# BMS-986397, a first-in-class Casein Kinase 1α (CK1α) Degrader in Patients with Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML) and High-Risk Myelodysplastic Syndrome (HR-MDS): A Phase 1 Dose Escalation Study

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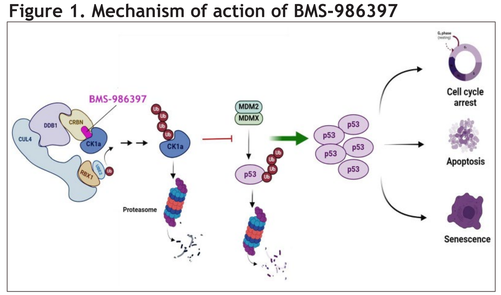
## Introduction

- Patients with relapsed or refractory (R/R) AML or high-risk MDS (HR-MDS) have limited therapeutic options and poor outcomes.
- BMS-986397 (CC-91633) repurposes the CRL4$^{CRBN}$ E3 ubiquitin ligase to target Casein kinase 1α (CK1α) for ubiquitination and potent proteasomal degradation, which leads to the stabilization and activation of p53 resulting in cell cycle arrest and induction of apoptosis in AML blasts (**Figure 1**).
- Extensive preclinical *ex vivo* and *in vivo* BMS-986397 data in AML and healthy models established key safety, efficacy and PK/PD relationships which critically informed the starting dose and schedule in the clinic[1,2].
- Here, we present the first clinical data from CC-91633-AML-001 (NCT04951778), a first-in-human, multicenter, open-label study of BMS-986397 in patients with R/R AML and R/R HR-MDS.

### Figure 1. Mechanism of action of BMS-986397

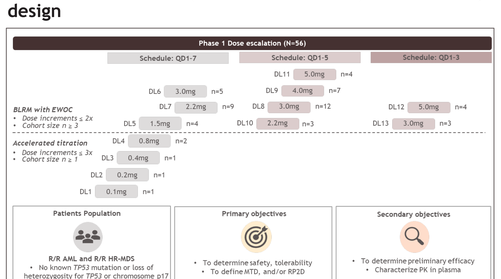



CK1α degradation via Cereblon (CRBN) by BMS-986397 leads to the stabilization and activation of p53, resulting in cell cycle arrest and induction of acute apoptosis in AML blasts.

## Methods

- Patients were ≥18 years with R/R AML or HR-MDS without known TP53 mutation or loss of 17p, who failed or were ineligible for any available therapies.
- BMS-986397 was administered orally once daily (QD) for 3, 5 or 7 consecutive days on 28-days cycle. The observation period for dose-limiting toxicities (DLT) was cycle 1 (28 to 42 days).
- Primary objectives were to determine the safety and tolerability of BMS-986397 and to define the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose(s) and schedule(s). Secondary endpoints were to assess the preliminary efficacy and to characterize the pharmacokinetics of BMS-986397. Exploratory pharmacodynamic objectives included to evaluate molecular and/or cellular biomarkers in the bone marrow (BM) and peripheral blood (PB) (**Figure 2**)

### Figure 2. CA091-P01 (CC-91633-AML-001) Phase 1 study design




## Results

### Baseline characteristics and disposition

- 56 patients were enrolled and treated with BMS-986397. Thirty-nine (70%) had AML (11 [28.2%] had secondary AML [sAML] from prior MDS) and 17 (30%) had HR-MDS (**Table 1**)
- **The most common reason for treatment discontinuation was progressive disease** (PD; 32 patients, 57.1%), followed by treatment-emergent AEs (TEAEs) and withdrawal by patient (5, 8.9% each), death (4, 7.1%), other reasons (6, 10.7%) and physician decision (3, 5.4%)

### Table 1. Patient characteristics

| | AML | HR-MDS | All patients |
|---|---|---|---|
| | N=39 | N=17 | N=56 |
| Age (median, range) | 74 (34-87) | 79 (58-85) | 76 (34-87) |
| Sex (n,%) | M:23 (59)<br>F:16 (41) | M:12 (71)<br>F:5 (29) | M:35 (63)<br>F:21 (38) |
| ECOG PS | | | |
| 0-1 | 30 (77%) | 13 (77%) | 43 (77%) |
| 2 | 9 (23%) | 4 (23%) | 13 (23%) |
| Median prior lines (range) | 2 (1-4) | 1 (1-3) | 2 (1-4) |
| Prior HMA | 22 (56%) | 16 (94%) | 38 (68%) |
| Prior Ven | 21 (54%) | 2 (12%) | 23 (41%) |
| Prior ICT | 20 (51%) | 3 (18%) | 23 (41%) |
| Prior SCT | 4 (10%) | 0 | 4 (7%) |
| ELN 2022 molecular risk (AML) | | | |
| Adverse | 23 (59%) | NA | 23 (59%) |
| Int/Low | 8 (21%) | NA | 8 (21%) |
| N/A | 8 (21%) | NA | 8 (21%) |
| IPSS-R (MDS) | | | |
| High/Very High | NA | 12 (71%) | 12 (71%) |
| Int/Low | NA | 5 (29%) | 5 (29%) |
| BM blasts at baseline (%) | 48 (21-92) | 12 (5-18) | 35 (5-92) |
| WBC at baseline (x10^9/L) | 4.1 (0.3-24.9) | 2.7 (0.4-6.2) | 3.7 (0.3-24.9) |

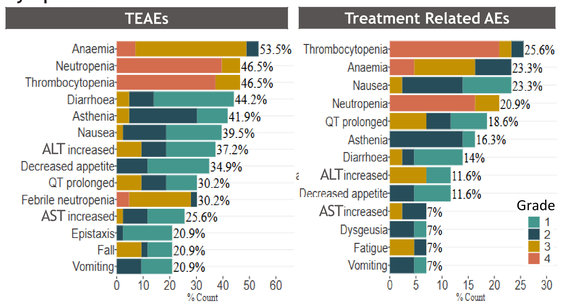
### Longer duration of treatment in HR-MDS patients

- Patients received BMS-986397 at doses ranging from 0.1mg to 5.0mg QDx3, QDx5 or QDx7 for a median of 1 cycle (range: 1-12).
- Median treatment duration was 5.6 weeks (range: 0.4-52.4) across indications. 17 weeks (range 0.7-52.4) in HR-MDS vs. 4.9 weeks (range: 0.4-18) in AML (*P*=0.0014)
- **Most of the BMS-986397 discontinuations (3/3), interruptions (10/18) and reductions (6/6) occurred in patients at 3.0mg or higher (Figure 3)**
- The TEAEs leading to treatment discontinuation included acute kidney injury, septic shock and pneumonia, all assessed events were assessed as not related to BMS-986397 and occurred in patients with HR-MDS patients
- At 2.2mg QDx7, 2 (3.6%) patients discontinued BMS-986397 due to Grade 5 TEAEs of pneumonia and septic shock. Both events were assessed as not related to BMS-986397
- To note, the majority of patients already presented cytopenias at baseline (mean Hb: 86.6 g/L [range 63 to 117], ANC: 0.8 x10^9/L [range 0-7.9], platelets: 45.6 x10^9/L [range 6-195])

### Compromised tolerability at ≥3.0mg doses especially in HR-MDS

- Four patients experienced a DLT: Grade 3 prolonged QT in 2 AML patients at 2.2mg and 3mg QDx7; and, Grade 4 prolonged cytopenias lasting >42 days (in the absence of active disease) in 2 patients (1 AML and 1 HR-MDS) at 3mg QDx7 and 3mg QDx5, respectively

### Figure 3. The most frequent TEAEs and TRAEs were Grade 3/4 cytopenias



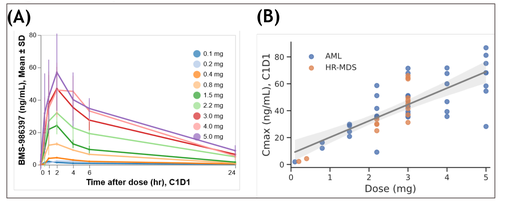

| | TEAEs | | | Treatment Related AEs | | |
|---|---|---|---|---|---|---|
| | AML | HR-MDS | All patients | AML | HR-MDS | All patients |
| | N=39 | N=17 | N=56 | N=39 | N=17 | N=56 |
| Num. of patients with at least 1 TEAE: | | | | | | |
| Any Grade | 38 (97.4%) | 17 (100%) | 55 (98.2%) | 24 (61.5%) | 15 (88.2%) | 39 (69.6%) |
| Grade 3/4 | 34 (87.2%) | 16 (94.1%) | 50 (89.3%) | 16 (41%) | 12 (70.6%) | 28 (50%) |
| SAE | 24 (61.5%) | 14 (82.4%) | 38 (67.9%) | 5 (12.8%) | 4 (23.5%) | 9 (16.1%) |
| Grade 5 | 2 (5.1%) | 0 | 2 (3.6%) | 0 | 0 | 0 |
| Leading to treatment discontinuation | 1 (2.6%) | 2 (11.8%) | 3 (5.4%) | 1 (2.6%) | 0 | 1 (1.8%) |
| Leading to treatment interruption | 9 (23.1%) | 9 (52.9%) | 18 (32.1%) | 6 (15.4%) | 4 (23.5%) | 10 (17.9%) |
| Leading to dose reduction | 2 (5.1%) | 4 (23.5%) | 6 (10.7%) | 2 (5.1%) | 4 (23.5%) | 6 (10.7%) |

Treatment-emergent adverse events (TEAEs) in at least 20% patients, and treatment-related adverse events (TRAEs) in at least 5% patients.

### Pharmacokinetics (PK)

- BMS-986397 was rapidly absorbed, with a median Tmax of ~2 hrs on Cycle 1 Day 1. Exposure increased in a dose-dependent manner across the 0.1 – 5mg range
- By Day 5, BMS-986397 reached steady state, with a median Cmax accumulation of ~13% and an estimated effective half-life of ~11hrs
- No notable differences were observed between AML and HR-MDS patients (**Figure 4**)

### Figure 4. Exposure data

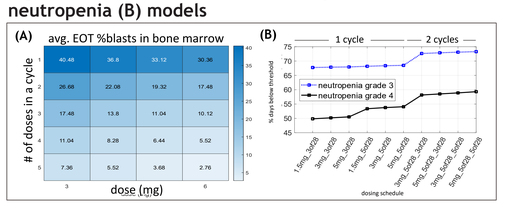



(A) PK profile of BMS-986397 on Cycle 1 Day 1 (C1D1) across the 0.1 – 5mg dose range. (B) Relationship between dose and C1D1 Cmax in subjects with AML and HR-MDS.

### Exposure-response (ER) modeling

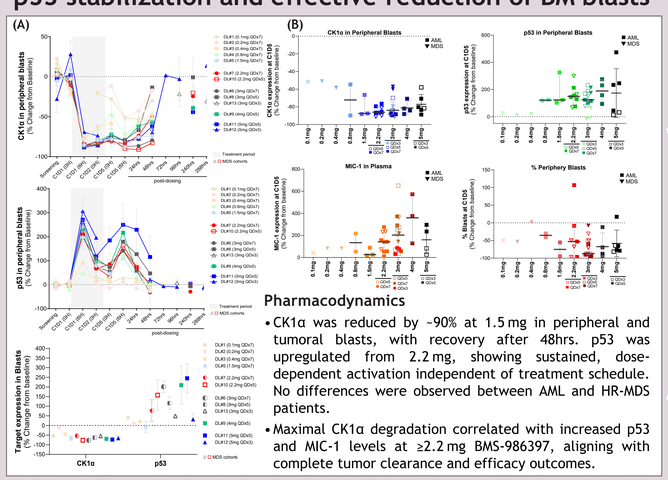
- PK/PD models were developed and calibrated to longitudinal clinical PD and ANC data to predict efficacy and neutropenia incidence with different dosing schedules.
- Model simulations showed that shorter schedules (QDx5, QDx3) help mitigate the duration of neutropenia while maintaining efficient blast reduction (**Figure 5**).

### Figure 5. Simulation of PK/PD efficacy (A) and neutropenia (B) models




(A) Average simulated %blasts in bone marrow after one cycle for different # of doses and dose amounts. (B) Average % of days for simulated neutrophil counts to fall below neutropenia thresholds on different dosing schedules.

## Potent CK1α degradation induced rapid and sustained p53 stabilization and effective reduction of BM blasts

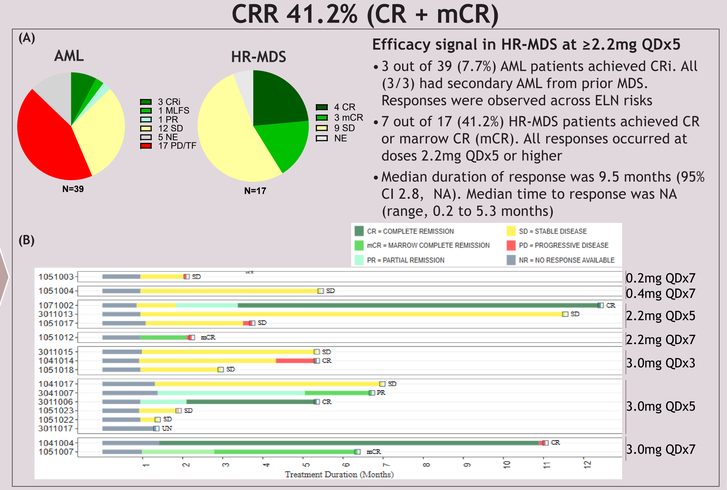



### Pharmacodynamics

- CK1α was reduced by ~90% at 1.5 mg in peripheral and tumoral blasts, with recovery after 48hrs. p53 was upregulated from 2.2 mg, showing sustained, dose-dependent activation independent of treatment schedule. No differences were observed between AML and HR-MDS patients.
- Maximal CK1α degradation correlated with increased p53 and MIC-1 levels at ≥2.2 mg BMS-986397, aligning with complete tumor clearance and efficacy outcomes.

**(A)** CK1α and p53 expression dynamics throughout Cycle 1 of BMS-986397 dosing in blasts from peripheral blood (upper panels) and bone marrow (bottom panel); (B) Maximal change from baseline of peripheral expression of CK1α, p53, MIC-1 (macrophage inhibitory cytokine-1) and blasts counts across different dose/schedules.

## Promising single-agent activity in R/R HR-MDS: CRR 41.2% (CR + mCR)




### Efficacy signal in HR-MDS at ≥2.2mg QDx5

- 3 out of 39 (7.7%) AML patients achieved CRi. All (3/3) had secondary AML from prior MDS. Responses were observed across ELN risks
- 7 out of 17 (41.2%) HR-MDS patients achieved CR or marrow CR (mCR). All responses occurred at doses 2.2mg QDx5 or higher
- Median duration of response was 9.5 months (95% CI 2.8, NA). Median time to response was NA (range, 0.2 to 5.3 months)

**(A) ORR and CRR in AML and HR-MDS.** Complete Remission Rate (CRR) = the percentage of subjects with best response CR, CRi or CRh for AML and CR, mCRHI/mCR for MDS; Overall Response Rate (ORR) = the percentage of subjects with best response is cCRR, MLFS, PR for AML and CR, HI, mCRHI and PR for MDS. (B) Swimmers plot for HR-MDS patients

## Conclusions

- BMS-986397 induced potent and rapid CK1α degradation in circulating and BM blasts from R/R AML and HR-MDS patients
- CK1α degradation correlated with sustained p53 stabilization, increased soluble MIC-1 levels and decrease on BM blasts at ≥2.2 mg doses in AML and HR-MDS patients
- The most frequent TEAEs and TRAEs were Grade 3/4 cytopenias, which compromised tolerability at ≥3.0mg doses specially in HR-MDS
- Promising efficacy (CRR 41.2%) in HR-MDS at ≥2.2mg doses. Activity signal in sAML from prior MDS
- ER modeling suggested that shorter schedules might mitigate the duration of neutropenia while maintaining efficient blast reduction
- Despite narrow therapeutic index as single agent, BMS-986397 showed potential for combinability in AML and HR-MDS patients

## References


1.Carmen Jimenez et al. Blood (2024); Volume 144 (Supplement 1): Abstract 4142.
2.Carmen Jimenez et al. Blood (2024); Volume 144 (Supplement 1): Abstract 1395.
3.Deborah Mortensen et al. ACS (2024). 4099774.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