BMS-986397, a first-in-class molecular glue degrader of Casein Kinase 1α (CK1α) for the treatment of AML and HR-MDS harboring functional TP53

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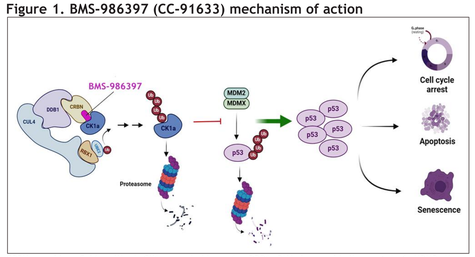
Introduction

- The Casein Kinase 1α (CK1α) gene is encompassed in the 5q commonly deleted region in del5q myelodysplastic syndrome (MDS), which leads to attenuated CK1α expression. Lenalidomide is a weak degrader of CK1α and is active in del5q MDS with lesser activity in non-del5q MDS and acute myeloid leukemia (AML). This provides clinical evidence for efficacy of degradation of CK1α in myeloid malignancies, and suggests that a stronger degrader could have broader activity.
- BMS-986397 (also known as CC-91633) is a novel, first-in-class cereblon E3 ligase modulator (CELMoD) degrader of CK1α with the potential to promote p53 activity. Degradation of CK1α by BMS-986397 leads to p53 stabilization and the consequent induction of p53 transcriptional targets including p21 (cyclin-dependent kinase inhibitor 1), PUMA, and BAX, thereby inducing cell cycle arrest and apoptosis in AML (**Figure 1**).
- BMS-986397 is being developed for the treatment of human relapse/refractory (R/R) AML or high-risk (HR)-MDS harboring functional TP53.
- Here, we present preclinical evidence of cereblon (CRBN) and p53-dependent efficacy of BMS-986397 in AML and MDS.

Figure 1. BMS-986397 (CC-91633) mechanism of action



CRBN, cereblon; Cul4, cullin 4; CK1α, casein kinase 1α; DDB1, DNA damage-binding protein 1; MDM2, Mouse double minute 2 homolog; MDMX, Mouse double minute 4 homolog; Roc1, regulator of cullins-1; p53, tumor protein p53; UB, ubiquitin.

Methods

- To assess the anti-proliferative activity and molecular mechanism of BMS-986397, AML parental and genetically engineered cell lines with CRISPR/Cas9-mediated knockout of CRBN or TP53 or overexpressing a non-degradable CK1α mutant (CK1α variant 2 G40N) were evaluated by proliferative assays, flow cytometry, and immunoblotting.
- Given BMS-986397's pharmacological activity across different species[7], *in vivo* studies in AML xenograft murine models, healthy cynomolgus monkeys and in *ex vivo* models using primary samples from healthy volunteers and AML patients were conducted to assess pharmacokinetics (PK), pharmacodynamics (PD), antitumor activity and safety.
- Preclinical data were integrated into PK/PD model to establish key safety, efficacy, and PD relationships informing the starting dose/schedules for FIH (first-in-human) study.

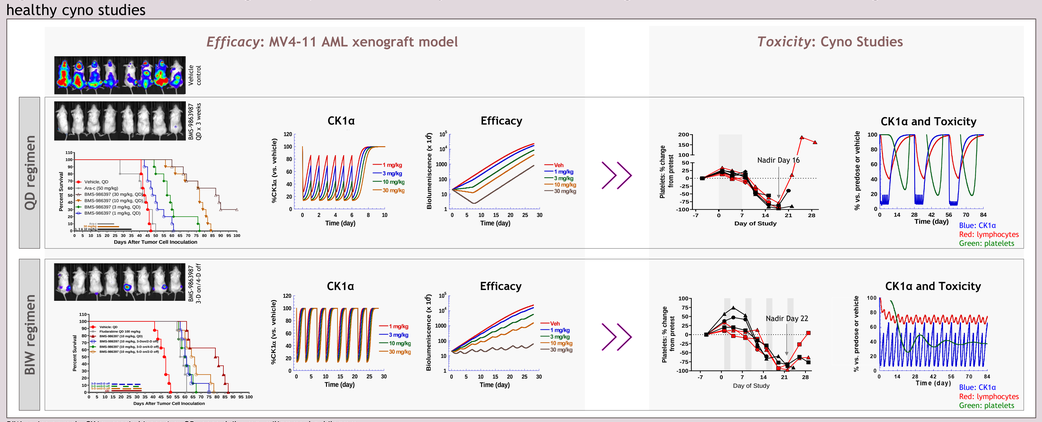
Results

BMS-986397 displayed potent and broad cell autonomous activity in TP53 WT (wild-type) AML cell lines

- BMS-986397 exhibited a strong antiproliferative activity in TP53 WT AML cancer cell lines regardless of FAB subtype or any common oncogenic-driver mutations, while those with TP53 loss or mutation were insensitive to BMS-986397 treatment (**Figure 2A**).
- BMS-986397 treatment promoted CK1α degradation, stabilization of p53 and its transcriptional targets such as p21, BAX and BBC3 (which encodes PUMA) and subsequent induction of γH2AX, and caspase-3 cleavage in a concentration- and time-dependent manner in different TP53 WT AML cancer cell lines (**Figure 2B**).
- Depletion of CRBN abolished BMS-986397-induced CK1α degradation, while CK1α G40N overexpression abrogated the activation of p53 signaling determining that the growth inhibitory effect of BMS-986397 is associated with G1 cell cycle arrest and induction of apoptosis in a cereblon-, CK1α-, and p53-dependent manner (**Figure 2C**).
- BMS-986397 selectively degraded CK1α, but did not degrade other well-established cereblon neosubstrates including Ikaros (IKAROS family zinc finger 1) and GSPT1 (G1 to S phase transition 1) (**Figure 3**).

BMS-986397 anti-tumor activity mediated by CK1α degradation demonstrated its value as a candidate for clinical development in AML and HR-MDS patients

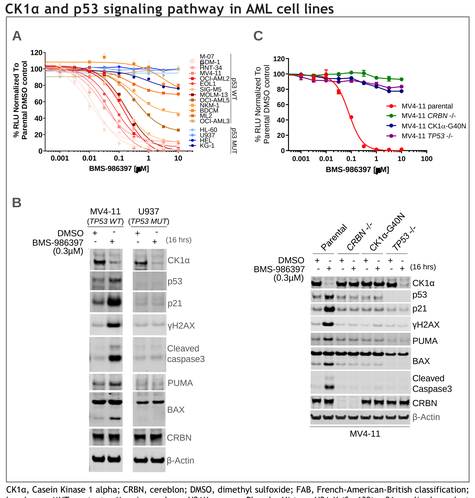
Figure 8. Model-simulated CK1α degradation, antitumor efficacy and normal blood counts generated from *in vivo* MV4-11 xenograft mouse model and healthy cyno studies



Preclinical model-approaches integrating available PK/PD/efficacy/toxicity data informed dose/schedule regimens for clinical development

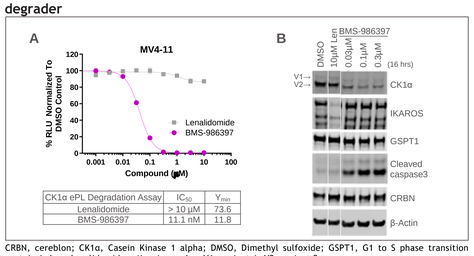
BIW, twice a week; CK1α, casein kinase 1 α; QD, once daily; mg, miligrams; kg, kilogram

Figure 2. BMS-986397 anti-proliferative activity mediated by CRBN, CK1α and p53 signaling pathway in AML cell lines



CK1α, Casein Kinase 1 alpha; CRBN, cereblon; DMSO, dimethyl sulfoxide; FAB, French-American-British classification; hrs, hours; MUT, mutant; μM, micromolar; γH2AX, gamma Phospho-Histone H2A.X (Ser139); p21, cyclin-dependent kinase inhibitor 1; p53, tumor protein p53; RLU, relative luminescence unit; WT, wild-type.

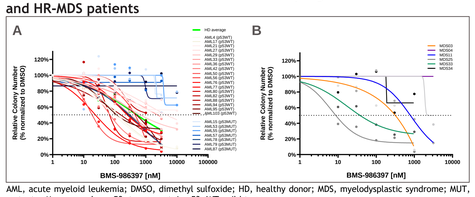
Figure 3. BMS-986397 (CC-91633), a selective and potent CK1α degrader



CK1α ePL Degradation Assay	IC_{50}	Y_{min}
Lenalidomide	> 10 μM	73.6
BMS-986397	11.1 nM	11.8

CRBN, cereblon; CK1α, Casein Kinase 1 alpha; DMSO, Dimethyl sulfoxide; GSPT1, G1 to S phase transition protein 1; Len, lenalidomide; μM, micromolar; V1, variant 1; V2, variant 2.

Figure 4. BMS-986397 effects in leukemic progenitor cells from AML and HR-MDS patients

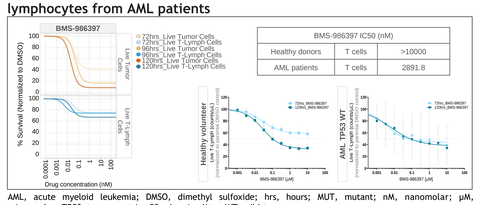


AML, acute myeloid leukemia; DMSO, dimethyl sulfoxide; HD, healthy donor; MDS, myelodysplastic syndrome; MUT, mutant; nM, nanomolar; p53, tumor protein p53; WT, wild-type.

BMS-986397 preferentially compromised cell fitness of leukemic progenitor cells over normal hematopoietic progenitors in TP53 WT AML patients

- BMS-986397 impacted the clonogenic potential in AML (**Figure 4A**) and HR-MDS (**Figure 4B**) patient samples harboring functional p53 by eliminating the leukemic progenitor cells (77.8% and 67%, respectively), while only mildly affecting normal hematopoietic progenitors, thereby establishing a narrow therapeutic index (TI) which suggest the need of dose/regimens adjustments to reduce the incidence of bone marrow toxicity.
- Viability of mature leukemic cells from TP53 WT AML patients was significantly compromised in response to BMS-986397 treatment (IC_{50} values ranging from 22 nM to 412 nM), while sparing normal T lymphocytes demonstrating a better profile to identify an efficacious TI (**Figure 5**).

Figure 5. Efficacy of BMS-986397 in leukemic cells and normal T lymphocytes from AML patients

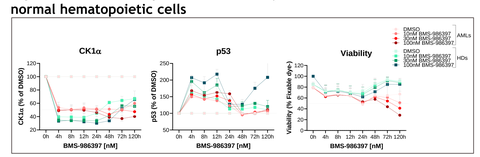


BMS-986397 IC50 (nM)		
Healthy donors	T cells	>10000
AML patients	T cells	2891.8

AML, acute myeloid leukemia; DMSO, dimethyl sulfoxide; hrs, hours; MUT, mutant; nM, nanomolar; μM, micromolar; TP53, tumor protein p53; μL, microliter; WT, wild-type.

- BMS-986397-induced target modulation suggesting that at least 70-80% CK1α degradation and 120% p53 stabilization for a minimum of 48 hours was required for achieving antileukemic efficacy and compromising blast viability in TP53 WT AML patients (**Figure 6**).

Figure 6. CK1α and p53 modulation by BMS-986397 in leukemic vs normal hematopoietic cells

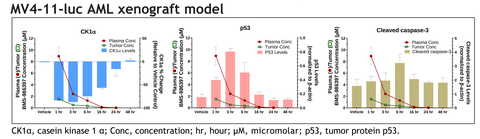


AML, acute myeloid leukemia; DMSO, dimethyl sulfoxide; HD, healthy donor; h, hours; nM, nanomolar; p53, tumor protein p53.

In vivo pharmacology studies were to determine the PK/PD relationship and antitumor activity of BMS-986397 as a single agent

- The PK/PD relationship in the MV4-11-luc tumor model indicated that up to 99% degradation of CK1α can be achieved when the tumor BMS-986397 concentrations were >0.3μM with a consequent dose-dependent induction of cleavage caspase-3. A level of 50% degradation through 24 hours at the minimum efficacious dose of 3mg/kg conferred a significant reduction in tumor burden and a marked prolonged survival of mice with disseminated AML (**Figure 7**).
- In monkeys, doses of 0.03 mg/kg/day for 7 consecutive days in each 4-week cycle for 2 cycles of BMS-986397 were considered well tolerated with no adverse findings in animals treated. However, higher doses were associated with a decreased hematopoietic cellularity in the bone marrow with correlating changes in the peripheral blood (mainly decreased red cell mass, leukocytes, and platelets) that could be addressed in a dose/schedule manner.
- Integrative modeling of PK/PD, efficacy, and toxicity data established key safety, efficacy, and target engagement relationships which suggested that short and intense schedules followed by prolonged off-treatment period (QD) instead of more frequent intermittent schedules (BIW) may maximize cytotoxicity on AML blasts while allowing for extended recovery period of hematopoietic progenitors (**Figure 8**).

Figure 7. Pharmacokinetics and pharmacodynamics of BMS-986397 in MV4-11-luc AML xenograft model



CK1α, casein kinase 1 α; Conc, concentration; hr, hour; μM, micromolar; p53, tumor protein p53.

Conclusions

- BMS-986397 is a novel CELMoD agent with a first in class mechanism targeting CK1α degradation that exhibit a strong anti-leukemic activity as a single agent in preclinical models of TP53 WT AML and HR-MDS.
- BMS-986397 moderately compromised the myeloid stem precursor of bone marrow and allowed a rapid recovery of normal lymphoid cells. Taken together, these results suggested an advantage of CK1α degrader to stablish dose/schedule regimens to manage myelosuppression in AML patients.
- The totality of the nonclinical toxicology and pharmacology assessments demonstrate that BMS-986397 may has an acceptable safety profile for an AML and MDS clinical candidate as a single agent and opens an avenue for combinations.
- These data support the clinical investigation of BMS-986397 in patients with R/R AML and HR-MDS patients (CA091-P01 study; NCT04951778).

References

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Acknowledgments

- The scientific teams who participated
- The study was supported by Bristol Myers Squibb
- All authors contributed to and approved the presentation

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Presented at the American Society of hematology (ASH) Annual Meeting, December 7-10, San Diego, CA

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