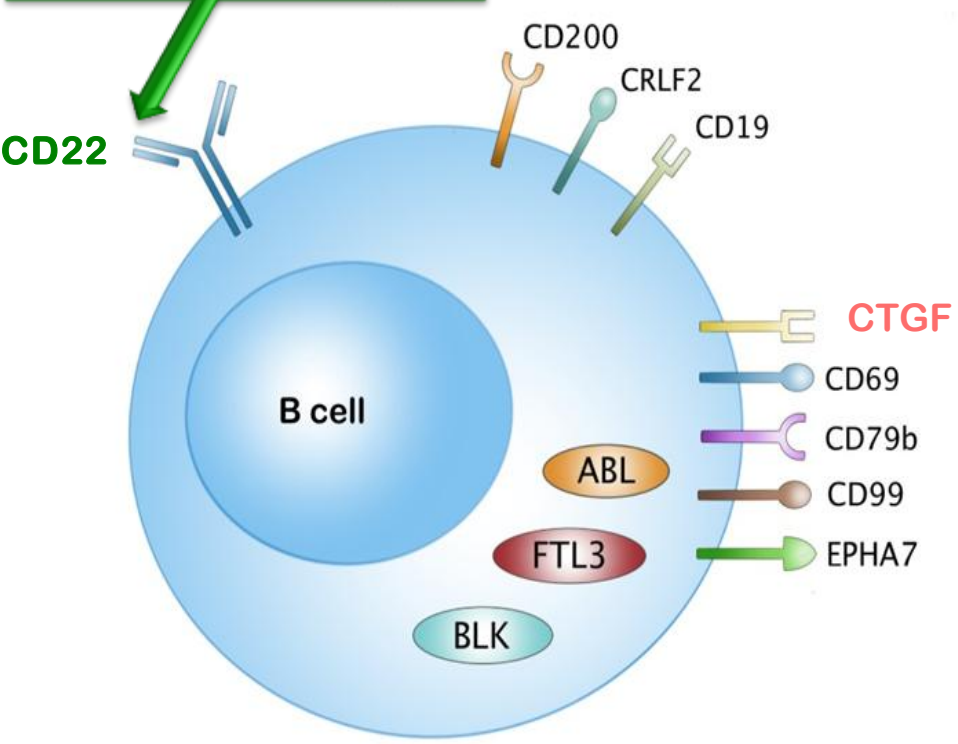
Potential targets on triple negative (Ph-/-/-) Gr2 ALL



Potential targets on 3c-UP (Ph like included)

CDK4-6 Inhibitors (experimental)

Inotuzumab



***anti*-CRLF2 Phase 1 dosing**

Blincyto

***a*-CTGF (Pancreatic Cancer Phase 3) FIBROGEN**

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

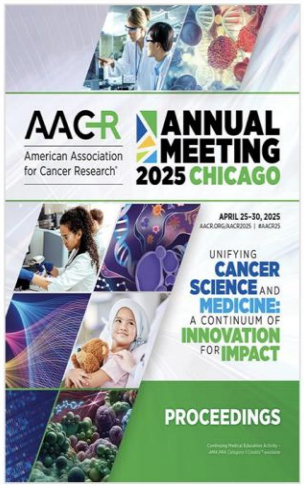
AM E3-SG3249

CANCER RESEARCH

ABOUT ARTICLES FOR AUTHORS ALERTS NEWS CANCER HALLMARKS WEBINARS

Volume 85, Issue 8_Supplement_1

15 April 2025



POSTER PRESENTATIONS - PROFFERED ABSTRACTS | APRIL 21 2025

Abstract 4773: AM E3-SG3249, a first-in-class α-CRLF2 antibody-drug conjugate for the treatment of CRLF2-rearranged Ph-like B-ALL FREE

Claudia Dall'Armi; Valentina Di Biasio; Chantal Paolini; Daniela Natale; Francesco Scalabrì; Antonino Missineo; Nadine Alaimo; Maurizio Nuzzo; Anna Demartis; Pamela Di Pasquale; Roberto Benoni; Fulvia Caretti; Elisa Beghetto; Fabrizio Colaceci; Romina Sasso; Vincenzo Pucci; Carlo Toniatti; Alessandro Carugo

+ Author & Article Information

Cancer Res (2025) 85 (8_Supplement_1): 4773.

https://doi.org/10.1158/1538-7445.AM2025-4773

Abstract

AM E3-SG3249

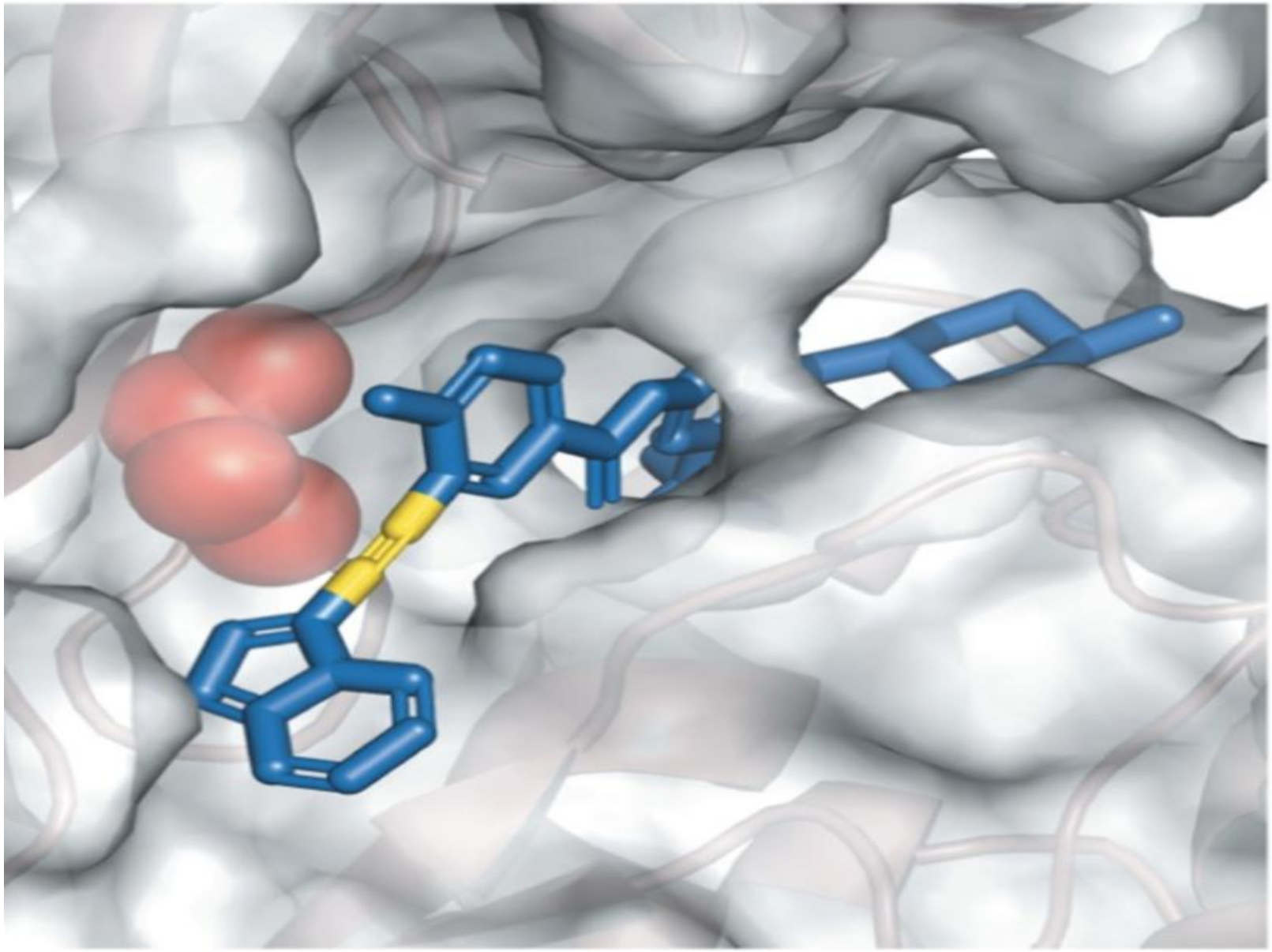
- AM E3-SG3249 was potently cytotoxic (**EC_{50} = 40pM**) against a panel of hCRLF2-rearranged B-ALL cell lines in vitro.
- Upon single injection in xenograft models, AM E3-SG3249 showed strong anti-tumor activity proportional to receptor density.
- Moreover, AM E3-SG3249 treatment extended survival of hCRLF2-rearranged B-ALL orthotopic xenografts over standard induction therapy combining vincristine, dexamethasone, and L-asparaginase (VXL).
- The ADC surrogate mB4 AM23-SG3249 was also efficacious and well-tolerated in xenograft models engineered to overexpress murine CRLF2.
- Conclusions:
- AM E3 is a novel monoclonal antibody with ideal features for the development of a first-in-class α-CRLF2 ADC therapy. AM E3 conjugated with the cytotoxic agent tesirine (SG3249) demonstrated remarkable anti-tumor efficacy and a reasonable therapeutic window for the treatment of CRLF2-rearranged Ph-like B-ALL.

ARIAD Pharmaceutical
Frank Haluska

now President, CEO, and Founder
at Kestrel Therapeutics, Inc.
Kestrel Therapeutics

Harvard University

Ponatinib



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

First Report of a GIMEMA LAL1811 Phase II Prospective Study of Combination of Steroid with Ponatinib in Frontline Therapy of Elderly or Unfit Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

Giovanni Martinelli, MD, Alfonso Piciocchi[2*], Cristina Papayannidis, MD, PhD[3], Stefania Paolini, MD, PhD[1*], Valentina Robustelli, PhD[4*], Simona Soverini, PhD[1,5], Carolina Terragna[1*], Roberto M Lemoli, MD[6], Fabio Guolo, MD[6*], Paolo Di Bartolomeo, M.D[7], Monia Lunghi[8*], Paolo de Fabritiis[9*], Anna Candoni, MD[10*], Carmine Selleri, MD[11], Federico Simonetti, MD[12*], Monica Bocchia[13*], Antonella Vitale[14*], Luca Frison[15*], Alessandra Tedeschi[16*], Antonio Cuneo, MD[17*], Massimiliano Bonifacio, MD[18*], Brunangelo Falini, MD[19], Stefano D'Ardia[20*], Silvia Trappolini[21*], Patrizia Tosi, MD[22*], Piero Galieni, MD[23*], Francesco Fabbiano, MD[24], Maria Chiara Abbenante[1*], Giovanni Marconi[25], Chiara Sartor[26*], Michele Cavo, MD[27*], Robin Foà, MD[28*], Paola Fazi[29*], Marco Vignetti[30*] and Michele Baccarani, MD[1]

ASH 2017

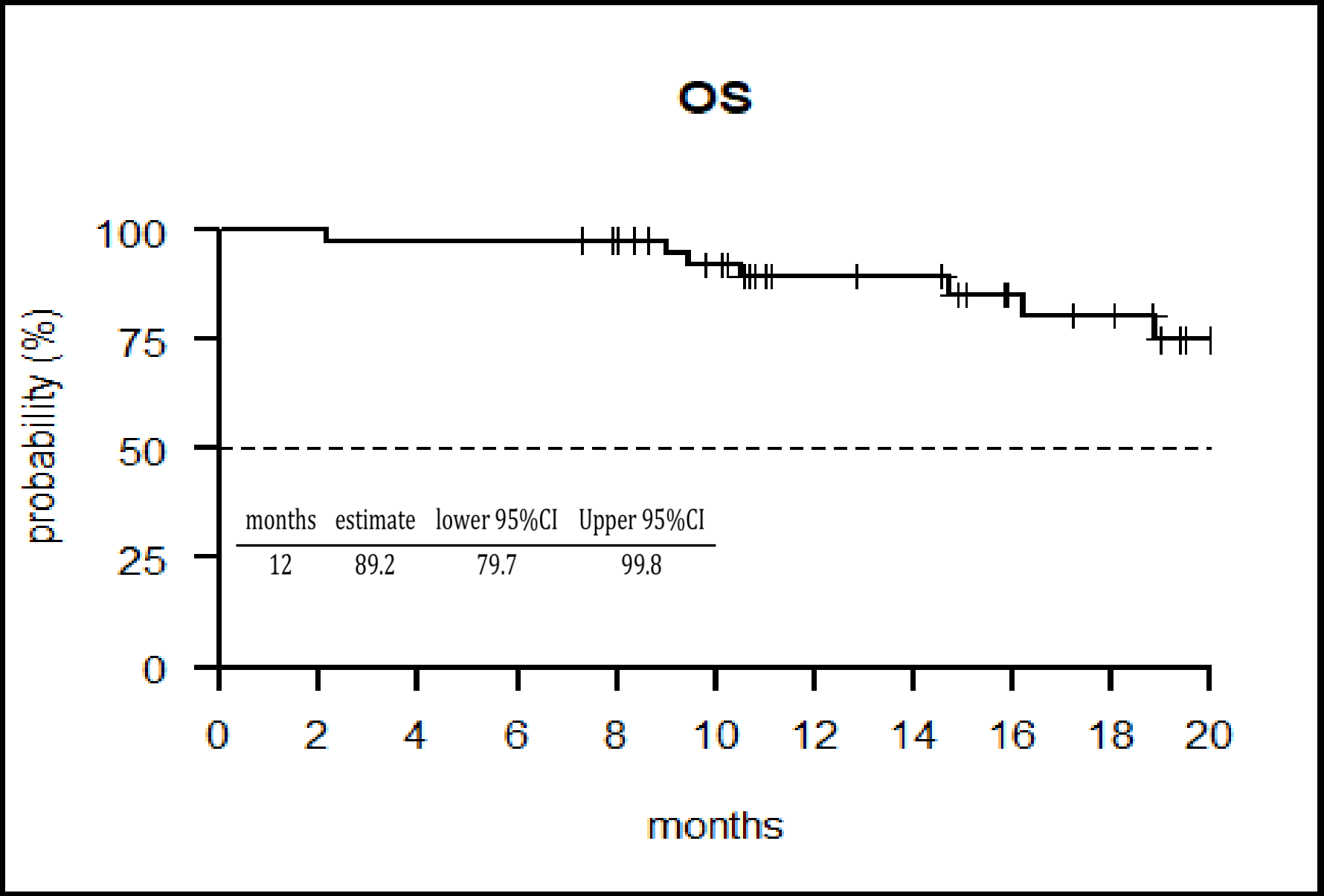
American Society of Hematology Annual meeting

Steroid + Ponatinib in Ph-Positive ALL. Patients' characteristics

Parameter (N=42)		N (%)/ Median [range]
Age (yrs)		67 (27-85)**
Sex	Male	20 (47)
	Female	22 (52)
PS	0-1	37 (87)
	2	5 (13)
WBC (x 10^9/L)		4960 (0.18-347.800)
CNS +		0(0)
CD20+		ND
Transcript	p190	26 (61)
	p210	4 (10)
	p190/p210	12 (29)*

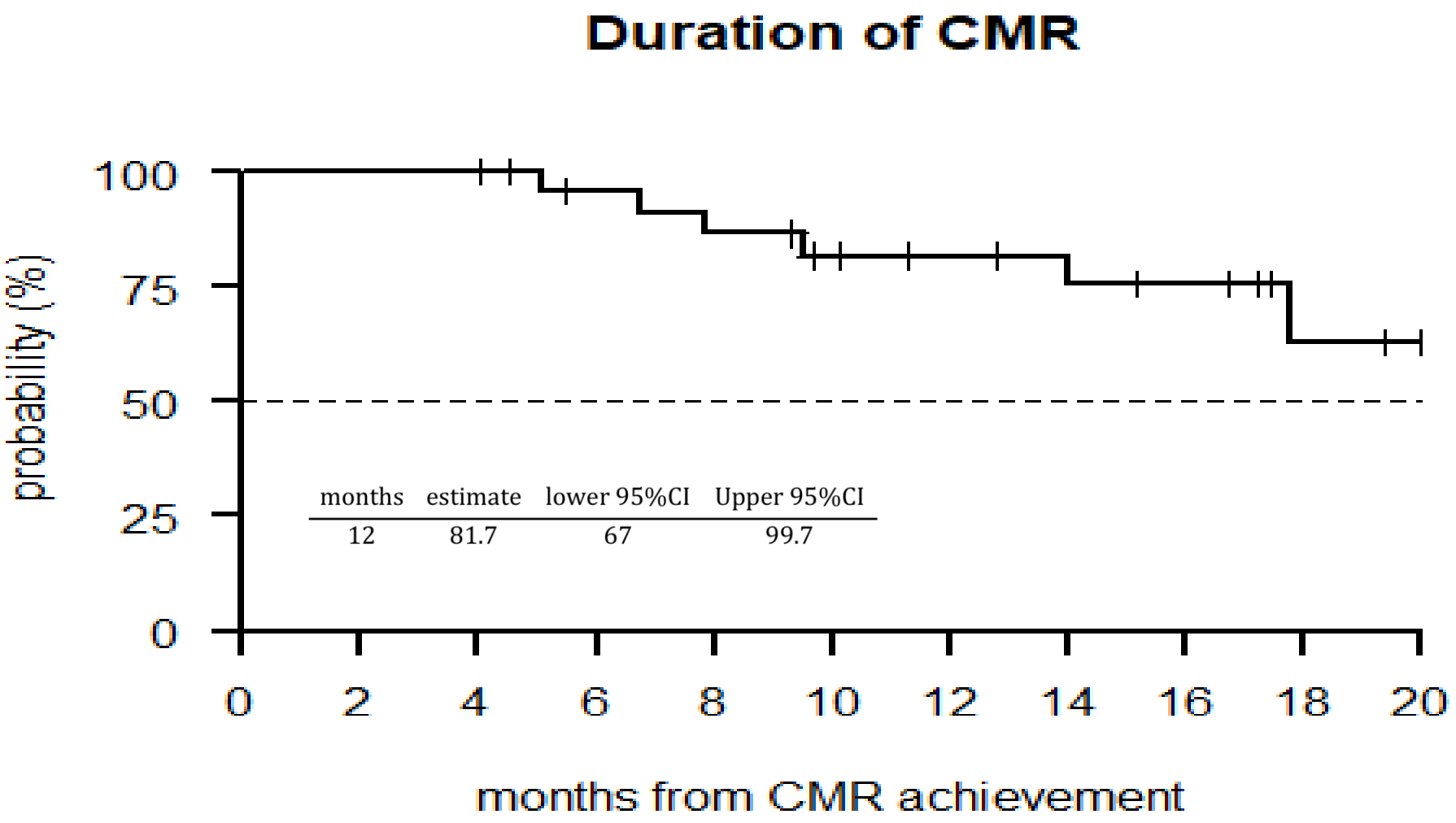
**9 (21.4%) patients with age <60 years

Gimema 1811 Survival

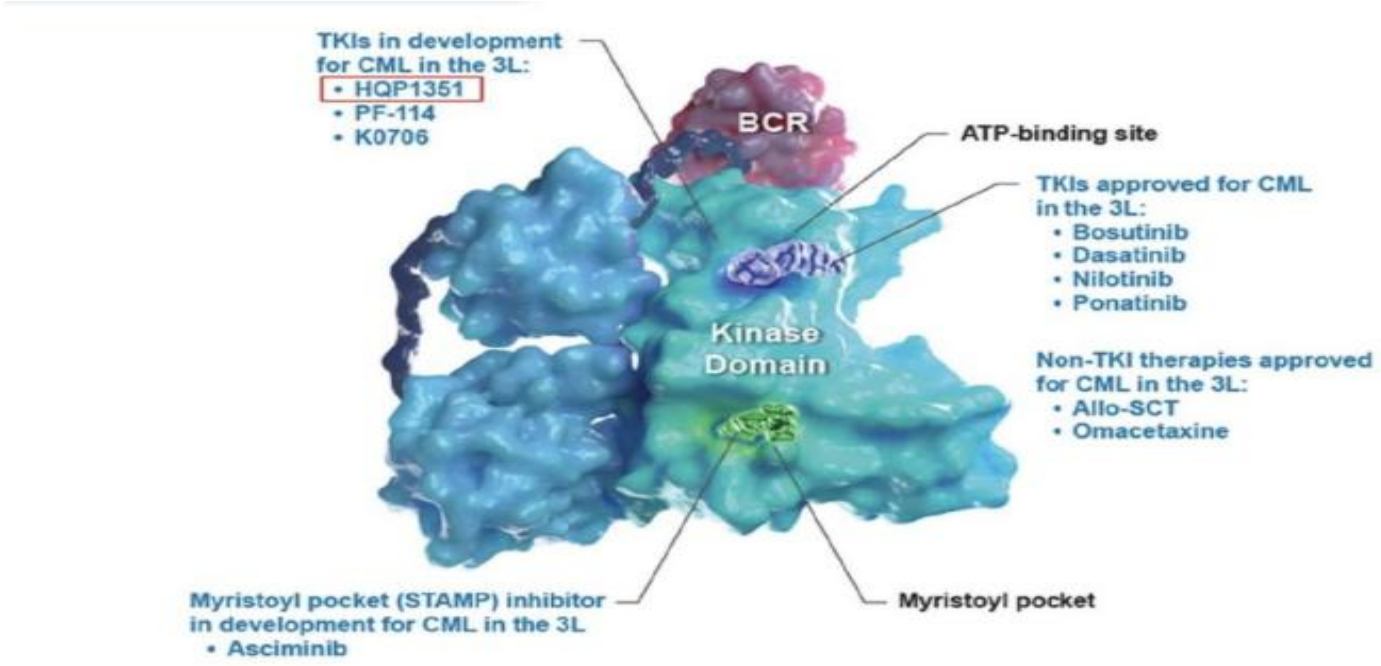


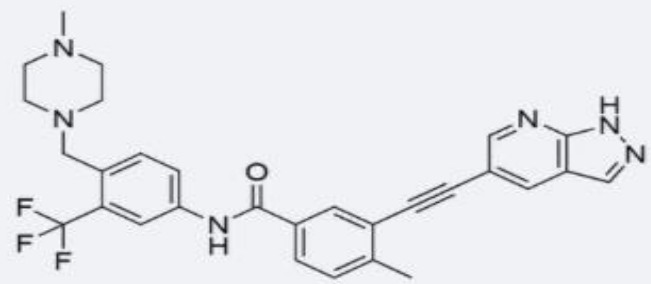
Martinelli G. ASH 2017

Gimema 1811
Duration of Complete Molecular remission

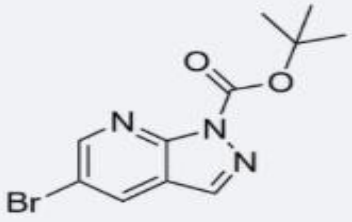


Overembatinib

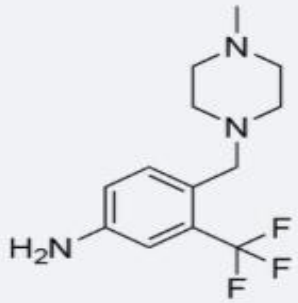




Olverembatinib
CAS 1257628-77-5

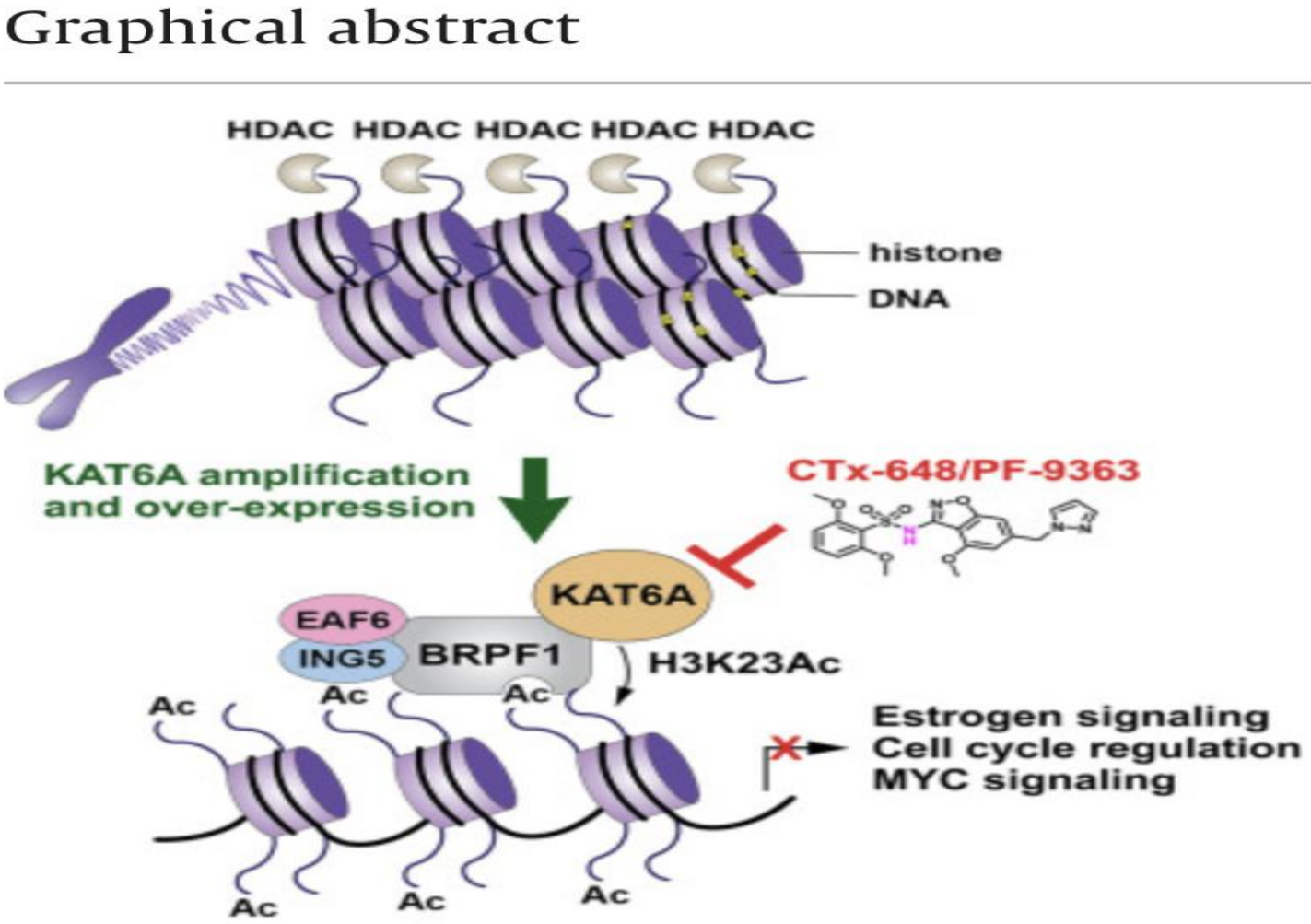


CM151955



CM169811

KAT6 is overexpressed in Ph Leukemias



Conclusions

- We identified a **new signature**, related to *CRLF2* high expression, **to classify triple negative (Ph-/-/-)** ALL B-based on **10 genes.**
- One group (Gr2) represents **11.3%** of all B-ALL and it is characterized by high expression of three main top genes: *CRLF2, CTGF* and *CD200*
- The second group (Gr1) represents **46%** of all B-ALL
- Gene Expression of the Gr2 is similar to Ph+ one, and have CRLF2, CTGF, FLT3, ABL, BLK, CD19, CD22, CD200 as a potential targets for specific therapies
- This new triple negative (Ph-/-/-) classification identify a new class of adult ALL potential **sensitive to Ponatinib and Inotuzumab.**

Thank you!

Clinical Acute Leukemia Team

Delia Cangini, Benedetta Giannini, Marianna Norata, Giovanni Marconi, Gerardo Musuraca, Claudio Cerchione, Alessandro Lucchesi, Valeria Di Battista.

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Istituto di Ricovero e Cura a Carattere Scientifico

ISTITUTO ROMAGNOLO PER LO STUDIO DEI TUMORI DINO AMADORI

OSHO

CHARITÉ

TIMELEX

AML BFM

KAUNO KLINIKOS

ALAN

Acknowledgments

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