POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

# Novità dal Meeting della Società Americana di Ematologia

Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

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## *Acute Myeloid Leukemia*

*A. CANDONI*

# ANNA CANDONI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario**: NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario **: NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board: **ASTELLAS, JAZZ, AMGEN, PFIZER, JANSSEN, INCYTE**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Relazioni ad Eventi (Corsi, Congressi, Riunioni Scientifiche) sponsorizzati: **ASTELLAS, JAZZ, AMGEN, PFIZER, JANSSEN, INCYTE, ABBVIE**

# -SOMMARIO-

**Spunti su……**

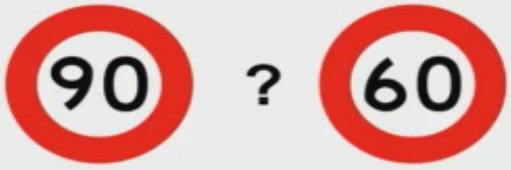
- **TERAPIA DI PRIMA LINEA FIT PER CHEMIOTERAPIA INTENSIVA (Abs 217, Abs 710)**
- **TERAPIA DI PRIMA LINEA UNFIT PER CHEMIOTERAPIA INTENSIVA (Abs 219, Abs 222)**
- **SETTING REFRACTORY/RELAPSED (Abs 221)**
- **AML/TRAPIANTO (Abs 04)**
- **«Nuovi Farmaci» (Abs 2757)**


**615. Acute Myeloid Leukemias: Commercially Available Therapies, Excluding Transplantation and Cellular Immunotherapies: New Approaches to Combination Chemotherapy and Venetoclax Plus Hypomethylating Agent Therapy in AML--Saturday, December 10**

- ✖ 217 Single Versus Double Induction with "7+3" Containing 60 Versus 90 Mg Daunorubicin for Newly Diagnosed AML: Results from the Randomized Controlled SAL Dauno-Double Trial
- 218 FLAG-Ida Combined with Gemtuzumab Ozogamicin (GO) Improves Event Free Survival in Younger Patients with Newly Diagnosed Acute Myeloid Leukaemia (AML) and Shows an Overall Survival Benefit in *NPM1* and *FLT3* mutated Subgroups. Results from the UK NCRI AML19 Trial
- ✖ 219 Long-Term Follow-up of the Phase 3 Viale-a Clinical Trial of Venetoclax Plus Azacitidine for Patients with Untreated Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy
- 220 A Randomized Comparison of the Fractionated Versus Single Dose Schedule of Gemtuzumab Ozogamicin at Induction with Determinants of Benefit for Older AML Patients: UK NCRI AML18 Trial Results
- ✖ 221 Updated Phase IIb Results of Venetoclax with FLAG-IDA in Relapsed or Refractory Acute Myeloid Leukemia
- ✖ 222 Reduced Venetoclax Exposition to Seven Days of Azacitidine Is Efficient in Treatment-Naïve Patients with Acute Myeloid Leukemia

# Single Versus Double Induction with "7+3" Containing 60 Versus 90 Mg Daunorubicin for Newly Diagnosed AML: Results from the Randomized Controlled SAL Dauno-Double Trial

Paper Number: 217
**Christoph Röllig, MD, MSC**
Universitätsklinikum Carl Gustav Carus




**864 pazienti arruolati !**

## The SAL DaunoDouble Trial

**Two research questions:**

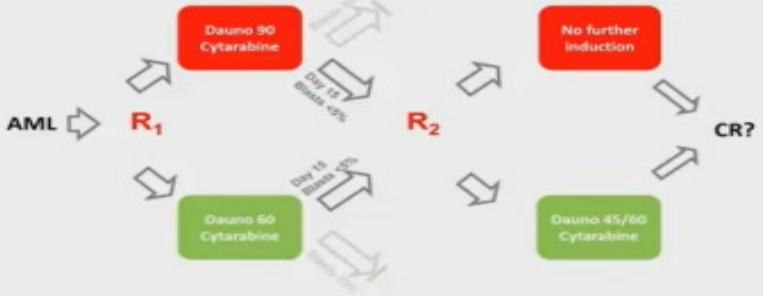
- Part 1: Is 90 mg superior to 60 mg daunorubicin in 7+3 induction?
- Part 2: Is double induction necessary in patients with good early response after single 7+3?

# 217 Single Versus Double Induction with "7+3" Containing 60 Versus 90 Mg Daunorubicin for Newly Diagnosed AML: Results from the Randomized Controlled SAL Dauno-Double Trial

## Eligibility criteria

- Newly diagnosed AML
- 18-65 years
- *de novo*/sAML
- LVEF ≥50%
- ECOG 0-2
- Absence of relevant hepatic, renal, pulmonary dysfunction

## Design DaunoDouble Trial

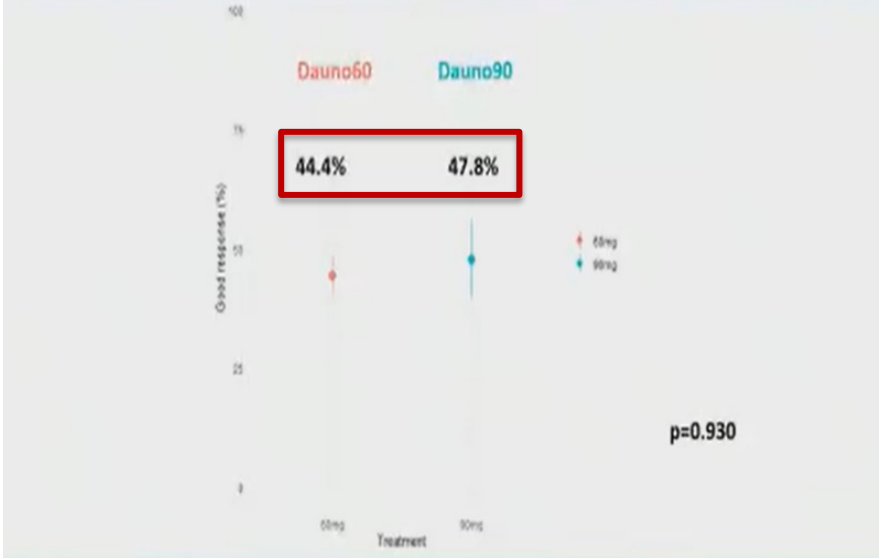


# Patient characteristics patients with first induction 7+3

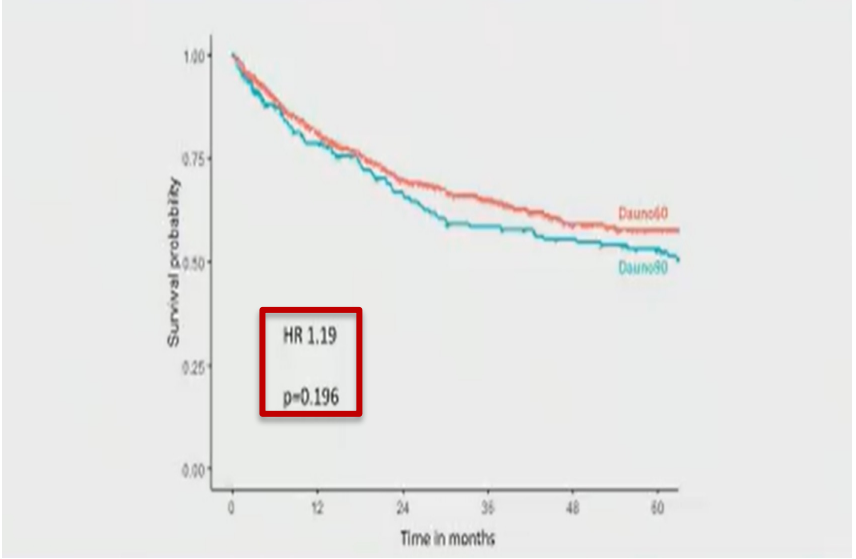
| | Total (n=864) | Arm 60 (n=160+547) | Arm 90 (n=157) |
|---|---|---|---|
| Age, median (IQR) | 52 (43-58) | 53 (43-59) | 52 (44-56) |
| ECOG, n (%) | | | |
| 0-1 | 813 (94.1) | 662 (95.1) | 151 (96.2) |
| >1 | 40 (4.7) | 34 (4.9) | 6 (3.8) |
| NPM1, n (%) | | | |
| pos | 273 (34.1) | 213 (32.4) | 60 (41.7) |
| neg | 528 (65.9) | 444 (67.6) | 84 (58.3) |
| FLT3-ITD, n (%) | | | |
| pos | 162 (20.7) | 131 (20.2) | 31 (23.1) |
| neg | 622 (79.3) | 519 (79.8) | 103 (76.9) |
| ELN 2017, n (%) | | | |
| Fav | 304 (37.2) | 246 (36.9) | 58 (38.7) |
| Int | 373 (45.7) | 305 (45.7) | 68 (45.3) |
| Adv | 150 (17.1) | 116 (17.4) | 24 (16.0) |
| Treatment n (%) | | | |
| Gemtuzumab Ozogamicin | 18 (2.1) | 18 (2.5) | 0 (0) |
| Midostaurin | 49 (5.7) | 49 (6.9) | 0 (0) |
| Allo HCT in CR1 | 282 (38.9) | 224 (37.9) | 58 (43.3) |

# 217 Single Versus Double Induction with "7+3" Containing 60 Versus 90 Mg Daunorubicin for Newly Diagnosed AML: Results from the Randomized Controlled SAL Dauno-Double Trial

## Primary endpoint:
## Blast clearance <5% day 15



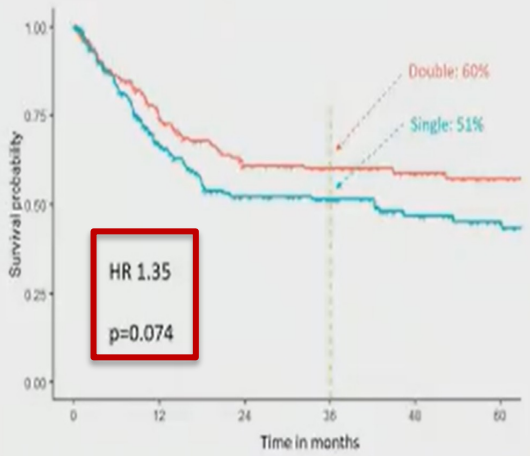

## Overall Survival
Median Follow-up 44 months



# 217 Single Versus Double Induction with "7+3" Containing 60 Versus 90 Mg Daunorubicin for Newly Diagnosed AML: Results from the Randomized Controlled SAL Dauno-Double Trial

## Relapse-free Survival ITT Population

Median Follow-up 44 months




## Relapse-free Survival: Multivariable Analysis (Per-Protocol Population)

| Parameter | log.HR | HR | ci.HR | se.HR | z | p |
|---|---|---|---|---|---|---|
| 'Age (years)' | 0.007 | 1.007 | (0.989 to 1.026) | 0.009 | 0.778 | 0.437 |
| 'Cytogenetic risk (ELN 2017)' favourable | -0.289 | 0.749 | (0.434 to 1.292) | 0.278 | -1.04 | 0.299 |
| 'Cytogenetic risk (ELN 2017)' adverse | 0.279 | 1.321 | (0.655 to 2.668) | 0.358 | 0.779 | 0.436 |
| NPM1Y | 0.052 | 1.053 | (0.588 to 1.886) | 0.297 | 0.175 | 0.861 |
| FLT3IY | -0.11 | 0.896 | (0.404 to 1.986) | 0.406 | -0.271 | 0.786 |
| 'Randomized single vs. double induction'S | 0.331 | 1.393 | (0.935 to 2.075) | 0.203 | 1.631 | 0.103 |
| ALSCTCR1 | -0.198 | 0.821 | (0.517 to 1.302) | 0.236 | -0.839 | 0.401 |
| NPM1Y:FLT3IY | 0.447 | 1.564 | (0.589 to 4.153) | 0.498 | 0.898 | 0.369 |

# 217 Single Versus Double Induction with "7+3" Containing 60 Versus 90 Mg Daunorubicin for Newly Diagnosed AML: Results from the Randomized Controlled SAL Dauno-Double Trial

## Conclusions

**In the first cycle of 7 + 3:**

- 90 mg daunorubicin did not result in a significantly better blast clearance than 60 mg
- Correlation between blast clearance and CR
- No impact on RFS or OS of 90 versus 60 mg daunorubicin
- No excess toxcitiy

**In good responders after 7+3:**

- CR/CRi rates were slightly higher after double induction, but difference was small and not significant
- Trend for RFS advantage in patients with double induction in univariable analysis, no difference in multivariable analysis
- No differences in overall survival after single versus double induction in good responders

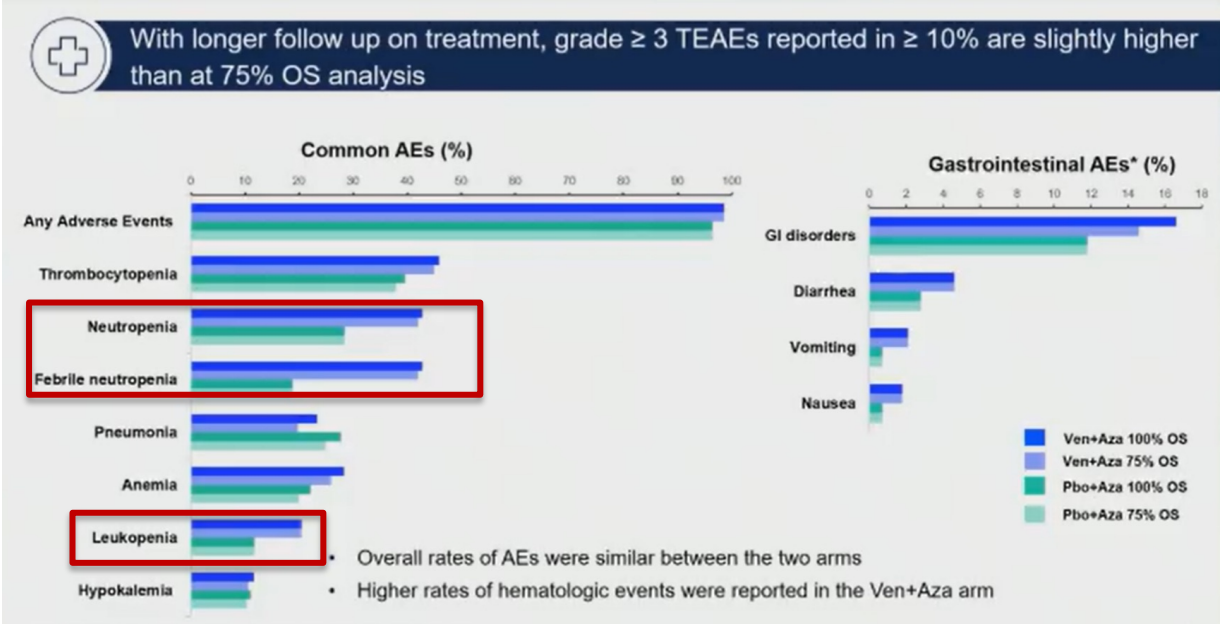
# Long-Term Follow-up of the Phase 3 Viale-a Clinical Trial of Venetoclax Plus Azacitidine for Patients with Untreated Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy

**+ 2 anni-Viale-A**

Paper Number: 219

**Keith Pratz, MD** ♡

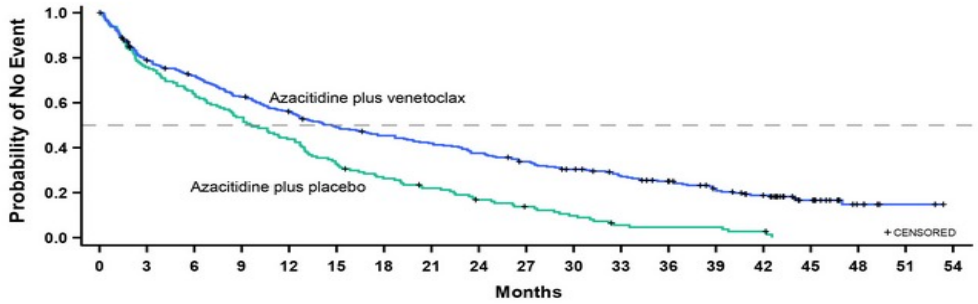
Abramson Cancer Center University of Pennsylvania



## 219 Long-Term Follow-up of the Phase 3 Viale-a Clinical Trial of Venetoclax Plus Azacitidine for Patients with Untreated Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy

- 2 additional 2-year follow-up
- At the time of analysis 25 patients ongoing treatment on VEN-AZA vs 0 on AZA

**Figure 1. Overall Survival**




**Patients at Risk**

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Azacitidine plus placebo | 145 | 109 | 92 | 77 | 63 | 47 | 37 | 30 | 22 | 17 | 12 | 6 | 5 | 5 | 3 | 0 | |
| Azacitidine plus venetoclax | 286 | 220 | 199 | 173 | 153 | 133 | 122 | 113 | 101 | 89 | 78 | 67 | 57 | 45 | 34 | 18 | 6 | 2 | 0 |

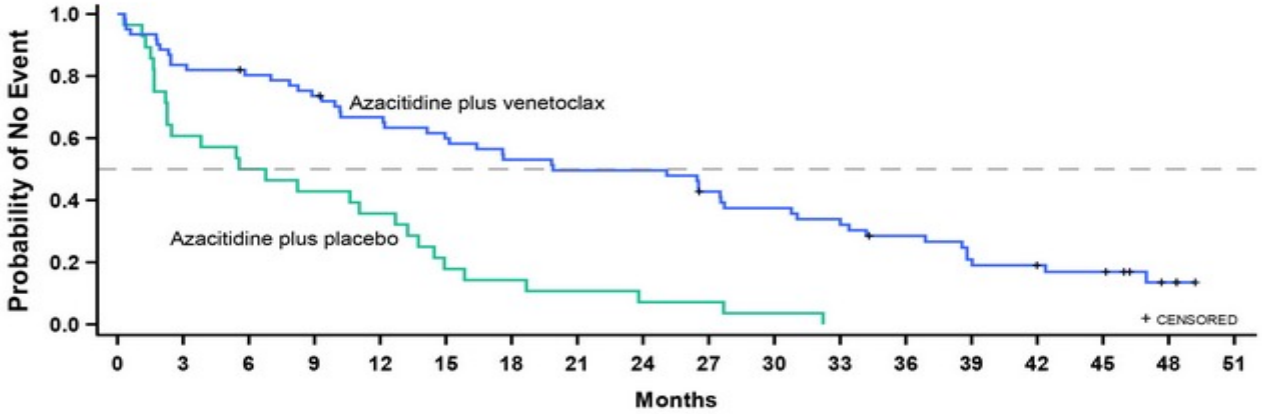
Median follow-up: 43.2 months
Median OS: 14.7 months (VEN+AZA)
9.6 months (PBO+AZA)

Median OS for pts with MRD $<10^{-3}$: 34.2 months
Median OS for pts with *IDH1/2* +:19.9 months

Pratz KW et al, ASH 2022

# 219 Long-Term Follow-up of the Phase 3 Viale-a Clinical Trial of Venetoclax Plus Azacitidine for Patients with Untreated Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy

**Figure 2. Median OS reached for patients with IDH1/2 mutations treated with azacitidine plus venetoclax**




**Patients at Risk**

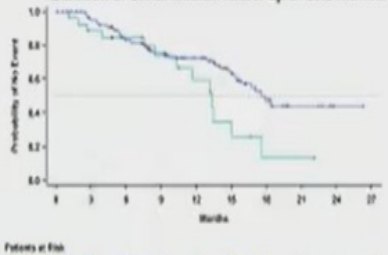
| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Azacitidine plus placebo | 28 | 17 | 14 | 12 | 10 | 5 | 4 | 3 | 2 | 2 | 1 | 0 | | | | | | |
| Azacitidine plus venetoclax | 61 | 51 | 48 | 44 | 39 | 35 | 31 | 29 | 29 | 24 | 21 | 19 | 15 | 11 | 9 | 8 | 3 | 0 |

Pratz KW et al, ASH 2022

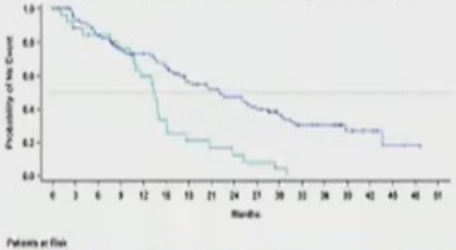
# 219 Long-Term Follow-up of the Phase 3 Viale-a Clinical Trial of Venetoclax Plus Azacitidine for Patients with Untreated Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy

**Median duration of CR for patients on Ven+Aza is ~5 months longer at 100% OS analysis than at primary analysis**

Duration of CR at median follow-up of 20.5 months[1]



Duration of CR at median follow-up of 43.2 months



| | DOR at 75% OS analysis (months) median (95% CI) | | DOR at 100% OS analysis (months) median (95% CI) |
|---|---|---|---|
| Ven+Aza (n=105) | 17.5 (15.3 – NE) | Ven+Aza (n=111) | 22.1 (16.7 – 27.0) |
| Pbo+Aza (n=26) | 13.3 (8.5 – 17.6) | Pbo+Aza (n=26) | 13.4 (10.3 – 15.1) |

**+ 5 MESI DOR**

**The VIALE-A study demonstrates favorable benefit risk of Ven+Aza in newly diagnosed AML patients who are ineligible to receive intensive chemotherapy**

**The 100% OS analysis shows that the OS benefit from Ven+Aza continues to be observed**

**No new safety signals are found for Ven+Aza or Aza monotherapy from the previous analysis**

# Reduced Venetoclax Exposition to Seven Days of Azacitidine Is Efficient in Treatment-Naïve Patients with Acute Myeloid Leukemia

Paper Number: 222

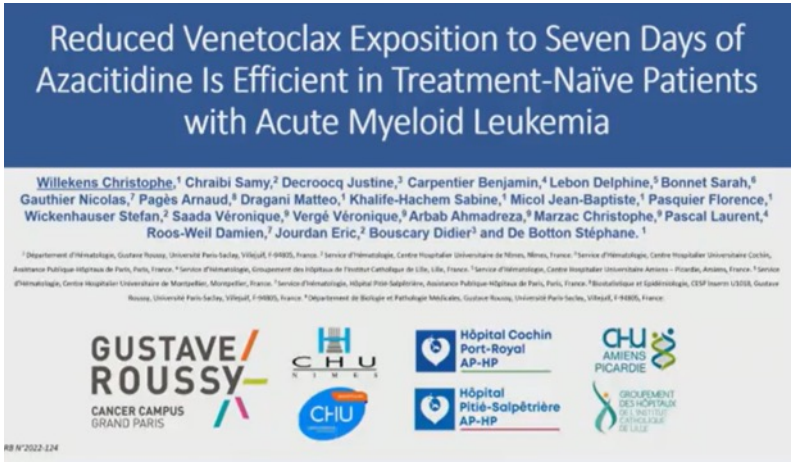
**Christophe Willekens, MD** ♡

Département d'Hématologie, Gustave Roussy, Université Paris-Saclay

> Ann Hematol. 2023 Jan 16. doi: 10.1007/s00277-023-05102-y. Online ahead of print.

**Shorter duration of venetoclax administration to 14 days has same efficacy and better safety profile in treatment of acute myeloid leukemia**

Masayuki Aiba [1], Akio Shigematsu [2], Toma Suzuki [2], Takuto Miyagishima [2]



# 222 Reduced Venetoclax Exposition to Seven Days of Azacitidine Is Efficient in Treatment-Naïve Patients with Acute Myeloid Leukemia

## Azacitidine – Venetoclax in AML patients ineligible to intensive chemotherapy – VIALE-A

- AZA + VEN combination is approved in previously untreated AML patients ineligible to intensive chemotherapy
  - ORR (CR+CRi): 66.4%
  - Median OS: 14.7 months
  - Median EFS: 9.8 months
- AZA for 7 days and **continuous VEN exposure** (VIALE-A)


DiNardo CD *et al.*, N Engl J Med 2020.

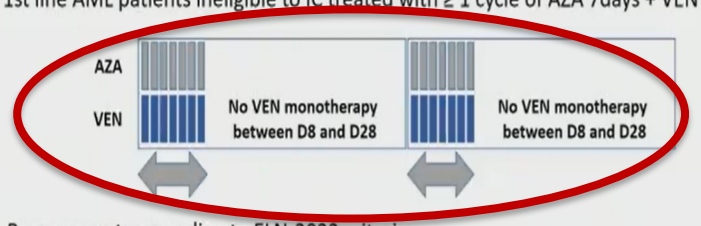
## Reduced VEN exposure to 7 days of AZA

**QUESTIONS**

- To assess efficacy and safety of only concurrent 7 days of **VEN+AZA per cycle in a « difficult to treat » population**

**METHODS**

- Multicentric retrospective study (7 centers in France)
- 1st line AML patients ineligible to IC treated with ≥ 1 cycle of AZA 7days + VEN 7days




- Response rate according to ELN-2022 criterias
- Evaluation of further dose reduction in responders

# 222 Reduced Venetoclax Exposition to Seven Days of Azacitidine Is Efficient in Treatment-Naïve Patients with Acute Myeloid Leukemia

## Patients characteristics (N = 82)

- Median age similar to VIALE-A study
- Frail/adverse risk patients:
  - **PS 2-4 in 37% of cases**
  - **Enrichment in therapy-related AML** (32%)
  - Ineligibility to IC (if <75y) mainly related to prior/concomitant neoplasia (47%)
  - **29.3% had comorbidities defined as exclusion criteria's in VIALE-A study**

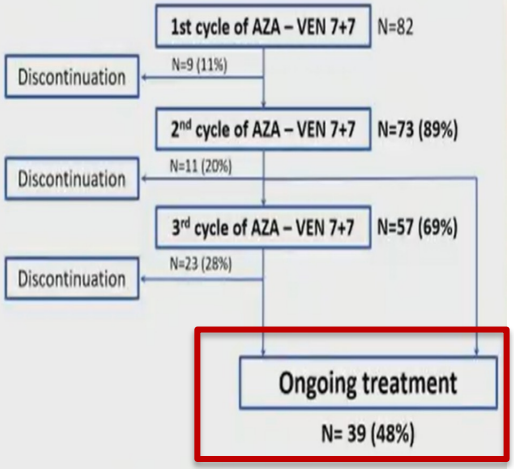
- Poor risk cytogenetic in 32.9%
- *TP53* mut (VAF≥1%) in 21.3%
- **ELN-2022 adverse risk: 69.5% of the cohort**

Frail and/or adverse risk cohort

# 222 Reduced Venetoclax Exposition to Seven Days of Azacitidine Is Efficient in Treatment-Naïve Patients with Acute Myeloid Leukemia

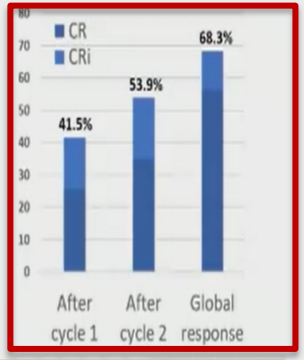
## Flowchart and follow-up

- Median FU: 4.8 months (0.3 – 25.8)
- Median number of cycles: 4 (1-28)
- Reasons for discontinuation:
  - Failure/relapse: 27/43 (63%)
  - Toxicity in CR/CRi/MLFS: 13/43 (30%)
  - Others: 3/43 (7%)




## Overall response rate / time to response

- ORR (CR+CRi): 68.3%
- Median number of cycle to obtain response : 2 (1-4)
- Subgroup analysis (Chi2) :
  - Normal karyotype: ORR 81.8% (P=0.0204)
  - NPM1 mutation: ORR 91.6% (P=0.0597)
  - IDH2 R140 mutation: ORR 100.0% (P=0.0955)
  - Complex karyotype: ORR 47.1% (P=0.0411)
  - TP53 mutation: ORR 43.7% (P=0.0104)
  - Adverse ELN-2022: ORR 61.4% (P=0.0404)



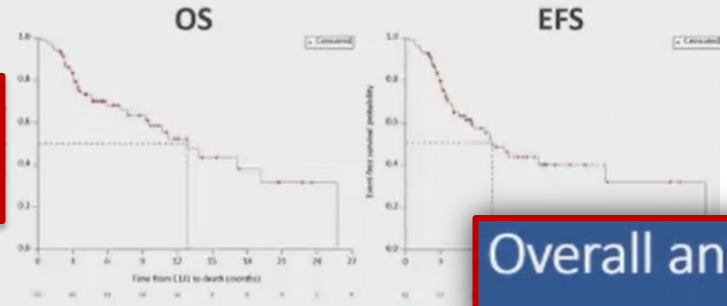

| Overall response (N=82) | |
|---|---|
| CR | 46 (56.1%) |
| CRi | 10 (12.2%) |
| PR / MLFS | 7 (8.5%) |
| SD / PD / Failure | 19 (23.2%) |

* Patients with blastes <5% and cytopenia at BM evaluation (i.e. MLFS or CRi) who recovered from cytopenia before next cycle were defined as CR or CRi

# 222 Reduced Venetoclax Exposition to Seven Days of Azacitidine Is Efficient in Treatment-Naïve Patients with Acute Myeloid Leukemia

## Overall and Event-Free Survival

- Median OS: 12.8 months (IC95: 9.2-19.2)
- Median EFS: 7.5 months (IC95: 5.1-17.1)




- Univariate analysis:

Estimated hazard-ratio using unstratified Cox model

| | OS - HR | P | EFS – HR | P |
|---|---|---|---|---|
| PS status 0-1 (vs 2-4) | 0.272 | **0.0003** | 0.407 | **0.0057** |
| Age < 75 years | 2.119 | **0.0334** | 3.242 | **0.0005** |
| Exclusion criteria's for VIALE-A protocol | 2.083 | **0.0413** | 2.012 | **0.0353** |
| Cytogenetic risk : intermediate (vs poor) | 0.329 | **0.0028** | 0.251 | **<.0001** |
| *TP53* mutation (VAF ≥5%) | 4.324 | **0.0001** | 3.993 | **<.0001** |

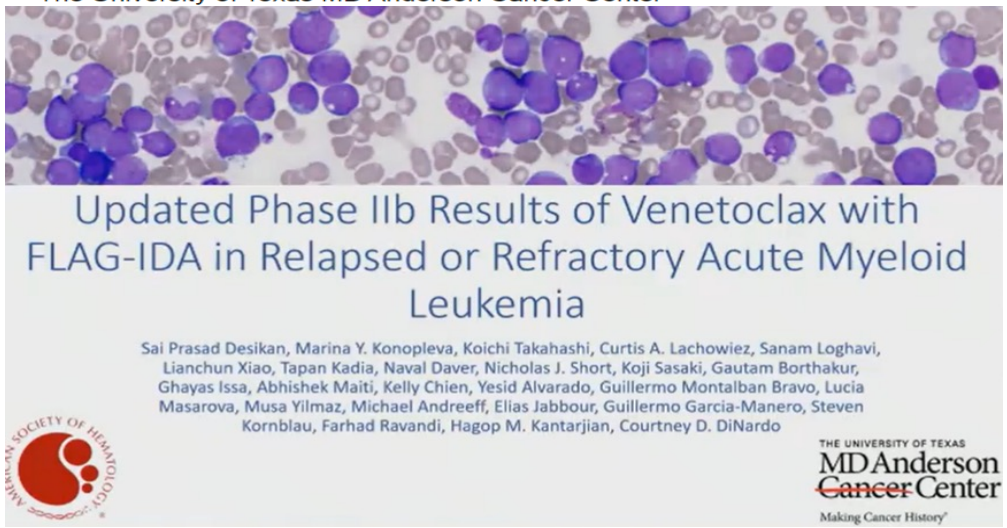
## Overall and Event-Free Survival

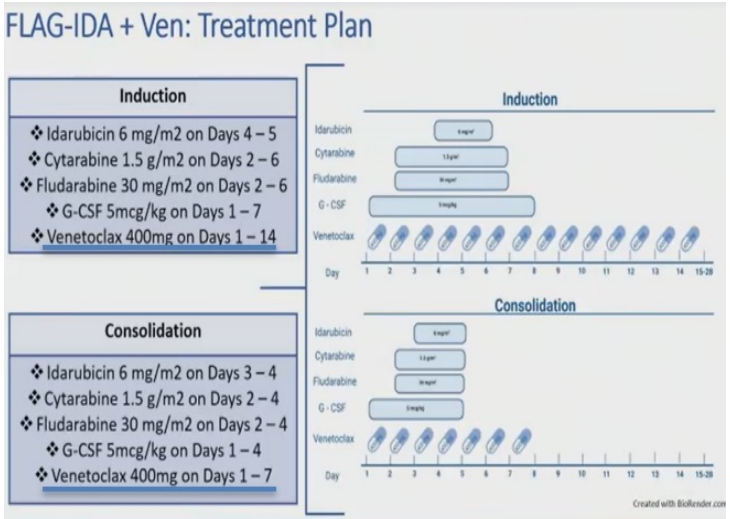
- **Absence of VIALE-A exclusion criterias - (N=58)**
  - Median OS: **13.80 months** (IC95: 10.68-NR)
  - Median EFS: **11.40 months** (IC95: 6.83-NR)

# Updated Phase IIb Results of Venetoclax with FLAG-IDA in Relapsed or Refractory Acute Myeloid Leukemia

Paper Number: 221

**Sai Desikan, MD**
The University of Texas MD Anderson Cancer Center



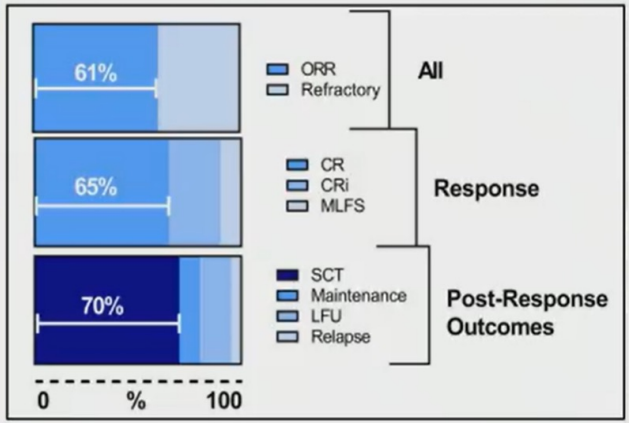




| | | |
|---|---|---|
| Median Blast % | | 55 [1-91] |
| ELN 2017 | Favorable | 7 (21) |
| | Intermediate | 4 (12) |
| | **Adverse** | **22 (67)** |

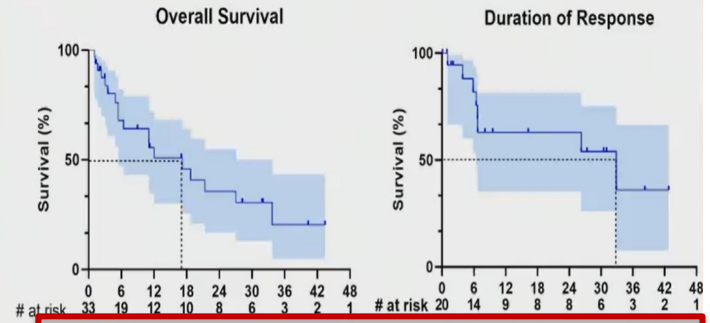
# 221 Updated Phase IIb Results of Venetoclax with FLAG-IDA in Relapsed or Refractory Acute Myeloid Leukemia

## FLAG-IDA + Ven: Outcomes

| Outcomes | |
|---|---|
| ORR | 20/33 (61%) |
| **Composite Response** | 18/33 (55) |
| CR | 13/33 (40) |
| CRi | 5/33 (15) |
| MRD (-) | 13/33 (40) |
| MLFS | 2/33 (6) |
| **Follow-up** | |
| Allogeneic SCT | 14/33 (42) |
| Maintenance | 2/33 (6) |
| Lost to F/U | 3/33 (9) |
| after response | |
| Relapsed on-trial | 1/33 (3) |
| Refractory | 13/33 (40) |




## FLAG-IDA + Ven: Overall Survival

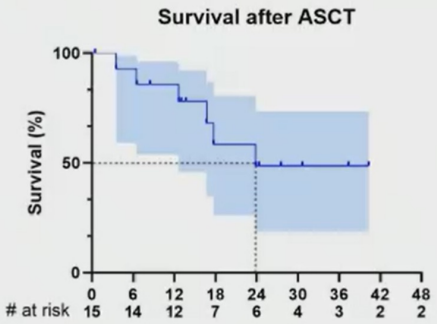


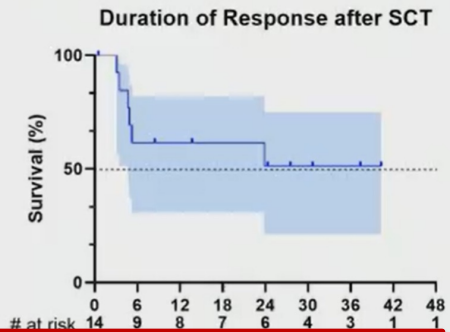

| N | Median OS (mo) | 1-year OS (%) |
|---|---|---|
| 33 | 17 | 56% |

| N | Median DOR (mo) | 1-year CIR (%) |
|---|---|---|
| 20 | 33 | 37% |

# 221 Updated Phase IIb Results of Venetoclax with FLAG-IDA in Relapsed or Refractory Acute Myeloid Leukemia

## FLAG-IDA + Ven: Stem Cell Transplant

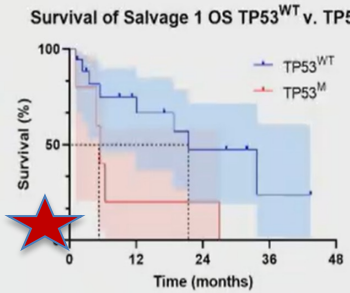


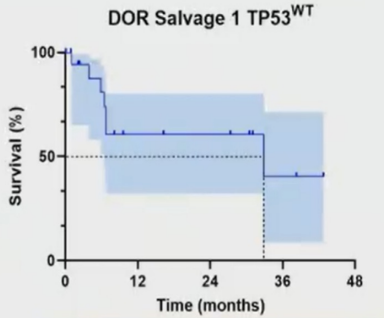

| N | Median OS (mo) | 1-year OS (%) |
|---|---|---|
| 14 | 24 | 86% |

| N | Median DOR (mo) | 1-year CIR (%) |
|---|---|---|
| 14 | NR | 39% |

## FLAG-IDA + Ven: Salvage 1 Survival and Response analysis




| Mutation | N | Median OS (mo) | 1-year OS (%) | P – Log rank |
|---|---|---|---|---|
| TP53WT | 18 | 21 | 75% | 0.03 |
| TP53M | 5 | 5 | 20% | |




| N | Median DOR (mo) | 1-year CIR (%) |
|---|---|---|
| 14 | 33 | 40% |

Ann Hematol. 2022 Aug;101(8):1719-1726. doi: 10.1007/s00277-022-04883-y. Epub 2022 Jun 23.

### Venetoclax in combination with FLAG-IDA-based protocol for patients with acute myeloid leukemia: a real-world analysis

Ofir Wolach [1 2], Avraham Frisch [3], Liat Shargian [4 5], Moshe Yeshurun [4 5], Arie Apel [5 6], Vladimir Vainstein [7], Yakir Moshe [8], Shai Shimony [4 5 9], Odelia Amit [8], Yael Bar-On [8], Yishai Ofran [10], Pia Raanani [4 5], Boaz Nachmias [# 7], Ron Ram [# 8]

## **Venetoclax** combined with induction chemotherapy in patients with newly diagnosed **acute myeloid** leukaemia: a post-hoc, propensity score-matched, cohort study.

Lachowiez CA, Reville PK, Kantarjian H, Jabbour E, Borthakur G, Daver N, Loghavi S, Furudate K, Xiao L, Pierce S, Short NJ, Maiti A, Yilmaz M, Sasaki K, Takahashi K, Konopleva M, Pemmaraju N, Popat U, Shpall E, Garcia-Manero G, Ravandi F, DiNardo CD, Kadia TM.

Lancet Haematol. 2022 May;9(5):e350-e360. doi: 10.1016/S2352-3026(22)00076-X.

## **Venetoclax** plus 3 + 7 daunorubicin and cytarabine chemotherapy as first-line treatment for adults with **acute myeloid** leukaemia: a multicentre, single-arm, phase 2 trial.

Wang H, Mao L, Yang M, Qian P, Lu H, Tong H, Xie W, Zhou D, Huang X, Wang Y, Xu G, Lu Y, Wei J, Mai W, Ye X, Meng H, Shen Y, Huang J, Yu W, Sun J, Sheng J, Yan X, Jin J, Zhu HH.

Lancet Haematol. 2022 Jun;9(6):e415-e424. doi: 10.1016/S2352-3026(22)00106-5. Epub 2022

## Advancing the standard: **venetoclax** combined with intensive induction and consolidation therapy for **acute myeloid leukemia**.

Lachowiez CA, Atluri H, DiNardo CD.

Ther Adv Hematol. 2022 Apr 29;13:20406207221093964. doi: 10.1177/20406207221093964.

## Venetoclax Combined With FLAG-IDA Induction and Consolidation in Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia.

DiNardo CD, Lachowiez CA, Takahashi K, Loghavi S, Xiao L, Kadia T, Daver N, Adeoti M, Short NJ, Sasaki K, Wang S, Borthakur G, Issa G, Maiti A, Alvarado Y, Pemmaraju N, Montalban Bravo G, Masarova L, Yilmaz M, Jain N, Andreeff M, Jabbour E, Garcia-Manero G, Kornblau S, Ravandi F, Konopleva MY, Kantarjian HM.

J Clin Oncol. 2021 Sep 1;39(25):2768-2778. doi: 10.1200/JCO.20.03736. Epub 2021 May 27.

PMID: 34043428 **Free PMC article.** Clinical Trial.

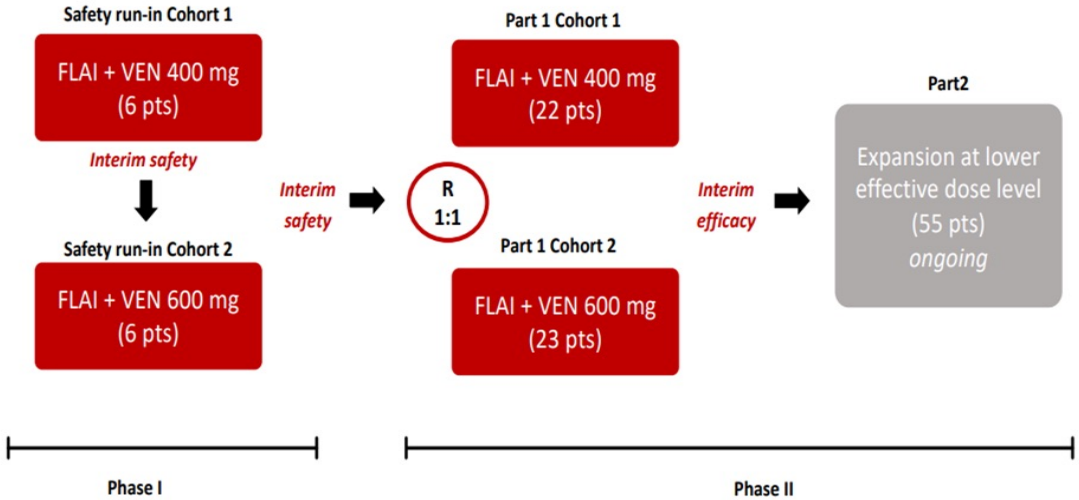
## Venetoclax combined with FLAG-IDA induction and consolidation in newly diagnosed acute myeloid leukemia.

DiNardo CD, Lachowiez CA, Takahashi K, Loghavi S, Kadia T, Daver N, Xiao L, Adeoti M, Short NJ, Sasaki K, Wang SA, Borthakur G, Issa G, Maiti A, Alvarado Y, Pemmaraju N, Bravo GM, Masarova L, Yilmaz M, Jain N, Andreeff M, Garcia-Manero G, Kornblau S, Ravandi F, Jabbour E, Konopleva MY, Kantarjian HM.

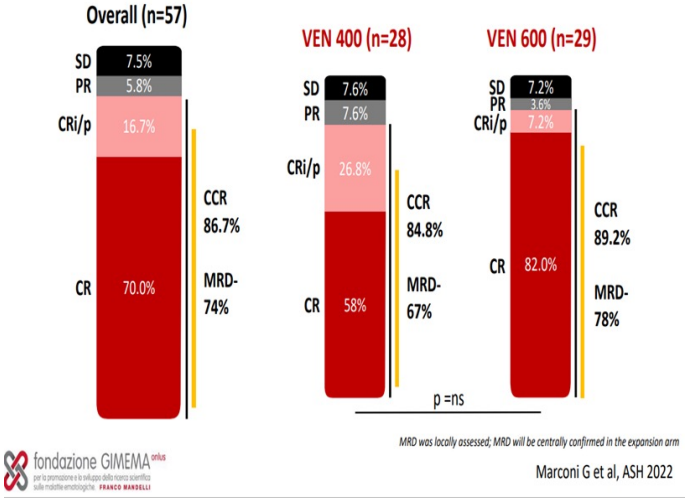
Am J Hematol. 2022 Aug;97(8):1035-1043. doi: 10.1002/ajh.26601. Epub 2022 May 30.

PMID: 35583199

# 710 Gimema AML1718 Part 1: Planned Interim Analysis of a Safety Run-in and Phase 2 Open-Label Study of Venetoclax, Fludarabine, Idarubicin and Cytarabine (V-FLAI) in the Induction Therapy of Non Low-Risk Acute Myeloid Leukemia




## Response




Marconi G et al, ASH 2022

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

Marconi G et al, ASH 2022

SCT

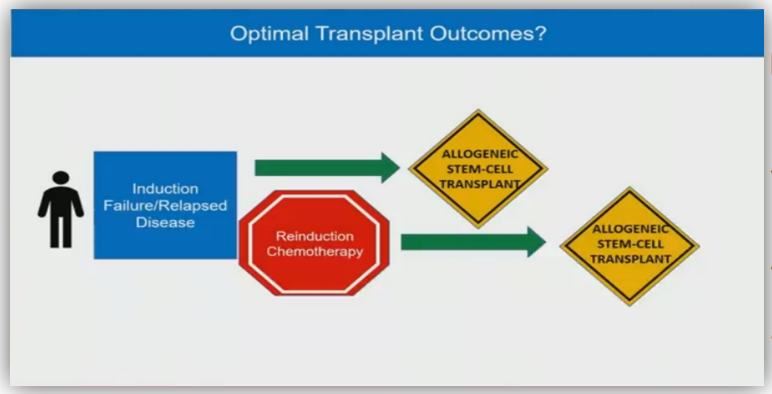
**UNICA PRESENTAZIONE SU AML in PLENARY SESSION**

# In Patients with Relapsed/Refractory AML Sequential Conditioning and Immediate Allogeneic Stem Cell Transplantation (allo-HCT) Results in Similar Overall and Leukemia-Free Survival Compared to Intensive Remission Induction Chemotherapy Followed By Allo-HCT: Results from the Randomized Phase III ASAP Trial

Paper Number: 4

**Johannes Schetelig, MD,MSc** ❤
University Hospital TU Dresden, Germany

Study Alliance Leukemia & the German Cooperative Transplant Study Group
DKMS for funding the trial with support from the Alfred und Angelika Gutermuth Stiftung
Martin Bornhäuser, Matthias Stelljes, Gesine Bug, Lutz P. Müller, Eva-Maria Wagner, Stefan Krause, Christoph Schmid, Moritz Middeke, Cathleen Petzold, Susanne Kiessling, Henning Baldauf, Alexander H. Schmidt, Elke Neujahr




Meeting Coverage > ASH: Hematology

## AML Study Suggests Intensive Chemo Unnecessary Before Allo-HCT

— Similar outcomes if patients went directly to transplant or received intensive salvage first

DESIGN OF THE ASAP TRIAL 3

## Hypothesis: Salvage Chemotherapy prior to alloHCT would not provide a net benefit.

(Remission Induction Strategy)

**RIST**

- Age 18 – 75 years
- poor response after first induction[2] of non-favorable AML OR first untreated relapse
- HLA compatible donor
- Fit for salvage CT and alloHCT[3]

R

1:1, stratified for disease status, AML biology and age

Salvage CT (HAM):
AraC 2 x 3 g/m² d 1-3[1]
Mitox 10 mg/m² d 3-5

137

Conditioning Intensity adapted to residual AML and patient condition

(Disease Control Strategy)

**DisC**

watchful waiting -76%
or
low-dose AraC
or
Mitoxantron 10 mg/m²

139

Sequential Conditioning:
- FLAMSA-RIC
- HD-Melphalan +Flu/TBI

Primary Endpoint:
DFS@d56 after HCT
OS from Rando

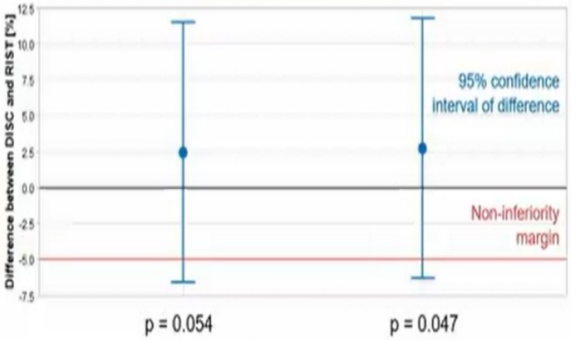
[1] Cytarabine 2 x 1 g/m² for patients >60 yrs
[2] poor response was defined as ≥5% marrow blasts after 1st induction; (see also Röllig *et al*, abstract 217, ASH 2022)
[3] Patients with WBC≥50 GPT/L, CNS manifestations, prior alloHCT, LVEF <50%, $O_2$ supplementation., bilirubin >1.5xULN, GFR <50 ml/min were not eligible

ASAP TRIAL: PRIMARY EFFICACY ANALYSIS 8

## Primary Endpoint: Disease-free Survival @d56 after HCT

| Arm | Intention-to-Treat | Per-Protocol |
|---|---|---|
| Disease-Control | 83.5% | 84.1% |
| Remission-Induction | 81.0% | 81.3% |

Confirmatory analysis done with Farrington-Manning test with one-sided significance level of 2.5%.



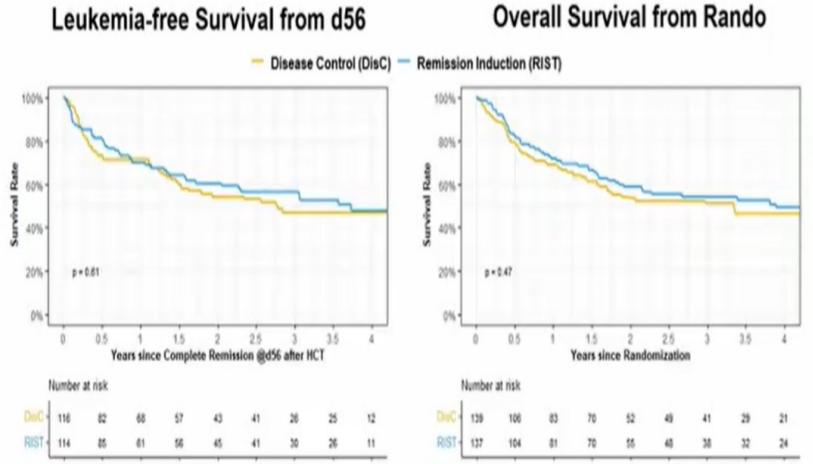

Given the observed edge of the disease control arm over the remission Induction arm,

- probability that true success rate of experimental arm is lower than the non-inferiority margin is 4.7%

DKMS-14-01 ITT/PP, data lock 2022-07-19, analysis as of 2022-11-04

ASAP TRIAL: SURVIVAL OUTCOMES 9

## No Difference in Leukemia-free from DFS@d56 and Survival from randomization!

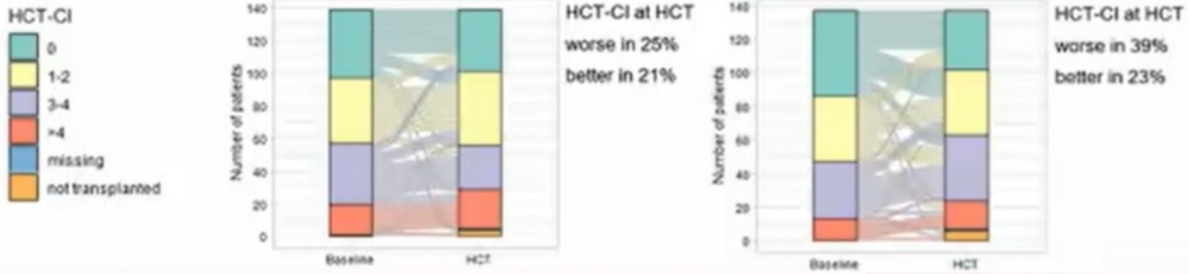



**Median follow-up from Randomization: 37 months**

DKMS-14-01 ITT/PP population, data lock 2022-07-19, analysis as of 2022-11-04

PATIENT SAFETY 12

## Less Adverse Events ≥ grade 3, less days in Hospital with Disease control Strategy

| | Disease Control arm | Remission Induction arm | |
|---|---|---|---|
| Change of HCT-CI from baseline to HCT |  | | |
| Number of patients (%) with AEs ≥ grade 3[1] | 32 (23%) | 87 (64%) | **p<0.001** |
| Days in hospital prior to HCT, mean (range) | 19 (7 - 63) days [2] | 42 (9 - 75) days [2] | **p<0.001** |
| Day 28 mortality from randomization | 3.6% (1.5% - 8.4%) | 1.5% (0.4% - 5.7%) | ns |
| Reasons no HCT | N=4; death due to sepsis (N=2) / leukemia (N=1); decision against alloHCT (N=1) | N=6; death due to pneumonia (N=3), ICB (N=1), refr. AML (N=1); decision against alloHCT (N=1) | |
| Discharged from Hospital | 75% [67%-82%] at 28 days from HCT | 73% [66%-81%] at 28 days from HCT | ns |
| In-hospital death before day 56 | 2.2% [0%-4.8%] | 0.8% [0%-2.4%] | ns |

[1] AEs were counted between randomization and start of conditioning; [2] Days in hospital prior to HCT were calculated for 80% of all patients

DKMS-14-01

ASAP ITT population, data lock 2022-07-19, analysis as of 2022-11-04

## Conclusions

- Patients with poor response after first induction therapy or relapsed AML do not benefit from salvage chemotherapy with high-dose cytarabine plus anthracycline administered for CR induction prior to alloHCT.
- Watchful waiting and sequential conditioning prior to alloHCT results in comparable CR rates and overall survival and may be the preferred option whenever a stem cell donor is readily available.
- Patients spent less time in hospital (42 days vs 19 days) with disease control compared to remission induction and experienced fewer adverse events grade ≥3.

- Impact of morphological CR at time of alloHCT less important than expected.
- Minimal disease burden at admission for transplantation per se is not a pre-requisite for good long-term outcome after alloHCT.
- The benefit of any treatment aiming at better long-term outcomes by inducing a CR prior to transplantation should be demonstrated in prospective intention-to-transplant trials.

# «Nuovi Farmaci-1-»

## 2757 Olutasidenib (FT-2102) Induces Durable Complete Remissions in Patients with Relapsed/Refractory mIDH1 Acute Myeloid Leukemia. Results from a Planned Interim Analysis of a Phase 2 Pivotal Clinical Trial

Program: Oral and Poster Abstracts
Session: 616. Acute Myeloid Leukemias: Investigational Therapies, Excluding Transplantation and Cellular Immunotherapies: Poster II
Hematology Disease Topics & Pathways:
Acute Myeloid Malignancies, AML, drug development, Diseases, Therapies, Myeloid Malignancies

Sunday, December 11, 2022, 6:00 PM-8:00 PM

***Jorge E. Cortes, MD***[1], *Pierre Fenaux*[2], *Karen Yee, MD*[3], *Christian Recher, MD*[4], *Andrew H. Wei, MBBS, FRACP, FRCPA, PhD*[5], *Pau Montesinos, PhD, MD*[6*], *David C Taussig, PhD, FRCPath, MRCP*[7], *Arnaud Pigneux, MD, PhD*[8*], *Thorsten Braun, MD, PhD*[9], *Antonio Curti, MD, PhD*[10], *Carolyn Grove, MBBS, PhD*[11*], *Brian A. Jonas, MD, PhD*[12], *Asim Khwaja, MD, FRCP, FRCPath*[13*], *Pierre Peterlin, MD*[14*], *Olga Polyanskaya, MS*[15*], *Jennifer Sweeney*[15*], *Julie Brevard, MPH*[15*], *Emma Barrett, MD*[15*] *and Stephane De Botton, MD, PhD*[16*]

**Olutasidenib (FT-2102)** is a potent, selective, oral, small-molecule inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1)

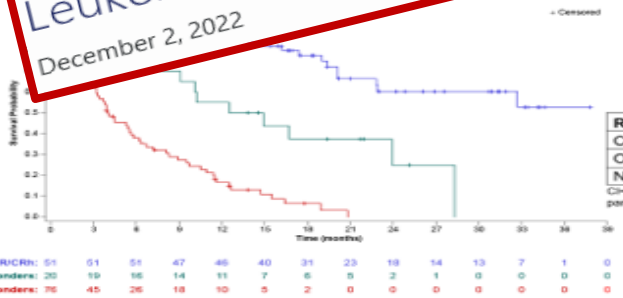
**153 IDH1 inhibitor-naïve pts with R/R mIDH1R132 AML received olutasidenib monotherapy 150 mg twice daily.**

**Table 1: Olutasidenib Response Rates in R/R m*IDH1* AML for the Efficacy Evaluable Cohort**

| Response Rates, n (%) | Efficacy Evaluable Cohort (N = 147) |
|---|---|
| ORR | 71 (48) |
| CR | 47 (32) |
| CRh | 4 (3) |
| CRi | |
| PR | |
| MLFS | |

CR = complete remission; CRh = CR with partial hematologic recovery; MLFS = morph

**Figur… Respo… …e Full Analysis Set by**




| Response Category | Median OS (95% CI) |
|---|---|
| CR/CRh Responders | NR (22.8–NR) |
| Other Responders | 13.7 months (6.0–NR) |
| Non-Responders | 4.0 months (3.2–5.8) |

CI=confidence interval; CR=complete remission; CRh=CR with partial hematologic recovery; NR=not reached; OS=overall survival

FDA Approves Olutasidenib for Relapsed/Refractory IDH1+ Acute Myeloid Leukemia
December 2, 2022

**Conclu…**

**…issions with a … manageable side-effect …**

**…ransfusion independence was achieved across all response groups.**

- ✓ **The observed activity is clinically meaningful and represents a therapeutic advance in the treatment of this molecularly defined, poor-prognosis patient population with R/R AML, including those with prior venetoclax failure.**
- ✓ **Investigation of olutasidenib as monotherapy and in combination with azacytidine is ongoing in other mIDH1 hematologic malignancies.**

POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

# Novità dal Meeting della Società Americana di Ematologia

## GRAZIE

Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

COORDINATORI
Angelo Michele Carella
Pier Luigi Zinzani

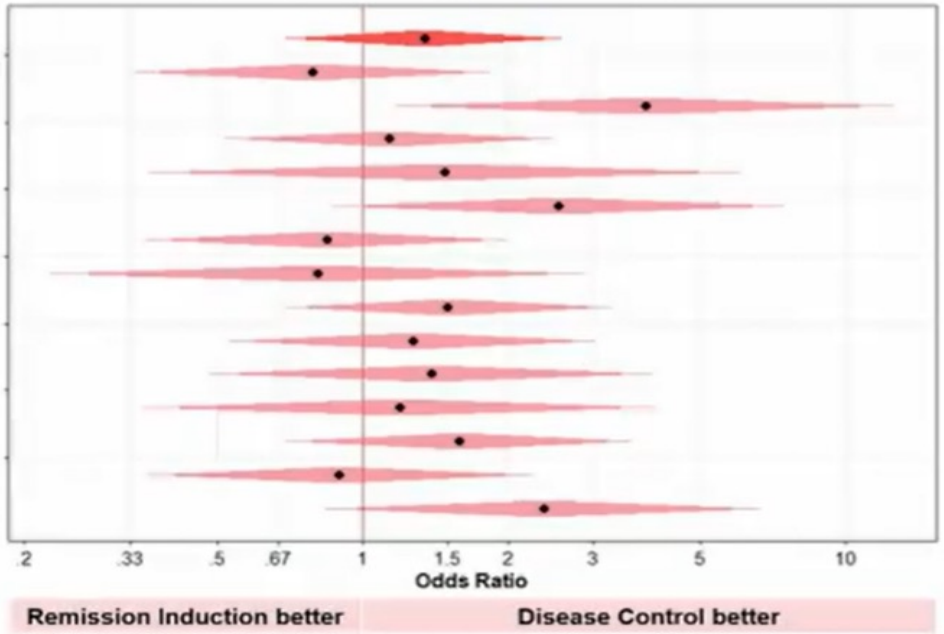
BOARD SCIENTIFICO
Paolo Corradini
Mauro Krampera
Fabrizio Pane
Adriano Venditti

ASAP-TRIAL: PREDICTIVE FACTORS – TEST FOR INTERACTIONS



# Treatment effect consistent across subgroups: DFS@d56 after HCT

| | | N | DISC | RIST |
|---|---|---|---|---|
| **Per Protocol** | | 272 | 138 | 134 |
| **Age** | >60ys | 143 | 71 | 72 |
| | ≤60ys | 129 | 67 | 62 |
| **Disease Status** | Poor response | 177 | 88 | 89 |
| | Relapse | 95 | 50 | 45 |
| **ELN risk *** | Adverse | 81 | 48 | 33 |
| | Fav/Int | 191 | 90 | 101 |
| **Diagnosis** | De-novo AML | 204 | 108 | 96 |
| | sAML / tAML | 68 | 30 | 38 |
| **Sex** | Male | 152 | 75 | 77 |
| | Female | 120 | 63 | 57 |
| **ECOG** | 0 | 102 | 58 | 44 |
| | 1-2 | 170 | 80 | 90 |
| **HCT-CI** | <3 | 169 | 82 | 87 |
| | ≥3 | 103 | 56 | 47 |




DKMS-14-01

* available information was classified according to ELN 2022; molecular typing profile did not comprise all recommended markers for ELN 2022
PP population, data lock 2022-07-19, analysis as of 2022-11-04