SUPPLEMENTARY APPENDIX

Phase 1 dose-finding study of rebastinib (DCC-2036) in patients with relapsed chronic myeloid leukemia and acute myeloid leukemia

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Supplementary Information

Cortes et al., "Phase 1 dose-finding study of rebastinib (DCC-2036) in patients with relapsed chronic myeloid leukemia and acute myeloid leukemia"

Inclusion Criteria

Subjects were required to meet all inclusion criteria to be considered eligible for study participation:

1. The subject had:

    a. Ph^+ CML (chronic phase chronic myeloid leukemia [CP-CML] or accelerated phase chronic myeloid leukemia [AP-CML]) as confirmed by the presence of the BCR-ABL1 translocation [t(9;22)] based on fluorescence *in situ* hybridization (FISH), cytogenetics, or quantitative reverse transcriptase-polymerase chain reaction (QRT-PCR); orFLT3/ITD+ AML with no prior treatment with a FLT3 TKI and 1) had failed to achieve morphologic complete remission (CR) or had relapsed after prior chemotherapy and was not a candidate for potentially curative treatment; or 2) was ≥ 60 years of age and not a candidate for standard induction chemotherapy. Subjects with CML had 1 of the following: a) T315I ABL1 mutation; b) known resistance to or intolerance of ≥ 2 TKIs with known efficacy (eg, imatinib, dasatinib, nilotinib); or c) resistance or intolerance to 1 TKI but was unable or unwilling to receive other TKIs of known efficacy. When enrollment into the CML Expansion Cohort was extended beyond the planned 15 subjects, only subjects with T315I(+) CP-CML were considered eligible.

3. The subject was ≥18 years old.

4. For CML, the subject had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. For AML, the subject had an ECOG performance status < 1.

5. The subject had adequate organ function as indicated by the following laboratory assessments performed within 14 days prior to the first dose of study drug:

    - Hepatic: Serum bilirubin ≤ 1.5 times upper limit of normal (x ULN) unless due to leukemic involvement or Gilbert's syndrome (≤ 3 x ULN if due to leukemic involvement or Gilbert's syndrome); aspartate aminotransferase or alanine aminotransferase ≤ 2.5 x ULN (≤ 5.0 x ULN if due to leukemic involvement); alkaline phosphatase ≤ 2.5 x ULN unless due to leukemic involvement (≤ 5.0 x ULN if due to leukemic involvement).Renal: Serum creatinine ≤ 1.5 x ULN or 24 hour creatinine clearance ≥ 50 mL/min (subjects with a serum creatinine > 1.5 ULN were eligible if the 24 hour creatinine clearance was ≥ 50 mL/min).Female subjects of childbearing potential were required to have a negative serum or urine beta-human chorionic gonadotropin (β-hCG) pregnancy test within 14 days prior to the start of study drug.

7. Sexually active subjects who were fertile agreed to use an effective barrier method of contraception (eg, latex condom, diaphragm, or cervical cap) while on therapy and for 30 days following discontinuation of study drug. Nonfertile subjects or those not sexually active were also eligible. A nonfertile female was defined as one who

was postmenopausal (amenorrheic for ≥ 12 months) or had undergone a tubal ligation, complete oophorectomy, or hysterectomy. A nonfertile male was defined as one who had undergone vasectomy.

8. The subject was capable of understanding and complying with the protocol and had signed the informed consent document (ICD).

Exclusion Criteria

Subjects who met any of the following criteria did not qualify for entry into the study:

1. For FLT3 AML, the subject had received prior treatment with a FLT3 TKI or had only extramedullary disease without bone marrow involvement.
2. The subject had received chemotherapy or a TKI ≤ 7 days, investigational agent ≤14 days, or radiotherapy ≤ 28 days prior to the start of study drug or had not recovered (to ≤ NCI-CTCAE v3.0 Grade 1 severity) from the acute toxicities associated with any prior treatments including approved therapies, investigational agents, and prior stem cell or bone marrow transplant. The following exceptions applied:
   - Hydroxyurea was permitted at any time prior to study enrollment. Glucocorticoids (natural or synthetic) were allowed up to 48 hours prior to the start of study drug (with the exception of steroids for premedication and topical/nasal steroid use which were allowed at any time).The subject had BP-CML. (Note that subjects with BP-CML were eligible to participate in the dose escalation portion of the trial, but were not eligible for the expansion cohort.)
4. The subject had received immunosuppressive therapy (eg, cyclosporine, steroids, tacrolimus for graft-versus-host disease) ≤ 28 days prior to the first dose of study drug and had not recovered (to ≤ NCI-CTCAE v3.0 Grade 1 severity) from associated acute toxicities.
5. The subject had New York Heart Association class III or IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension, or congestive heart failure.
6. Myocardial infarction within 3 months of the start of study drug.
7. The subject had an active, uncontrolled systemic infection considered opportunistic, life-threatening, or clinically significant.
8. The subject had any other severe concurrent disease and/or uncontrolled medical conditions, which, in the judgment of the investigator, could predispose subjects to unacceptable safety risks or compromise compliance with the protocol.
9. The subject was known to be positive for human immunodeficiency virus .
10. If female, the subject was pregnant or lactating.
11. The subject had a known allergy or hypersensitivity to any component of the investigational drug product.

Table S1. Adverse Events by Dose Level (Incidence ≥ 15%)

	Dose of Rebastinib at Onset of Adverse Event by Protocol Dose Level (mg/dose)											
	57 QD (N=1)	114/150 QD (N=4)	225/228/300 QD (N=7)	450/456 QD (N=6)	600 QD (N=7)	300 BID (N=4)	1200 QD (N=3)	100 T[b] QD (N=4)	100 T[b] BID (N=16)	150 T[b] BID (N=34)	200 T[b] BID (N=4)	Total (N=57)
Preferred Term[a]	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Any Adverse Event	1 (100)	3 (75)	7 (100)	6 (100)	5 (71)	4 (100)	3 (100)	3 (75)	15 (94)	34 (100)	4 (100)	57 (100)
Dry mouth	1 (100)	0	3 (43)	3 (50)	3 (43)	2 (50)	1 (33)	0	3 (19)	13 (38)	2 (50)	27 (47)
Constipation	0	1 (25)	2 (29)	3 (50)	1 (14)	1 (25)	0	0	5 (31)	13 (38)	2 (50)	25 (44)
Fatigue	0	1 (25)	0	0	1 (14)	1 (25)	1 (33)	0	3 (19)	17 (50)	1 (25)	22 (39)
Muscular weakness	0	0	0	0	0	0	2 (67)	0	4 (25)	17 (50)	1 (25)	21 (37)
Headache	0	0	1 (14)	0	1 (14)	0	3 (100)	1 (25)	5 (31)	11 (32)	1 (25)	20 (35)
Nausea	0	1 (25)	3 (43)	1 (17)	0	0	0	0	5 (31)	11 (32)	1 (25)	19 (33)
Vision blurred	0	0	1 (14)	1 (17)	0	1 (25)	2 (67)	0	5 (31)	10 (29)	0	19 (33)
Diarrhoea	0	1 (25)	5 (71)	1 (17)	3 (43)	1 (25)	1 (33)	1 (25)	1 (6)	7 (21)	0	17 (30)
Dizziness	0	0	0	1 (17)	0	0	1 (33)	0	6 (38)	11 (32)	0	17 (30)
Dysgeusia	0	0	0	2 (33)	0	0	0	0	2 (13)	11 (32)	0	15 (26)
Vomiting	0	0	1 (14)	0	0	1 (25)	1 (33)	0	6 (38)	6 (18)	1 (25)	15 (26)
Dyspnoea	0	1 (25)	0	0	0	1 (25)	0	0	3 (19)	7 (21)	1 (25)	12 (21)
Paraesthesia	0	0	2 (29)	1 (17)	1 (14)	1 (25)	0	0	1 (6)	6 (18)	1 (25)	12 (21)
Arthralgia	0	0	0	0	1 (14)	1 (25)	1 (33)	0	3 (19)	5 (15)	1 (25)	11 (19)
Hypertension	0	0	1 (14)	1 (17)	0	0	0	0	2 (13)	6 (18)	1 (25)	11 (19)
Pain in extremity	0	0	0	1 (17)	0	0	2 (67)	1 (25)	2 (13)	7 (21)	0	11 (19)
Abdominal pain	1 (100)	0	0	0	2 (29)	0	1 (33)	0	2 (13)	4 (12)	0	10 (18)
Cough	0	0	2 (29)	0	1 (14)	0	0	0	1 (6)	5 (15)	1 (25)	10 (18)
Myalgia	0	0	0	0	1 (14)	0	0	0	0	7 (21)	2 (50)	10 (18)
Chest pain	0	0	0	0	0	2 (50)	1 (33)	0	1 (6)	4 (12)	1 (25)	9 (16)
Decreased appetite	0	0	0	0	0	0	0	0	1 (6)	8 (24)	0	9 (16)
Hypoaesthesia	0	0	1 (14)	0	1 (14)	0	0	0	0	7 (21)	0	9 (16)

BID=twice daily; QD=once daily; T=tablet

[a] Preferred terms are sorted by descending frequency, as reported in the total column

[b] Doses received in tablet form

Table S2. Treatment-related Serious Adverse Events by Dose Level

	Dose of Rebastinib at Onset of Adverse Event by Protocol Dose Level (mg/dose)											
	57 QD (N=1)	114/150 QD (N=4)	225/228 /300 QD (N=7)	450/456 QD (N=6)	600 QD (N=7)	300 BID (N=4)	1200 QD (N=3)	100 T[b] QD (N=4)	100 T[b] BID (N=16)	150 T[b] BID (N=34)	200 T[b] BID (N=4)	Total (N=57)
Preferred Term[a]	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any Related SAE	0	0	0	0	0	1 (25)	1 (33)	0	4 (25)	12 (35)	1 (25)	18 (32)
Muscular weakness	0	0	0	0	0	0	1 (33)	0	1 (6)	1 (3)	1 (25)	4 (7)
Acute myocardial infarction	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Atrial fibrillation	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Cardiomyopathy	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Death	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Dysarthria	0	0	0	0	0	0	1 (33)	0	0	0	0	1 (2)
Ejection fraction decreased	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Intraocular pressure increased	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Left ventricular dysfunction	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Malignant hypertension	0	0	0	0	0	0	0	0	1 (6)	0	0	1 (2)
Melanocytic naevus	0	0	0	0	0	1 (25)	0	0	0	0	0	1 (2)
Nausea	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Optic nerve disorder	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Pancreatitis	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Pericardial effusion	0	0	0	0	0	0	0	0	1 (6)	0	0	1 (2)
Pulmonary oedema	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Retinal vein occlusion	0	0	0	0	0	0	0	0	1 (6)	0	0	1 (2)
Viral cardiomyopathy	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Vision blurred	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)
Vomiting	0	0	0	0	0	0	0	0	0	1 (3)	0	1 (2)

BID=twice daily; QD=once daily; SAE=serious adverse event; T=tablet

If a subject had more than 1 treatment-emergent adverse event that codes to the same preferred term, the subject was counted once for that preferred term

[a] Preferred terms are sorted by descending frequency, as reported in the total column

[b] Doses received in tablet form

Table S3. Adverse Event Preferred Terms Included in the Safety Analysis by Exposure

Category	Preferred Terms
Musculoskeletal disorders	Muscular weakness, Myopathy, Muscle spasms, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Myalgia, Pain in extremity
Nervous System disorders	Hypoaesthesia, Hypoaesthesia facial, Hypoaesthesia oral, Neuropathy peripheral, Paraesthesia, Paraesthesia oral, Peripheral sensory neuropathy, Dysarthria
Cardiac disorders	Cardiac failure congestive, Cardiomyopathy, Ejection fraction decreased, Left ventricular dysfunction, Left ventricular hypertrophy, Viral cardiomyopathy, Acute myocardial infarction, Arrhythmia, Atrial fibrillation, Bradycardia, Palpitations, Pericardial effusion, Sinus arrhythmia, Sinus tachycardia, Tachycardia, Troponin I increased.
Visual abnormalities	Vision blurred, Visual field defect, Visual impairment, Ocular Hypertension, Optic nerve disorder, Papilloedema, Retinal vein occlusion, Intraocular pressure increased, Intraocular pressure test

Table S4. Summary of Adverse Events of Special Interest (Incidence ≥5%)

Preferred Term	Grade 1 N=57	Grade 2 N=57	Grade 3 N=57	Grade 4 N=57	Grade 5 N=57	All Grades N=57
Musculoskeletal disorders	10 (17.5%)	8 (14.0%)	15 (26.3%)	1 (1.8%)	0 (0.0%)	34 (59.6%)
Muscle spasms	3 (5.3%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	5 (8.8%)
Muscular weakness	5 (8.8%)	3 (5.3%)	13 (22.8%)	0 (0.0%)	0 (0.0%)	21 (36.8%)
Musculoskeletal pain	4 (7.0%)	3 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (12.3%)
Myalgia	6 (10.5%)	1 (1.8%)	3 (5.3%)	0 (0.0%)	0 (0.0%)	10 (17.5%)
Pain in extremity	6 (10.5%)	3 (5.3%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	11 (19.3%)
Nervous system disorders	19 (33.3%)	7 (12.3%)	4 (7.0%)	0 (0.0%)	0 (0.0%)	30 (52.6%)
Hypoaesthesia	9 (15.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (15.8%)
Neuropathy peripheral	2 (3.5%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	3 (5.3%)
Paraesthesia	9 (15.8%)	3 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (21.1%)
Peripheral sensory neuropathy	3 (5.3%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	5 (8.8%)
Cardiac disorders	6 (10.5%)	3 (5.3%)	4 (7.0%)	0 (0.0%)	2 (3.5%)	15 (26.3%)
Cardiac failure congestive	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.5%)	3 (5.3%)
Visual abnormalities	14 (24.6%)	5 (8.8%)	5 (8.8%)	0 (0.0%)	0 (0.0%)	24 (42.1%)
Intraocular pressure increased	2 (3.5%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	4 (7.0%)
Retinal vein occlusion	2 (3.5%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.3%)
Vision blurred	14 (24.6%)	2 (3.5%)	3 (5.3%)	0 (0.0%)	0 (0.0%)	19 (33.3%)
Visual impairment	3 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.3%)

Table S5. Causes of Death and Presumed Causality

Pt –ID	Diagnosis	Dose cohort	Cycle	Study Day of Last Dose of Study Drug Prior to Death (Day of Death)	Cause of Death*
01-001	CML-AP	57 mg QD	7	186 (199)	Disease Progression
03-001	CML-CP	225/228 mg QD	8	224 (225)	Acute Exacerbation of CHF; Cardiomegaly due to Aortic Stenosis
03-003	CML-AP	600 mg QD	13	364 (368)	Disease Progression
03-005	CML-CP	1200 mg QD	2	56 (61)	Disease Progression
01-019	CML-CP	150 mg BID	1	21 (30)	Pneumonia
02-008	AML	150 mg BID	1	1 (7)	Unknown[#]
03-012	CML-CP	150 mg BID	4	96 (111)	Pulmonary Hemorrhage
07-001	CML-CP	150 mg BID	1	5 (7)	CHF

AP = Accelerated phase; CP = Chronic phase; CHF = Congestive Heart Failure
*None of the deaths were deemed related and were attributed to causes other than DCC-2036
[#]Listed in Table 3 as 'treatment-related AE'

Table S6. Adverse Events of Special Interest by Worst Common Terminology Criteria for Adverse Event (AE) Grade and Rebastinib Maximum Concentration and Area Under the Curve from 0 to 4 hours Subgroup during Cycles 1 and 2

		Low[a]		Medium[a]		High[a]	
SOC	**Worst CTC Grade of AE**	**C_{max} Subgroup** (N=17) n (%)	**$AUC_{(0-4h)}$ Subgroup** (N=15) n (%)	**C_{max} Subgroup** (N=15) n (%)	**$AUC_{(0-4h)}$ Subgroup** (N=14) n (%)	**C_{max} Subgroup** (N=18) n (%)	**$AUC_{(0-4h)}$ Subgroup** (N=18) n (%)
Cardiac disorders	Grade 1	1 (6%)	1 (7%)	1 (7%)	1 (7%)	2 (11%)	2 (11%)
	Grade 2	0	0	0	0	0	0
	Grade 3	1 (6%)	1 (7%)	0	0	1 (6%)	1 (6%)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
	Total	2 (12%)	2 (13%)	1 (7%)	1 (7%)	3 (17%)	3 (17%)
Musculoskeletal disorders	Grade 1	4 (24%)	3 (20%)	1 (7%)	1 (7%)	3 (17%)	4 (22%)
	Grade 2	1 (6%)	1 (7%)	2 (13%)	2 (14%)	2 (11%)	2 (11%)
	Grade 3	1 (6%)	0	4 (27%)	4 (29%)	5 (28%)	3 (17%)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
	Total	6 (32%)	4 (27%)	7 (47%)	7 (50%)	10 (56%)	9 (50%)
Nervous system disorders	Grade 1	2 (12%)	2 (13%)	5 (33%)	5 (36%)	6 (33%)	6 (33%)
	Grade 2	1 (6%)	1 (7%)	1 (7%)	0	5 (28%)	5 (28%)
	Grade 3	0	0	1 (7%)	1 (7%)	1 (6%)	1 (6%)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
	Total	3 (18%)	3 (20%)	7 (47%)	6 (43%)	12 (67%)	12 (67%)
Visual abnormalities	Grade 1	3 (18%)	3 (20%)	5 (33%)	4 (29%)	2 (11%)	2 (11%)
	Grade 2	0	0	0	0	2 (11%)	1 (6%)
	Grade 3	0	0	0	0	1 (6%)	1 (6%)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
	Total	3 (18%)	3 (20%)	5 (33%)	4 (29%)	5 (28%)	4 (22%)
Any of the above	Grade 1	6 (35%)	5 (33%)	6 (40%)	6 (43%)	6 (33%)	7 (39%)
	Grade 2	0	0	3 (20%)	2 (14%)	3 (17%)	4 (22%)
	Grade 3	2 (12%)	1 (7%)	4 (27%)	4 (29%)	7 (39%)	5 (28%)
	Grade 4	0	0	0	0	0	0
	Grade 5	0	0	0	0	0	0
	Total	8 (47%)	6 (40%)	13 (87%)	12 (86%)	16 (89%)	16 (89%)

$AUC_{(0-4h)}$=area under the curve from 0 to 4 hours; C_{max}=maximum concentration; CTC=Common Terminology Criteria; SOC=system organ class

[a]The ranges from the lowest to the highest C_{max} and AUC values were divided into tertiles. Low, Medium and High represent the corresponding tertiles for each parameter

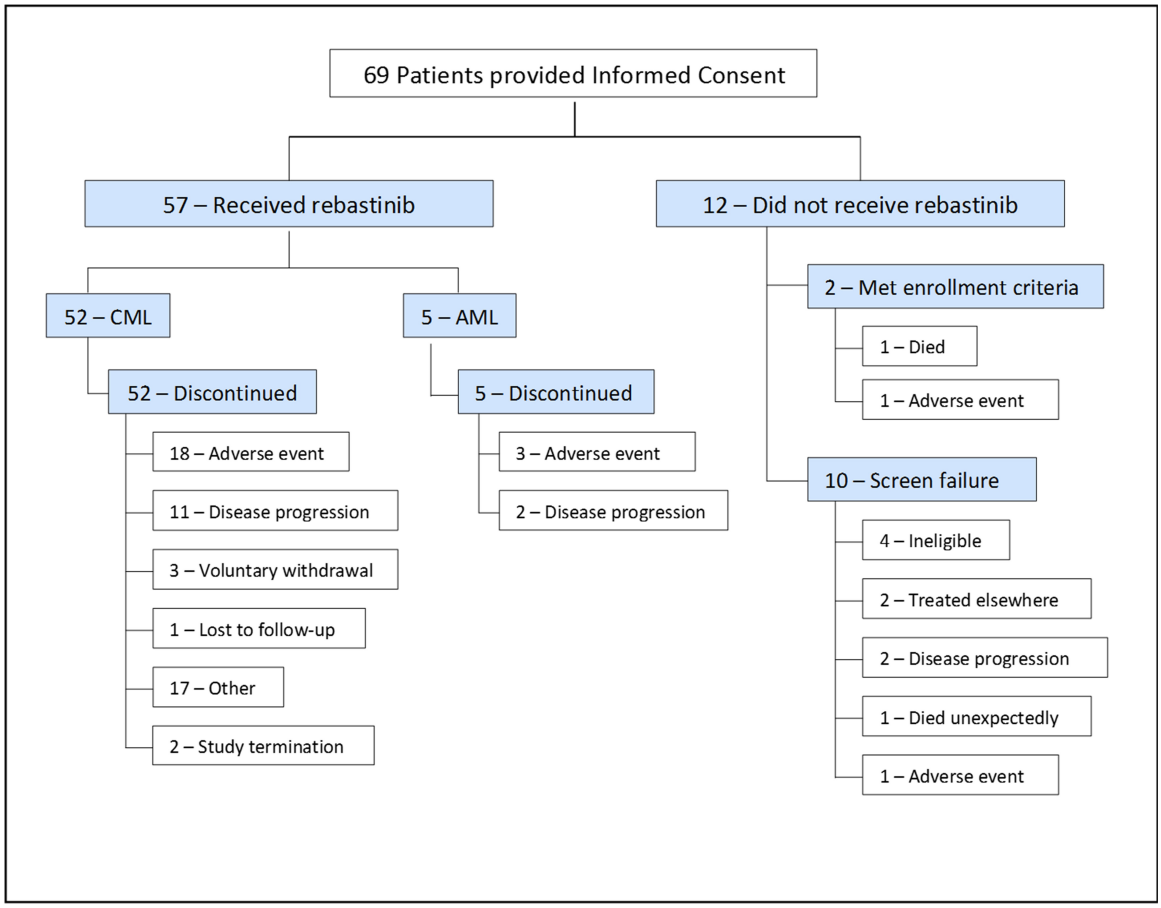

Figure S1. Study flow chart. Schematic representation of the outcomes of patients accrued to the Phase 1 study of rebastinib.

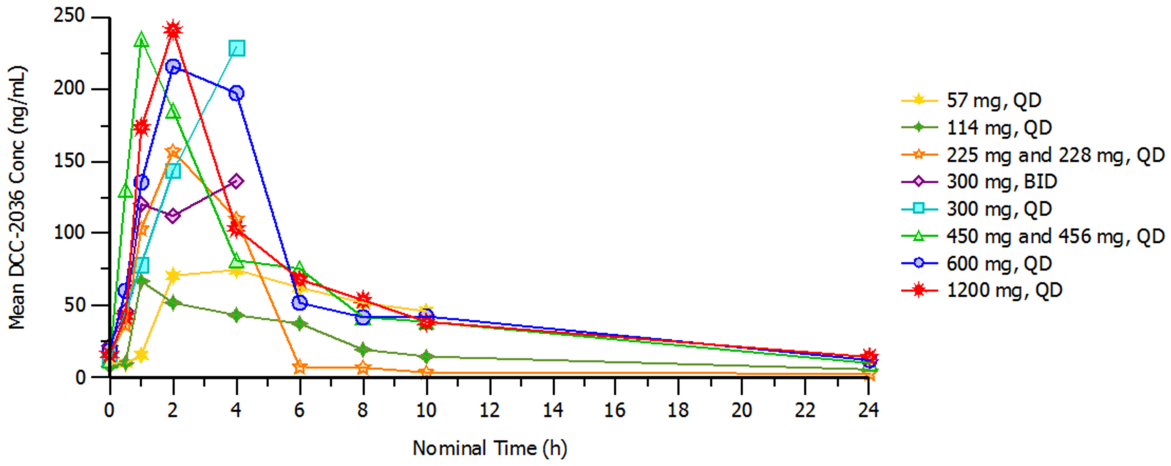

Figure S2. Mean plasma rebastinib concentration-time profile following multiple dose administration of rebastinib PIC to steady state. Mean peak plasma concentrations of rebastinib were determined for individual patients receiving rebastinib as powder-in-capsule formulation at the indicated dose level, following at least one week of continuous dosing.