50 ANNIVERSARIO

Leucemia Acuta Linfoblastica

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Disclosures of CRISTINA PAPAYANNIDIS

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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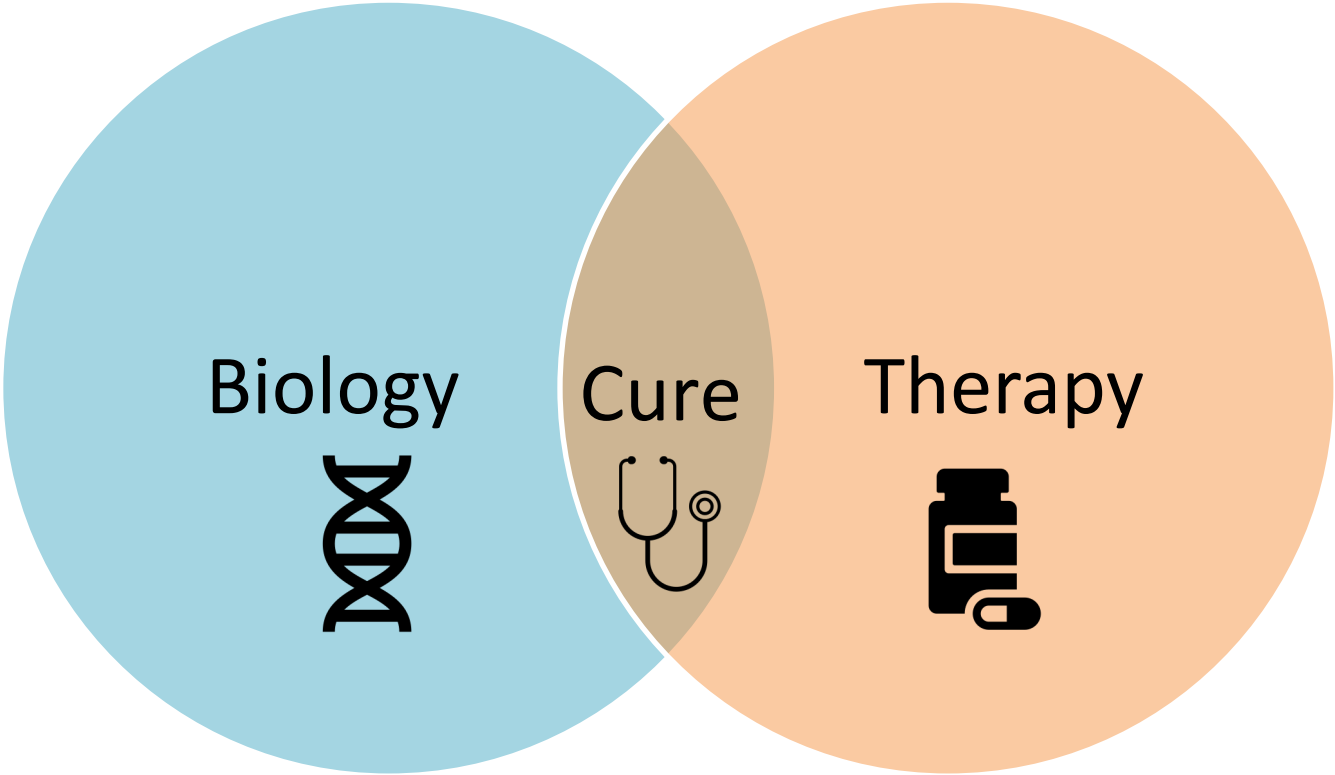
Astellas						X	X
Servier							X
Menarini							X
BMS							X
Pfizer						X	X
Amgen							X
Janssen						X	
GSK						X	
Blueprint						X	
Incyte						X	X
Paladin Labs Inc							X
Jazz pharmaceuticals						X	
Novartis						X	
Delbert Laboratoires						X	

ALL: a translational approach to drive patient's cure



Ph+ ALL: the GIMEMA strategy over the years

Study protocol	Age (years)	Induction therapy	CHR (%)
LAL 0201-B[1]	60–89	IMA + PDN	100%
LAL 1205[2]	18–84	DAS + PDN	100%
LAL 0904 3rd amendment[3]	16–60	IMA + HAM (± transplant)	96%
LAL 1408[4]	>60	NIL + IMA + PDN*	94%
LAL 1509[5]	18–60	Total therapy strategy (DAS)	97%

High CR rates (94-100%)

Alternating 6 week schedules of nilotinib/imatinib; CHR, complete hematologic remission; DAS, dasatinib; HAM, high-dose cytarabine and mitoxantrone; IMA, imatinib; NIL, nilotinib; PDN, prednisone; PON, ponatinib

1. Vignetti M, et al. Blood 2007;109:3676–8; 2. Foà R, et al. Blood 2011;6521–8
3. Chiaretti S, et al. Haematologica 2016, 101:1544-1552
4. Martinelli G, et al. AACR 2014, Abstract 5552 and poster presentation
5. Chiaretti S, et al. Under revision
6. Martinelli G. et al ASH 2017

SCT for all young/fit patients

Ph+ ALL: not a single entity

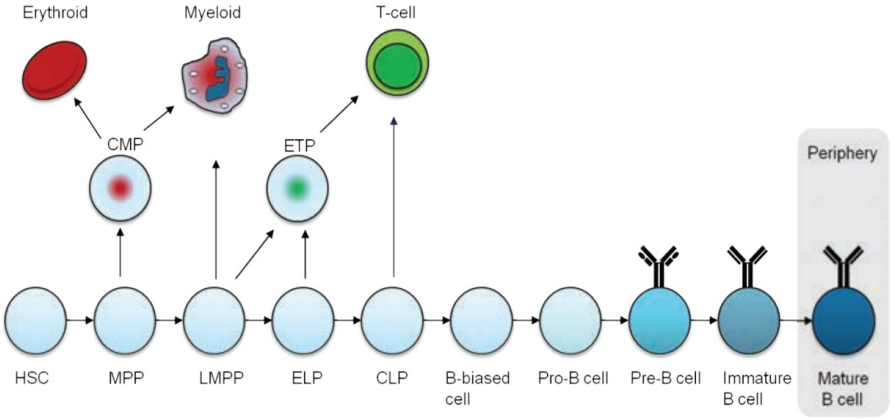
CYTOGENETIC AND MOLECULAR PROGNOSTIC RISK STRATIFICATION FOR B-ALL[h]

RISK GROUPS	CYTOGENETIC AND MOLECULAR ALTERATIONS
Standard risk	• Hyperdiploidy (51–65 chromosomes) ▸ Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome • t(12;21)(p13;q22): *ETV6::RUNX1*[i] • t(1;19)(q23;p13.3): *TCF3::PBX1* • *DUX4* rearranged • *PAX5* P80R • t(9;22)(q34;q11.2): *BCR::ABL1*[j] without *IKZF1* plus[k] and without antecedent chronic myeloid leukemia (CML)
Poor risk	• Hypodiploidy[l,m] (<44 chromosomes) • *TP53* mutation • *KMT2A* rearranged (t[4;11] or others) • *IgH* rearranged[n] • *HLF* rearranged • *ZNF384* rearranged • *MEF2D* rearranged • *MYC* rearranged • *BCR::ABL1*-like (Philadelphia chromosome [Ph]-like) ALL ▸ JAK-STAT (*CRLF2r*,[o] *EPORr*, *JAK1/2/3r*, *TYK2r*, mutations of *SH2B3*, *IL7R*, *JAK1/2/3*) ▸ ABL class (rearrangements of *ABL1*, *ABL2*, *PDGFRA*, *PDGFRB*, *FGFR*) ▸ Other (*NTRKr*, *FLT3r*, *LYNr*, *PTK2Br*) • *PAX5alt* • t(9;22)(q34;q11.2): *BCR::ABL1*[j] with *IKZF1* plus[k] and/or antecedent CML • Intrachromosomal amplification of chromosome 21 (iAMP21) • Alterations of *IKZF1*[k,p,q] • Complex karyotype (5 or more chromosomal abnormalities)

IKZF1 deletion coexisting with *PAX5*, *CDKN2A/2B*, or PAR1 region deletions

NCCN guidelines v 4.2023

Transcription factors in lymphopoiesis: IKAROS (*IKZF1*)



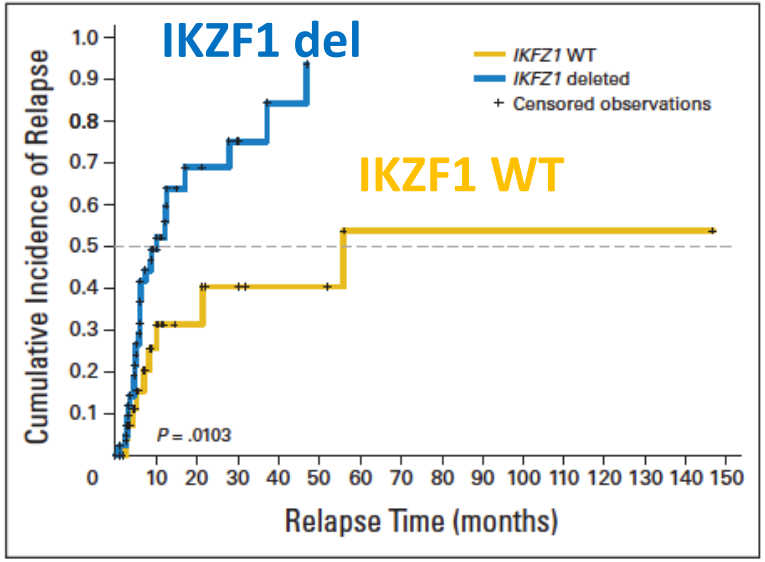
Up-regulated genes:
Cell cycle/apoptosis
JAK-STAT signaling
Stem cell self-renewal

Down-regulated genes:
DNA repair

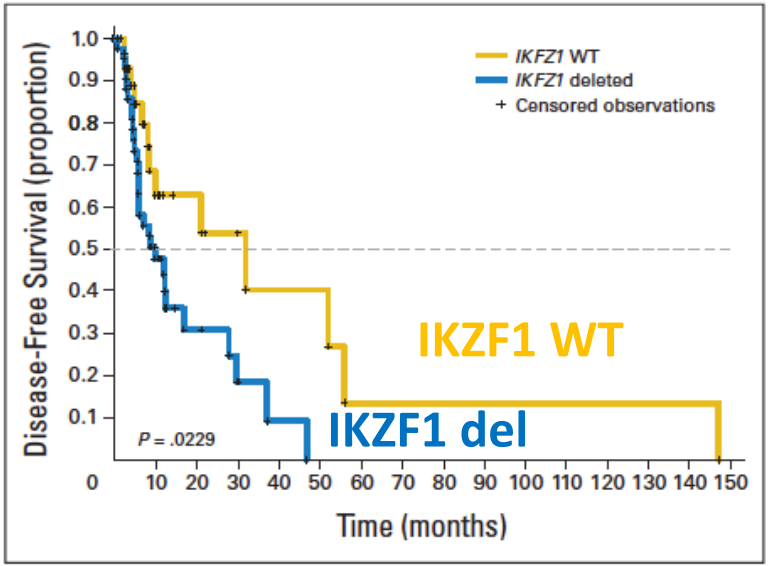
Iacobucci I et al, PlosOne 2012

IKZF1 deletions in BCR-ABL positive ALL are associated with short Disease Free Survival and high rate of Cumulative Incidence of Relapse

CUMULATIVE INCIDENCE OF RELAPSE

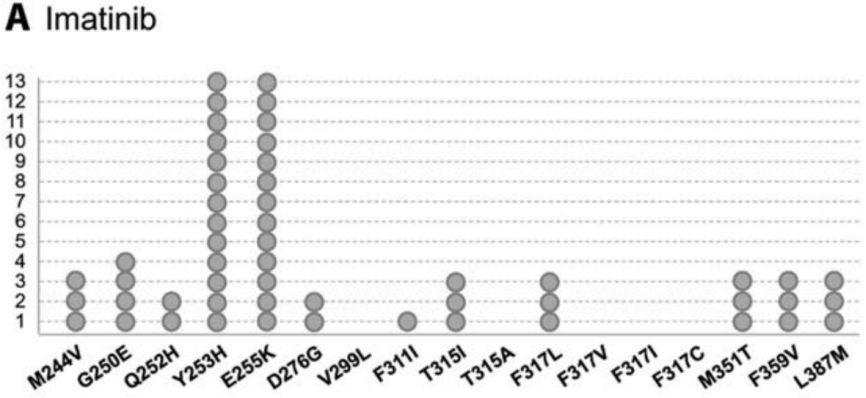


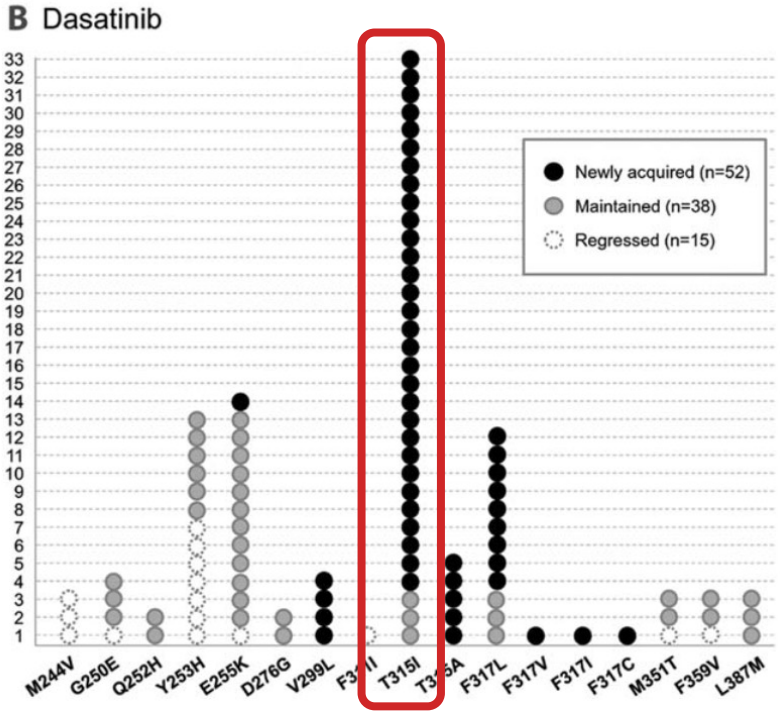
DISEASE FREE SURVIVAL



Martinelli G et al, JCO 2009

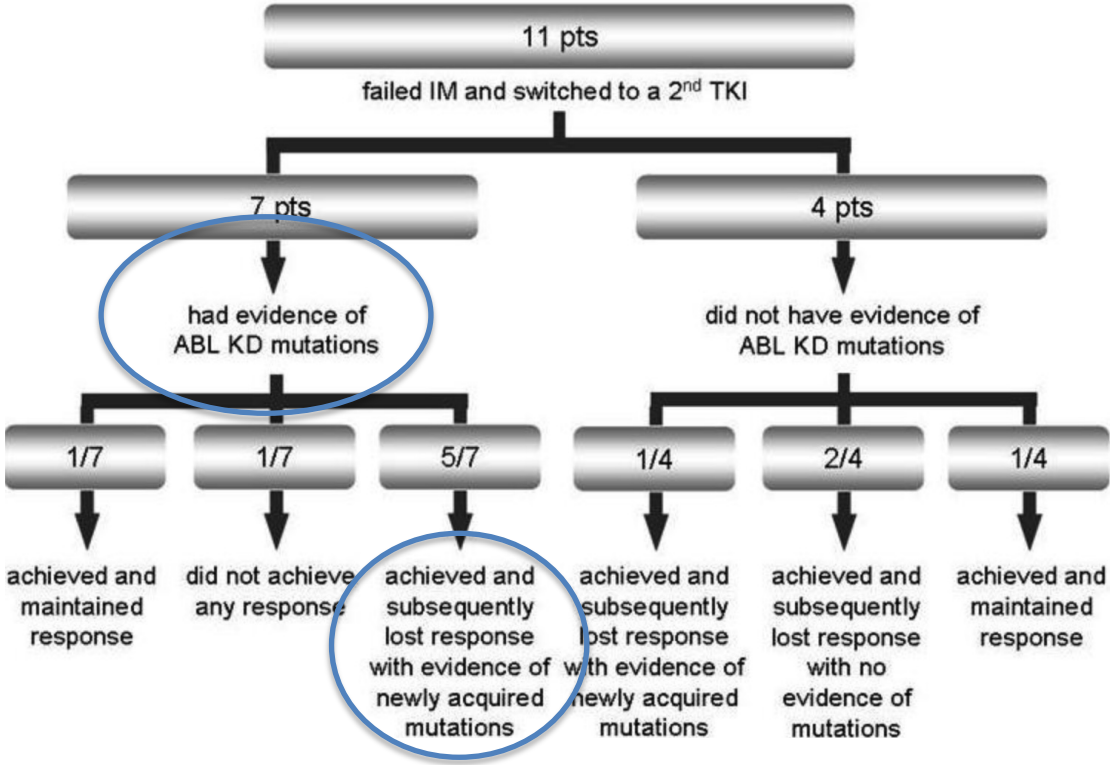
ABL mutations are responsible for resistance to TKIs





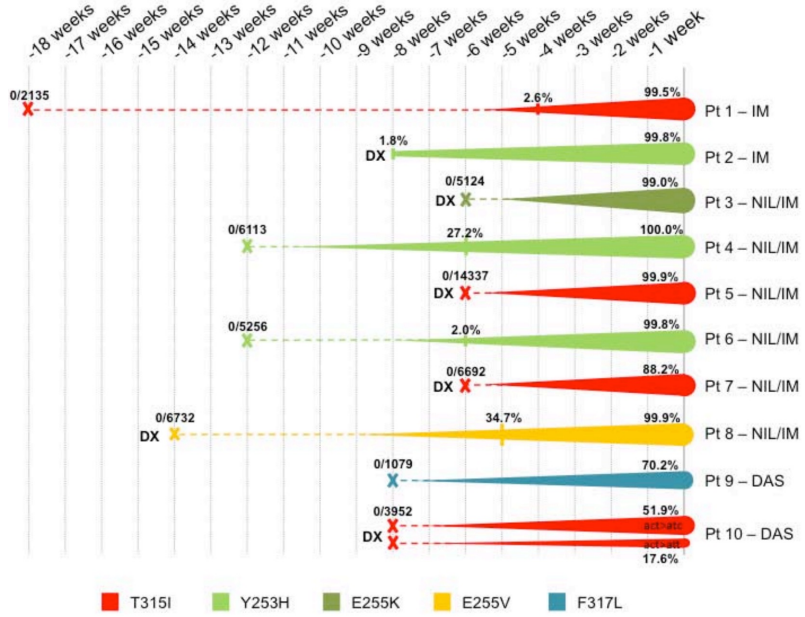
Soverini S et al, Cancer 2013

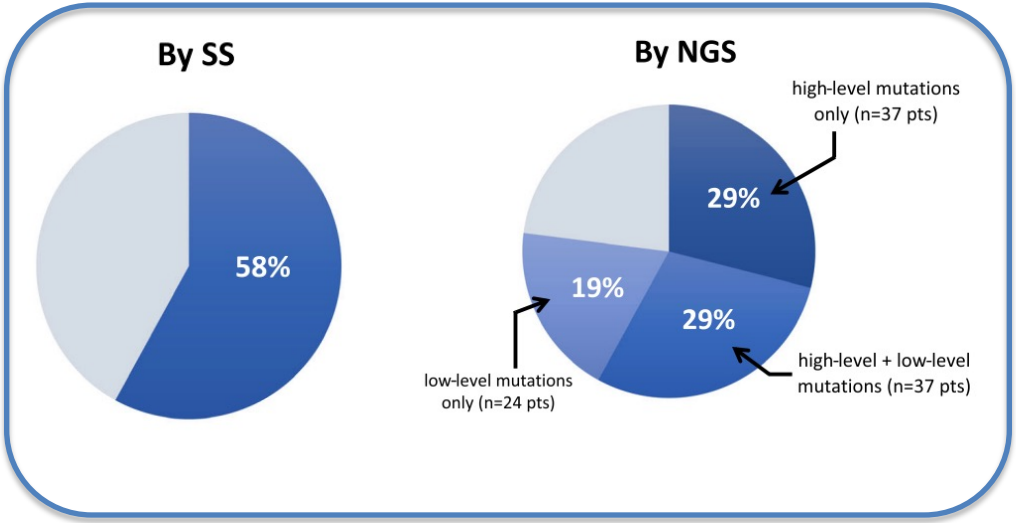
Patients with Imatinib resistant ABL mutations have a higher likelihood of developing additional mutations associated with second or third line TKIs



Soverini S et al, Blood 2009

NGS approach improves their identification over time



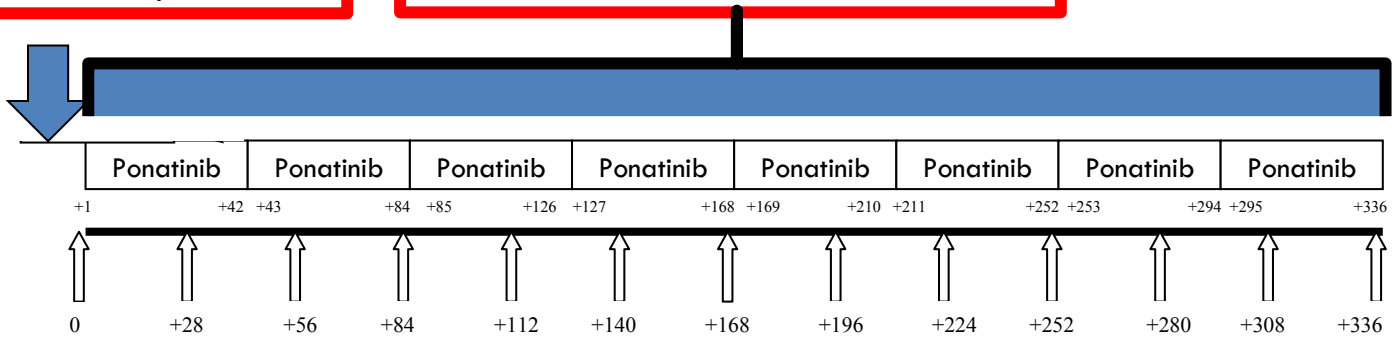


Soverini S et al, Leukemia 2016
Soverini S et al, Br J Haematol 2021

Ponatinib+steroids in newly diagnosed unfit Ph+ALL patients: GIMEMA LAL 1811 clinical trial

Steroid pre-treatment x 7-14 days

Ponatinib 45 mg/daily x 6 weeks (1 course) x 8 courses



= Intrathecal therapy: MTX 10 mg, AraC 40 mg, Dex 4 mg

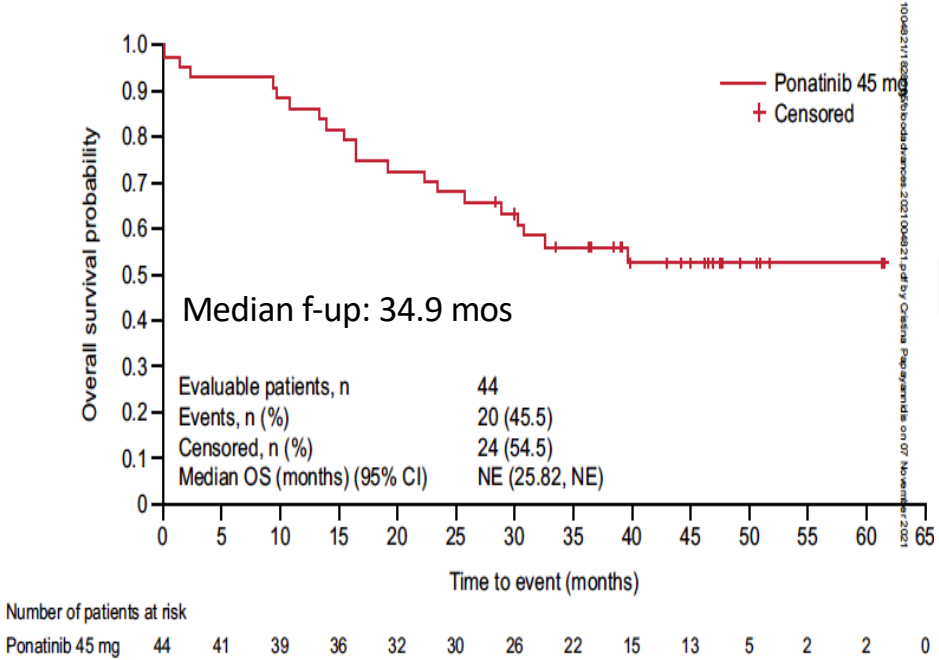
Extension Phase:
Ponatinib until disease relapse or progression

Primary endpoint: CHR @ 6months
Secondary Endpoints: CCyR @ 6, 12, 24, 36 and 48 weeks; CMolR and MMR @ 12, 24, 36 and 48 weeks

Martinelli G et al, Blood Advances 2021

Ponatinib+steroids in newly diagnosed unfit Ph+ALL patients: GIMEMA LAL 1811 clinical trial

PONATINIB+STEROIDS
OVERALL SURVIVAL



Martinelli G et al, Blood Advances 2021

Legge 648

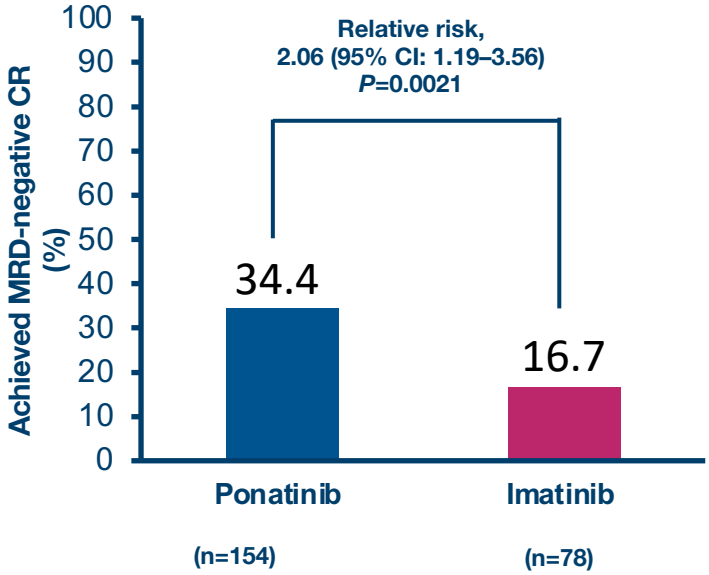
Trattamento di I linea, comprendente Induzione e consolidamento in associazione o meno alla chemioterapia intensiva dei pazienti adulti affetti da LAL Ph+ eleggibili o non al trapianto allogenico

Ponatinib+low intensity chemotherapy is superior to Imatinib+low intensity chemotherapy: phase III PhALLCON trial

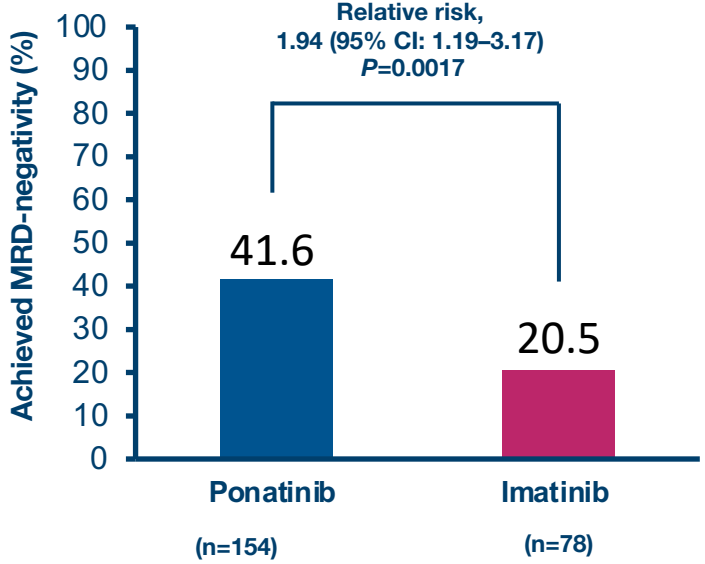
- **Primary endpoint: MRD-negative CR at the end of induction:**
  hematologic CR (for ≥4 weeks) + MRD negativity (≤0.01% *BCR::ABL1*)

FDA APPROVED

Primary endpoint: MRD-negative (MR4) CR at end of induction



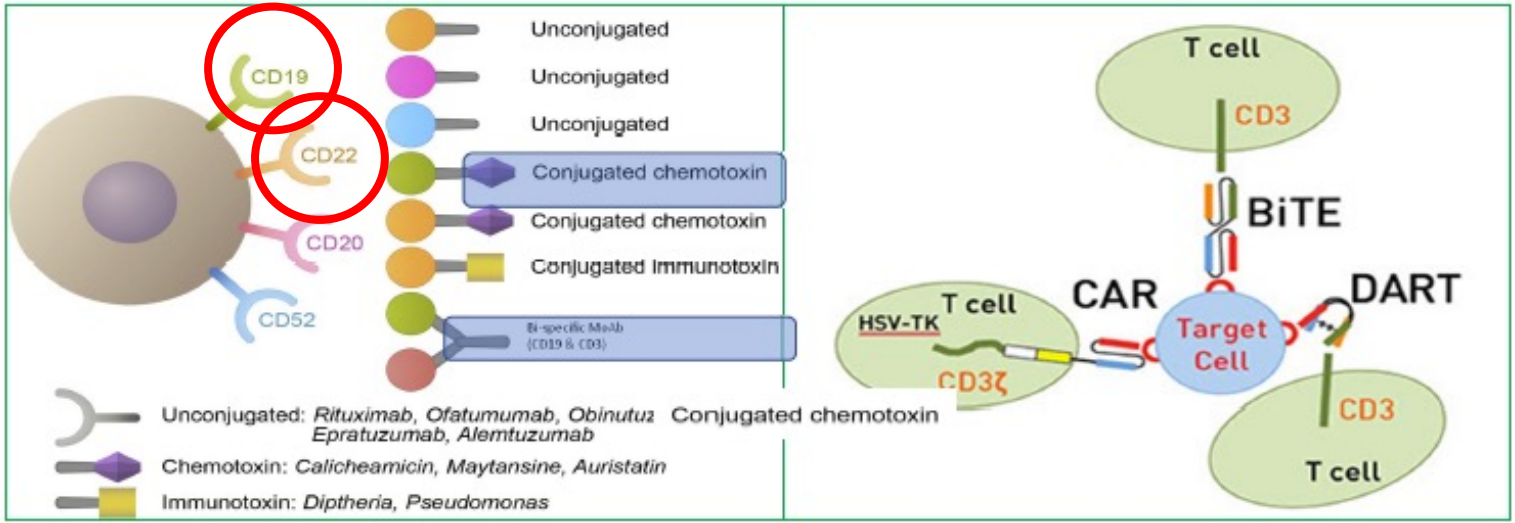
MRD-negativity (MR4) at end of induction, regardless of CR assessment



Jabbour E et al, JAMA 2024

Immunotherapy in ALL

- **Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR-T cells[1,2]**



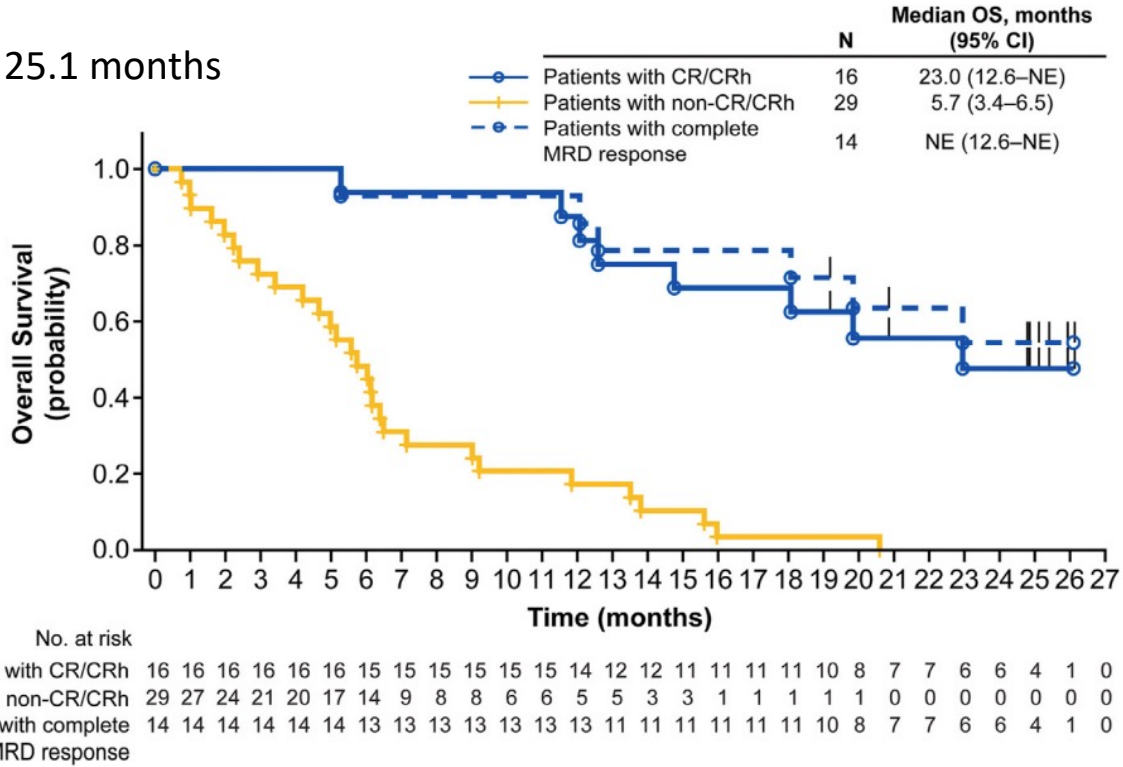
ADC, antibody–drug conjugate; ALL, acute lymphoblastic leukaemia; BITE, bi-specific T-cell engagers; CAR, chimeric antigen receptor; DART, dual affinity retargeting molecules; HSV-TK, Herpes Simplex virus thymidine kinase

1. Adapted from Jabbour. Blood 2015;125:4010; 2. http://www.dipersiolab.org/index.html (accessed 20 March 2016)

Blinatumomab in R/R Ph+ ALL: Alcantara Trial

Median follow up: 25.1 months

CR/CRh 36%
MRD neg 88%
AlloHSCT 25%

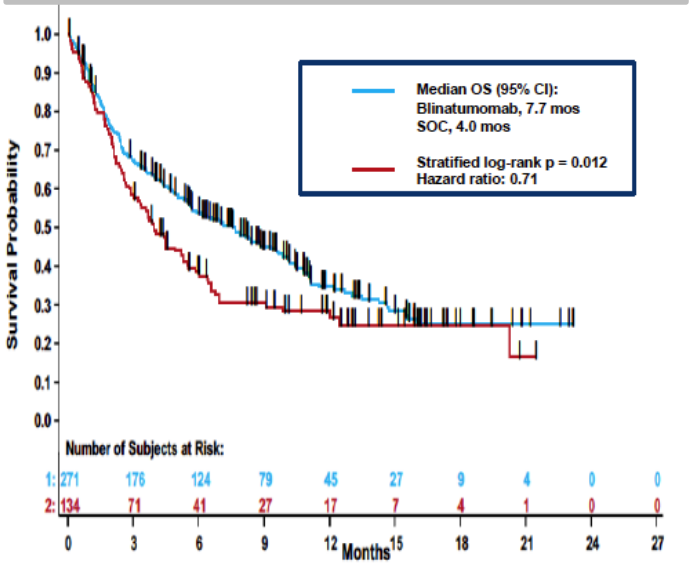


Martinelli G et al, JCO 2017

Martinelli G et al, Eur J Cancer 2021

Blinatumomab and Inotuzumab Ozogamicin are superior to SOC in R/R Ph neg ALL

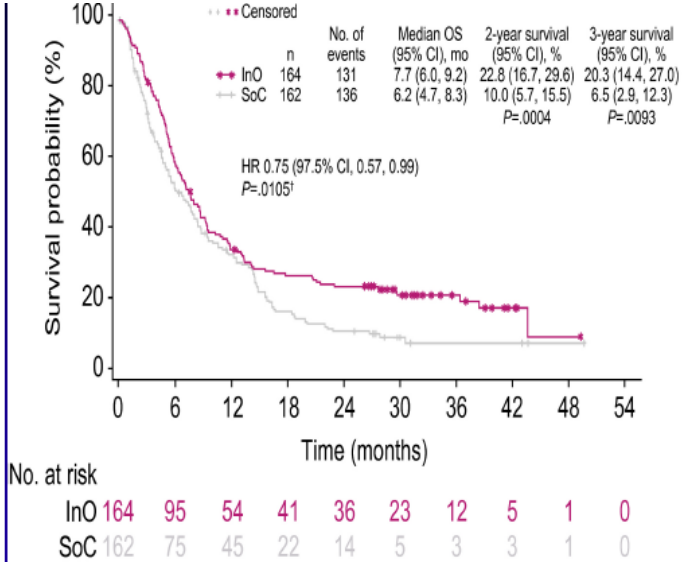
Blinatumomab vs SOC (Tower trial)



CR/CRi rate: 44% vs 25%

Kantarjian H et al, NEJM 2017

Inotuzumab Ozogamicin vs SOC (INOVATE trial)

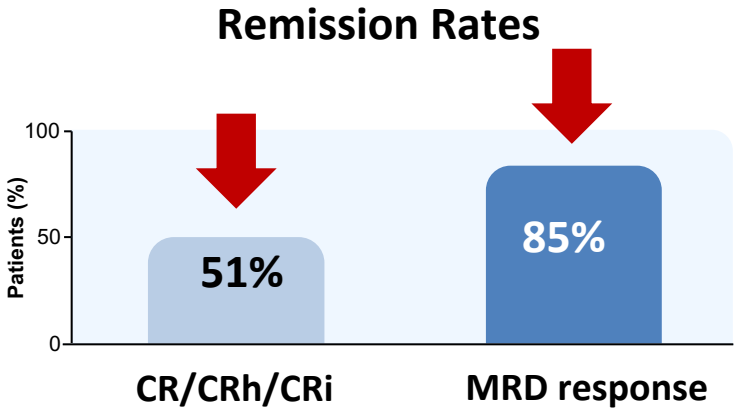


CR/CRi rate: 80% vs 29%

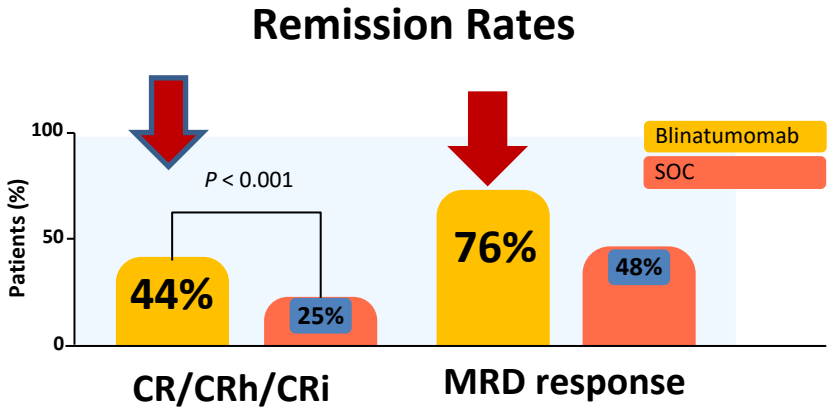
Kantarjian H et al, NEJM 2016

Blinatumomab results confirmed also in a «real life» setting: the NEUF study

NEUF Study: R/R Ph-Negative ALL



TOWER Study

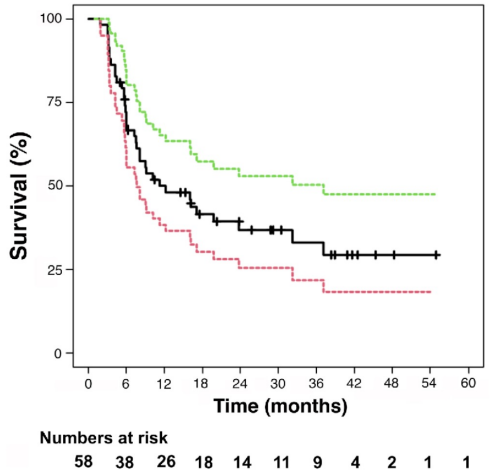


Remission rates observed in the NEUF real-world study were consistent with those in a previous clinical (TOWER) study of blinatumomab in R/R Ph-negative ALL

Boissel N et al, Blood Cancer Journal 2023; Kantarjian NEJM 2017

Impact of inotuzumab ozogamicin on outcome in relapsed or refractory acute B-cell lymphoblastic leukemia patients prior to allogeneic hematopoietic stem cell transplantation and risk of sinusoidal obstruction syndrome/venous occlusive disease

Kayser S, Sartor C,Giglio F, Bruno A, Webster J, Chiusolo P, Saraceni F, Guerzoni S, Pochintesta L, Borlenghi E, Marconi G, Zacheo I, Cerrano M, Salutari P, Restuccia F, Abbenante MC, Levis MJ, Schlenk RF, Papayannidis C



Median follow up 30.5 months
Median OS 11.2 months

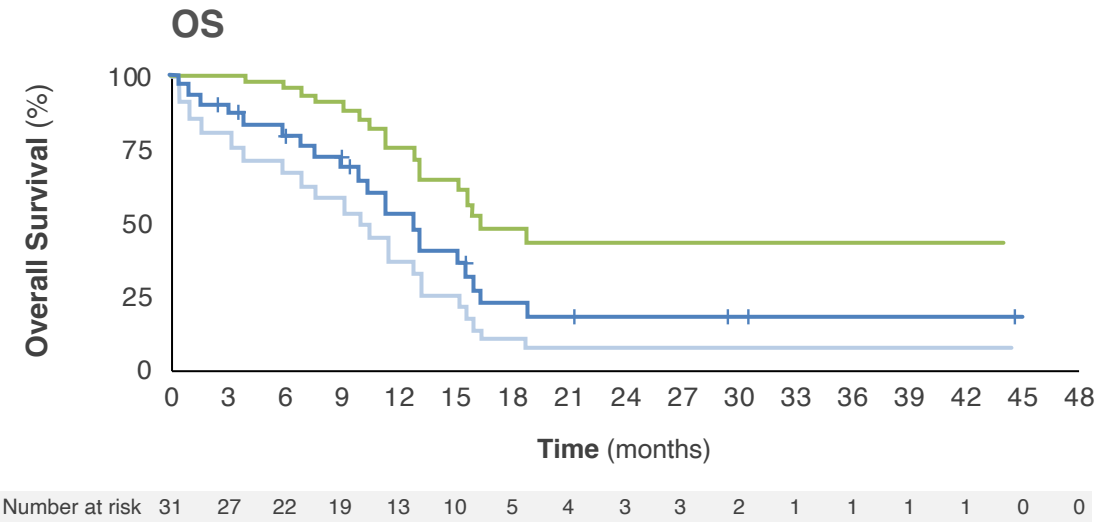
1 year OS 50%
2 year OS 36.7%

Haematologica 2024

Outcome of Relapsed or Refractory Acute B-lymphoblastic Leukemia Patients with Extramedullary Disease Receiving Inotuzumab Ozogamicin

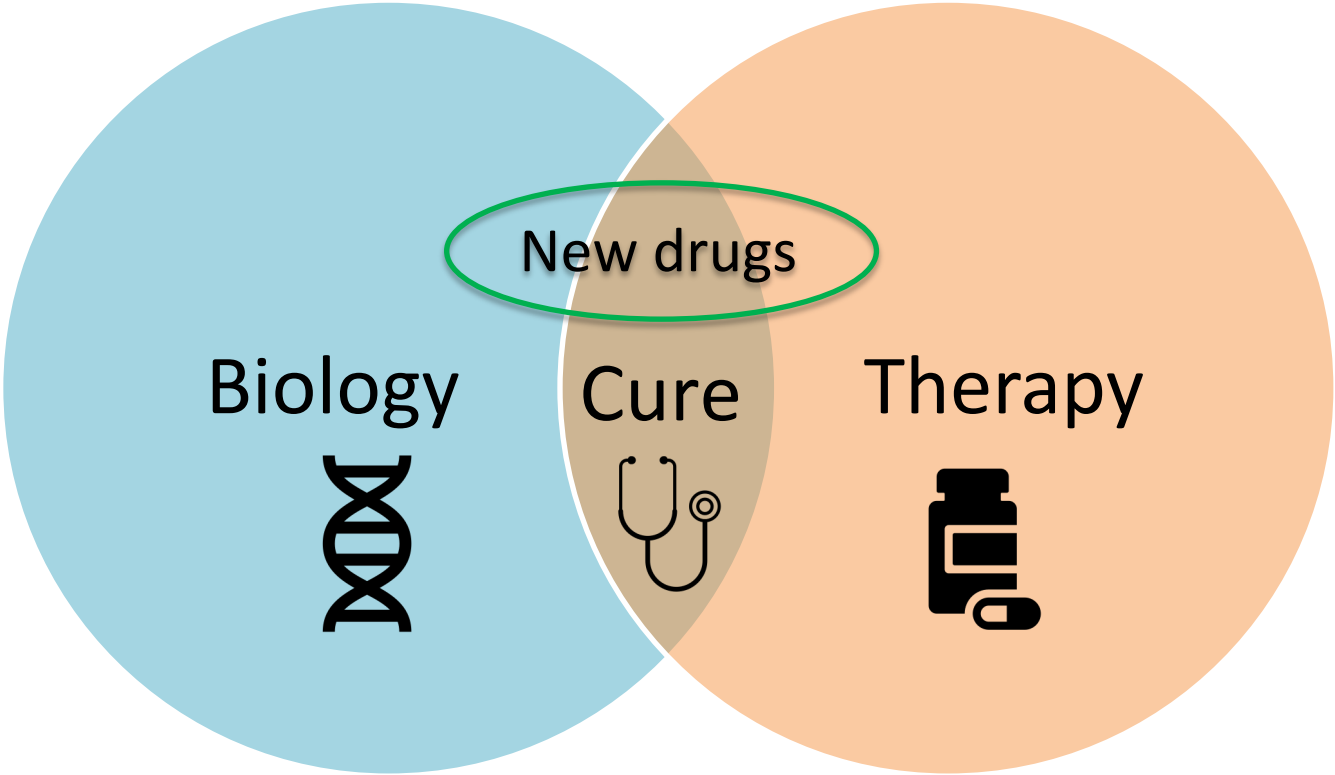
Kayser S, Sartor C, Luskin MR, Webster J, Giglio F, Panitz N, Brunner AM, Fante M, Lutz C, Wolff D, Ho AD, Levis MJ, Schlenk RF, Papayannidis C

	After 1 course
CR	42% (10/24)
PR	37.5% (9/24)
SD	8% (2/24)
RD/PD	12.5% (3/24)
Early death	1 patient

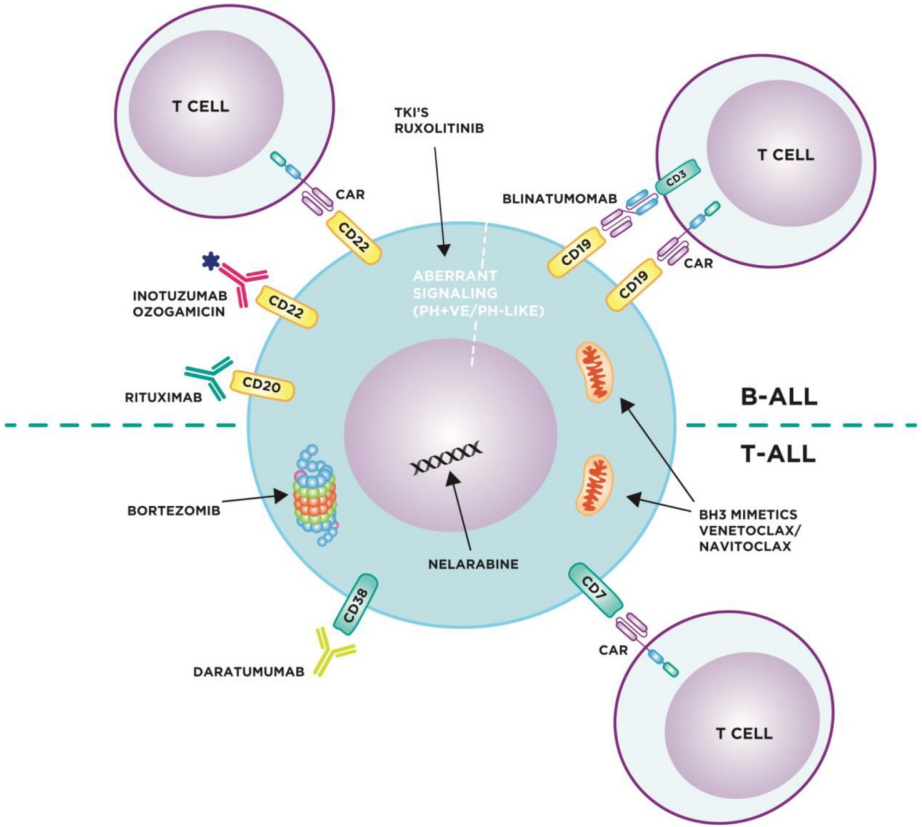


Haematologica 2022

ALL: a translational approach to drive patient's cure



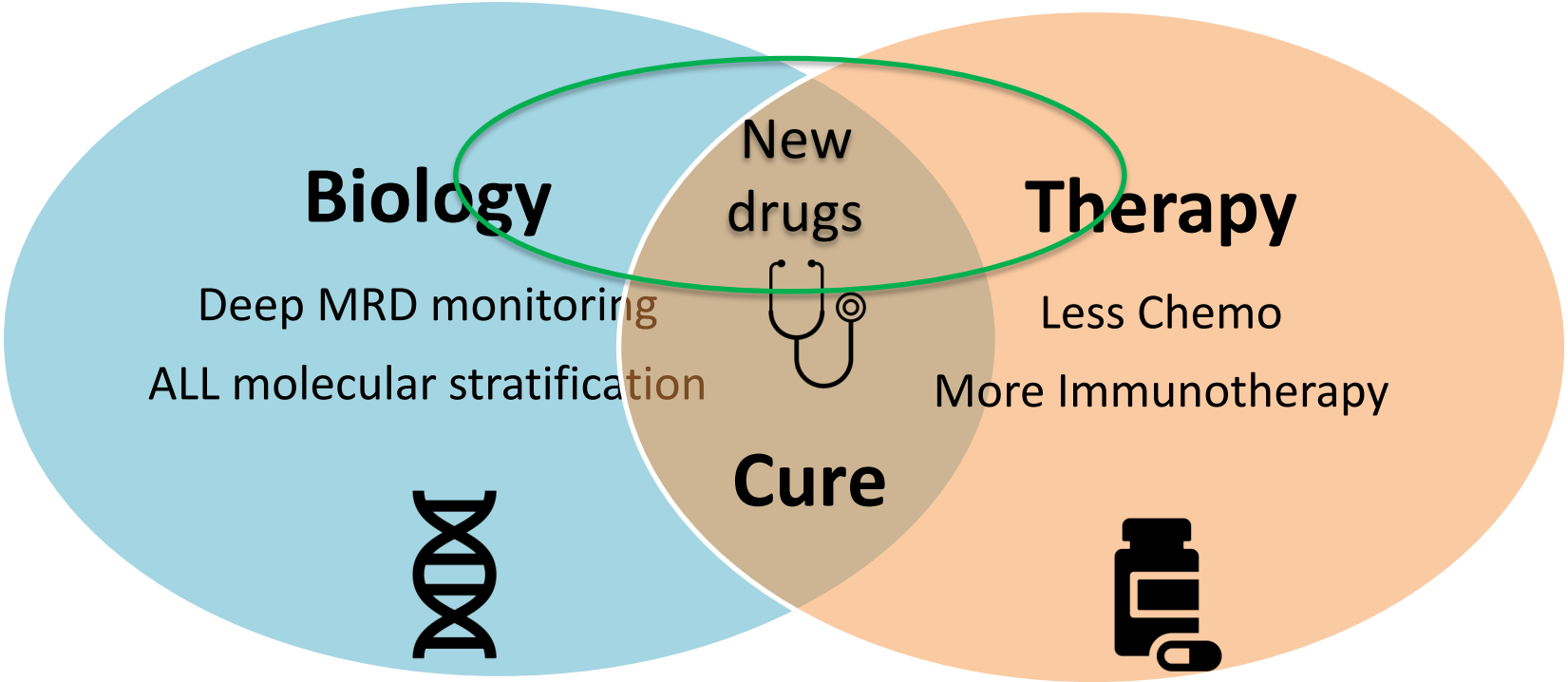
Experimental drugs over the years: B and T ALL



- Blinatumomab + AMG-404
  (Papayannidis C et al, ASCO 2022)
- PHA 739358
- MK0457 (Seymour JF Blood Cancer J 2014)
- s.c. Blinatumomab
- Menin inhibitors
- Olverembatinib

- PF-03084014
  (Papayannidis et al, Blood Cancer J 2015)
- Nelarabine
  (Candoni A et al, Am J Hematol 2020)
- Navitoclax+Venetoclax
  (Malfona F et al, Haematologica 2024)

Present (and future) in ALL



Thank you!

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