A phase 2 randomized study of BMS-986012, an anti-fucosyl-GM1 monoclonal antibody, plus carboplatin, etoposide, and nivolumab as first-line therapy in patients with extensive-stage small cell lung cancer (ES-SCLC)

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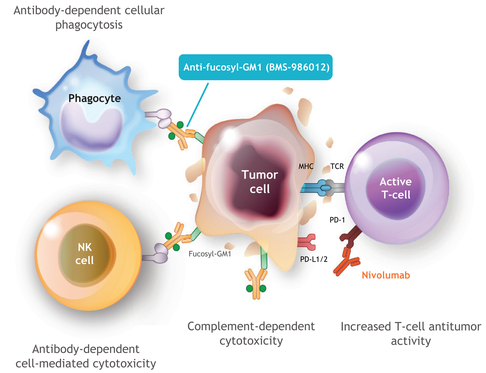
Background

- Small cell lung cancer (SCLC) is an aggressive disease with limited treatment options and represents approximately 13%-15% of all lung cancer worldwide[1]
- Historically, patients with extensive-stage SCLC (ES-SCLC) had a poor prognosis with standard-of-care platinum/etoposide chemotherapy[2]
  - Most patients experienced disease relapse within 6 months of treatment, and median overall survival (OS) ranged from 9-10 months[3,4]
- The addition of anti-programmed death-(ligand) 1 (PD-[L]1) regimens to chemotherapy in first-line (1L) therapy has demonstrated significant but modest benefit[5-7]
  - Therefore, combination regimens with the addition of novel compounds are needed in order to improve patient outcomes

Study rationale

- Fucosyl-GM1 is a monosialoganglioside with limited expression in normal tissues, but it is highly expressed on the surface of SCLC cells in 50%-70% of tumors[8-10]
- BMS-986012 is a nonfucosylated, first-in-class, fully human IgG1 monoclonal antibody that binds to fucosyl-GM1 with high affinity and specificity[11] (**Figure 1**)
- Preclinically, binding of BMS-986012 to tumor cells resulted in tumor cell death via antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity activity (CDC)[11] (**Figure 1**)
  - Lack of fucosylation was associated with greater binding on natural killer (NK) cells and increased ADCC[11]
- Using SCLC cells and mouse xenograft and syngeneic models, BMS-986012 also demonstrated antitumor activity as monotherapy with synergistic effects in combination with chemotherapy, anti-CD137 agonist antibodies, or immunomodulating agents, including anti-PD-1 antibodies[11]

Figure 1. BMS-986012 and nivolumab mechanism of action



Preclinically, binding of BMS-986012 to tumor cells activates ADCC, ADCP, and CDC,[11] while nivolumab functions to increase T-cell antitumor activity[12]

MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1/2, programmed death-ligand 1/2; TCR, T-cell receptor.

- BMS-986012 was previously evaluated as monotherapy and in combination with standard-of-care platinum/etoposide chemotherapy or nivolumab in patients with SCLC[12-14]
- Treatment with BMS-986012 monotherapy was well tolerated in patients with relapsed/refractory (R/R) SCLC, with manageable low-grade pruritus observed as the most common treatment-related adverse event (TRAE)[12]
- In previously untreated patients with ES-SCLC, the safety profile of BMS-986012 plus platinum/etoposide chemotherapy was comparable to the profile observed historically with platinum/etoposide chemotherapy alone except for clinically manageable pruritus, which self-resolved after the first 2 cycles of therapy and did not recur[13]
- In an interim analysis, BMS-986012 also demonstrated a manageable safety profile and clinical activity when combined with nivolumab in a small number of patients with R/R SCLC not previously treated with checkpoint inhibitors[14]
  - Pruritus was the most common TRAE (n = 27; 93%) and resolved in most cases
  - A high objective response rate (ORR; 38%) was observed, with durability and a median duration of response (DOR) of 26.4 months
  - Median OS was 18.7 months
  - Responses were seen in both platinum-sensitive and -refractory patient populations
- Based on these findings, it was hypothesized that checkpoint inhibition in combination with BMS-986012 and standard-of-care platinum/etoposide chemotherapy might have benefit in previously untreated patients with SCLC

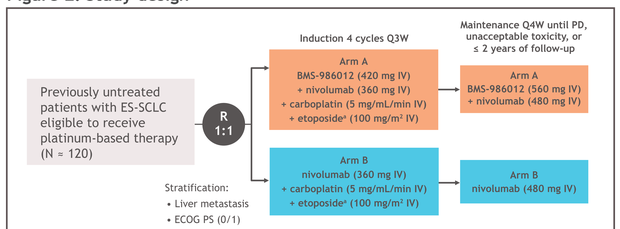
Study objective

- To evaluate the safety and efficacy of BMS-986012 combined with carboplatin/etoposide and nivolumab as 1L therapy in patients with ES-SCLC

Study design

- This is a randomized, open-label, phase 2, global study (NCT04702880)
- Approximately 120 patients will be randomized 1:1 to receive nivolumab + carboplatin + etoposide ± BMS-986012 (**Figure 2**)

Figure 2. Study design



Primary endpoints: safety/tolerability and PFS by BICR
Key secondary endpoints: PFSR by BICR; PFS and PFSR by investigator per RECIST v1.1; ORR, TTR, and DOR per RECIST v1.1; OS, OSR, fucosyl-GM1 and PD-L1 expression and associations with antitumor activity, and immunogenicity of BMS-986012

Patients will be randomized to receive carboplatin/etoposide in combination with BMS-986012 and nivolumab induction followed by BMS-986012 and nivolumab maintenance or carboplatin/etoposide in combination with nivolumab followed by nivolumab maintenance.

BICR, blinded independent central review; PD, progressive disease; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PFS, progression-free survival; PFSR, progression-free survival rate; OSR, overall survival rate; Q3W, every 3 weeks; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
[a] Etoposide was administered on days 1, 2, and 3 of each cycle.

Enrollment criteria

- Key enrollment criteria are shown in **Table 1**

Table 1. Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Histologically or cytologically documented ES-SCLC and extensive-stage disease (AJCC, 7th edition, stage IV [T any, N any, M1a, or M1b], or T3-4)	Prior chemotherapy, radiation therapy, or biologic therapy for SCLC
Mandatory tumor biopsies from primary disease site or any metastatic site when primary is not available	Symptomatic brain or other CNS metastases
ECOG PS of 0 or 1	Paraneoplastic autoimmune syndrome requiring systemic treatment
≥ 1 measurable lesion by CT or MRI per RECIST v1.1 criteria	Active or history of interstitial lung disease
	Grade ≥ 2 peripheral sensory neuropathy at study entry
	Active known or suspected autoimmune disease

AJCC, American Joint Committee on Cancer; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging.

Study sites

- The study is expected to take place at 34 sites in 11 countries (**Figure 3**)

Figure 3. Study sites

Summary

- BMS-986012 previously demonstrated a tolerable safety profile when combined with chemotherapy or nivolumab in patients with previously untreated ES-SCLC or R/R SCLC, respectively
- This phase 2 study (NCT04702880) will evaluate the safety and therapeutic benefit of BMS-986012, a fucosyl-GM1 monoclonal antibody, when combined with carboplatin, etoposide, and nivolumab to address the unmet need in patients with newly diagnosed ES-SCLC

References

1. Rosti G, et al. *Ann Oncol* 2006;17(suppl 2):ii5-10.
2. Früh M, et al. *Ann Oncol* 2013;24(suppl 6):vi99-v105.
3. Rossi A, et al. *J Clin Oncol* 2012;30:1692-1698.
4. Demedts IK, et al. *Eur Respir J* 2010;35:202-215.
5. Leal T, et al. *J Clin Oncol* 2020;38(suppl 15). Abstract 9000.
6. Horn L, et al. *N Engl J Med* 2018;379:2220-2229.
7. Paz-Ares L, et al. *Lancet* 2019;394:1929-1939.
8. Brezicka FT, et al. *APMIS* 1991;99:797-802.
9. Brezicka FT, et al. *Tumour Biol* 1992;13:308-315.
10. Zhang S, et al. *Int J Cancer* 1997;73:42-49.
11. Ponath P, et al. *Clin Cancer Res* 2018;24:5178-5189.
12. Chu QSC, et al. *Ann Oncol* 2016;27(suppl 6):vi494. Abstract 1427PD.
13. Paz-Ares L, et al. *J Thorac Oncol* 2021;16:S345-S346. Abstract P15.06.
14. Chu QSC, et al. *J Thorac Oncol* 2021;16:S195. Abstract FP.03.03.

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