Should AML patients in CR1 unfit for HSCT receive maintenance? YES

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Disclosures of Paola Minetto

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NA							

Acute Lymphoblastic Leukemia Therapy

A

B

low-intensity chemotherapy lasting for 1 to 3 years

WHICH ARE THE FEATURES THAT AN IDEAL MAINTENANCE THERAPY SHOULD HAVE?

- Suppress the evolution of the relapse from residual leukemic cells, without leading to additional therapy-related genomic instability.
- Not lead to significant additional toxicity burden to the patient through increased risk of infections, need for recurrent transfusions and overall poor quality of life
- Easy to administer
- In post HSCT setting, not increase risks of GVHD or interfere with post-transplant immunosuppressive medications.

Teachey DT, et al. Optimizing therapy in the modern age: differences in length of maintenance therapy in acute lymphoblastic leukemia. *Blood* 2021; 137: 168–177.

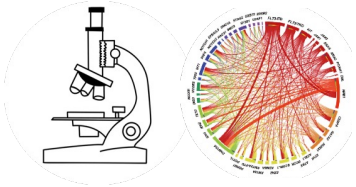
UNMET NEED

Relapse after intensive induction and consolidation therapy remains the most important cause of treatment failure in AML. Risk of relapse increases with age

HISTORICAL EVIDENCES

Should AML patients in CR1 unfit for HSCT receive maintenance?

YES!



BETTER UNDERSTANDING OD DISEASE BIOLOGY
ROLE OF MINIMAL RESIDUAL DISEASE

or at least

WHY NOT

NEW THERAPEUTIC OPTIONS AVAILABLE
WITH LOW TOXICITY PROFILE

LOW-INTENSIY CHEMO

Low dose cytarabine
Attenuated chemo[1]

IMMUNE ADJUVANTS

IL-2/IL-2 + HDC
IFN α
LENALIDOMIDE
Checkpoint inhibitors → RISK OF GvHD

OTHER
Androgen analog

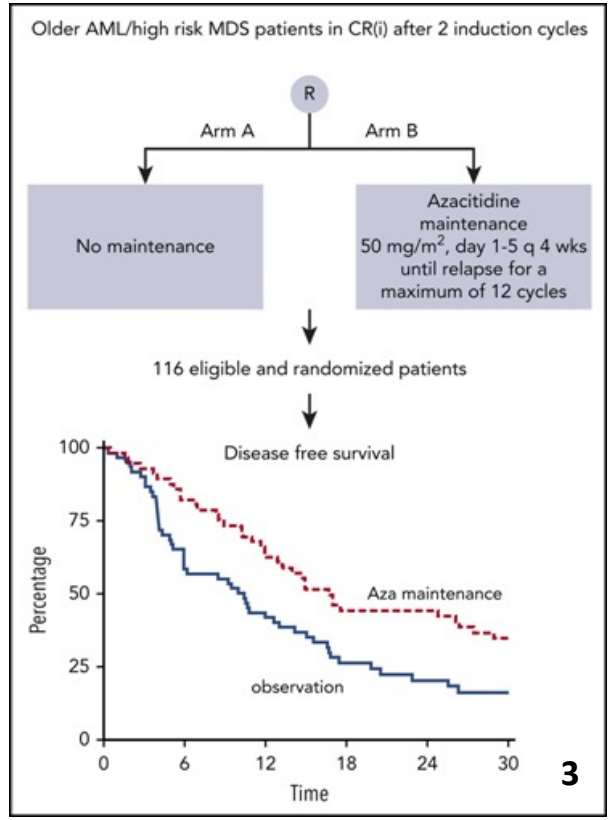
EPIGENETIC MODIFIERS

AZACITIDINE → OS ADVANTAGE IN MRD NEG, > 60 YRS[2]
DECITABINE → GOOD TOLERABILITY

HMA + VENETOCLAX[4]

TARGETED THERAPIES

GO
FLT3-INHIBITORS
IDH- INHIBITORS
DASATINIB (CBF)



1. Rashidi A, et al. Maintenance therapy in acute myeloid leukemia: an evidence-based review of randomized trials. Blood. 2016 Aug 11;128(6):763-73.
2. Burnett A, et al. A Comparison of Limited Consolidation Chemotherapy Therapy Or Not, and Demethylation Maintenance Or Not in Older Patients with Aml and High Risk Mds: Long Term Results of the Uk Ncri Aml16 Trial. Haematologica. 2015;100(s1):194.
3. Huls G, et al. Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. Blood. 2019;133(13):1457-1464.
4. Bazinet A, et al. A Phase II Study of Azacitidine Plus Venetoclax As Maintenance Therapy in Acute Myeloid Leukemia: Durable Responses with Longer Term Follow-up. Blood. 2022;140(Supplement 1):9005-9007.

Oral Azacitidine – QUAZAR AML-001

N= 472
(≥ 55yrs)
INT/ADV

INDUCTION/CONSOLIDATION

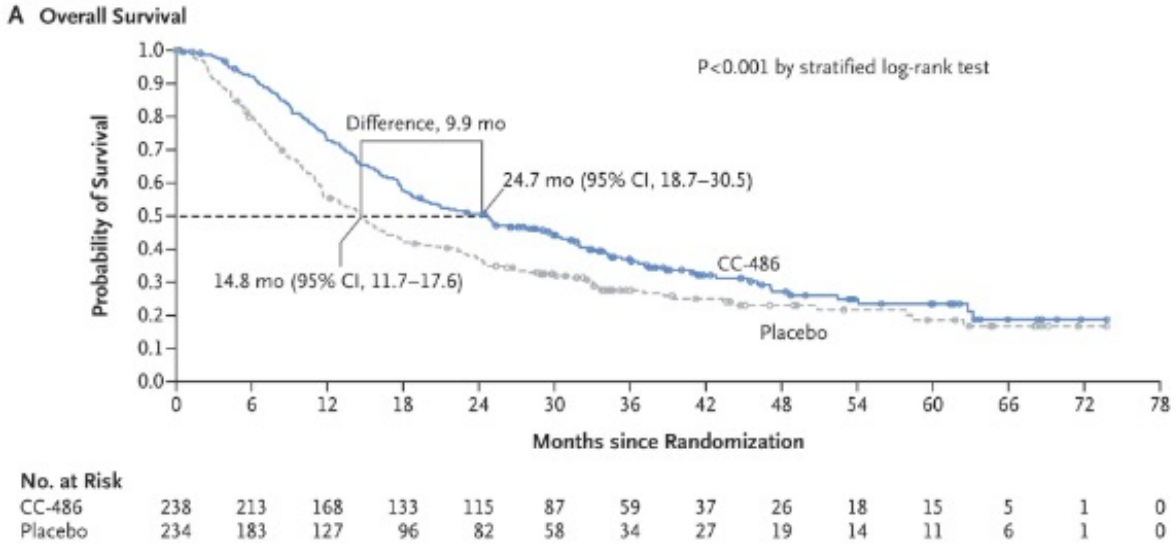
CR/CRi

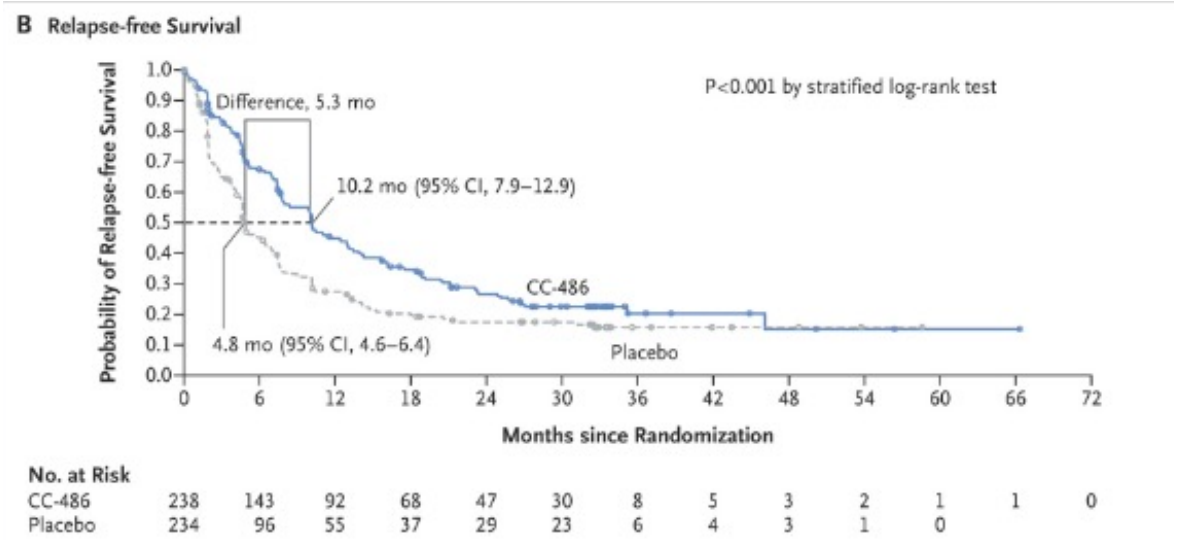
1:1

PLACEBO

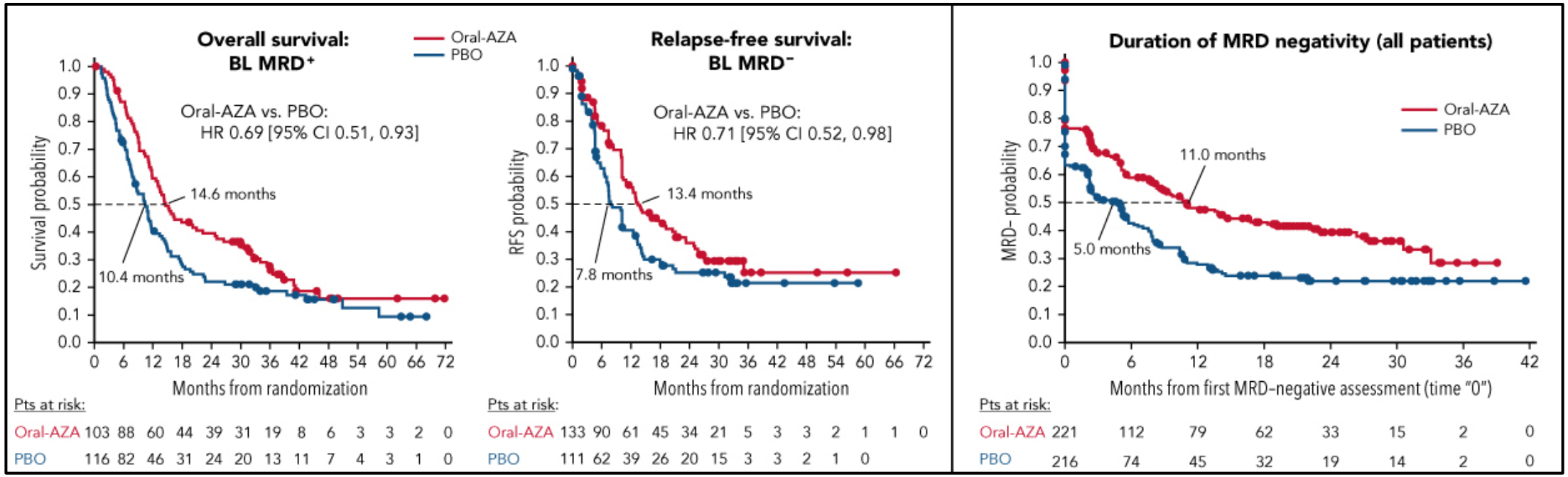
MAINTENANCE

CC-486 (oral azacitidine) 300 mg/die d 1-14 [28 day cycle]





Wei AH, et al. QUAZAR AML-001 Trial Investigators. Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission. N Engl J Med. 2020 Dec 24;383(26):2526-2537.



- MRD POSITIVITY CONFIRMED AS PROGNOSTICALLY POOR
- MRD + ALSO BENEFIT OF ORAL AZA VS PLACEBO (SUBSET WITH MRD CONVERSION 37%) – POST HOC

Roboz GJ, et al. Oral azacitidine prolongs survival of patients with AML in remission independently of measurable residual disease status. *Blood* 2022; 139 (14): 2145–2155.

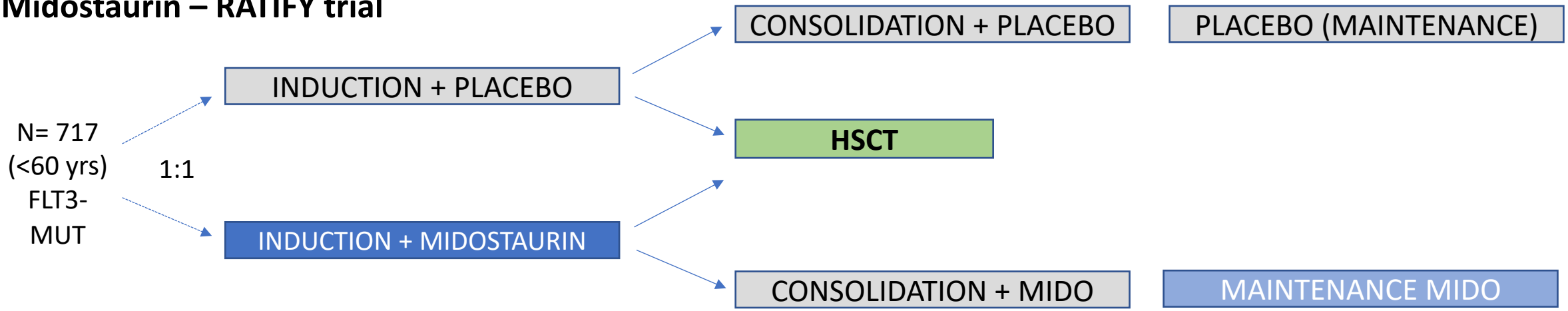
Oral Azacitidine – QUAZAR AML-001

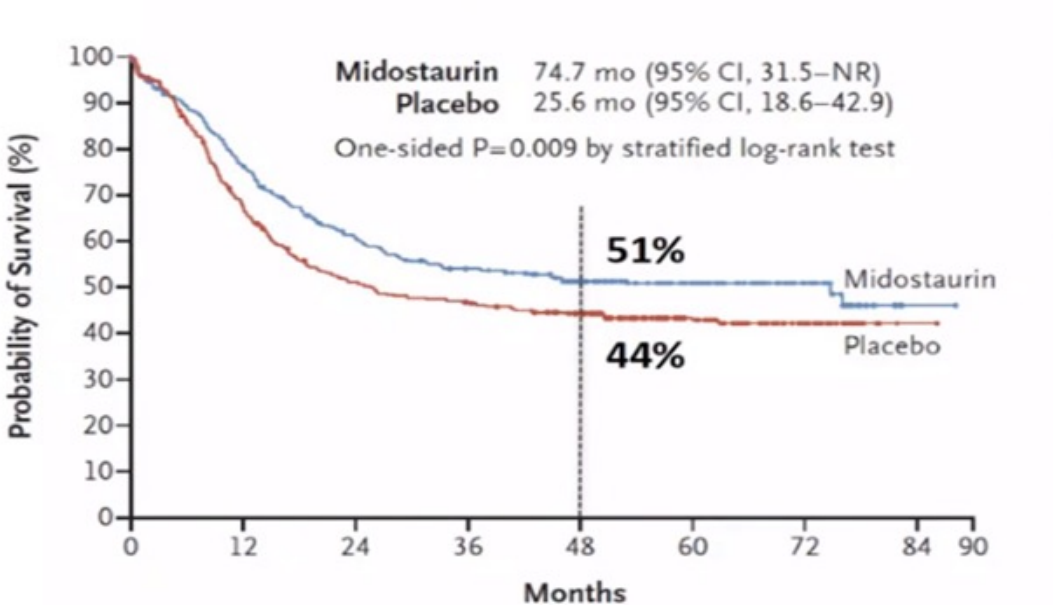
Safety

- AEs: GASTROINTESTINAL AND HAEMATOLOGICAL (neutropenia)
- QoL: MAINTENANCE ARM NON INFERIOR

- INCIDENCE OF GI AEs DECREASE OVER TIME

Midostaurin – RATIFY trial

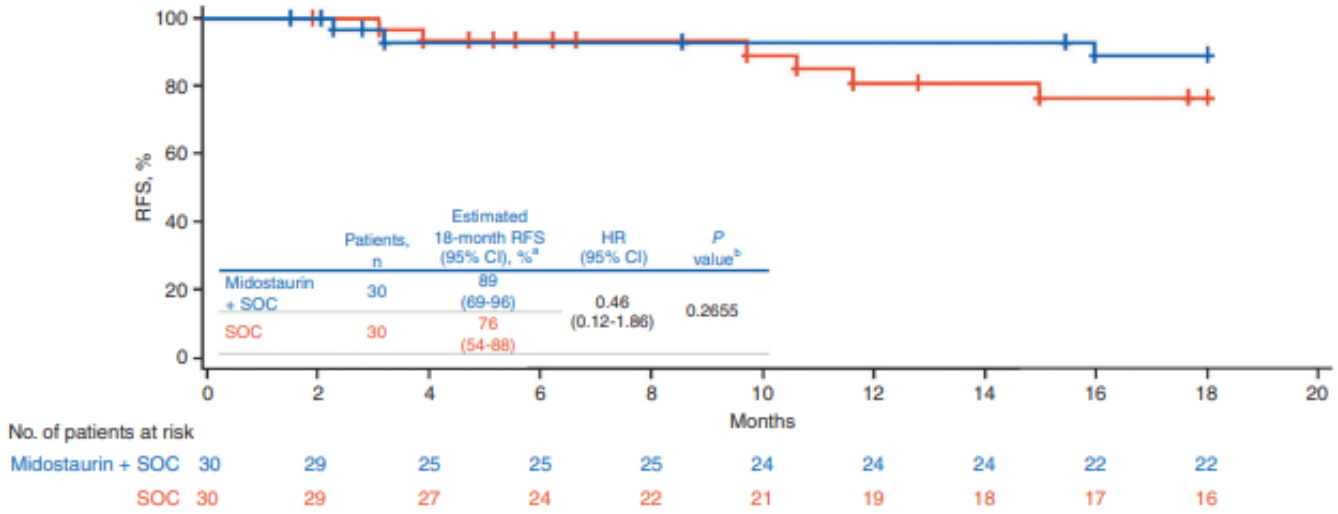




- EMA approved maintenance
- Added value not assessed

Stone RM,et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017 Aug 3;377(5):454-464.

RADIUS - Phase 2 trial investigating whether the addition of midostaurin to standard-of-care (SOC) treatment post-alloHSCT improves RFS over SOC alone in patients with *FLT3*-ITD-positive AML



Adults (aged 18-70 y) who had undergone myeloablative alloSCT in first complete remission (CR1), had achieved hematologic recovery, and were transfusion independent were eligible.

- AEs in 100% and 87% of patients, respectively in MIDO+SOC and SOC respectively.
- Most AEs in both arms were grade 1/2. The most common AEs were low-grade gastrointestinal AEs Gastrointestinal AEs were more common in the MIDO +SOC arm than in the SOC arm.

Maziarz RT, et al. Midostaurin after allogeneic stem cell transplant in patients with *FLT3*-internal tandem duplication-positive acute myeloid leukemia. *Bone Marrow Transplant* **56**, 1180–1189 (2021).

Other options?

Combinations - HMA/VENETOCLAX

- Bazinet et al, 2021 - AZA 50 mg/m ^{2} IV/SQ on days 1-5 and VEN 400 mg PO on days 1-14 every 28 days, for up to 24 cycles. 27 patients in CR1 and CR2 treated with intensive chemotherapy (defined as including standard or higher-dose cytarabineor low-intensity chemotherapy (defined as including a low-dose cytarabine (LDAC) or hypomethylating agent (HMA) backbone)
- VIALE-M (NCT04102020) - A Study of Oral Venetoclax Tablets and Oral Azacitidine Versus Oral Azacitidine as Maintenance Therapy in Adult Participants With Acute Myeloid Leukemia in First Remission After Conventional Chemotherapy

Other FLT3-TARGETED AGENTS

- **Sorafenib (post HSCT) -** Burchert et al, 2020 - Randomized, placebo-controlled, double-blind phase II trial (SORMAIN; German Clinical Trials Register: DRKS00000591), 83 adult patients with *FLT3*-ITD-positive AML
  The 24-month RFS probability was 53.3% with placebo versus 85.0% with sorafenib

Conclusions and open questions

- Far from replacing HSCT, maintenance therapy in AML generally prolongs DFS and recently oral AZA showed for the first time that maintenance therapy can improve OS
- New available options with acceptable toxicity profile
- Possibility to exploit combinations (HMA backbone)
- New therapeutic options as front line-treatment increase the percentage of elderly patients achieving CR (and then?)
- Are we preventing or delaying relapse? Open question, however delaying relapse in elderly patient is a positive goal
- Which is the optimal timing and which patient may benefit most from maintenance? Open question

Thank you for your attention