BMS-986458, a first-in-class, highly selective, and potent ligand-directed degrader (LDD) of B-cell lymphoma 6 (BCL6) combined with T-cell engagers (TCEs) demonstrates preclinical synergistic antitumor efficacy for the treatment of B-cell non-Hodgkin lymphoma (NHL)

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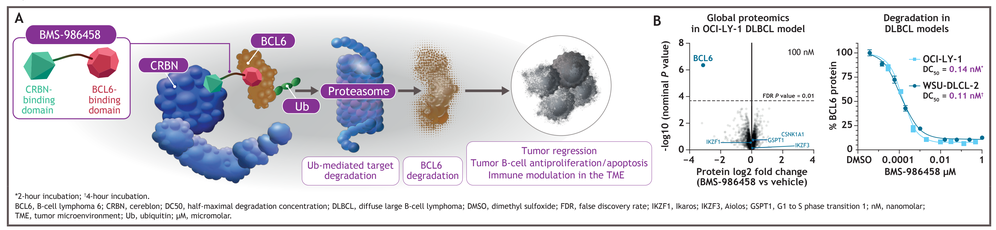
Background

- Up to half of patients with diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL) experience relapse or have treatment-refractory disease, which are associated with poor prognosis[1-3]
- BCL6 is a transcriptional repressor required for tolerance of immunoglobulin hypermutation and normal B-cell maturation[4]
  - In DLBCL and FL, BCL6 is misregulated in approximately 15%-40% of cases, leading to increased proliferation and apoptosis resistance in the tumor cells[4,5]
- BMS-986458 is a first-in-class, oral, highly selective bifunctional cereblon (CRBN)-dependent LDD of BCL6 (**Figure 1A** and **1B**)
  - BMS-986458-mediated BCL6 degradation occurs through recruitment of the CRBN E3 ligase, ubiquitination, and subsequent proteolytic processing by the proteasome[6]
  - BMS-986458-mediated degradation of BCL6 leads to anti-proliferation and apoptosis of tumor B cells, and immune modulation[6]
    - In vitro, BMS-986458 phenotypically modulates T follicular helper (Tfh) and T regulatory cells without affecting cell viability[6]
  - In an ongoing phase 1/2 trial (NCT06090539), BMS-986458 has shown promising preliminary efficacy and acceptable tolerability in heavily pretreated patients with relapsed/refractory DLBCL and FL[7]
- In BCL6-expressing NHL models, BMS-986458 potently and rapidly degraded BCL6, modulated lymph-resistant Tfh cells, and enhanced the expression and surface clustering of cluster of differentiation (CD)20, leading to antitumor activity[6]
  - The immunomodulatory properties of BMS-986458 together with enhanced CD20 surface expression led to an observed synergistic effect when combined with rituximab in relapsed or refractory NHL[6]

Figure 1. BMS-986458 mechanism of action[6]

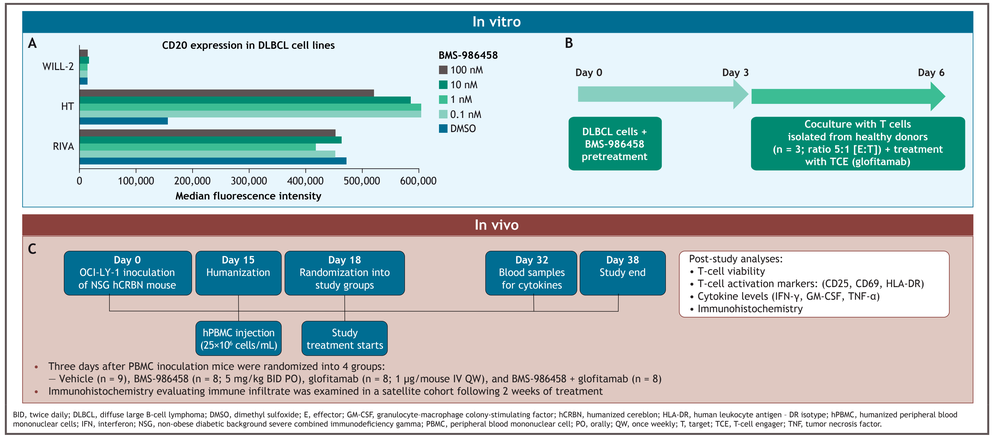


*2-hour incubation; †4-hour incubation.
BCL6, B-cell lymphoma 6; CRBN, cereblon; DC50, half-maximal degradation concentration; DLBCL, diffuse large B-cell lymphoma; DMSO, dimethyl sulfoxide; FDR, false discovery rate; IKZF1, Ikaros; IKZF3, Aiolos; GSPT1, G1 to S phase transition 1; nM, nanomolar; TME, tumor microenvironment; Ub, ubiquitin; µM, micromolar.

Methods

- This study aimed to evaluate the antitumor synergy of BMS-986458 when combined with TCEs in preclinical models of NHL, both in vitro and in vivo (**Figure 2A-C**)
- Of the NHL cell lines tested, WILL-2, a BCL6-negative activated B-cell model, exhibited low expression of CD20 at baseline (**Figure 2A**) and was consequently selected as a key cell line of interest for evaluation of the synergy of BMS-986458 and TCE in vitro

Figure 2. Study design



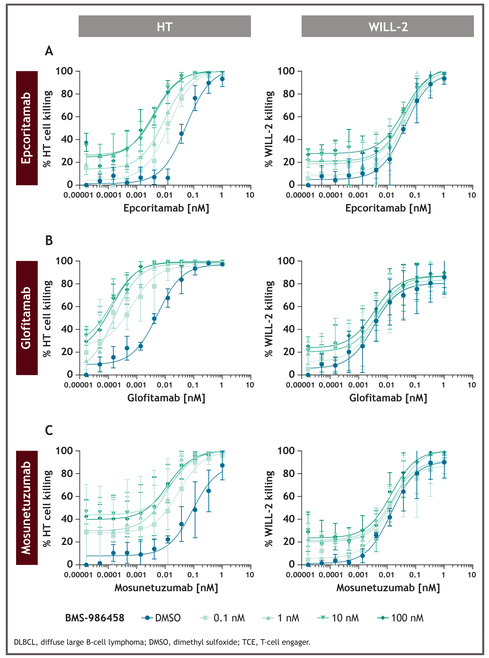
BID, twice daily; DLBCL, diffuse large B-cell lymphoma; DMSO, dimethyl sulfoxide; E, effector; GM-CSF, granulocyte-macrophage colony-stimulating factor; hCRBN, humanized cereblon; HLA-DR, human leukocyte antigen – DR isotype; hPBMC, humanized peripheral blood mononuclear cells; IFN, interferon; NSG, non-obese diabetic background severe combined immunodeficiency gamma; PBMC, peripheral blood mononuclear cell; PO, orally; QW, once weekly; T, target; TCE, T-cell engager; TNF, tumor necrosis factor.

Results

In vitro

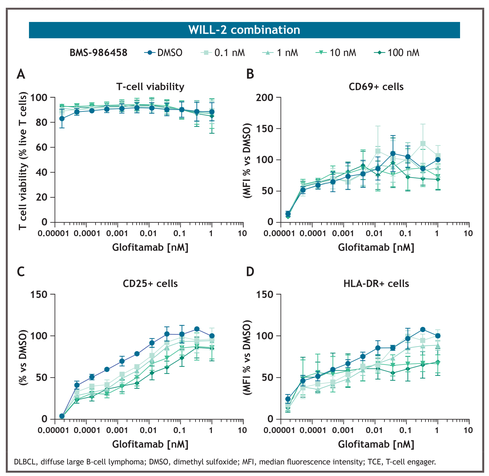
- Tumor cell killing assays evaluating the synergy of BMS-986458 with CD20xCD3 TCEs (glofitamab, epcoritamab, and mosunetuzumab) in DLBCL cell lines revealed HT cells had the highest synergistic response (**Figure 3**)
  - HT cells had the largest CD20 fold-induction from baseline
- Responses to BMS-986458 with CD20xCD3 TCEs were milder in RIVA cells
  - RIVA cells had higher CD20 baseline expression than HT cells, but a smaller fold-change following treatment
- WILL-2 cells had very mild antitumor response and combination synergy
- BMS-986458 + glofitamab did not significantly impact T-cell viability (**Figure 4A**) or expression of T-cell activation markers CD25, CD69 during coculture with WILL-2 cells vs glofitamab + dimethyl sulfoxide control (**Figure 4B** and **C**); there was a small decrease in human leukocyte antigen - DR isotype (HLA-DR, **Figure 4D**)

Figure 3. Impact of BMS-986458 + TCE on tumor cell killing in DLBCL cells



DLBCL, diffuse large B-cell lymphoma; DMSO, dimethyl sulfoxide; TCE, T-cell engager.

Figure 4. Effect of BMS-986458 + TCE on T-cell viability and T-cell activation in DLBCL cells

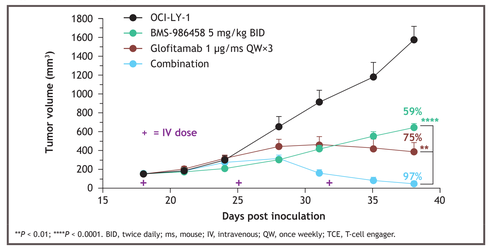


DLBCL, diffuse large B-cell lymphoma; DMSO, dimethyl sulfoxide; MFI, median fluorescence intensity; TCE, T-cell engager.

In vivo

- In humanized (h)DLBCL and peripheral blood mononuclear cell (PBMC) hCRBN non-obese diabetic background severe combined immunodeficiency gamma (NSG) xenografts, monotherapy with BMS-986458 or glofitamab led to a 59% and 75% tumor volume reduction, respectively, vs the OCI-LY-1 control (**Figure 5**)
  - BMS-986458 + glofitamab led to a synergistic reduction in tumor volume of 97% vs the OCI-LY-1 control
  - Six of 8 mice treated with the combination of BMS-986458 + glofitamab were tumor-free at the end of treatment

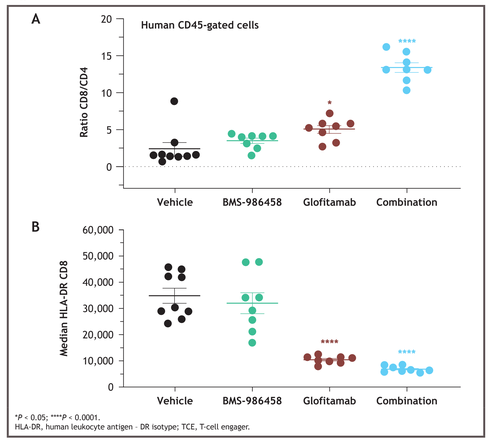
Figure 5. Synergy and tolerability of BMS-986458 + TCE in vivo



**P < 0.01; ****P < 0.0001. BID, twice daily; ms, mouse; IV, intravenous; QW, once weekly; TCE, T-cell engager.

- At study end, peripheral blood samples showed increased T-cell expansion and CD8/CD4 ratio with the combination of BMS-986458 + glofitamab vs BMS-986458 or glofitamab monotherapy (**Figure 6A**)
- HLA-DR expression on CD8 T cells was significantly reduced in the glofitamab monotherapy and BMS-986458 + glofitamab groups (**Figure 6B**), consistent with in vitro observations
  - No changes in HLA-DR expression occurred with BMS-986458 alone vs vehicle

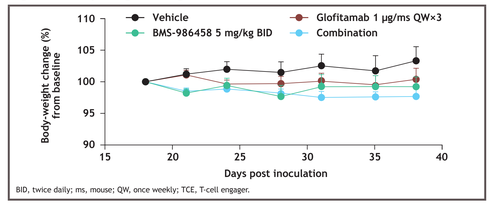
Figure 6. Immunomodulatory effects of BMS-986458 + TCE in vivo



*P < 0.05; ****P < 0.0001.
HLA-DR, human leukocyte antigen – DR isotype; TCE, T-cell engager.

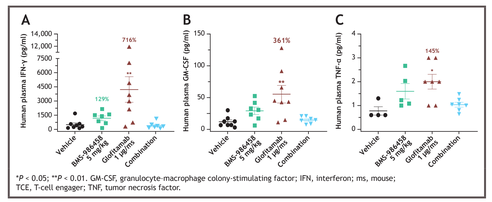
- The BMS-986458 + TCE combination was well tolerated, with no significant body-weight loss (**Figure 7**)
- No significant changes in human cytokines (interferon [IFN]-γ, granulocyte-macrophage colony-stimulating factor [GM-CSF], or tumor necrosis factor [TNF]-α were observed with BMS-986458 ± glofitamab (**Figure 8A-C**)
  - Treatment with glofitamab alone significantly enhanced IFN-γ ($P < 0.01$), GM-CSF ($P < 0.01$), and TNF-α ($P < 0.05$) vs vehicle
- In hPBMC hCRBN NSG mice treated with BMS-986458 or glofitamab monotherapy, immunohistochemistry showed a modest increase of CD3+ cells, predominantly at the tumor's edge (**Figure 9**)
- The combination of BMS-986458 + glofitamab resulted in a significant increase in CD3+ cells infiltrating the tumor compared with monotherapy or vehicle

Figure 7. Body-weight changes in mice treated with BMS-986458 + TCE



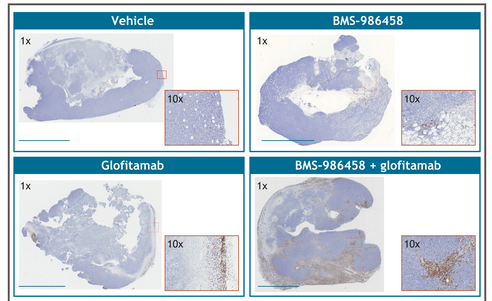
BID, twice daily; ms, mouse; QW, once weekly; TCE, T-cell engager.

Figure 8. Impact of BMS-986458 + TCE on human cytokine levels in vivo



*P < 0.05; **P < 0.01. GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; ms, mouse; TCE, T-cell engager; TNF, tumor necrosis factor.

Figure 9. Tumor infiltration of CD3+ cells with BMS-986458 + glofitamab



Scale bars represent 5mm.

Conclusions

- Combining BMS-986458 with TCEs results in synergistic T cell-driven tumor cell killing across multiple DLBCL models
- In vivo, using a hPBMC mouse DLBCL model, BMS-986458 + glofitamab resulted in synergistic antitumor efficacy and increased infiltration of CD3+ T cells into the tumor microenvironment
- No evidence of T-cell activation based on HLA-DR expression or plasma-measured cytokines was observed with BMS-986458 ± glofitamab
- In vitro studies showed synergy was observed irrespective of CD20 fold-induction following BMS-986458 treatment, and was also observed in models lacking BCL6 expression
  - This indicates that additional immune mechanisms may be contributing to the antitumor activity beyond direct cytotoxic tumor-intrinsic effects

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