# BMS-986458, a first-in-class, bifunctional, cereblon-dependent ligand-directed degrader of B-cell lymphoma 6 (BCL6) in patients with relapsed/refractory non-Hodgkin lymphoma: initial phase 1 results

PF934

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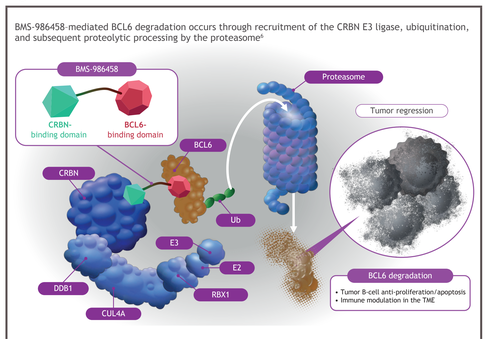
## Introduction

- Approximately 20%-50% of patients with diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL) experience relapsed or refractory (R/R) disease, which is associated with poor outcomes[1-3]
- BCL6 is a transcriptional repressor required for tolerance of immunoglobulin hypermutation and normal B-cell maturation; it inhibits cell cycle arrest and DNA damage checkpoints, and prevents apoptosis[4]
- Along with BCL2 and c-Myc, BCL6 is one of the most frequently genetically misregulated proteins in DLBCL (~20%-40%).[4,5] BCL6 overexpression in DLBCL and FL leads to increased tumor cell proliferation, making it a relevant therapeutic target for the treatment of B-cell lymphomas[4]
- BMS-986458 is a first-in-class, oral, highly selective, cereblon-dependent ligand-directed degrader of BCL6[6]
  - BMS-986458 links BCL6 to cereblon and promotes the degradation of BCL6, leading to anti-proliferation, apoptosis of tumor B cells, and immune modulation (**Figure 1**)[6]
  - Daily oral dosing of BMS-986458 in preclinical models of DLBCL demonstrated selective and potent BCL6 degradation, tumor regression, and improved survival while sparing normal bone marrow cells[6]
- Here, we present the first clinical findings from the dose-escalation part of CA123-1000 (NCT06090539), a first-in-human, multicenter, open-label, phase 1/2 study of BMS-986458 in patients with R/R non-Hodgkin lymphoma (NHL)

**Figure 1. BMS-986458 mechanism of action**

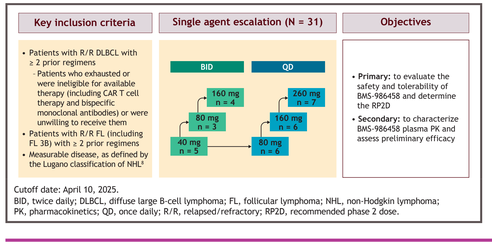



BCL6, B-cell lymphoma 6; CRBN, cereblon; CUL4A, cullin-4A; DDB1, DNA damage-binding protein 1; RBX1, ring-box 1; TME, tumor microenvironment; Ub, ubiquitin.

## Methods

- Eligible patients had de novo or transformed R/R DLBCL previously treated with ≥ 2 prior regimens, or R/R FL (including FL 3B) previously treated with ≥ 2 prior regimens
- The dosing schedule and study objectives are shown in **Figure 2**
- The efficacy-evaluable population included patients who received ≥ 1 dose of BMS-986458, had undergone baseline and post-baseline tumor assessment, had experienced clinical disease progression, or died
- For pharmacodynamic analyses, flow cytometry was used to measure the expression of BCL6 in peripheral blood

**Figure 2. Study design[7]**




Cutoff date: April 10, 2025.
BID, twice daily; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; PK, pharmacokinetics; QD, once daily; R/R, relapsed/refractory; RP2D, recommended phase 2 dose.

## Results

### Patient characteristics and disposition

- A total of 31 patients with R/R DLBCL and FL were treated with BMS-986458
- A heavily pre-treated population was enrolled as indicated by the patient characteristics shown in **Table 1**
  - Patients received a median of 4 (range, 2-12) prior lines of treatment
  - In total, 24 (77.4%) patients had received prior CAR T cell therapy and 18 (58.1%) patients had received prior bi/tri-specific antibody therapy
  - Twenty-two (71.0%) patients had disease that was refractory to prior therapy regimens
- At the database cutoff (April 10, 2025), treatment was ongoing for 14 (45.2%) patients, and 17 (54.8%) patients had discontinued treatment
  - The reasons for discontinuing treatment included progressive disease (n = 10, 32.3%), adverse events (n = 5, 16.1%), death (n = 1, 3.2%), and withdrawal of consent (n = 1, 3.2%)

**Table 1. Patient characteristics and disposition**

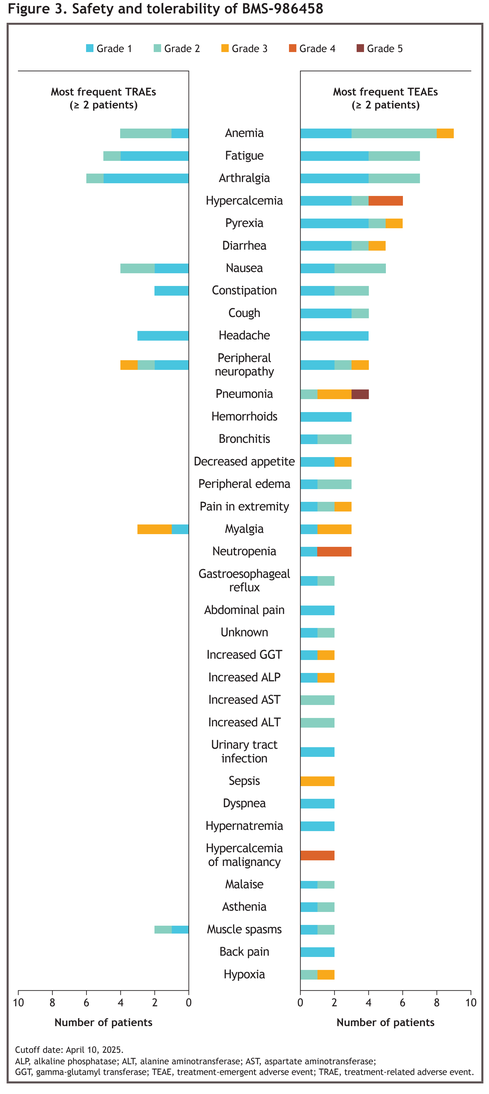
| | N = 31 |
|---|---|
| **Age, years, median (range)** | 62 (26-76) |
| **Sex, n (%)** | |
| Female | 10 (32.3) |
| Male | 21 (67.7) |
| **Disease stage at entry, n (%)** | |
| Stage I | 2 (6.5) |
| Stage II | 4 (12.9) |
| Stage III | 5 (16.1) |
| Stage IV | 18 (58.1) |
| Unknown | 2 (6.5) |
| **Disease type[a], n (%)** | |
| DLBCL (not otherwise specified) | 14 (45.2) |
| DLBCL/high grade B-cell lymphoma with *MYC*/*BCL2* rearrangements | 5 (16.1) |
| FL | 10 (32.3) |
| **Cell of origin, n (%)** | |
| ABC, non-GCB | 5 (16.1) |
| GCB | 7 (22.6) |
| Unknown | 9 (29.0) |
| **Risk category for IPI (DLBCL), n (%)** | |
| High (4-5) | 2 (6.5) |
| High-intermediate (3) | 5 (16.1) |
| Low-intermediate (2) | 9 (29.0) |
| Low (0-1) | 3 (9.7) |
| **Risk category for FLIPI (FL), n (%)** | |
| High (3-5) | 6 (19.4) |
| Intermediate (2) | 1 (3.2) |
| Low (0-1) | 2 (6.5) |
| Unknown | 1 (3.2) |
| **Hit status, n (%)** | |
| Double-hit | 0 |
| Triple-hit | 5 (16.1) |
| **ECOG PS, n (%)** | |
| 0 | 11 (35.5) |
| 1 | 20 (64.5) |
| **Prior lines of therapy, n (%)** | |
| 2 | 4 (12.9) |
| 3 | 6 (19.4) |
| ≥ 4 | 21 (67.7) |
| **Median prior lines of therapy (range)** | 4 (2-12) |
| **Types of prior anticancer therapy, n (%)** | |
| CAR T cell therapy | 24 (77.4) |
| Bi-/tri-specific mAb | 18 (58.1) |
| IMiD/CELMoD™ agent | 19 (61.3) |
| **Refractory to prior therapy, n (%)** | 22 (71.0) |

Cutoff date: April 10, 2025. [a]Two patients with high-grade B-cell lymphoma were entered after data cutoff.
ABC, activated B-cell-like; BCL, B-cell lymphoma; CELMoD, cereblon E3 ligase modulator; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GCB, germinal center B-cell-like; IMiD, immunomodulatory imide drug; IPI, International Prognostic Index; mAb, monoclonal antibody.

### Safety and tolerability

- A summary of safety and tolerability results is shown in **Figure 3**
  - The most common treatment-emergent adverse events (TEAEs) were anemia (n = 9, 29.0%), arthralgia (n = 7, 22.6%), and fatigue (n = 7, 22.6%)
  - Grade 3/4 TEAEs occurred in 16 (51.6%) patients
  - Serious TEAEs occurred in 17 (54.8%) patients and the most common serious TEAEs included hypercalcemia (n = 4, 13%), pneumonia (n = 3, 9.7%), and pyrexia (n = 3, 9.7%)
- TEAEs led to dose interruption in 15 (48.4%) patients, dose reduction in 2 (6.5%) patients, and discontinuation in 5 (16.1%) patients
- The most common treatment-related adverse events (TRAEs) were arthralgia (n = 6, 19.4%) and fatigue (n = 5, 16.1%)
  - Grade 3/4 TRAEs occurred in 5 (16.1%) treated patients and included pneumonia, arthritis, bone pain, peripheral neuropathy, prolonged QT (n = 1 for each), and myalgia (n = 2)
  - Serious TRAEs occurred in 2 (6.5%) patients, and were pneumonia (n = 1, 3.2%) and a prolonged QT (n = 1, 3.2%)
  - There were no grade ≥ 3 hematologic TRAEs
  - No dose discontinuations or death occurred due to TRAEs
- A total of 2/25 (8%) experienced a dose-limiting toxicity (DLT); these DLTs were arthritis and bone pain in one patient dosed at 40 mg twice daily (BID), and a prolonged QT interval in a patient dosed at 260 mg once daily (QD)

**Figure 3. Safety and tolerability of BMS-986458**

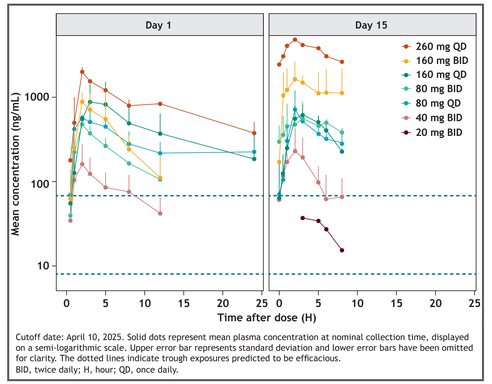



Cutoff date: April 10, 2025.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

### BMS-986458 pharmacokinetics

- BID and QD dosing of BMS-986458 produced efficacious exposures (**Figure 4**)

**Figure 4. BMS-986458 concentration at day 1 and day 15**

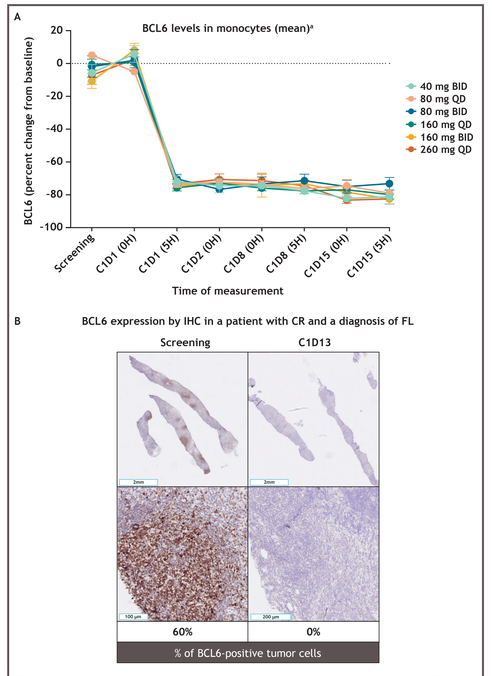



Cutoff date: April 10, 2025. Solid dots represent mean plasma concentration at nominal collection time, displayed on a semi-logarithmic scale. Upper error bar represents standard deviation and lower error bars have been omitted for clarity. The dotted lines indicate trough exposures predicted to be efficacious.
BID, twice daily; H, hour; QD, once daily.

### BCL6 degradation

- The maximum detectable degradation of BCL6 in peripheral blood was observed at all doses evaluated (**Figure 5A**)
- **Figure 5B** shows BCL6 expression by immunohistochemistry in a patient with complete response (CR)

**Figure 5. BMS-986458 induces rapid and sustained BCL6 degradation in peripheral blood (A) and in the tumor (B)**

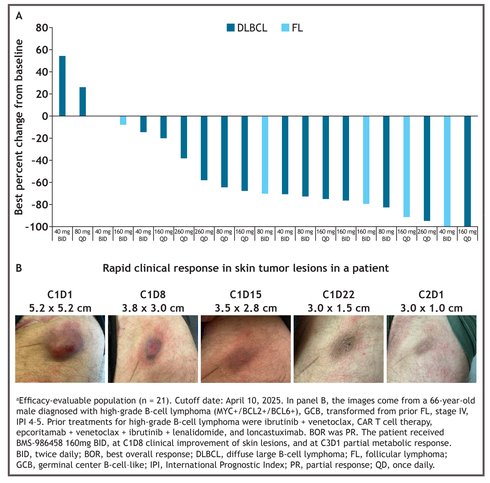



[a]The maximum detectable degradation of BCL6 during assay validation was 80%. Cutoff date: April 10, 2025.
BCL6, B-cell lymphoma 6; BID, twice daily; CR, complete response; C, cycle; D, day; FL, follicular lymphoma; H, hour; IHC, immunohistochemistry; QD, once daily.

### Preliminary efficacy

- The median follow-up for treated patients was 2.8 months (range, 0.3-11.7)
- The objective response rate (ORR) was 81.0% (17/21), with 5/21 (23.8%) patients achieving a CR and 12/21 (57.1%) patients achieving a partial response
  - One patient with triple-hit status achieved a CR
  - In patients with DLBCL, the ORR was 80% (n = 12) and the CR rate was 7% (n = 1); in patients with FL, the ORR was 83% (n = 5) and the CR rate was 67% (n = 4)
- Among responders, the median (range) time to first objective response was 1.77 (1.6-2.4) months, and the median (range) duration of response was 3.71 (1.15-not reached) months
- Individual patient tumor burden change from baseline is shown in **Figure 6A**
- Skin tumor lesions showed rapid clinical response in a patient with CR (**Figure 6B**)

**Figure 6. Deep responses across dose levels in patients[a] with DLBCL and FL (A) and change in size in skin lesion (B)**




[a]Efficacy-evaluable population (n = 21). Cutoff date: April 10, 2025. In panel B, the images come from a 66-year-old male diagnosed with high-grade B-cell lymphoma (*MYC*+/*BCL2*+/*BCL6*+), GCB, transformed from prior FL, stage IV, IPI 4-5. Prior treatments for high-grade B-cell lymphoma were ibrutinib + venetoclax, CAR T cell therapy, epcoritamab + venetoclax + ibrutinib + lenalidomide, and loncastuximab. BOR was PR. The patient received BMS-986458 160mg BID, at C1D8 clinical improvement of skin lesions, and at C3D1 partial metabolic response.
BID, twice daily; BOR, best overall response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell-like; IPI, International Prognostic Index; PR, partial response; QD, once daily.

## Conclusions

- BMS-986458 was well tolerated in patients with R/R NHL, with mainly low-grade adverse events, no grade ≥ 3 treatment-related cytopenias, and no treatment discontinuations due to TRAEs
- BMS-986458 induced rapid and sustained degradation of BCL6 in peripheral blood and in the tumor
- Strong antitumor activity was confirmed in heavily pretreated patients with DLBCL and FL
  - Response rates were favorable, with an ORR of 81% (80% in DLBCL and 83% in FL) and a CR rate of approximately 24% (7% in DLBCL and 67% in FL)
- Overall, in these initial phase 1 results, BMS-986458 showed promising preliminary efficacy and acceptable tolerability in heavily pre-treated R/R DLBCL and FL, supporting its continued development as monotherapy or combination therapy for NHL

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