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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: updated results from the phase 1 dose-escalation study

Franck Morschhauser,¹ David Qualls,² Jennifer Lue,³ Anastasios Stathis,⁴ Marcel Nijland,⁵ Avyakta Kallam,⁶ Jörg Bittenbring,⁷ Guillaume Cartron,⁸ Noémie Lang,⁹ Marjolein van der Poel,¹⁰ Loïc Ysebaert,¹¹ Vladan Vučinić,¹² Alejandro Martin García-Sancho,¹³ Antonio Rueda Dominguez,¹⁴ Noelia Purroy,¹⁵ Berengere de Moucheron,¹⁶ Xiaosong Li,¹⁵ Carla Guarinos,¹⁶ Joseph Burnett,¹⁵ Alicia Benítez Rondán,¹⁶ Michael Pourdehnad,¹⁷ Jessica Voetsch,¹⁵ Diego Sobradillo,¹⁶ Jean-Marie Michot¹⁸

¹Hôpital Claude Huriez - CHU de Lille, Lille, France; ²Dana-Farber Cancer Institute, Boston, MA, USA; ³Memorial Sloan Kettering Cancer Center, New York, NY, USA; ⁴Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland; ⁵University Medical Center Groningen, Groningen, The Netherlands; ⁶City of Hope Comprehensive Cancer Center, Duarte, CA, USA; ⁷Universitätsklinikum des Saarlandes, Homburg, Germany; ⁸CHU, Montpellier, UMR-CNRS 5535, Montpellier, France; ⁹Hôpitaux Universitaires de Genève (HUG), Geneva, Switzerland; ¹⁰Maastricht University Medical Center, Maastricht, The Netherlands; ¹¹Institut Claudius Regaud, Toulouse, France; ¹²Universitätsklinikum Leipzig, Leipzig, Germany; ¹³Hospital Universitario de Salamanca, Salamanca, Spain; ¹⁴Hospital Universitario Virgen de la Victoria, Málaga, Spain; ¹⁵Bristol Myers Squibb, Princeton, NJ, USA; ¹⁶Bristol Myers Squibb, Center for Innovation and Translational Research Europe (CITRE), Seville, Spain; ¹⁷Bristol Myers Squibb, Early Clinical Development, Hematology/Oncology and Cell Therapy, San Francisco, CA, USA; ¹⁸Institut Gustave Roussy, Villejuif, France

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Introduction

- Approximately 20%-50% of patients with DLBCL or FL experience R/R disease, which is associated with poor outcomes¹⁻³
- BCL6 is a transcriptional repressor required for tolerance of Ig hypermutation and normal B-cell maturation; it inhibits cell cycle arrest and DNA damage checkpoints, and prevents apoptosis⁴
- Along with BCL2 and c-Myc, BCL6 is one of the most frequently genetically misregulated proteins in DLBCL (~20%-40%)^{4,5}
- BMS-986458 is an oral, highly selective bifunctional cereblon-dependent LDD of BCL6⁶
- Here, we present updated 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 NHL

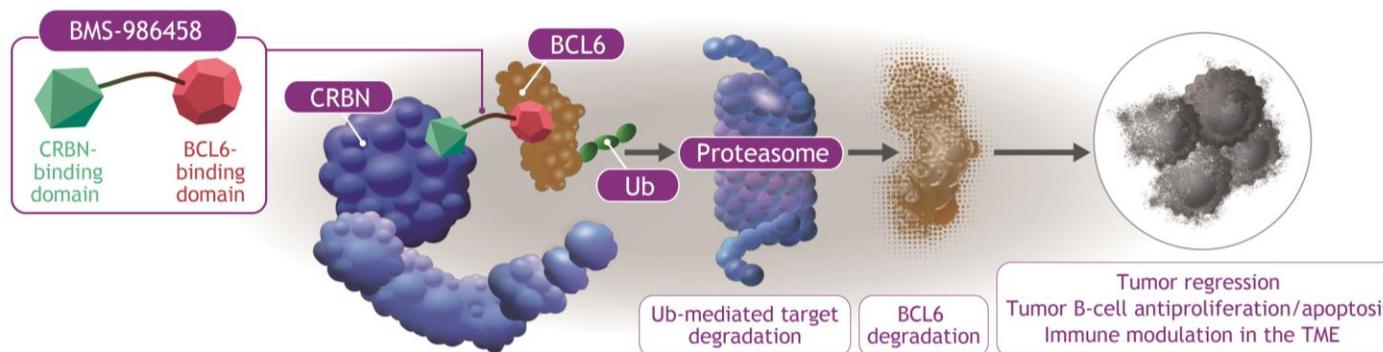
BCL2, B-cell lymphoma/leukemia 2; BCL6, B-cell lymphoma 6; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; Ig, immunoglobulin; LDD, ligand-directed degrader; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory.

1. Coiffier B, et al. *Blood* 2010;116:2040-2045. 2. Casulo C, et al. *J Clin Oncol* 2015;33:2516-2522. 3. Crump M, et al. *Blood* 2017;130:1800-1808. 4. Basso K and Dalla-Favera R. *Nat Rev Immunol* 2015;15:172-184. 5. Grau M, et al. *Best Pract Res Clin Haematol* 2023;36:101513. 6. Grocock L, et al. Oral presentation at the American Society of Hematology (ASH) Annual Meeting 2024; December 5-10, 2024; San Diego, CA, USA. Abstract 957.

BMS-986458 is a first-in-class, highly selective, BCL6 ligand-directed degrader¹

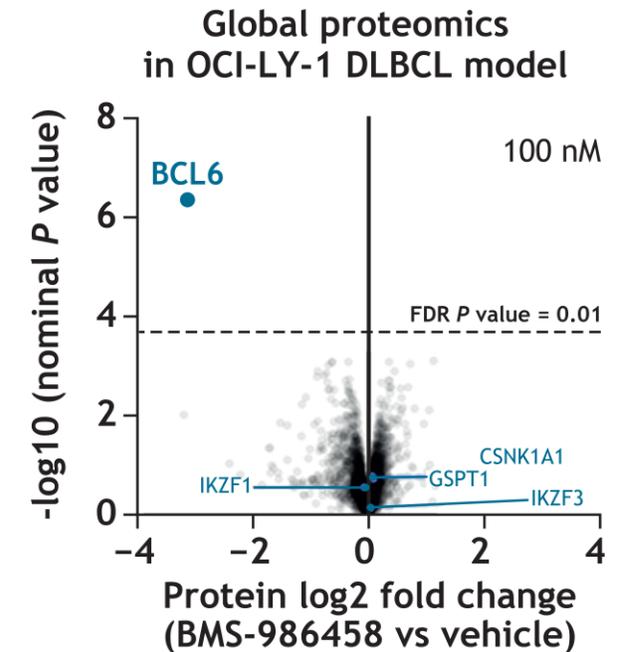
BMS-986458 mediates degradation of BCL6

- BMS-986458 is a hetero-bifunctional LDD that degrades BCL6 through CRBN E3 ligase recruitment, ubiquitination, and subsequent proteolytic processing by the proteasome
 - This results in anti-proliferation and apoptosis of tumor B cells, and immune modulation
 - In vitro, BMS-986458 modulates Tfh and Treg cells towards more effector-like phenotype without affecting cell viability



BMS-986458 is highly BCL6 selective

- Rapid and highly selective BCL6 degradation is observed with BMS-986458 in OCI-LY-1 cells



BCL6, B-cell lymphoma 6; CRBN, cereblon; CUL4A, cullin 4A; DDB1, DNA damage-binding protein 1; DLBCL, diffuse large B-cell lymphoma; DMSO, dimethyl sulfoxide; FDR, false discovery rate; GSPT1, G1 to S phase transition 1; IKZF1, Ikaros; IKZF3, Aiolos; LDD, ligand-directed degrader; nM, nonmolar; RBX1, RING-box protein 1; Tfh, T follicular helper; TME, tumor microenvironment; Treg, regulatory T; Ub, ubiquitin; μ M, micromolar.

1. Grocock L, et al. Oral presentation at the American Society of Hematology (ASH) Annual Meeting 2024; December 5-10, 2024; San Diego, CA, USA. Abstract 957.

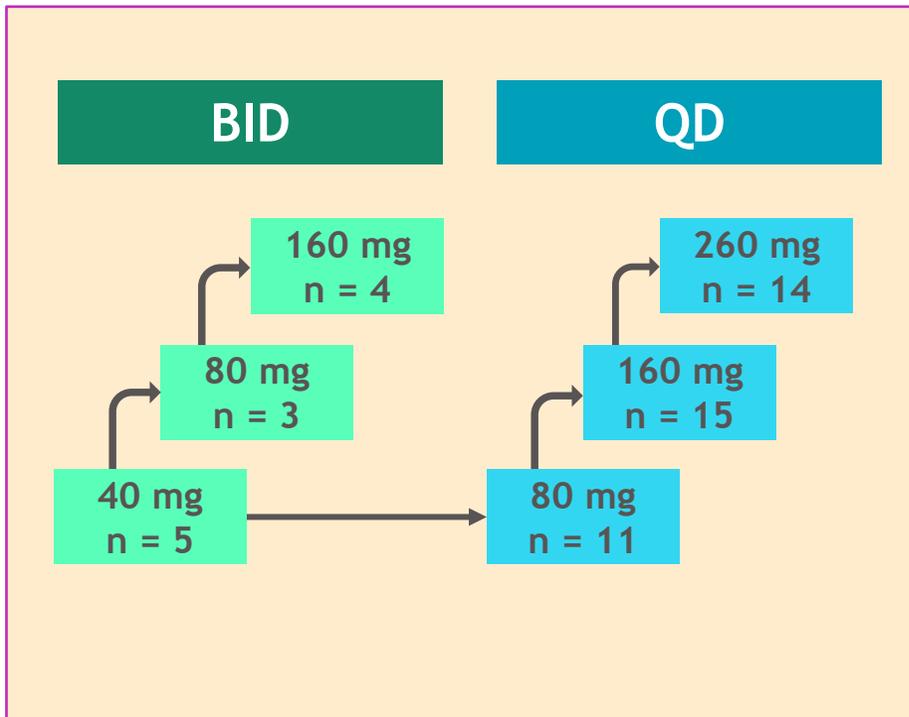
Phase 1/2 study (CA123-1000): dose escalation of BMS-986458 in patients with R/R NHL¹

- Phase 1/2 study includes multiple monotherapy and combination escalation and expansion cohorts across NHL

Key inclusion criteria

- Patients with R/R DLBCL with ≥ 2 prior regimens
 - Patients who exhausted or were ineligible for available therapy (including CAR T cell therapy and bispecific mAbs) or were unwilling to receive them
- Patients with R/R FL with ≥ 2 prior regimens
- Measurable disease, as defined by the Lugano classification of NHL²

Single-agent escalation: part A1 (N = 52)



Objectives

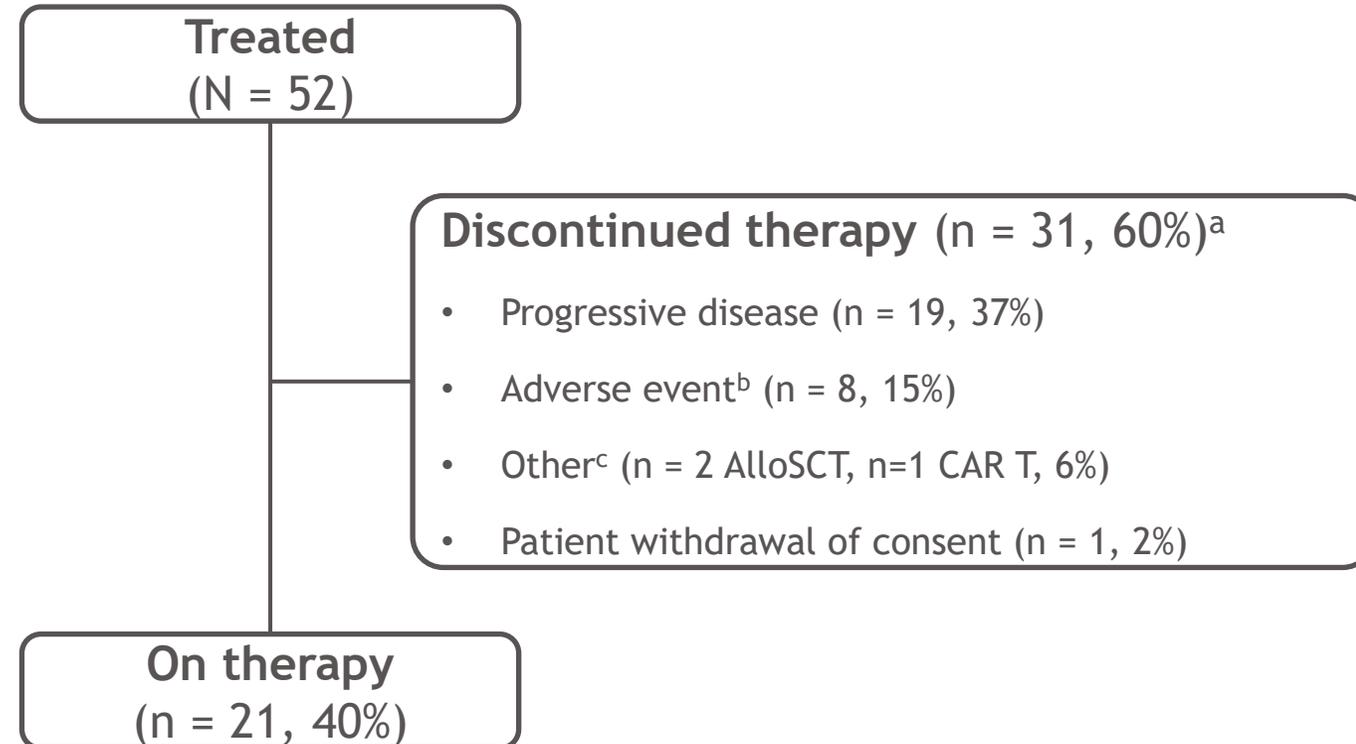
- Primary:** to evaluate the safety and tolerability of BMS-986458 and determine the RP2D
- Secondary:** to characterize BMS-986458 plasma PK and assess preliminary efficacy^a

Cutoff date: September 26, 2025. ^aThe 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.

BID, twice daily; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; mAb, monoclonal antibody; NHL, non-Hodgkin lymphoma; PK, pharmacokinetics; QD, once daily; R/R, relapsed/refractory; RP2D, recommended phase 2 dose.

1. ClinicalTrials.gov. NCT06090539. <https://www.clinicaltrials.gov/study/NCT06090539>. Accessed September 9, 2025. 2. Cheson BD, et al. *J Clin Oncol* 2014;32:3059-3068.

Patient disposition



- Median follow-up was 4.29 months (range, 0.4-17.1)

Cutoff date: September 26, 2025. ^aAt the April 10, 2025 data cutoff, one death was listed as a reason for discontinuation. This has been reclassified as an adverse event. ^b6 were due to treatment-emergent adverse events (thrombocytopenia, hypercalcemia, secondary primary malignancy, peripheral neuropathy, respiratory failure, and hypovolemic shock [n = 1 each]), 2 were due to treatment-related adverse events (peripheral neuropathy and arthralgia [n = 1 each]). ^cThree patients, all of whom achieved a response, discontinued therapy and underwent allogeneic stem cell transplant (n = 2) or chimeric antigen receptor T cell therapy (n = 1).

Patient characteristics: a heavily pre-treated population was enrolled

N = 52	
Age, years, median (range)	63 (26-85)
Sex, n (%)	
Female	16 (31)
Male	36 (69)
Disease stage at entry, n (%)	
Stage I	1 (2)
Stage II	5 (10)
Stage III	12 (23)
Stage IV	31 (60)
Unknown	3 (6)
Disease type ^a , n (%)	
DLBCL (not otherwise specified) ^b	23 (44)
DLBCL/HGBCL with MYC and BCL2 rearrangements ^c	8 (15)
FL	21 (40)
Cell of origin (DLBCL/HGBCL), n/N (%)	
ABC, non-GCB	7/31 (23)
GCB	10/31 (32)
Unknown	14/31 (45)
ECOG PS, n (%)	
0	22 (42)
1	29 (56)
2	1 (2)

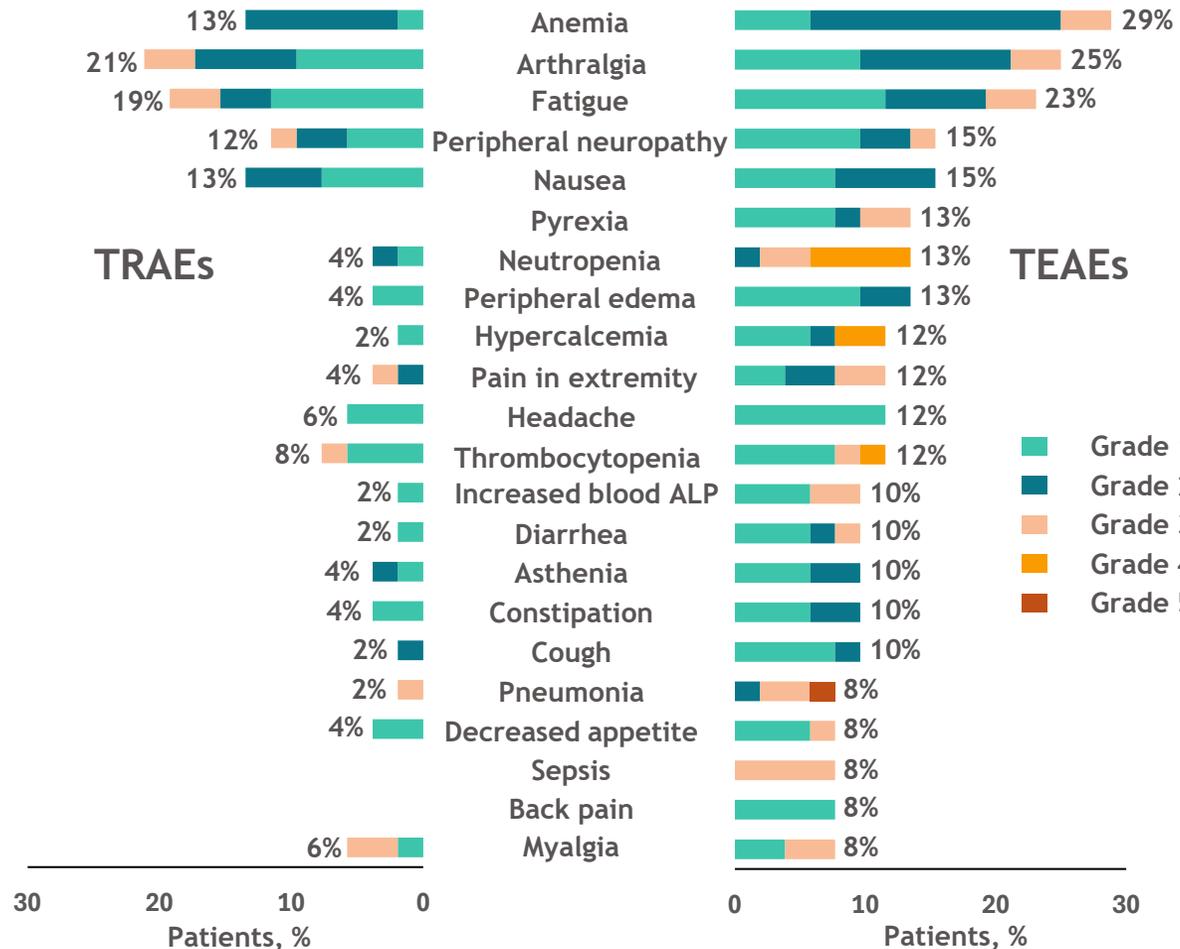
N = 52	
Risk category for IPI (DLBCL), n/N (%)	
High (3-5)	9/24 (38)
Low-intermediate (2)	9/24 (38)
Low (0-1)	3/24 (13)
Not reported	3/24 (13)
Risk category for FLIPI (FL), n/N (%)	
High (3-5)	9/19 (47)
Intermediate (2)	4/19 (21)
Low (0-1)	2/19 (11)
Unknown	4/19 (21)
Prior lines of therapy, n (%)	
2	6 (12)
3	13 (25)
≥ 4	33 (63)
Median prior lines of therapy, n (range)	
DLBCL (n = 24)	5 (2-12)
FL (n = 19)	4 (2-9)
Types of prior anticancer therapy, n (%)	
CAR T cell therapy	32 (62)
Bi-/tri-specific mAb	30 (58)
CAR T and bi-/tri-specific mAb	19 (37)
IMiD/CELMoD™ agent	31 (60)
Refractory to prior therapy, n (%)	33 (63)
Bulky disease, n (%)	
≥ 7 cm	13 (25)
≥ 10 cm	8 (15)

Cutoff date: September 26, 2025. ^aTwo patients with HGBCL were entered after data cutoff. ^bTwelve patients had transformed DLBCL (FL, n = 7; MZL, n = 2; NPL-HL, n = 2; CLL, n = 1).

^cA total of 6/8 patients had triple-hit status; 2/8 patients had double-hit status. ABC, activated B-cell-like; CLL, chronic lymphocytic leukemia; 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; HGBCL, high-grade B-cell lymphoma; IMiD, immunomodulatory imide drug; IPI, International Prognostic Index; mAb, monoclonal antibody; MZL, marginal zone lymphoma; NPL-HL, nodular lymphocyte-predominant Hodgkin lymphoma.

Safety and Tolerability of BMS-986458

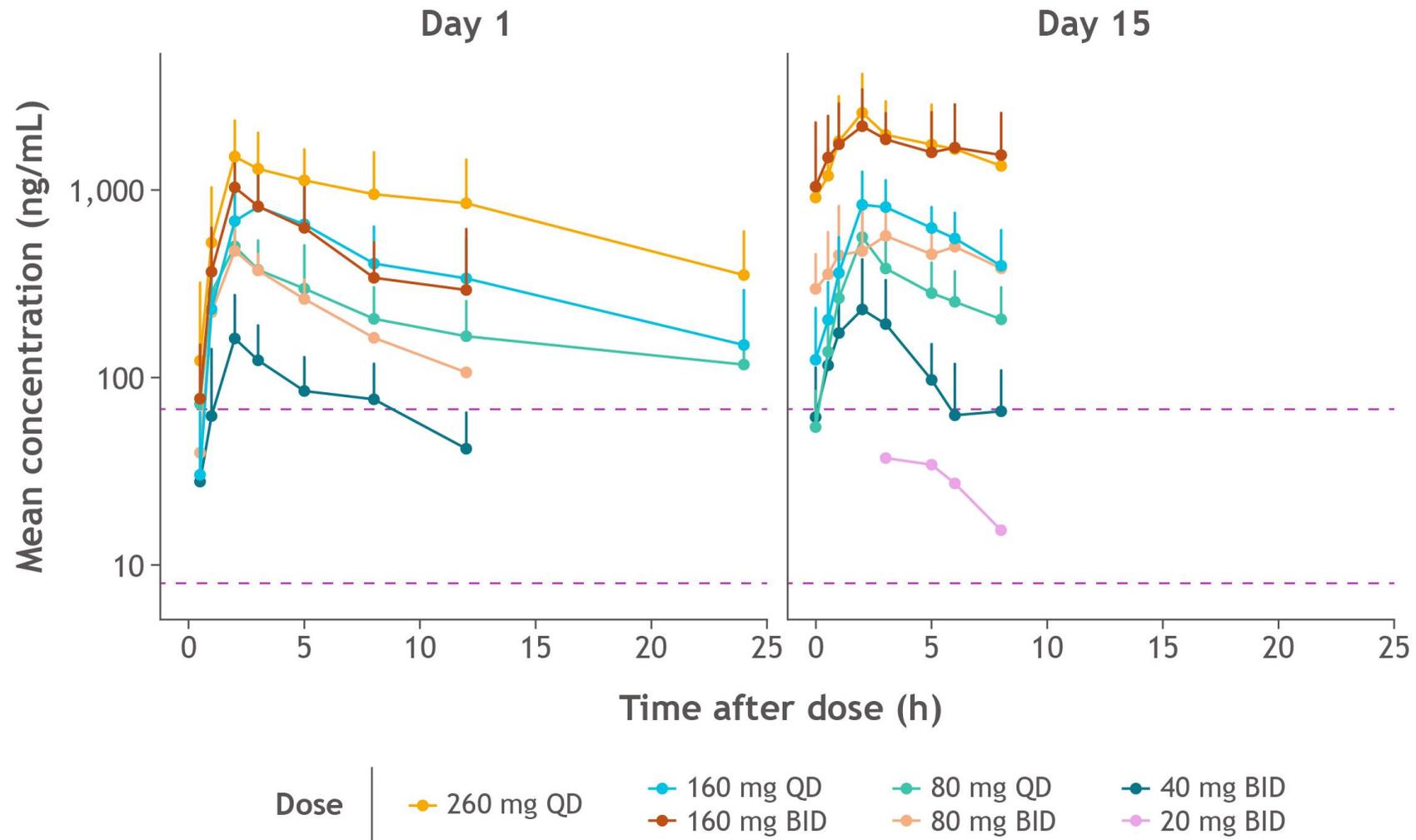
Most frequent TRAEs and TEAEs (≥ 4 patients in either category)^a



- The most frequent TRAEs were arthralgia (21%) and fatigue (19%)^b
 - Grade 3/4 TRAEs occurred in 23.1% of patients
 - Serious TRAEs occurred in 2 (4%) patients^c
 - No grade 4 treatment-related cytopenia was reported
- The most common TRAEs that led to treatment interruption or reductions were within the SOC of musculoskeletal and connective tissue disorders (n = 7, 13%) and included arthralgia, myalgia^d, pain in extremity, arthritis^e, and bone pain^e
- TRAEs led to 2 (4%) treatment discontinuations
 - Peripheral neuropathy and arthralgia (n = 1 each)
- There were no deaths due to TRAEs
- 2/47^f (4%) patients experienced a DLT^g

Cutoff date: September 26, 2025. ^an = 52 treated patients. ^bThe most frequent TRAEs per SOC were musculoskeletal and connective tissue disorders (35%), general disorders and administration site conditions (27%), and nervous system disorders (27%). ^cSerious TRAEs were pneumonia and prolonged QT interval (n = 1 each). ^dTwo myalgia events occurred in the same patient. ^eArthritis and bone pain occurred in the same patient. ^fn = 47 DLT-evaluable patients. ^gDLTs were arthritis and bone pain in 1 patient dosed at 40 mg BID, and a prolonged QT interval in a patient dosed at 260 mg QD. ALP, alkaline phosphatase; BID, twice daily; DLT, dose-limiting toxicity; QD, once daily; SOC, System Organ Class; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

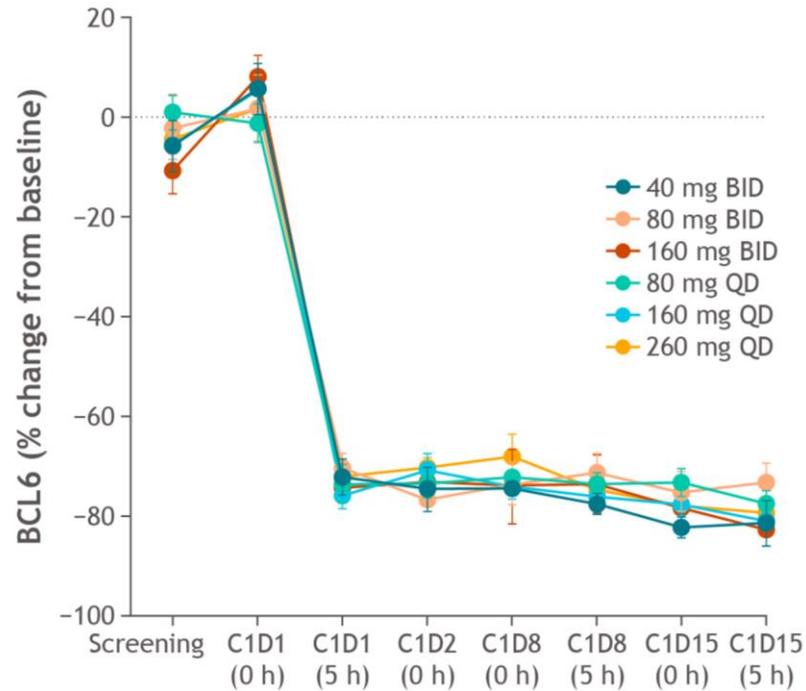
BID and QD dosing of BMS-986458 achieved exposures above the preclinical efficacy benchmark on day 1 and at steady state



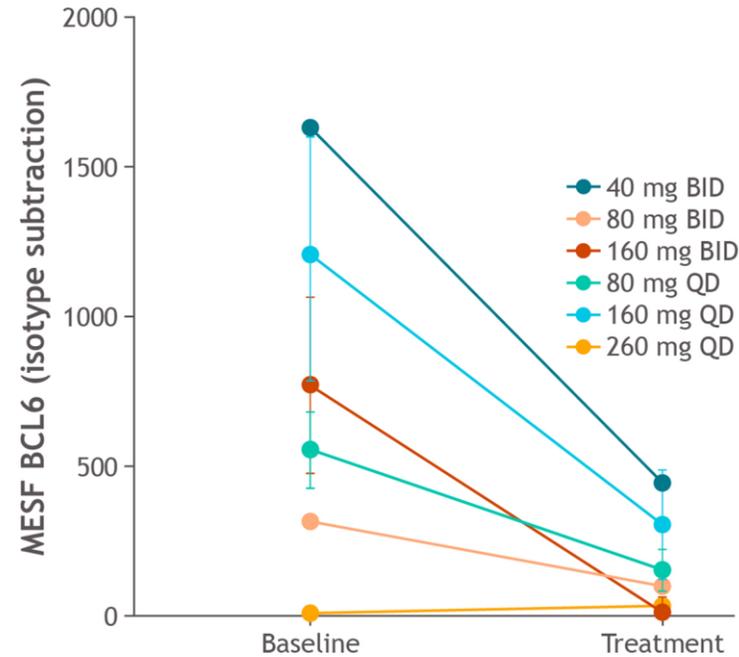
Cutoff date: September 11th, 2025. Solid dots represent mean plasma concentration at nominal collection time, displayed on a semi-logarithmic scale. Upper error bar represents standard deviation and lower error bars have been omitted for clarity. The dotted lines indicate trough exposures predicted to be efficacious. BID, twice daily; h, hour; QD, once daily.

BMS-986458 induces rapid and sustained BCL6 degradation in both peripheral blood and the tumor

BCL6 degradation in peripheral blood monocytes by flow cytometry



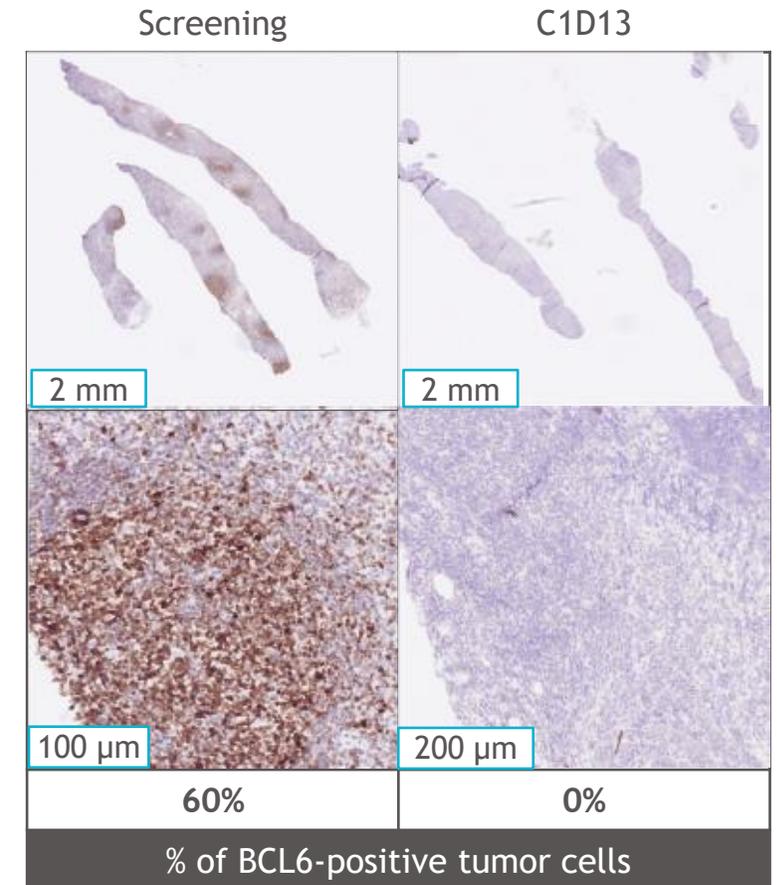
BCL6 degradation in tumoral B cells (from FNA samples) by flow cytometry



Baseline: screening samples. Treatment: C1D15 + 3 days, except pt71 (C1D10) and pt59 (C2D1), both received 160 mg BID, collected out of window

- The maximum detectable degradation of BCL6 in peripheral blood was observed at all doses evaluated^a

BCL6 expression by IHC in a patient with CR and a diagnosis of FL



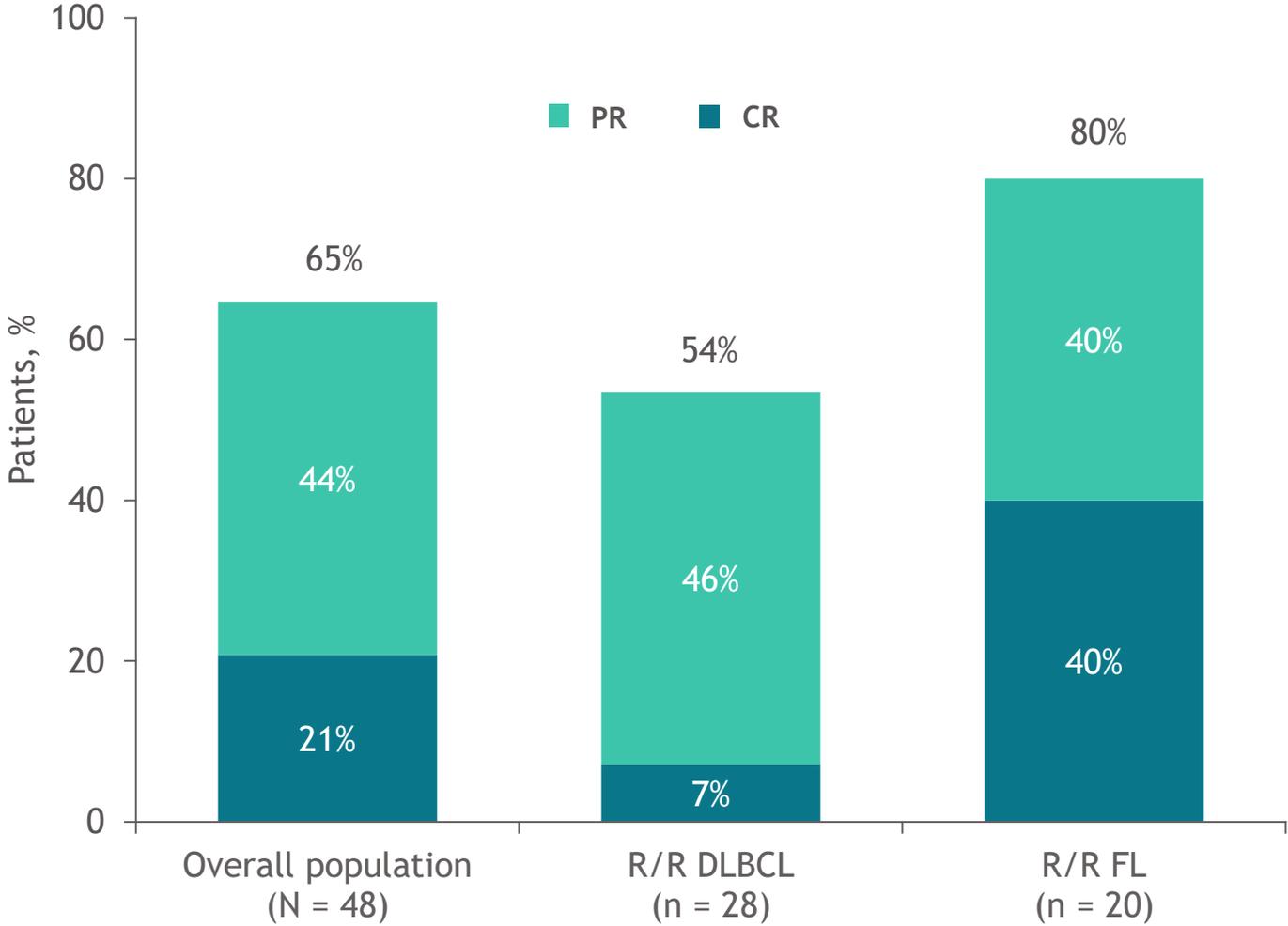
As of October 2025. ^aThe maximum detectable degradation of BCL6 during assay validation via flow cytometry was 80%.

BCL6 degradation in peripheral blood monocytes and tumoral B cells was determined by flow cytometry.

BCL6, B-cell lymphoma 6; BID, twice daily; C, cycle; CR, complete response; D, day; FL, follicular lymphoma; FNA, fine-needle aspiration; H, hour; IHC, immunohistochemistry; MESF, molecules of equivalent soluble fluorescein; QD, once daily; SCR, screening.

BMS-986458 achieved a high ORR in a heavily pre-treated population with DLBCL and FL

ORR across dose levels^a

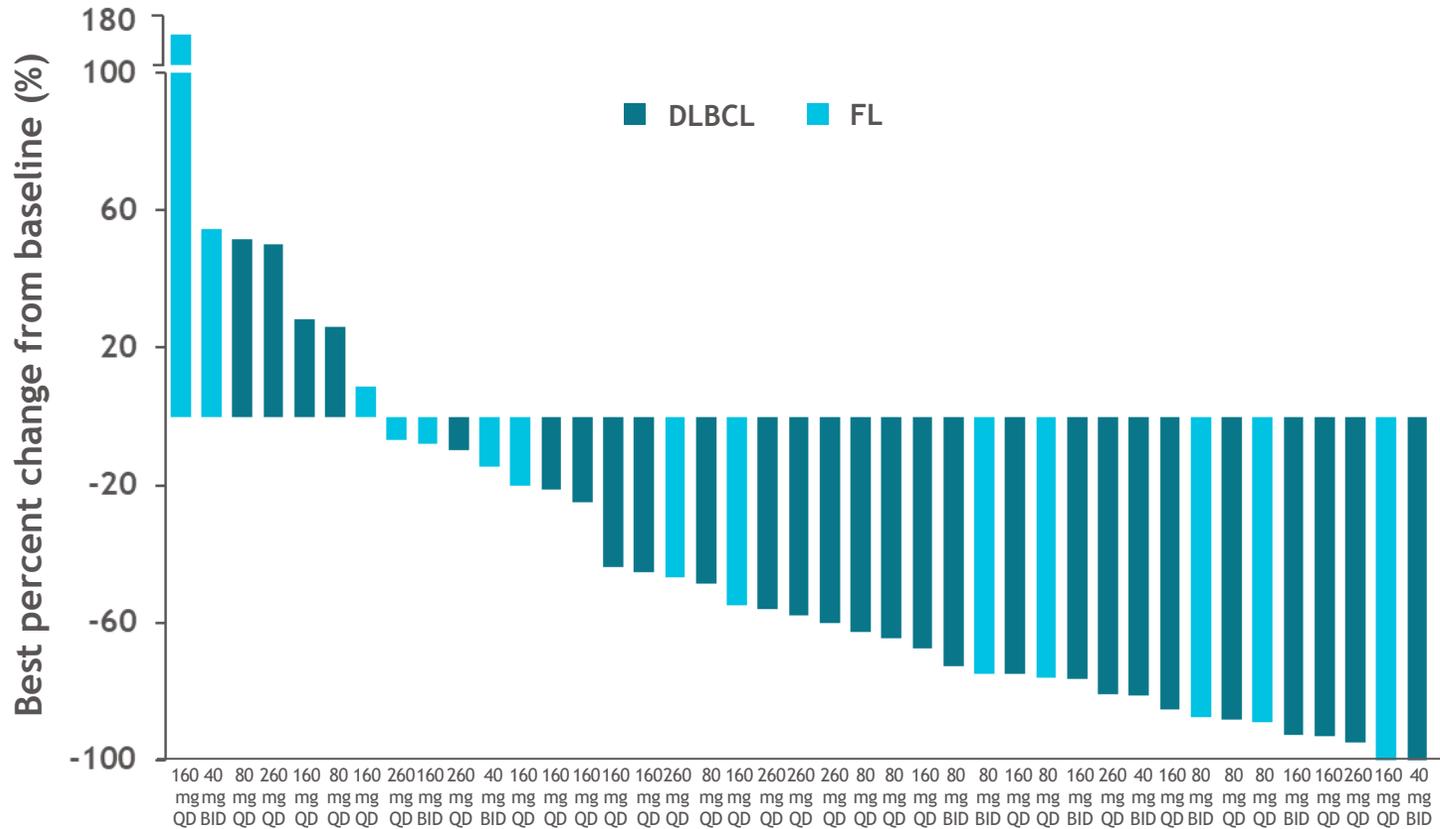


- Among responders, the median (range):
 - Time to first response: 1.8 months (1.0-2.4)
 - Duration of response: 5.8 months (0-11.7)
 - Duration of CR: NR (0-11.7)
- Responses were observed across subgroups of interest, including Prior CAR-T cell therapy, HGBCL, tDLBCL, GCB/non-GCB, and BCL6 expression

Cutoff date: November 6, 2025. ^aEfficacy-evaluable patients. BCL6, B-cell lymphoma 6; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; GCB, germinal center B-cell-like; HGBCL, high-grade B-cell lymphoma; NR, not reached; ORR, objective response rate; PR, partial response; R/R, relapsed/refractory; tDLBCL, transformed DLBCL.

BMS-986458 produced deep responses in both DLBCL and FL across dose levels

Best tumor burden change from baseline in patients with DLBCL and FL



Cutoff date: September 26, 2025. ^aEfficacy-evaluable patients.

BCL6, B-cell lymphoma 6; BID, twice daily; BOR, best overall response; CMR, complete metabolic response;

CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma;

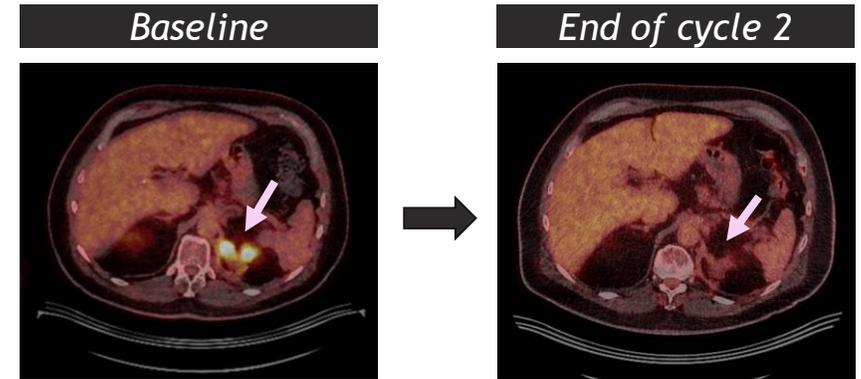
GCB, germinal center B-cell-like; HGBCL, high-grade B-cell lymphoma; ORR, objective response rate; PD, progressive disease; PMR, partial metabolic response; PR, partial response;

QD, once daily; R/R, relapsed/refractory.

Example of metabolic responses in DLBCL

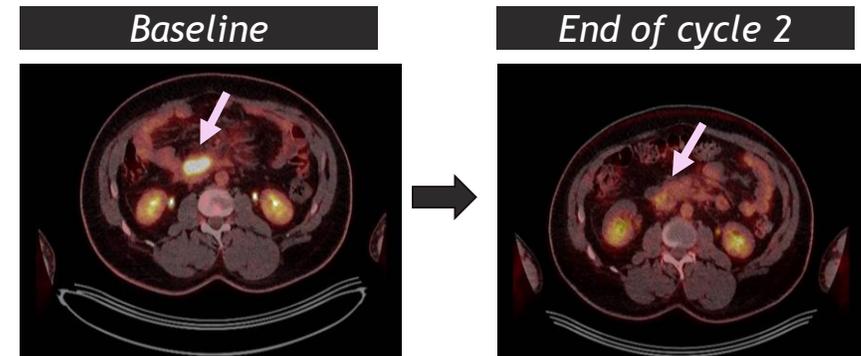
R/R DLBCL, 260 mg QD, 4 prior lines of therapy

- Liso-cel (BOR: CMR), glofitamab (BOR: PMR)



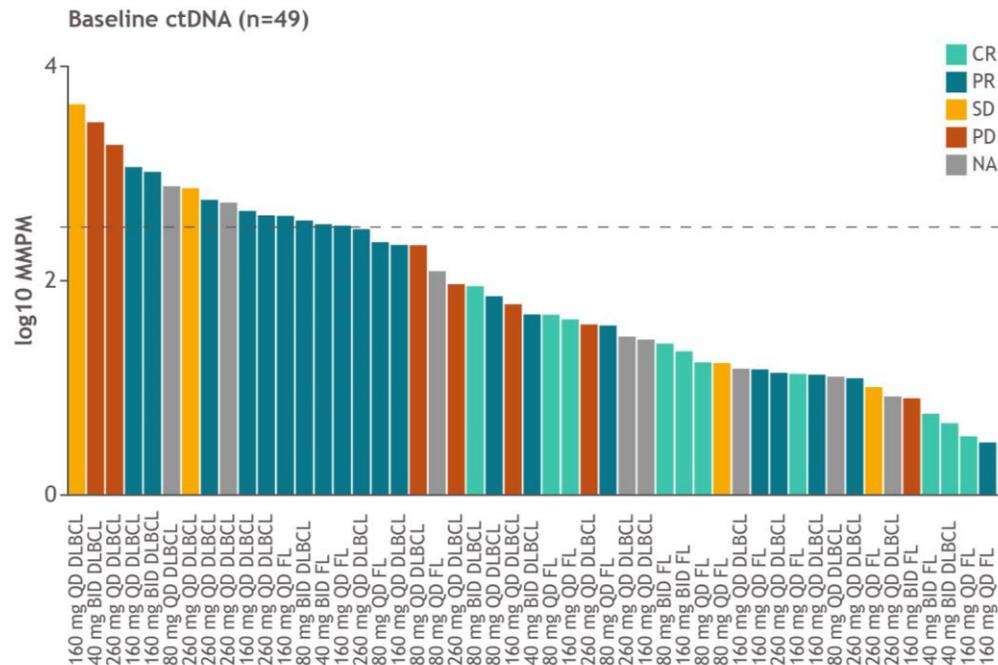
R/R DLBCL, 260 mg QD, 3 prior lines of therapy

- Axi-cel (BOR: PD)



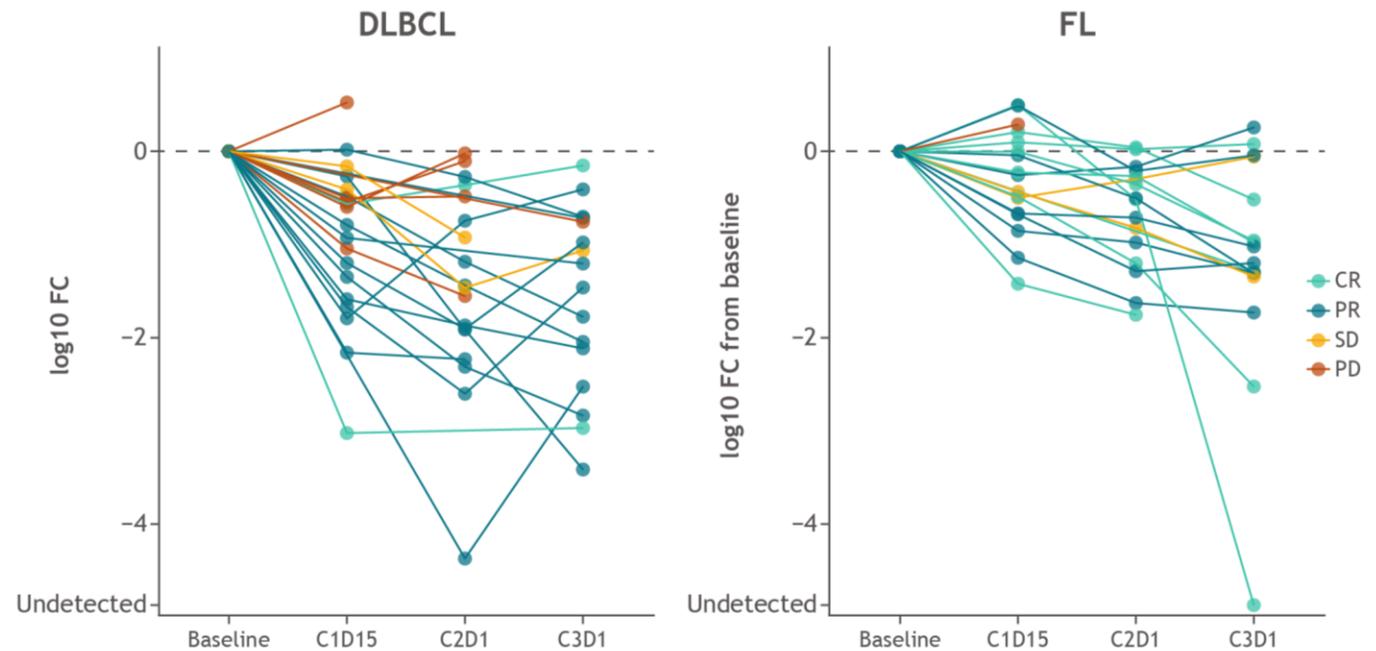
BMS-986458 achieved responses regardless of baseline ctDNA and induced rapid reductions in ctDNA

Responses were observed regardless of baseline ctDNA levels



- Among 49 patients with available ctDNA data, 15 (31%) had high tumor burden^a at baseline
- 60% (9/15) of patients with high tumor burden achieved a response

Rapid reductions in ctDNA were observed in patients with DLBCL and FL



- Reductions in ctDNA were generally associated with clinical response, particularly in DLBCL
- MRD negativity^b was achieved in 3 patients (2 DLBCL and 1 FL)

As of October 2025. ^aDefined as $> 2.5 \log_{10}$ of tumor-specific mutant sequence. ^bUndetectable ctDNA (1×10^{-4} threshold) by CAPP-Seq assay. BCL6, B-cell lymphoma 6; BID, twice daily; Bsln, baseline; C, cycle; CR, complete response; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; FC, fold change; FL, follicular lymphoma; MMPM, mutant molecules per million; MRD, minimal residual disease; NA, not applicable; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease.

Conclusions

- BMS-986458 was tolerable in patients with R/R NHL
 - The most common TRAEs that led to treatment interruption or reductions were within the SOC of musculoskeletal and connective tissue disorders (n = 7, 13%)
 - No grade 4 treatment-related cytopenia was reported
- BMS-986458 induced a rapid and sustained degradation of BCL6 in peripheral blood and the tumor
- Strong antitumor activity was confirmed in heavily pre-treated patients with DLBCL and FL
 - Response rates were favorable, with an ORR of 65% (54% in DLBCL and 80% in FL) and a CR rate of 21% (7% in DLBCL and 40% in FL)
 - Responses were achieved regardless of baseline ctDNA levels, and rapid ctDNA reductions were observed
- Overall, in these updated phase 1 results, BMS-986458 continued to show 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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