ALAN network -update on AML EHA

Dr E Nikolousis

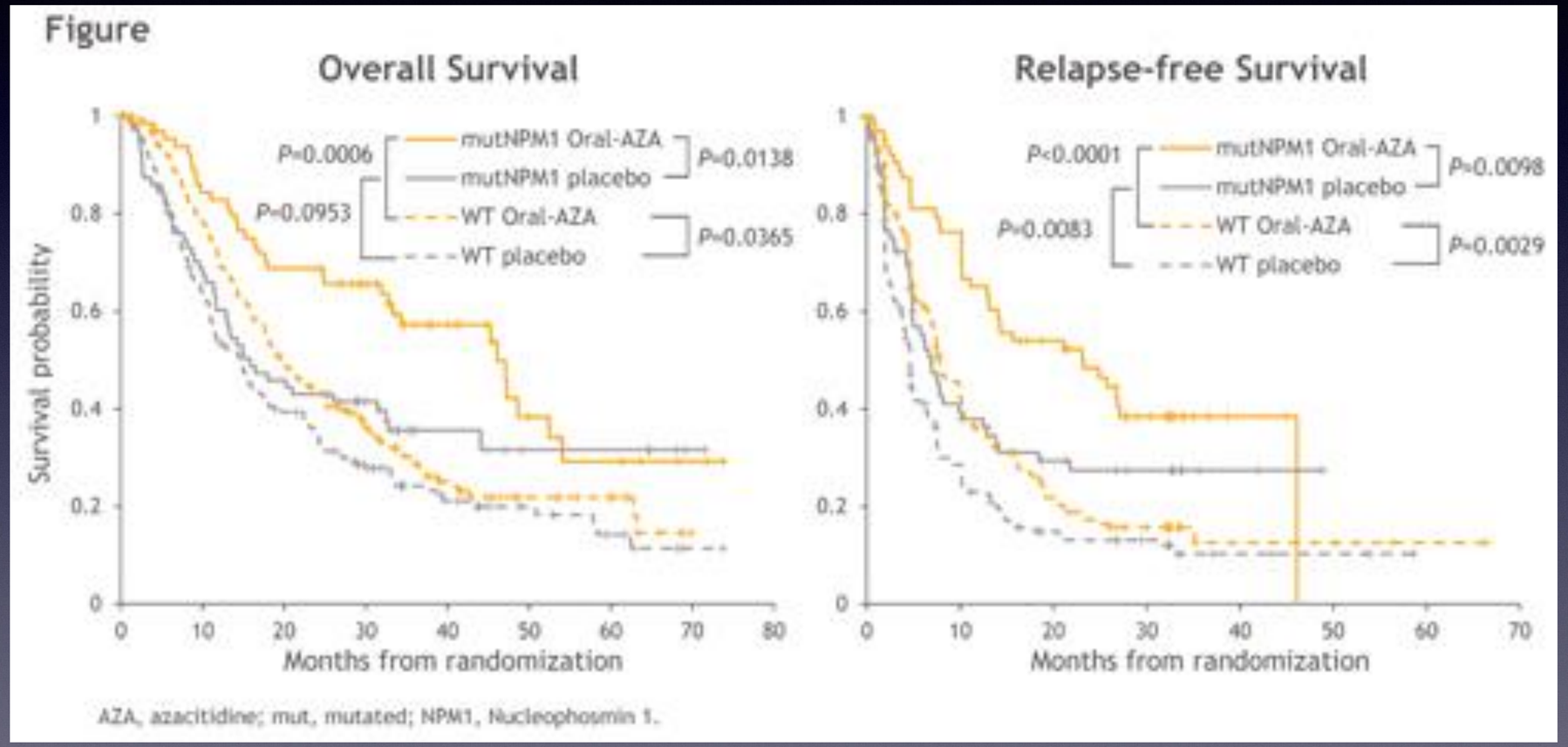
AML in the COVID era

- All these patients, were affected by Acute Leukemia (8 pts AML, 2 pts ALL ph negative)
- the majority of them was in peak of cytopenia at the Covid-19 infection time
- Nine patients had been treated with intensive chemotherapy before SARS-CoV-2 confirmation.
- At SARS-CoV-2 diagnosis, only one patient had untreated, newly diagnosed AML
- 3 patients had refractory/relapsed AML.
- Deep vein thrombosis complicated by pulmonary embolism and interstitial pneumonia was observed in a patients despite anticoagulation and in thrombocytopenia.
- After SARS-CoV-2 infection, no leukemia-specific treatment was adjusted.
- Three patients (30%) died due to severe acute respiratory distress syndrome (ARDS) despite extracorporeal membrane oxygenation (ECMO) in deep aplasia, all of them was in refractory disease.
- Seven patients delayed in chemotherapy treatment for a media of 34 days; chemotherapy started until COVID-19 symptoms have completely resolved and two viral testing becomes negative

Oral Azacitidine AZA001

- Oral azacitidine (Oral-AZA; CC-486) is approved in the US for adult patients (pts) with acute myeloid leukemia (AML) who have achieved first complete remission (CR) or CR with incomplete blood count recovery (CRi) after intensive chemotherapy and are ineligible for intensive curative therapy
- Oral-AZA considerably improved survival for pts with *de novo* AML and int-risk cytogenetics.
- Additionally, pts with mut*NPM1* in the Oral-AZA arm derived an extended OS benefit of more than 2.5 years vs PBO, whereas OS for all pts in QUAZAR AML-001 was lengthened by 9.9 months with Oral-AZA vs PBO

Oral Azacitidine AZA001



V-FAST study

- V-FAST (Vyxeos – First Phase Assessment With Targeted Agents) an open-label, multicenter, phase 1b master trial (NCT04075747)
- evaluate CPX-351 in combination with targeted agents in patients aged 18 to 75 years with untreated AML who are fit for intensive chemotherapy
- Patients received CPX-351 (dose level 1 for first induction [DL1]: 100 units/m^2 on Days 1, 3, and 5) plus venetoclax (Arm A; DL1: 400 mg on Days 1 to 14), midostaurin (Arm B; DL1: 50 mg BID on Days 8 to 21), or the IDH2 inhibitor enasidenib (Arm C; DL1: 100 mg on Days 8 to 28) based on mutation testing.

PEVOLAM trial

- PEVOLAM: TRIAL DESIGN FOR A RANDOMIZED PHASE 3 MULTICENTER STUDY COMPARING AZACITIDINE PLUS **PEVONEDISTAT** VS AZACITIDINE IN OLDER OR UNFIT PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA
- its novel mechanism of action and non-myelosuppressive safety profile,
- PEVO as an additional combination therapy partner for pts with AML to improve survival outcomes while preserving QoL-study still ongoing

Menin inhibitors another small molecule!

- Histone-lysine-*N*-methyltransferase 2A (*KMT2A*) gene (formerly known as mixed-lineage leukemia (*MLL*)) plays an essential role in regulating gene expression including that of *MEIS1* and the homeobox gene family
- important for maintenance of leukemic cells when dysregulated
- In 5-10% of acute myeloid leukemia (AML) cases, specific *KMT2A* gene perturbations can occur which result in poor prognosis
- The Menin-KMT2A complex also appears to play a central role in the epigenetic dysregulation in AMLs with co-mutations in genes such as *NPM1*, *IDH1/2*, *FLT3*, *EZH2*, and *DNMT3A*, with *NPM1* mutation accounting for 25-30%
- Therefore targeting these AML subsets, which may be exquisitely sensitive to the menin-KMT2A complex inhibition

Menin inhibitors another small molecule!

- KOMET-001 (NCT04067336) is an ongoing Ph1/2 open-label study evaluating KO-539 in adult patients (pts) with relapsed or refractory (R/R) AML
- R/R AML defined as the appearance of > 5% blasts in the bone marrow who have failed or are ineligible for any approved standard of care therapies, including transplant, ECOG performance status of 0 to 2, and adequate organ function
- Determine a recommended Ph2 dose (RP2D), and investigate early signs of anti-leukemic activity
- The Ph1 expansion cohorts will assess anti-leukemic activity, PK, safety and tolerability in AML pts with *NPM1* mutation or *KMT2A* rearrangement at doses that have already met the safety threshold

ADMIRAL follow up

- Follow-up of ADMIRAL assessed long-term survivors, hematopoietic stem cell transplantation (HSCT) outcomes, and gilteritinib safety beyond 1 year
- A data cut was performed on September 20, 2020—2 years after the primary analysis. Patients who were alive without relapse, patients who underwent HSCT, and adverse events (AEs) of interest in Years 1 (≤12 months) and 2 (>12 months) of gilteritinib therapy were evaluated

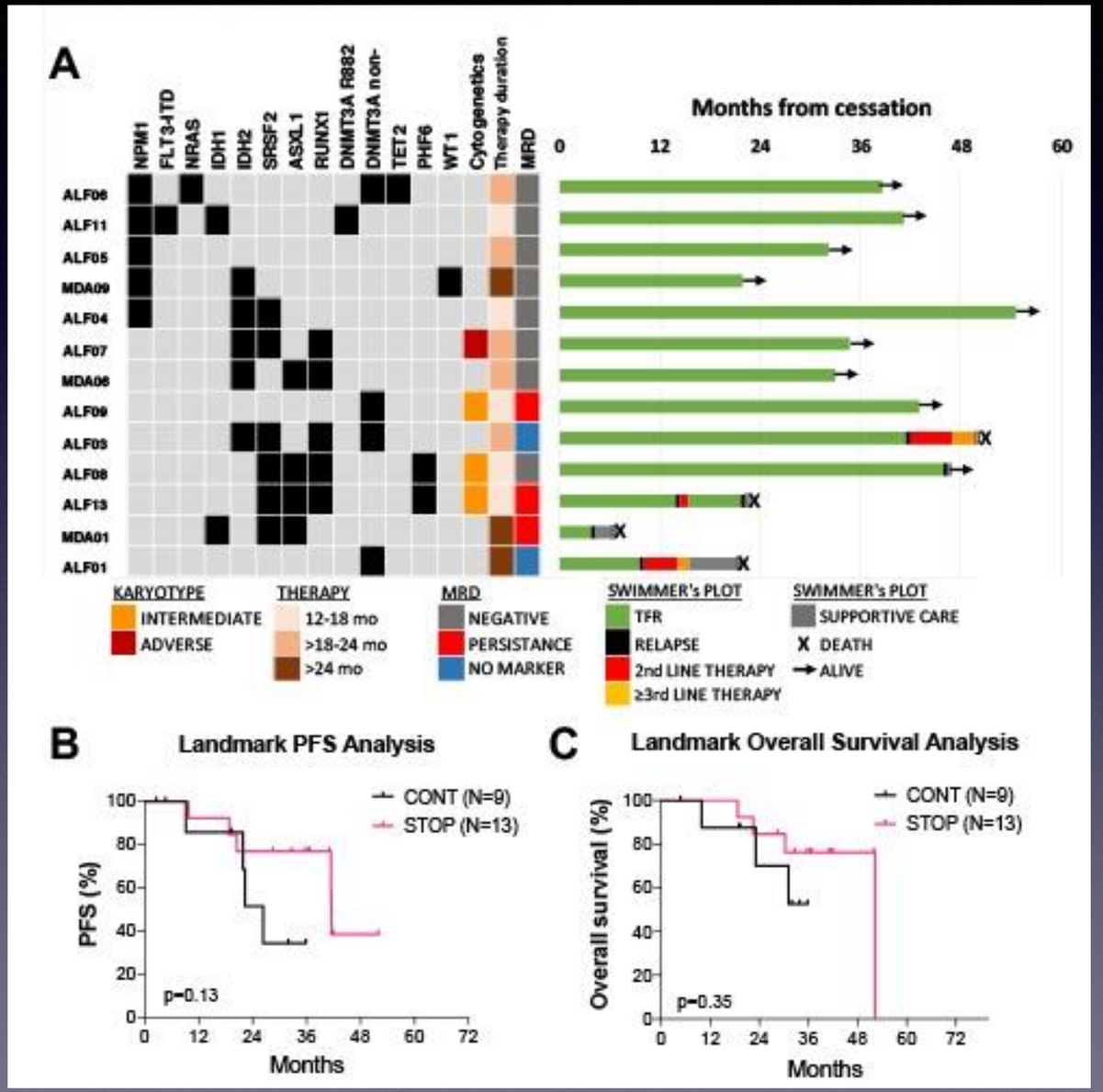
ADMIRAL follow up

- Cumulative 24-month relapse rates in gilteritinib-treated patients who achieved pre-HSCT CR and CRc were 20% and 45%, respectively.
- Median post-HSCT overall survival (landmarked to the date of HSCT) was similar across arms (gilteritinib, 16.1 months; SC, 15.3 months; HR=1.076; 95% CI: 0.536, 2.160)
- Overall, 10.2% of patients (n=25/246) had ≥24 months of gilteritinib exposure. The most common AEs of interest during Years 1 and 2 of gilteritinib therapy were elevated alanine or aspartate aminotransferase levels.
- Incidences of all AEs of interest declined in Year 2.
- One case of differentiation syndrome and cutaneous squamous cell carcinoma occurred in Years 1 and 2, respectively.

TFR-is it feasible?

- Phase 3 studies have confirmed the benefit of adding venetoclax (VEN) to azacitidine (AZA) or low dose cytarabine (LDAC) in older/unfit patients (pts) with newly diagnosed AML
- AML receiving VEN combined with either hypomethylating agents (HMA) or LDAC for ≥12 months and in first remission were included in this retrospective analysis.
- Two treatment approaches were compared: elective cessation of therapy in remission followed by monitoring (STOP cohort) or continued therapy until relapse (CONT cohort)

TFR-is it feasible



Magrolimab-the solution for p53?

- Magrolimab (Hu5F9-G4) is an antibody blocking CD47
- It induces tumor phagocytosis and eliminates leukemia stem cells.
- Azacitidine (AZA) synergizes with magrolimab by inducing eat me signals on leukemic blasts
- In 12 untreated TP53 mutant AML patients unfit for induction chemotherapy, the CR/CRi rate was 75% - DoR NR

MRD- what can we do best?

- MRD results may vary by method and laboratory, and comparability of MRD results across different laboratories is limited
- Next-generation sequencing (NGS) has been shown to be a sensitive and prognostic methodology for MRD detection
- High sensitivity and specificity for the various local protocols for the majority of participating laboratories-a standardized protocol can be quickly and successfully incorporated

MRD-when and HSCT vs chemo

- *Nucleophosmin1* mutated (*NPM1*$_{mut}$) based minimal residual disease (MRD) monitoring allows the early identification of patients (pts) with acute myeloid leukemia (AML) at high risk of relapse

- 611 *NPM1*$_{mut}$ pts were enrolled in one of four AMLSG treatment trials. Treatment comprised 1 to 2 cycles of induction therapy followed by HIDAC (n=363, 59%), autologous (n=19, 3%) or alloSCT (n=162, 27%)

- Outcome of pts who became MRD negative was superior after HIDAC consolidation versus alloSCT

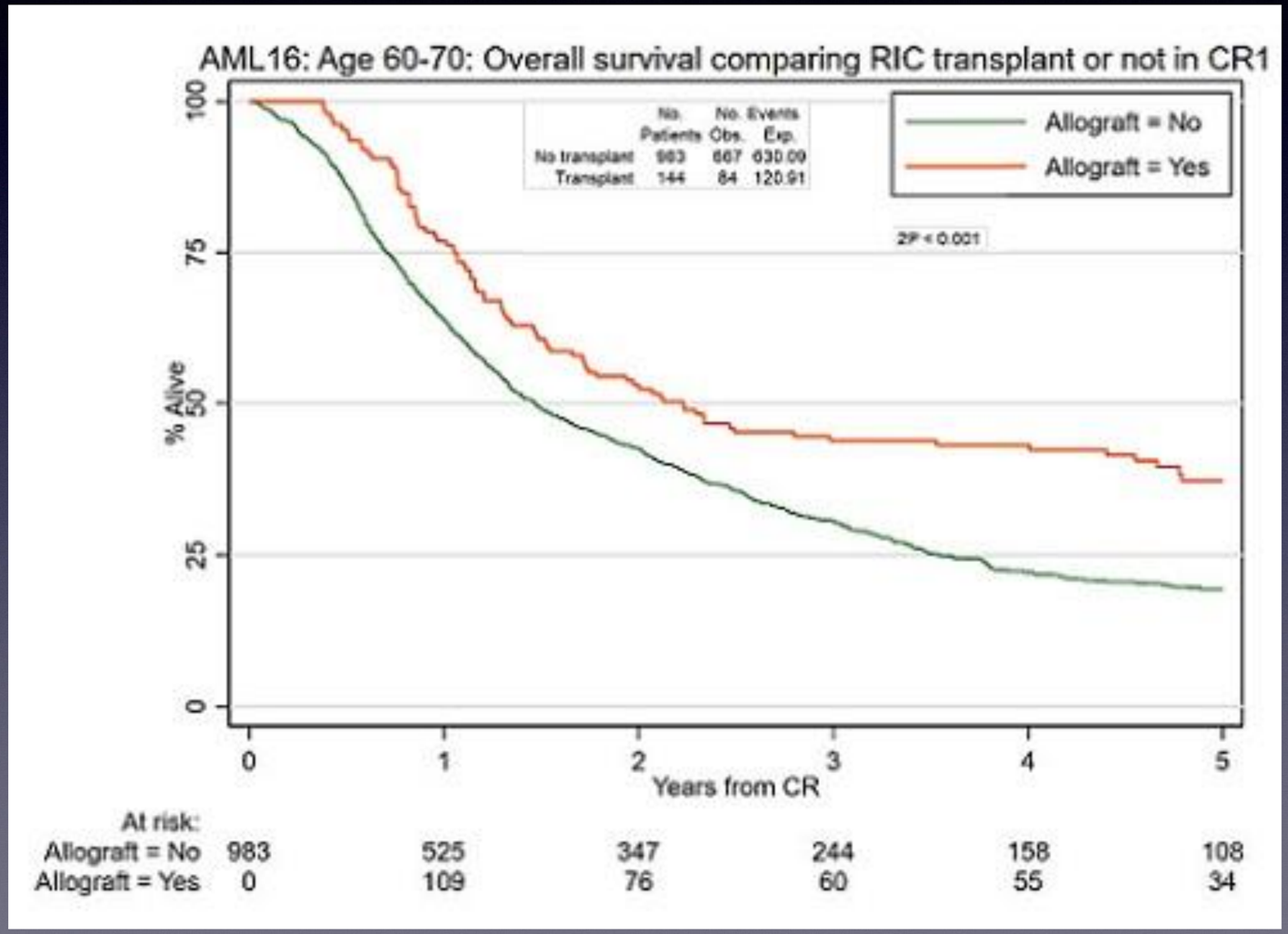
Allo-HSCT maintenance

- 2009 and 2018, including 736 patients
- Maintenance therapy was comprised of tyrosine kinase inhibitors (TKI): sorafenib - 2 studies; midostaurin - 1 study, and hypomethylating agents (HMAs): decitabine and azacytidine - one study each
- Maintenance after allogeneic HSCT was associated with an improved OS, HR=0.61 (95% CI 0.47-0.80, I^2=2%, 547 patients). Subgroup analyses by type of maintenance therapy also revealed advantage in OS with either TKI or HMA maintenance [HR=0.50 (95% CI 0.33-0.77, 3 trials, 345 patients) and HR=0.69 (95% CI 0.49-0.98, 2 trials, 391 patients), respectively]
- Data from five trials were available for RFS analysis and showed improved RFS in the maintenance group compared with the control arm HR=0.51 [95% CI 0.40 - 0.66]. Relapse rate was significantly decreased in the maintenance arm compared to the control arm, RR=0.41 (95% CI 0.20-0.88, 4 trials, 668 patients)

RIC Allo for AML- MRD

- Two consecutive front line NCRI trials for patients >60 years, the AML16 trial (2006-2012) and AML18 (2015-) performed with the aim of identifying which patients benefit from RIC transplantation in CR1
- Both trials employed a double induction with daunorubicin and clofarabine or AraC +/- Gemtuzumab in AML16 and daunorubicin and AraC (DA) + Gemtuzumab in AML18
- In AML16, 983 patients in CR1 were studied, with RIC transplant given to 144 (15%) with median follow-up for survival from CR of 60 months.
- In AML18, 648 out of 847 patients achieved CR of whom 201 (31%) were transplanted with a median follow up of survival from CR of 45 months.

RIC Allo for AML-MRD



RIC Allo for AML-MRD

- RIC transplant in first remission for older adults that is independent of post course 1 response and MRD status.
- A feasible and curative option via GvL effect