New drugs in leukemia

Istituto "Seragnoli"
University of Bologna

Giovanni Martinelli, MD

Istituto "L. e A. Seragnoli"

University of Bologna

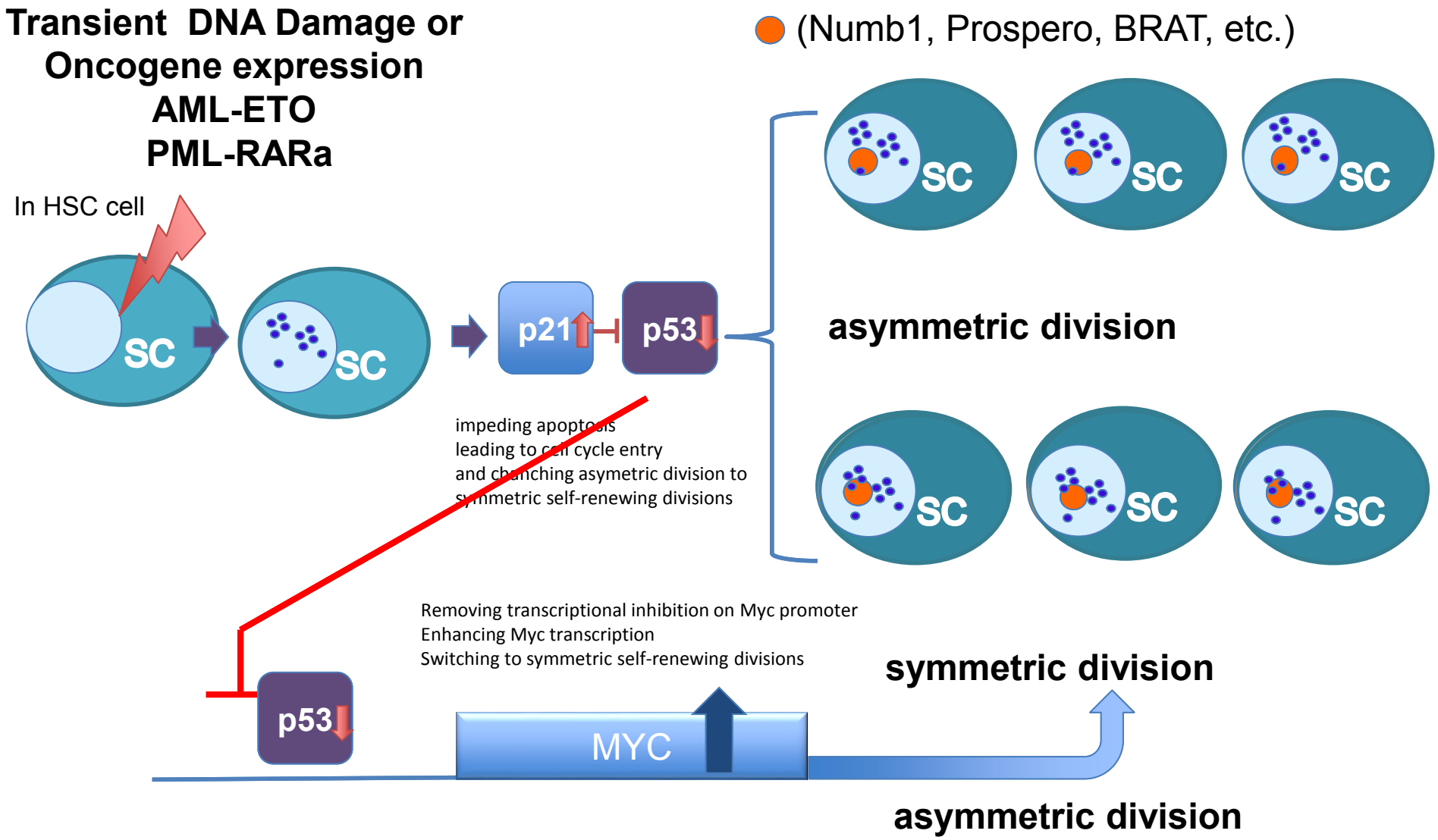
Udine 2016

SEVENTH FRAMEWORK PROGRAMME

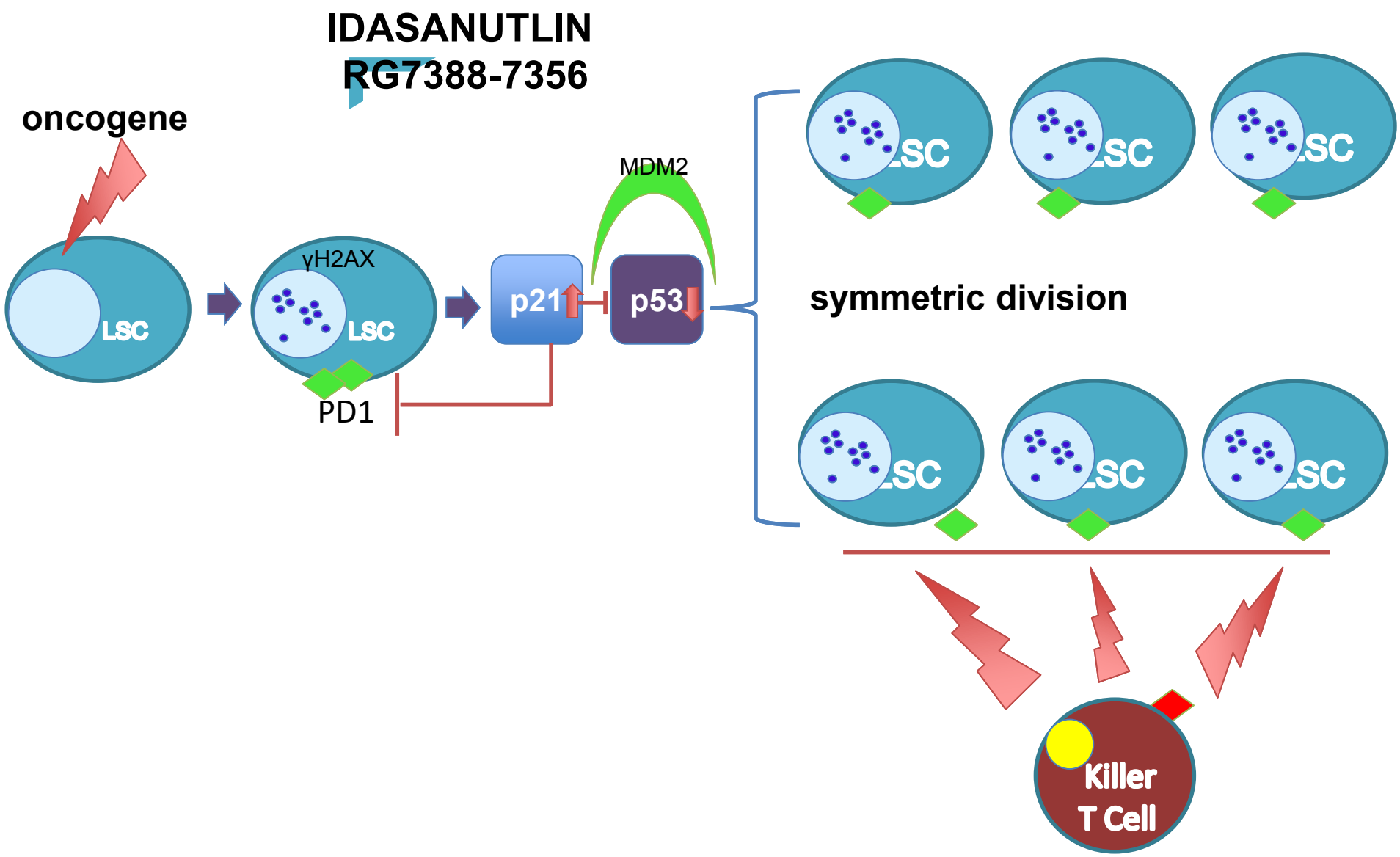
NEXT GENERATION SEQUENCING for Targeted Personalized Therapy of Leukemia

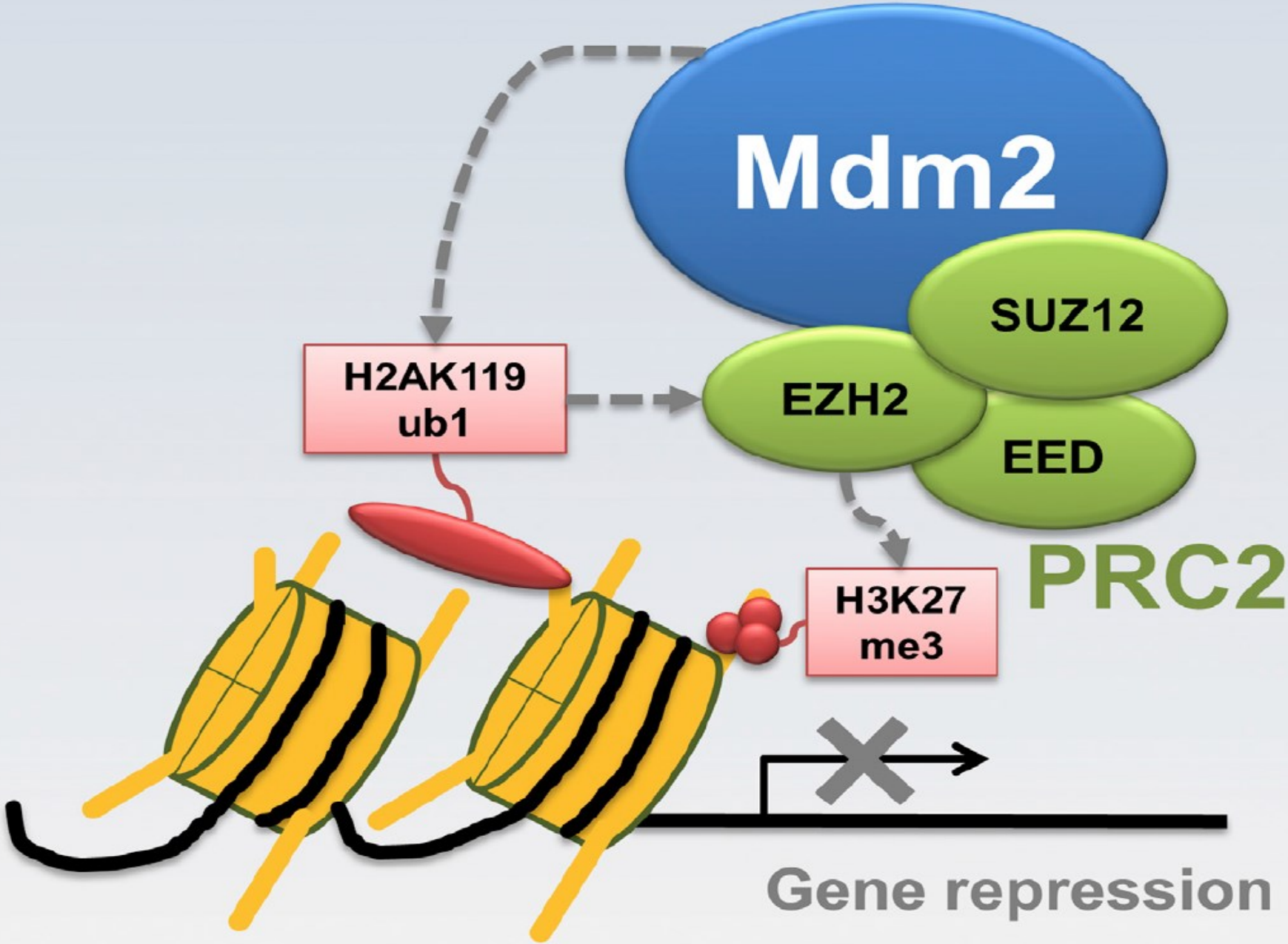
WHY we don't cure Ph+ leukemias?

P53 (and Myc) as a target !



The mdm2-mdm4 inhibition restore P53 dependent activation of immunological surveillance




Mdm2
SUZ12
EZH2
EED
PRC2
H2AK119
ub1
H3K27
me3
Gene repression

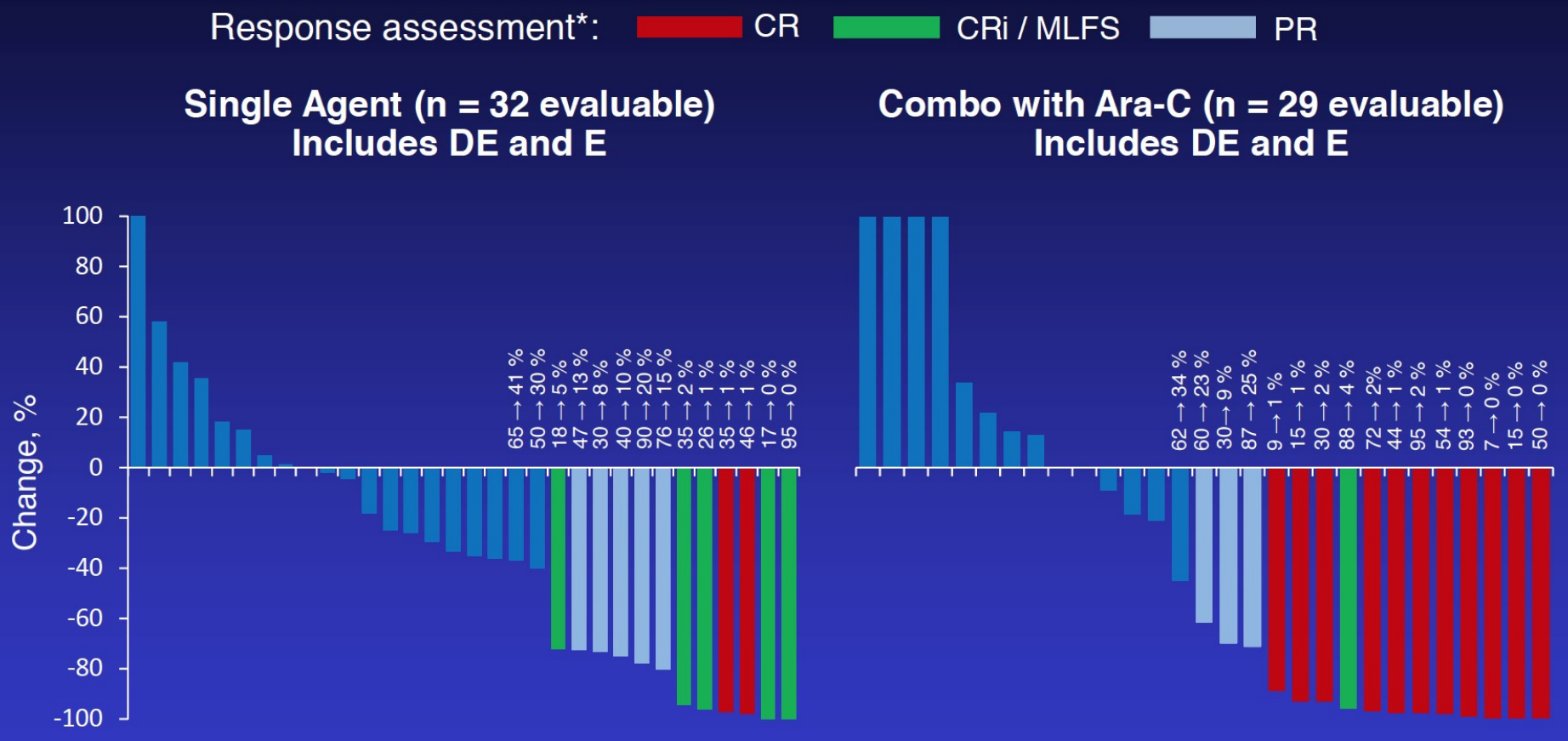
Phase 1/1b Study of RG7388, a Potent MDM2 Antagonist, in Acute Myelogenous Leukemia (AML) Patients (Pts)

Karen Yee[1], Giovanni Martinelli[2], Norbert Vey[3], Michael J. Dickinson[4], Karen Seiter[5], Sarit Assouline[6], Mark Drummond[7], Sung-Soo Yoon[8], Margaret Kasner[9], Je-Hwan Lee[10], Kevin R. Kelly[11], Steven Blotner[12], Brian Higgins[12], Steven Middleton[12], Gwen Nichols[12], Gong Chen[12], Hua Zhong[12], William E. Pierceall[12], Jianguo Zhi[12] and Lin-Chi Chen[12]

[1]Princess Margaret Hospital, Toronto, Canada; [2]Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [3]Hematology Department, Institut Paoli Calmettes, Marseille, France; [4]Department of Haematology, Peter MacCallum Cancer Centre, Melbourne, Australia; [5]New York Medical College, Valhalla, NY; [6]Division of Hematology, Jewish General Hospital, McGill University, Montreal, QC, Canada; [7]Beatson West of Scotland Cancer Centre, Gartnavel General Hospital, Glasgow, Scotland; [8]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea; [9]Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; [10]Department of Hematology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [11]Cancer Therapy and Research Center, University of Texas Health Science Center at San Antonio, San Antonio, TX; [12]Roche Innovation Center New York, Roche Pharma Research & Early Development, New York, NY

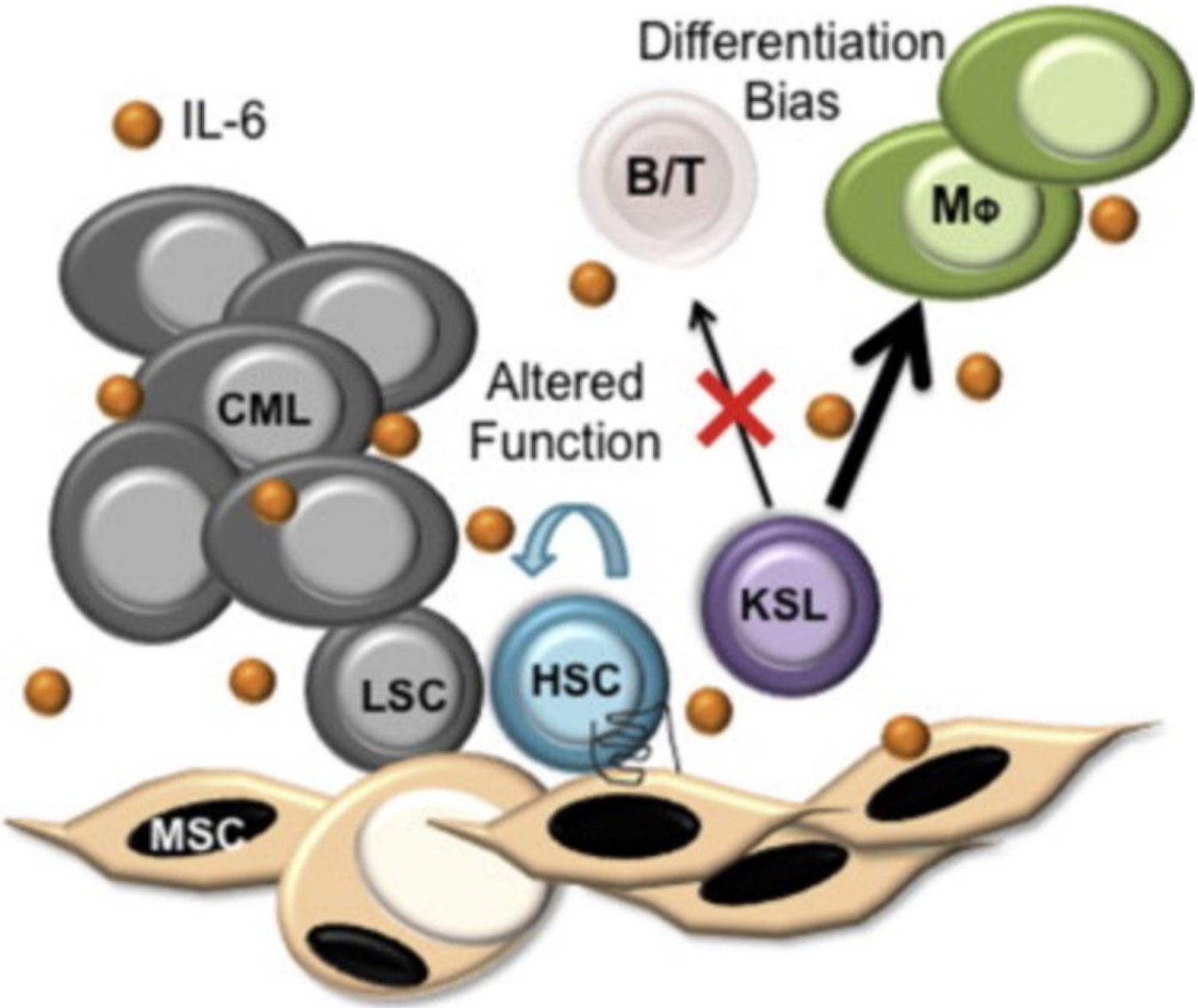
RG7388 AML Phase 1/1b Responses

Change in bone marrow blasts from baseline



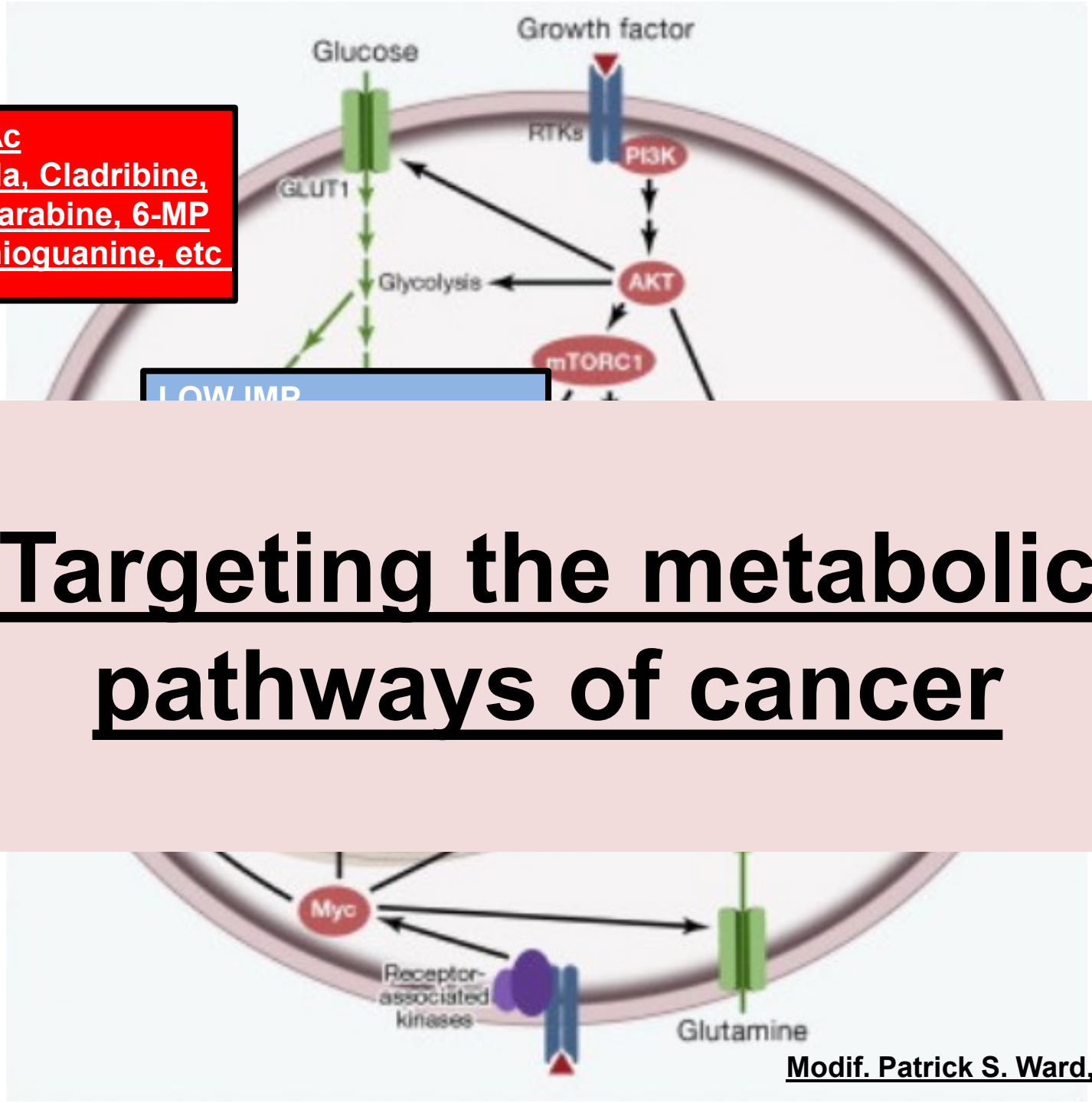
Response definitions:
CR: < 5% marrow blasts with complete recovery of peripheral counts
CRi/MLFS: < 5% marrow blasts with incomplete/no recovery of peripheral counts
PR: > 50% decrease in marrow blasts

*All bone marrow assessments performed at d28 or later except for one patient each in the single agent and combination therapy arms.



Targeting the micro-enviromental?

Cancer Cell 2015



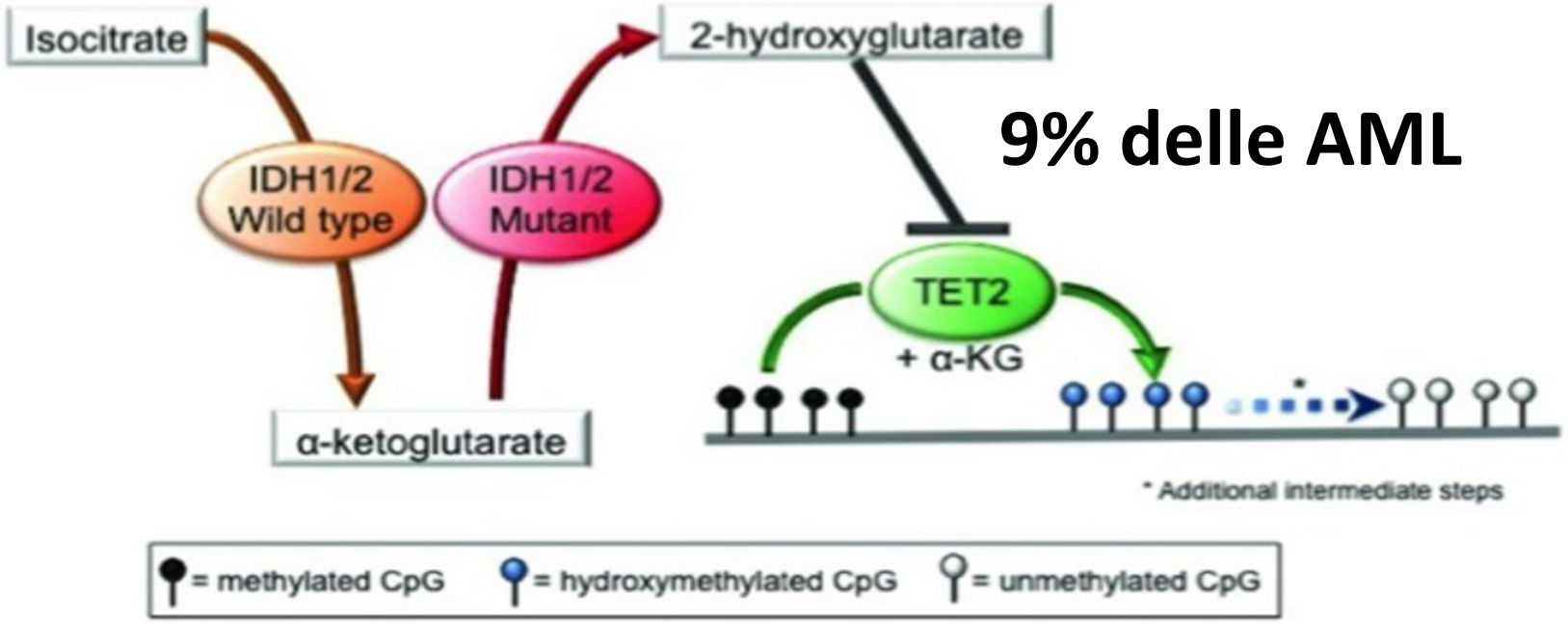
Targeting the metabolic pathways of cancer

Modif. Patrick S. Ward, Cancer Cell 2

IDH1/IDH2 as a target!

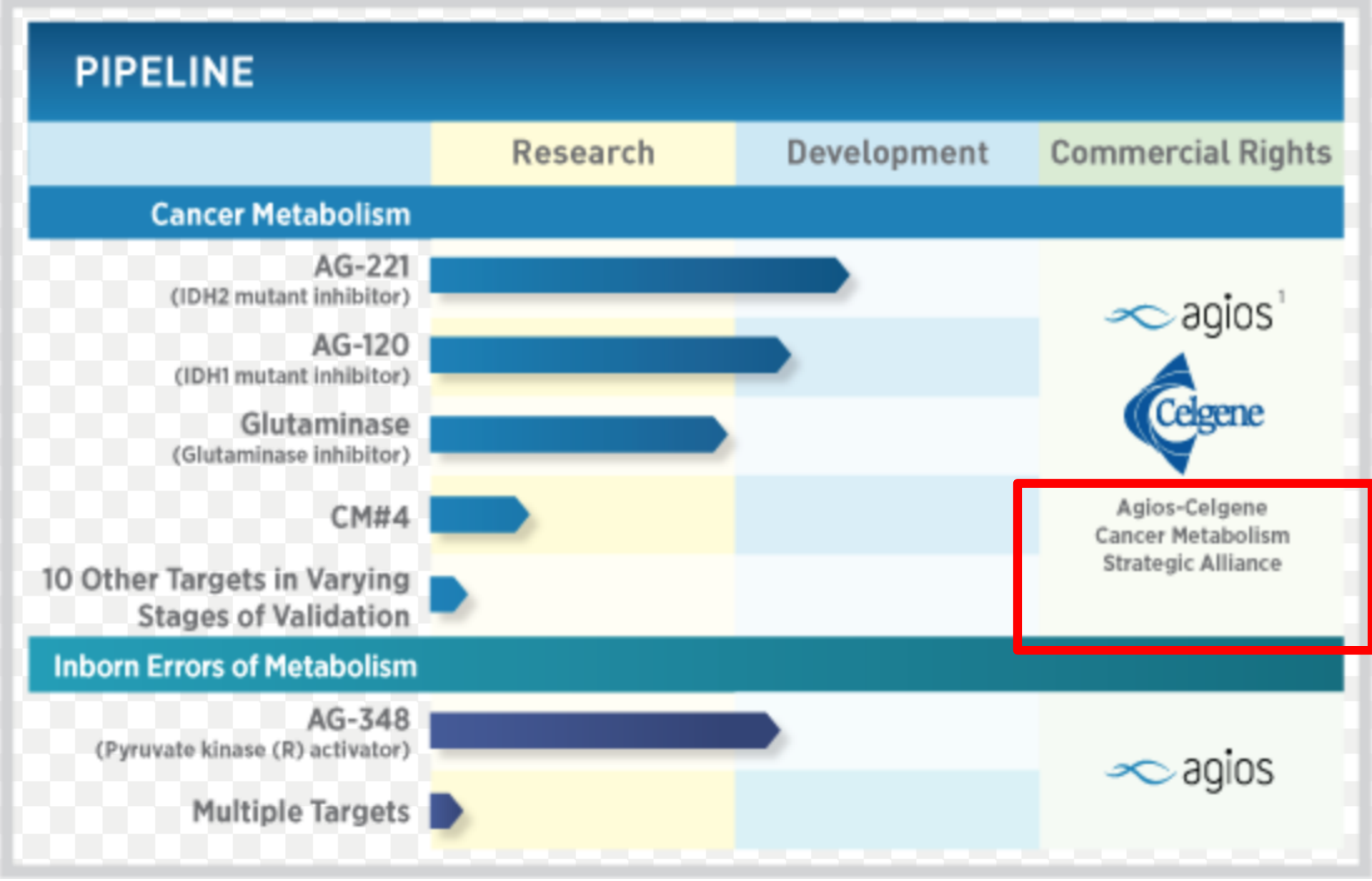
Mu ion.

17% delle AML



9% delle AML

Abdel-Wahab O , and Figueroa M E Hematology 2012;2012:56-64


PIPELINE
Research
Development
Commercial Rights
Cancer Metabolism
AG-221
(IDH2 mutant inhibitor)
AG-120
(IDH1 mutant inhibitor)
Glutaminase
(Glutaminase inhibitor)
CM#4
10 Other Targets in Varying Stages of Validation
agios[1]
Celgene
Agios-Celgene
Cancer Metabolism
Strategic Alliance
Inborn Errors of Metabolism
AG-348
(Pyruvate kinase (R) activator)
Multiple Targets
agios

Abstract 115 (Stein) AG-221, an Oral, Selective, First-in-Class, Potent Inhibitor of the IDH2 Mutant Metabolic Enzyme, Induces Durable Remissions in a Phase I Study in Patients with IDH2 Mutation Positive Advanced Hematologic Malignancies

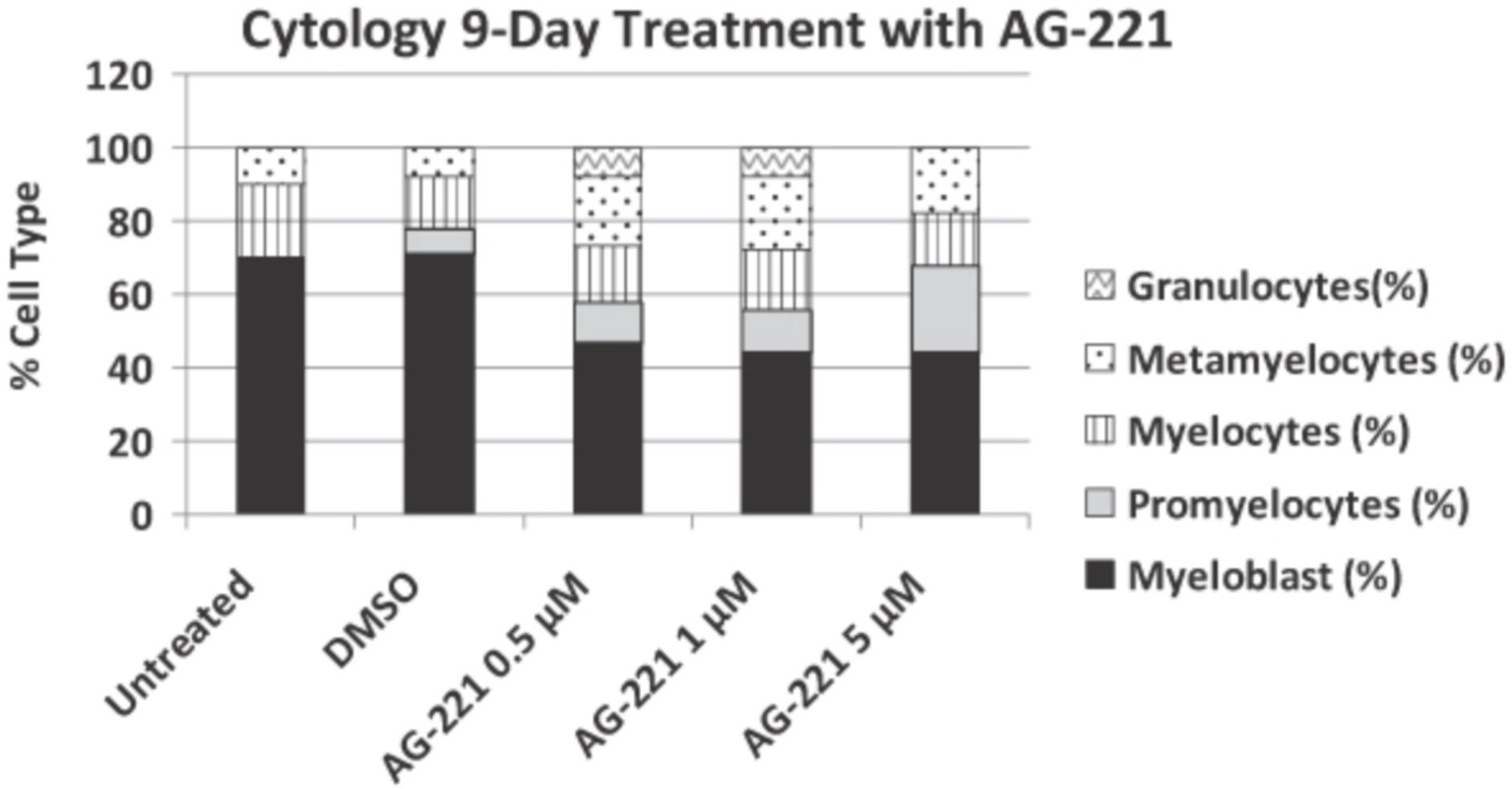
Best Overall Response by Cumulative Daily Dose*

	≤75 mg (n=9)	100 mg (n=14)	≥150 mg (n=22)	Total (n=45 efficacy evaluable)
CR	3	3	-	6
CRp	1	1	2	4
mCR	-	2	2	4
CRi	-	-	1	1
PR	-	3	7	10
SD	5	3	9	17
PD	-	1	1	2
Disease Not Evaluable	-	1	-	1
Overall Response Rate**	4/9 (44%)	9/14 (64%)	12/22 (55%)	25/45 (56%) 95% CI (40%, 70%)

CR = complete response
CRp = complete response, incomplete platelet recovery
Marrow CR = ≤5% blasts in BM; no hematological recovery
CRi = complete response, incomplete hematologic recovery
PR = partial response
SD = stable disease
PD = progressive disease

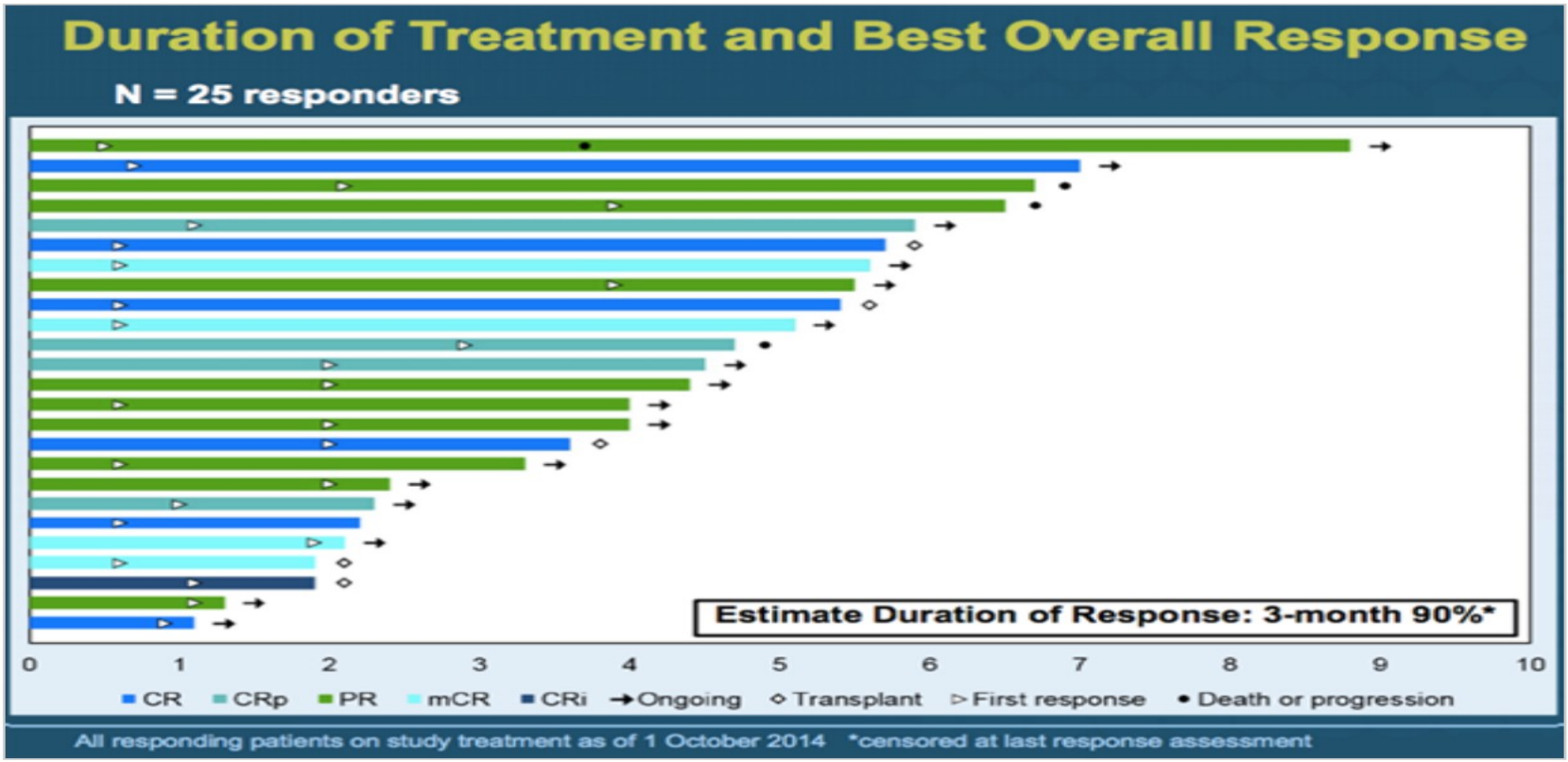
* Includes patients with a Day 28 response assessment as of October 1, 2014. Excludes 12 on-going patients with Day 28 not yet available and 16 patients off study without a Day 28 assessment.
** ORR = CR + CRp + mCR + CRi + PR

“Atra Like”


Cytology 9-Day Treatment with AG-221
% Cell Type
120
100
80
60
40
20
0
Untreated
DMSO
AG-221 0.5 µM
AG-221 1 µM
AG-221 5 µM
Granulocytes(%)
Metamyelocytes (%)
Myelocytes (%)
Promyelocytes (%)
Myeloblast (%)

Top 7 Highlights From the 2014 ASH Meeting

December 12, 2014
By Anna Azvolinsky, PhD



Slide 5: Activity of First-in-Class IDH2 Inhibitor in AML Validates IDH2 as Therapeutic Target—A phase I study of AG-221, an oral, first-in-class inhibitor of isocitrate dehydrogenase 2 (IDH2), has validated IDH2 as a therapeutic target in *IDH2*-mutated hematologic cancers, including acute myeloid leukemia (AML). Of a total of 45 patients who could be evaluated for efficacy, 25 patients (56%) responded, including 6 patients who achieved complete responses. The most common adverse

Investigational therapy

A Phase 1/2 Study of ABT-199 in Combination with Low-Dose Cytarabine in Treatment-Naïve Subjects with Acute Myelogenous Leukemia Who Are ≥ 65 Years of Age and Who Are Not Eligible for Standard Anthracycline-Based Induction Therapy

abbvie

ABT-199
M14-387 Protocol
EudraCT 2014-002610-23

Investigational therapy

abbvie

ABT-199
M14-387 Protocol
EudraCT 2014-002610-23

Study rationale

- Bcl-2 over-expression has been implicated in the maintenance and survival of AML cells and has been associated with resistance to chemotherapeutics. In addition, high levels of Bcl-2 were associated with poor survival in a subset of patients with this disease
- Combinations of ABT-199 and chemotherapeutic agents commonly used in the treatment of AML were tested against a panel of 20 AML cell lines. While most combinations resulted in additive cell killing, ABT-199 combined with cytarabine or azacitidine showed synergistic effects on several AML cell lines

Souers AJ, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med. 2013
Tsao T, et al. Concomitant inhibition of DNA methyltransferase and BCL-2 protein function synergistically induce mitochondrial apoptosis in acute myelogenous leukemia cells. Ann Hematol. 2012

Investigational therapy

abbvie

ABT-199
M14-387 Protocol
EudraCT 2014-002610-23

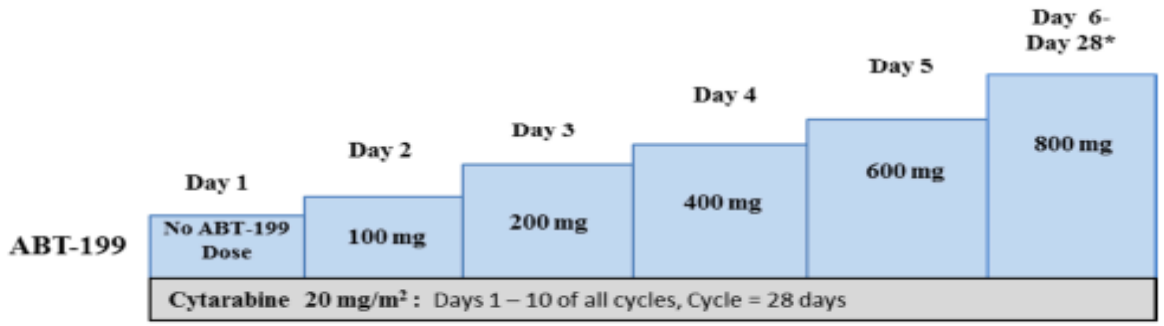
Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

A subject will be eligible for study participation if he/she meets the following criteria within 21 days prior to the first day of therapy:

1. Subject must be ≥ 65 years of age.
2. Subject must have a projected life expectancy of at least 12 weeks.
3. Subject must have histological confirmation of AML and be ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to co-morbidity or other factors.
4. Subject must have received no prior treatment for AML with the exception of hydroxyurea, allowed through the first cycle of study treatment. **Note:** Subject may have been treated for prior Myelodysplastic Syndrome.
5. Subject must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
6. Subject must have adequate renal function as demonstrated by a calculated creatinine clearance ≥ 50 mL/min; determined via urine collection for 24-hour creatinine clearance or by the Cockcroft-Gault formula.
7. Subject must have adequate liver function as demonstrated by:
   - aspartate aminotransferase (AST) ≤ 2.5 × ULN*
   - alanine aminotransferase (ALT) ≤ 2.5 × ULN*
   - bilirubin ≤ 1.5 × ULN*

Dose level 2



* Cycle = 28 days. ABT-199 dose will be administered on Day 1 – Day 28 starting with Cycle 2, at the designated cohort dose of 800 mg.

Investigational therapy

A Phase 1/2 Open-Label, Dose Escalation Study Investigating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ASP2215 in Patients with Relapsed or Refractory Acute Myeloid Leukemia

Protocol for Phase 1/ 2 Study of ASP2215

Gimema Clinical Trial LAL1811

Front-line treatment of Philadelphia positive **(Ph+)/BCR- ABL positive Acute Lymphoblastic Leukemia (ALL)** with AP24534 (Ponatinib), a new potent tyrosine kinase inhibitor (TKI).

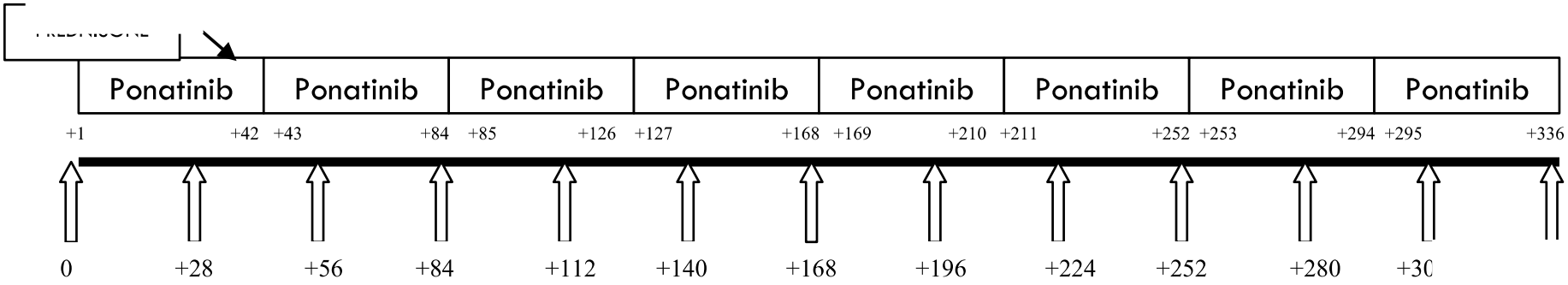
A phase II exploratory **multicentric study** in patients **more than 60 years** old **or unfit** for a program of intensive chemotherapy and stem cell transplantation

ClinicalTrial number CT01641107

Treatment Schedule

Steroid pre-treatment x 7-14 days
(and for 28 days
during Ponatinib administration)

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



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

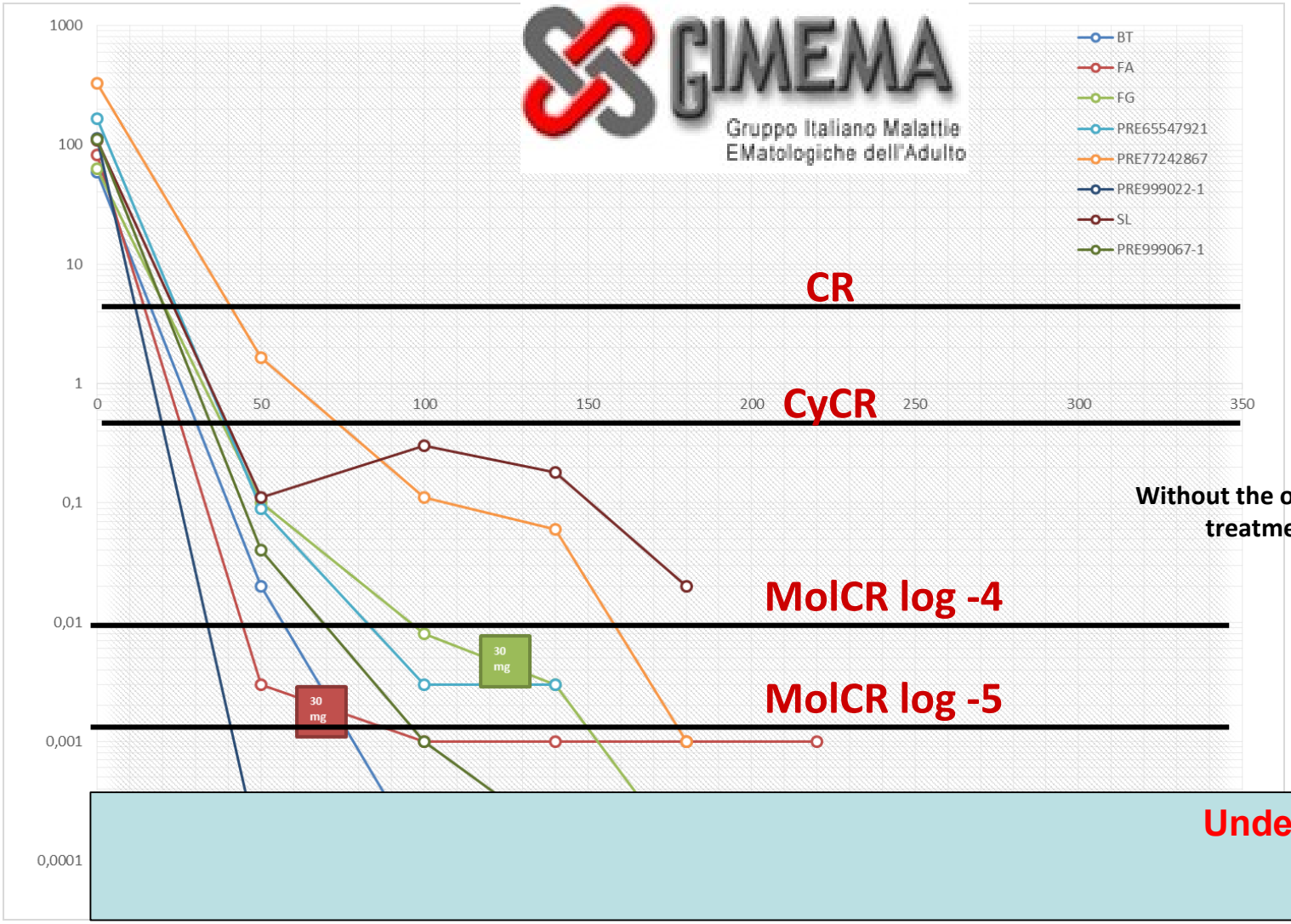
Extension Phase:
Ponatinib until disease relapse

Efficacy measure: Clinical and Response Data

	n
M/F	9/5
Median age (range)	68(42-74)
WBC/mmc median (range)	4660 (1900-186900)
Hb g/dl median (range)	8.7 (7.1-9.9)
PLTs/mmc median (range)	38000 (11000-121000)
p190/p210	8/6
CHR@6 weeks	11/11 (3 not already evaluated)
Relapsed	1 (no treatment adherence @ day +250)
Transplanted	1 in CR

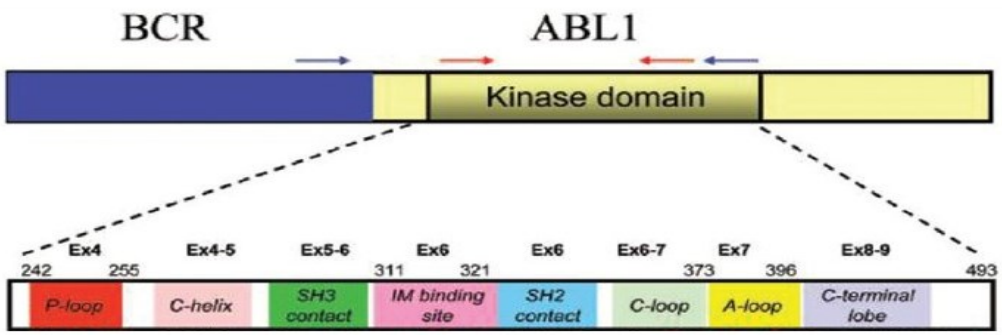
Efficacy outcome:

ALL pts experienced rapid and very deep molecular responses



Without the only patient with no treatment adherence

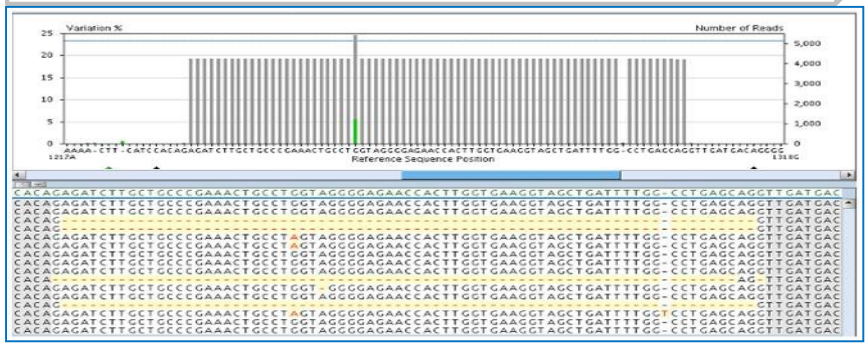
No evidence of emerging point mutations resistant to Ponatinib in until now treated patients



GIMEMA
Gruppo Italiano Malattie EMatologiche dell'Adulto

185DEL

Frameshift deletion
185bp deletion (nt 1233-1417) exons 6 and 7
Loss of 61 residues (Δ362-424)



PRE11837136: 2,76%
FI.GO82694832: 6,24%

35INS

Frameshift insertion
35bp insertion (nt 1571) between exons 8 and 9
Loss of 653 residues

PRE11837136: 1,66%
FI.GO82694832: 1,11%

Why Ponatinib works?
It targets Hck LSC gene?

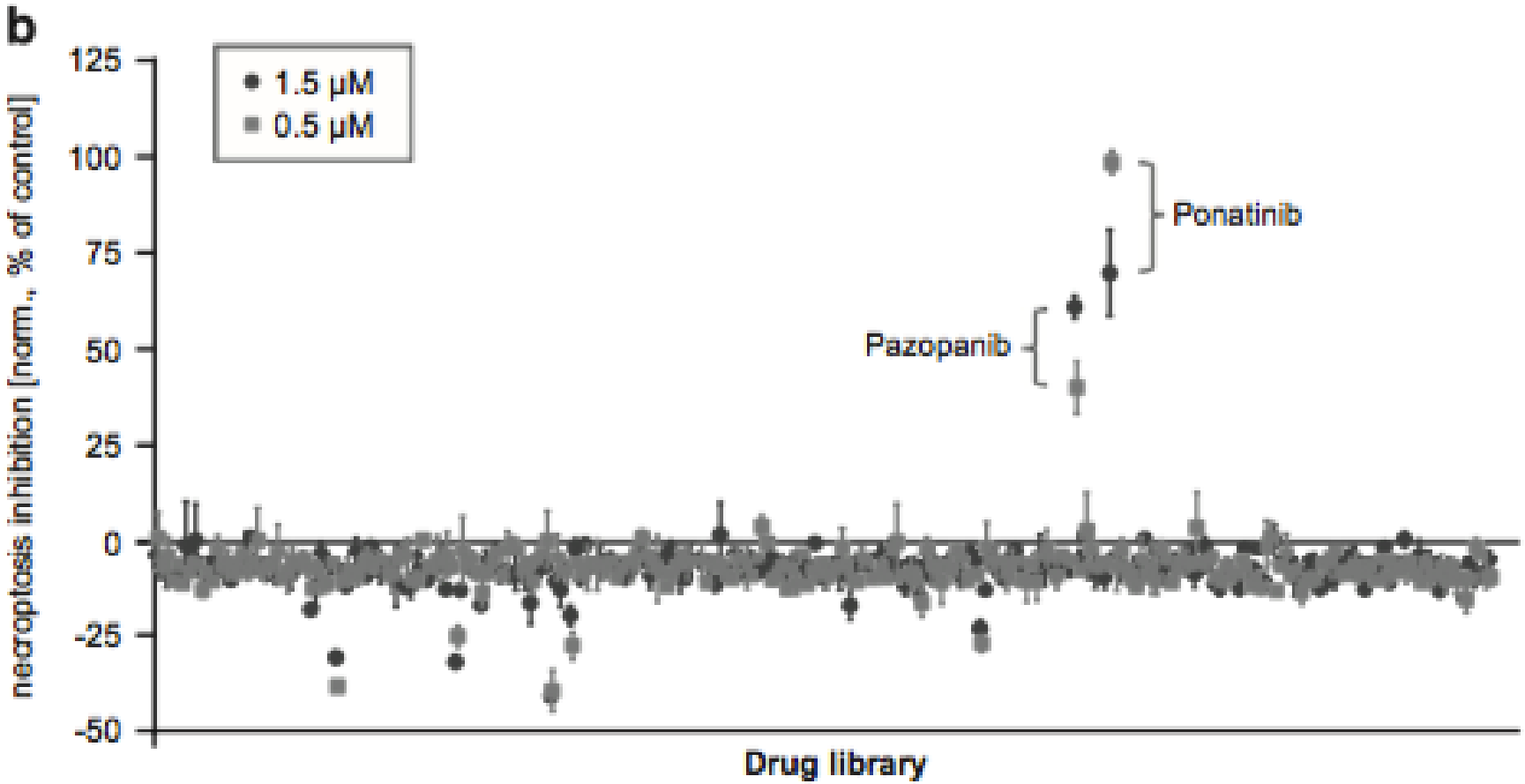
Sci Transl Med. 2010 February 3; 2(17): 17ra9. doi:10.1126/scitranslmed.3000349.

Identification of Therapeutic Targets for Quiescent, Chemotherapy-Resistant Human Leukemia Stem Cells

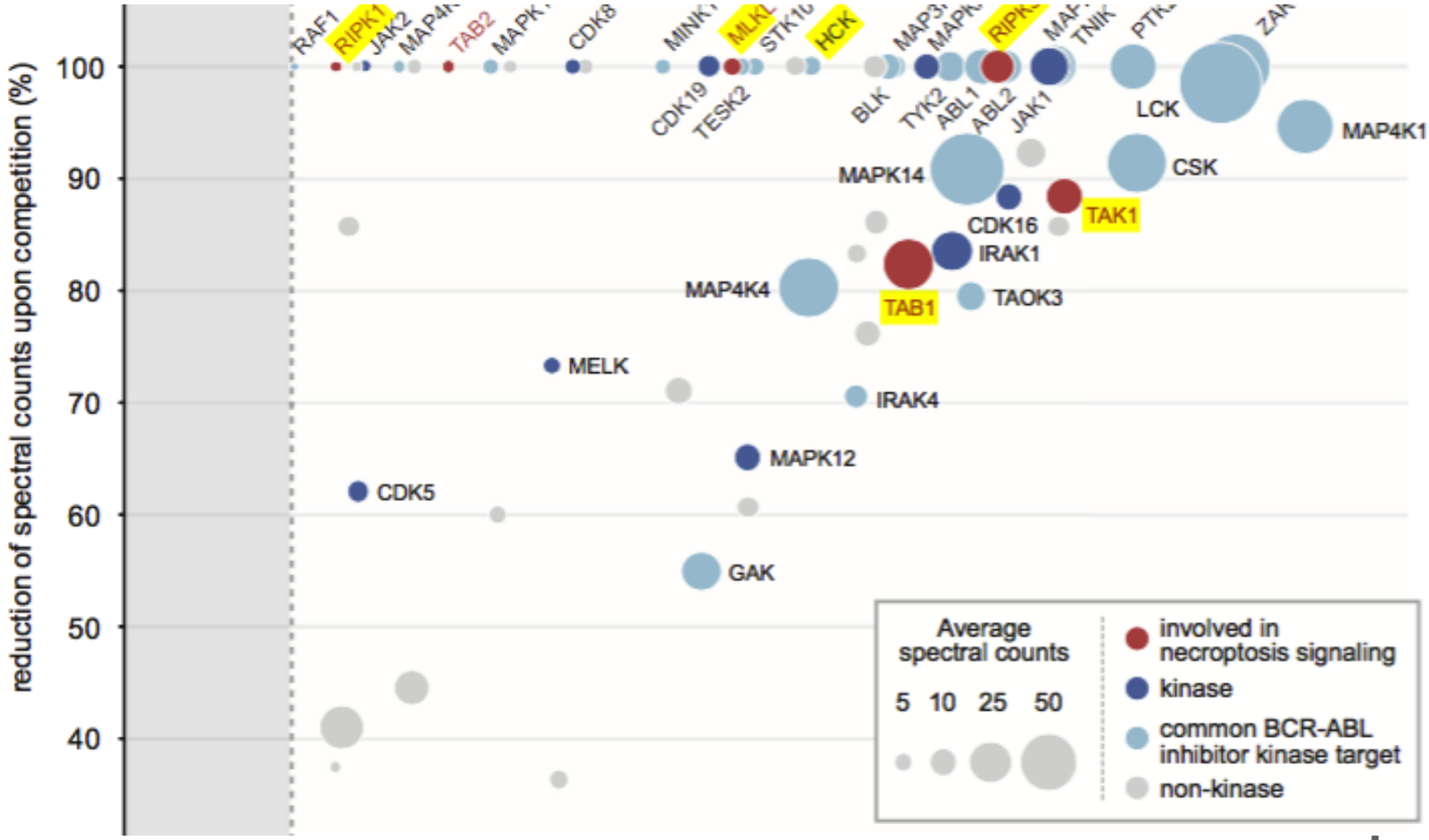
Yoriko Saito[1,*], **Hiroshi Kitamura**[2,*], **Atsushi Hijikata**[2], **Mariko Tomizawa-Murasawa**[1], **Satoshi Tanaka**[3], **Shinsuke Takagi**[1], **Naoyuki Uchida**[4], **Nahoko Suzuki**[1], **Akiko Sone**[1], **Yuho Najima**[1], **Hidetoshi Ozawa**[1], **Atsushi Wake**[4], **Shuichi Taniguchi**[4], **Leonard D. Shultz**[5], **Osamu Ohara**[2], and **Fumihiko Ishikawa**[1,†]

[1] Research Unit for Human Disease Models, RIKEN Research Center for Allergy and Immunology, Yokohama, 230-0045 Japan

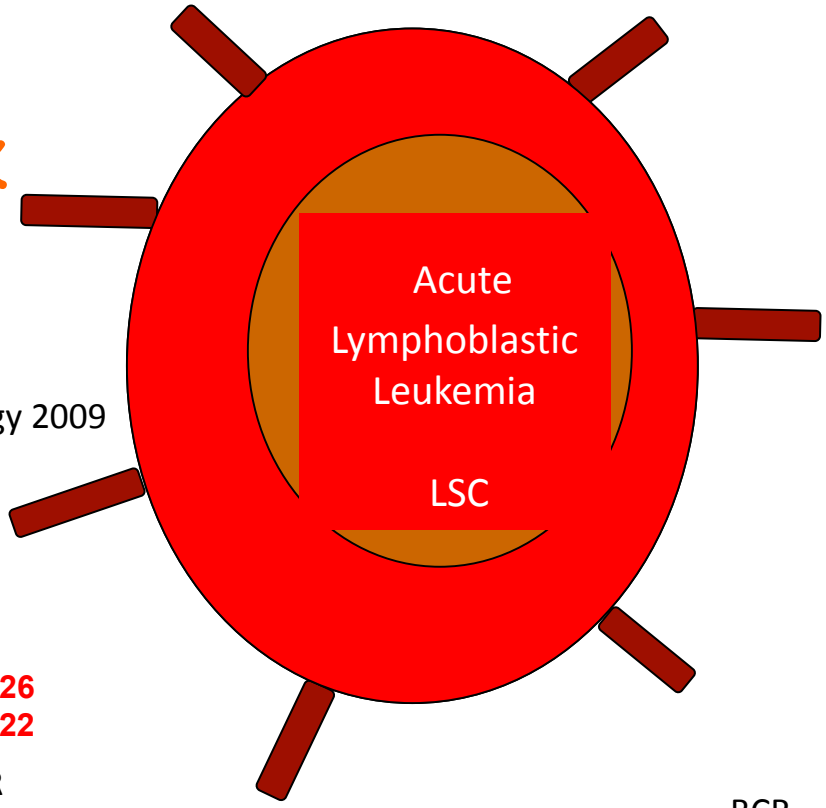
Ponatinib inhibits necroptosis



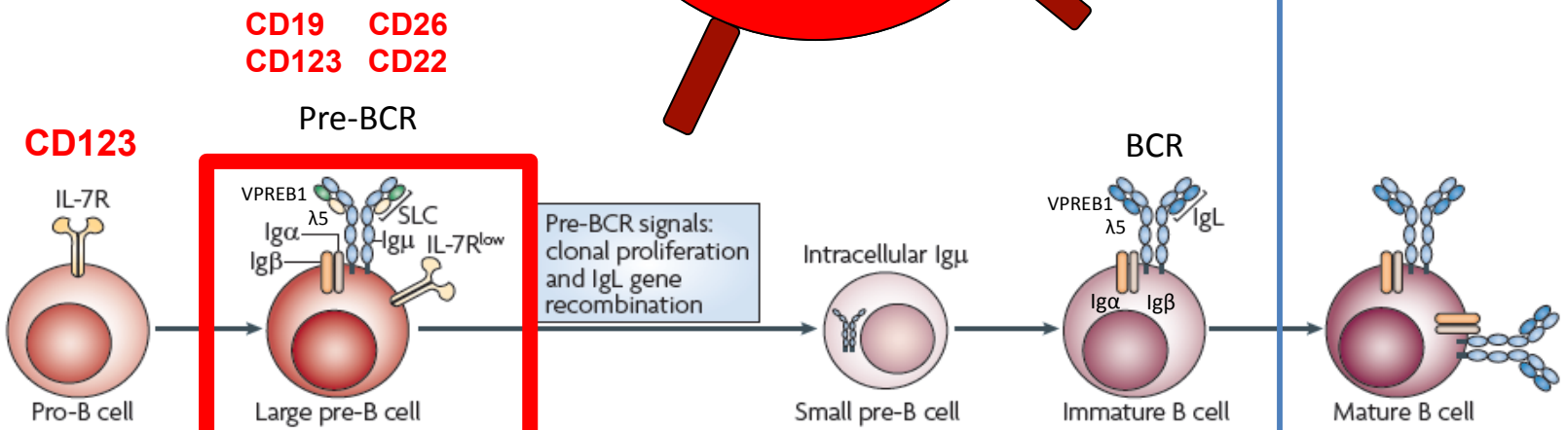
Ponatinib and necroptosis



New Targets for Acute Leukemia Stem Cell Therapy

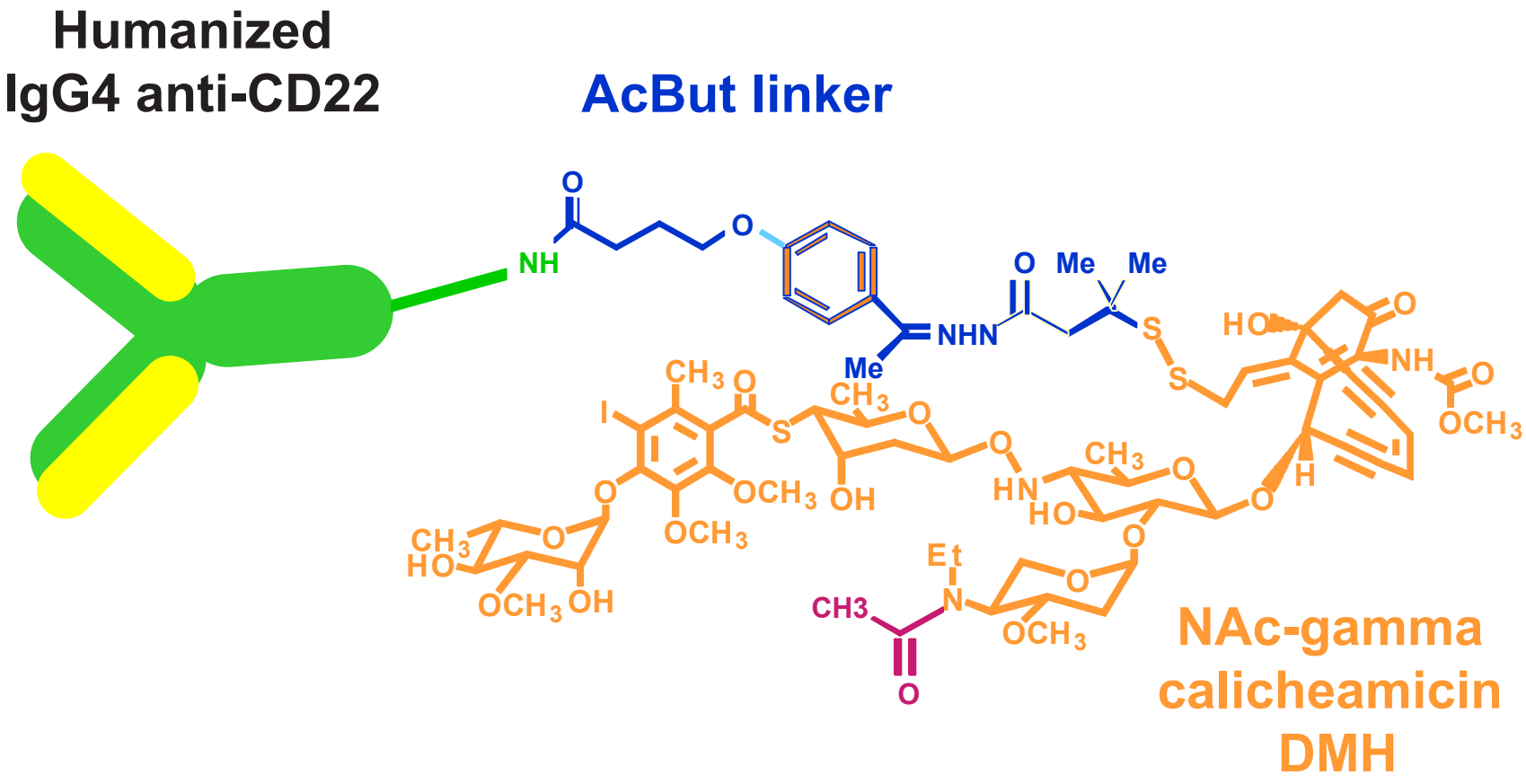


Herzog S. et al. Nature Reviews | Immunology 2009



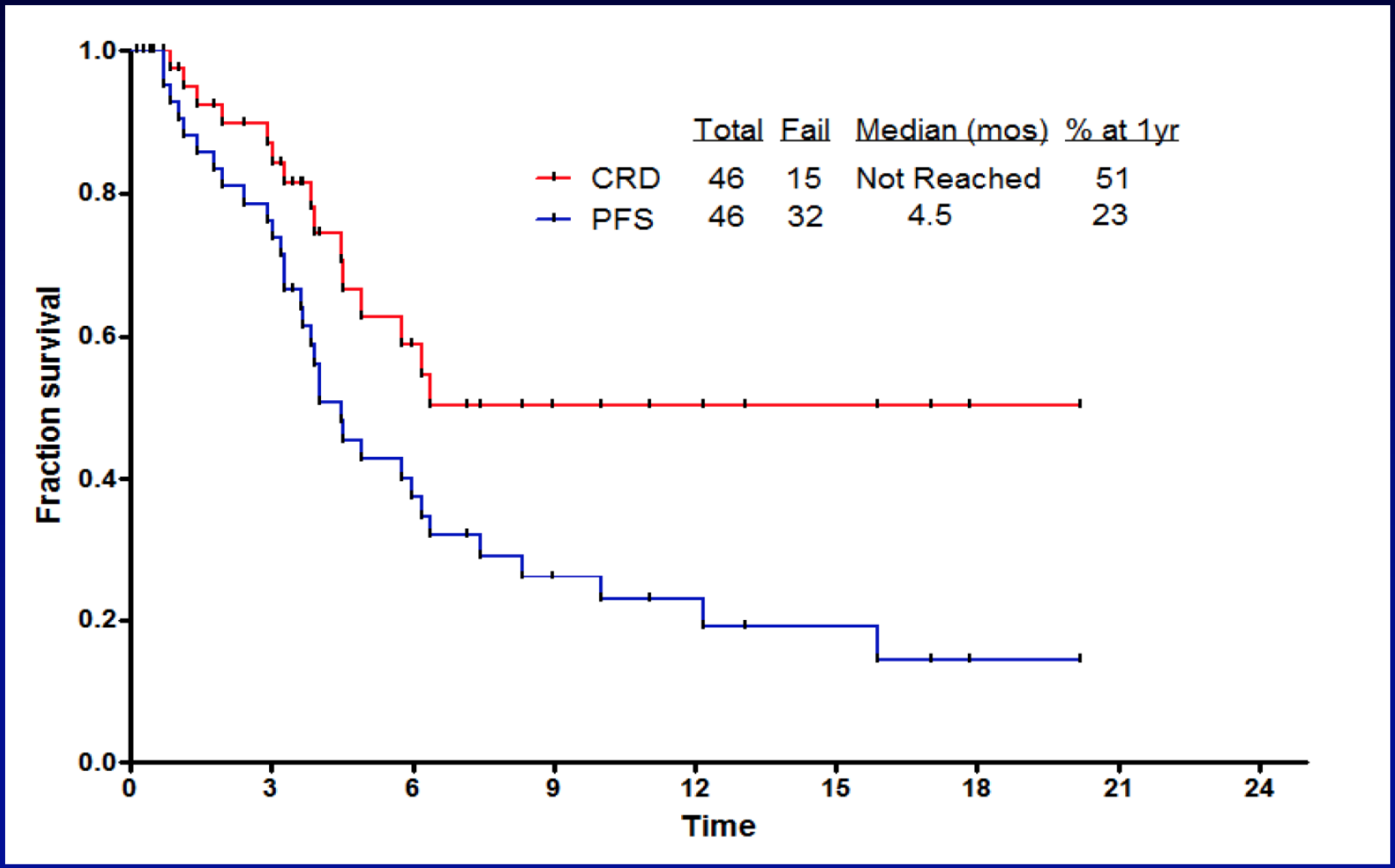
Gene locus	IgH	DJ	VDJ	VDJ	VDJ	VDJ
	IgL	Germline	Germline	VJ	VJ	VJ
Surface immunoglobulin		–	Igμ and SLC (pre-BCR)	–	Igμ (IgH) and Igκ and Igλ (IgL)	Igμ (IgH) and Igκ and Igλ (IgL)

Inotuzumab Ozogamicin (CMC-544)
CD22-targeted



Advani A, et al. *J Clin Oncol* 2010;28:2085–2093

Inotuzumab in ALL. Complete Remission Duration & Progression Free Survival



EFFICACY AND SAFETY OF INOTUZUMAB OZOGAMICIN (INO) VS STANDARD OF CARE (SOC) IN SALVAGE 1 OR 2 PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): ONGOING GLOBAL PHASE 3 STUDY

Daniel J. DeAngelo,[1] Matthias Stelljes,[2] Giovanni Martinelli,[3] Hagop M. Kantarjian,[4] Michaela Liedtke,[5] Wendy Stock,[6] Nicola Goekbuget,[7] Kongming Wang,[8] Luisa Pacagnella,[9] Barbara Sleight,[9] Erik Vandendries,[8] Anjali S. Advani[10]

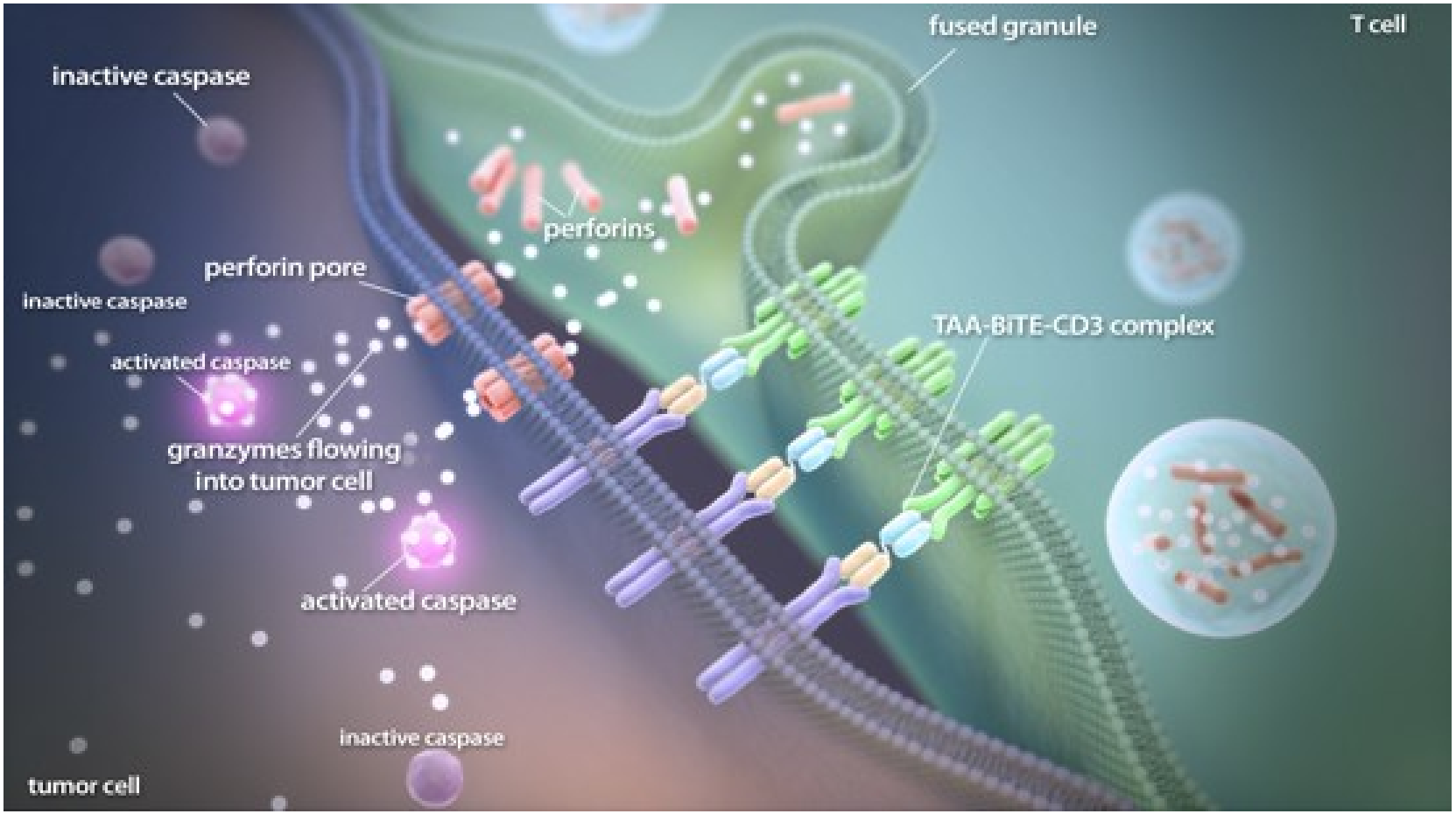
[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Universitätsklinikum Münster, Münster, Germany; [3]Institute Seragnoli, University of Bologna, Bologna, Italy; [4]MD Anderson Cancer Center, Houston, TX, USA; [5]Stanford Cancer Institute, Stanford, CA, USA; [6]University of Chicago,

EHA 2015 InO Study 1022 data LBA (Subm. Deadline: April 27)
April 22, 2015 Draft 1
INO15189.2005

% (95% CI)	InO (n=109)	SOC (n=109)	1-sided *P*-Value
CR/CRi[a]	80.7 (72–88)	29.4 (21–39)	<0.0001
S1	87.7	31.3	<0.0001
S2	66.7	37.9	0.0011
Median DOR, mo	4.6 (3.9–5.4)	3.1 (1.4–4.9)	0.0169
MRD-neg in pts with CR/CRi	78.4 (68–87)	28.1 (14–47)	<0.0001

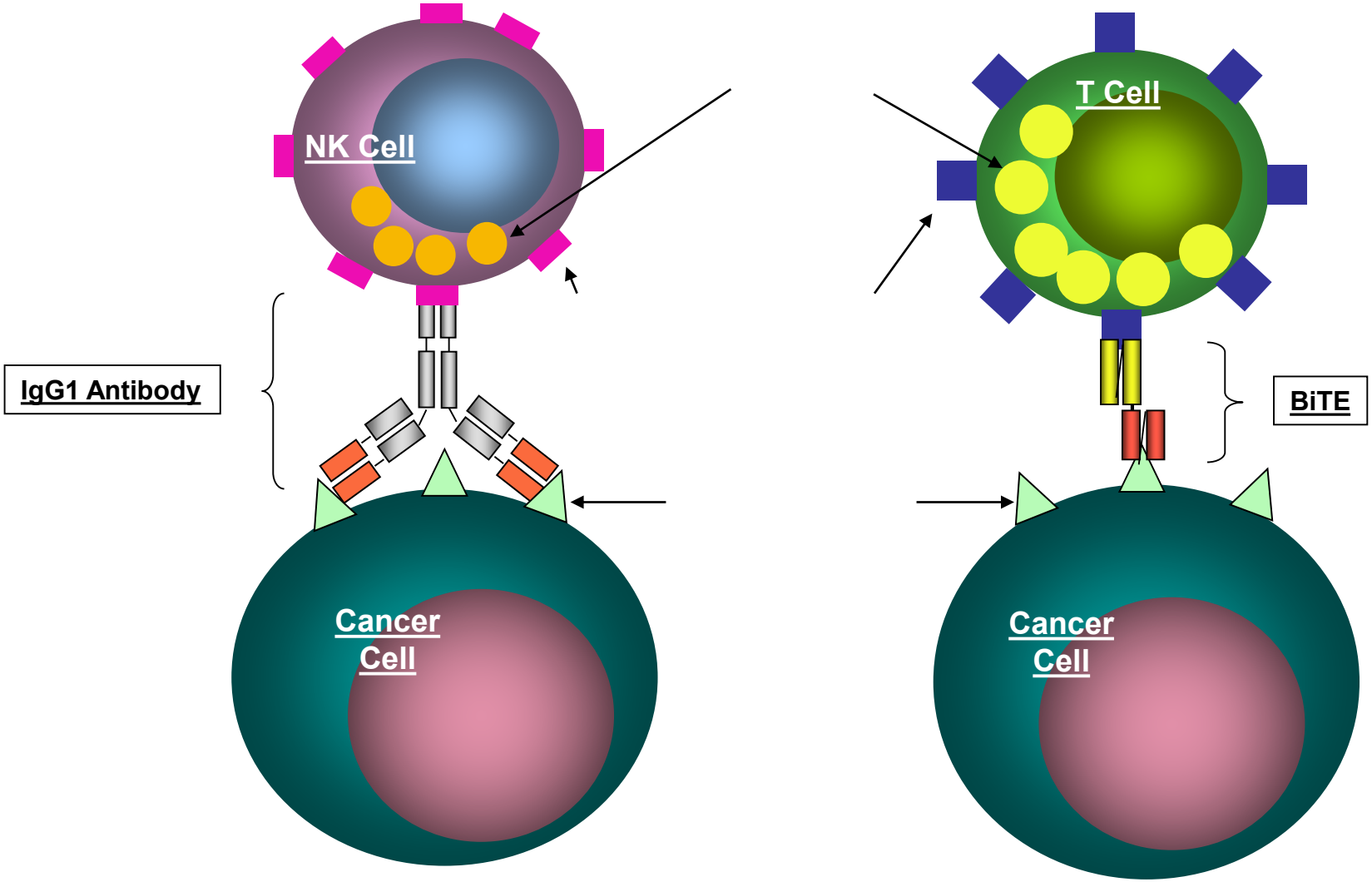
[a]Modified ITT analysis excluding 13 untreated SOC pts; assessed per independent endpoint adjudication committee

BiTE® (Bispecific T Cell Engager) Antibodies



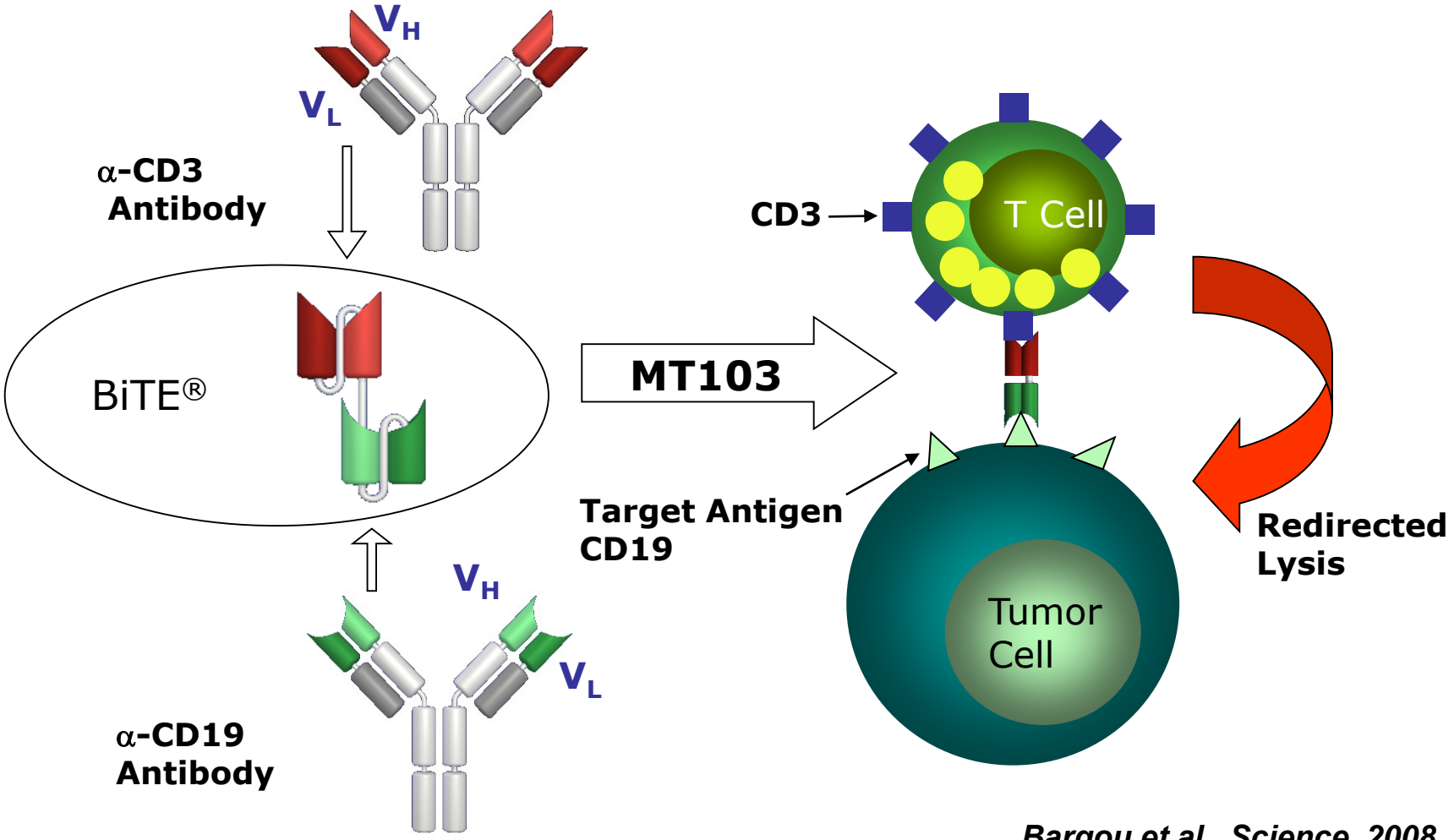
1. Baeuerle PA, et al. *Bispecific Antibodies.* 2011:273-287. 2. Baeuerle PA, et al. *Cancer Vaccines. From Research to Clinical Practice.* 2011:250-262. 3. Hoffman P, et al. *Int J Cancer.* 2005;115:98-104. 4. Kurschus FC, et al. *Immunol Rev.* 2010;235:159-171.

BiTE® Mediate T Cell Recognition of Surface Antigens



1. Baeuerle PA, et al. *Cancer Res* 2009;69:4941-4944. 2. Baeuerle PA, et al. *Bispecific Antibodies.* 2011:273-287. 3. Adams GP, et al. *Nat Biotechnol.* 2005;23:1147-1157.

Blinatumomab (MT103), a Bispecific T Cell Engaging Single-chain BiTE® Antibody



Bargou et al., Science, 2008

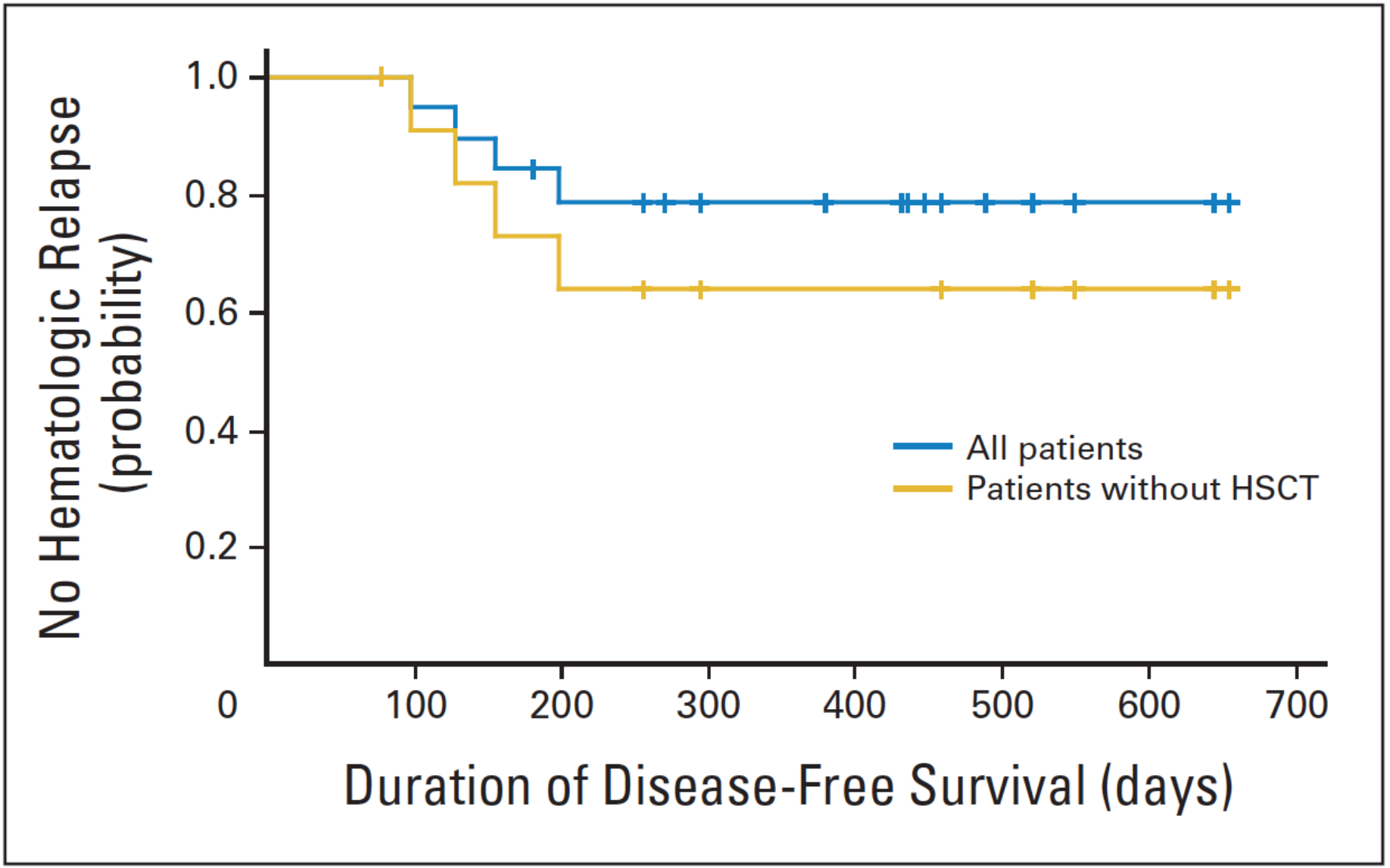
Löffler et al., Blood, 2000

Mack et al., PNAS, 1995

VOLUME 29 · NUMBER 18 · JUNE 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT



Complete Molecular and Hematologic Response in Adult Patients With Relapsed/Refractory (R/R) Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia (ALL) Following Treatment With Blinatumomab: Results From a Phase 2 Single-Arm, Multicenter Study (ALCANTARA)

Giovanni Martinelli,[1] Hervé Dombret,[2] Patrice Chevallier,[3] Oliver Ottmann,[4] Nicola Gökbuget,[5] Max S. Topp,[6] Adele K. Fielding,[7] Lulu Ren Sterling,[8] Jonathan Benjamin,[9] Anthony Stein[10]

[1]Institute of Hematology and Medical Oncology "L. e A. Seragnoli", Bologna, Italy; [2]University Paris Diderot, Hôpital Saint-Louis, Paris, France; [3]Hematology, CHU Nantes, Nantes, France; [4]Department of Haematology, Cardiff University, Cardiff, UK; [5]Department of Medicine II, Goethe University, Frankfurt, Germany; [6]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany; [7]Department of Haematology, UCL, London, UK; [8]Amgen Inc., San Francisco, CA, USA; [9]Amgen Inc., Thousand Oaks, CA, USA; [10]Gehr Family Center for Leukemia Research, City of Hope, Duarte, CA, USA

Outcomes Are Poor for Adults with Philadelphia Chromosome-Positive (Ph+) R/R ALL

- Ph+ is the most common single cytogenetic abnormality in B-precursor ALL
  - ~25% of adult ALL is Ph+ and frequency of Ph+ disease increases with age
- Ph+ ALL historically has a poor prognosis
- TKIs have improved outcomes
  - Addition to firstline therapy has increased response rates and likelihood of achieving alloHSCT[1]
  - Sequential use of chemotherapy ± alternative TKIs is the dominant approach to treating Ph+ R/R ALL when alloHSCT is not an option
  - Emergence of single and compound point mutations in *BCR-ABL* is responsible for a significant proportion of TKI resistance[2]

TKI monotherapy	Nilotinib[3] (N = 41)	Dasatinib[4] (N = 36)	Ponatinib[5] (N = 32)
Complete hematologic response	45%	33%	41% (MHR)
Median overall survival (OS) OS at 1 year	5.2 months 27%	3.3 months* NA	8.0 months 40%

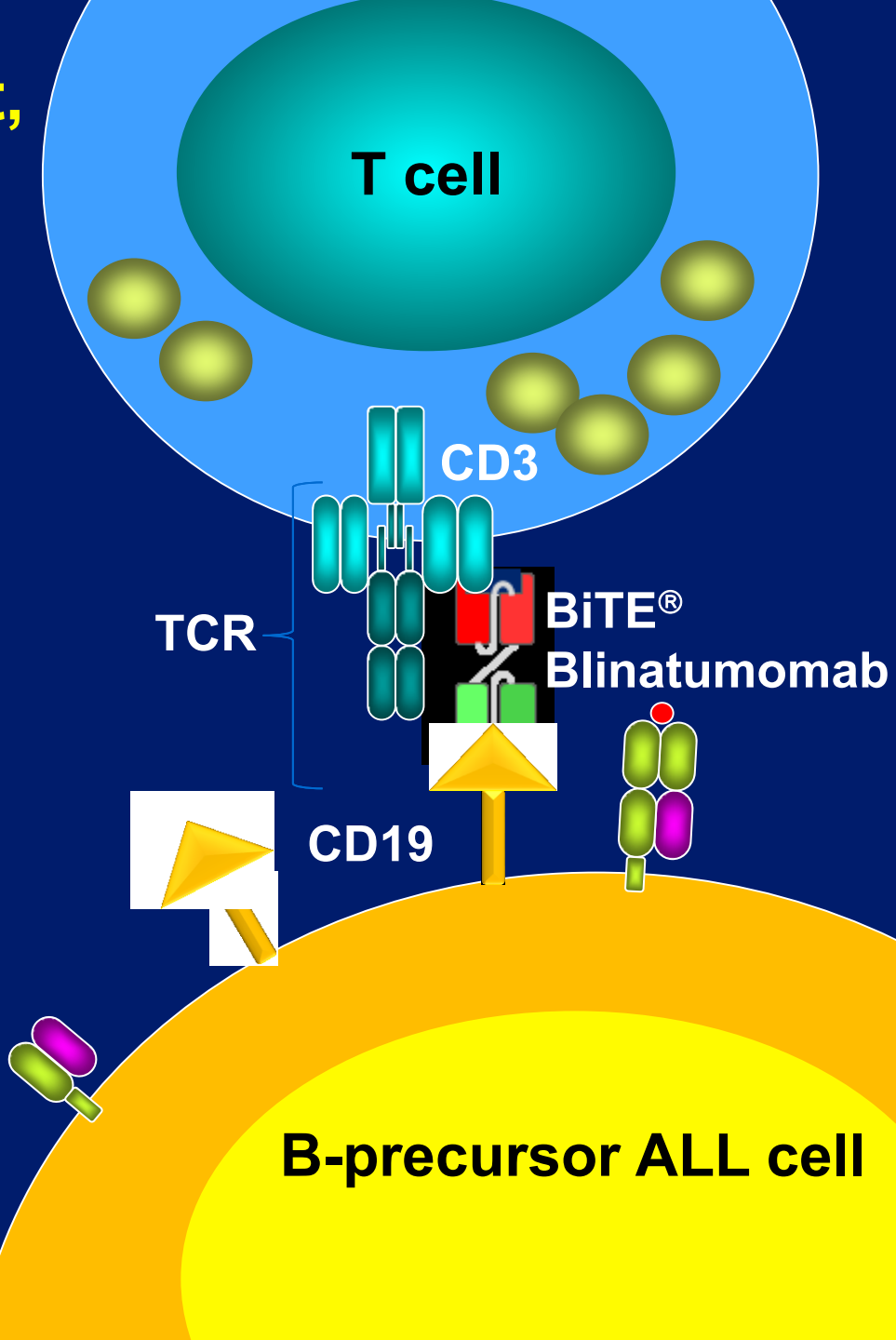
* Progression-free survival

alloHSCT, allogeneic hematopoietic stem cell transplantation; MHR, major hematologic response; NA, not available; TKI, tyrosine kinase inhibitor

1. Fielding AK, et al. *Blood* 2014;123(6):843-850.
2. Zabriskie MS, et al. *Cancer Cell* 2014;26:428-442.
3. Ottmann OG, et al. *Leukemia* 2013;27:1411-1413.
4. Ottmann OG, et al. *Blood* 2007;110(7):2309-2315.
5. Cortes JE, et al. *N Eng J Med* 2013;369(19):1783-1796.

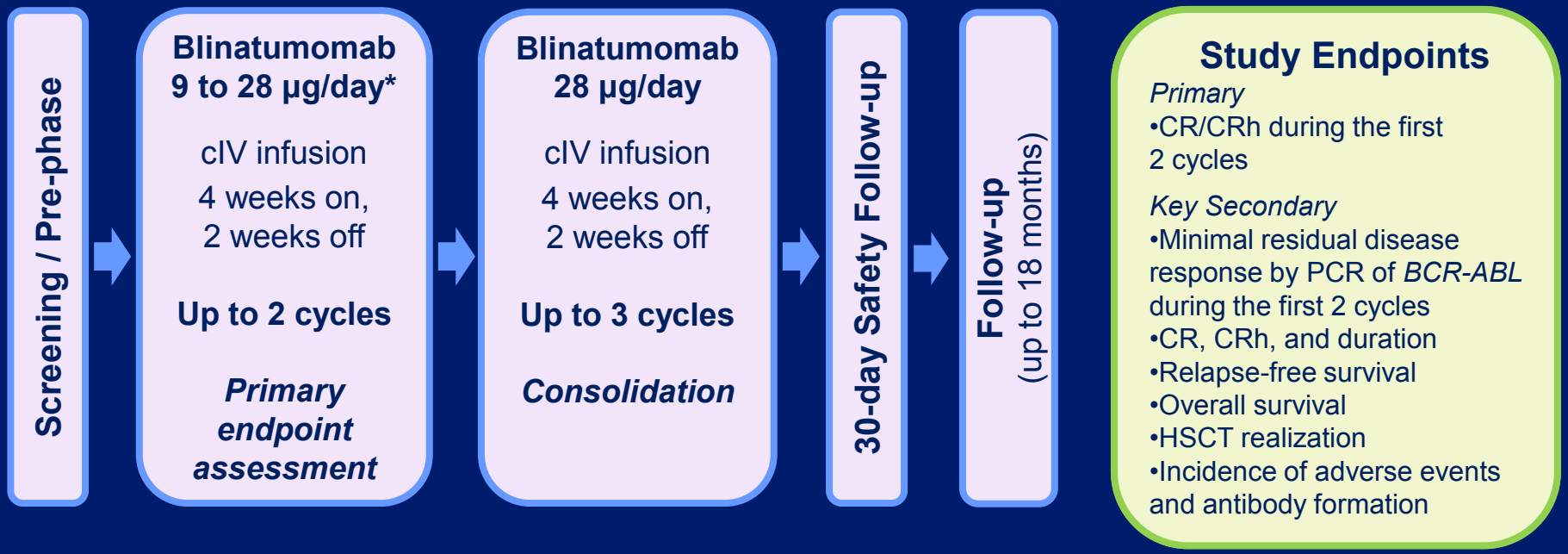
BiTE® Antibody Construct, Blinatumomab

- Blinatumomab is a bispecific T-cell engaging antibody (BiTE®) construct
- Blinatumomab redirects T cells to lyse CD19-positive malignant and nonmalignant B cells[1]
- CD19 is expressed in virtually all tested B-lineage ALL cells and throughout B-cell development[2,3]
- 43% CR/CRh as monotherapy in Ph-negative R/R ALL[4]



1. Bargou R, et al. *Science*. 2008;321:974–977.
2. Raponi S, et al. *Leuk Lymphoma*. 2011;52:1098–1107.
3. Piccaluga P, et al. *Leuk Lymphoma*. 2011;52:325–327.
4. Topp MS, et al. *Lancet Oncol*. 2015;16:57-66.

Open-Label, Single-Arm, Multicenter Phase 2 Study in Ph+ R/R ALL



* Only cycle 1, days 1 to 7: 9 µg/day

CR, complete remission; CRh, complete remission with partial hematological recovery of peripheral blood counts (platelets > 50,000/µL and ANC > 500/µL); cIV, continuous intravenous; HSCT, hematopoietic stem cell transplantation

Eligibility

Key Inclusion Criteria

- Adults (≥ 18 years) with Ph+ B-precursor ALL
  - Relapsed or refractory to at least one 2+ generation TKI or
  - Intolerant to 2+ generation TKI and intolerant/refractory to imatinib
- > 5% bone marrow blasts
- ECOG performance status ≤ 2

Key Exclusion Criteria

- Allogeneic HSCT within 12 weeks prior to start of blinatumomab
- Active acute or active chronic (grade 2−4) GvHD, or systemic treatment for GvHD within 2 weeks before treatment start
- History or presence of clinically relevant CNS pathology (epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis)

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; GvHD, graft-versus-host disease

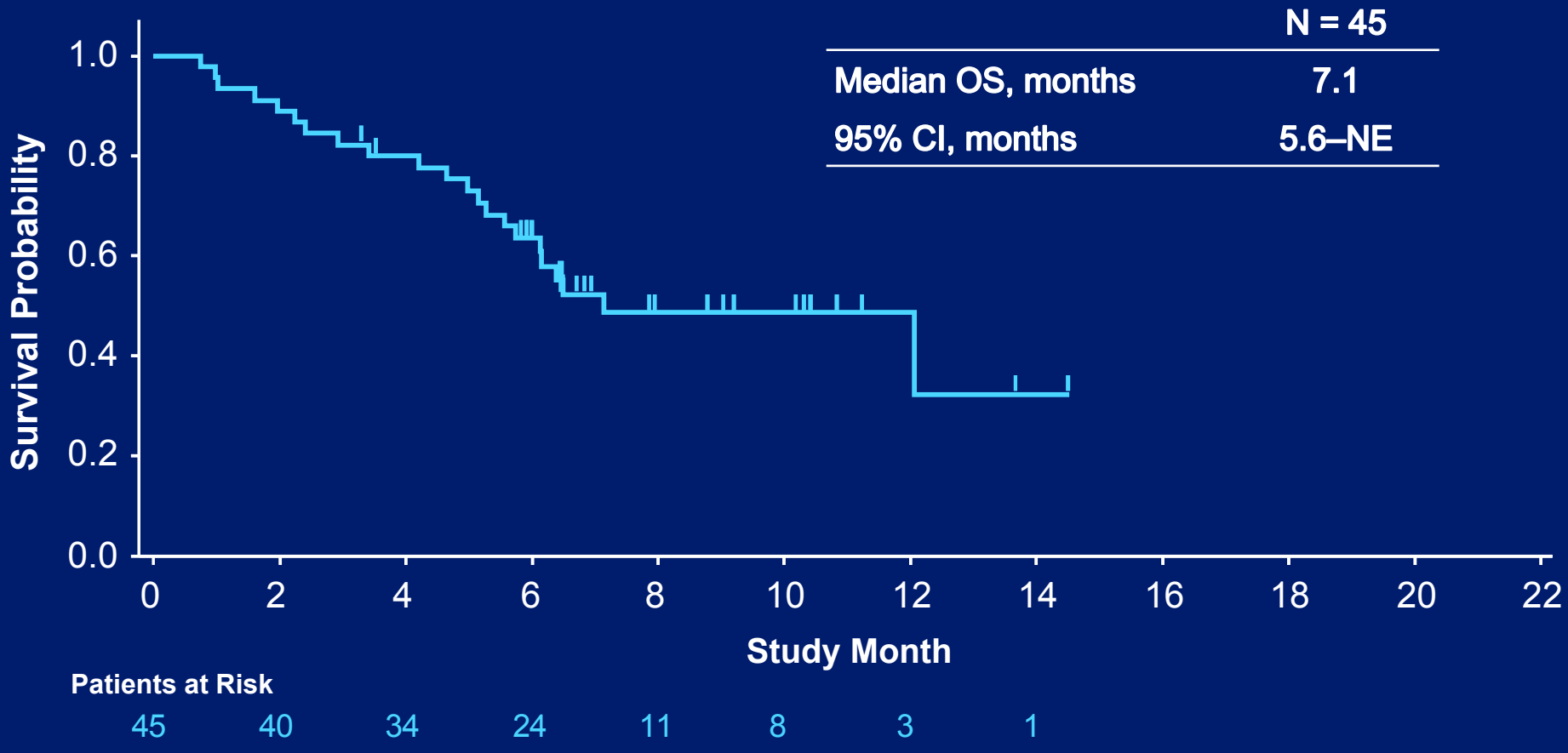
Response During First Two Cycles

	n / N		95% CI
Primary endpoint			
CR/CRh	16 / 45	**36%**	22–51
T315I mutation	4 / 10	40%	
≥ 2 prior 2+ generation TKI	11 / 27	41%	
Prior ponatinib treatment	8 / 23	35%	
Age 18 to < 55 years	8 / 22	36%	17–59
Age ≥ 55 years	8 / 23	35%	16–57
Secondary endpoints			
Best response			
CR	14 / 45	31%	18–47
CRh	2 / 45	4%	1–15
CRi (not qualifying for CRh)	2 / 45	4%	1–15
Complete MRD response*	14 / 16	**88%**	62–98
HSCT after blinatumomab-induced remission	4 / 16	**25%**	
100-day post-transplant mortality rate	1 / 4	25%	4–87

* Among CR/CRh responders only; includes all four CR/CRh patients with the T315I mutation.
Complete MRD response = no detectable PCR amplification of Ig or TCR genes in central lab with a sensitivity of 10^{-5}

CR, complete remission; CRh, complete remission with partial hematological recovery of peripheral blood counts; CRi, complete response incomplete; MRD, minimal residual disease

Overall Survival



NE, not estimable

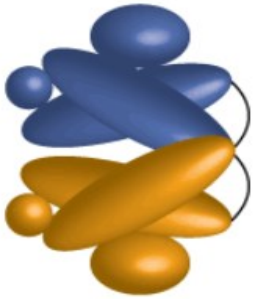
Median follow-up: 8.8 months

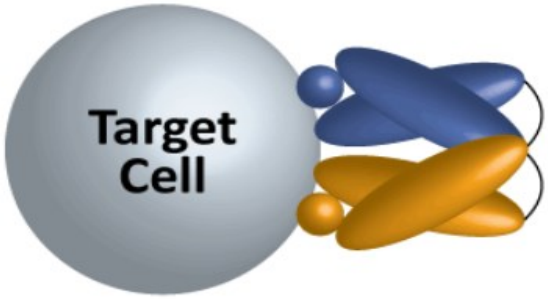
Conclusions

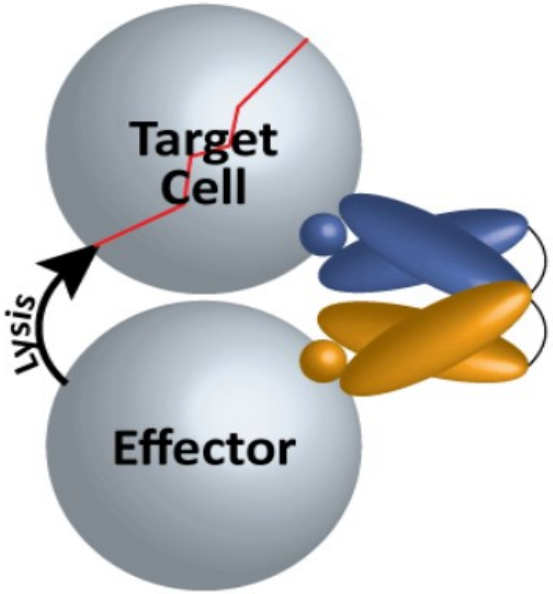
- The present study showed single-agent antileukemia activity of blinatumomab in patients with Ph+ R/R ALL who had failed 2+ generation TKI therapy, with a CR/CRh rate of 36% (95% CI, 22–51)
- Hematologic and molecular responses were independent of mutational status, including presence of the T315I mutation
  - Equivalent CR/CRh and RFS observed in patients < 55 and ≥ 55 years of age
- Among responders, 88% (14/16) achieved complete MRD response
  - Of these, 100% (6/6) with ABL-kinase domain mutations had complete MRD response
- Median OS of 7.1 months was observed in this poor prognostic Ph+ patient population
- Adverse events were consistent with previous blinatumomab treatment experience in the setting of Ph-negative R/R ALL

DART™ Platform

Anti CD123







Ligand Targeting
(i.e., cytokine blockade)

Signaling Modulation
(i.e., suppression or blockade of an activating signal)

Redirected Effector Cell Killing

STANDARD COVER PAGE

Document title	***CLINICAL STUDY PROTOCOL***
Study title	A phase I, dose escalation study of S 80880, a CD123 x CD3 Dual Affinity Re-Targeting (DART) bi-specific antibody-based molecule given as monotherapy in continuous intravenous infusion, in patients with acute leukaemias and other haematological malignancies expressing CD123
Test drug code	S 80880
Indication	AML, MDS, B-ALL, BAL, BPDCN
Development phase	Phase I
Protocol code	***CL1-80880-001***
EudraCT Number	***To be completed if applicable (otherwise "Not applicable")***
Universal Trial Number	***To be completed if applicable(otherwise "Not applicable")***
Sponsor	I.R.I.S.
Date of the document	24/01/2014

Acknowledgments

Supported by: FP7, European LeukemiaNet, AIL, AIRC, FIRB 2006, Fondazione del Monte di Bologna e Ravenna

Acknowledgments

Hematology/Oncology University of Bologna:

Manuela Mancini
Caterina De Benedittis
Luca Zazzeroni
Cristina Papayannidis
Giovanni Martinelli

Personal Genomics & University of Verona:

Massimo Delledonne
Alberto Ferrarini
Elisa Zago
Marianna Garonzi
Anna Scandola

Department of Hematology and Hemostaseology, Medical University of Vienna:

Peter Valent
Sabine Cerny-Reiterer

U.O.Corelab- Hematology Cesena:

Michela Rondoni

SEVENTH FRAMEWORK PROGRAMME

NEXT GENERATION SEQUENCING for Targeted Personalized Therapy of Leukemia