PACE Basic Results Summary

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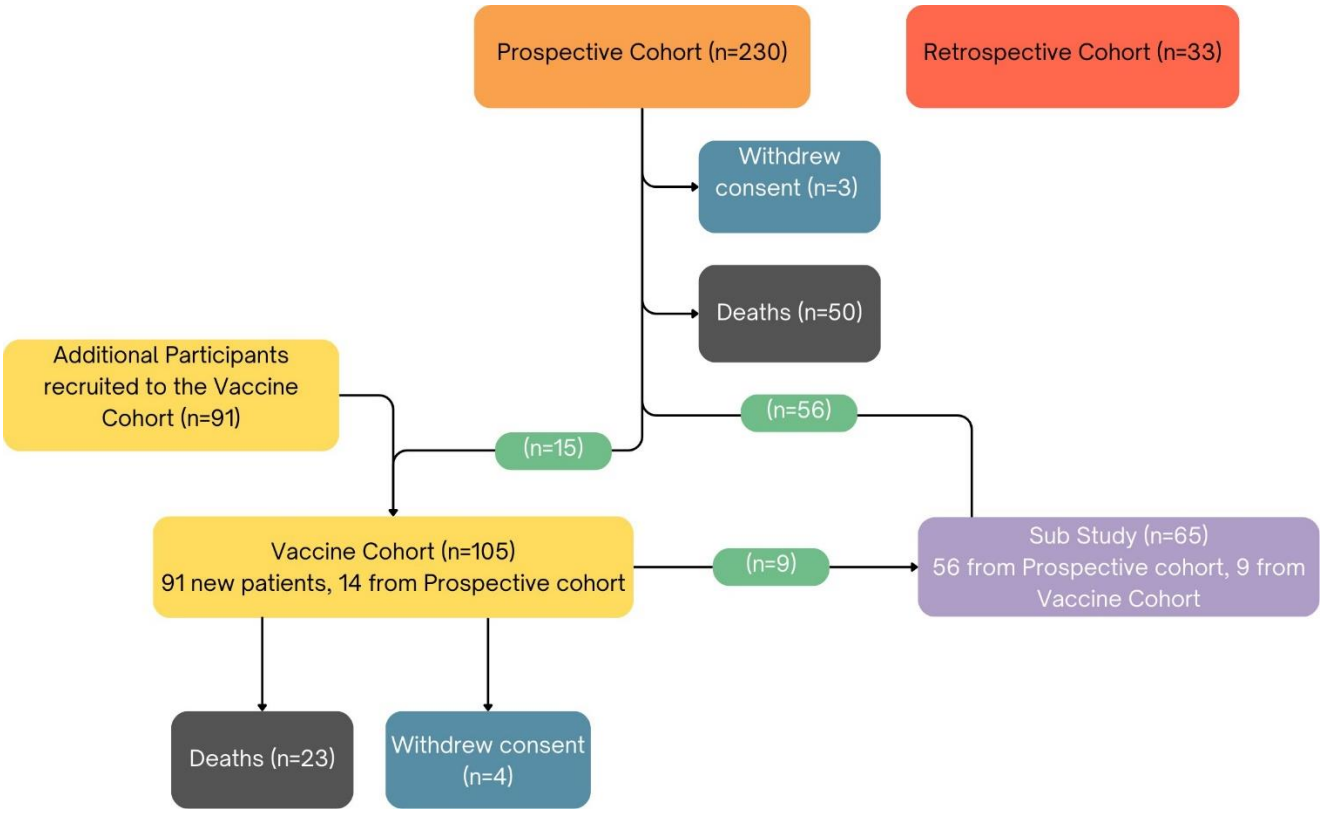
Participant Flow:



Baseline Characteristics:

1.a. Prospective Cohort: demographics at baseline

	Intensive (N=127)	Not Intensive (N=99)	Unknown (N=4)	Total (N=230)
Age (years)	59 [16; 76]	72 [19; 86]	68 [37; 75]	65 [16; 86]
Sex				
Female	61 (48%)	38 (38%)	3 (75%)	102 (44%)
Male	66 (52%)	61 (62%)	1 (25%)	128 (56%)
Ethnicity				
African	1 (1%)	1 (1%)	0 (0%)	2 (1%)
Arab	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Caribbean	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Indian	4 (3%)	0 (0%)	0 (0%)	4 (2%)
Pakistani	0 (0%)	1 (1%)	0 (0%)	1 (0%)
British*	111 (87%)	90 (91%)	4 (100%)	205 (89%)
White Irish	0 (0%)	2 (2%)	0 (0%)	2 (1%)
Other**	8 (6%)	5 (5%)	0 (0%)	13 (6%)
Unknown	1 (1%)	0 (0%)	0 (0%)	1 (0%)
ECOG Performance Status				
0	44 (35%)	35 (35%)	1 (25%)	80 (35%)
1	64 (50%)	48 (48%)	2 (50%)	114 (50%)
2	11 (9%)	11 (11%)	0 (0%)	22 (10%)
3	2 (2%)	4 (4%)	0 (0%)	6 (3%)
Unknown	6 (5%)	1 (1%)	1 (25%)	8 (3%)
Disease Type				
AML	119 (94%)	80 (81%)	3 (100%)	202 (88%)
MDS	8 (6%)	19 (19%)	0 (0%)	27 (12%)
AML Type***				
Secondary AML	13 (11%)	21 (26%)	2 (67%)	36 (18%)
Primary AML	106 (89%)	59 (74%)	1 (33%)	166 (82%)

Frequency (%); Median [Range]

* Including English/Welsh/Scottish/Northern Irish/British.

** Other ethnicities have been reported in the appendix

*** Answered only for patients diagnosed with AML

b. Prospective Cohort: disease and treatment status at study entry:

	Intensive (N=127)	Not Intensive (N=99)	Unknown (N=4)	Total (N=230)
Disease Status				
First diagnosis	115 (91%)	80 (81%)	2 (67%)	197 (86%)
Relapsed	11 (9%)	19 (19%)	1 (33%)	31 (14%)
Unknown	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Time From Diagnosis (weeks)*	4.1 [0.1; 292.4]	19.4 [0.0; 784.1]	120.3 [1.9; 238.7]	8.9 [0.0; 784.1]
Time From Relapse (weeks)*	4.0 [0.4; 74.3]	7.4 [0.9; 325.6]	1.7 [1.7; 1.7]	5.0 [0.4; 325.6]
Treatment Started				
No	39 (31%)	19 (19%)	3 (100%)	61 (27%)
Unknown	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Yes	87 (69%)	80 (81%)	0 (0%)	167 (73%)
Disease Response**				
CR	21 (24%)	18 (22%)	0 (.%)	39 (23%)
CR1	2 (2%)	5 (6%)	0 (.%)	7 (4%)
CRi	5 (6%)	6 (8%)	0 (.%)	11 (7%)
Not applicable	4 (5%)	3 (4%)	0 (.%)	7 (4%)
Not reassessed	48 (55%)	33 (41%)	0 (.%)	81 (49%)
PR	4 (5%)	7 (9%)	0 (.%)	11 (7%)
RD	1 (1%)	5 (6%)	0 (.%)	6 (4%)
Relapsed disease	0 (0%)	1 (1%)	0 (.%)	1 (0%)
Unknown	2 (2%)	2 (2%)	0 (.%)	4 (2%)
Categorised Disease Response**				
CR/CR1/CRi	28 (32%)	29 (36%)	0 (.%)	57 (34%)
PR/RD/Relapsed/Not Reassessed	53 (60%)	46 (57%)	0 (.%)	99 (59%)
Unknown/Not Applicable	7 (8%)	5 (6%)	0 (.%)	12 (7%)

Frequency (%); Median [Range]
* Time to registration date
** Only answered by those who were receiving treatment at trial entry

c. Prospective Cohort: disease characteristics at baseline

	Intensive (N=127)	Not Intensive (N=99)	Unknown (N=4)	Total (N=230)
Cytogenetics				
Adverse risk	20 (16%)	20 (20%)	0 (0%)	40 (17%)
Favourable risk	21 (17%)	15 (15%)	0 (0%)	36 (16%)
Intermediate risk	64 (50%)	42 (42%)	0 (0%)	106 (46%)
Not applicable	1 (1%)	6 (6%)	0 (0%)	7 (3%)
Other	5 (4%)	4 (4%)	0 (0%)	9 (4%)
Risk not known	3 (2%)	4 (4%)	0 (0%)	7 (3%)
Unknown	13 (10%)	8 (8%)	4 (100%)	25 (11%)
NPM1				
Present	36 (28%)	25 (25%)	0 (0%)	61 (27%)
Not Present	91 (72%)	74 (75%)	4 (100%)	169 (73%)
FLT3-ITD				
Present	34 (27%)	14 (14%)	1 (25%)	49 (21%)
Not Present	93 (73%)	85 (86%)	3 (75%)	181 (79%)
Other Molecular Marker				
Present	46 (36%)	48 (48%)	1 (25%)	95 (41%)
Not Present	81 (64%)	51 (52%)	3 (75%)	135 (59%)

d. Prospective Cohort: previous treatment information

	Intensive (N=127)	Not Intensive (N=99)	Unknown (N=4)	Total (N=230)
Previous Treatment Reported				
Yes	10 (8%)	19 (19%)	1 (25%)	30 (13%)
No	117 (92%)	80 (81%)	3 (75%)	200 (87%)
Previous Treatment Received*				
Azacitidine	1 (10%)	1 (5%)	0 (0%)	2 (7%)
Azacitidine; Other	0 (0%)	1 (5%)	0 (0%)	1 (3%)
CPX	3 (30%)	1 (5%)	0 (0%)	4 (13%)
DA	1 (10%)	2 (11%)	0 (0%)	3 (10%)
DA; FLAG-IDA; Gemtuzumab Ozogamacin; Other	0 (0%)	1 (5%)	0 (0%)	1 (3%)
DA; FLAG-IDA; Other	0 (0%)	1 (5%)	0 (0%)	1 (3%)
DA; Gemtuzumab Ozogamacin	1 (10%)	3 (16%)	0 (0%)	4 (13%)
DA; Gemtuzumab Ozogamacin; Other	0 (0%)	2 (11%)	0 (0%)	2 (7%)
DA; Midostaurin; Gemtuzumab Ozogamacin; Other	1 (10%)	0 (0%)	0 (0%)	1 (3%)
DA; Midostaurin; Other	0 (0%)	1 (5%)	0 (0%)	1 (3%)
DA; Other	1 (10%)	3 (16%)	0 (0%)	4 (13%)
DA; Venetoclax; Other	1 (10%)	0 (0%)	0 (0%)	1 (3%)
FLAG-IDA; Gemtuzumab Ozogamacin	0 (0%)	1 (5%)	0 (0%)	1 (3%)
FLAG-IDA; Gemtuzumab Ozogamacin; Other	1 (10%)	1 (5%)	0 (0%)	2 (7%)
Other	0 (0%)	0 (0%)	1 (100%)	1 (3%)
Venetoclax	0 (0%)	1 (5%)	0 (0%)	1 (3%)

Frequency (%)

2. a. Retrospective Cohort: patient characteristics at time of positive SARS-CoV2 result

	Summary (N=33)
Gender	
Female	17 (52%)
Male	16 (48%)
Age (years)	67 (18; 91)
Ethnicity	
African	2 (6%)
Other Asian Background	2 (6%)
Other White Background	1 (3%)
Other Ethnic Group	1 (3%)
Bangladeshi	2 (6%)
Caribbean	1 (3%)
Indian	2 (6%)
White*	20 (62%)
White and Asian	1 (3%)
ECOG Performance Status	
0	4 (12%)
1	11 (33%)
2	8 (24%)
3	2 (6%)
Not applicable	1 (3%)
Unknown	7 (21%)
Weight (kg)	74 (42; 111)
Height (cm)	163 (149; 190)

Frequency (%); Median [Range]

* Including English/Welsh/Scottish/Northern Irish/British

** Other ethnicities are given to be: Not reported (n=1); Phillipino (n=1); Unknown (n=2);

b. Retrospective Cohort: COVID-19 vaccination status at the time of infection

	Summary (N=33)
Covid Vaccination Received	
No	31 (94%)
Unknown	1 (3%)
Yes	1 (3%)
Vaccine Type	
Oxford/Astrazeneca	1 (100%)

Frequency (%)

c. Retrospective Cohort: Disease characteristics at time of positive SARS-CoV2 result

	Summary (N=33)
Disease Type	
AML	30 (91%)
MDS	3 (9%)
AML Type*	
Secondary AML	10 (33%)
Primary AML	20 (67%)
Cytogenetics	
Adverse risk	12 (36%)
Favourable risk	1 (3%)
Intermediate risk	14 (42%)
Risk not known	4 (12%)
Unknown	2 (6%)
NPM1	
Present	7 (21%)
Not Present	26 (79%)
FLT3-ITD	
Present	9 (27%)
Not Present	24 (73%)
Other Molecular Marker **	
Present	17 (52%)
Not Present	16 (48%)
Disease Status	
First diagnosis	26 (79%)
Relapsed	7 (21%)

Frequency (%)

* Answered only by those diagnosed with AML at entry to the study

** Other molecular markers given to be: loss of 17p13 (TP53) (n=1); CEBPA & GATA2 (n=1); Clinically significant variance in DNMT3A, ID2 and RUNX1 (n=1); IDH1 (n=1); IDH2 (n=1); IDH2 mutation, U2AF1 mutation (n=1); IDH2, NRAS (n=1); JAK 2, TP53 (n=1); JAK2 (n=1); JAK2, USAF1 (n=1); NRAS (n=1); NRAS, DNMT3A, ASXL1 (n=1); SETBP1, ASXL1 (n=1); SRSF2, ASXL1, RUNX1 (n=1); TET2, KRAS, NRAS (n=1); p53 (n=2);

3. a. Vaccine cohort: patient characteristics at study entry

	Newly Consented (N=91)	Reconsented (N=14)	Total (N=105)
Age (years)	69 [24; 91]	68 [33; 74]	68 [24; 91]
Sex			
Female	37 (41%)	7 (50%)	44 (42%)
Male	54 (59%)	7 (50%)	61 (58%)
Ethnicity			
African	1 (1%)	0 (0%)	1 (1%)
Pakistani	1 (1%)	0 (0%)	1 (1%)
British*	77 (85%)	13 (93%)	90 (86%)
White and Asian	1 (1%)	0 (0%)	1 (1%)
Other	10 (11%)	1 (7%)	11 (10%)
Unknown	1 (1%)	0 (0%)	1 (1%)
Disease Type			
AML	81 (89%)	10 (71%)	91 (87%)
MDS	10 (11%)	4 (29%)	14 (13%)
AML Type**			
Secondary AML	15 (19%)	2 (20%)	17 (19%)
Primary AML	66 (81%)	8 (80%)	74 (81%)

Frequency (%); Median [Range]
* Including English/Welsh/Scottish/Northern Irish/British.
** Answered only for patients diagnosed with AML

Outcome Measures:

1. **Prospective Cohort**

Primary outcome measure:	
Incidence of COVID-19 infection developing during AML or MDS-EB2 before or during treatment until 4 weeks after the last cycle of treatment	40/225 evaluable patients reported a confirmed COVID-19 diagnosis. 17.8% incidence rate (90% Confidence Interval: 22.5,13.7) 24/127 patients receiving intensive chemotherapy reported a confirmed COVID-19 diagnosis (18.9%), and 16/95 patients receiving non-intensive chemotherapy reported a confirmed COVID-19 infection (16.8%).
Secondary outcome measures:	
Symptoms and severity of COVID-19 infection in patients with AML or MDS-EB2	Symptoms of COVID-19 infection: **Symptom** — **Events (Patients, %)** Asymptomatic — 21 (15, 34.9%) Fever — 19 (16, 37.2%) Cough — 15 (12, 27.9%) Fatigued — 11 (8, 18.6%) Unknown — 9 (6, 14.0%) Shortness of Breath — 9 (7, 16.3%) Headache — 8 (8, 18.6%) Diarrhoea — 6 (5, 11.6%) Loss of Smell/Taste — 5 (3, 7.0%) Vomiting — 3 (3, 7.0%) Sore Throat — 3 (3, 7.0%) Abdominal Pain — 2 (2, 4.7%) Myalgia — 1 (1, 2.3%) Rhinorrhea — 1 (1, 2.3%)

<table>
<tr><td></td><td>Severity of confirmed COVID-19 infections prior to study entry:
<table>
<tr><th></th><th>Intensive (7)</th><th>Not Intensive (5)</th><th>Overall (12)</th></tr>
<tr><td colspan="4">Hospitalised (N (%))</td></tr>
<tr><td>No</td><td>2 (28.6)</td><td>1 (20.0)</td><td>3 (25.0)</td></tr>
<tr><td>Yes</td><td>5 (71.4)</td><td>4 (80.0)</td><td>9 (75.0)</td></tr>
<tr><td>Total</td><td>7 (100.0)</td><td>5 (100.0)</td><td>12 (100.0)</td></tr>
<tr><td colspan="4">Oxygen Required (N (%))</td></tr>
<tr><td>No</td><td>3 (60.0)</td><td>1 (25.0)</td><td>4 (44.4)</td></tr>
<tr><td>Yes</td><td>2 (40.0)</td><td>3 (75.0)</td><td>5 (55.6)</td></tr>
<tr><td>Total</td><td>5 (100.0)</td><td>4 (100.0)</td><td>9 (100.0)</td></tr>
<tr><td colspan="4">ITU Admission (N (%))</td></tr>
<tr><td>No</td><td>5 (100.0)</td><td>2 (50.0)</td><td>7 (77.8)</td></tr>
<tr><td>Yes</td><td>0 (0.0)</td><td>2 (50.0)</td><td>2 (22.2)</td></tr>
<tr><td>Total</td><td>5 (100.0)</td><td>4 (100.0)</td><td>9 (100.0)</td></tr>
</table>

Severity of confirmed COVID-19 infections during study:
13.8% (4/29) with oxygen <92%; all patients with oxygen <92% received oxygen supplementation. 13.8% (4/29) patients had a sustained respiratory rate >25/min. 10.3% (3/29) patients had blood pressure <90 mmHg.</td></tr>
<tr><td>Survival at Day 30 and 60 with or without a diagnosis of COVID-19 at presentation or at any stage</td><td>214 of 225 patients were alive at day 30 (95.1%)
201 of 225 patients were alive at day 60 (89.3%)

Of 40 patients who had a confirmed COVID-19 test, 37 were alive at day 30 (92.5), and 36 were alive at day 60 (90%)</td></tr>
<tr><td>Overall survival (OS)</td><td>60 Day OS: 89.3% (90% CI: 85.4%, 92.3%)
12 Month OS: 62.5% (90% CI: 56.9%, 67.6%)</td></tr>
<tr><td>The number of episodes of bacteraemia/presumed fungal infection in AML or MDS-EB2 patients</td><td>160 of 225 patients reported at least 1 significant infection (not COVID-19) during their time on study. 389 infections were reported in patients receiving intensive chemotherapy (107 patients), and 102 infections were reported in patients receiving non-intensive chemotherapy (52 patients).</td></tr>
<tr><td>The severity of episodes of bacteraemia/presumed fungal infection in AML or MDS-EB2 patients (as measured by length of episode, days in ICU and duration of hypotension, CTCAE V5 grading)</td><td>Median number of hospitalised infections (non-COVID-19) over the duration of the study:
<table>
<tr><th></th><th>Intensive (127)</th><th>Not Intensive (95)</th><th>Unknown (3)</th><th>Overall (225)</th></tr>
<tr><td colspan="5">Number of Infections</td></tr>
<tr><td>N</td><td>107</td><td>52</td><td>1</td><td>160</td></tr>
<tr><td>Median</td><td>3.0</td><td>2.0</td><td>1.0</td><td>2.0</td></tr>
<tr><td>Range</td><td>1.0, 11.0</td><td>1.0, 7.0</td><td>1.0, 1.0</td><td>1.0, 11.0</td></tr>
</table>

Length of hospital stay for patients with a non-COVID-19 infection
<table>
<tr><td colspan="2">Length of Hospital Stay (days)</td></tr>
<tr><td>N</td><td>542</td></tr>
<tr><td>Mean (sd)</td><td>19.4 (23.0)</td></tr>
<tr><td>Range</td><td>1.0, 345.0</td></tr>
<tr><td colspan="2">Discharge Status (N (%))</td></tr>
<tr><td>Discharge date not known*</td><td>86 (13.7)</td></tr>
<tr><td>Discharge date reported</td><td>542 (86.3)</td></tr>
<tr><td>Total</td><td>628 (100.0)</td></tr>
</table></td></tr>
</table>

Prevalence of prior COVID-19 infection at time of AML or MDS-EB2 presentation, defined by positive IgG	At the time of final analysis there were no positive IgG or IgM tests reported at study entry.
Development of COVID-19 antibodies (IgG and/or IgM) during AML or MDS-EB2 treatment	At the time of final analysis, 16 patients had either an IgG or IgM test. However, in the main, these tests were not performed.
Exploratory outcome measures:	
Investigate dysregulated immune responses to COVID-19 infection in patients with AML/MDS-EB2. Assess if patients with AML or MDS-EB2 who suffer COVID-19 infection will excrete SARS-CoV-2 for a prolonged period. Lastly, to explore the influence of the respiratory and gastrointestinal microbiome on COVID-19 severity	Data will be reported at a later date following further analysis.

2. Retrospective Cohort

Exploratory outcome measures:	
Symptoms and severity of COVID-19 infection in patients with AML or MDS-EB2	Symptoms of COVID-19 reported at time of diagnosis of COVID-19: **Symptom** — **Count (%)** Fever — 20 (61%) Shortness Of Breath — 16 (48%) Coughing — 11 (33%) Fatigue — 7 (21%) Asymptomatic — 6 (18%) Diarrhoea — 6 (18%) Myalgia — 4 (12%) Sore Throat — 3 (9%) Rhinorrhea — 1 (3%) Loss Of Smell Or Taste — 1 (3%) Vomiting — 1 (3%) Abdominal Pain — 0 (0%) Headache — 0 (0%) Severity of symptoms: 28 of 33 patients required hospitalisation (84.8%), 23 patients required oxygen (82.1%), 8 patients required non-invasive ventilation (28.6%), 6 were admitted to an Intensive Care Unit (ICU) (21.4%), and 4 were intubated (66.7%). Median number of days on ICU was 9.5 (range 0.0, 14.0), and median days hospitalised was 15.5 (range 1.0, 54.0)
Survival at Day 30 and 60 in AML or MDS-EB2 patients who contract COVID-19	Survival 30 days after COVID-19 positive test: 10 of 33 patients alive (30.3%) Survival 60 days after COVID-19 positive test: 7 of 33 patients alive (21.2%)

3. Vaccine Cohort

Exploratory outcome measures:	
Immune response to COVID-19 vaccination at 4 weeks following vaccination (both first, second, third and fourth vaccine where possible), and at month 6 post 2nd vaccination, in patients with AML or MDS-EB2	Only 3 samples were received post vaccine 1, therefore no conclusions could be made regarding patients' response to the first vaccine. 49 of 49 patients (100%) with a post vaccine 2 sample, and 59 of 59 patients (100%) with a post vaccine 3 sample demonstrated a positive antibody response to the COVID-19 spike protein (≥0.8 U/mL was interpreted as positive). Antibody levels were on average higher post vaccine 3 than post vaccine 2. Post vaccine 2 median was 860.0 U/mL (IQR: 298.0, 1599.0 U/mL, versus a median of 4910.0 U/mL post vaccine 3 (IQR:1193.0, 21490.0 U/mL). Post vaccine 4 median levels of anti-spike antibodies were higher still at 13600 U/ml (IQR: 4870, 25000 U/ml). Antibody levels remained above the threshold for positivity in individuals sampled more than once. Neutralizing antibody titres against all tested variants correlated positively with total S-antibody titre, suggesting that the antibody measured in patient serum post vaccination on is functionally relevant. There was minimal variation in antibody levels collected within or after 6 months post vaccine 2. Only 2 samples were available from patients after their 1st vaccine, therefore no conclusions could be drawn on the T-cell response post vaccine 1. Post vaccine 2, only 17 of 47 samples (36.2%) demonstrated an adequate T-cell response (Oxford Immunotec Panel 1 assay result of >16). Post vaccine 3, this increased slightly; only 25 of 57 samples showed an adequate T-cell response (43.9%). Post vaccine 4, 27 of 49 samples demonstrated an adequate T-cell response (55.1%).
Explore the influence of treatment regimen and disease status on immune response to COVID-19 vaccination in patients with AML or MDS-EB2	Frequentist regression models with stepwise regression were used to identify any significant covariates; exploring the effect of age, sex, treatment intensity, time from vaccination to sample and disease response (CR/CRi vs. not). Post vaccine 2, disease response for those not in CR/CRi, and age were significant covariates (−159.11 SFU/106 cells [95%CI: −341.92, 23.7] and −4.14 SFU/106 cells per year of age from median [95% CI: −9.5, 1.22] respectively). Post vaccine 3, time from vaccine to sample (−17.15 SFU/106 cells per week [95% CI: −40.01, 5.71]) was the only significant covariate.

Adverse Events:

This study was non-interventional; therefore, no adverse event data was collected.