Supplemental Figure 1
A) Propensity score matching for age, European Leukemia Network risk group and transplantation status. Blue represents venetoclax + azacitidine and red represents intensive chemotherapy. “All” boxplots represent the degree to which these factors are matched in the entire dataset. “Matched” boxplots represents the degree to which these factors are matched in the propensity matched cohorts.

B) Propensity score matching for age. Blue represents venetoclax + azacitidine and red represents intensive chemotherapy. “All” boxplots represents the degree to which age is matched in the entire dataset. “Matched” boxplots represents the degree to which age is matched in the propensity matched cohorts.

C) Propensity score matching for transplantation. Top (darker) bar in “matched” and “all” are patients who received venetoclax + azacitidine; blue are venetoclax + azacitidine patients who received transplantation and red are venetoclax + azacitidine patients who did not receive transplantation. Bottom (lighter) bars in “matched” and “all” are patients who received intensive chemotherapy. Blue are intensive chemotherapy patients who received transplantation and red are intensive chemotherapy patients who did not receive transplantation. “All” represents the entire cohort and “matched” represents the propensity matched cohort.

D) Propensity score matching for European Leukemia Network (ELN) risk. Top (darker) bar in “matched” and “all” are patients who received venetoclax + azacitidine; blue are venetoclax + azacitidine patients with ELN non-adverse risk and red are venetoclax + azacitidine patients with ELN adverse risk. Bottom (lighter) bar in “matched” and “all” are patients who received intensive chemotherapy. Blue are intensive chemotherapy patients with ELN non-adverse risk and red are intensive chemotherapy patients with ELN adverse risk. “All” represents the entire cohort and “matched” represents the propensity matched cohort.
Favors Venetoclax + Azacitidine  Favors Intensive Chemotherapy

Supplemental Figure 2. Factors that favored progression free survival for intensive chemotherapy versus venetoclax + azacitidine.
Supplemental Figure 3. In a cohort of patients propensity matched for age, European Leukemia Network risk group and transplantation status, factors that favored progression free survival for intensive chemotherapy compared to venetoclax + azacitidine.
Supplemental Figure 4. Correlation between the presence of RUNX1 mutations and primitive AML disease biology, as represented by FAB M0/M1, in the Cancer Genome Atlas database.
**Supplemental Table 1:** Types of intensive chemotherapy regimens for patients who received intensive chemotherapy (N=149)

| Regimen                                           | N   (%) |
|---------------------------------------------------|--------|
| 7+3                                               | 110 (74%) |
| 7+3 + targeted therapy*                           | 26 (17%) |
| Cytarabine +/- clofarabine                        | 5 (4%)  |
| FLAG +/- idarubicin                               | 7 (5%)  |
| Liposomal cytarabine and daunorubicin             | 1 (1%)  |

7+3 = 7 days of infusional cytarabine with 3 days of anthracycline (N=106 idarubicin, N=4 daunorubicin); FLAG = fludarabine + cytarabine + colony stimulating factor

*Targeted therapies included dasatinib (N=2), enasidenib (N=4), glasdegib (N=3), ivosidenib (N=1), pravastatin (N=3) and midostaurin (N=13)
**Supplemental Table 2**: Median follow up times for all patients by treatment category, and median follow up times for all patients by treatment category two, three and five years after treatment. Within the different follow up time groups, the differences with respect to median overall survival and progression free survival did not change.

|                      | All Data | 2-year Survival | 3-year Survival | 5-year Survival |
|----------------------|----------|-----------------|-----------------|-----------------|
|                      | Median (95% CI) | Median (95% CI) | Median (95% CI) | Median (95% CI) |
| **Median Follow-up** |           |                 |                 |                 |
| Venetoclax/Azacitidine | 808 days (659, 1001) | 730 days (659, 730) | 808 days (659, 1001) | 808 days (659, 1001) |
| Intensive Chemotherapy | 1697 days (1386, 2118) | 730 days (NR, NR) | 1095 days (NR, NR) | 1697 days (1386, 1825) |
| **OS All Individuals** |           |                 |                 |                 |
| Logrank p-value | p = 0.0020 | p = 0.0029 | p = 0.0035 | p = 0.0017 |
| Venetoclax/Azacitidine | 483 days (335, 638) | 483 days (335, 638) | 483 days (335, 638) | 483 days (335, 638) |
| Intensive Chemotherapy | 884 days (730, 1973) | NR (730, NR) | 884 days (730, NR) | 884 days (730, NR) |
| **PFS All Individuals** |           |                 |                 |                 |
| Logrank p-value | p = 0.0007 | p = 0.0031 | p = 0.0009 | p = 0.0006 |
| Venetoclax/Azacitidine | 332 days (256, 469) | 332 days (256, 469) | 332 days (256, 469) | 332 days (256, 469) |
| Intensive Chemotherapy | 814 days (503, 1110) | 203 days (74, 570) | 814 days (503, 1095) | 814 days (503, 1110) |

CI=Confidence interval; NR=not reached; OS=overall survival; PFS=progression free survival
### Supplemental Table 3: Baseline characteristics of the propensity matched cohorts for patients who received venetoclax + azacitidine and intensive chemotherapy

| Variable                                | Intensive Chemotherapy | Venetoclax + Azacitidine | p-value   |
|-----------------------------------------|------------------------|--------------------------|-----------|
|                                         | **N = 48**             | **N = 48**               |           |
| Sex                                     |                        |                          |           |
| Male, N (%)                             | 27 (56.3%)             | 22 (45.8%)               | 0.3532a   |
| Female, N (%)                           | 21 (43.7%)             | 26 (54.2%)               |           |
| Median age (range)                      | 61 (21-81)             | 65 (22-82)               | 0.1737b   |
| Median bone marrow blast % (range)      | 62 (15-95)             | 42.5 (10-95)             | 0.1574b   |
| FAB M0/M1, N (%)                        | 24 (50.0%)             | 32 (66.7%)               | 0.1167a   |
| FAB M5, N (%)                           | 3 (6.3%)               | 4 (8.3%)                 | 0.6547a   |
| KMT2A rearranged, N (%)                 | 1 (2.1%)               | 5 (10.4%)                | 0.1025a   |
| ELN risk group                          |                        |                          |           |
| Adverse, N (%)                          | 34 (70.8%)             | 34 (70.8%)               | 0.4073a   |
| Favorable, N (%)                        | 8 (16.7%)              | 8 (16.7%)                |           |
| Intermediate, N (%)                     | 6 (12.5%)              | 6 (12.5%)                |           |
| FLT3 ITD, N (%)                         | 16 (38.1%)             | 7 (16.7%)                | 0.0290*a  |
| NPM1, N (%)                             | 12 (28.6%)             | 9 (21.4%)                | 0.4386a   |
| NPM1 and ≥65 years, N (%)               | 4 (8.3%)               | 3 (6.3%)                 | 0.6547a   |
| IDH, N (%)                              | 10 (25.0%)             | 14 (35.0%)               | 0.2482a   |
| IDH1, N (%)                             | 2 (5.3%)               | 4 (10.5%)                | 0.4142a   |
| IDH2, N (%)                             | 8 (20.0%)              | 10 (25.0%)               | 0.5637a   |
| RAS pathway, N (%)                      | 4 (11.8%)              | 6 (17.7%)                | 0.5271a   |
| TP53, N (%)                             | 2 (5.9%)               | 7 (20.6%)                | 0.0588a   |
| ASXL1, N (%)                            | 8 (23.5%)              | 7 (20.6%)                | 0.7630a   |
| Splice Gene, N (%)                      | 4 (11.8%)              | 8 (23.5%)                | 0.2059a   |
| RUNX1, N (%)                            | 6 (17.7%)              | 2 (5.9%)                 | 0.1573a   |
| RUNX1 and ≥65 years, N (%)              | 4 (8.3%)               | 2 (4.2%)                 | 0.4142a   |
| Secondary AML, N (%)                    | 19 (39.6%)             | 21 (43.7%)               | 0.6698a   |
| Treatment-Related AML, N (%)            | 5 (10.4%)              | 9 (18.7%)                | 0.2850a   |
| Prior therapy for MDS or MPN, N (%)     | 6 (12.5%)              | 7 (14.6%)                | 0.7630a   |
| Received allogeneic stem cell transplantation, N (%) | 30 (62.5%)              | 31 (64.6%)               | 0.6547a   |
a = McNemar’s Test; b = Paired T-test
*=meets statistical significance at an alpha level of 0.05
FAB=French American British classification system; ELN=European Leukemia Network;
SWOG=Southwest oncology group; ITD=Internal tandem duplication;
MDS=myelodysplastic syndrome; MPN=myeloproliferative neoplasm
**Supplemental Table 4:** Multiple comparisons corrections for the entire cohort for response, overall survival and progression-free survival

| Variable               | CR/CRi p-value | CR/CRi q-value | OS p-value | OS q-value | PFS p-value | PFS q-value |
|------------------------|----------------|----------------|------------|------------|-------------|-------------|
| All Individuals        | 0.436          | 0.700          | **0.002**  | 0.022      | 0.001       | 0.011       |
| Age >=65               | **0.019**      | 0.139          | 0.607      | 0.703      | 0.762       | 0.838       |
| FAB M0/M1              | 0.509          | 0.700          | **0.025**  | 0.092      | **0.018**   | 0.066       |
| FAB M5                 | **0.008**      | **0.089**      | 0.054      | 0.170      | 0.057       | 0.139       |
| ELN adverse risk       | 0.065          | 0.204          | 0.183      | 0.366      | 0.056       | 0.139       |
| ELN intermediate risk  | 0.480          | 0.700          | **0.001**  | **0.022**  | **0.0001**  | **0.002**   |
| KMT2A rearrangement    | 0.139          | 0.340          | 0.568      | 0.694      | **0.006**   | **0.033**   |
| FLT3 ITD               | 0.305          | 0.610          | **0.015**  | 0.075      | **0.017**   | 0.066       |
| NPM1                   | 0.977          | 1.000          | 0.244      | 0.413      | 0.589       | 0.682       |
| NPM1 and Age >=65      | 0.063          | 0.204          | 0.419      | 0.576      | 0.289       | 0.422       |
| IDH                    | 0.581          | 0.752          | 0.240      | 0.413      | 0.307       | 0.422       |
| IDH2                   | 1.000          | 1.000          | 0.098      | 0.240      | 0.114       | 0.222       |
| IDH1                   | 0.398          | 0.700          | 0.404      | 0.576      | 0.349       | 0.452       |
| RAS pathway            | 0.100          | 0.275          | **0.011**  | 0.075      | **0.003**   | **0.022**   |
| TP53                   | 0.707          | 0.819          | 0.941      | 0.986      | 0.861       | 0.895       |
| ASXL1                  | 0.486          | 0.700          | 0.354      | 0.556      | 0.121       | 0.222       |
| Splice gene mutation   | 0.807          | 0.888          | 0.913      | 0.986      | 0.895       | 0.895       |
| RUNX1                  | **0.040**      | 0.176          | 0.560      | 0.694      | 0.576       | 0.682       |
| RUNX1 and Age >=65     | NA             | NA             | **0.017**  | 0.075      | **0.036**   | 0.113       |
| Secondary AML          | **0.038**      | 0.176          | 0.131      | 0.288      | 0.086       | 0.189       |
| Treatment-related AML  | 0.235          | 0.517          | 0.071      | 0.195      | 0.267       | 0.422       |
| Prior therapy for MDS or MPN | 0.648 | 0.792          | 0.987      | 0.987      | 0.285       | 0.422       |

CR=complete remission; CRi=complete remission with incomplete peripheral blood count recovery; OS=overall survival; PFS=progression free survival; ELN=European Leukemia Network; FAB=French American British; AML=acute myeloid leukemia; MDS=myelodysplastic syndrome; MPN=myeloproliferative neoplasm
### Supplemental Table 5: Multiple comparisons corrections for the propensity matched cohort for overall survival and progression free survival

| Variable                        | OS p-value | OS q-value | PFS p-value | PFS q-value |
|---------------------------------|------------|------------|-------------|-------------|
| All Individuals                 | 0.064      | 0.222      | 0.392       | 0.641       |
| Age >=65                        | **0.002**  | **0.036**  | **0.010**   | 0.078       |
| FAB M0/M1                       | 0.428      | 0.593      | 0.575       | 0.739       |
| FAB M5                          | 0.133      | 0.266      | 0.149       | 0.443       |
| ELN adverse risk                | **0.021**  | 0.126      | 0.176       | 0.443       |
| ELN intermediate risk           | **0.048**  | 0.216      | NA          | NA          |
| FLT3 ITD                        | 0.750      | 0.844      | 0.762       | 0.887       |
| NPM1                            | 0.412      | 0.593      | 0.549       | 0.739       |
| IDH                             | 0.104      | 0.234      | 0.089       | 0.353       |
| IDH2                            | 0.351      | 0.574      | 0.298       | 0.596       |
| RAS pathway                     | 0.571      | 0.685      | 0.197       | 0.443       |
| TP53                            | 0.948      | 0.948      | 0.985       | 0.985       |
| ASXL1                           | 0.273      | 0.491      | 0.457       | 0.686       |
| Splice gene mutation            | 0.074      | 0.222      | 0.098       | 0.353       |
| RUNX1                           | **0.013**  | 0.117      | **0.013**   | 0.078       |
| Secondary AML                   | 0.541      | 0.685      | 0.788       | 0.887       |
| Treatment-related AML           | 0.856      | 0.906      | 0.856       | 0.906       |
| Prior therapy for MDS or MPN    | 0.092      | 0.234      | 0.334       | 0.601       |

OS=overall survival; PFS=progression free survival; FAB=French American British; ELN=European Leukemia Network; AML=acute myeloid leukemia; MDS=myelodysplastic syndrome; MPN=myeloproliferative neoplasm