Online Supplement:

Included in the Supplement are

- Supplemental methods text
- Supplemental results text
- Supplemental Table 1-5
- Supplemental Figure 1

Methods

There were 10 imputed data sets generated from a model with 68 variables using random forest imputation with 500 trees for missing continuous and unordered categorical data, and polytomous logistic regression for missing ordered categorical data. These methods restricted the imputed data to take plausible values found within the original data. Standard combining rules were used to provide p-values and 95% confidence intervals (95%CI) for the estimates of the HR and OR in a way that accounted for the increased uncertainty due to missing data. The fraction of missing information (fmi), reported for each variable in Supplemental tables 1 and 3, represented the impact the missing data have on the estimation of HR and OR. Univariate models and a full multivariate model containing all variables of interest were fit. The CPH and logistic regression models were fit on each of the 10 imputed data sets and standard multiple imputation combining rules were used to compute estimates of the hazard ratio (HR) for OS from CPH models and odds ratio (OR) for response from logistic regression models.

Results

The anti-CD33 antibody drug conjugate gemtuzumab ozogamicin (GO) was most commonly administered concurrently with HMA (12% of patients). The histone deacetylase inhibitor valproic acid (VPA) was administered either alone or in combination with all-trans retinoic acid (ATRA) in 1.3% and 4.5% of patients, respectively. Hydroxyurea and chemotherapy was added to HMA in 2.3% and 1.2% of patients, respectively. Tyrosine kinase inhibitor (TKI) such as sorafenib, hedgehog inhibitors and isocitrate dehydrogenase (IDH) inhibitors were combined with HMA in 3.5% of patients. Finally, 15 patients received growth factor support in the addition to HMA either erythropoiesis-stimulating agents (ESAs, 1.3%) or granulocyte colony-stimulating factor (G-CSF, 1.5%). During the observation period, 98.5% of patients stopped HMA therapy, mostly due to progressive disease or lack of response while only 6.3% of patients stopped therapy because of HMA-related toxicities.

Supplemental Table 1: Univariate Logistic Regression Models for Response (CR or CRi).

	Predictive Factor		
Variable	**p-value**	**OR (95% CI)**	**fmi**
Patient Demographics and HMA therapy			
Sex (Female vs. Male)	0.7405	1.0741 (0.703, 1.6412)	0.0326
Age at diagnosis (years)	0.6616	1.0036 (0.9874, 1.0201)	0.0367
Age (> 55 vs. ≤ 55)	0.3691	1.2605 (0.76, 2.0907)	0.0312
HMA Therapy (Decitabine vs. Azacitidine)	0.6039	1.1249 (0.7202, 1.7569)	0.1324
HMA treatment schedule: Decitabine 10-days (Yes vs. No)	0.043	1.9716 (1.0218, 3.8042)	0.0203
Clinical parameters prior to initiation of HMA			
WHO type at diagnosis (4 categories)			
AML with recurrent genetic abnormalities vs. AML with MDS-related features	0.0927	2.0851 (0.8849, 4.9132)	0.0562
AML not otherwise specified vs. AML with MDS-related features	0.457	1.2065 (0.7352, 1.98)	0.0103
Therapy-related AML vs. AML with MDS-related features	0.3669	0.6263 (0.2264, 1.7328)	0.0239
Therapy-related AML (Yes vs. No)	0.1839	0.5247 (0.2025, 1.3597)	0.0268
Treatment related at diagnosis (Yes vs. No)	0.6866	0.8716 (0.4464, 1.7018)	0.0971
Therapy prior to HMA (Relapsed AML vs. Refractory AML)	0.0586	1.5175 (0.9848, 2.3382)	0.0215
Allogeneic SCT prior to initiation of HMA (Yes vs. No)	0.0639	1.6035 (0.973, 2.6428)	0.0582
Duration of CR1 (months)	0.102	1.0101 (0.998, 1.0224)	0.0432
Duration of CR1 (> 6 vs. ≤ 6 months)	0.0063	1.8111 (1.1831, 2.7724)	0.0156
ECOG status at diagnosis (2 or 3 vs. 0 or 1)	0.8263	0.9199 (0.4197, 2.0164)	0.6842
Number of prior lines of therapy before initiation of HMA	0.2114	0.8583 (0.6751, 1.091)	0.0489
Number of prior lines of therapy before initiation of HMA (3 categories)			
2 Prior Lines vs. 1 Prior Line	0.0563	0.583 (0.335, 1.0147)	0.0802
3 or More Prior Lines vs. 1 Prior Line	0.5049	0.8226 (0.4628, 1.4621)	0.0576
Laboratory parameters at initiation of HMA			
WBC (x 10^9 cells per liter)	0.2822	0.9892 (0.9697, 1.0091)	0.3179
WBC (x 10^9 cells per liter) (> 10 vs. ≤ 10)	0.2599	0.682 (0.3483, 1.3355)	0.346
Peripheral blast (%)	0.0212	0.9879 (0.9778, 0.9981)	0.3279
Peripheral blast (≤ 5% vs. > 5%)	0.0042	2.0074 (1.2500, 3.2239)	0.2179
Bone marrow cellularity (%)	0.7807	0.9989 (0.9911, 1.0068)	0.3173
Bone marrow cellularity (> 20% vs. ≤ 20%)	0.4592	1.2345 (0.7028, 2.1685)	0.3131
Bone marrow blast (%)	0.7457	0.9983 (0.9879, 1.0088)	0.4199
Bone marrow blast (> 20% vs. ≤ 20%)	0.1668	0.7267 (0.462, 1.1431)	0.0232
Cytogenetic risk group (3 categories)			
Intermediate/Normal vs. Poor	0.6356	1.1823 (0.5823, 2.4007)	0.4646
Good vs. Poor	0.284	1.4782 (0.7158, 3.0528)	0.4267
Complex cytogenetics (Yes vs. No)	0.5212	0.7928 (0.383, 1.6409)	0.5085
Chromosome 7 abnormality (Yes vs. No)	0.607	0.8503 (0.4554, 1.5877)	0.3088
Chromosome 5 abnormality (Yes vs. No)	0.4712	0.7633 (0.3613, 1.6126)	0.4318
Platelet Count (x 10^9 cells per liter)	0.0879	1.0024 (0.9996, 1.0051)	0.2528
Platelet Count (x 10^9 cells per liter) (≤ 30 vs. > 30)	0.1184	0.623 (0.3424, 1.1337)	0.4446
Mutational Status prior to initiation of HMA			
TP53 mutation (Yes vs. No)	0.8405	1.1193 (0.3647, 3.4351)	0.4467
FLT3 mutation (Yes vs. No)	0.6132	1.1862 (0.6013, 2.3398)	0.5053
NPM1 mutation (Yes vs. No)	0.5901	1.1624 (0.6671, 2.0257)	0.3651
CEBPa mutation (Yes vs. No)	0.7501	1.2279 (0.3333, 4.5234)	0.5474

Supplemental Table 2: Multivariate Regression Model for Response (CR or CRi).

	Predictive Factor		
Variable	**p-value**	**OR (95% CI)**	**fmi**
Patient Demographics and HMA therapy			
Sex (Female vs. Male)	0.6575	1.1099 (0.6995, 1.7609)	0.0517
Age (> 55 vs. ≤ 55)	0.3826	1.3165 (0.7095, 2.443)	0.0659
HMA Therapy (Decitabine vs. Azacitidine)	0.5856	1.2001 (0.6179, 2.3311)	0.3372
HMA treatment schedule: Decitabine 10-days (Yes vs. No)	0.0374	2.3667 (1.0516, 5.3265)	0.0587
Clinical parameters prior to initiation of HMA			
Therapy-related AML (Yes vs. No)	0.1524	0.4309 (0.1359, 1.3663)	0.0468
Treatment related at diagnosis (Yes vs. No)	0.5864	1.263 (0.5433, 2.9358)	0.1265
Therapy prior to HMA (Relapsed AML vs. Refractory AML)	0.8322	1.0674 (0.583, 1.9544)	0.0617
Allogeneic SCT prior to initiation of HMA (Yes vs. No)	0.1424	1.6396 (0.8456, 3.1788)	0.1797
Duration of CR1 (> 6 vs. ≤ 6 months)	0.3301	1.3519 (0.7362, 2.4825)	0.0684
ECOG status at diagnosis (2 or 3 vs. 0 or 1)	0.746	0.8561 (0.3165, 2.3155)	0.7232
Number of prior lines of therapy before initiation of HMA (3 categories)			
2 Prior Lines vs. 1 Prior Line	0.0467	0.5175 (0.2704, 0.9905)	0.1343
3 or More Prior Lines vs. 1 Prior Line	0.3383	0.7005 (0.3374, 1.4545)	0.1404
Laboratory parameters at initiation of HMA			
WBC (x 10^9 cells per liter) (> 10 vs. ≤ 10)	0.6346	0.8386 (0.4015, 1.7517)	0.3718
Peripheral blast (≤ 5% vs. > 5%)	0.0278	1.8694 (1.0724, 3.2589)	0.2947
Bone marrow cellularity (> 20% vs. ≤ 20%)	0.3911	1.2991 (0.7105, 2.3756)	0.3073
Bone marrow blast (> 20% vs. ≤ 20%)	0.5056	0.8375 (0.4965, 1.4127)	0.0598
Cytogenetic risk group (3 categories)			
Intermediate/Normal vs. Poor	0.7702	0.8849 (0.3816, 2.052)	0.48
Good vs. Poor	0.3602	1.4945 (0.6208, 3.5975)	0.4884
Complex cytogenetics (Yes vs. No)	0.5964	0.7974 (0.336, 1.8927)	0.5578
Chromosome 7 abnormality (Yes vs. No)	0.8231	0.9173 (0.4234, 1.9874)	0.4394
Chromosome 5 abnormality (Yes vs. No)	0.5754	0.7635 (0.2873, 2.0289)	0.5845
Platelet Count (x 10^9 cells per liter) (≤ 30 vs. > 30)	0.4332	0.7648 (0.3849, 1.5197)	0.5093
Mutational Status prior to initiation of HMA			
TP53 mutation (Yes vs. No)	0.8015	1.1625 (0.3503, 3.858)	0.4455
FLT3 mutation (Yes vs. No)	0.4515	1.326 (0.6235, 2.8199)	0.5364
NPM1 mutation (Yes vs. No)	0.7409	1.1083 (0.5959, 2.0613)	0.408
CEBPa mutation (Yes vs. No)	0.7647	1.2138 (0.3303, 4.461)	0.4873

Supplemental Table 3: Univariate Cox Proportional Hazards Models for overall survival.

	Predictive Factor		
Variable	**p-value**	**HR (95% CI)**	**fmi**
Patient Demographics and HMA therapy			
Sex (Male vs. Female)	0.1195	0.8727 (0.7352, 1.0359)	0.0363
Age at diagnosis (years)	0.7568	0.9989 (0.9922, 1.0057)	0.0893
Age (> 55 vs. ≤ 55)	0.285	0.8993 (0.7402, 1.0925)	0.032
HMA Therapy (Decitabine vs. Azacitidine)	0.029	1.2167 (1.0204, 1.4509)	0.1134
A treatment schedule: Decitabine 10-days (Yes vs. No)	0.8101	1.0385 (0.7631, 1.4133)	0.0505
Clinical parameters prior to initiation of HMA			
WHO type at diagnosis (4 categories)			
AML with recurrent genetic abnormalities vs. AML with MDS-related features	0.4774	0.8656 (0.5814, 1.2889)	0.0075
AML not otherwise specified vs. AML with MDS-related features	0.8075	1.025 (0.8403, 1.2503)	0.0676
Therapy-related AML vs. AML with MDS-related features	0.1677	1.2674 (0.9051, 1.7749)	0.0242
Therapy-related AML (Yes vs. No)	0.1439	1.2589 (0.9244, 1.7143)	0.0249
Treatment related at diagnosis (Yes vs. No)	0.994	0.999 (0.7638, 1.3065)	0.1852
Therapy prior to HMA (Relapsed AML vs. Refractory AML)	0.4593	1.0659 (0.9001, 1.2621)	0.0409
Allogenic SCT prior to initiation of HMA (Yes vs. No)	0.9349	0.9908 (0.7937, 1.2369)	0.0771
Duration of CR1 (months)	0.011	0.7368 (0.5824, 0.9322)	0.1036
Duration of CR1 (> 12 vs. ≤ 12 months)	0.011	0.7368 (0.5824, 0.9322)	0.1036
ECOG status at diagnosis (2 or 3 vs. 0 or 1)	0.3972	1.1286 (0.8447, 1.5078)	0.6437
Number of prior lines of therapy before initiation of HMA	0.0733	1.0942 (0.9915, 1.2075)	0.2302
Number of prior lines of therapy before initiation of HMA (3 categories)			
2 Prior Lines vs. 1 Prior Line	0.0299	1.2496 (1.0219, 1.528)	0.0571
3 or More Prior Lines vs. 1 Prior Line	0.4117	1.1084 (0.8664, 1.418)	0.171
Laboratory parameters at initiation of HMA			
WBC (x 10^9 cells liter)	0.1561	1.0046 (0.9982, 1.0109)	0.3279
WBC (x 10^9 cells per liter) (> 10 vs. ≤ 10)	0.0919	1.2227 (0.9673, 1.5456)	0.2891
Peripheral blast (%)	0.0002	1.0055 (1.0026, 1.0085)	0.1259
Peripheral blast (> 5% vs. ≤ 5%)	0.0003	1.4866 (1.2082, 1.8291)	0.3343
Bone marrow cellularity (%)	0.8084	0.9995 (0.9954, 1.0036)	0.589
Bone marrow cellularity (> 20% vs. ≤ 20%)	0.6121	0.9276 (0.6861, 1.2543)	0.6406
Bone marrow blast (%)	0.0836	1.0039 (0.9995, 1.0084)	0.5013
Bone marrow blast (> 20% vs. ≤ 20%)	0.0031	1.3278 (1.1004, 1.6021)	0.0192
Cytogenetic risk group (3 categories)			
Intermediate/Normal vs. Poor	0.046	0.7969 (0.6377, 0.9959)	0.2512
Good vs. Poor	0.0734	0.784 (0.6004, 1.0238)	0.3162
Complex cytogenetics (Yes vs. No)	0.1874	1.2034 (0.91, 1.5914)	0.5274
Chromosome 7 abnormality (Yes vs. No)	0.6245	1.0742 (0.8002, 1.4422)	0.5383
Chromosome 5 abnormality (Yes vs. No)	0.1077	1.2232 (0.9563, 1.5646)	0.2876
Platelet Count (x 10^9 cells per liter)	0.0188	0.9982 (0.9968, 0.9997)	0.3002
Platelet Count (x 10^9 cells per liter) (≤ 30 vs. > 30)	0.0082	1.3121 (1.0742, 1.6027)	0.2831
Mutational Status Prior to HMA			
TP53 mutation (Yes vs. No)	0.9042	1.0317 (0.6094, 1.7467)	0.5901
FLT3 mutation (Yes vs. No)	0.9371	0.9889 (0.7446, 1.3134)	0.5242
NPM1 mutation (Yes vs. No)	0.9537	0.993 (0.7783, 1.2669)	0.457
CEBPa mutation (Yes vs. No)	0.7651	0.921 (0.5283, 1.6056)	0.5472

Supplemental Table 4: Multivariate Proportional Hazards Model for overall survival.

	Predictive Factor		
Variable	**p-value**	**HR (95% CI)**	**fmi**
Patient Demographics and HMA therapy			
Sex (Female vs. Male)	0.1761	0.881 (0.7331, 1.0586)	0.1002
Age (> 55 vs. ≤ 55)	0.4811	0.9179 (0.7231, 1.1652)	0.1336
HMA Therapy (Decitabine vs. Azacitidine)	0.0885	1.222 (0.97, 1.5394)	0.2121
HMA treatment schedule: Decitabine 10-days (Yes vs. No)	0.464	0.8783 (0.6206, 1.2432)	0.0682
Clinical parameters prior to initiation of HMA			
Therapy-related AML (Yes vs. No)	0.3286	1.2026 (0.8303, 1.7418)	0.1018
Treatment related at diagnosis (Yes vs. No)	0.8667	0.974 (0.7159, 1.3253)	0.153
Therapy prior to HMA (Relapsed AML vs. Refractory AML)	0.0924	1.193 (0.9713, 1.4654)	0.1088
Allogeneic HSCT prior to initiation of HMA (Yes vs. No)	0.735	0.9548 (0.7302, 1.2487)	0.1528
Duration of CR1 (> 12 vs. ≤ 12 months)	0.0747	0.7689 (0.5758, 1.0268)	0.2028
ECOG status at diagnosis (2 or 3 vs. 0 or 1)	0.1407	1.2727 (0.9181, 1.7641)	0.6357
Number of prior lines of therapy before initiation of HMA (3 categories)			
2 Prior Lines vs. 1 Prior Line	0.1168	1.2206 (0.951, 1.5667)	0.2415
3 or More Prior Lines vs. 1 Prior Line	0.8015	1.0438 (0.7439, 1.4645)	0.3702
Laboratory parameters at initiation of HMA			
WBC (x 10^9 cells per liter) (> 10 vs. ≤ 10)	0.5153	1.0905 (0.8372, 1.4206)	0.3757
Peripheral blast (> 5% vs. ≤ 5%)	0.0151	1.29 (1.0509, 1.5834)	0.2004
Bone marrow cellularity (> 20% vs. ≤ 20%)	0.6424	0.9253 (0.6565, 1.3041)	0.6898
Bone marrow blast (> 20% vs. ≤ 20%)	0.0408	1.2441 (1.0092, 1.5337)	0.0705
Cytogenetic risk group (3 categories)			
Intermediate/Normal vs. Poor	0.5334	0.9212 (0.7102, 1.1949)	0.2919
Good vs. Poor	0.1618	0.8172 (0.6151, 1.0856)	0.2924
Complex cytogenetics (Yes vs. No)	0.5089	1.1151 (0.7988, 1.5568)	0.5937
Chromosome 7 abnormality (Yes vs. No)	0.9455	1.0113 (0.7259, 1.4088)	0.5704
Chromosome 5 abnormality (Yes vs. No)	0.3158	1.1651 (0.8605, 1.5775)	0.4508
Platelet Count (x 10^9 cells per liter) (≤ 30 vs. > 30)	0.0774	1.2052 (0.9795, 1.4829)	0.2427
Mutational Status prior to initiation of HMA			
TP53 mutation (Yes vs. No)	0.9742	1.009 (0.5732, 1.7762)	0.6143
FLT3 mutation (Yes vs. No)	0.7585	0.9541 (0.7004, 1.2996)	0.5614
NPM1 mutation (Yes vs. No)	0.986	1.0021 (0.7882, 1.274)	0.3914
CEBPa mutation (Yes vs. No)	0.7369	0.905 (0.496, 1.6515)	0.5822

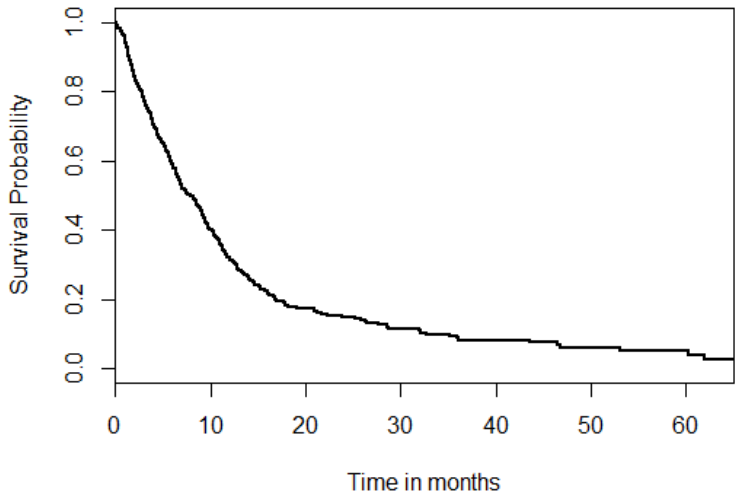
Supplemental Table 5: Response rates and OS based on HMA administration schedules

Characteristic	Number of responders	% of Responders	Median OS (95% CI)
HMA Administration Schedule (n= 587)			
Azacitidine (n=336):			
7-0 (n=257)	34	13.3	6.7 (5.8 – 8.7)
5-2-2 (n=18)	4	25.0	11.1 (5.7 – Inf)
5-0 (n=60)	11	19.0	8.4 (5.7 – 10.6)
10-0 (n=1)	0	0.0	NA (NA)
Decitabine (n=251):			
7-0 (n=3)	0	0.0	12.7 (NA)
5-2-2 (n=2)	1	50.0	18.0 (NA)
5-0 (n=181)	28	16.1	6.0 (4.8 – 7.7)
10-0 (n=50)	14	28.0	8.0 (6.4 – 16.3)
Others (n=15)	1	6.7	2.4 (0.7 – 7.3)

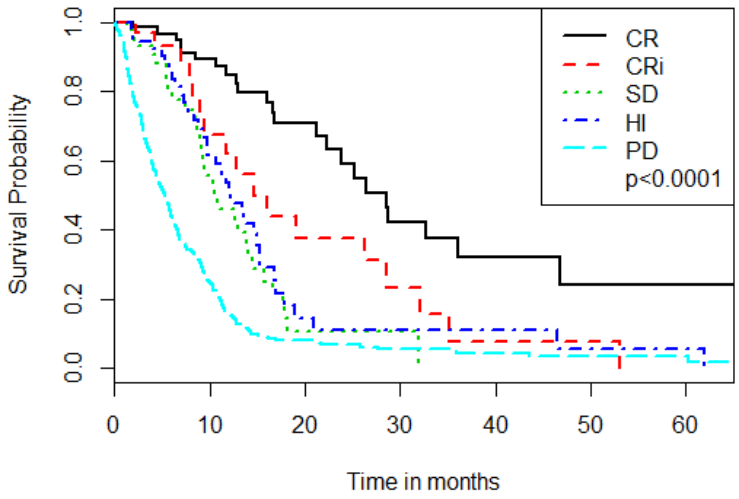
Supplemental Figure 1: Probability of overall survival (OS) of RR-AML patients treated with HMAs

(A) From onset of HMA treatment in the global cohort censored at time of alloSCT
(B) From onset of HMA treatment according to AML IWG response criteria (for CR/CRi/PD) and MDS IWG response criteria (SD/HI) censored at time of alloSCT
(C) From onset of HMA treatment according to treatment schedule used (decitabine 10 days vs all others)
(D) From onset of HMA treatment according to mutational status (TP53 non mutated vs. mutated)
(E) From onset of HMA treatment according to mutational status (FLT3 non mutated vs. mutated)

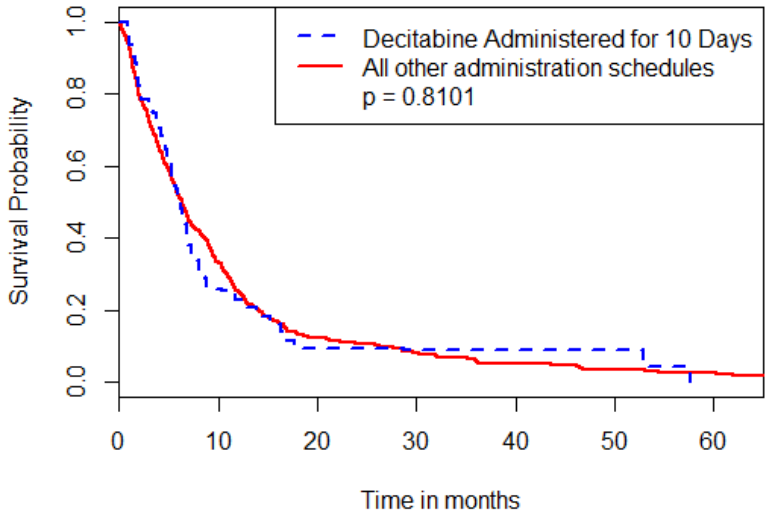
(A)



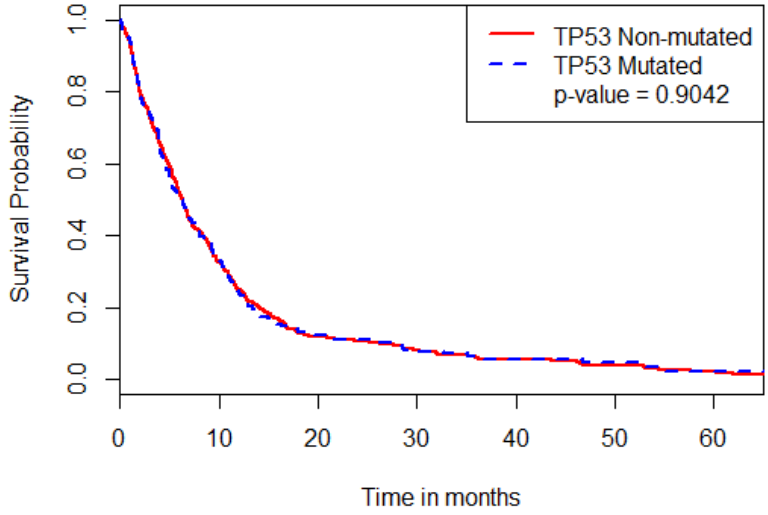
(B)



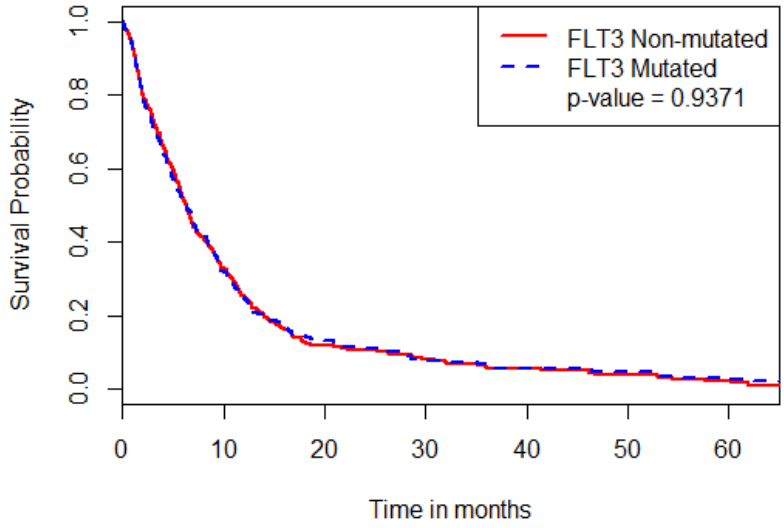
(C)


Decitabine Administered for 10 Days
All other administration schedules
p = 0.8101
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60
Time in months

(D)


TP53 Non-mutated
TP53 Mutated
p-value = 0.9042
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60
Time in months

(E)


FLT3 Non-mutated
FLT3 Mutated
p-value = 0.9371
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60
Time in months