ALAN

Acute Leukemia Advocates Network

WEBINAR:
UNRAVELLING EHA'S KEY TOPICS: PATIENT AND HCP PERSPECTIVES

JULY 02, 2024

www.acuteleuk.org

Agenda

Time (CEST)	Topic
12:30 PM	Welcome Moderator: James Badman, Colab Health
12:35 PM	Presentation of topics from EHA Speaker: Dr. Pramila Krishnamurthy, Consultant Hematologist, Kings College London
1:00 PM	Discussion on the implications of the clinical data at EHA on the patient community Moderator: Anne-Pierre Pickaert, Patient Advocate
1:10 PM	Q&A session Moderator: James Badman. Anne-Pierre Pickaert and Dr. Pramila Krishnamurthy to answer questions
1:30 PM	Close

Housekeeping

Q&A Session

Please use the Q&A window to write a question and the moderator will ask it on your behalf

Technical Issues

If you are facing any technical difficulties, please let us know in the chat function and someone from our technical team will reach out to you

Recorded

Will be available on the ALAN website www.acuteleuk.org

Why are we holding the webinar today?

- **Webinar part of ALAN's broader initiative:** Includes detailed reports, infographics, and interactive webinars (all available on the website)

- **Our aim is to:**
  - **Take the complex acute leukemia medical research from the recent European Hematology Association (EHA) Congress and communicate key highlights in a format and language that is easily understood by advocates and patients**

Presentation of topics from EHA

Dr. Pramila Krishnamurthy:

- Consultant Hematologist, Kings College London
- She has contributed significantly to the field through her clinical practice and research endeavors
- Dr. Krishnamurthy is known for her expertise in leukemia treatment and her commitment to advancing medical knowledge and improving patient outcomes

Updates from EHA 2024

ACUTE PROMYELOCYTIC LEUKEMIA (APL)

FIRST RESULTS OF THE APOLLO TRIAL: A RANDOMIZED PHASE III STUDY TO COMPARE ATO COMBINED WITH ATRA VERSUS STANDARD AIDA REGIMEN FOR PATIENTS WITH NEWLY DIAGNOSED, HIGH-RISK ACUTE PROMYELOCYTIC LEUKEMIA

Background

- For patients with low- or intermediate-risk APL, the standard front-line treatment involves a combination of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO)
- Patients with high-risk APL are typically treated with ATRA plus chemotherapy (AIDA being the gold standard)
- The combination of ATRA /ATO had not been studied in high-risk APL in randomized clinical trials

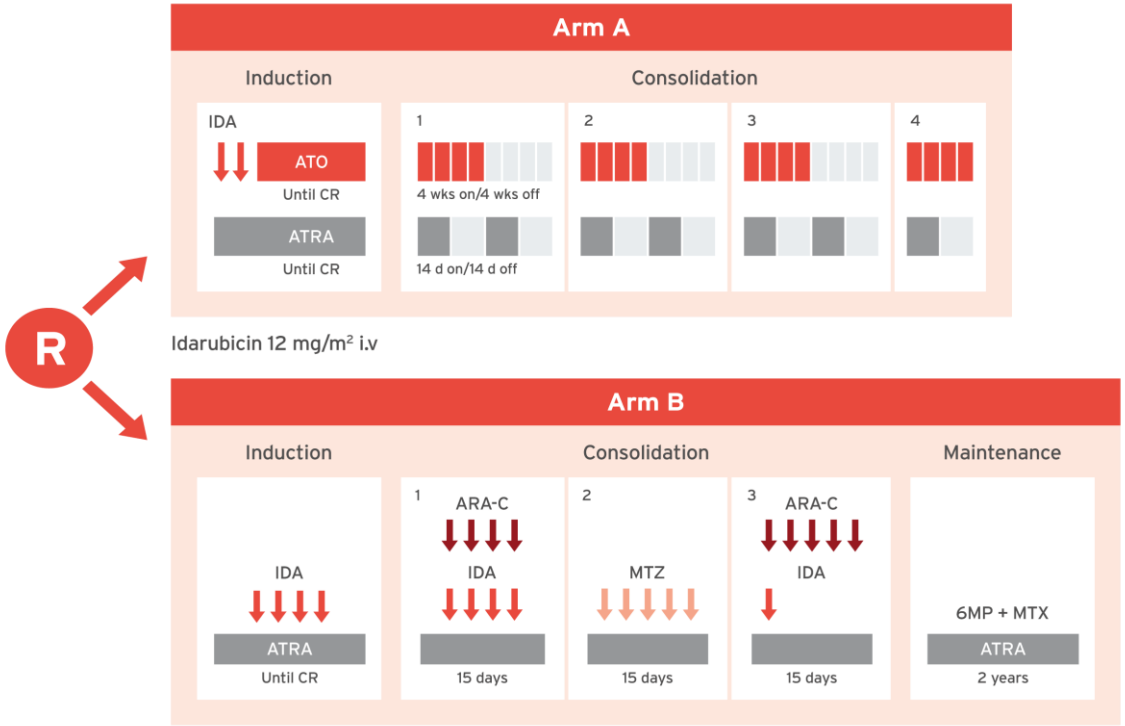
Abbreviations: AIDA, ATRA + idarubicin; APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; ATO, arsenic trioxide.

Reference: Platzbecker U, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S102.

APOLLO: Open-label, multicenter, Phase III trial

Select inclusion criteria:

- Newly-diagnosed APL
- Age 18–65 years
- WBC at diagnosis >10 GPt/l
- ECOG PS 0–3



Abbreviations: ARA-C, cytarabine; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CR, complete response; d, day; IDA, idarabucin; ECOG PS, Eastern Cooperative Oncology Group Performance Status; i.v., intravenous; MTX, methotrexate; MTZ, mitoxantrone; R, randomized; 6MP, 6-mercaptopurine.

Reference: Platzbecker U, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S102.

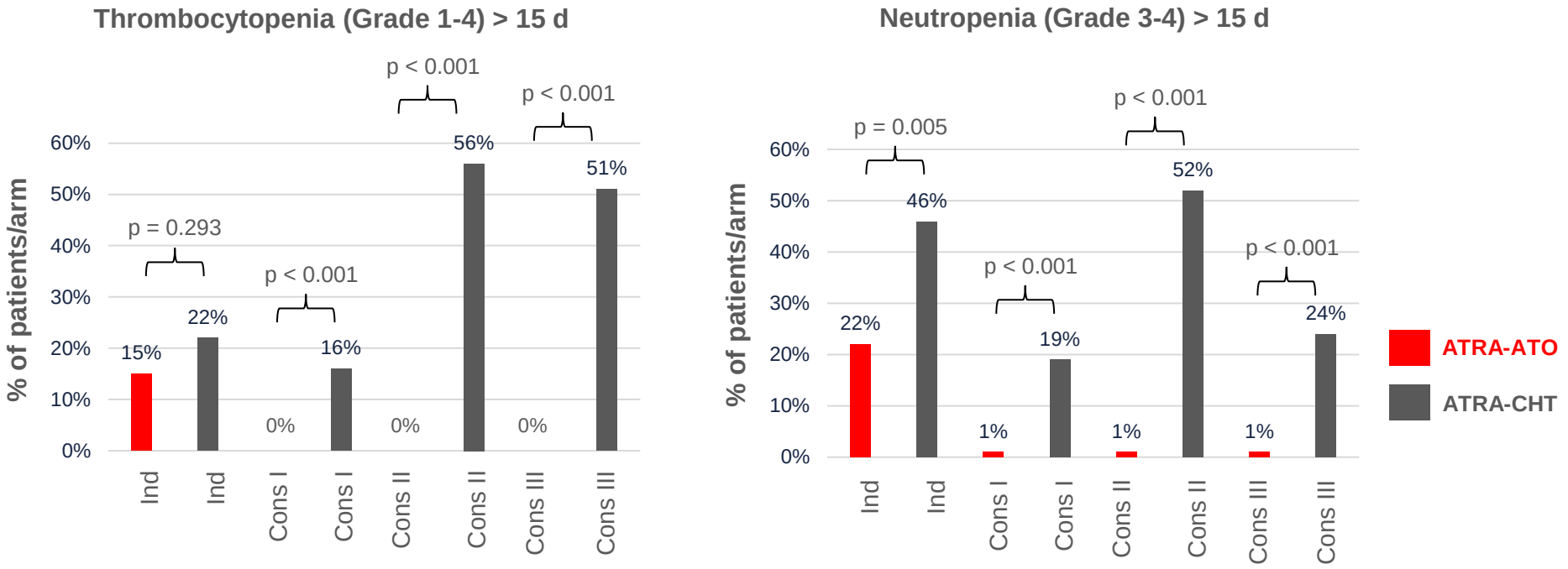
APOLLO: Patient characteristics

	ATRA-ATO (n=68)	ATRA-CHT (n=63)	Total (n=131)	P value
Age, (years)				
Median	46.5	44.0	**46.0**	0.910
Range	18–66	18–65	18–66	
Sex, n (%)				
Female	34 (50%)	29 (46.0%)	63 (48.1%)	0.650
Male	34 (50%)	34 (54.0%)	68 (51.9%)	
WBC count (x10^9/L)				
Median	33.5	36.4	**35.7**	0.866
Range	10.4-489.0	10.1–339.0	10.1–489.0	
ECOG PS				
Median	1	1	**1**	0.381
Range	0–3	0–3	0–3	

Abbreviations: ATO, arsenic trioxide; ATRA, all-trans retinoic acid; ECOG PS, Eastern Cooperative Oncology Group Performance Status; WBC, white blood cell.

Reference: Platzbecker U, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S102.

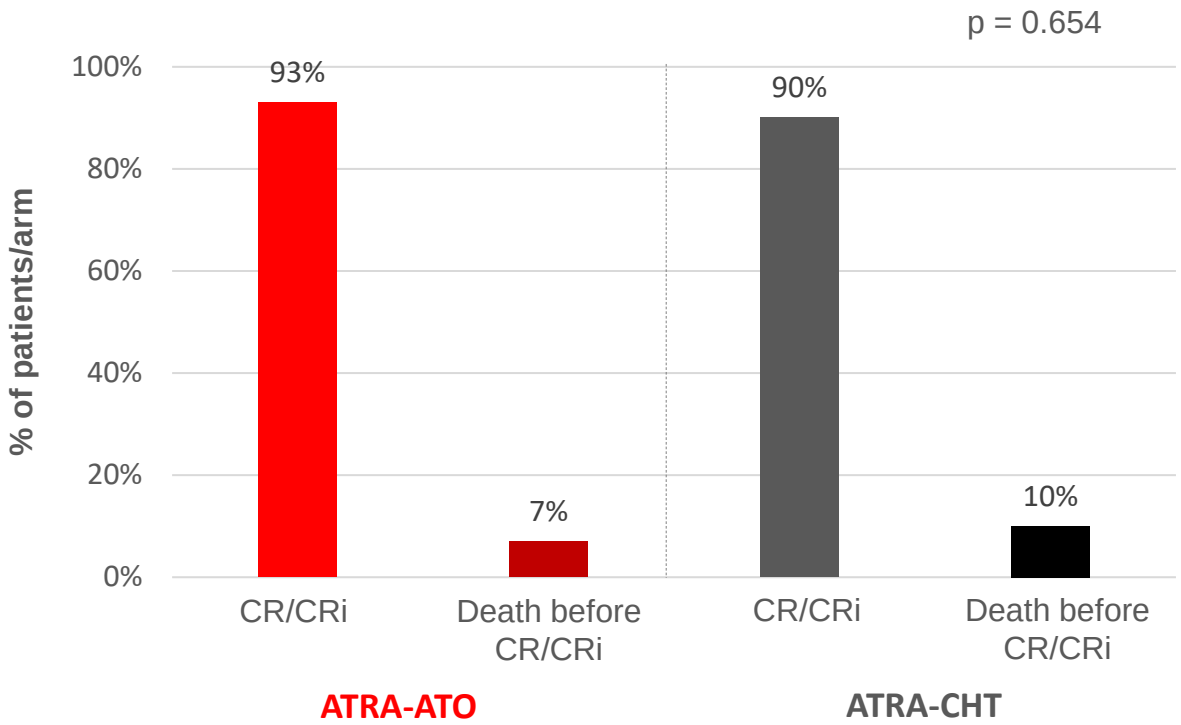
APOLLO: Hematologic toxicity



Abbreviations: ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CHT, chemotherapy; Cons, consolidation; Ind, induction.

Reference: Platzbecker U, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S102.

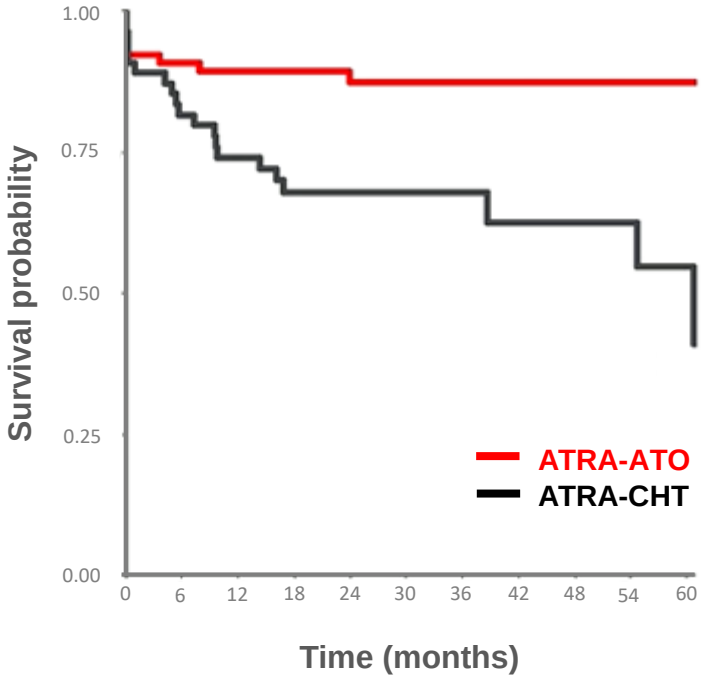
APOLLO: Induction outcome



Abbreviations: ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CHT, chemotherapy; CR(i), complete response (with incomplete count recovery).

Reference: Platzbecker U, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S102.

APOLLO: Primary endpoint - event-free survival (EFS)



Primary endpoint: 2-year EFS

	2-year survival	95% CI	P value
ATRA-ATO	88%	80– 96%	0.02
ATRA-CHT	70%	59–83%	

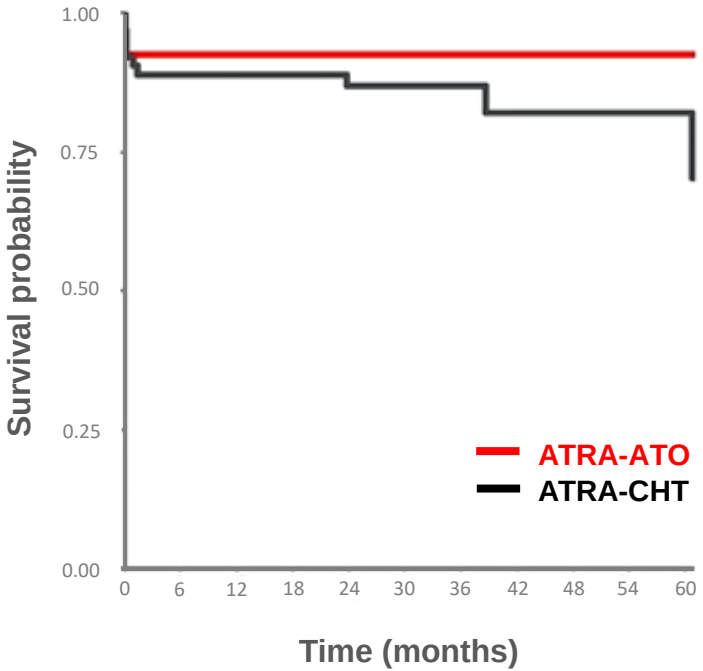
5-year EFS

	5-year survival	95% CI	P value
ATRA-ATO	87%	79– 96%	0.0034
ATRA-CHT	55%	38–78%	

Abbreviations: ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CHT, chemotherapy; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EFS, event-free survival; WBC, white blood cell.

Reference: Platzbecker U, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S102.

APOLLO: Overall survival (OS)



2-year OS

	2-year survival	95% CI	P value
ATRA-ATO	93%	87– 99%	0.17
ATRA-CHT	87%	78–96%	

5-year OS

	5-year survival	95% CI	P value
ATRA-ATO	93%	87– 99%	0.17
ATRA-CHT	82%	71–95%	

Abbreviations: ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CHT, chemotherapy; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; OS, overall survival; WBC, white blood cell.

Reference: Platzbecker U, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S102.

APOLLO: Conclusions

- **First-line therapy with ATRA-ATO** with two initial doses of idarubicin results in **superior EFS compared with conventional ATRA-CHT in patients with HR-APL**

- Further analysis of the APOLLO trial may support the implantation of this regimen as the **new standard of care in patients with high-risk APL**

Abbreviations: ATO, arsenic trioxide; ATRA, all-trans retinoic acid; CHT, chemotherapy; EFS, event-free survival; HR-APL, high-risk acute promyelocytic leukemia.

Reference: Platzbecker U, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S102.

Updates from EHA 2024

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

BLINATUMOMAB FOR FIRST LINE TREATMENT IN INTERMEDIATE AND HIGH RISK DOWN SYNDROME B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA: INITIAL FINDINGS FROM THE ALLTOGETHER1 DS TRIAL

Background

- Down syndrome leads to a 10–20-fold increased risk of ALL, accounting for 2–3% of all pediatric cases
- Children with Down Syndrome ALL (DS-ALL) have inferior outcomes, due to the twin challenges of **disease resistance** and **higher treatment-related mortality**, underscoring the need for innovative strategies
- Blinatumomab is a CD3-/CD19-directed bispecific T-cell engager
- Given the promising outcomes in relapsed/refractory B-ALL, the hypothesis was that blinatumomab could be used as a chemotherapy replacement:
  - For increased efficacy – greater measurable residual disease (MRD) clearance
  - For increased safety – reduce treatment-related mortality

Abbreviations: ALL, acute lymphoblastic leukemia; DS, Down Syndrome; MRD, measurable residual disease.

Reference: Samarasinghe S, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S111.

ALLTogether1: Presentation summary

- Initial results of the Phase 2, ALLTogether1 DS trial, investigating blinatumomab as chemotherapy-replacement for children/young adults with newly-diagnosed DS B-ALL
- ALLTogether1 met the primary endpoint
  - Blinatumomab shows impressive activity (91% patients [31/33] MRD undetectable)
- No relapse, second cancers, or deaths so far
- Need further follow-up (median 15 months)
- High rate of seizure in patients aged over 10 years old despite prophylaxis
  - Led to updated seizure prophylaxis aiming to achieve therapeutic levels prior to the start of blinatumomab
- Lower rate of Grade 3/4 toxicity events vs historical controls (UKALL 2011 trial)

Abbreviations: ALL, acute lymphoblastic leukemia; DS, Down Syndrome; MRD, measurable residual disease.

Reference: Samarasinghe S, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S111.

PONATINIB VERSUS IMATINIB IN PATIENTS WITH NEWLY DIAGNOSED PH+ ACUTE LYMPHOBLASTIC LEUKEMIA IN THE PHASE 3 PHALLCON TRIAL: IN-DEPTH RESPONDER ANALYSIS

Background

- Ponatinib is a third-generation BCR::ABL1 tyrosine kinase inhibitor (TKI) that has potent activity against all clinically-relevant variants of BCR::ABL
- In March 2024, the US FDA approved ponatinib + chemotherapy for the treatment of adults with newly diagnosed Ph+ ALL based on the results of the Phase 3 PhALLCON trial
- PhALLCON is the first global, Phase III trial to compare two TKIs in adults with newly diagnosed Ph+ ALL
  - The primary endpoint, the MRD-negative CR rate at EOI, was clinically meaningful and significantly higher with ponatinib vs imatinib + reduced-intensity chemotherapy (34.4% vs 16.7%; P=0.002)
  - Safety data indicate that ponatinib has a comparable safety profile to imatinib
- The analysis presented at EHA 2024 investigated rates of MRD negativity at any time, PFS by age, and BCR::ABL1 variant subgroups, as well as exploring outcomes in patients who proceeded to HSCT

Abbreviations: CR, complete response; EOI, end of induction; EHA, European Hematology Association; HSCT, hematopoietic stem cell transplantation; TKI, tyrosine kinase inhibitor; US FDA, United States Food and Drug Administration; MRD, measurable residual disease; PFS, progression-free survival; Ph+ ALL, Philadelphia chromosome-positive ALL.

Reference: Ribera J-M, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S115.

PhALLCON: Patient demographics and baseline characteristics well balanced

- N=245 patients randomized
  - n=164 ponatinib
  - n=81 imatinib
- N=232 patients had p190/p210 confirmed
  - n=154 ponatinib
  - n=78 imatinib
- At data cut-off (Aug 12, 2022), median follow-up was 19.4 months for patient with confirmed p190/p210

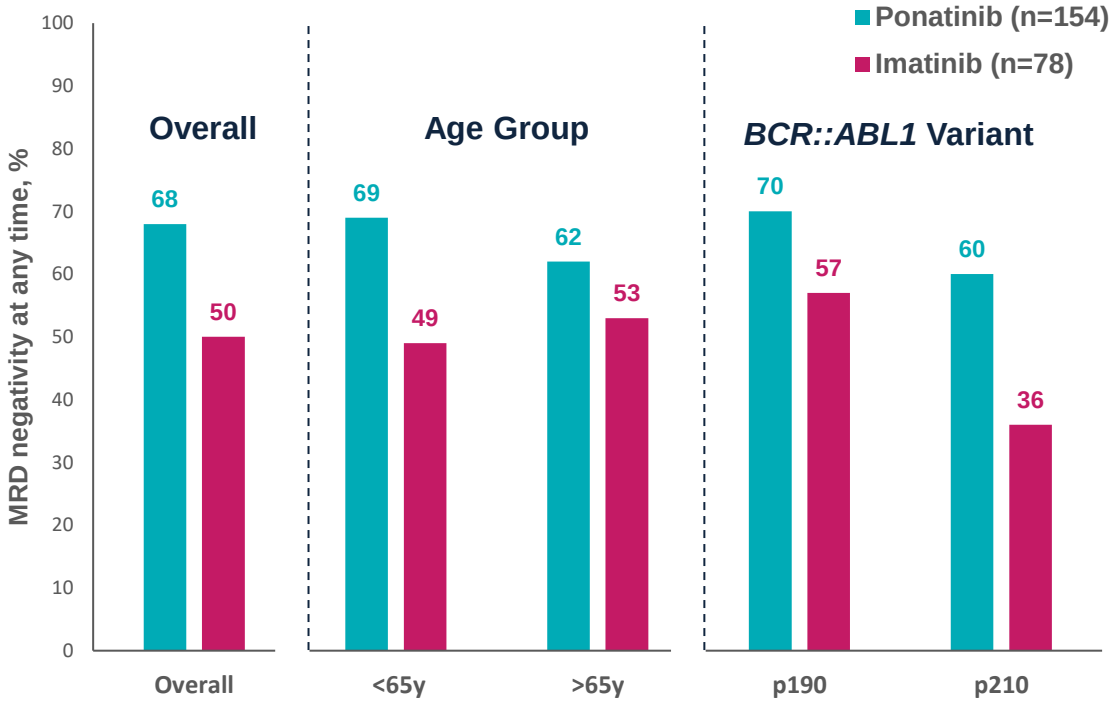
Characteristic	Ponatinib arm (n=154)	Imatinib arm (n=78)
Age, y, median (range) ≥65 y, %	54.5 (19–82) 22	52.5 (19–75) 19
Female, %	55	51
ECOG PS 0 or 1, %	95	95
Leukocyte count, x 10^9/L, median (range)	4.4 (0.4–197.3)	3.0 (0.2–81.2)
Leukemic blasts, %, median (range)	80 (0–100)	73 (0–100)
BCR::ABL1 dominant variant, % p190 p210	 74 26	 68 32

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Reference: Ribera J-M, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S115.

PhALLCON: MRD negativity at any time

- Rates of MRD negativity at any time were higher with ponatinib
- Although not statistically significant in all subgroups, the trend for the benefit of ponatinib was similar across age and variant subgroups

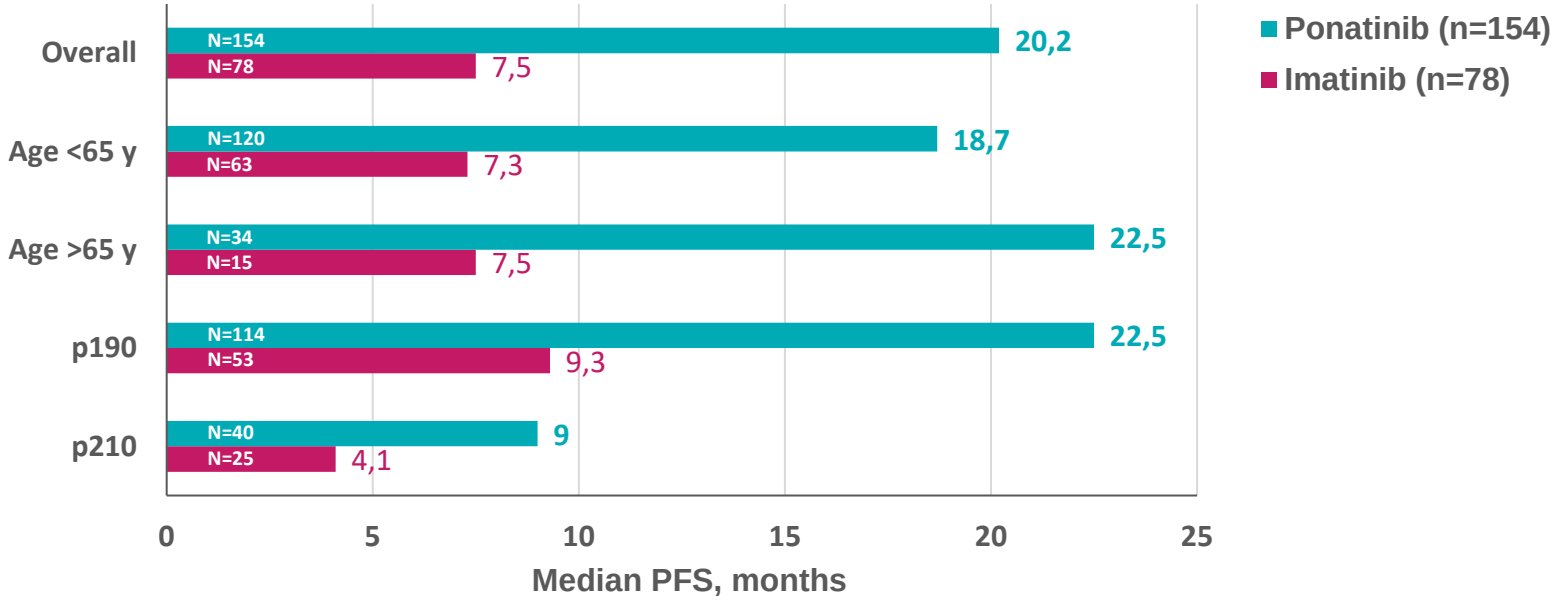


Abbreviations: ALL, acute lymphoblastic leukemia; MRD, measurable residual disease; RR, response rate.

Reference: Ribera J-M, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S115.

PhALLCON: Progression free survival

- Median PFS was longer with ponatinib vs imatinib, with similar benefit of ponatinib across age and variant subgroups

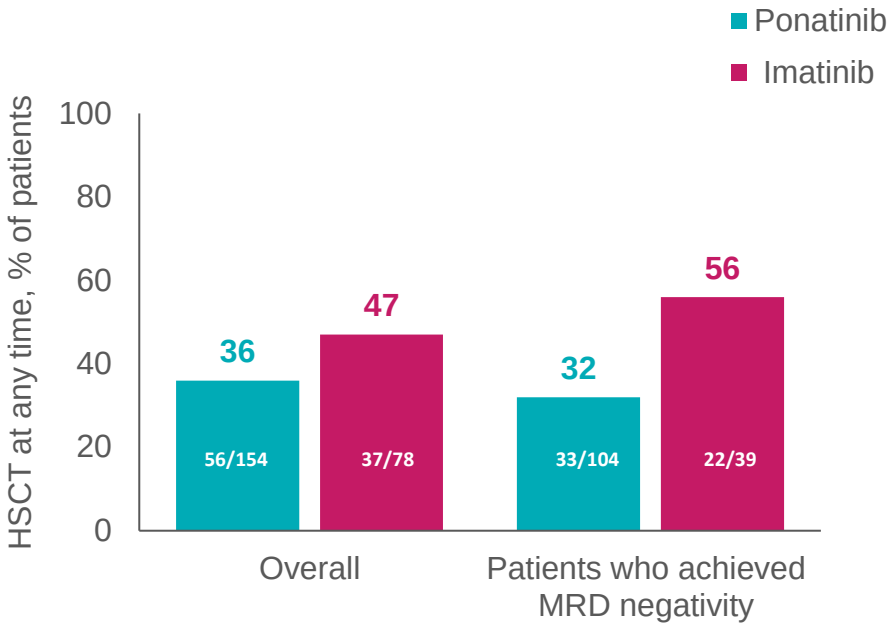


Abbreviations: ALL, acute lymphoblastic leukemia; PFS, progression free survival.

Reference: Ribera J-M, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S115.

PhALLCON: Outcomes by HSCT status

- The proportion of patients proceeding to HSCT (per investigator's discretion) at any time was lower in the ponatinib arm than in the imatinib arm (36% vs 47%)
- Among patients who achieved MRD negativity, the proportion who received HSCT was lower in the ponatinib arm than in the imatinib arm (32% vs 56%)



Abbreviations: ALL, acute lymphoblastic leukemia; HSCT, hematopoietic stem cell transplantation; MRD, measurable residual disease.

Reference: Ribera J-M, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S115.

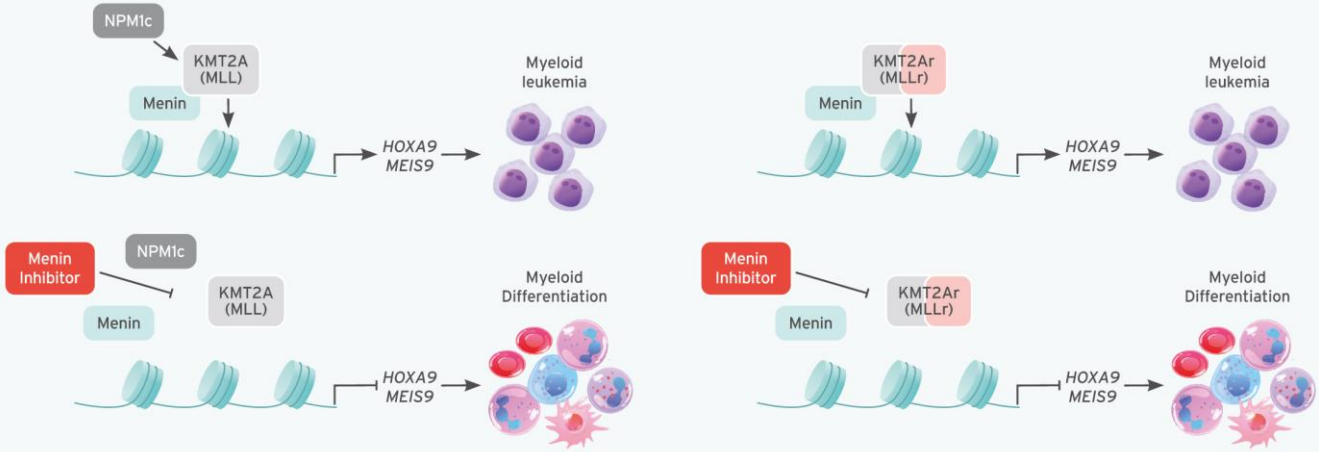
Updates from EHA 2024

ACUTE MYELOID LEUKEMIA (AML)

MENIN INHIBITORS

Menin inhibitors in acute leukemias

- Menin inhibitors in clinical development have shown promise for patients with AML and *KMT2A* rearrangements or *NPM1* mutations



MLL/KMT2A rearranged (KMT2Ar) and cytosolic resticted NPM1 (NPM1c) acute leukemias are driven by aberrant expression of HOX/MEIS1 that are dependent on menin-KMT2A interation.

Figure adapted from Hertlein E, et al. EHA Congress; June 14, 2024: Madrid, Spain. Abstract S130.

Abbreviations: AML, acute myeloid leukemia.

Reference: Hertlein E, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S130.

Common side effects and clinical challenges of menin inhibitors

- **QT interval prolongation** and **differentiation syndrome** (including severe and fatal) have been adverse events observed with some menin inhibitors[1]
  - These require close monitoring and interventions (including steroid prophylaxis for DS) to prevent such potentially life-threatening consequences
- Dose adjustment due to **Drug-Drug interactions** with CYP3A4 inhibitors such as azole antifungal agents are needed with some menin inhibitors[1]
- **Resistance mutations**: Early trials with menin inhibitors have reported that some patients develop mutations in the *MEN1* gene, representing a mechanism of acquired resistance during therapy[2]

Abbreviations: DS, differentiation syndrome.

References: 1. Daver N, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S132; **2.** Hertlein E, et al. Presentation at 29th EHA Congress, Madrid. June 13–16, 2024. Abstract #S130.

Phase 1–2 trials and pre-clinical studies of menin inhibitors were presented at EHA 2024, including:

1. **DSP-5336**

   First-in-human Phase 1/2 study of the menin-MLL inhibitor **DSP-5336** in patients with relapsed or refractory acute leukemia: updated results from dose escalation[1]

2. **Bleximenib (JNJ-75276617)**

   A phase 1b study of the menin-KMT2A inhibitor **JNJ-75276617 in combination with venetoclax and azacitidine** in relapsed/refractory acute myeloid leukemia with alterations in KMT2A or NPM1[2]

3. **Balomenib ZE63-0302**

   The novel menin inhibitor **ZE63-0302** has an impressive safety profile and unique chemistry that suggests improved efficacy against resistance mutations[3]

References: 1. Daver N, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S132; **2.** Wei H, et al. Presentation at 29th EHA Congress, Madrid. June 13–16, 2024. Abstract #S133; **3.** Hertlein E, et al. EHA Congress, Madrid. June 13–16, 2024. Abstract #S130.

1. DSP-5336: Presentation summary

- Phase 1 dose escalation/optimization and Phase 2 dose expansion of DSP 5336
- Patients with R/R acute leukemia (AML or ALL) were eligible, with no limit on prior therapies and a focus on patients with *KMT2Ar* and *NPM1m* (N=57)
- DSP-5336 was well tolerated with no DLTs and no clinical severe DS episodes to date
- Overall response rate of 57% and CR + CRh of 24% in patients with R/R AML and *KMT2Ar* or *NPM1m* receiving therapeutic doses (n=21; ≥140mg twice a day)
- Dose optimization is ongoing in the global study to identify a recommended dose for Phase 2 expansion (RP2D)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CR, complete response; DLT, dose-limiting toxicity; DS, differentiation syndrome; EHA, European Hematology Association; RP2D, recommended phase II dose; R/R, relapsed/refractory.

Reference: Daver N, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S132.

2. Bleximenib (JNJ-75276617): Presentation summary

- Single agent activity of bleximenib was previously reported in a Phase 1 study in patients with R/R AML harboring *KMT2A* or *NPM1* alterations
- Synergistic antiproliferative activity of bleximenib in combination with venetoclax (VEN) + azacitidine (AZA) has been demonstrated in preclinical studies
- The ongoing Phase 1b is determining the safety and preliminary clinical activity of bleximenib in combination with VEN + AZA in adults with *KMT2A*- and *NPM1*-altered AML
- Bleximenib combination therapy well tolerated (n=60). DS observed in 3%. No bleximenib-related events of QT prolongation or TLS
- Preliminary clinical activity observed
  - Efficacy population (n=34; 250 mg BID): ORR 79%; CR/CRh/CRi 41%
  - In participants with prior VEN exposure (n=17): ORR 65%; CR/CRh/CRi 29%
- Phase 1 dose escalation ongoing to identify RP2D

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine, CR(h)[i], complete remission (with partial count recovery) [with incomplete hematological recovery]; ORR, overall response rate; RP2D, recommended Phase II Dose; R/R, relapsed/refractory, TLS, tumour lysis syndrome; VEN, venetoclax.

Reference: Wei H, et al. Presentation at 29th EHA Congress, Madrid. June 13–16, 2024. Abstract #S133.

3. Balomenib (ZE63-0302): Pre-clinical study summary

- Balomenib (ZE63-0302) is a next generation menin inhibitor
- The aim was to develop a novel potent selective menin inhibitor with fewer cardiac side effects and reduced likelihood of developing treatment resistant mutations
- Balomenib demonstrated a favorable PK profile in mice and exhibited good single-agent efficacy
- No cardiac side effects were observed in dogs after balomenib dosing
- Balomenib exhibited unique chemistry that suggests improved efficacy against resistance mutations
- Combination strategies with balomenib + BLC2 inhibitor or + FLT3 inhibitor demonstrated improved survival in mice models vs single agent alone
- Currently a Phase I trial in healthy volunteers is underway to further investigate the safety and PK of balomenib

Abbreviation: PK, pharmacokinetic.

Reference: Hertlein E, et al. Presentation at 29th EHA Congress, Madrid. June 13–16, 2024. Abstract #S130.

PHASE 1/2 STUDY OF ORAL DECITABINE/ CEDAZURIDINE WITH VENETOCLAX AND GILTERITINIB IN PATIENTS WITH NEWLY DIAGNOSED AND RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA

Background

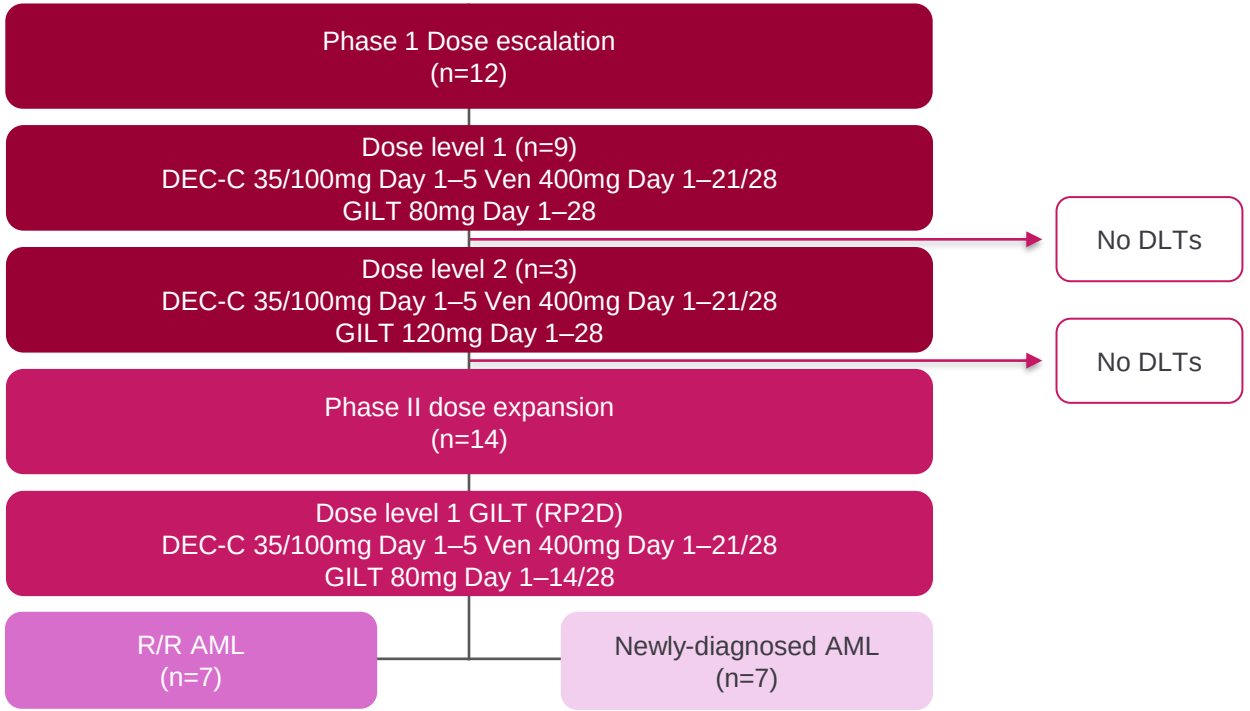
- Hypomethylating agents (HMA) combined with venetoclax (VEN) is standard of care for patients with AML ineligible for intensive chemotherapy
- *FLT3* activating mutations are frequent in AML (*FLT3-ITD* in 20–25%, *FLT3-TKD* in 5–10%) and associated with adverse outcomes particularly in the elderly
- Promising results in *FLT3* mutated AML with the addition of FLT3 inhibitors to HMA plus VEN
- Decitabine/cedazuridine 35mg/100mg (DEC-C), an oral fixed-dose HMA formulation, is approved for MDS (USA) and AML (EU)
- **The objective of the study was to determine the safety and efficacy of a fully oral combination of DEC-C with VEN and gilteritinib (GILT) in patients with newly diagnosed and R/R AML or MDS with *FLT3* mutations**

Abbreviations: AML, acute myeloid leukemia; DEC-C, decitabine/cedazuridine; GILT, gilteritinib; HMA, hypomethylating agents; MDS, myelodysplastic syndrome; R/R; relapsed/refractory; VEN, venetoclax.

Reference: Bataller A, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S139.

Single-center, open-label, Phase 1/2 trial

Inclusion criteria
Newly diagnosed or R/R AML or HR-MDS with mutated *FLT3*



Abbreviations: AML, acute myeloid leukemia; DEC-C, decitabine/cedazuridine; DLT, dose-limiting toxicity; GILT, gilteritinib; HR- MDS, high-risk myelodysplastic syndrome; RP2D, recommended Phase II dose; R/R, relapsed/refractory; VEN, venetoclax.

Reference: Bataller A, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S139.

Baseline characteristics

	R/R AML and MDS cohort (n=19)	ND AML cohort (n=7)
Age, years, median (range)	**67 (38–84)**	**79 (61–83)**
Sex, male, n (%)	12 (63)	3 (43)
Performance status, n (%)		
0	1 (5)	0
1	14 (74)	1 (14)
2	4 (21)	6 (86)
Disease subtype, n (%)		
AML	18 (95)	7 (100)
CMML	1 (5)	0
Previous lines of AML therapy, median (range)	1 (1–12)	0
Previous types of therapy, n (%)		
Previous HMA	16 (84)	1 (14)
Previous Ven	15 (79)	0
Previous FLT3 inhibitor	4 (21)	0
Previous SCT	8 (42)	0
Karyotype, n (%)		
Normal	10 (53)	4 (57)
Complex	3 (16)	2 (29)
ELN 2022, n (%)		
Favorable	0	0
Immediate	9 (47)	5 (71)
Adverse	10 (53)	2 (29)

Abbreviations: AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; ELN, European Leukemia Net; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; ND, newly-diagnosed; R/R, relapsed/refractory; SCT, stem cell transplant; VEN, venetoclax.

Reference: Bataller A, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S139.

Efficacy

	R/R AML cohort (n = 18)*	Newly-diagnosed AML (n = 7)
ORR, (%)	44	86
CR, (%)	17	71
CRi, (%)	28	14
MLFS, (%)	33	0
Median treatment cycle to first response, (range)	1 (1–2)	1 (1–1)
Median treatment cycle to best response, (range)	1 (1–2)	1 (1–2)
Median cycles received, (range)	2 (1–8)	3 (1–5)
Median DoR, (range)	7.6 (7.2–NR)	NR (NR–NR)
HSCT	17	43

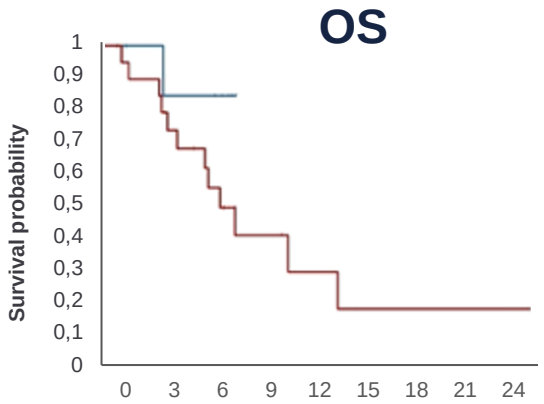
***One patient was excluded due to withdrawal.**

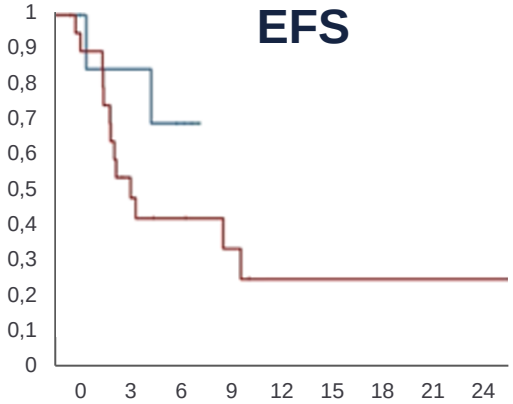
Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete hematological recovery; DoR, duration of response; HSCT, hematopoietic stem cell transplantation; MLFS, morphologic leukemia-free state; NR, not reached; ORR, overall response rate.

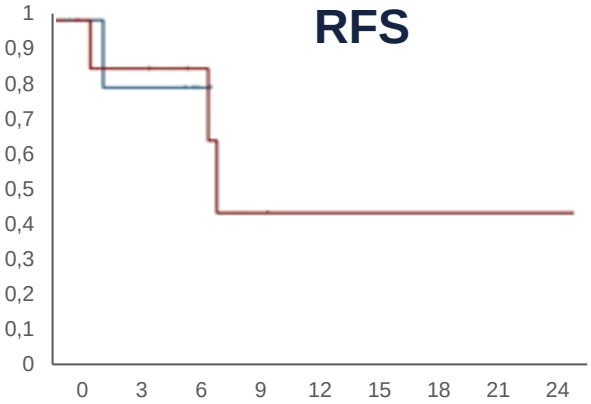
Reference: Bataller A, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S139.

Survival

Median follow-up: 7.5 months (7–NR)







Cohort	n	Median OS	6m OS	1yr OS
ND	7	NR	83%	-
RR	19	6.8	59%	25%

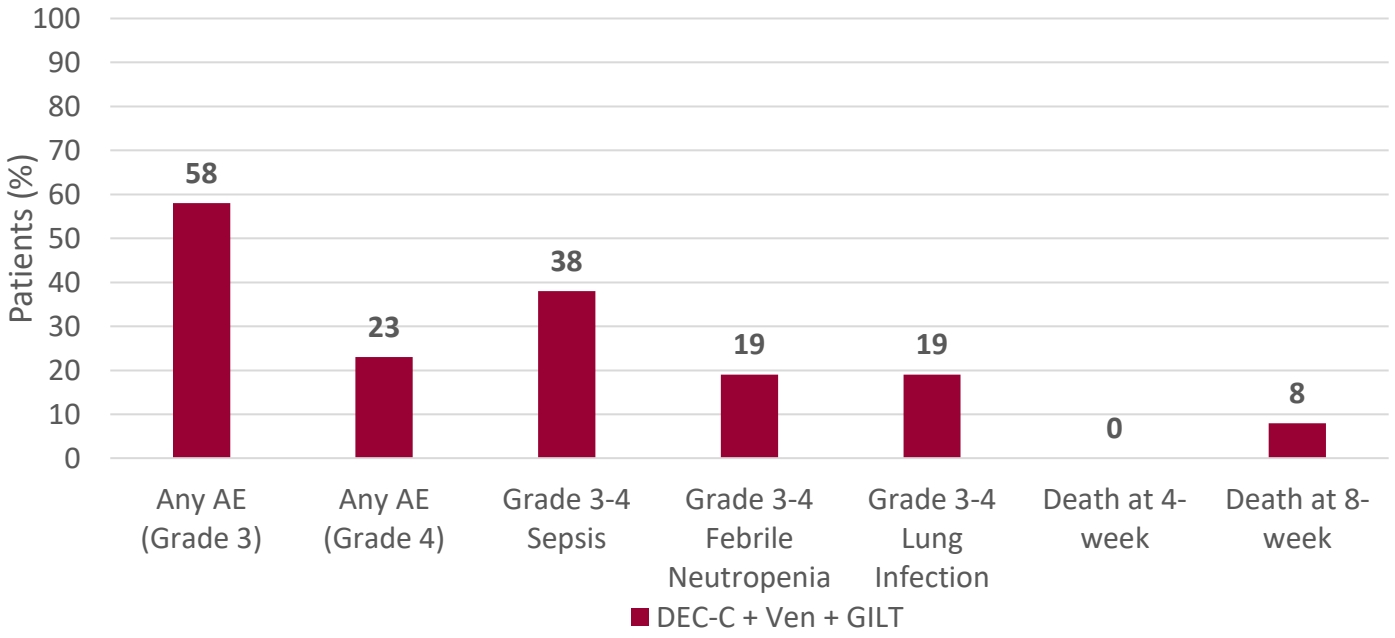
Cohort	n	Median EFS	6m EFS	1yr EFS
ND	7	NR	67%	-
RR	19	3.7	38%	19%

Cohort	n	Median RFS	6m RFS	1yr RFS
ND	6	NR	80%	-
RR	8	7.6	86%	43%

Abbreviations: EFS, event-free survival; ND, newly diagnosed; NR, not reached; OS, overall survival; RFS, relapse-free survival; R/R, relapsed/refractory.

Reference: Bataller A, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S139.

Safety



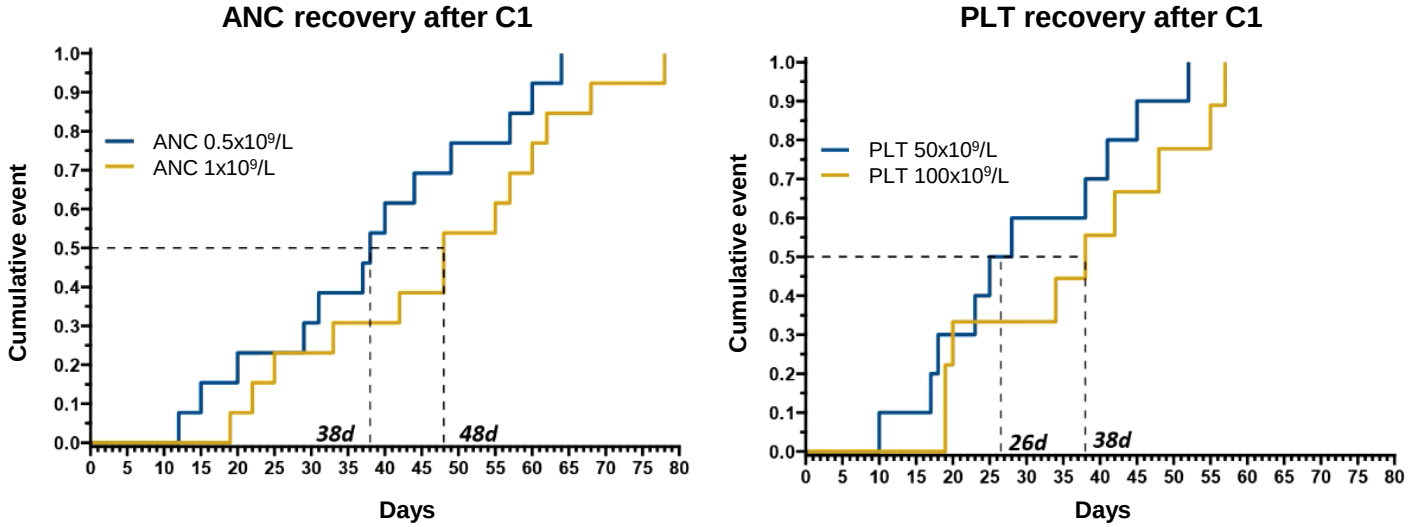
Grade 5 events (n=2, 8%) were in the R/R cohort due to septic shock at C1 and C2

Abbreviations: AE, adverse event; DEC-C, decitabine/cedazuridine; GILT, gilteritinib; R/R, relapsed/refractory; VEN, venetoclax.

Reference: Bataller A, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S139.

Count recovery

- Ven/GILT could be held around C1D14–21 due to complete remission or hypoplastic/aplastic marrow
- All patients that proceeded to C2 underwent dose reduction in the subsequent cycles



Abbreviations: ANC, absolute neutrophil count; C, cycle; D, day; GILT, gilteritinib; PLT, platelet; R/R, relapsed/refractory; VEN, venetoclax.

Reference: Bataller A, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S139.

DEC-C with VEN and GILT: Conclusions

- The fully oral combination of DEC-C with VEN and GILT was tolerable and feasible in patients with R/R and ND AML with *FLT3* activating mutations
- Encouraging overall response rate (86% in ND AML; 44% in R/R AML); achieved in the first 2 cycles
- Cytopenia and delayed count recovery were the main limiting factors of this combination; dose adjustments often needed to avoid prolonged cytopenia
- Acceptable toxicity and prolonged survival especially for those responding and proceeding to HSCT
- A larger cohort and longer follow-up needed to fully assess the utility of this regimen

Abbreviations: AML, acute myeloid leukemia; DEC-C, decitabine/cedazuridine; GILT, gilteritinib; HSCT, hematopoietic stem cell transplantation; ND, newly diagnosed; R/R, relapsed/refractory; VEN, venetoclax.

Reference: Bataller A, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S139.

AML presentation

COMPLETED DOSE ESCALATION FROM THE FIRST-IN-HUMAN, PHASE 1/2 STUDY OF CD123 NK CELL ENGAGER, SAR443579, IN RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA OR HIGH RISK-MYELODYSPLASIA

Background

- CD123 is frequently overexpressed on leukemic blasts; high levels are associated with poor outcomes in various hematologic malignancies
- SAR443579 is a natural killer (NK) cell engager facilitating the formation of a cytolytic synapse between CD16 and NKp46 on NK cells and CD123 on tumor cells, leading to NK-cell activation and tumor death
- Early clinical results in patients with R/R AML demonstrated that SAR443579 had a manageable toxicity profile up to 6.0 mg/kg/infusion QW; complete remissions were identified at a maximal target dose of 1.0 mg/kg/infusion

Abbreviations: AML, acute myeloid leukemia; QW, once a week; NK, natural killer; R/R, relapsed/refractory.

Reference: Garciaz S, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S146.

SAR443579: Presentation summary

- First-in-human, open-label, study to characterize the overall safety and tolerability profile of SAR443579 along with preliminary anti-leukemic activity
  - N=59 adult patients: 58 R/R AML & 1 HR-MDS
- SAR443579 had a manageable toxicity profile up to a dose of 6 mg/kg QW
  - Low grade infusion-related reaction (Grade 1–2) was the most common TRAE
  - CRS events were rare (one Grade 3) and no ICANS
- Among 15 patients with AML treated at a target dose of 1 mg/kg
  - 5 patients (33.3%) achieved CR/Cri
  - Durable remission >10 months in 3 of 5 responders
    - One responder proceeded to HSCT
    - Two remain on maintenance therapy
- SAR443579 received Fast Track designation by the US FDA, and the dose optimization and expansion phase of the trial is ongoing

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRS, cytokine release syndrome; FDA, Food and Drug Administration; HR-MDS, high-risk myelodysplastic syndrome; HSCT, hematopoietic stem cell transplantation; ICANS, immune effector cell-associated neurotoxicity syndrome; QW, once a week; R/R, relapsed/refractory; TRAE, treatment-related adverse event.

Reference: Garciaz S, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S146.

AML presentation

ADVERSE PROGNOSTIC IMPACT OF SECONDARY-TYPE MUTATIONS IN ELN 2022 FAVORABLE RISK ACUTE MYELOID LEUKEMIA

Risk classification of AML

- AML is a biologically heterogeneous disease characterized by various genetic abnormalities which impact clinical outcomes[1]
- The 2022 European LeukemiaNet (ELN) risk classification stratifies patients into three risk groups[2]
- The prognostic impact of secondary-type mutations in patients with concurrent favorable risk alterations has remained unclear[1]
- The study presented at EHA assessed the prognostic impact of secondary-type mutations on outcomes in 549 patients with ELN 2022 favorable-risk AML[1]

2022 ELN risk classification by genetics at initial diagnosis[2]

Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ • Mutated *TP53*[a]

Abbreviations: AML, acute myeloid leukemia; ELN, European Leukemia Net.

References: 1. Kotsos D, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S147; **2.** Döhner H, et al. *Blood.* 2022;140(12):1345–1377.

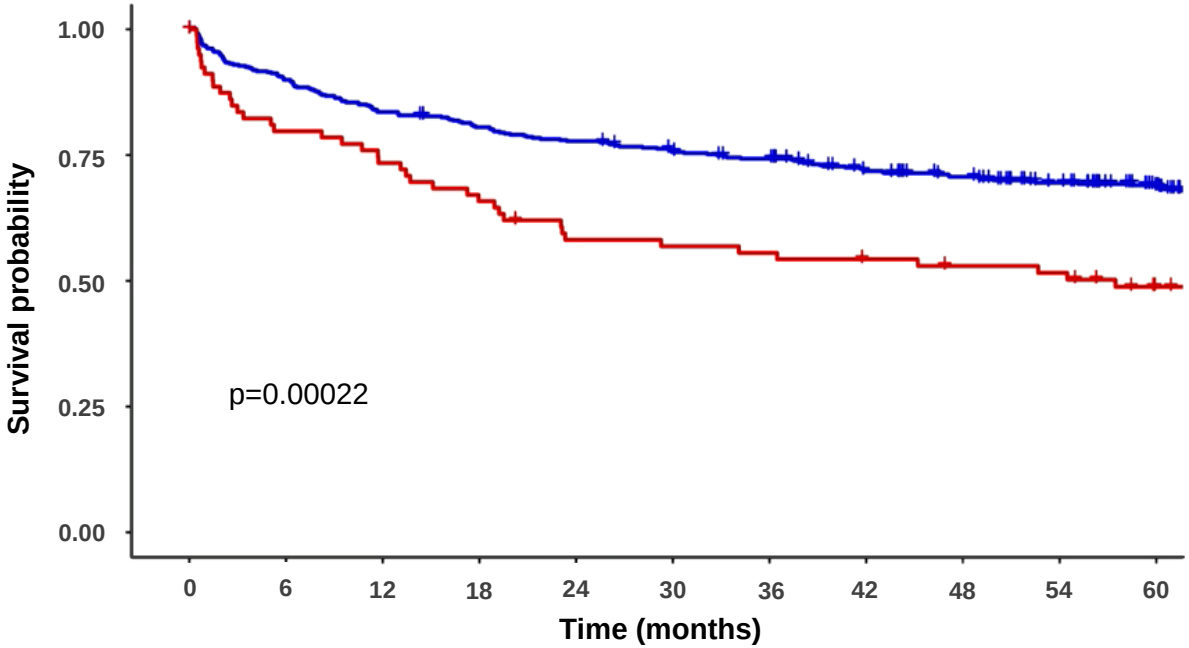
Higher CRi rates in patients without STM

Variable	STM present, n (%) n=80	STM absent, n (%) n=469	p-value
Response to induction treatment			0.007
CRi	68 (85.0)	440 (93.8)	
Refractory disease	9 (11.3)	16 (3.4)	
Induction death	3 (3.8)	13 (2.8)	
Post-remission treatment in CR(i)			0.04
No treatment	24 (35.3)	93 (21.1)	
Chemotherapy	18 (26.5)	114 (25.9)	
Autologous HCT	15 (22.1)	152 (34.5)	
Allogeneic HCT	11 (16.2)	81 (18.4)	

Abbreviations: CRi, complete remission with incomplete hematological recovery; HCT, hematopoietic cell transplantation; STM, secondary-type mutation.

Reference: Kotsos D, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S147.

Significantly worse OS in ELN-favourable patients with STM



5-year OS

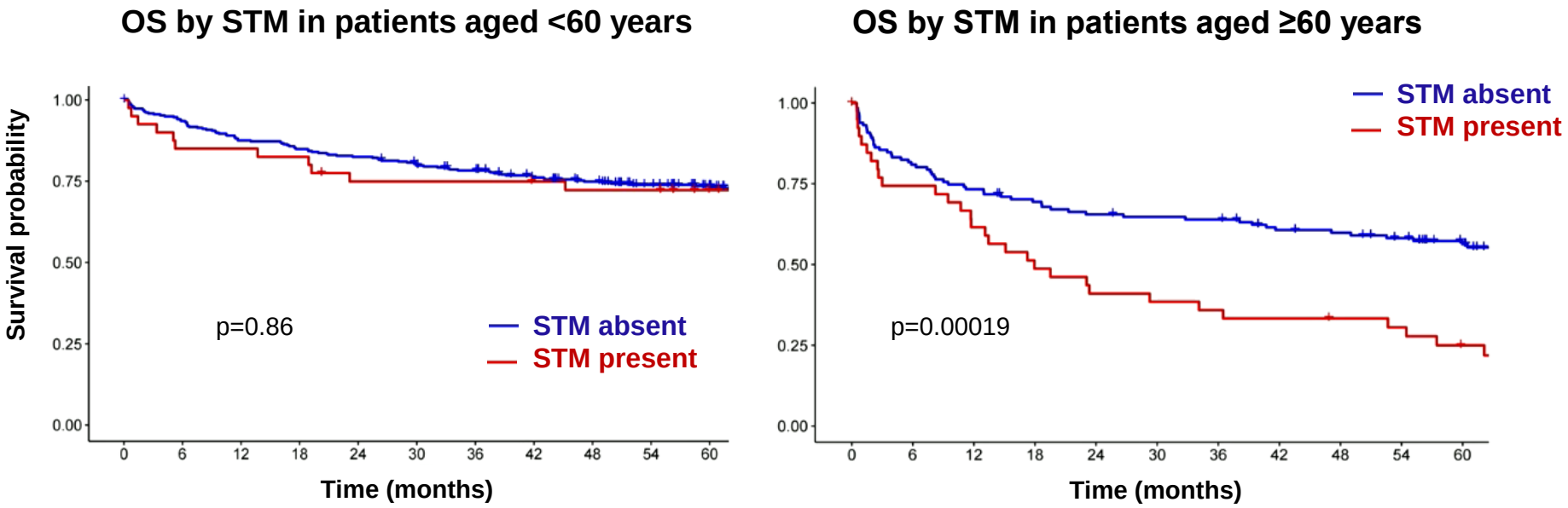
STM absent: **68.7%** (64.6–73.1)

STM present: **48.8%** (38.8–61.3)

Abbreviations: ELN, European Leukemia Net; OS, overall survival; STM, secondary-type mutation.

Reference: Kotsos D, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S147.

Worse OS by STM in patients aged ≥60 years, but not <60 years



Abbreviations: OS, overall survival; STM, secondary-type mutation.

Reference: Kotsos D, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S147.

Conclusions

- Secondary-type mutations were found in 15% of ELN 2022 favorable-risk patients treated within HOVON-SAKK clinical trials
  - SRSF2 and STAG2 most common
- CRi rates and OS were significantly lower in patients with secondary-type mutations compared with patients without secondary-type mutations
  - Particularly in patients aged ≥60 years
- AML risk stratification might consider secondary-type mutations in NPM1 mutated without FLT3-ITD and CEBPα with in-frame bZIP mutation
  - Role of MRD needs to be assessed

Abbreviations: AML, acute myeloid leukemia; CRi, complete remission with incomplete hematological recovery; ELN, European Leukemia Net, MRD, measurable residual disease; OS, overall survival.

Reference: Kotsos D, et al. Presentation at 29th European Hematology Association (EHA) Congress, Madrid. June 13–16, 2024. Abstract #S147.

Discussion on the implications of the clinical data at EHA on the patient community

Anne-Pierre Pickaert:

- A dedicated Patient Advocate with extensive experience in supporting leukemia patients and promoting awareness
- She has been actively involved in various initiatives to improve patient care and provide essential resources to those affected by acute leukemia
- Her work emphasizes the importance of patient perspectives in medical research and healthcare delivery

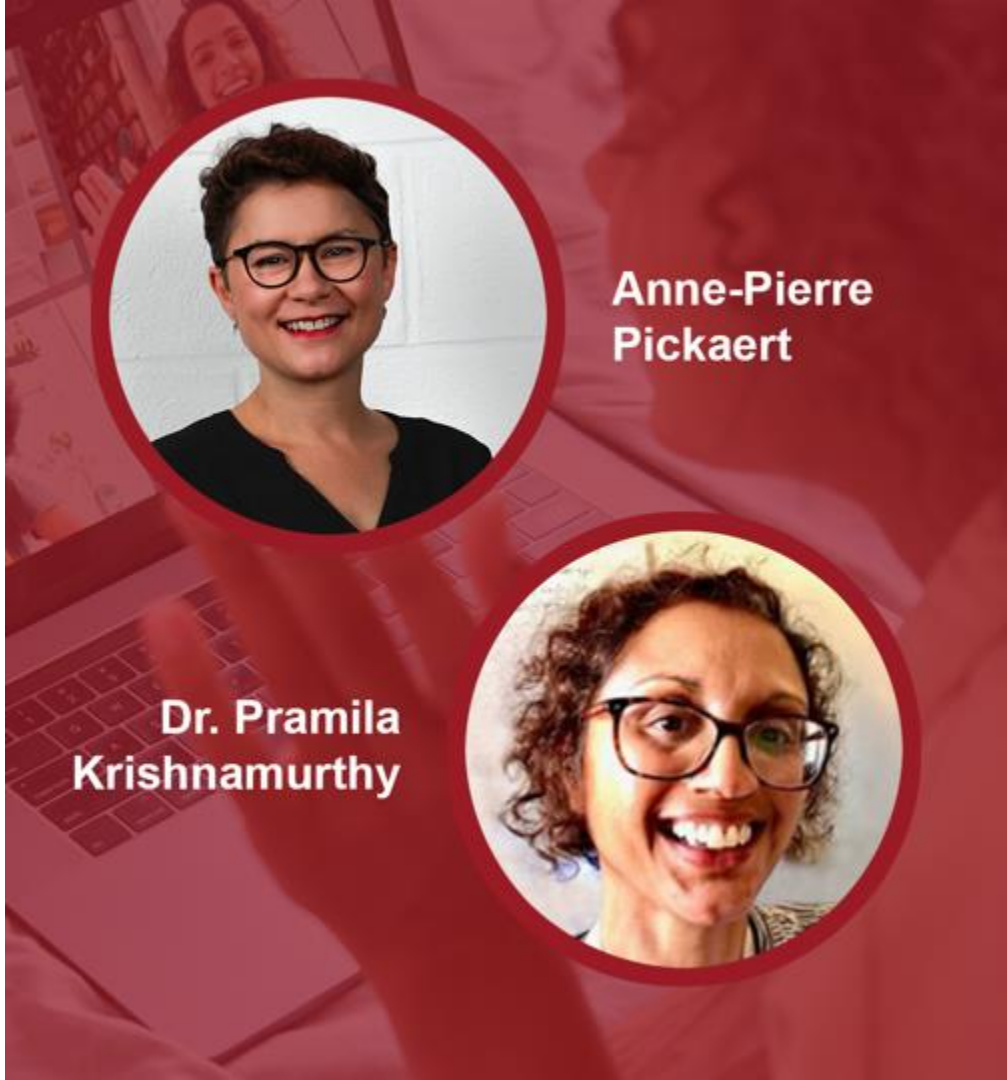
10 minutes

Discussion on the implications of the clinical data at EHA on the patient community

Anne-Pierre Pickaert, Patient advocate

NEXT UP ON THE AGENDA: Q&A SESSION

Submit your questions in the chat



Ask a question

Q&A Session

Please, use the Q&A window to write a question and the moderator will ask it on your behalf

THANK YOU!