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S134 FLAG-IDA COMBINED WITH GEMTUZUMAB OZOGAMICIN (GO) REDUCED MRD LEVELS AND IMPROVED OVERALL SURVIVAL IN NPM1MUT AML INDEPENDENT OF FLT3 AND MRD STATUS, RESULTS FROM THE AML19 TRIAL

Topic: Novel combinations in the treatment of AML

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Background:

The NCRI AML17 trial established the prognostic impact of measurable residual disease (MRD) by RT-qPCR in patients with *NPM1*^{mut} AML. Patients testing MRD+ve in the peripheral blood (PB) following the second course of chemotherapy (PC2) had a high risk of relapse (77% at 3 years) and poor overall survival (OS, 25% at 3 years). The subsequent NCRI AML19 trial randomised 1033 patients with newly diagnosed AML or MDS-EB2 between FLAG-Ida and DA3+10 and either a single dose of GO (GO1) or a fractionated schedule (GO2). No *FLT3* inhibition was used. The outcomes for this trial have been reported with no OS benefit (Russell et al, ASH, 2022), however in *NPM1*^{mut} patients (n=307) there was an OS benefit with FLAG-Ida-GO (5y OS 82% vs 64%, HR 0.50, CI O31-0.81, p <0.005).

Aims:

To analyse the impact of FLAG-Ida-GO on MRD and outcome of post-induction therapy in *NPM1*^{mut} AML with and without a *FLT3* mutation

Methods:

NPM1^{mut} MRD was measured following each chemotherapy course. *P*atients who were PC2 PB MRD+ve were recommended for transplant in CR1 Post-remission therapy for MRD-ve patients consisted of up to 2 courses of HDAC.

Results:

The survival benefit for FLAG-Ida-GO was seen in both *FLT3*^{mut} (HR 0.32, 95CI 0.17-0.62) and *FLT3*^{wt} patients (HR 0.75, 95CI 0.37-1.51) with no evidence of differential benefit on tests for heterogeneity (Figure 1). FLAG-Ida-GO increased the number of patients who were PC2 PB MRD-ve (88% vs 77% with DA-GO, p=0.02), as well as the number with an MRD-ve bone marrow (BM) both PC2 (56% vs 37%, p=0.004) and at end of treatment (70% vs 58%, p=0.32). In those with undetectable PB MRD, the BM response was deeper in the FLAG-Ida-GO arm, with 60% also BM MRD-ve compared to 47% with DA-GO (p=0.069). The same trend for a deeper BM response was

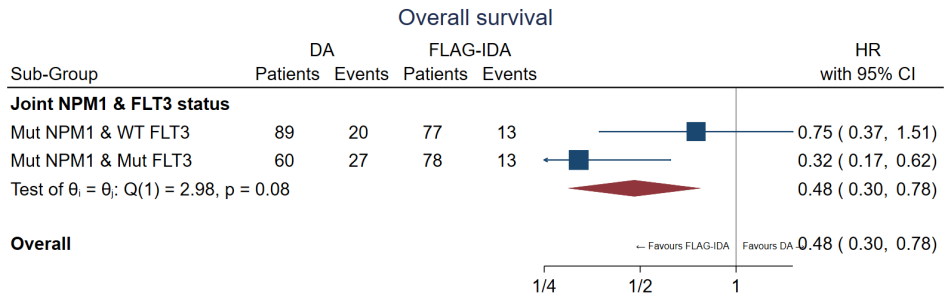
seen in those who were PB PC2 MRD+ve. The improved FLAG-Ida-GO MRD response was seen in both *FLT3*^{mut} (PC2 PB-ve 83% vs 68%) and *FLT3*^{wt} (PC2 PB-ve 92% vs 82%). Within the DAGO arm, GO2 resulted in an increase in the number testing PB PC2 MRD-ve (84% vs 69% for GO1, p=0.04) but did not improve survival. There was no effect of GO dose on MRD in the FLAG-Ida-GO arm.

For PB PC2 MRD+ve patients, 61% proceeded to transplant in CR and this did not differ by randomisation. For these patients 3y OS was 59%, those randomised to FLAG-Ida-GO had a trend to better survival than those allocated DA-GO (74% vs 51% at 3 years, HR 0.52, 95CI 0.17-1.57). For PC2 PB MRD-ve patients, outcomes were excellent with both therapies, but here again survival was superior in patients treated with FLAG-Ida-GO (3y OS 90% vs 78%, HR 0.43, 95CI 0.22-0.87). There was no heterogeneity in the FLAG-Ida-GO benefit based on MRD response (Figure 1). Patients could receive up to 2 cycles of consolidation with HDAC, for patients who were PB MRD-ve after FLAG-Ida-GO (n=115) there was no evidence that overall or relapse-free survival (RFS) was improved by consolidation (for 0, 1 and 2 cycles of consolidation respectively, 3 year OS 90% vs 83% vs 93%, p=0.53; 3 year RFS 75% vs 65% vs 81%, p=0.14)

Summary/Conclusion:

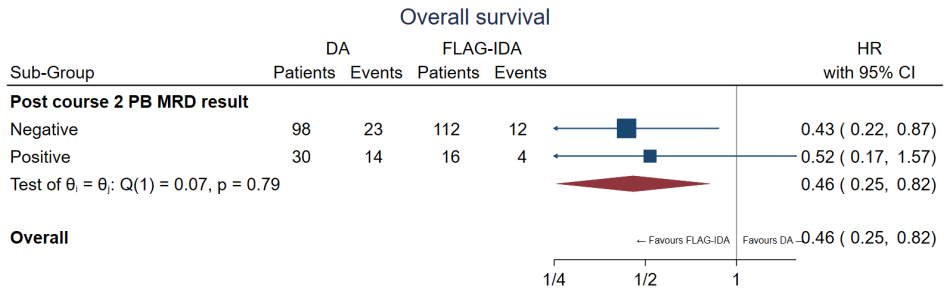
FLAG-Ida-GO improved the OS of patients with *NPM1*^{mut} AML and reduced the number who were PB PC2 MRD+ve compared to DA-GO. This survival benefit was independent of *FLT3* mutation status and was seen in both PB PC2 MRD+ve and MRD-ve patients and was supported by the finding that BM MRD levels in both groups were lower with FLAG-Ida-GO including those testing PB post C2 negative. For those patients who were PB MRD-ve after 2 cycles of FLAG-Ida-GO, this treatment appears sufficient.

A



Note: Unadjusted analyses with DA as referent and FLT3 grouping TKD and ITD patients receiving GO1/GO2

B



Note: Unadjusted analyses with DA as referent, all patients receiving GO1/GO2

Figure 1 – overall survival by randomisation arm.

A. By NPM1 and FLT3 status

B. By Post course 2 peripheral blood MRD result