Supplementary Table 1. Reasons for Discontinuation

	CC-486 300 mg QD 14 days/cycle (n=28) n (%)	CC-486 300 mg QD 21 days/cycle (n=27) n (%)	Total (N=55) n (%)
No response*	11 (39)	6 (22)	17 (31)
Loss of response†	5 (18)	4 (15)	9 (16)
Adverse event	3 (11)	9 (33)	12 (22)
Allogeneic Hematopoietic Stem Cell Transplant (allo-HSCT)	1 (4)	3 (11)	4 (7)
Withdrew consent	1 (4)	2 (7)	3 (5)
Other‡	3 (11)	1 (4)	4 (7)
Death	2 (7)	0	2 (4)

*Median number (range) of treatment cycles for patients with no response was 7 (3 - 11) cycles in the 14-day group, and 7 (1 - 9) cycles in the 21-day group.

†Median number (range) of treatment cycles for patients who lost response was 10 (7 - 24) cycles in the 14-day group, and 12.5 (11 - 14) cycles in the 21-day group.

‡1 patient had transportation difficulties, 1 patient discontinued due to investigator decision, and 2 patients completed 6 treatment cycles and did not enter the extension phase of the study.

Supplementary Table 2. PK parameters for SC azacitidine on day 1 and 7 and for CC-486 on day 1 and the last dosing day (day 14 or 21) of cycle 1

		AUC_{∞} (ng*h/mL)	C_{max} (ng/mL)	T_{max}[a] (h)	$t_{1/2}$ (h)	Cl/F (L/h)	Vz/F (L)
Azacitidine SC 75 mg/m2							
Mean ±SD (%CV[d]) Median [min, max]	Day 1 (n=44[b])	1011 ± 434 (46) 964 [195, 2927]	663 ± 269 (48) 602 [114, 1310]	0.50 [0.23, 1.08]	1.5 ± 0.66 (50) [1.41] [0.53, 2.93]	177 ± 125 (48) 159 [46, 894]	381 ± 397 (71) 288 [92, 2718]
	Day 7 (n=44[b])	1021 ± 401 (41) 985 [209, 2782]	623 ± 250 (48) 616 [151, 1150]	0.50 [0.17, 1.00]	1.9 ± 1.3 (68) 1.45 [0.47, 5.18]	168 ± 93 (44) 158 [48, 670]	460 ± 397 (89) 298 [91, 1730]
CC-486 300 mg QD							
Mean ± SD (%CV) Median [min, max]	Day 1 (n=25)	193 ± 139 (72) 154 [28, 687]	124 ± 84.9 (69) 92 [24, 388]	1.00 [0.47, 2.00]	0.53 ± 0.17 (32) 0.46 [0.34, 0.98]	2391 ± 2062 (86) 1948 [437, 10817]	1791 ± 1407 (79) 1332 [355, 6202]
	Day 14/21 (n=14)	182 ± 102[c] (56) 135 [47, 419]	98 ± 53 (54) 75 [24, 206]	1.23 [0.50, 3.50]	0.62 ± 0.20[c] (32) 0.57 [0.41, 0.99]	2221 ± 1435[c] (65) 2225 [716, 6427]	2218 ± 2254[c] (102) 1423 [539, 9142]

%CV = coefficient of variation; AUC_{∞} = the area under the concentration-time curve (AUC) from the time of dosing extrapolated to infinity; CL/F = apparent total clearance; C_{max} = maximum observed concentration; $t_{1/2}$ = terminal half-life; T_{max} = time to maximum concentration; Vz/F = apparent volume of distribution.

[a]Median [min, max].

[b]PK data were unavailable for 1 patient on Day 1 and 1 different patient on Day 7.

[c]n=13

[d]Geometric CV

Supplementary Table 3. Patient demographics and disease characteristics by response

Characteristic	Responders (n=21)	Non-responders (n=34)
Age (years), median (range)	71.0 (53 - 86)	72.0 (31 - 87)
RBC transfusion-dependent,* n (%)	13 (62)	19 (56)
Platelet transfusion-dependent,[†] n (%)	1 (5)	5 (15)
Hematology, median (range)		
Hgb (g/dL)	8.6 (6.0 - 11.6)	8.7 (6.4- 13.0)
ANC (10^9/L)	1.4 (0.3 - 16.3)	1.7 (0 - 30.3)
Platelets (10^9/L)	144.0 (19.0 - 454.0)	47.0 (6.0 - 564.0)
MDS WHO classification, n (%)		
RA/RARS[‡]	10 (48)	8 (24)
RCMD/RCMD-RS[‡]	5 (24)	12 (35)
RAEB-1	2 (10)	6 (18)
RAEB-2	1[§] (5)	0
MDS-U	1 (5)	5 (15)
Del(5q)	1 (5)	1 (3)
Missing	1 (5)	2 (6)
IPSS risk classification, n (%)		
Low	4(19)	10 (29)
Intermediate-1	17 (81)	24 (71)
Cytogenetics, n (%)		
Normal/diploid	9 (43)	18 (53)
≥ 1 Abnormality	10 (48)	9 (26)
Indeterminate	2 (10)	6 (18)
Prior treatment, n (%)		
Erythropoiesis-stimulating agents	10 (48)	16 (47)
WBC growth factors	4 (19)	5 (15)
Other	5 (24)	8 (24)
None[‖]	7 (33)	14 (41)

*Defined as receipt of ≥ 4 units of packed RBC within 56 days of the first dose of CC-486.
[†]Defined as receipt of ≥ 2 platelet transfusions within 56 days of the first dose of CC-486.
[‡]Because of the limited number of patients in the study, these classifications were grouped prospectively.
[§]Assessed as lower-risk MDS by the treating physician on the case report form.
[‖]Other than transfusions.
RBC = red blood cell; Hgb = hemoglobin; ANC = absolute neutrophil count; RA = refractory anemia; RARS = RA with ringed sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia; RCMD-RS = RCMD with ringed sideroblasts; RAEB = RA with excess blasts; MDS-U = myelodysplastic syndrome-unclassified; IPSS = International Prognostic Scoring System; WBC = white blood cell.

Supplementary Table 4. Hematologic response by IPSS-R score

Parameter	IPSS-R Score* n Responders/N Evaluable (%)		
	Low[†] n=25	**Intermediate n=14**	**High n=15**
Overall Response (CR, PR, any HI, TI)[‡]	11/25 (44)	5/14 (36)	5/15 (33)
CR[§]	0/0	0/3	1/9 (11)
PR	0/0	0/2	0/5
Any HI	9/25 (36)	5/14 (36)	4/15 (27)
HI-E	7/21 (33)	5/14 (36)	1/14 (7)
HI-P	4/13 (31)	2/8 (25)	2/12 (17)
HI-N	0/0	1/5 (20)	2/11 (18)
Marrow CR	0/0	1/3 (33)	3/9 (33)
RBC TI[‖]			
Sustained for 56 days	7/13 (54)	3/10 (30)	1/8 (13)
Platelet TI[‖]			
Sustained for 56 days	0/2	0/2	0/2

IWG 2006 criteria[28]

*1 patient was not evaluable for IPSS-R score

†1 patient had very low risk MDS per IPSS-R

‡Patients are counted only once for Overall Response, but may be counted more than once in individual response categories. marrow CR (mCR) is not included in Overall Response

§Subjects who had a CR are not counted for PR, any HI, or (mCR.

‖To be evaluated for RBC TI, patients must have been RBC transfusion-dependent at baseline and been on-study at least 56 days. RBC transfusion dependence at baseline was defined as receipt of ≥ 4 units of packed RBC within 56 days of the first dose of CC-486. To be evaluated for platelet TI, patients must have been platelet transfusion-dependent at baseline and been on-study at least 56 days. Platelet transfusion dependence at baseline was defined as receipt of ≥ 2 platelet transfusions within 56 days of the first dose of CC-486.

CR = complete remission; PR = partial remission; HI = hematologic improvement; HI-E = hematologic improvement-erythroid; HI-P = hematologic improvement-platelet; HI-N = hematologic improvement-neutrophil; TI = transfusion independence; IWG = International Working Group.

Supplementary Table 5. Grade 3-4 hematologic adverse events (≥5%) by treatment cycles

	300 mg QD CC-486: 14 days/cycle (n=28)				300 mg QD CC-486: 21 days/cycle (n=27)			
Treatment Cycles	**1 – 2 (n=28)**	**3 – 4 (n=27)**	**5 – 6 (n=23)**	**7 + (n=17)**	**1 – 2 (n=27)**	**3 – 4 (n=19)**	**5 – 6 (n=15)**	**7 + (n=12)**
Anemia, n (%)	1 (4)	3 (11)	1 (4)	1 (6)	3 (11)	0	0	1 (8)
Neutropenia, n (%)	1 (4)	0	1 (4)	1 (6)	5 (19)	2 (11)	2 (13)	2 (17)
Thrombocytopenia, n (%)	2 (7)	1 (4)	1 (4)	0	2 (7)	0	0	3 (25)
Febrile neutropenia, n (%)	1 (4)	0	0	0	2 (7)	2 (11)	0	0
n = number of patients evaluable for safety in each 2-cycle period or who received 7 or more cycles.								