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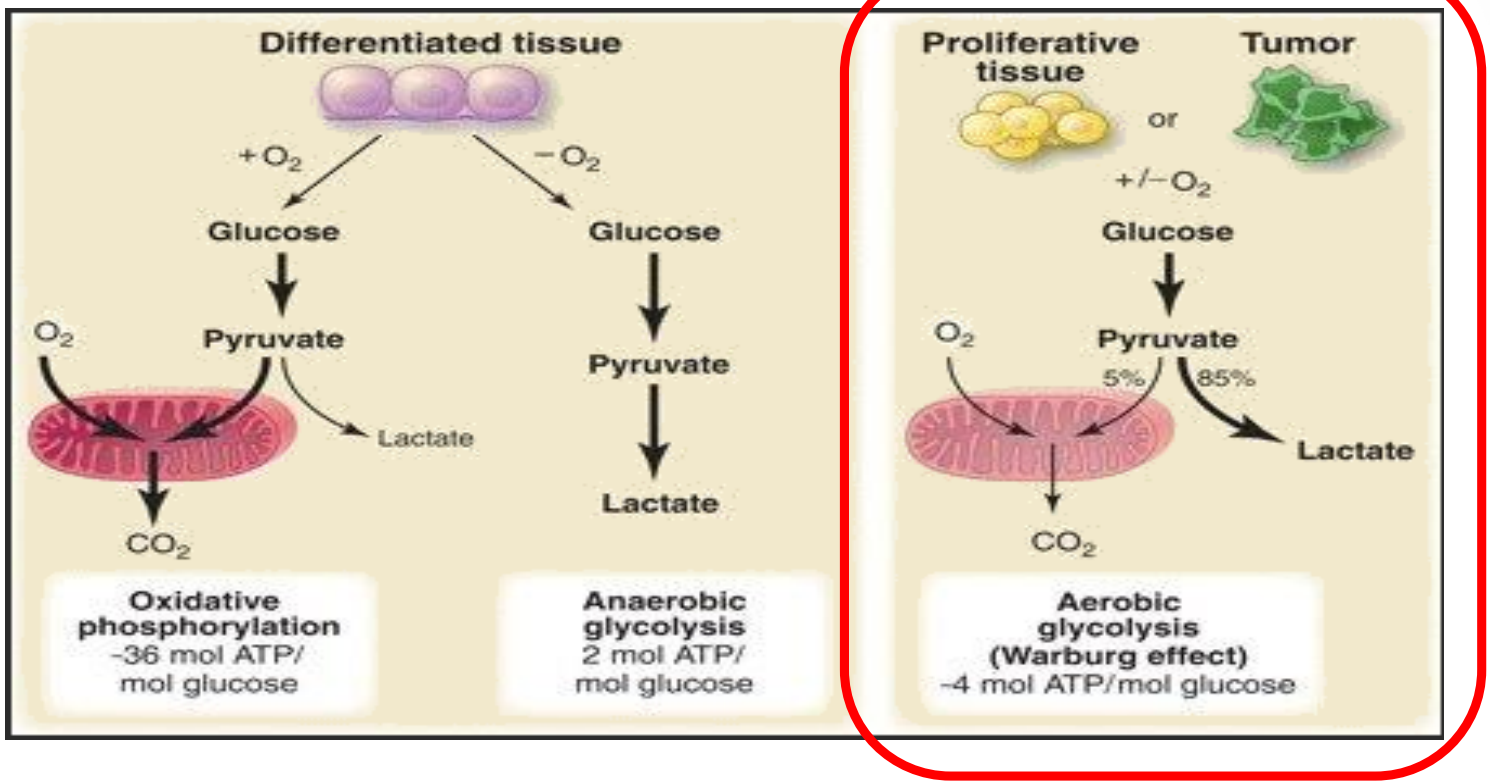
ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

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

Metabolism: a new cancer selectively vulnerability?

Prof. Giovanni Martinelli, MD, PhD
Scientific Director IRCCS della Romagna

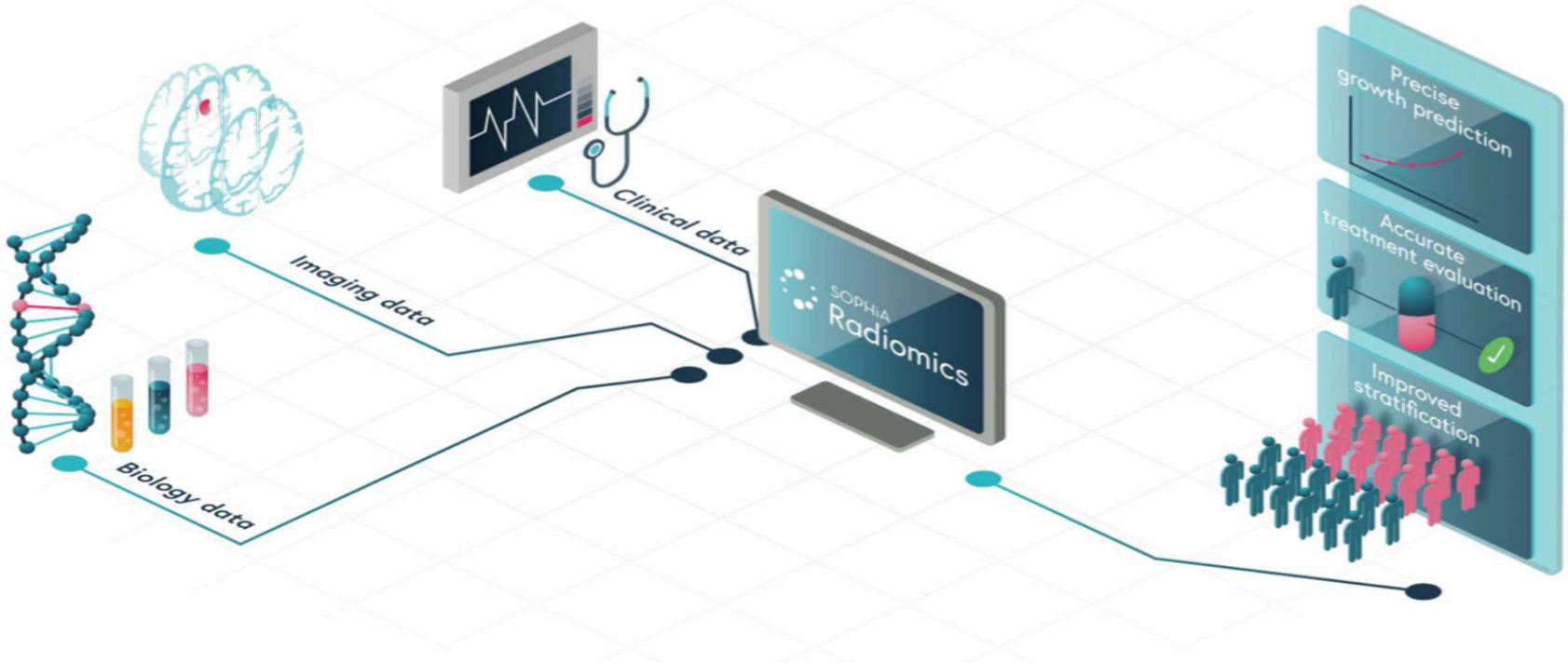
Aberrant metabolism of cancer cells



The **Warburg effect** is the observation that most cancer cells predominantly produce energy by a **high rate of glycolysis** followed by lactic acid fermentation in the cytosol, rather than by a comparatively low rate of glycolysis followed by oxidation of pyruvate in mitochondria as in most normal cells

Esscientificconsulting

Il Progetto **IRST-IRCCS** Radiomics



The personalized dru[illegible]ble genome in myeloid

AG221
ENASIDENIB

AG120
IVOSIDENIB

ABL1		**HRAS**	**MYD88**	SF3B1
ASXL1	[illegible]	**IDH1**	**NOTCH1**	SMC1A
ATRX	CUX1	**IDH2**	NPM1	SMC3
BCOR	**DNMT3A**	**IKZF1**	**NRAS**	SRFS2
BCORL1	ETV6/TEL	**JAK2**	**PDGFRA**	STAG2
BRAF	EZH2	JAK3	PHF6	TET2
CALR	FBXW7	KDM6A	PTEN	**TP53**
CBL	**FLT3**	**KIT**	PTPN11	U2AF1
CBLB	GATA1	**KRAS**	RAD21	WT1
CBLC	GATA2	MLL	RUNX1	ZRSR2
CDKN2A	GNAS	MPL	SETBP1	

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Mutant IDH1 Inhibitor Ivosidenib (IVO; AG-120) in Combination With Azacitidine (AZA) for Newly Diagnosed Acute Myeloid Leukemia (ND AML)

Courtney D. DiNardo[1], Anthony S. Stein[2], Eytan M. Stein[3], Amir T. Fathi[4], Olga Frankfurt[5], Andre C. Schuh[6], Hartmut Döhner[7], Giovanni Martinelli[8], Prapti A. Patel[9], Emmanuel Raffoux[10], Peter Tan[11], Amer Zeidan[12], Stéphane de Botton[13], Hagop M. Kantarjian[1], Richard M. Stone[14], Du Lam[15], Xiwei Wang[15], Jing Gong[15], Stephanie M. Kapsalis[16], Denice Hickman[16], Vickie Zhang[16], Thomas Winkler[16], Bin Wu[16], Paresh Vyas[17]

Figure 1. Study design for phase 1b dose-finding and expansion ivosidenib + azacitidine arm (N=23; enrollment complete)

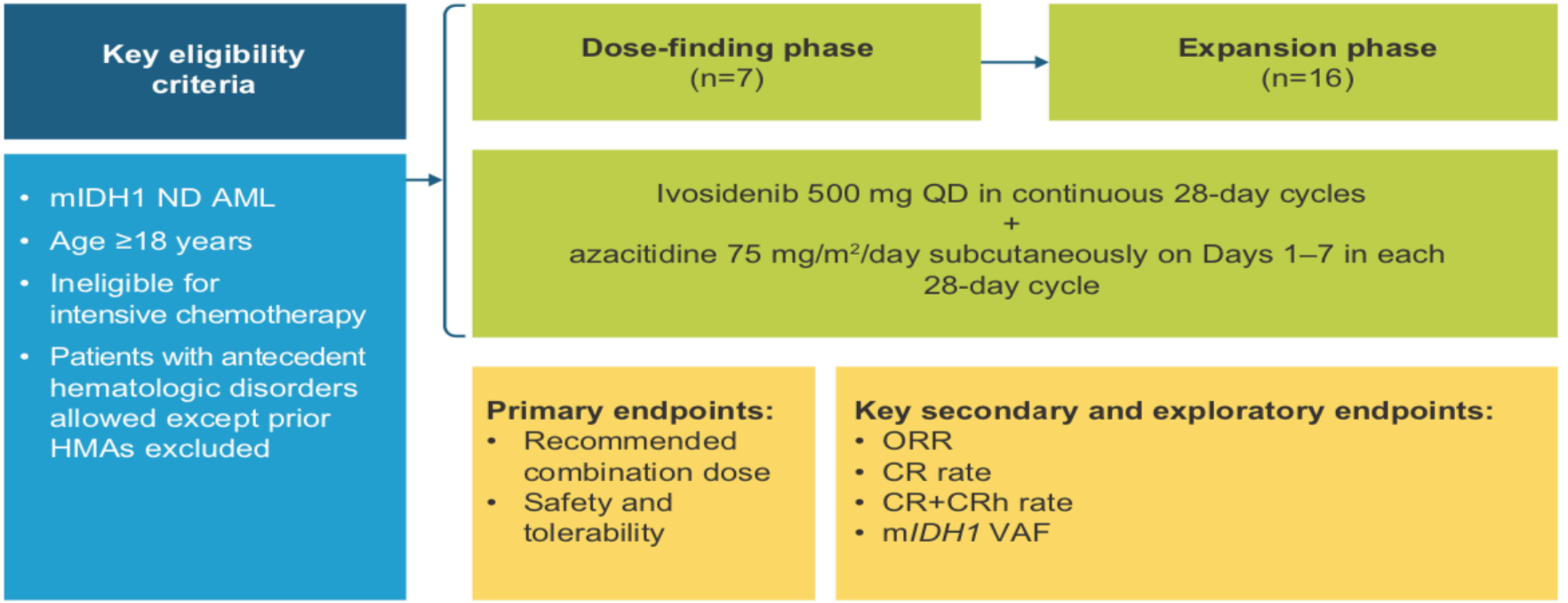
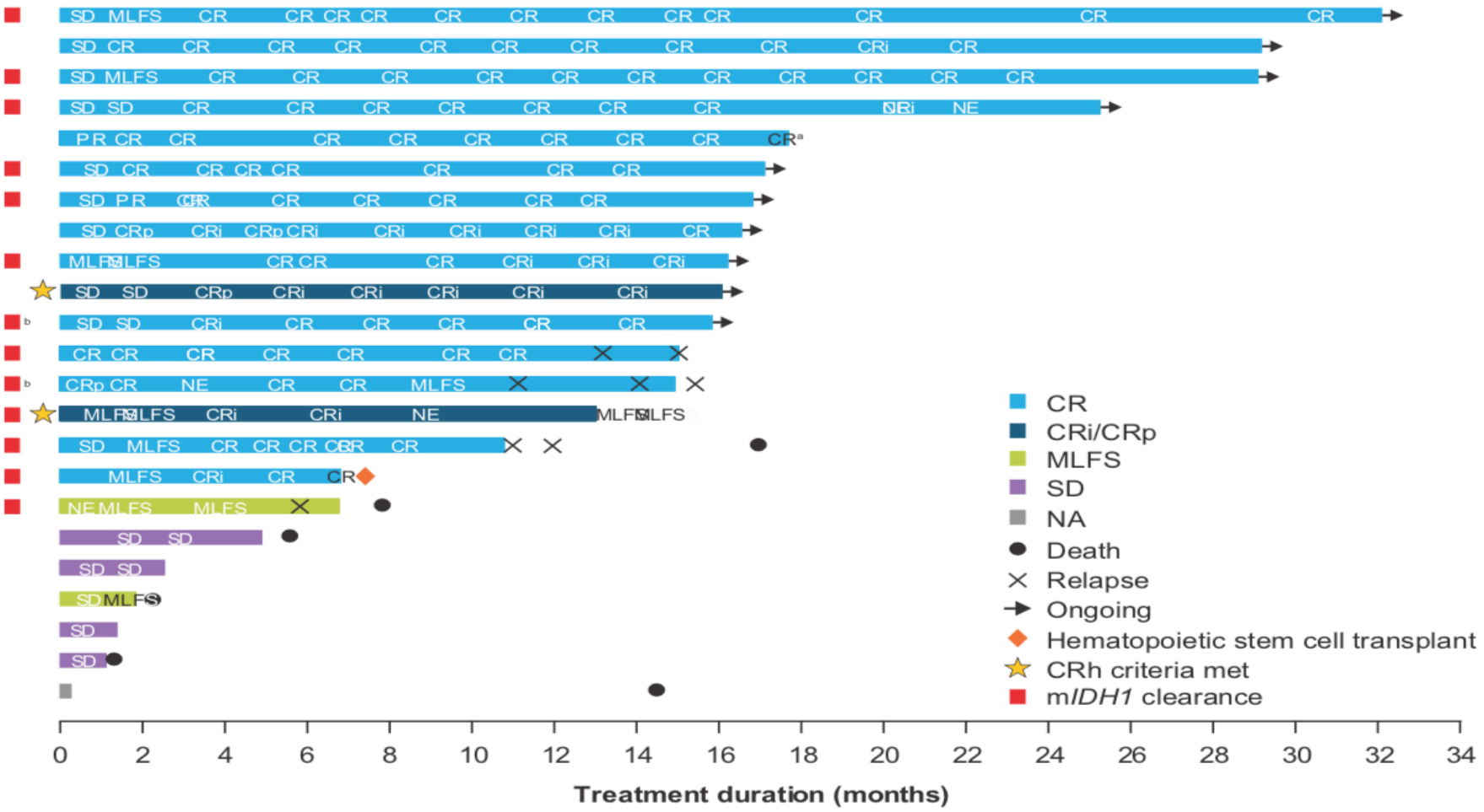


Figure 3. Treatment duration and best overall response



[a]Patient continued on commercially available ivosidenib
[b]Patient had m*IDH1* clearance in PBMCs only (BMMCs not available); all other patients had m*IDH1* clearance in both BMMCs and PBMCs
NA = not assessed; NE = not evaluable

The personalized dru[illegible]ble genome in myeloid

VENETOCLAX

VENETOCLAX

ABL1	[illegible]	***HRAS***	***MYD88***	*SF3B1*
ASXL1	[illegible]	***IDH1***	***NOTCH1***	*SMC1A*
ATRX	*CUX1*	***IDH2***	*NPM1*	*SMC3*
BCOR	***DNMT3A***	***IKZF1***	***NRAS***	*SRFS2*
BCORL1	*ETV6/TEL*	***JAK2***	***PDGFRA***	*STAG2*
BRAF	*EZH2*	*JAK3*	*PHF6*	*TET2*
CALR	*FBXW7*	*KDM6A*	*PTEN*	***TP53***
CBL	***FLT3***	***KIT***	*PTPN11*	*U2AF1*
CBLB	*GATA1*	***KRAS***	*RAD21*	*WT1*
CBLC	*GATA2*	*MLL*	*RUNX1*	*ZRSR2*
CDKN2A	*GNAS*	*MPL*	*SETBP1*	

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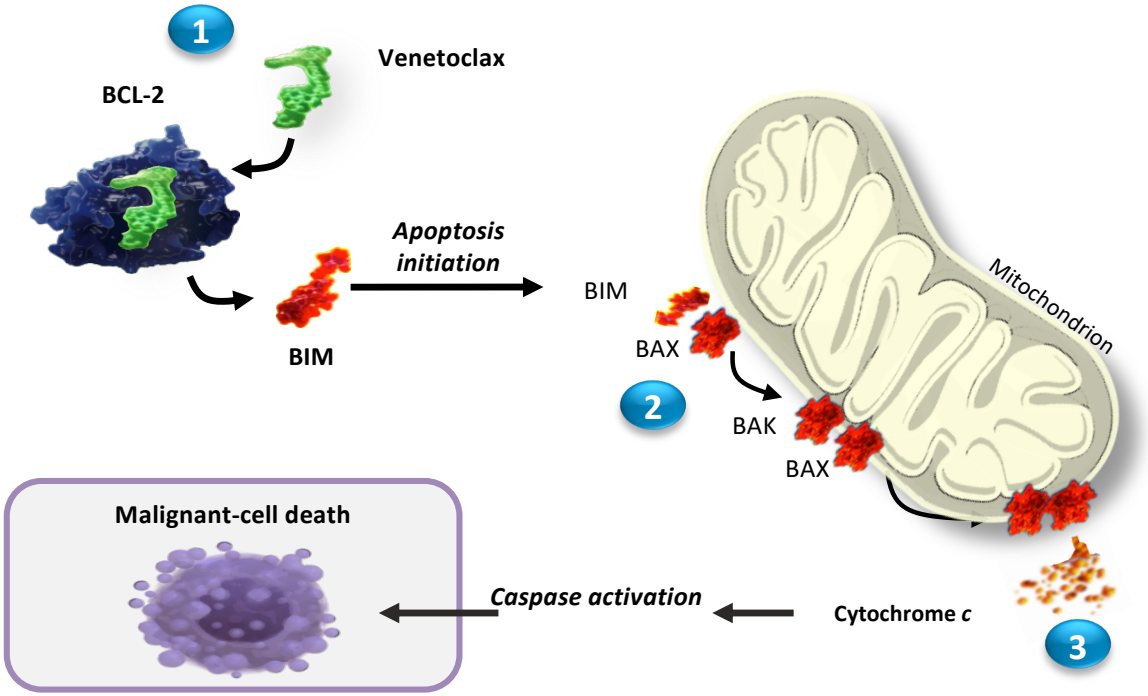
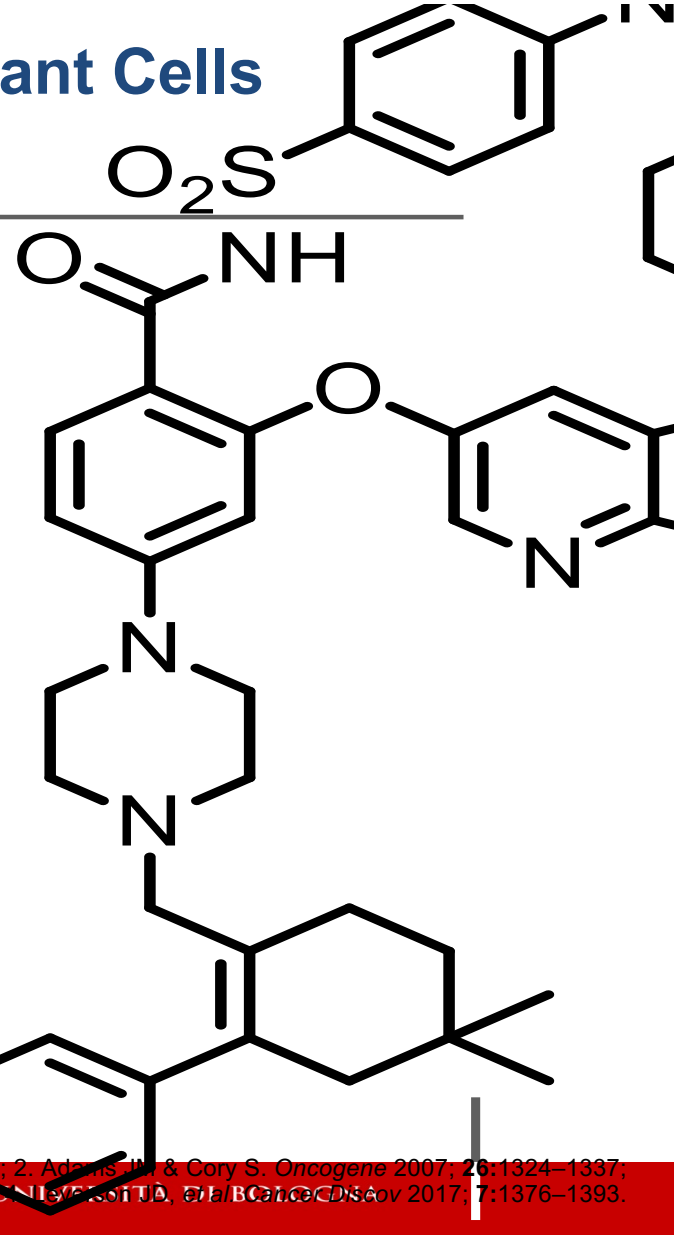
Venetoclax Induces Apoptosis in Malignant Cells



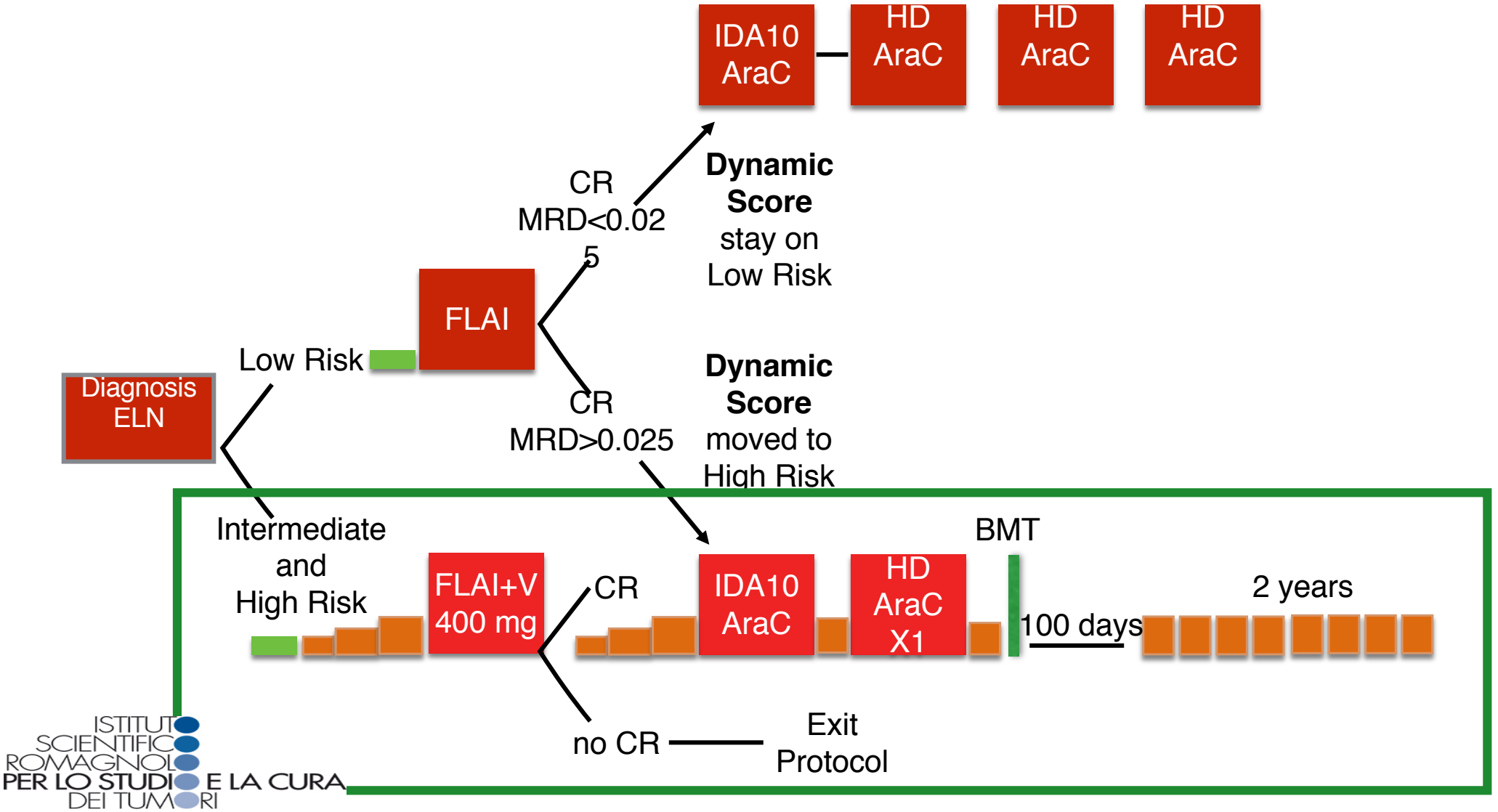


1. Letai A, *et al. Cancer Cell* 2002; **2:**183–192; 2. Adams JM & Cory S. *Oncogene* 2007; **26:**1324–1337;
3. Souers AJ, *et al. Nat Med* 2013; **19:**202–208; Roberts AW, *et al. Cancer Discov* 2017; **7:**1376–1393.

Gimema Clinical Trial Open V-FLAI

AML de novo patients with intermediate or complex karyotype

G. Martinelli Et Al.


IDA10 AraC
HD AraC
HD AraC
HD AraC
CR MRD<0.025
Dynamic Score stay on Low Risk
FLAI
Low Risk
Diagnosis ELN
CR MRD>0.025
Dynamic Score moved to High Risk
Intermediate and High Risk
FLAI+V 400 mg
CR
IDA10 AraC
HD AraC X1
BMT
100 days
2 years
no CR
Exit Protocol
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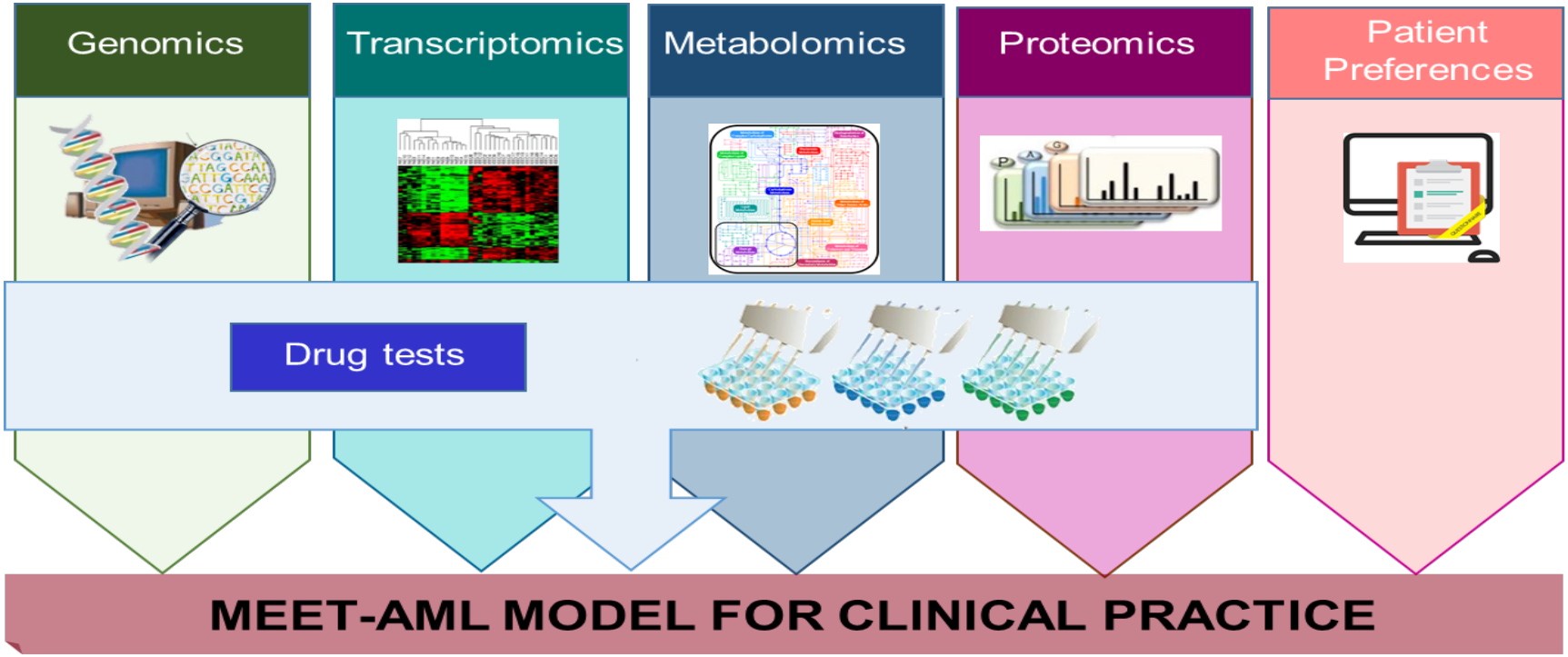
Metabolic vulnerabilities for personalized therapeutic approaches in acute myeloid leukemia - MEET-AML

Project partners 2019

Lars Bullinger, Charité University Medicine Berlin, Germany; Caroline Heckman, University of Helsinki, Finland Michel Salzet, Inserm Délégation Régionale Nord Ouest, Villeneuve d'ascq Cedex, France Feliè Prosper, University of Navarra, Spain Ulrik Kihlbom, Uppsala University, Sweden



EULAC PerMed has been funded by the European Union's Horizon 2020 Research and Innovation programme under Grant Agreement Num. 825173

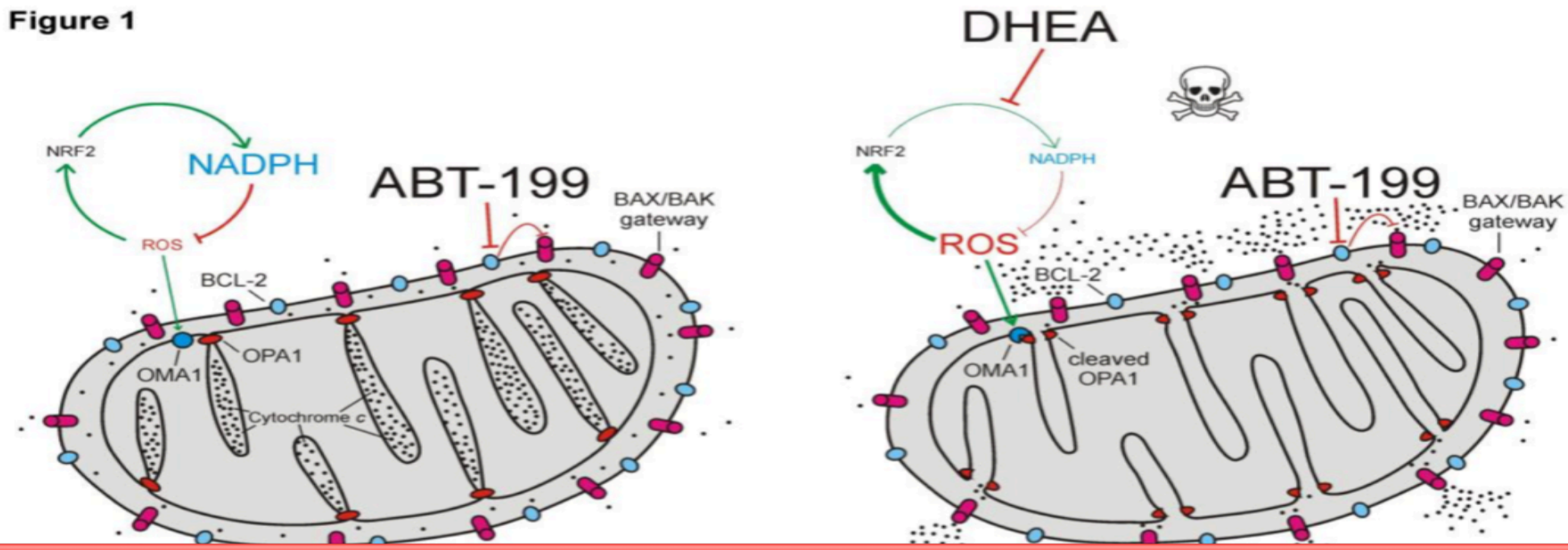
Bandi ERAPERMED
Progetti Finanziati

- **GRAMMY:** InteGRAtive analysis of tuMor, Microenvironment, immunitY and patient expectation for personalized response prediction in Gastric Cancer.
  PI: Molinari. Collaborator: Monti, Angeli, De Padova, De Matteis, Vagheggini, Battistelli, Mariotti, Imbrogno

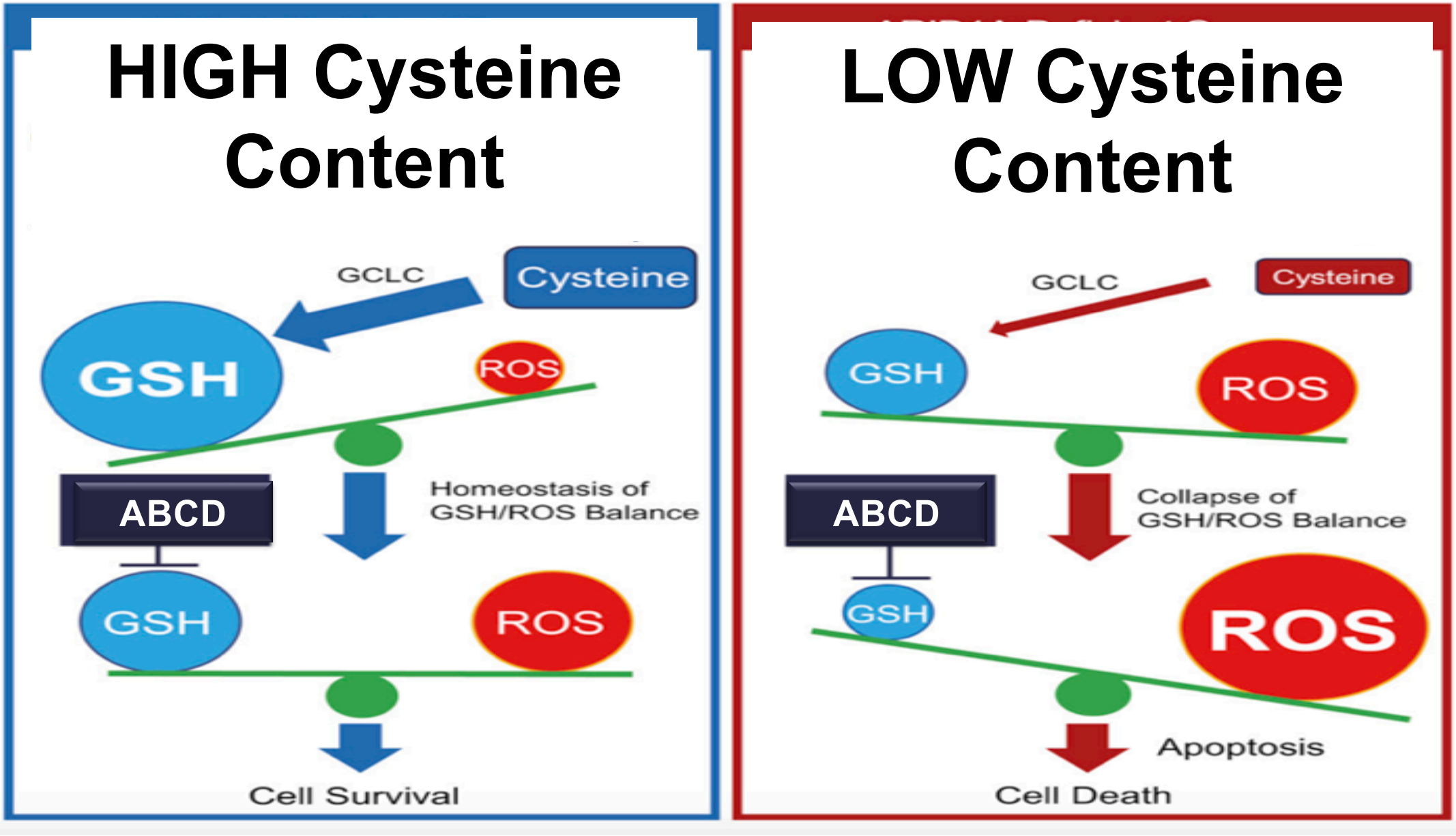
- **Bronc-HOC**: Proteomic screening of bronchoscopic biopsies-on-chip for improved prediction of anti-PD-1 responses in real-time.
  PI: Delmonte. Collaborator: Ulivi, Crinò, Battistelli, Mariotti, Imbrogno

- **MEET-AML: Metabolic vulnerabilities** for personalized therapeutic approaches in acute myeloid leukemia.
  PI: Martinelli. Collaborator: Simonetti, Petracci, Zingaretti, Battistelli, Mariotti, Imbrogno.

RIDUCENDO IL NADPH?



Come incrementare i ROS?


HIGH Cysteine Content
GCLC
Cysteine
GSH
ROS
ABCD
Homeostasis of GSH/ROS Balance
GSH
ROS
Cell Survival
LOW Cysteine Content
GCLC
Cysteine
GSH
ROS
ABCD
Collapse of GSH/ROS Balance
GSH
ROS
Apoptosis
Cell Death

nature > scientific reports > articles > article

SCIENTIFIC REPORTS

cancers

MDPI

Review

The Non-Essential Amino Acid Cysteine Becomes Essential for Tumor Proliferation and Survival

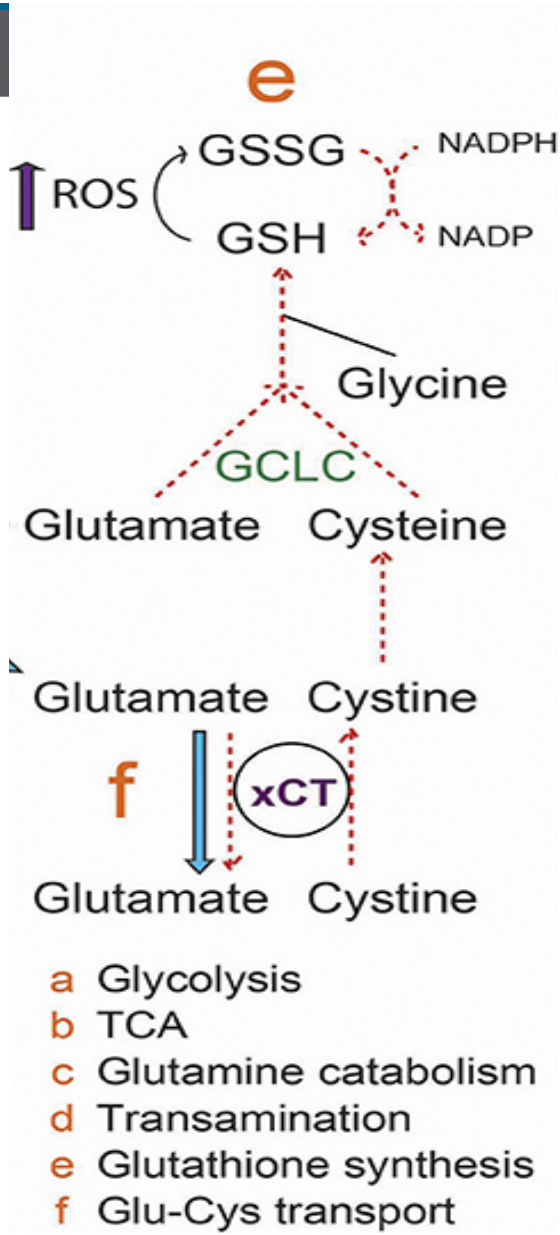
Joseph A. Combs and Gina M. DeNicola *

Department of Cancer Physiology, H. Lee Moffitt Cancer Center, Tampa, FL 33612, USA

* Correspondence: Gina.DeNicola@Moffitt.org

Received: 24 April 2019; Accepted: 14 May 2019; Published: 16 May 2019

check for updates



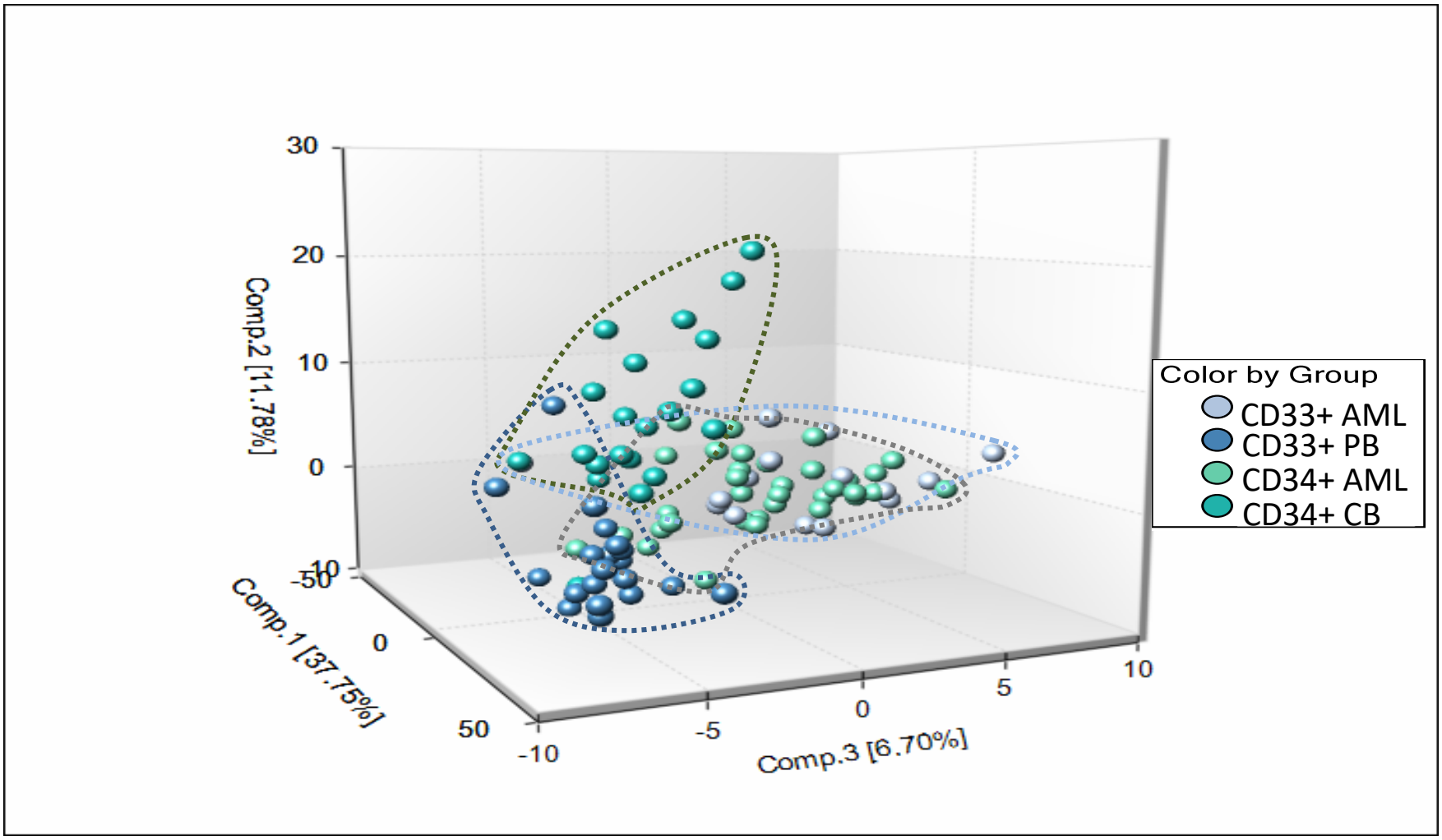
Analysing >2400 metabolites by Mass Spect of CD34+ AML at diagnosis

Experimental design

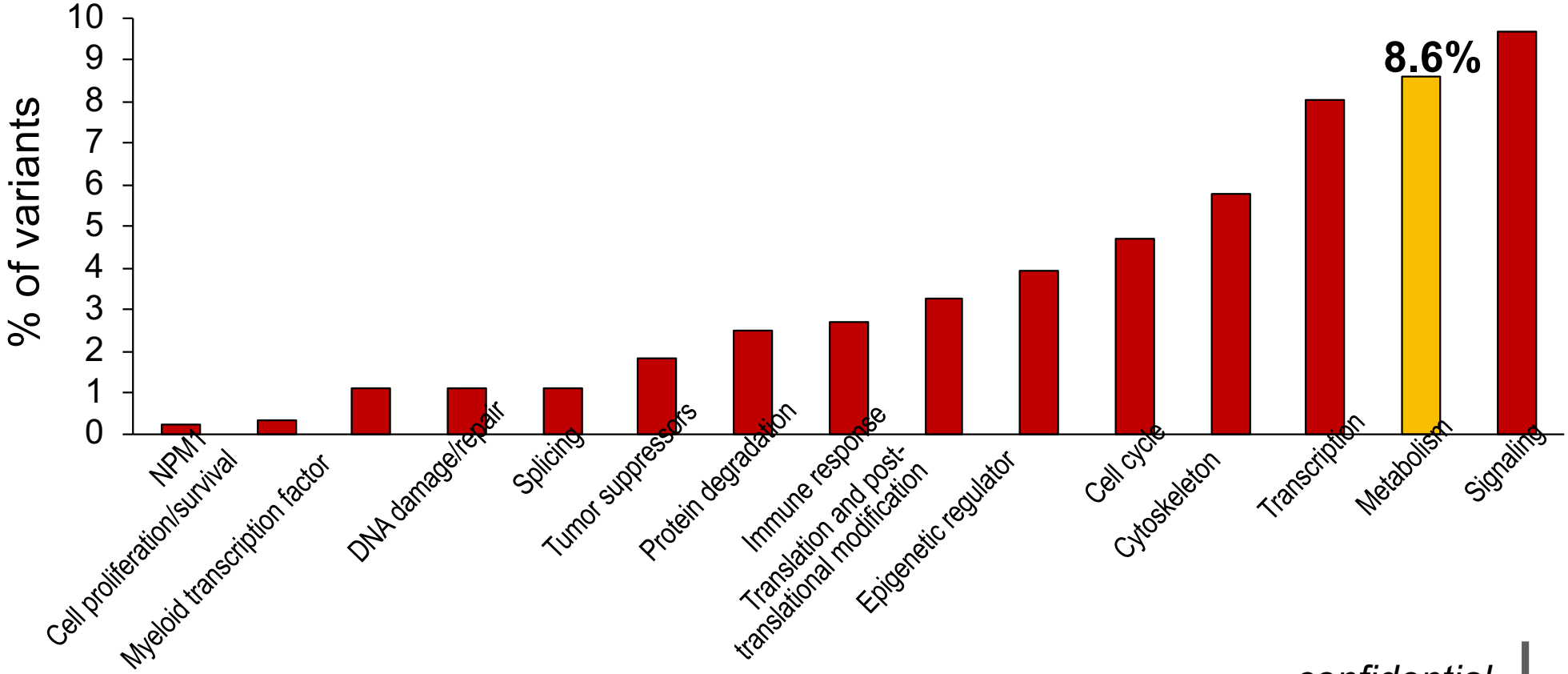
Global biochemical profiles were determined in submitted cell samples as below.

Group	n	Description
CD34+ CB	21	CD34+ cord blood cells
CD34+ AML	35	CD34+ AML patient bone marrow stem progenitor cells
CD33+ PB	21	CD33+ healthy donor peripheral blood cells
CD33+ AML	16	CD33+ AML patient bone marrow blast cells

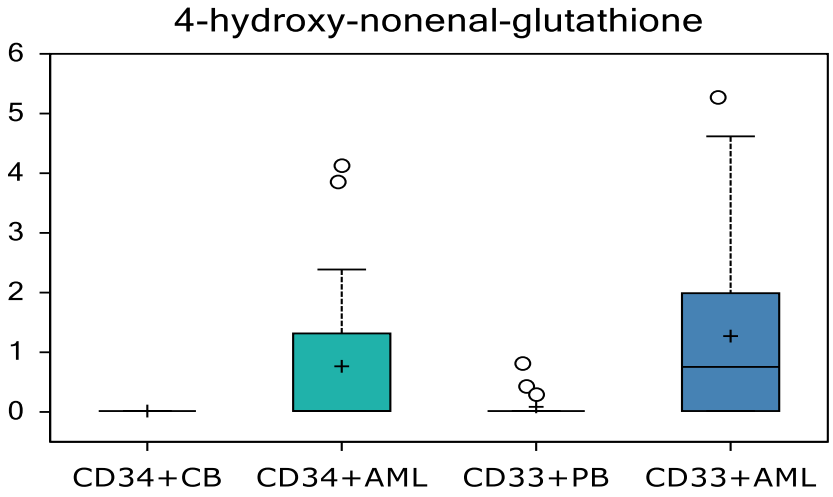
Principal Component Analysis

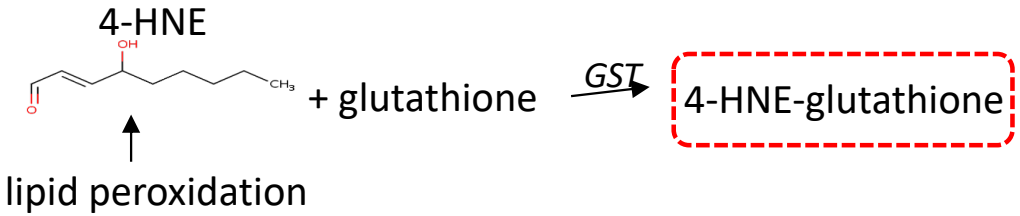


Metabolism is a novel putative functional category of mutated genes in AML



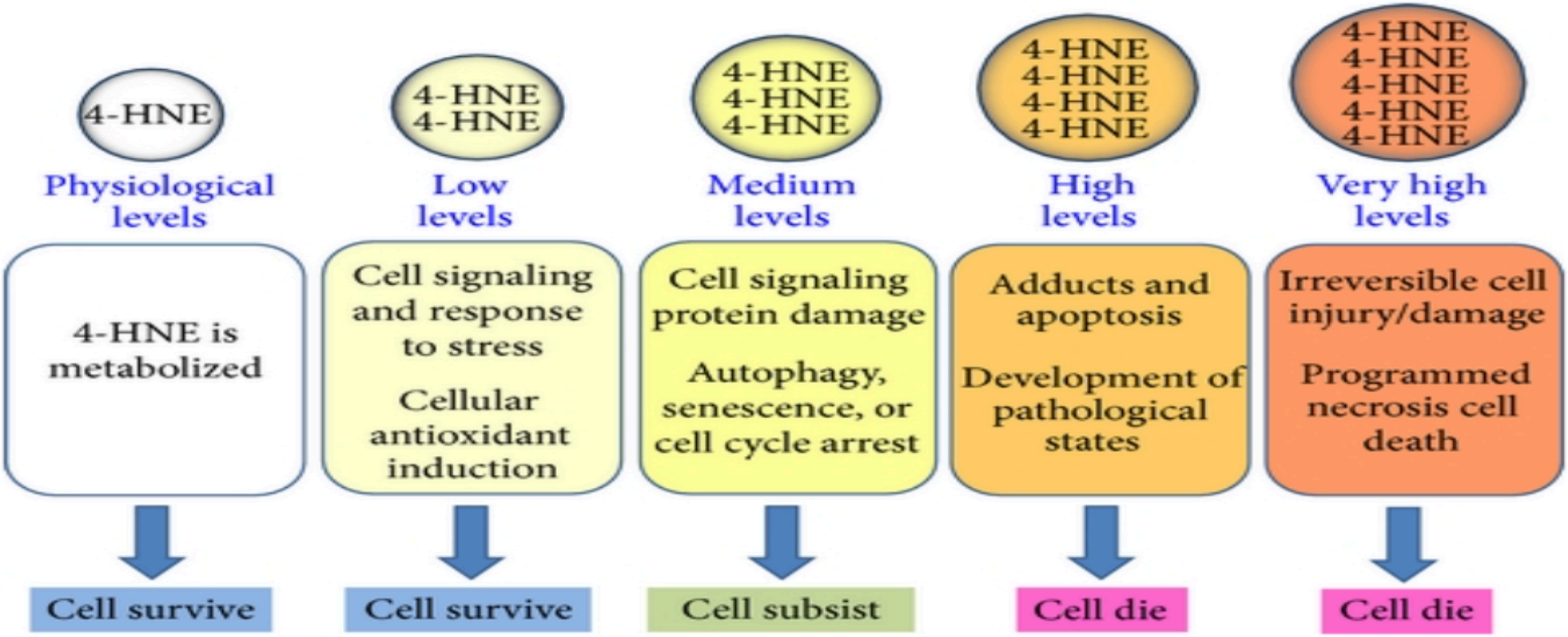
Altered Redox Homeostasis: >40 times 4-Hydroxynonenal-Glutathione (GS-4-HNE)

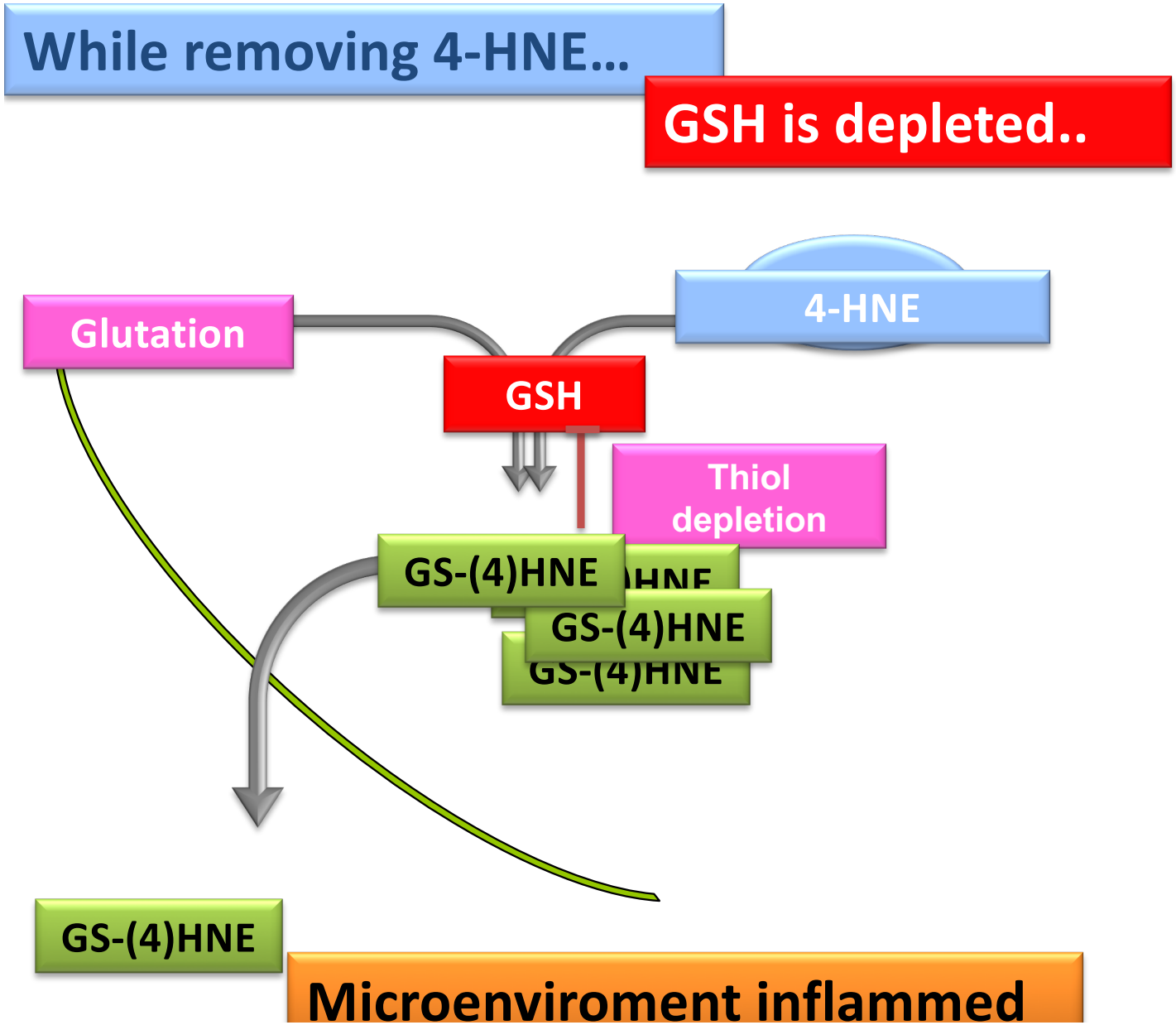




Elevated 4-HNE detoxification in the CD34 AML increase apoptotic resistance
(PMID: 15288119).

il 4-HNE va rimosso dalla cellula… perche’ e’ tossico.




While removing 4-HNE…
GSH is depleted..
Glutation
4-HNE
GSH
Thiol depletion
GS-(4)HNE
GS-(4)HNE
GS-(4)HNE
GS-(4)HNE
Microenviroment inflammed

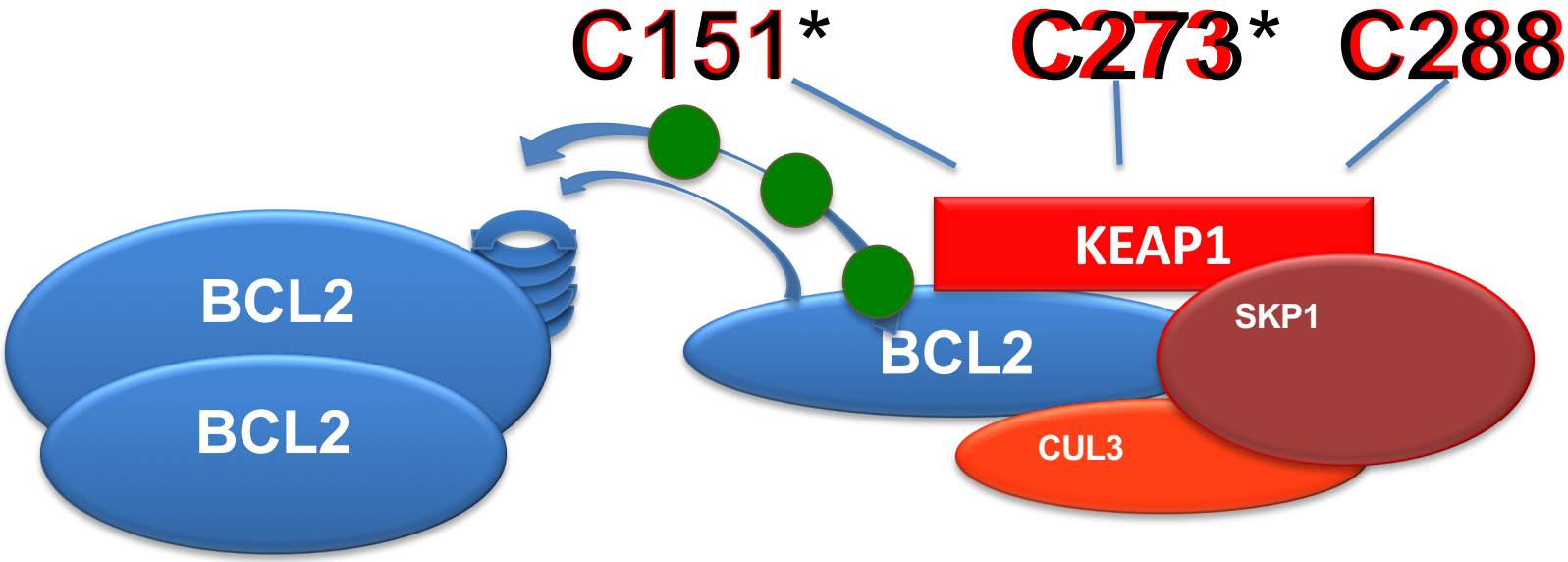
What's the consequence of Thiol depletion?

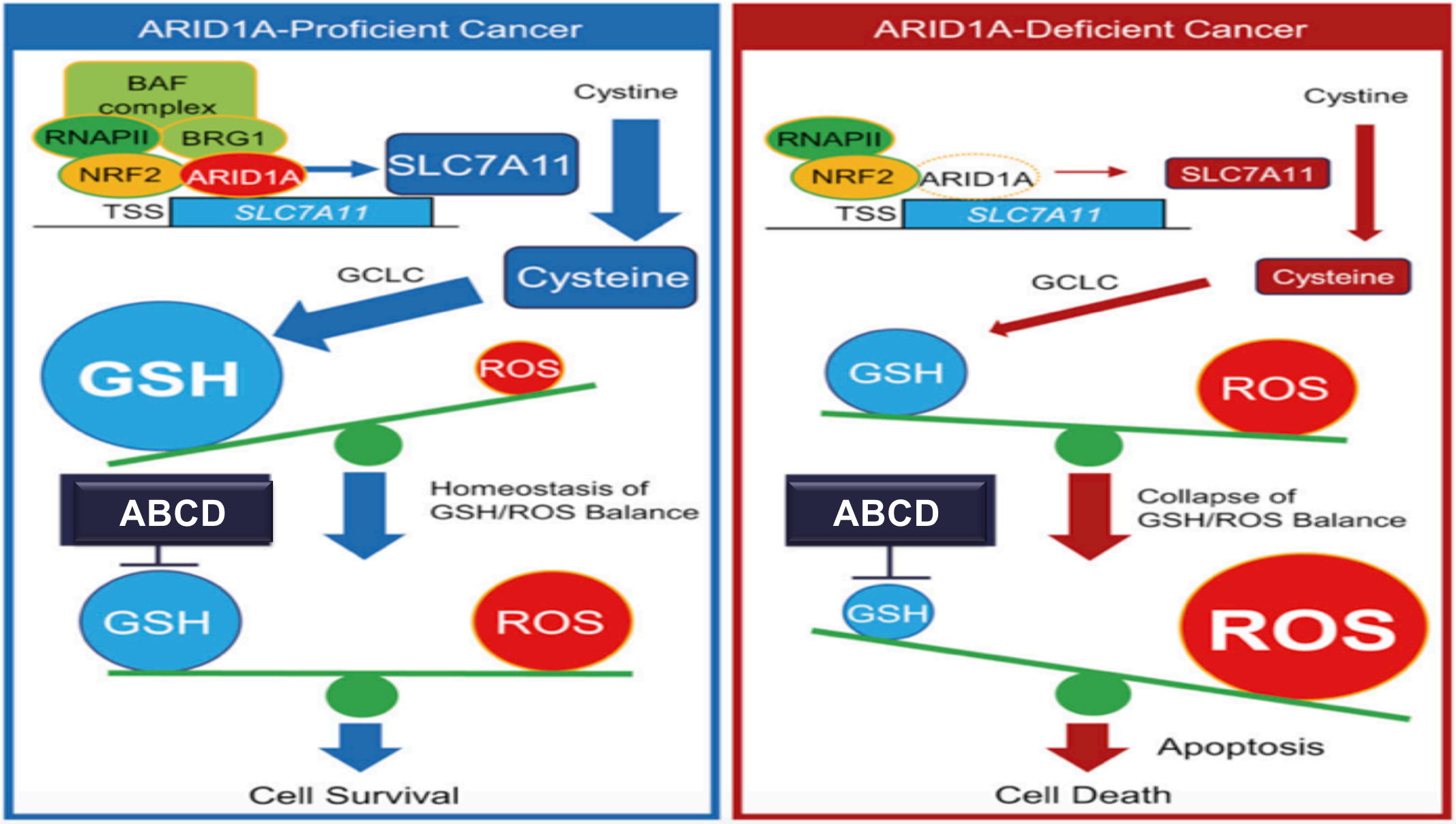
Is 4-HNE related to apoaptosis?
Is BCL2 involved?

Thiol depletion produces a structural modification of cysteine C151, C273, e C288 of

Keap1

a Ubiquitin E-Ligasi-protein




ARID1A-Proficient Cancer
BAF complex
RNAPII
BRG1
NRF2
ARID1A
TSS
SLC7A11
SLC7A11
Cystine
Cysteine
GCLC
GSH
ROS
ABCD
Homeostasis of GSH/ROS Balance
GSH
ROS
Cell Survival
ARID1A-Deficient Cancer
RNAPII
NRF2
ARID1A
TSS
SLC7A11
SLC7A11
Cystine
Cysteine
GCLC
GSH
ROS
ABCD
Collapse of GSH/ROS Balance
GSH
ROS
Apoptosis
Cell Death

Take-home message

- The metabolic features of AML cells are only partly dependent on their differentiation stage.
- Common and patient-specific metabolic alterations co-operate to the leukemic phenotype.
- Dissecting the link between genomic and metabolic alterations may improve therapeutic strategies and guide clinical decisions (e.g. *IDH1/2* mutations).

ALLEANZA CONTRO IL CANCRO

Thank you!

Clinical Acute Leukemia Team

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UNA SCOPERTA CHE TI CAMBIA LA VITA