A phase 1, multicenter, single-arm, dose-escalation study of BMS-986353 (CC-97540), a CD19-directed chimeric antigen receptor T cell therapy manufactured using a next-generation process, evaluating safety and tolerability in patients with relapsing or progressive forms of multiple sclerosis (Breakfree-2)

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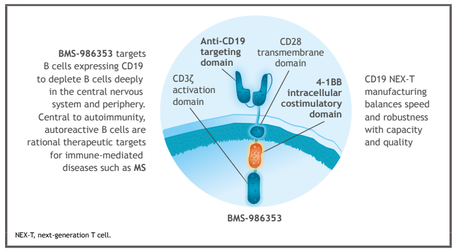
Introduction

- Approved therapies for relapsing multiple sclerosis (RMS) and progressive multiple sclerosis (PMS) have limited effect on disease progression and have concerning long-term toxicities[1-3]
- Novel chimeric antigen receptor (CAR) T cell therapies may exert anti-inflammatory and immunomodulatory effects at multiple sites, including within the central nervous system, and induce an immune reset, possibly leading to durable, treatment-free disease control[4]
- BMS-986353 (CC-97540) is an investigational CAR T cell therapy expressing the CD19-directed CAR used in US Food and Drug Administration-approved lisocabtagene maraleucel (liso-cel; **Figure 1**)

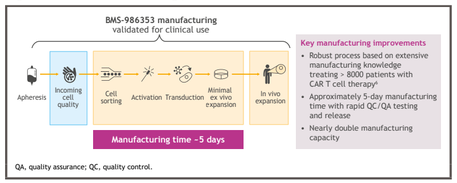
Figure 1. CD19 NEX-T® CAR construct



NEX-T, next-generation T cell.

- The NEX-T manufacturing process shortens manufacturing time and optimizes phenotypic attributes[5] (**Figure 2**)
- The phase 1 Breakfree-2 (NCT06220201) study investigates BMS-986353 in patients with RMS or PMS in 2 separate dose escalation cohorts
- Here, we report initial data from Breakfree-2 for the first 3 treated patients with RMS and 1 treated patient with PMS
- The objective of this study is to evaluate the safety and tolerability of a single infusion of BMS-986353 in patients with RMS or PMS and determine recommended phase 2 dose (RP2D)

Figure 2. NEX-T manufacturing process



QA, quality assurance; QC, quality control.

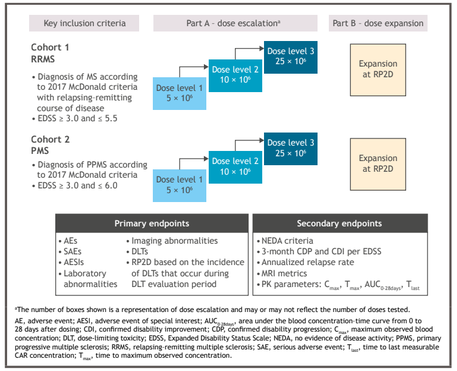
Methods

- Breakfree-2 is a phase 1, multicenter, open-label study investigating BMS-986353 in patients with RMS or PMS (**Figure 3**)
- Disease-modifying therapies were not administered after leukapheresis
- Two to 9 days after lymphodepletion (3 days of fludarabine and cyclophosphamide), a single BMS-986353 infusion was administered
- All patients shown in this report were treated with 5 x 10^6 CAR+ T cells (dose level 1)
- Baseline MRI was performed prior to the start of lymphodepletion. Patients underwent MRI scanning of the brain and cervical spinal cord. The use of gadolinium-based contrast agents was required at all timepoints
- CAR T pharmacokinetics (PK) were evaluated using droplet digital polymerase chain reaction to detect transgene copy numbers, and pharmacodynamics were measured using flow cytometry

At data cutoff (December 16, 2024), with a median (range) follow-up of 87.0 (25-192) days for patients with highly active RMS and 60 days for the patient with PMS, treatment with BMS-986353 demonstrated a promising initial safety profile

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; PMS, progressive multiple sclerosis; RMS, relapsing multiple sclerosis; TRAE, treatment-related adverse event.

Figure 3. Breakfree-2 study design



[a]The number of boxes shown is a representation of dose escalation and may or may not reflect the number of doses tested.

AE, adverse event; AESI, adverse event of special interest; $AUC_{0-28days}$, area under the blood concentration-time curve from 0 to 28 days after dosing; CDI, confirmed disability improvement; CDP, confirmed disability progression; C_{max}, maximum observed blood concentration; DLT, dose-limiting toxicity; EDSS, Expanded Disability Status Scale; NEDA, no evidence of disease activity; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SAE, serious adverse event; T_{last}, time to last measurable CAR concentration; T_{max}, time to maximum observed concentration.

Results

Baseline demographics and disease characteristics

- At data cutoff (December 16, 2024), 4 patients with highly active RMS and 5 with PMS had been enrolled. There were 3 patients with highly active RMS and 1 with PMS treated with BMS-986353, all at dose level 1
- Baseline characteristics are reported in **Table 1**
- Median (range) follow-up was 87.0 (25-192) days for patients with RMS; follow-up was 60 days for the patient with PMS
- All treated patients were evaluable for safety and 1 (RMS) was evaluable for efficacy

Safety

- All patients experienced treatment-emergent AEs (TEAEs; **Table 2**) and treatment-related AEs (TRAEs; **Table 3**)
- One patient (RMS) experienced a serious TEAE, grade 1 non-cardiac chest pain not related to BMS-986353
  - TEAE was considered serious due to prolonged hospitalization by 1 day
  - This was a mild recurrence of a previous MS symptom with quick resolution and confirmed not to be a relapse via MRI
- Two (66.7%) patients with RMS experienced cytopenias (lymphopenia, n = 2; anemia, n = 1), one of which (anemia) was related to BMS-986353
  - Both occurrences of lymphopenia were grade 3/4; anemia was grade 1
- The patient with PMS also experienced cytopenias: grade 4 lymphopenia and grade 3 neutropenia, neither related to BMS-986353

Table 3. Summary of TRAEs

TRAE, n (%)	RMS (n = 3)		PMS (n = 1)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAE	3 (100.0)	1 (33.3)	0	0
Hematologic				
Anemia	1 (33.3)	0	0	0
Non-hematologic				
CRS	2 (66.7)	0	0	0
Increased C-reactive protein	1 (33.3)	0	0	0
Decreased neutrophil count	1 (33.3)	1 (33.3)	0	0
Headache	1 (33.3)	0	0	0

TRAEs were defined as any TEAEs related to BMS-986353.

Table 1. Baseline demographics and disease characteristics

	RMS (n = 3)	PMS (n = 1)
Median (range) age, years	30.0 (30-33)	45.0
Sex, n (%)		
Female	2 (66.7)	0
Male	1 (33.3)	1 (100.0)
Race, n (%)		
White	3 (100.0)	1 (100.0)
Median (range) number of prior MS therapies	3.0 (1-7)	3.0
Median (range) EDSS score at screening	3.5 (3-4)	6.0
Median (range) time from disease diagnosis to BMS-986353 infusion, years	9.5 (2.3-13.4)	20.4

Table 2. Summary of TEAEs

TEAE, n (%)	RMS (n = 3)		PMS (n = 1)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TEAE	3 (100.0)	3 (100.0)	1 (100.0)	1 (100.0)
Hematologic				
Lymphopenia	2 (66.7)	2 (66.7)	1 (100.0)	1 (100.0)
Anemia	1 (33.3)	0	0	0
Neutropenia	0	0	1 (100.0)	1 (100.0)
Non-hematologic				
Headache	3 (100.0)	0	1 (100.0)	0
Nausea	2 (66.7)	0	1 (100.0)	0
Fatigue	2 (66.7)	0	1 (100.0)	0
CRS	2 (66.7)	0	0	0
Constipation	1 (33.3)	0	0	0
Flatulence	1 (33.3)	0	0	0
Vomiting	1 (33.3)	0	0	0
Non-cardiac chest pain	1 (33.3)	0	0	0
Pyrexia	1 (33.3)	0	0	0
Hypoesthesia	1 (33.3)	0	0	0
Resting tremor	1 (33.3)	0	0	0
Increased C-reactive protein	1 (33.3)	0	0	0
Decreased neutrophil count	1 (33.3)	1 (33.3)	0	0
Alopecia	1 (33.3)	0	0	0
Spider nevus	1 (33.3)	0	0	0
Sinus bradycardia	1 (33.3)	0	0	0
Cushingoid	1 (33.3)	0	0	0
Dry eye	1 (33.3)	0	0	0
Insomnia	1 (33.3)	0	0	0
Epistaxis	1 (33.3)	0	0	0
Hypotension	1 (33.3)	0	0	0
Ear infection	0	0	1 (100.0)	0
Myalgia	0	0	1 (100.0)	0
Micturition urgency	0	0	1 (100.0)	0

CRS, cytokine release syndrome.

Table 4. Summary of CRS and ICANS

	RMS (n = 3)	PMS (n = 1)
Any grade CRS, n (%)	2 (66.7)	0
Grade 1	2 (66.7)	0
Grade 2	0	0
Grade ≥ 3	0	0
Median (range) onset of CRS, days	9.5 (9-10)	—
Median (range) longest duration of CRS, days	1.5 (1-2)	—
Any grade ICANS, n (%)	0	0

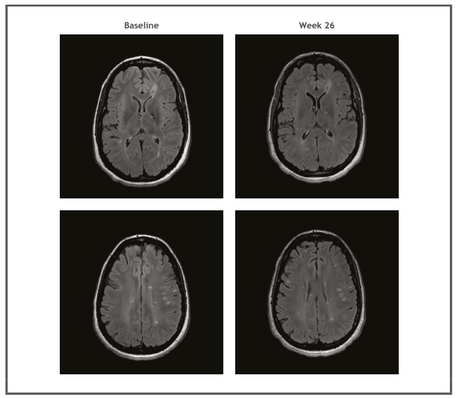
CRS was graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System (Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25:625-638).

- Two (66.7%) patients with RMS experienced grade 1 cytokine release syndrome (CRS) related to BMS-986353 (**Table 4**); the patient with PMS did not experience CRS
  - CRS resolved after a median of 1.5 days
- There were no grade 5 TEAEs, DLTs, infections, or immune effector cell-associated neurotoxicity syndrome (ICANS) reported

Imaging

- In 2 evaluable patients, MRI showed no new gadolinium-enhanced lesions or worsening T2 lesions from screening to week 26 in 1 patient with RMS (**Figure 4**) and from screening to week 12 in another patient with RMS (the other 2 patients were not evaluable). No new lesions concerning for infectious or other demyelinating etiology were observed

Figure 4. Axial fluid-attenuated inversion recovery images of T2 lesion load from baseline to week 26, demonstrating no change in 1 patient with RMS evaluable at week 26



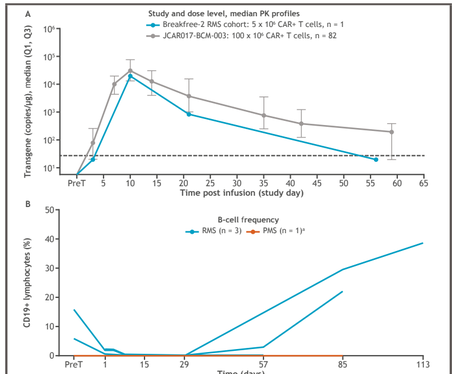
Efficacy

- One patient (RMS) had an EDSS score of 3 at pretreatment evaluation and 2.5 at week 26 (the other 3 patients were not evaluable)
- None of the 4 patients had experienced disease relapse at data cutoff

PK and pharmacodynamics

- Robust CD19 NEX-T cell expansion was observed in 1 evaluable patient (RMS) thus far, consistent with that at > 10-fold of the approved dose of liso-cel (RP2D, 100 × 10^6 CAR+ T cells) in patients with non-Hodgkin lymphoma (**Figure 5A**)
- In all patients, deep B-cell depletion was observed in which B cells became undetectable in the periphery by approximately 8 days after BMS-986353 infusion (**Figure 5B**)
  - In 2 patients with RMS, B-cell frequency increased after 29 days post-infusion

Figure 5. BMS-986353 CAR T cell expansion compared with liso-cel (A) and B-cell depletion and repopulation (B)



Dotted line indicates limit of detection of transgene levels.
[a]Patient with PMS had B cell depleting treatment prior to beginning trial.
PreT, pretreatment.

Conclusions

- Robust CAR T cell expansion was observed in the evaluable patient (RMS) and complete B-cell depletion was observed in all patients
- Treatment with BMS-986353 demonstrated a promising initial safety profile in patients with highly active RMS and PMS, with no DLT or ICANS observed; 2 patients had transient grade 1 CRS
- In the 2 evaluable patients with RMS, MRI showed no new gadolinium-enhanced lesions or worsening T2 lesions from screening to week 26 in 1 patient and from screening to week 12 in the other
- Trial enrollment is ongoing

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