**CONSORT 2010 Flow Diagram**

Allocated to LDAC-T Ara-C 20mg twice a day for 10 days with Tosedostat120mg once a day for up to 6 months (n= 123)

 Received allocated intervention (n= 114)

 Did not receive allocated intervention (n=9)

 Patient died before starting treatment (n=6)

 Did not start treatment (n=2)

 Randomised in error (n=1)

Figure 1. CONSORT flow diagram

## Allocation

## Follow-Up

## Analysis (ITT)

## Enrollment

Randomized (n= 247)

Allocated to LDAC Ara-C 20mg twice a day for 10 days (n=124)

 Received allocated intervention (n=116 )

 Did not receive allocated intervention (n=8)

 Patient died before starting treatment (n=4)

 Did not start treatment (n=1)

 Randomised in error (n=3)

No survival data (n=0)

Withdrew from trial treatment (n=11)

No survival data (n=0)

Withdrew from trial treatment (n=8)

Analysed (n= 122)
 Excluded from analysis (n= 0)

Analysed (n=121)
 Excluded from analysis (n= 0)



Figure 2. Co-morbidities



Figure 3a. Overall survival (OS)



Figure 3b. Overall survival from complete response (OS from CR)



Figure 3c. Survival from relapse



Figure 3d. Relapse free survival (RFS)



Figure 4a: Course 1 toxicity (expressed as percentage of patients) and resources used (the only significant difference between arms was an increased use of platelets in course 1 (mean 5.0 vs 3.5 pools p=0.006).



Figure 4b: Course 2 toxicity (expressed as percentage of patients) and resources used (no significant differences).

|  |  |  |  |
| --- | --- | --- | --- |
|   | **Treatment comparison** |   |   |
|   | **LDAC** | **LDAC+Tosedostat** | **Total** |
|   | N=121 | N=122 | N=243 |
| **Age at entry (years)** |   |   |   |   |   |   |
| Mean (SD) | 76.6 | (5.2) | 76.9 | (5.7) | 76.8 | (5.4) |
| Median (IQR) | 76.8 | (73.8, 79.9) | 76.9 | (73.0, 81.4) | 76.8 | (73.2, 80.7) |
| Min, max |   | (60.9, 88.9) |   | (61.6, 88.8) |   | (60.9, 88.9) |
| Missing (%) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| **Age group (years)** |   |   |   |   |   |   |
| 60-64 | 2 | (1.7) | 4 | (3.3) | 6 | (2.5) |
| 65-69 | 12 | (9.9) | 9 | (7.4) | 21 | (8.6) |
| 70-74 | 29 | (24.0) | 30 | (24.6) | 59 | (24.3) |
| 75-79 | 49 | (40.5) | 41 | (33.6) | 90 | (37.0) |
| 80+ | 29 | (24.0) | 38 | (31.1) | 67 | (27.6) |
| Missing (%) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| **Sex** |   |   |   |   |   |   |
| Female | 47 | (38.8) | 51 | (41.8) | 98 | (40.3) |
| Male | 74 | (61.2) | 71 | (58.2) | 145 | (59.7) |
| Missing (%) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| **WHO performance status** |   |   |   |   |   |
| 0 | 27 | (22.3) | 27 | (22.1) | 54 | (22.2) |
| 1 | 68 | (56.2) | 66 | (54.1) | 134 | (55.1) |
| 2 | 21 | (17.4) | 23 | (18.9) | 44 | (18.1) |
| 3 | 5 | (4.1) | 6 | (4.9) | 11 | (4.5) |
| Missing (%) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| **AML type** |   |   |   |   |   |   |
| De novo | 81 | (66.9) | 80 | (65.6) | 161 | (66.3) |
| Secondary | 34 | (28.1) | 35 | (28.7) | 69 | (28.4) |
| High risk MDS | 6 | (5.0) | 7 | (5.7) | 13 | (5.3) |
| Missing (%) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| **WBC categories (10^9/L)** |   |   |   |   |   |
| 0.0 - 9.9 | 78 | (64.5) | 75 | (61.5) | 153 | (63.0) |
| 10.0 - 49.9 | 28 | (23.1) | 29 | (23.8) | 57 | (23.5) |
| 50 - 99.9 | 8 | (6.6) | 12 | (9.8) | 20 | (8.2) |
| 100+ | 7 | (5.8) | 6 | (4.9) | 13 | (5.3) |
| Missing (%) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| **Cytogenetic status** |   |   |   |   |   |   |
| Favourable | 1 | (0.8) | 1 | (0.8) | 2 | (0.8) |
| Normal/Intermediate | 79 | (65.3) | 78 | (63.9) | 157 | (64.6) |
| Adverse | 25 | (20.7) | 29 | (23.8) | 54 | (22.2) |
| Unknown | 16 | (13.2) | 14 | (11.5) | 30 | (12.3) |
| Missing (%) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| **Wheatley Index** |   |   |   |   |   |   |
| Good | 8 | (6.6) | 5 | (4.1) | 13 | (5.3) |
| Standard | 45 | (37.2) | 43 | (35.2) | 88 | (36.2) |
| Poor | 68 | (56.2) | 74 | (60.7) | 142 | (58.4) |
| Missing (%) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Numbers are Mean (SD), Median (IQR), Minimum and Maximum or Frequency (%). |

Table 1: Patient Characteristics.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   | **Randomisation** |   |   |  |  |
|   | **LDAC+Tosedostat** | **LDAC** | **OR/HR (95% CI)** | **P value** |  |  |
|   | N=121 | N=122 |   |   |  |  |
| **Patient status, n(%)** |   |   |   |   |  |  |
| Resistant disease | 73 (60.3) | 83 (68.0) |   |   |  |  |
| Induction death | 19 (15.7) | 16 (13.1) |   |   |  |  |
| Achieved CR/CRi | 30 (24.8) | 22 (18.0) |   |   |  |  |
| **Response outcomes, n(%)** |   |   |   |   |  |  |
| CR | 23 (19.0) | 15 (12.3) | 0.61 (0.30-1.23)  |   0.17 |  |  |
| CRi | 7 (5.8) | 7 (5.7) |   |   |  |  |
| ORR (CR+CRi) | 30 (24.8) | 22 (18.0) | 0.68 (0.37, 1.27) | 0.22 |  |  |
| **Survival endpoints** |   |   |   |   |  |  |
| 30 day mortality | 16.2 | 13.5 | 1.26 (0.65, 2.46) | 0.5 |  |  |
| 60 day mortality | 31.2 | 27.5 | 1.20 (0.74, 1.93) | 0.5 |  |  |
| 1 year survival | 29.1 | 30.6 | 1.03 (0.76, 1.41) | 0.8 |  |  |
| 2 year survival | 15.5 | 11.7 | 0.97 (0.73, 1.28) | 0.8 |  |  |
| 1 year RFS | 46.7 | 54.5 | 1.63 (0.74, 3.59) | 0.22 |  |  |
| 2 year RFS | 26.7 | 27.3 | 1.41 (0.74, 2.68) | 0.3 |  |  |
| 2 year survival after remission | 46.7 | 36.4 | 0.88 (0.43, 1.80) | 0.7 |  |  |
| 1 year survival after relapse | 30.0 | 16.7 | 0.93 (0.45, 1.92) | 0.8 |  |  |
| 1 year survival no CR/CRi | 7.7 | 15.9 | 1.24 (0.90, 1.71) | 0.18 |  |  |
| Notes: |  |  |  |  |  |  |
| Response endpoints are reported as n (%) and odds ratios comparing LDAC to LDAC+Tosedostat. |
| Survival endpoints are reported as Kaplan-Meier estimates (%) and hazard ratios comparing LDAC+Tosedostat to LDAC. |

Table 2: Overall Outcomes: CR = complete remission, CRi = remission with incomplete counts, RFS = relapse free survival.



Supplementary Figure 2: Tests for Subgroup Interactions.