

IRCCS

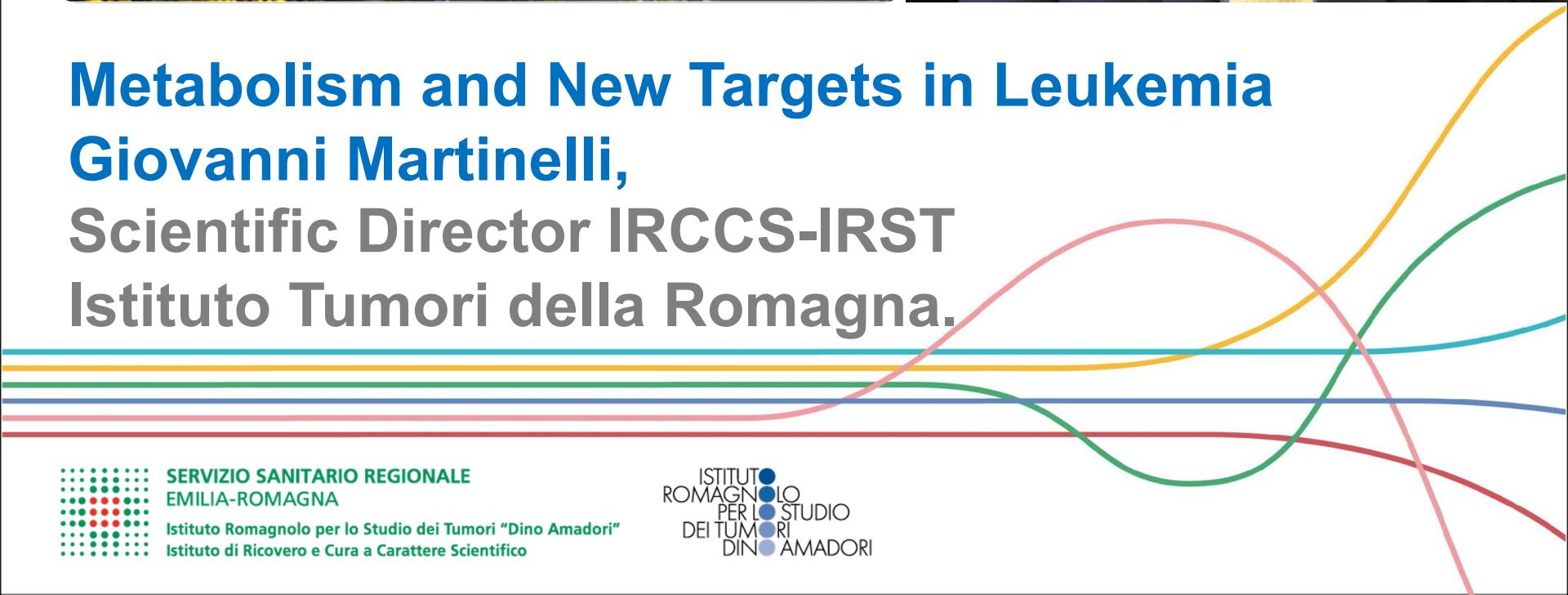
Istituto Romagnolo per lo Studio dei
Tumori

«Dino Amadori»

IRST S.r.l.



Metabolism and New Targets in Leukemia
Giovanni Martinelli,
Scientific Director IRCCS-IRST
Istituto Tumori della Romagna.



SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori"
Istituto di Ricovero e Cura a Carattere Scientifico

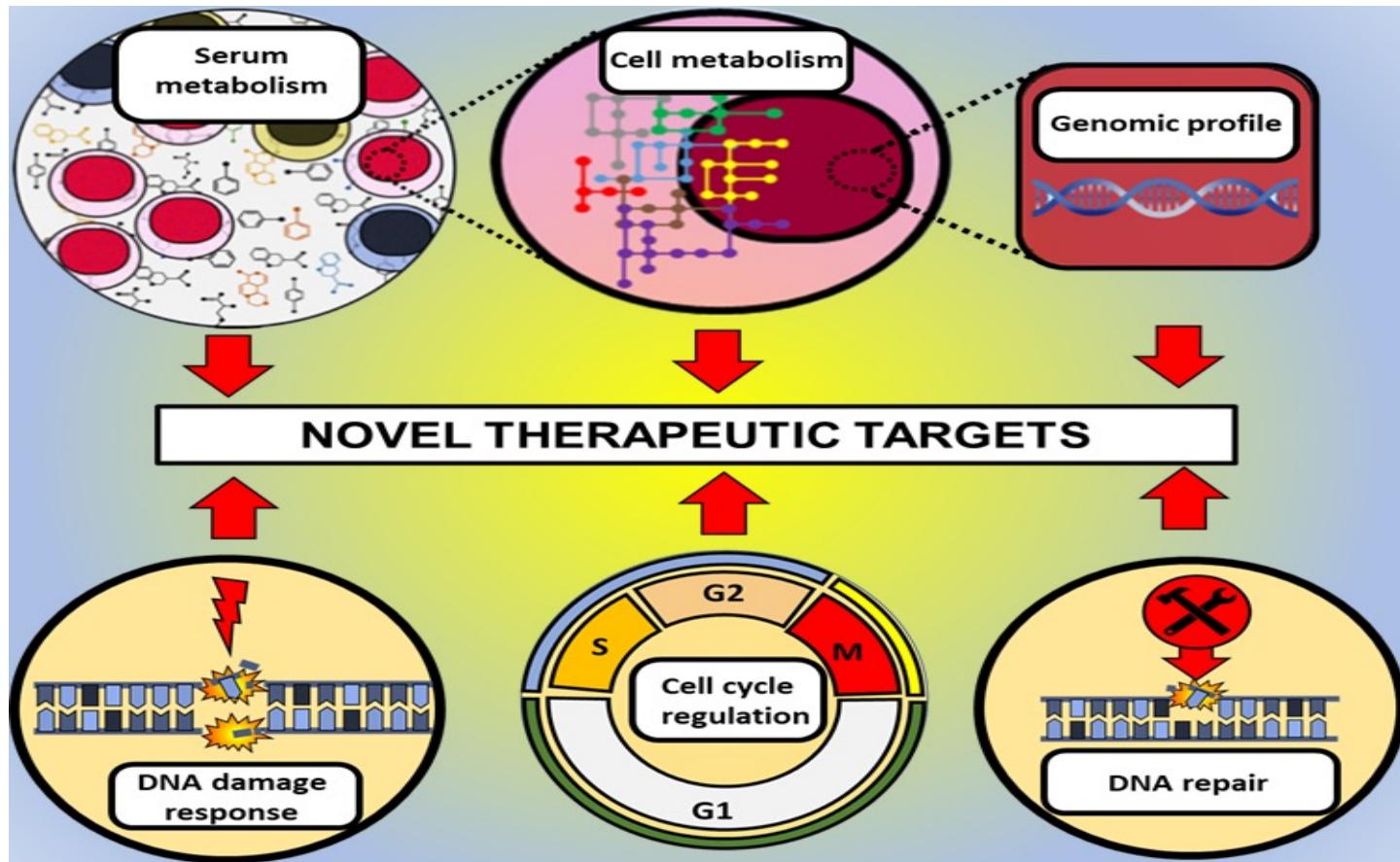
ISTITUTO
ROMAGNOLO
PER LO STUDIO
DEI TUMORI
DINO AMADORI

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

Metabolism

“Approcci terapeutici innovativi nelle leucemie mieloidi acute e infoblastiche acute basati sul metabolismo e sul targeting del danno al DNA”



REGIONE DEL VENETO



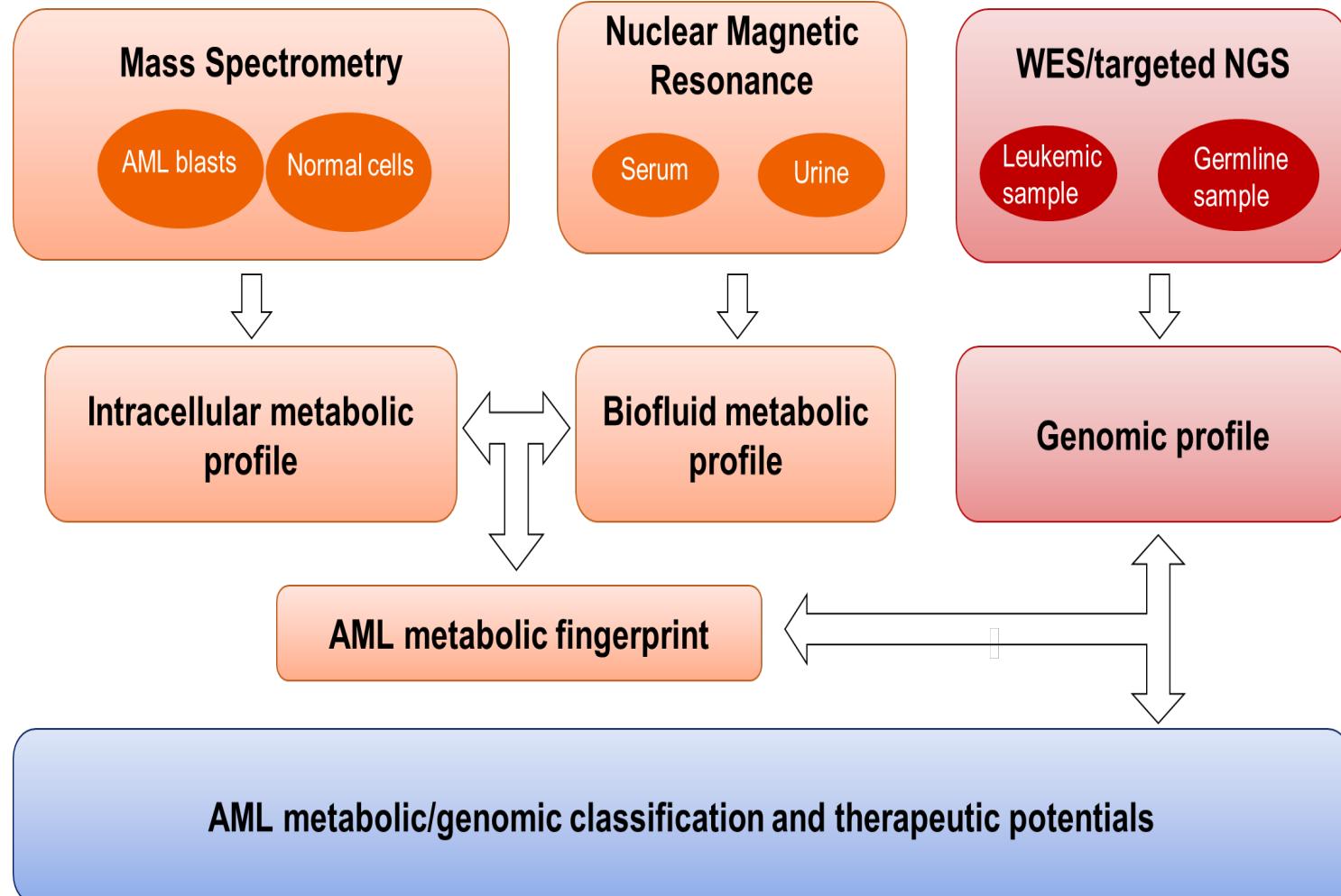
ULSS2
MARCA TREVIGIANA

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DEI TUMORI
DINO AMADORI



Treviso
ASSOCIAZIONE ITALIANA
CONTRO LEUCEMIE
LINFOMI E MIELOMA

Integrated genomic and metabolomic AML characterization

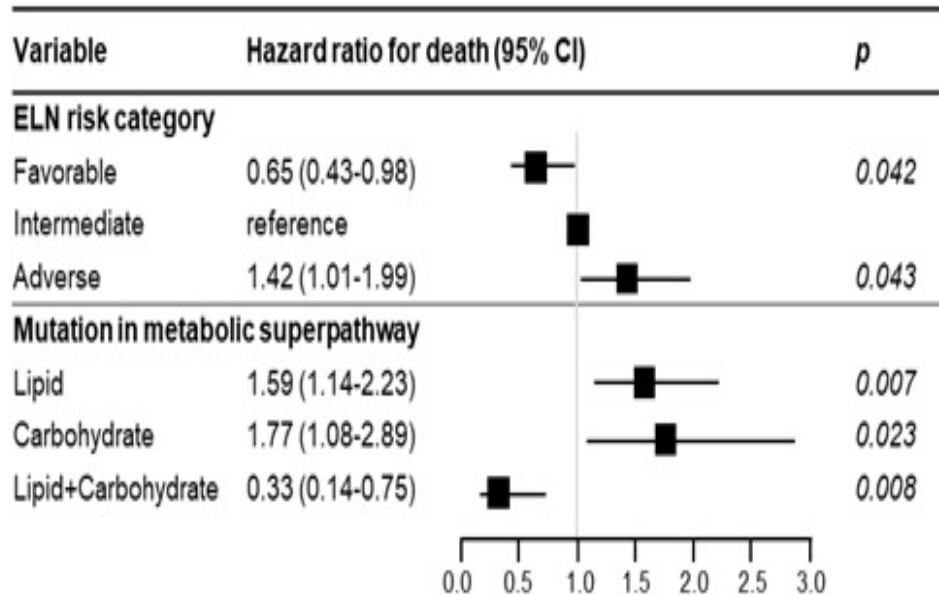
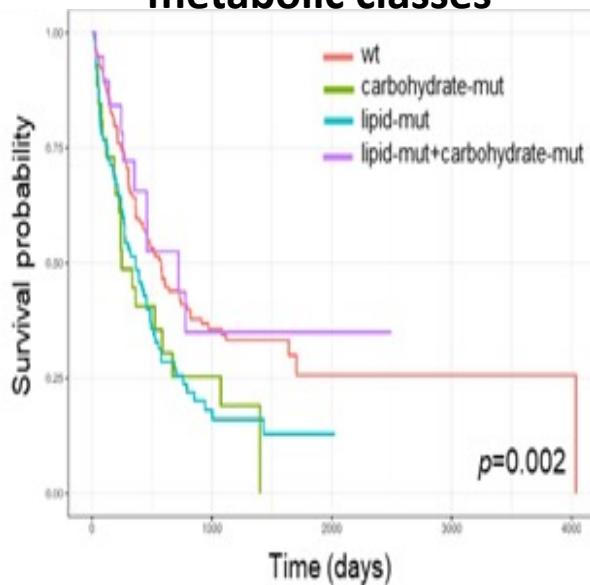


Mutations in metabolism-related genes predict prognosis in AML



Antonella
Padella

Prognosis according to mutations in some metabolic classes



The prognostic value of mutations in metabolism-related genes is confirmed in multivariate analysis with ELN risk classification

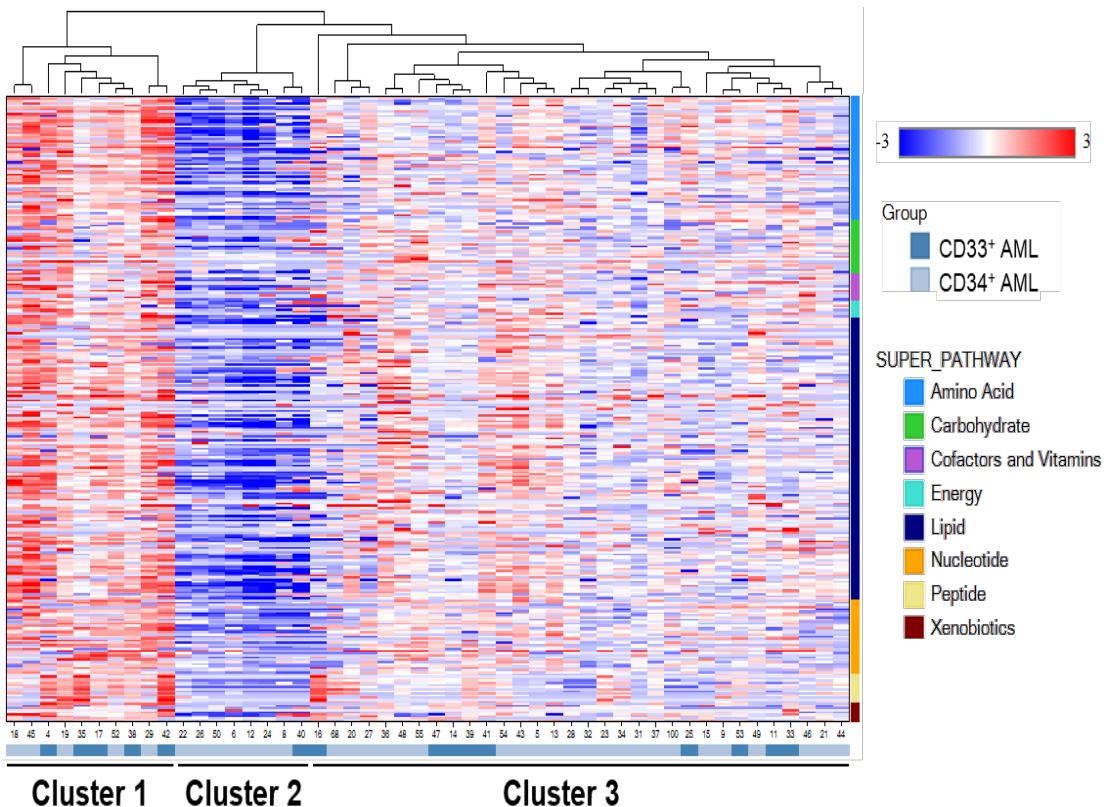
Confidential

AML intracellular metabolic clusters show association with molecular subgroups



Giorgia Simonetti

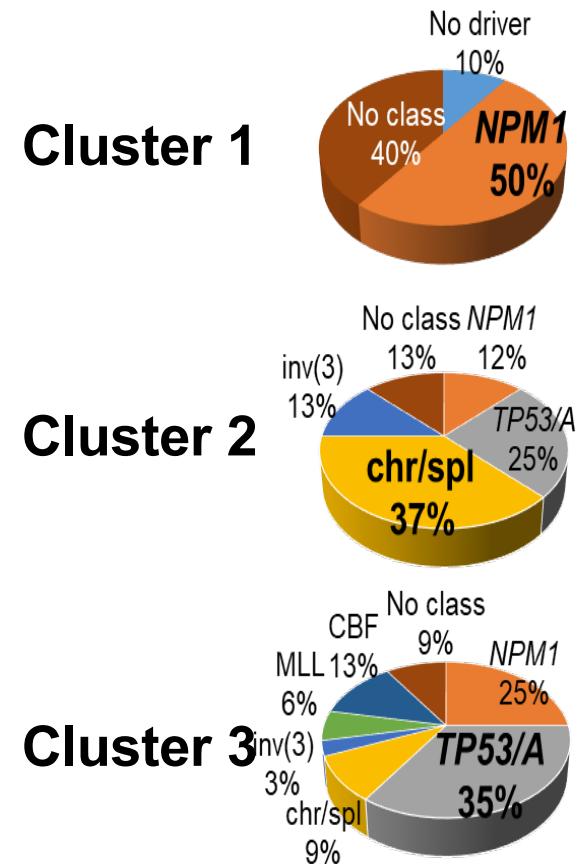
Metabolite analysis in AML blasts by mass spectrometry



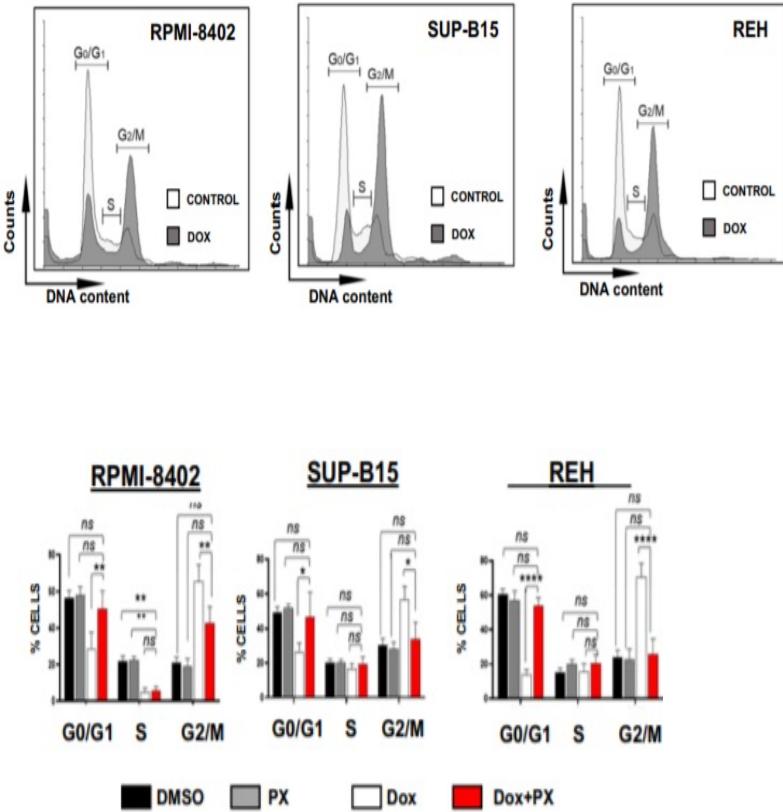
Cluster 1

Cluster 2

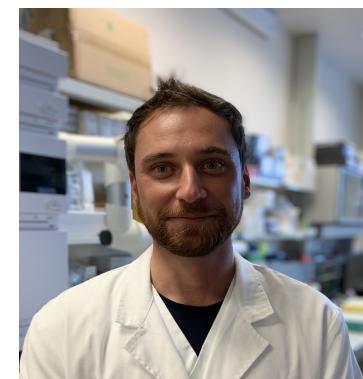
Cluster 3



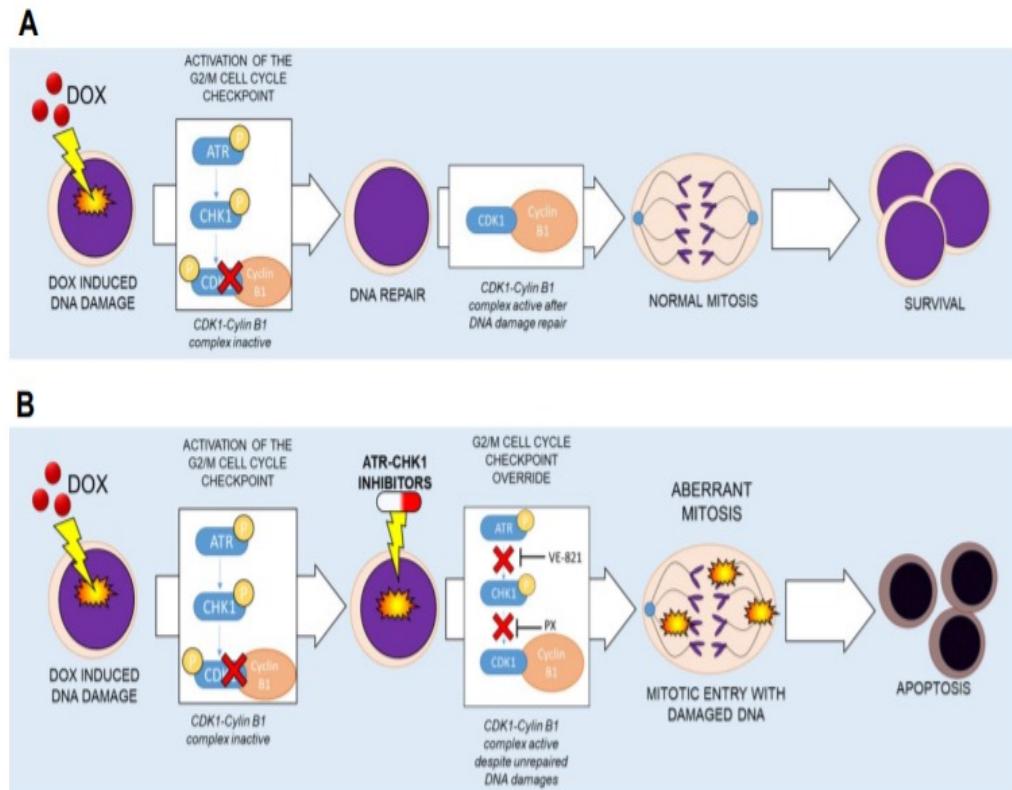
Crucial biological role of DNA damage response (DDR) pathway in Acute Lymphoblastic Leukemia (ALL)



ALL cells respond to chemotherapy agent doxorubicin activating the DDR pathway to survive



Andre Ghelli



Using DDR inhibitor we can restore the sensitivity of ALL cells to doxorubicin and enhance the therapeutic potential

Results of the project:

- Gemtuzumab ozogamicin in acute myeloid leukemia: past, present and future. Minerva Med. 2020 Oct;111(5):395-410. doi: 10.23736/S0026-4806.20.07019-6.
- Adrenomedullin Expression Characterizes Leukemia Stem Cells and Associates With an Inflammatory Signature in Acute Myeloid Leukemia. Front Oncol. 2021 Jun 2;11:684396. doi: 10.3389/fonc.2021.684396
- Targeting of Acute Myeloid Leukemia by Gemtuzumab Ozogamicin. Cancers (Basel). 2021 Sep 11;13(18):4566. doi: 10.3390/cancers13184566.



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Acknowledgements

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Ospedale Ca' Foncello, Treviso*

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(IOV), Castelfranco Veneto, Padua*

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Memphis*

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*Munich Leukemia Laboratory,
Munich*



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Treviso

Torsten Haferlach

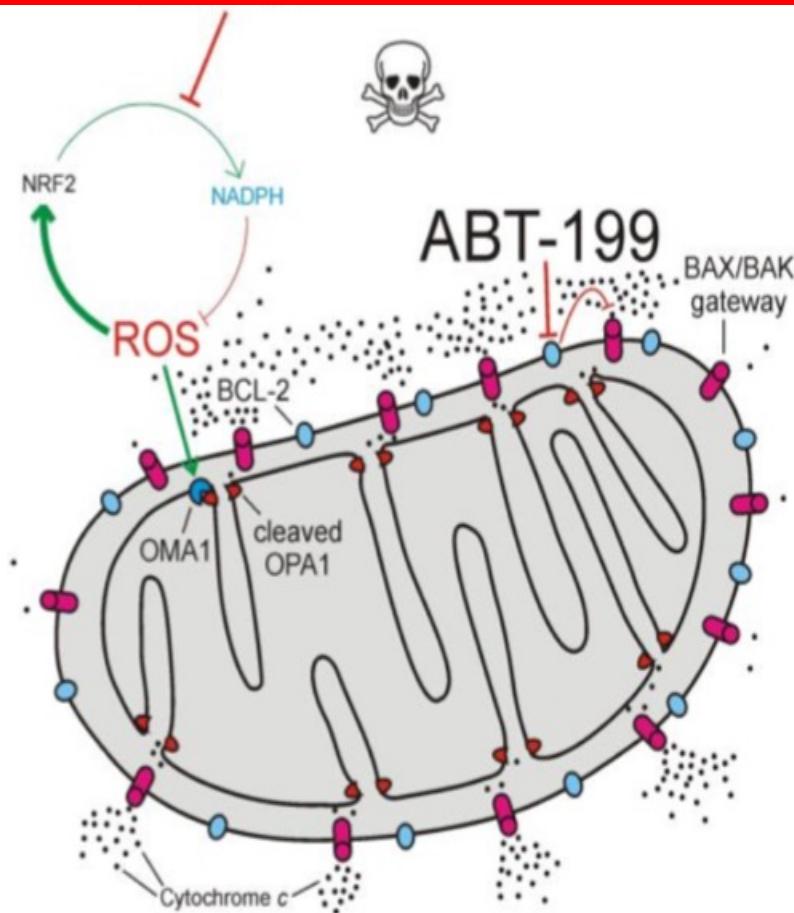
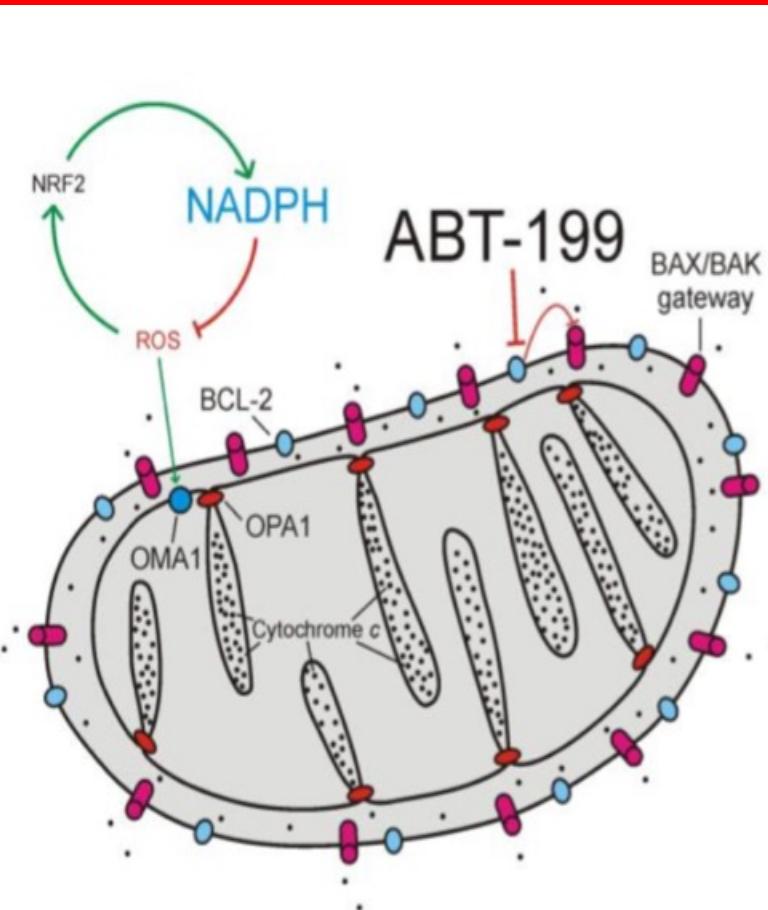
IRST Hematology research and diagnostic group



Energetic Pathway and Metabolism:

VENETOCLAX

NAVITOCLAX



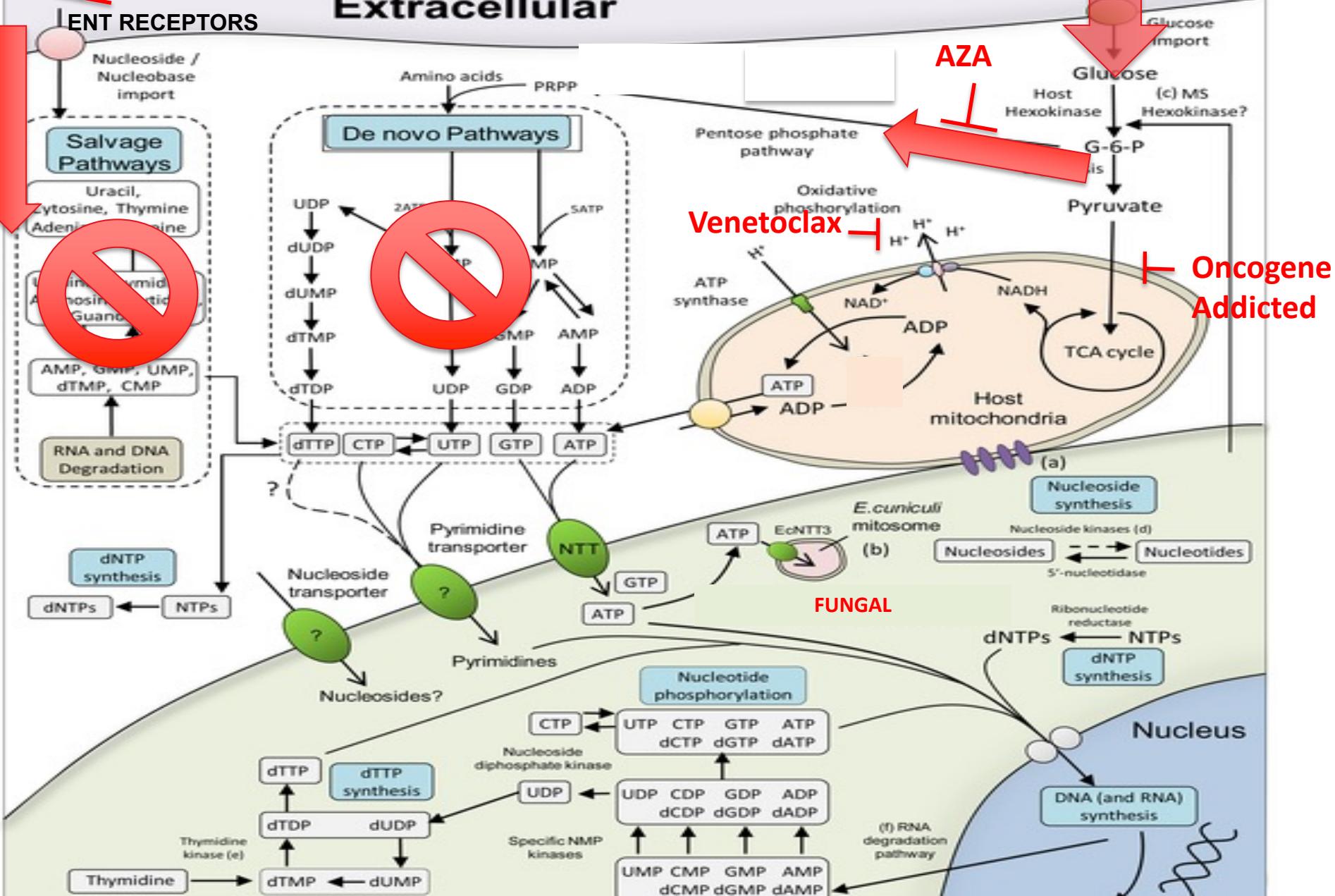
NUCLEOSIDE SALVAGE PATHWAY

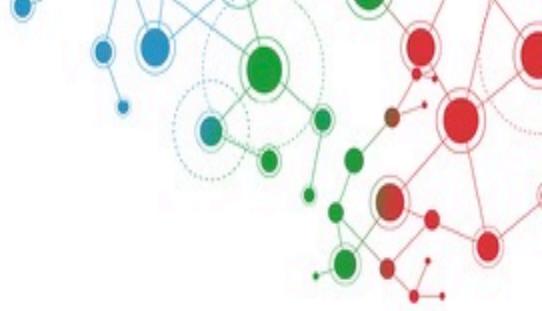
ENT RECEPTORS

Fludarabine

Leukemia Stem Cell Nucleoside Neo-Synthesis and Acquisition

Extracellular



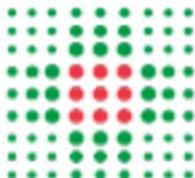


Gimema Clinical Trial Open V-FLAI (Venetoclax +FLAI)

**AML de novo patients with intermediate
or complex karyotype**

Preliminary data:

Arm Venetoclax 600mg: CR 89% CMR 69%



**SERVIZIO SANITARIO REGIONALE
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Istituto di Ricovero e Cura a Carattere Scientifico

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DEI TUMORI

A new double BCL2 / BCLx inhibitor



AstraZeneca
D8241C00001

“A Modular Phase I/II, Open-Label, Multi-Centre, Dose Escalation and Expansion Study to Assess Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of AZD0466 Monotherapy or in Combination in Patients with Advanced Haematological Malignancies”
254945

AZD0466 is a drug-dendrimer conjugate that consists of the active moiety,
the dual Bcl-2/Bcl-xL-specific inhibitor AZD4320,
covalently conjugated to a pegylated poly-L-lysine type dendrimer, which gradually
releases the active moiety by hydrolysis.

To be activated at IRST in November 2021

NUCLEOSIDE SALVAGE PATHWAY
ENT RECEPTORS as a TARGET

Workshop CCCRN-IRST

Metabolism and Leukemia

SEPTEMBER 4, 2022

Virtual Meeting

PROGRAM

Please Note: All session times for the CCNR Virtual Meeting.

Chair:

Giovanni Martinelli

Co Chair:

Giovanni Marconi, Cristina Papayannidis*, Claudio Cerchione, Giorgia Simonetti, Gerardo Musuraca, Angelo del Monte.

Article | [Open Access](#) | Published: 30 June 2021

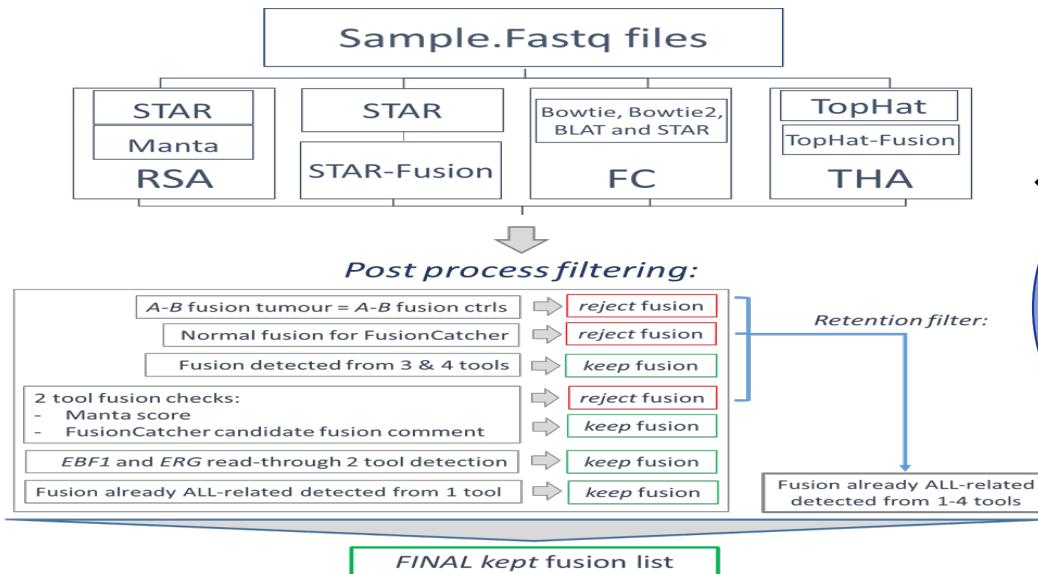
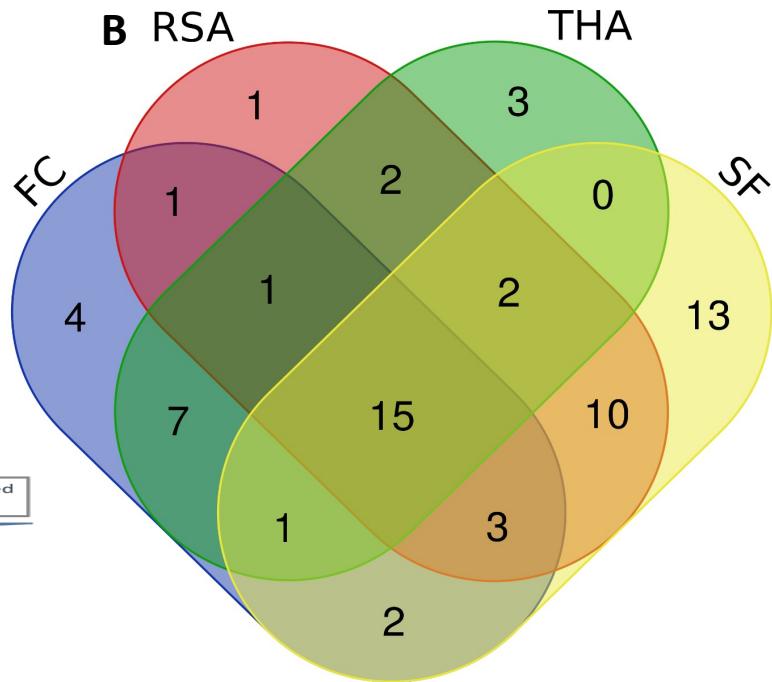
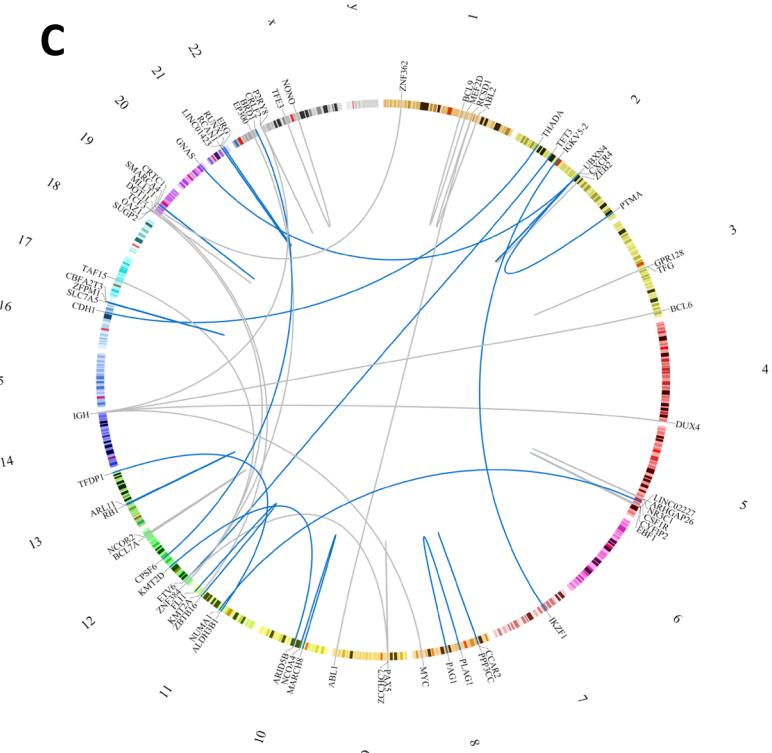
ACUTE MYELOID LEUKEMIA

Integrated genomic-metabolic classification of acute myeloid leukemia defines a subgroup with *NPM1* and cohesin/DNA damage mutations

Giorgia Simonetti , Carlo Mengucci, [...]Giovanni Martinelli

Leukemia (2021) | [Cite this article](#)

1163 Accesses | 3 Altmetric | [Metrics](#)

A**B****C**

Ferrari A. et Martinelli G. 2021
Patent registered

Ferrari A. et Al. SIE 2019 Oral communication

Ferrari et Al. Cancer Research 2019 and oral communication, and EHA 2021

Ferrari A. & Martinelli G, Patent registered n°3256790897

Krzywinski, M. et al. [Circos: an Information Aesthetic for Comparative Genomics](#). *Genome Res* (2009) 19:1639-1645

Any Acute Lymphoblastic Leukemia has a drugable “Fusion Transcript” ?

TRANSCRIPTIONAL REGULATION

BRD1 → *BETi*

CBFA2T3 → *diMF*

DUX4 → *DUX4i*

FLI1 → *TK216*

NR3C1 → *GRi*

TAF15 → *α -amanitin*

ZNF362 → *JAKi*

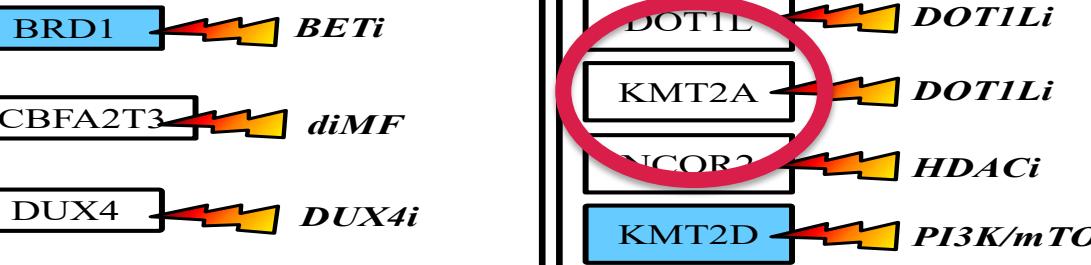
BCL6 → *BCL6i*

MYC → *MYCi361*
BETi

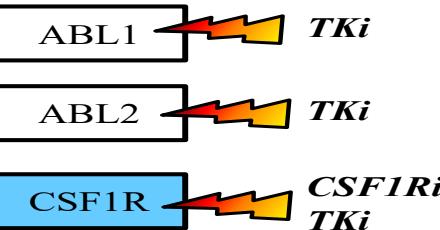
TFE3 → *PI3K/mTORi*

MEF2D → *HDACi*

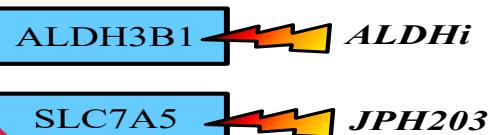
EPIGENOMIC



SIGNALING



METABOLISM



JAK-STAT PATHWAY

CRLF2 → *PI3K/mTORi*
JAKi
TKi

PI3-AKT PATHWAY

GNAS → *PI3K/AKTi*

OTHER PATHWAYS

CXCR4 → *CXCR4i*

PPP3CC → *CyclosporineA*
Tacrolimus

PTMA → *JNKi*
ERKi
PI3Ki

RCAN1 → *Dipyridamole*

MARCH8 → *AKTi*

“Triple negative” adult B-cell Acute Lymphoblastic Leukemia: molecular characterization, identification of new stratification Evaluation of rare fusions in Philadelphia positive Acute Lymphoblastic Leukemia (ALL) samples

“Research and Development of new NGS approaches to introduce in our Advance Molecular and Predictive Diagnostic Laboratory, with main focus on lymphoid hematological diseases”

Ferrari A. et Al. SIE 2019 Oral communication

Ferrari et Al Cancer Research 2019 and oral communication, and EHA 2021

Ferrari A. & Martinelli G, Patent registered n°3256790897

**Menin
traslocazioni coinvolgenti
MLL/KMT2A rearranged**

MLL-ENL



**metabolic
vulnerability**

PKM2



glycolysis

diet



**serine
glycine**

lactate

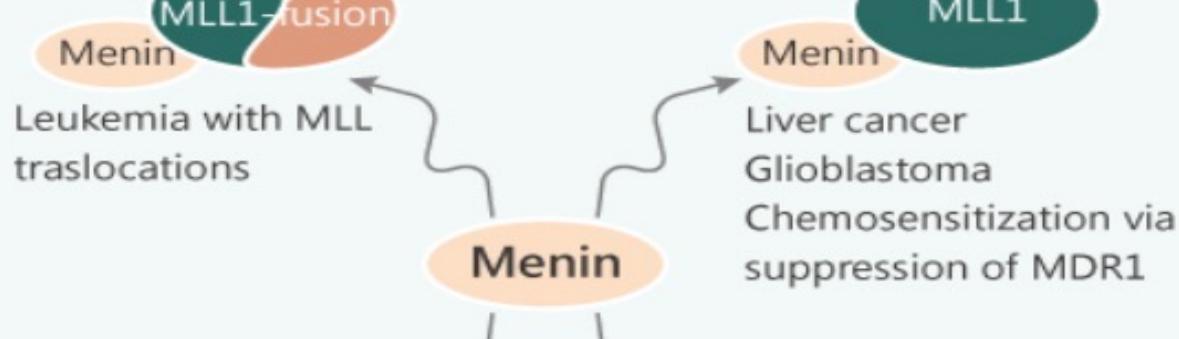
energy



M-525

NOW/SOON ENROLLING AT IRST

is a First-in-class



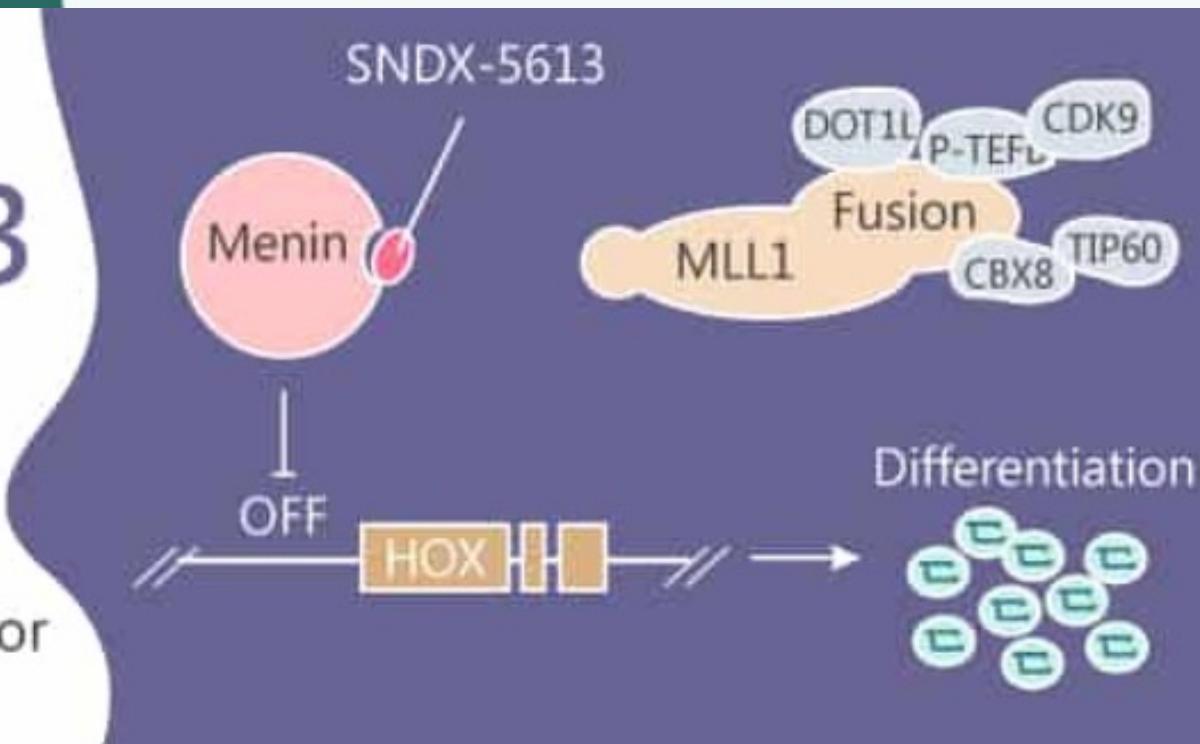
KOMET-001: A Phase 1/2A First in Human Study of the Menin-MLL(KMT2A) Inhibitor KO-539 in Patients With Relapsed or Refractory Acute Myeloid Leukemia (KO-MEN-001)

SNDX-5613

NOW/SOON ENROLLING AT IRST

is a Potent and

Specific Menin-MLL Inhibitor



ITALIAN OBSERVATIONAL STUDY OF PATIENTS WITH ACUTE MYELOID LEUKEMIA TREATED WITH SMALL MOLECULE INHIBITING BCL-2

An Italian, multi-center, retrospective observational study



The study is Sponsored by IRST IRCCS in collaboration with Rete Ematologica Lombarda and is endorsed by GIMEMA



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Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori"
Istituto di Ricovero e Cura a Carattere Scientifico



ITALIAN
OBSERVATIONAL
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WITH ACUTE MYELOID
LEUKEMIA
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INHIBITING BCL-2



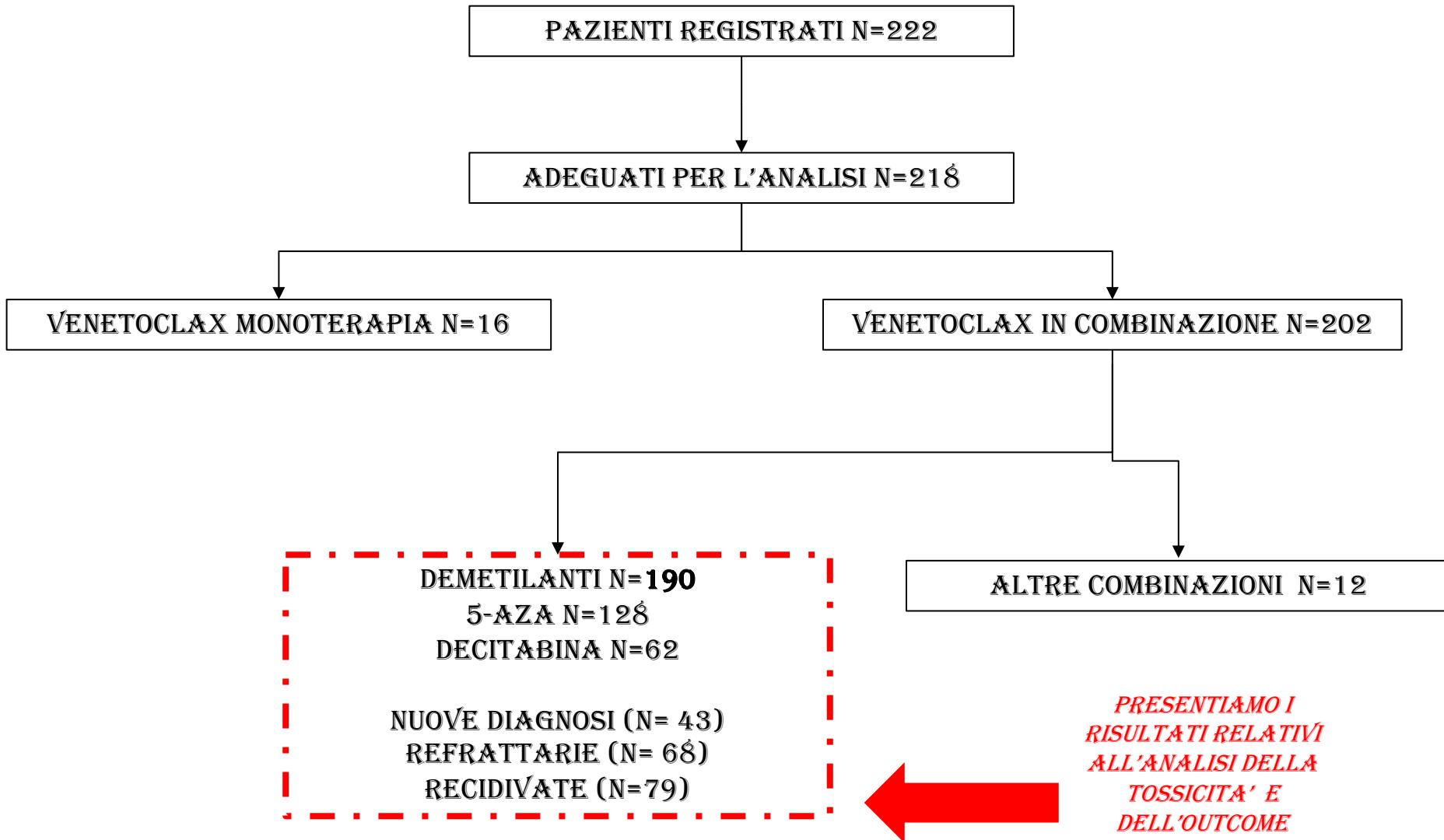
COPROMOTORI

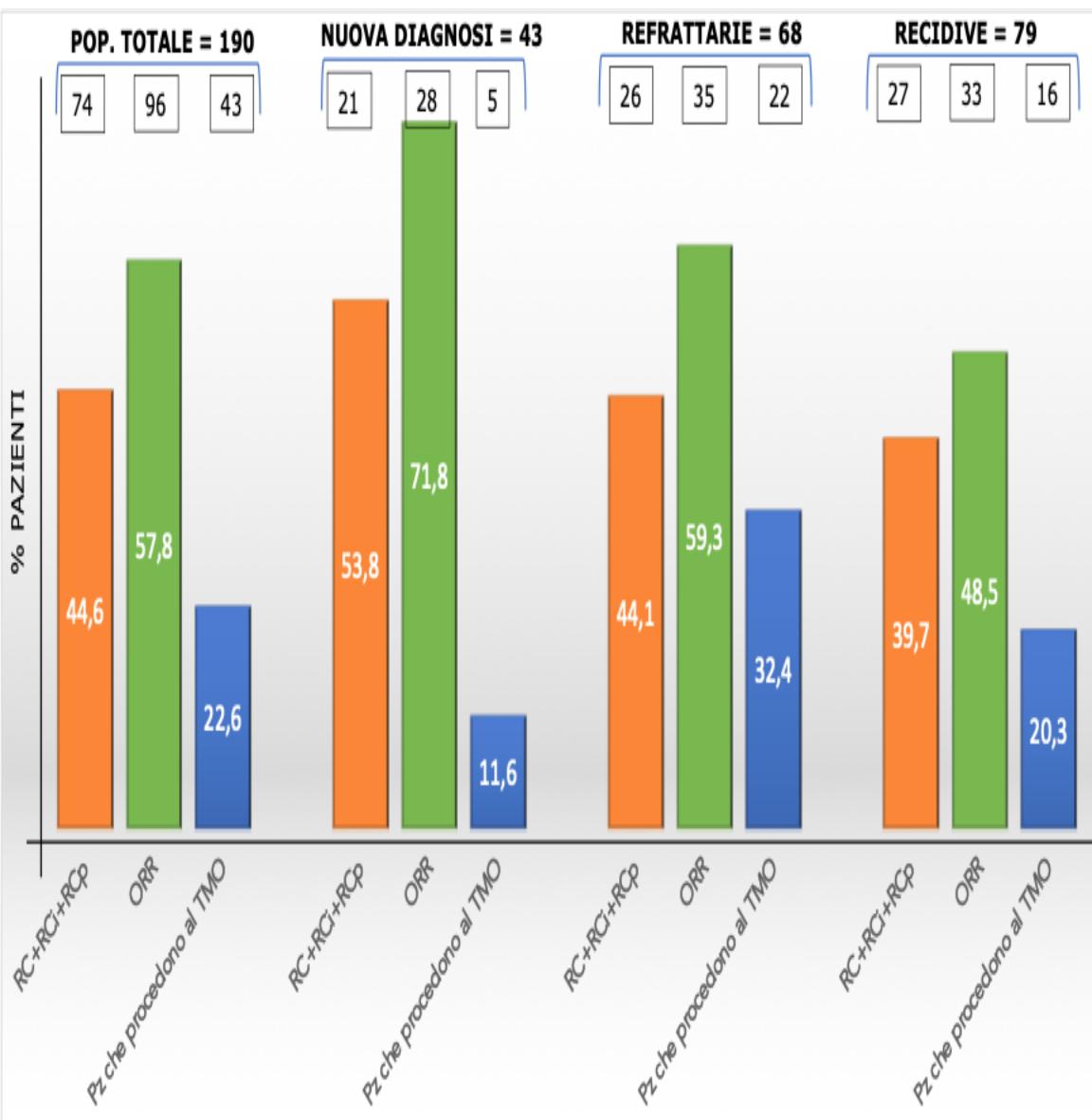
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IEO
Istituto Europeo di Oncologia

 **RELab**
RETE
EMATOLOGICA
LOMBARDA

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





POP. TOTALE 190 **NUOVA DIAGNOSI** 43 **REFRATTARIE** 68 **RECIDIVE** 79

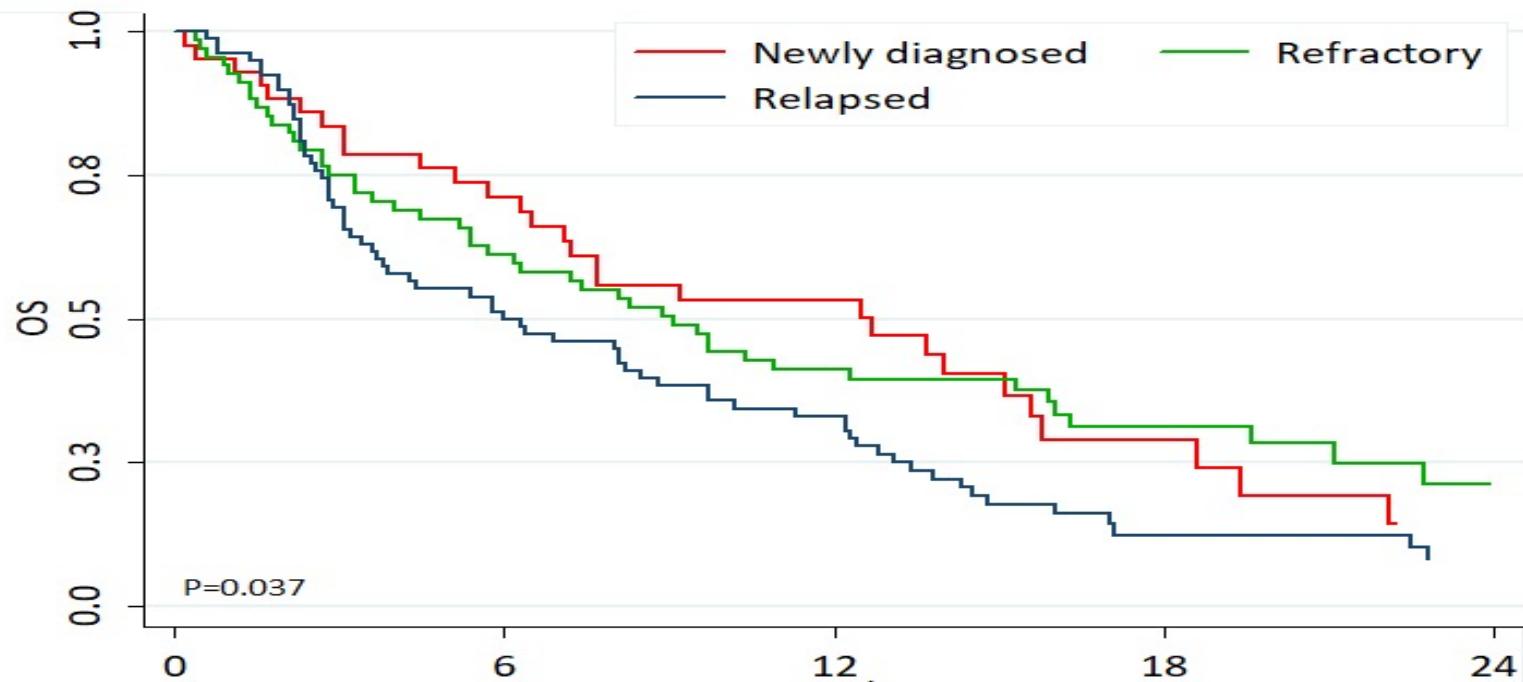
Tempo mediano alla risposta (mesi + QI range)

2,2 (1,2-4,4)	2,8 (1,8-5,9)	1,9 (1,1-4)	2,3 (1,2-3,8)
---------------	---------------	-------------	---------------

Durata mediana della risposta (mesi + QI range)

7,6 (5-11)	10,6 (4-12)	6,8 (4,4-12,6)	8,3 (4,7-12)
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OS

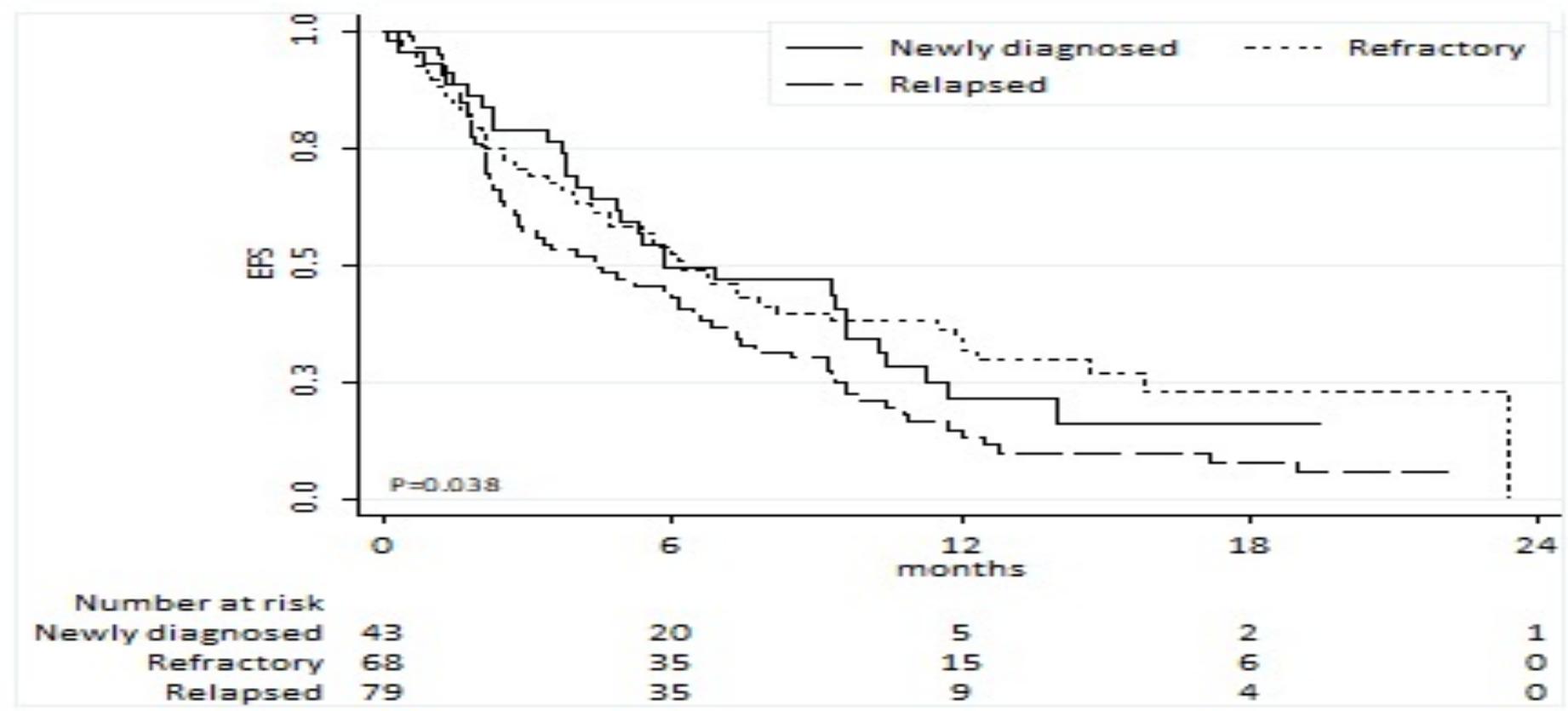


Number at risk

	0	6	12	18	24
Newly diagnosed	43	28	18	6	2
Refractory	68	40	24	13	5
Relapsed	79	40	25	6	4

VIALE-A MEDIAN OS DOPO VEN+ AZA: 17.4 MESI (11,9-18,7)

EFS



The AVALON collaborative group:

Giovanni Martinelli, IRST IRCCS	Fracchiolla Nicola Stefano, Fond IRCCS Cà Granda Milano	Cascavilla Nicola, Casa Sollievo della Sofferenza, S.Giovanni Rotondo
Claudio Cerchione, IRST IRCCS	Sciumè Mariarita, Fond IRCCS Cà Granda Milano	Mariachiara Abbenante, Casa Sollievo della Sofferenza, S.Giovanni Rotondo
Giovanni Marconi, IRST IRCCS	De Roberto Pasquale, Fond IRCCS Cà Granda Milano	Bocchia Monica, A.O.U. Senese Policlinico
Chiara Zingaretti, IRST IRCCS	Cairolì Roberto, ASST Niguarda, Milano	S. Maria delle Scotte, Siena
Roberta Volpi IRST IRCCS	Fumagalli Monica, ASST Monza	Audisio Ernesta, Città della Salute e della Scienza, Torino
Irene Valli, IRST IRCCS	Ferrara Felicetto, A.O.R.N. A. Cardarelli, Napoli	Priolo Giorgio, Città della Salute e della Scienza, Torino
Elisabetta Petracchi, IRST IRCCS	Oliva Valentina, A.O.R.N. A. Cardarelli, Napoli	Urbino Irene, Città della Salute e della Scienza, Torino
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Ciceri Fabio, Ospedale S.Raffaele	Pepe Rita A.O.U. S. Giovanni di Dio e Ruggi d'Aragona,	Lunghi Monia, A.O.U. Osp. Della Carità, Novara
Fabio Giglio, Ospedale S.Raffaele	Salerno	Cilloni Daniela, A.O.U. S. Luigi Gonzaga, Orbassano
	Dargenio Michelina, PO. Vito Fazzi Lecce	

Metabolic vulnerabilities for personalized therapeutic approaches in acute myeloid leukemia

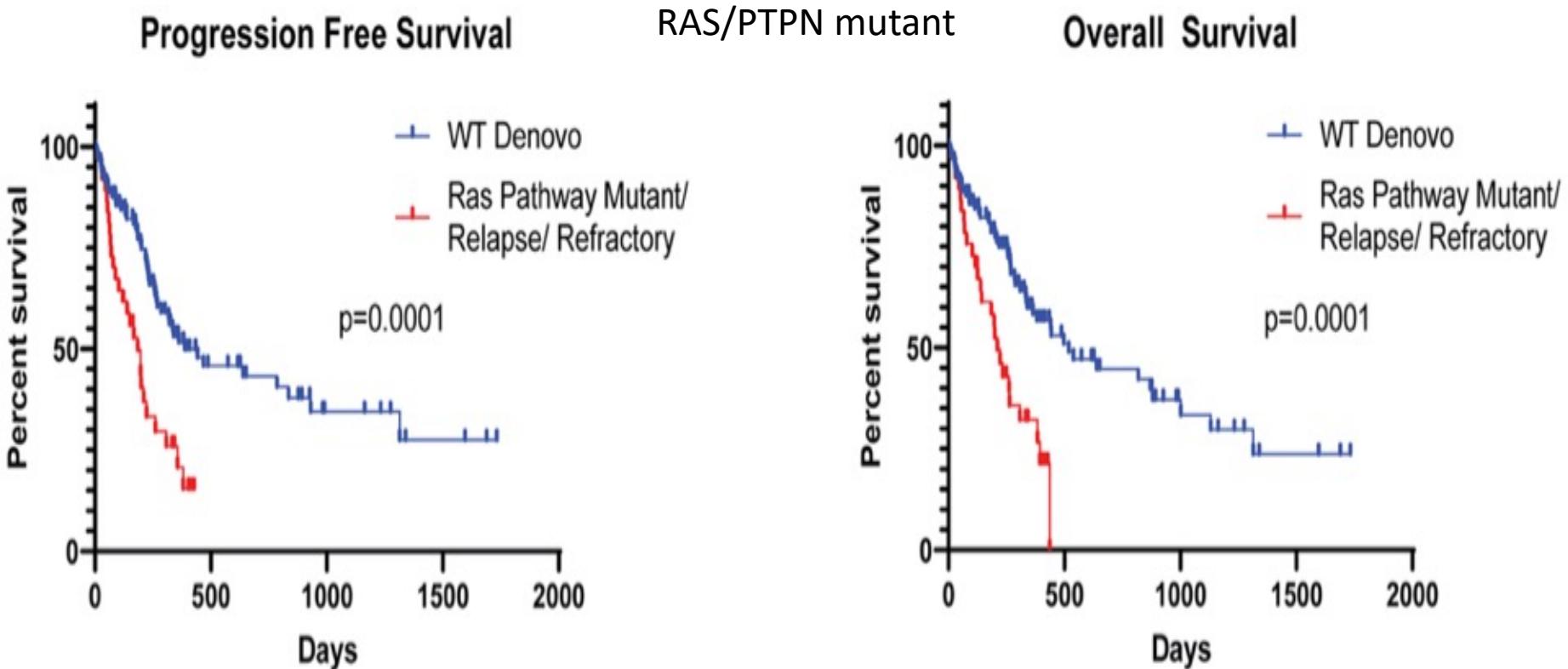
MEET-AML

MEET-AML virtual meeting
2021-11-19

#ERA PerMed



Resistance to ven/aza occurs via up-regulation of fatty acid oxidation (FAO), occurs due to **RAS** pathway mutations



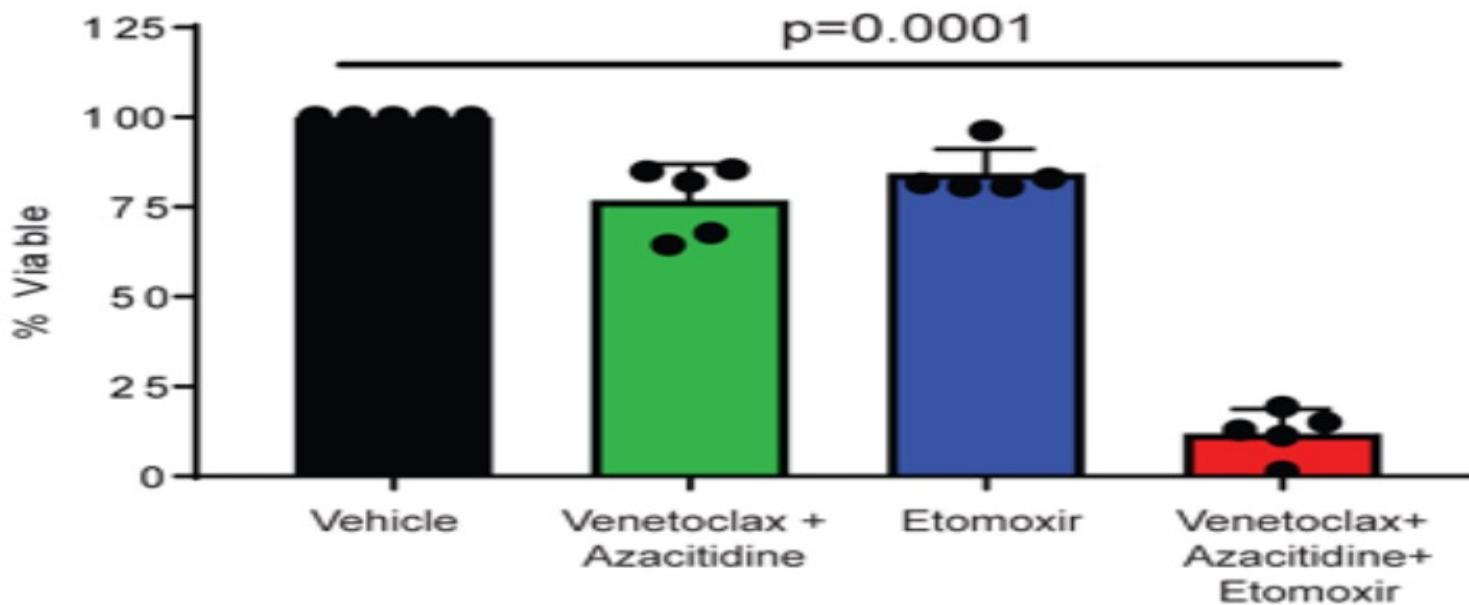
RAS pathway mutations G12x inhibitors on clinical development

Compounds	Company	Mechanism	Clinical trial
AMG 510	Amgen/Carmot Therapeutics	KRAS ^{G12C} inhibitor	NCT03600883
MRTX849	Mirati (ex Array)	KRAS ^{G12C} inhibitor	NCT03785249
KRAS TCR	Gilead (ex Kite/NCI)	Anti-KRAS ^{G12D} engineered T-cell receptor	NCT03745326
AZD4785	AstraZeneca/Ionis	KRAS antisense oligonucleotide	NCT03101839

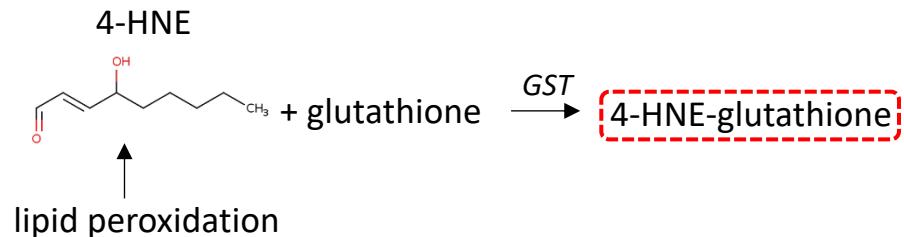
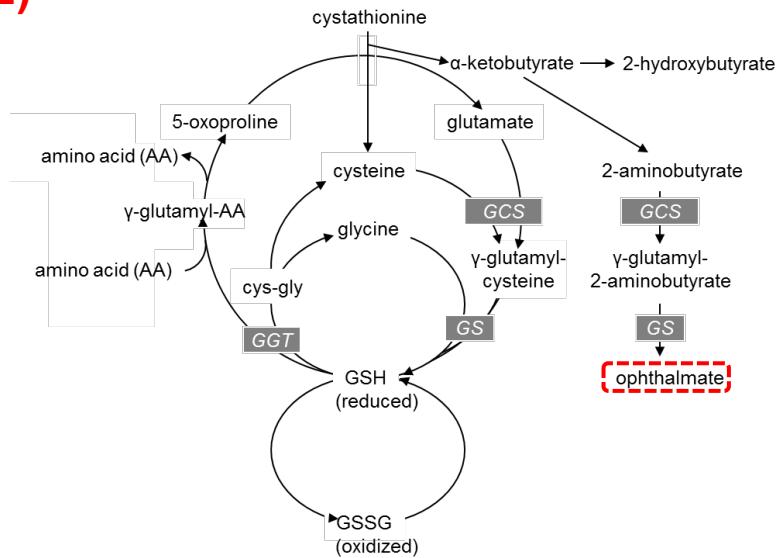
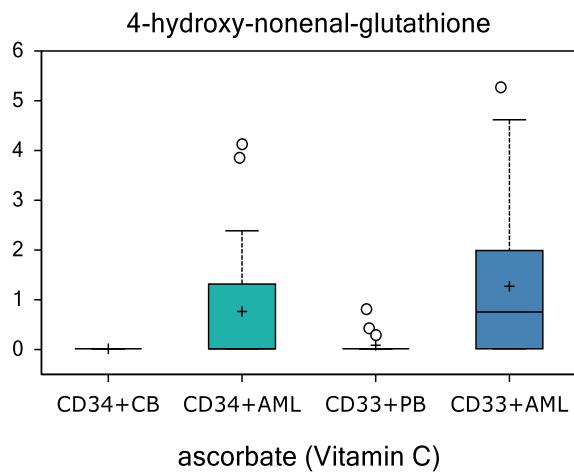
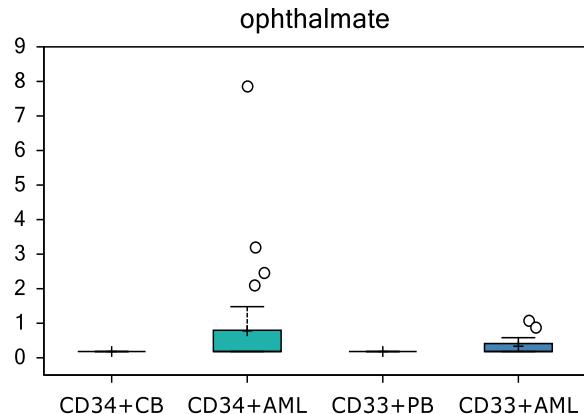
Fatty acid oxidation (FAO), inhibitors in RAS+mut

Lipid biosynthesis

	FASN	TVB-2640	Phase II
ACC		ND-646	
ACC		ND-654	



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



4-HNE is a second messenger of oxidative/electrophilic stress

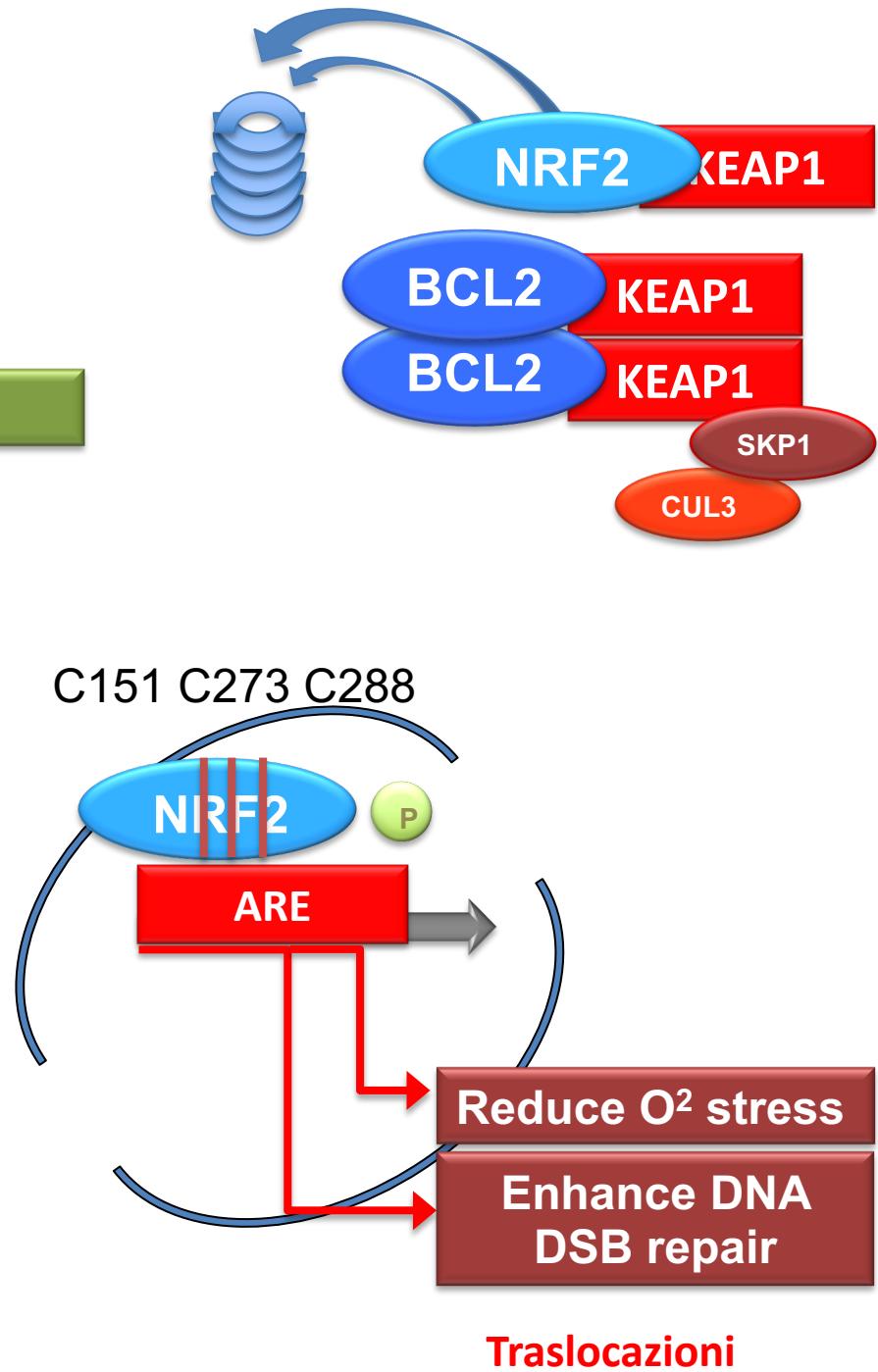
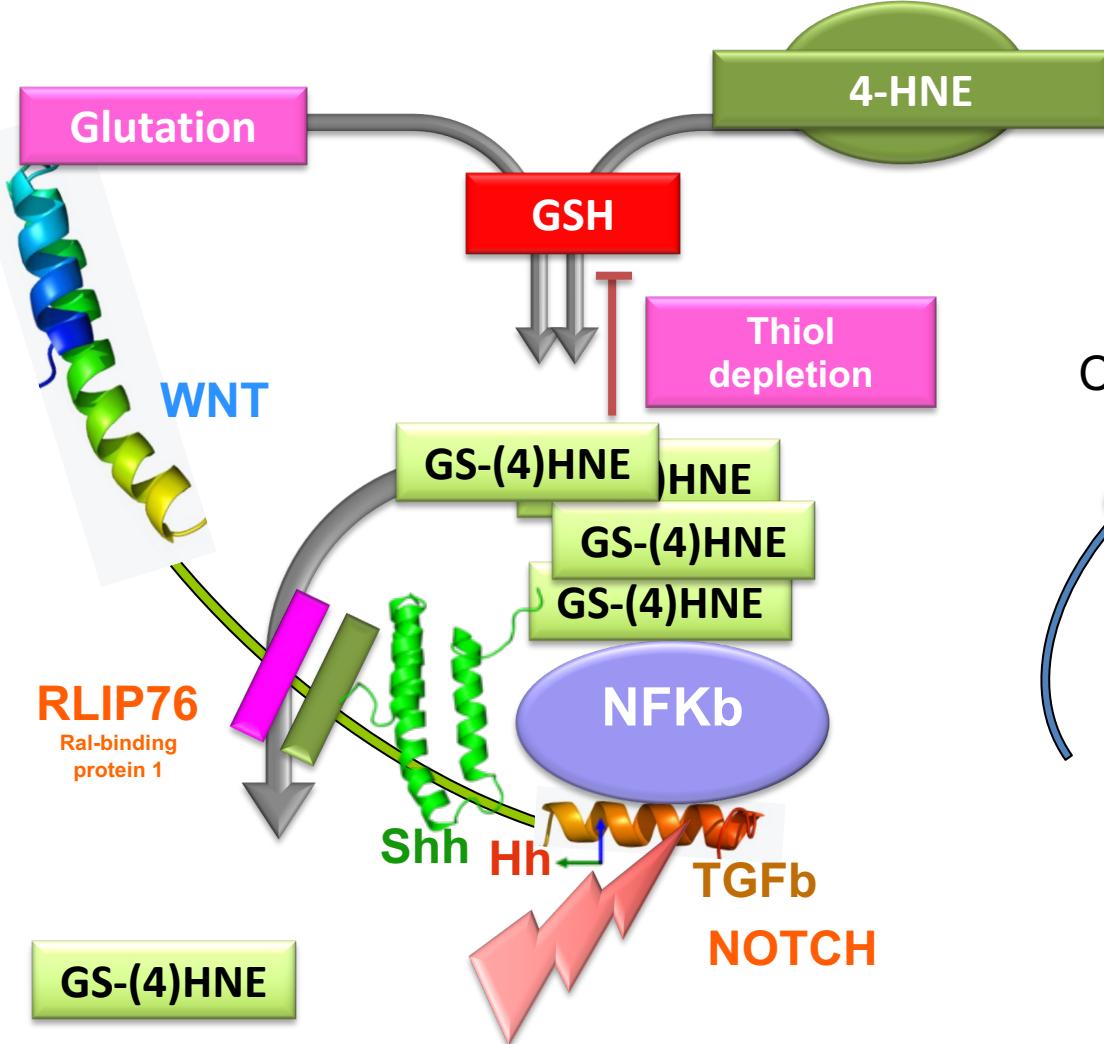
4

dehydroascorbate

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

Venetoclax

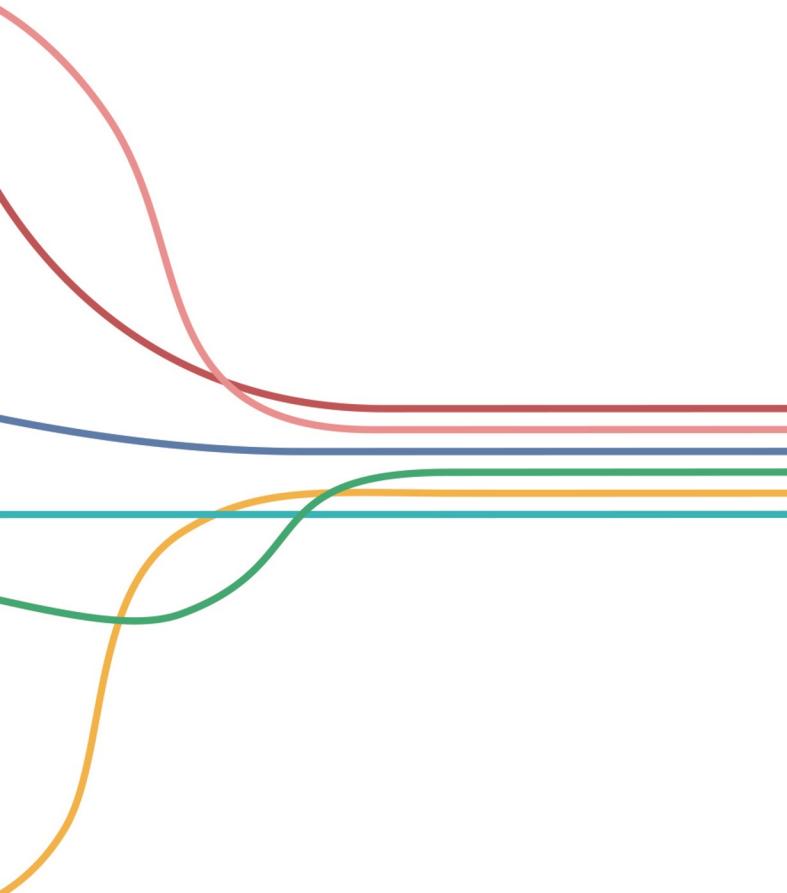
NO APOPTOSIS



Venetoclax + Fludarabine + HDA +/-

Ketogenic diet in cancer
treatment

IRST



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EMILIA-ROMAGNA

Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori"
Istituto di Ricovero e Cura a Carattere Scientifico

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