

Venetoclax in combinazione con chemioterapia o terapia demetilante nel trattamento di mielodisplasie pediatriche ad alto rischio e leucemia mieloide acuta recidivata/refrattaria

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Bologna, 2 Ottobre 2023

XLVIII

CONGRESSO NAZIONALE

AIEOP

Bologna

2-4 Ottobre 2023

// sottoscritto **Francesco Baccelli**

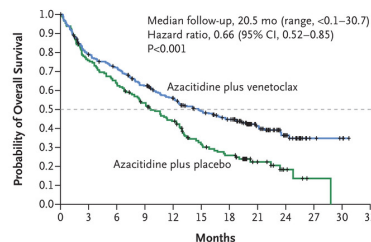
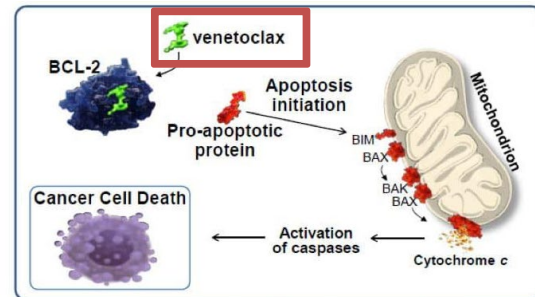
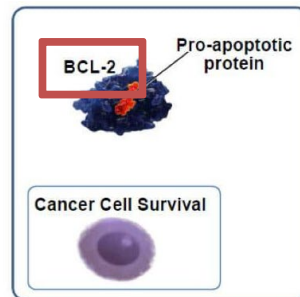
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

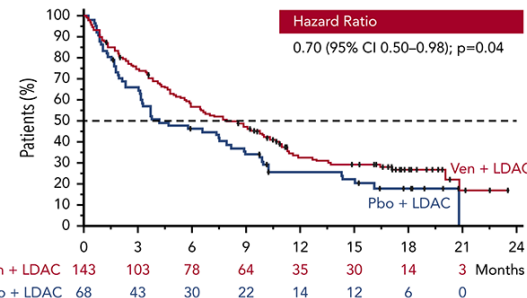
che negli ultimi due anni **NON** ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

Venetoclax

- ❖ l'iperespressione di **Bcl-2** rappresenta un meccanismo di «evasione dall'apoptosi» da parte delle cellule tumorali
- ❖ **Venetoclax** (ABT-199) è un potente inibitore orale selettivo di Bcl-2 (BH3-mimetico) che ripristina il meccanismo di morte cellulare
- ❖ sinergia con farmaci citotossici (citarabina, idarubicina) e ipometilanti (azacitidina)
- ❖ terapie di combinazioni efficaci nel trattamento delle LAM in pazienti adulti «unfit»



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33
Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0



No. at Risk	0	3	6	9	12	15	18	21	24
Ven + LDAC	143	103	78	64	35	30	14	3	0
Pbo + LDAC	68	43	30	22	14	12	6	0	0

Venetoclax in combination with cytarabine with or without idarubicin in children with relapsed or refractory acute myeloid leukaemia: a phase 1, dose-escalation study

Seth E Karol, Thomas B Alexander, Amit Budhreja, Stanley B Pounds, Kristin Canavera, Lei Wang, Joshua Wolf, Jeffery M Klco, Paul E Mead, Soumyasri Das Gupta, Su Y Kim, Ahmed Hamed Salem, Tammy Palenski, Norman J Lacayo, Ching-Hon Pui, Joseph T Opferman, Jeffrey E Rubnitz

- ❖ venetoclax + citarabina alte dosi +/- idarubicina
- ❖ recommended phase2 dose (RP2D) **360 mg/m² (28d)**
- ❖ **CR (+CRi) 14/20 (70%)** nei pazienti trattati a R2PD dopo un ciclo di terapia

Dose	Venetoclax	Cytarabine	Idarubicin	N	CR (MRD-)	CRi (MRD-)	PR	NR
1	240 mg/m ² (max 400 mg)	100 mg/m ² q12h x 20 doses	0	7	14% (14%)	29% (14%)	14%	33%
2a	360 mg/m ² (max 600 mg)	100 mg/m ² q12h x 20 doses	0	5	0	20%	20%	60%
2b	240 mg/m ² (max 400 mg)	1000 mg/m ² q12h x 8 doses	0	3	67% (22%)	0	0	33%
3	360 mg/m ² (max 600 mg)	1000 mg/m ² q12h x 8 doses	0	11	64% (55%)	9% (9%)	9%	18%
4	360 mg/m ² (max 600 mg)	1000 mg/m ² q12h x 8 doses	12 mg/m ²	9	66% (33%)	0	11%	22%

Venetoclax off-label in patologie mieloidi pediatriche

First author, Year, Journal	N° of pts, age	Disease	Combination therapies	Best response	HSCT post ven	Survival post HSCT	Toxicities
<i>Winters 2021 PBC</i>	8 (11 yrs, 2-20)	MDS-EB (2) t-MDS/AML (1) FLT3-ITD AML (3) AML (2) refractory/relapsed	VenX28 + HMA (aza) median 2 cycles (1-9)	CR 75% (6; 1 Cri) NR 25% (2)	4 + 2 pending (50%)	N/A	Neutropenia
<i>Bobeff 2023 Children</i>	National survey: 4 (<10 yrs)	MDR-AML (2), MLL-AML (1) AML (1) refractory/relapsed	VenX28 + chemo (IDA-FLA, ARA-C) (3) / aza (1)	CR 75% (2; 1 Cri), NR 25% (1)	2 (50%)	1 alive disease-free, 1 dead (relapse)	<i>Not reported</i>
<i>Marinoff 2023 PBC</i>	10 (10 yrs, 1-29)	t-MDS/AML (2), ref/rel AML (4), GATA2 MDS (1), MLL AML (2) AML (1)	VenX28 + chemo (ARA-C) (5) / HMA (decitabine, aza) (5)	CR 10% (1), PR/SD 50% (5), NR/PD 40% (4)	2 (25%)	1 alive disease-free, 1 dead	Cytopenia, infections (grade3 50%)
<i>Pfeiffer 2023 BMT</i>	28 (13, 1-21)	AML refractory (5) relapsed (23)	VenX28 + chemo (ARA-C, ida) (25) / HMA (decitabine, aza) (3)	CR 92% (26) (2 Cri), PR/NR 18% (2)	28 (100%)	20 alive disease-free, 8 relapse	<i>Not reported</i>
<i>Trabal 2023 Cancers</i>	43 (18, 1-21)	AML relapsed/refractory, MLL (17), WT1 (13), FLT3-ITD (10) NUP98 (1)	VenX28/X14 + HMA (decitabine, aza) (37) / chemo (6) + GO, gilteritinib, sorafenib, midostaurin, median 2 cycles (1-9)	CR 37% (16, 6 Cri), PR 5% (2), NR 51% (22) n.e. 7% (3)	11 (26%)	6 alive disease-free	Grade 3 neutropenia / febrile neutropenia (49%)
Summary	93 (1-29)	MDS-EB (3), MDR-AML (3), t-MDS/AML (2), rel/refr AML (83)	//	CR 10-92% ORR 42-92%	25-100% bridged to HSCT	50-71% alive disease-free after HSCT	//

On going

- First-line

AML23: Clinical Trial Studying the Safety of Using Venetoclax and Chemotherapy to Treat Newly Diagnosed Childhood AML



St. Jude Children's
Research Hospital

A Collaborative Phase 2 Study of Venetoclax in Combination with Conventional Chemotherapy in Pediatric Patients with Acute Myeloid Leukemia

- Relapsed

ASH meeting 2022; abstract #1459

ITCC-101/APAL2020D: A RANDOMIZED PHASE 3 TRIAL OF FLUDARABINE/CYTARABINE/ GEMTUZUMAB OZOGAMICIN WITH OR WITHOUT VENETOCLAX IN CHILDREN WITH RELAPSED ACUTE MYELOID LEUKEMIA - TRIAL IN PROGRESS -

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Key points dai report pediatrici

Terapia bridge al trapianto
(efficace, sicura, no impatto su
TRM/take/GVHD)

Utilizzo in MDS, MDR-AML,
t-MDS/AML

Fattori associati con la
risposta (genetica? burden
di malattia?)

	Age	Diagnosis	Prev lines	Ven combination therapy	Response	HSCT	Survival post HSCT
<i>Winters 2021</i>	11	t-MDS/AML (RUNX1)	1	Ven/aza	CR MRD+	No	
	7	MDS-EB/RAEB (mon7, ETV6, GATA2, SDS)	0	Ven/aza	CR (<5%)	Yes	Alive disease-free
	8	MDS-EB/RAEB-t (del17p/lossTP53, ASXL1, TET2, NF1)	0	Ven/aza	CR (<5%)	Yes	Alive disease-free (aza post-HSCT)
<i>Bobeff 2023</i>	<6	MDR-AML (mon7, NF1)	1	Ven/chemo	CR	Yes	Dead (relapse post HSCT)
	6-10	MDR-AML (RUNX1)	4	Ven/chemo	NR	No	Dead (PD pre HSCT)
<i>Marinof2023</i>	17	t-AML (mon7, t7;11, PTPN11, SED2, RUNX1, BCOR)	3	Ven/decitabine	PR	No	Dead (PD pre HSCT)
	17	MDS (GATA2)	1	Ven/aza	NR	Yes	Dead (relapse postSCT)
	9	t-MDS (PTPN11)	1	Ven/decitabine	PR (stable disease)	No	Dead (PD pre HSCT)
<i>Raedler 2020</i>	16	MDR-AML (complex karyotype)	2	Ven/decitabine	CR 10 months, then molecular relapse	No	Therapy ongoing (maintenance)
<i>Naviglio 2023</i>	14	MDR-AML (SDS)	2	Ven/aza	PR (92% to 52%)	-No	Dead (PD pre HSCT)

RESEARCH LETTER



TO THE EDITOR:

Venetoclax-based therapies in pediatric advanced MDS and relapsed/refractory AML: a multicenter retrospective analysis

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Design e metodi dello studio

- ❖ Studio retrospettivo multicentrico
- ❖ Pazienti pediatrici con patologie mieloidi ad alto rischio
- ❖ Terapie di combinazione contenenti venetoclax
- ❖ Analisi di risposta clinica, sicurezza, outcome post-TCSE

- **risposta completa (CR)** = blasti $\leq 5\%$ (BM) in assenza di malattia extra-midollare
- **risposta parziale (PR)** = blasti 5-20% o riduzione $> 50\%$
- **non risposta (NR)** = aumento o persistenza blasti $\geq 20\%$ o riduzione $< 50\%$

Roma (OPBG), Friburgo, Bologna, Monza, Padova, Pisa

- LAM r/r
- t-MDS/AML
- MDS-EB (ICC 2022)

- chemioterapici citotossici
- agenti ipometilanti (azacitidina, decitabina)

Popolazione

Patients (n = 31)

n (% or range)

Sex

Male	18 (58.1)
Female	13 (41.9)

Diagnosis

Advanced MDS	4 (23.5)
Relapsed AML	11 (35.5)
Refractory AML	7 (22.6)
Postcytotoxic therapy MDS/AML	9 (29.0)

Age, y, median (range)

10.2 (1.3-17.4)

Extramedullary disease

No	29 (93.5)
Yes	2 (6.5)

BM blast at diagnosis, median (range)

25% (0-95)

BM blasts before the first venetoclax therapy, median (range)

20% (0-80)

Previous lines of therapies since last complete response, median (range)

3 (1-7)

0	4 (23.5)
1	3 (17.6)
2	2 (11.8)
≥ 2	8 (45.1)

Previous HSCT

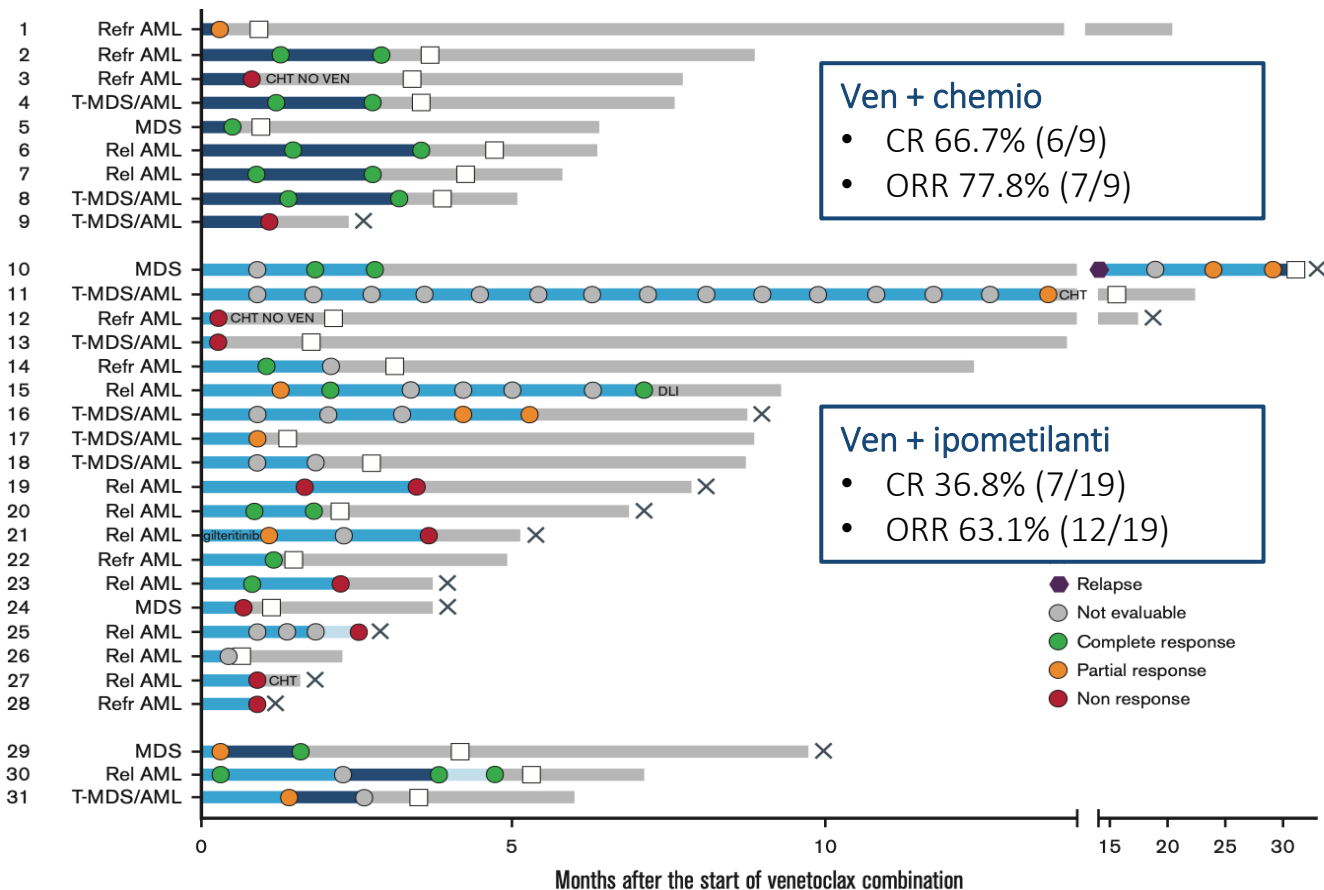
0	18 (58.1)
1	9 (29.0)
2	4 (12.9)

Unfavorable genetics

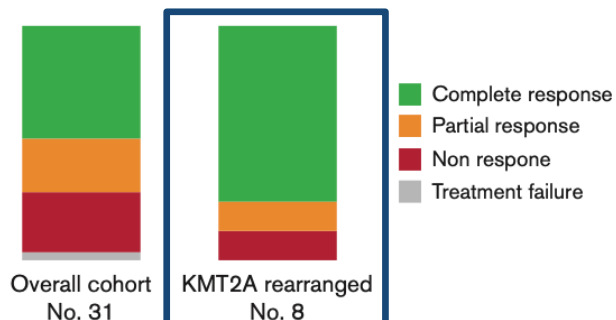
KMT2A rearrangements	8 (25.8)
- 7/del7q	6 (19.3)
FLT3-ITD	5 (16.1)
Complex karyotype	2 (6.5)
KRAS	2 (6.5)
PTPN11	1 (3.2)
No. of venetoclax cycles per patient, median (range)	2 (1-15)

Terapia con venetoclax

- ❖ dose **350 mg/mq/d** (escalation d1-3 in 25/31 pts)
- ❖ ciclo **28 giorni** (14-28)
- ❖ combinazione con **farmaci ipometilanti** (19 pts), **citotossici** (9) o **entrambi** (3)
- ❖ buon profilo di tossicità → 1 pancitopenia grado IV CTCAE, stop Ven dopo 9 giorni (**1 TF - treatment failure**)

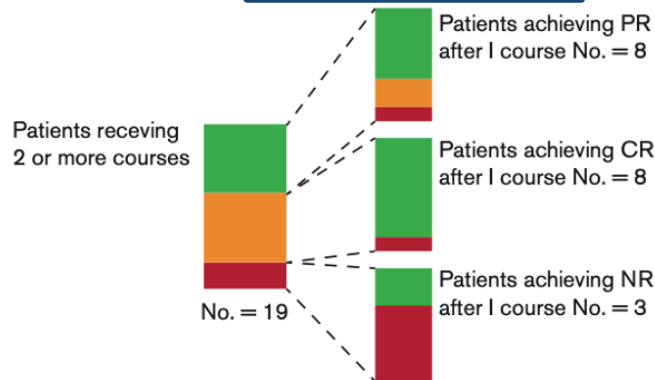


Best response to venetoclax combination

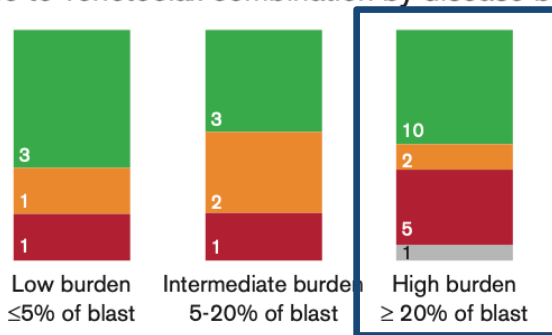


N° di cicli mediano per ottenere la migliore risposta = **1 (1-7)**

Response after 11 courses of venetoclax

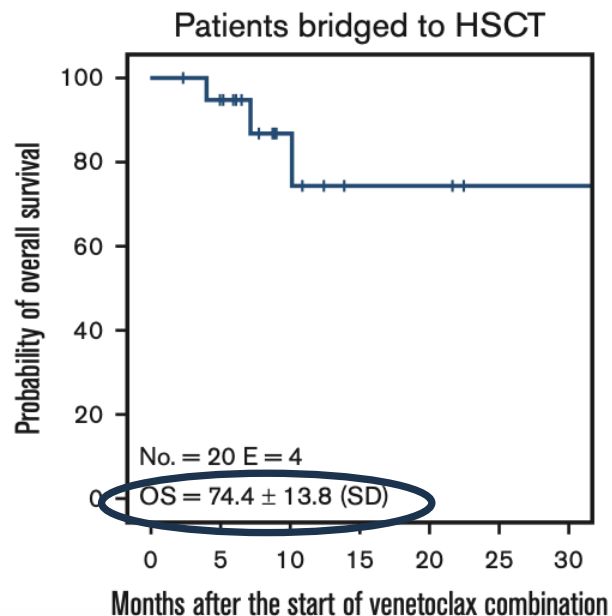
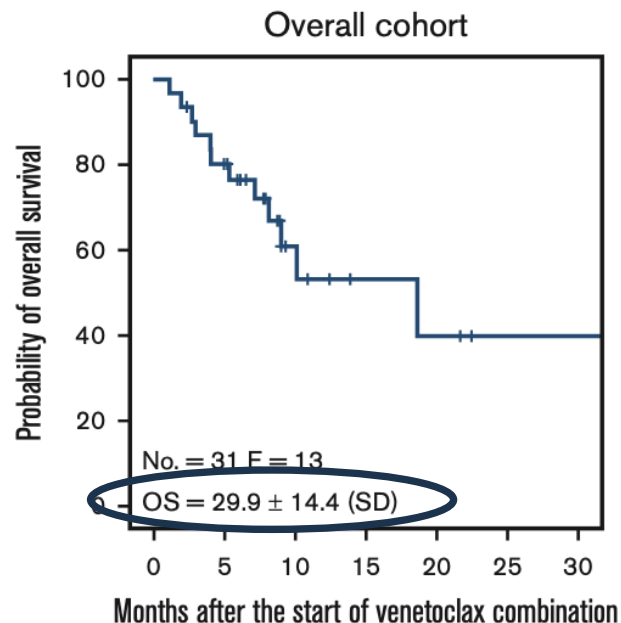


Best response to venetoclax combination by disease burden



Outcome

- ❖ follow-up mediano **7.7 mesi** (1.1-32.3)



Conclusioni e limiti

- ❖ Le terapie di combinazioni contenenti venetoclax hanno indotto una risposta nei pazienti pediatrici con patologie mieloidi ad alto rischio, anche in presenza di elevato burden di malattia
- ❖ Efficace bridge al TCSE in una popolazione intensamente pretrattata
- ❖ OS favorevole nei pazienti sottoposti a TCSE
- ❖ Limiti: breve follow-up, piccola coorte, eterogeneità

Domande aperte

- ☐ Valutazione della risposta pre-trapianto nei pazienti con MDS
- ☐ Definizione dell'endpoint clinico (riduzione % blasti pre-trapianto? EFS e TRM post-trapianto?)
- ☐ Scelta della terapia di combinazione (FLA, HD-ARAC, AZA?)
- ☐ Dose e durata ottimale della terapia nei pazienti pediatrici (formulazione orale pediatrica)
- ☐ Fattori biologici predittivi di risposta (espressione Bcl-2, BH3 profiling, risposta in vitro?)
- ☐ Sottogruppi genetici con particolare suscettibilità (KN)

Received: 20 March 2023 | Accepted: 5 June 2023

DOI: 10.1111/bjh.18936

LETTER TO THE EDITOR



Successful treatment of a chemotherapy-resistant t(17;19) paediatric ALL with a combination of inotuzumab, venetoclax and navitoclax

HemaSphere



P405 IN VITRO RESPONSE TO BCL-2 INHIBITION IN PEDIATRIC B PRECURSOR ALL WITH HIGH RISK CYTOGENETICS

Topic: 2. Acute lymphoblastic leukemia - Clinical

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**GRUPPO DI RICERCA SUL MICROBIOTA E TRAPIANTO DI
CELLULE STAMINALI EMOPOIETICHE PEDIATRICO**