Immune Checkpoint Inhibition in Sepsis: A Phase 1b Randomized, Placebo-Controlled, Single Ascending Dose Study of Antiprogrammed Cell Death-Ligand 1 Antibody (BMS-936559)

Richard S. Hotchkiss, Washington University
Elizabeth Colston, Bristol Myers Squibb
Sachin Yende, Veterans Affairs Pittsburgh Healthcare System
Derek C. Angus, University of Pittsburgh
Lyle L. Moldawer, University of Florida
Elliot D. Crouser, Ohio State University
Gregory Martin, Emory University
Craig Coopersmith, Emory University
Scott Brakenridge, University of Florida
Florian B. Mayr, Veterans Affairs Pittsburgh Healthcare System

Only first 10 authors above; see publication for full author list.

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Immune checkpoint inhibition in sepsis: a Phase 1b randomized, placebo-controlled, single ascending dose study of anti-PD-L1 (BMS-936559)

Richard S. Hotchkiss, MD1, Elizabeth Colston, MD, PhD2, Sachin Yende, MD3,4, Derek C. Angus, MD, MPH4, Lyle L. Moldawer, PhD5, Elliott D. Crouser, MD6, Greg S. Martin, MD, MSc, FCCM7, Craig M. Coopersmith, MD8, Scott Brakenridge, MD, MScS5, Florian B. Mayr, MD3,4, Pauline K. Park, MD9, June Ye, PhD2, Ian M. Catlett, PhD2, Ihab G. Girgis, PhD2, Dennis M. Grasela, PharmD PhD2

1. Washington University School of Medicine, St Louis, MO, USA
2. Innovative Medicines Development, Bristol-Myers Squibb, Princeton, NJ, USA
3. Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, PA, USA
4. The CRISMA Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
5. Department of Surgery, University of Florida College of Medicine, Gainesville, FL, USA
6. The Ohio State University, Columbus, OH, USA
7. Department of Medicine, Division of Pulmonary, Allergy, Critical Care & Sleep Medicine, Emory University, Atlanta, GA, USA
8. Department of Surgery and Emory Critical Care Center, Emory University, Atlanta, GA, USA
9. Department of Surgery, University of Michigan, Ann Arbor, MI, USA

Abstract

OBJECTIVES—To assess for the first time the safety and pharmacokinetics of an anti-PD-L1 immune checkpoint inhibitor (BMS-936559, Bristol-Myers Squibb) and its effect on immune biomarkers in participants with sepsis-associated immunosuppression.

DESIGN—Randomized, placebo-controlled, dose-escalation.

Contact information for corresponding author: Richard S. Hotchkiss, MD, Departments of Anesthesiology, Medicine, and Surgery, Washington University School of Medicine, St Louis, 660 South Euclid Avenue, St Louis, MO 63110-1093, USA., Phone no: +1 (314) 454 8224, Fax no: +1 (314) 454 8279, richardshotchkiss@wustl.edu.

No reprints of the paper are required.

Data sharing

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Tweet

In a Ph1 study of anti-PD-L1 in sepsis, BMS-936559 was well tolerated and increased a marker of immune function at the two highest doses.

Financial support for the study:

Financial support for this work was provided by Bristol-Myers Squibb.
SETTING—Seven US hospital intensive care units.

STUDY POPULATION—Twenty-four participants with sepsis, organ dysfunction (hypotension, acute respiratory failure, and/or acute renal injury) and absolute lymphocyte count ≤1100 cells/μL.

INTERVENTIONS—Participants received single-dose BMS-936559 (10–900 mg; n=20) or placebo (n=4) infusions. Primary endpoints were death and adverse events (AEs); key secondary endpoints included receptor occupancy (RO) and monocyte human leukocyte antigen (mHLA)-DR levels.

MEASUREMENTS AND MAIN RESULTS—The treated group was older (median 62y treated pooled versus 46y placebo), and a greater percentage had >2 organ dysfunctions (55% treated pooled versus 25% placebo); other baseline characteristics were comparable. Overall mortality was 25% (10 mg dose: 2/4; 30 mg: 2/4; 100 mg: 1/4; 300 mg: 1/4; 900 mg: 0/4; placebo: 0/4). All participants had AEs (75% Grade 1–2). Seventeen percent had a serious AE (3/20 treated pooled, 1/4 placebo), with none deemed drug-related. AEs that were potentially immune-related occurred in 54% of participants; most were Grade 1–2, none required corticosteroids, and none were deemed drug-related. No significant changes in cytokine levels were observed. Full RO was achieved for 28 days after BMS-936559 (900 mg). At the two highest doses, an apparent increase in mHLA-DR expression (>5000 mAb/cell) was observed and persisted beyond 28 days.

CONCLUSIONS—In this first clinical evaluation of PD-1/PD-L1 pathway inhibition in sepsis, BMS-936559 was well tolerated, with no evidence of drug-induced hyper-cytokinemia or cytokine storm, and at higher doses, some indication of restored immune status over 28 days. Further randomized trials on PD-1/PD-L1 pathway inhibition are needed to evaluate its clinical safety and efficacy in patients with sepsis.

Study registration number (clinicaltrials.gov)—NCT02576457E

Keywords
sepsis; anti-PD-L1; sepsis-associated immunosuppression; immunotherapy; immune checkpoint inhibition; BMS-936559

Introduction
Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection (1,2), with high mortality rates worldwide (3,4).

For years it was presumed that sepsis morbidity and mortality were secondary to an exaggerated systemic inflammatory response, but therapies intended to dampen this response failed to improve survival (5,6). Although the causes of these failures are multifactorial, sepsis-associated immune dysregulation may play an important role (7,8). Studies suggest that sepsis-associated immune dysregulation increases the risk of secondary infections and mortality (8–11).

Immune checkpoint pathways are endogenous components of the immune system that keep the immune response ‘in check’ under normal physiological conditions; tumor cells exploit these pathways to avoid recognition by the host. One of these immune checkpoint pathways
is the programmed cell death protein-1/programmed cell death-ligand 1 (PD-1/PDL1) pathway (12). PD-1 is a receptor that is inducibly expressed on T-cells and functions as a negative regulator of T-cell function (12). Tumor cells express its primary ligand, PD-L1, which binds to PD-1 and triggers T-cell inactivation; PD-L1 expression on tumor cells is associated with poor prognosis (12,13). Monoclonal antibodies that block PD-1 and PD-L1 activity have proved highly successful at reducing tumor burden and are licensed for therapeutic use in patients with certain cancer types (14–18).

Immune dysregulation in sepsis bears similarities to that seen in certain cancers, particularly the up-regulation of the PD-1/PD-L1 pathway (19–21), and PD-1 and PD-L1 may be important in sepsis-associated immunosuppression. PD-1 and PD-L1 are also key mediators of T-cell exhaustion in infections (12,22,23); blocking their interaction prevents T-cell death, modulates cytokine production, and is associated with reduced organ dysfunction and fewer deaths in mice with cecal ligation and puncture (CLP)-induced sepsis (24–27). PD-1 knockout mice also have marked protection against sepsis lethality versus wild-type mice (28). PD-1 and PD-L1 are also up-regulated on immune cells of patients with sepsis, and higher expression of these proteins is associated with increased mortality (9,27–34). Moreover, ex vivo studies using blood samples from patients with sepsis have reported decreased apoptosis and improved immune cell function with antibodies against PD-1 and PD-L1 (31,33,34). Therefore, anti-PD-L1 could be a promising approach for patients with sepsis-associated immunosuppression.

As with any agent that inhibits immune checkpoint pathways there is a theoretical risk that this approach could induce an unbridled pro-inflammatory response or ‘cytokine storm’. Therefore, any novel agent under investigation in the oncology or sepsis fields should be monitored carefully for such a response. However, while animal and ex vivo sepsis studies have reported some cytokine changes with anti-PD-1 and anti-PD-L1 antibodies (e.g. increased interferon-gamma, interleukin-6, and tumor necrosis factor-alpha), no excessive pro-inflammatory changes were reported (24–26,31,33). Furthermore, to the authors’ knowledge no clinical finding of cytokine storm in cancer patients receiving anti-PD-1 or antiPD-L1 therapy has been reported.

BMS-936559 (Bristol-Myers Squibb, Princeton, NJ, USA), an investigational, fully human IgG4 monoclonal antibody that inhibits binding of PD-L1 to both PD-1 and CD80, has been explored in Phase 1 studies in individuals with cancer (35) and those with HIV-1 infection on suppressive antiviral therapy (36). Anti-PD-L1 was effective in augmenting host immunity, as indicated by its ability to induce tumor regression and prolong disease stabilization in patients with cancer, and to enhance HIV-1 Gag-specific CD8+ T-cell function, respectively (35,36). The present study is the first clinical trial of checkpoint inhibitors in sepsis and represents a unique new immunotherapeutic approach to sepsis by targeting T-cell exhaustion and defective host adaptive immunity.

This study was undertaken primarily to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of anti-PD-L1 (BMS-936559) in patients with sepsis-associated immunosuppression. The study also explored biologic efficacy by examining the effects on immune system biomarkers.
Materials and Methods

Ethics statement

Written informed consent was obtained from all participants. Institutional Review Boards/Independent Ethics Committees approved the protocol and amendments. The study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation, and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

Study design and population

This was a Phase 1b, prospective, randomized, double-blind, placebo-controlled, multicenter study of BMS-936559 in adults with sepsis-associated immunosuppression (clinicaltrials.gov identifier: NCT02576457), and was a sequential, single ascending-dose assessment at seven US sites (December 2015–March 2017; see online supplement).

Inclusion criteria—Eligible participants were ≥18 years old with documented/suspected infection and sepsis onset ≥24 hours prior to study treatment administration based on one of three organ dysfunction criteria: hypotension (defined as treatment with any vasopressor[s] for ≥6 hours to maintain systolic pressure ≥90 mmHg or mean arterial pressure ≥70 mmHg), acute respiratory failure (mechanical ventilation for ≥24 hours), or acute kidney injury (creatinine >2.0 mg/dL [from a normal pre-sepsis value] or urine output <0.5 mL/kg/h for >2 hours despite adequate fluid resuscitation). Pre-existing renal impairment required the participant to meet another organ dysfunction criterion. Participants were required to have sepsis-associated immunosuppression (in this study, operationally defined as absolute lymphocyte count [ALC] ≤100 cells/μL within 96 hours before study treatment administration) (8,11), and needed to be receiving treatment in an intensive care unit (ICU).

Exclusion criteria—Key criteria were a previous episode of sepsis with ICU admission during the current hospitalization, an advanced directive for withholding/withdrawing life-sustaining treatment/do not resuscitate order/comfort measures-only order, active autoimmune disease, history of transplantation, or cancer diagnosis or treatment in the preceding 6 months (see online supplement).

Treatment assignment and study procedures—Participants were assigned to a single dose of BMS-936559 or placebo; study treatment assignment was to one of five sequential groups (BMS-936559 10, 30, 100, 300, 900 mg). BMS-936559 was given as an intravenous (IV) infusion on Day 1 (maximum infusion time: 180 min) (Figure 1). The decision to wait ≥24 hours after the onset of organ dysfunction before starting treatment was taken in order to account for resolution of the peak pro-inflammatory response associated with sepsis (37).

All participants received standard-of-care therapy (38), and were followed for 90 days after dosing, unless they died or were lost to follow-up, or access to the participant was denied. After completing dosing in any group, subsequent group dosing was not initiated until

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blinded safety data through Day 14 (or earlier for dosed participants who discontinued or died before Day 14) in the earlier dose group(s) were reviewed and deemed acceptable by the sponsor’s Medical Monitor in consultation with the investigators. Doses in groups 4 (300 mg) and 5 (900 mg) were selected based on a review of safety, receptor occupancy (RO), and PK data available through Day 14 from earlier groups. Study stopping rules are described in the online supplement.

Participants were randomized 4:1 (BMS-936559 to placebo) using a computer-generated randomization scheme, provided by the sponsor. The site pharmacist (who prepared the infusion) was notified of a participant’s treatment assignment. All other site staff and the sponsor remained blinded.

Endpoints and assessments

Key objectives and endpoints—The primary objective was to assess safety and tolerability over 90 days following single-dose administration of BMS-936559 10–900 mg to participants with sepsis. Safety was assessed based on review of physical examination findings, vital sign measurements, electrocardiogram (ECG), adverse event (AE) reports, ophthalmoscopic examinations, and laboratory tests (see online supplement for definitions of AEs and serious adverse events [SAEs]).

Key secondary objectives were to assess PK and RO of BMS-936559 following single-dose administration, and the effect of a single dose of BMS-936559 on immune function.

Assessments—Serial blood samples for PK/PD and biomarker analyses were collected at pre-dose and selected post-dose time points.

Pharmacokinetics—BMS-936559 serum concentrations were measured using a validated enzyme-linked immunosorbent assay (ELISA) method (39). PK parameters (maximum observed serum concentration [C_max], time of maximum observed serum concentration, area under the curve from time 0 to time of the last measurable concentration after drug administration/extrapolated to infinity [AUC_{0-T}/AUC_{(INF)}], total body clearance, volume of distribution, and terminal half-life were derived by non-compartmental analysis using Phoenix™ WinNonlin®, v6.3 or higher [Pharsight Corporation, Phoenix, Mountain View, CA, USA]). Dose proportionality, based on C_max, AUC_{(0-T)}, and AUC_{(INF)}, was assessed using the power model approach (40).

BMS-936559 receptor occupancy and immune system status—PD-L1 RO on CD3+ T cells and immune system status (monocyte human leukocyte antigen-DR [mHLA-DR] expression and ALC) up to Day 90 were measured. In vitro data suggest that T-cell function (as assessed by interferon (IFN)-γ production (BMS data on file) or T-cell proliferation (41)), is dose-dependently enhanced by PD-1/PD-L1 blockade. PD-L1 RO on T cells and T-cell activity saturate/plateau similarly; at saturating RO, there is a plateau in IFN-γ production (BMS data on file). BMS-936559 doses that achieved ≥80% RO were expected to restore or enhance T-cell function, and ≥80% was thus regarded as a relevant RO level.
The mHLA-DR levels were assessed using whole blood in flow-cytometry-based assays; an mHLA-DR level of <5000 monoclonal antibodies (mAb)/cell has been generally considered indicative of immunoparalysis (42). ALC was determined using a standard hematology analyzer. Cytokine levels (IL-6, IL-8 [CXCL8], IL-10) were also measured up to Day 90. IL-6 and IL-8 are markers of generalized immune system activation and inflammation, and IL-10 expression is considered an appropriate anti-inflammatory marker.

**Statistical methods**

The study employed a single ascending-dose design of four participants dosed with BMS-936559 and one with placebo at each dose level. Sample size was not based on statistical power considerations. Rather, if the incidence of an AE was 10%, then the sample size provided a 34.4% probability to observe at least one event in a given dose group.

Safety, PK, RO, and immunologic outcomes analyses were conducted on a modified intent-to-treat population (ITT-exposed), comprising all participants who received at least a partial dose of study treatment. Descriptive statistics were used to summarize safety, PK, RO, and immunologic data.

**Results**

**Participant disposition and baseline characteristics**

Thirty-five participants were enrolled, of whom 25 were randomized. Ten participants were excluded for the following reasons (in some cases, participants were excluded for more than one reason): one participant did not have documented or suspected infection; one participant had active autoimmune disease or documented history of autoimmune disease; three participants did not meet organ dysfunction criteria; six participants did not have ALC ≥100 cells/μL; five participants were not in the ICU at the time of study drug administration; and for one participant, the enrollment milestone had already been reached. One randomized participant’s status changed to ‘Do Not Resuscitate’ after randomization but prior to dosing, and so did not receive study treatment. Therefore, 24 participants received BMS-936559 (n=20 [n=4 per dose group]) or placebo (n=4). Fourteen (58.3%) participants completed the 90-day study period (Supplementary Figure S1).

Baseline characteristics were comparable across groups, except for age and number of organ dysfunctions (Table 1).

**Safety**

Six deaths occurred 2–52 days following BMS-936559 administration (Table 2); these were considered unrelated to study treatment by the investigator. Deaths occurred in 2/4 participants (50%) receiving BMS-936559 10 mg, 2/4 (50%) receiving 30 mg, 1/4 (25%) receiving 100 mg, and 1/4 (25%) receiving 300 mg (Table 2). The causes of death were not unexpected for these severely-ill patients (Supplementary Table S1).

SAEs occurred in four participants (16.7%; BMS-936559, n=3/20 [15.0%]; placebo, n=1/4, [25.0%]); all were considered unrelated to study treatment (Table 2; Supplementary Table S2). The most frequent (≥20%) on-treatment AEs (pooled BMS-936559 doses) were
hypotension (n=11; 55%), diarrhea and delirium (n=7; 35% each), anemia (n=6; 30%),
increased lipase and pleural effusion (n=5; 25% each), and decreased weight, hypokalemia,
and malnutrition (n=4; 20% each) (Table 2). Most AEs were mild to moderate (Grade 1–2),
with similar frequency and intensity across dose groups. The observed AEs were not
unexpected for this population. One participant (BMS-936559 30 mg) had AEs considered
related to study treatment: increased amylase (Grade 2) and lipase (Grade 1), and increased
blood lactate dehydrogenase (LDH) (Grade 1). The increased amylase and lipase events
began approximately 24 hours after infusion and resolved after 5 days, with neither event
requiring treatment. The increased blood LDH event began 6 days after infusion, resolved
after approximately 14 hours, did not require treatment, and was not associated with
hemolysis or anemia. No AEs led to discontinuation from the study.

Adverse events of special interest (AEOSIs, i.e., AEs with potential immune-related causes
as identified in the anti-PD-L1 study in cancer patients (35)) occurred in 13/24 participants
(54.2%; BMS-936559, n=11/20 [55.0%; placebo, n=2/4 [50.0%]) (Table 3). Most were
Grade 1–2; none were deemed related to study treatment or were suggestive of a drug-
induced exaggerated inflammatory response. Two participants (10%) had Grade 3 AEOSIs
of diarrhea: in one, the event began on Day 7, resolved on Day 12, was treated with
loperamide, and did not require corticosteroids; in the other, the event began on Day 6,
resolved on Day 23, was treated with diphenoxylate atropine, and did not require
corticosteroids. One participant (5%) had a Grade 3 AEOSI of lung infiltration, beginning
18 hours after study treatment infusion and resolving by 33 hours. It was treated with
antibiotics and did not require corticosteroids. No case of pneumonitis was reported.

Post-dose ophthalmoscopic data (at index hospitalization discharge and/or Day 90) were
available for 15 participants. No cases of focal retinal lesions were reported.

Pharmacokinetics

The PK findings are presented and discussed in more detail in the online supplement
(Supplementary Tables S3 to S5, Supplementary Figure S2). BMS-936559 mean terminal
half-life ranged from 29 hours (10 mg) to 189 hours (300 mg). BMS-936559 exhibited
nonlinear PK and target-mediated drug disposition kinetics, with faster elimination rates and
higher volumes of distribution observed compared with patients with cancer. After
dosenormalization, anti-PD-L1 observed concentrations were generally higher and
decreased more slowly in participants with solid tumors than in participants with sepsis.

Biomarkers

Receptor occupancy—A dose-dependent increase in RO duration was observed (Figure
2A). There was also a dose-dependent increase in the time period over which ≥80% RO was
achieved; full RO was achieved for 28 days following the 900-mg single dose (Figure 2A).

mHLA-DR—Increased mHLA-DR expression over time was demonstrated, with the
greatest increase observed at the two highest doses (Figure 2B). From Days 15 to 90, median
mHLA-DR levels with BMS-936559 300 mg and 900 mg were >5000 mAb/cell (between
~6000 and ~18,000 mAb/cell) (Figure 2B).
A post hoc analysis combined the 10, 30, and 100 mg dose groups (‘low-dose’) and 300 mg and 900 mg groups (‘high-dose’) for RO and mHLA-DR to Day 29 (Figure 2C). Full RO was maintained until Day 8 (low-dose) and until Day 29 (high-dose). mHLA-DR expression rose above 5000 mAb/cell at Day 8 in the low-dose group and at Day 4 in the high-dose group; beyond Day 8, mHLA-DR expression was consistently higher at each time point in the high-dose versus low-dose group.

**Other biomarkers**—No clear dose-related changes or trends were observed in ALC or cytokine levels (Supplementary Figures S3 to S5).

**Discussion**

These data describe the first clinical evaluation of an anti-PD-L1 monoclonal antibody in patients with sepsis-associated immunosuppression. Single doses of BMS-936559 (10–900 mg) were well tolerated. Most AEOSIs were of mild-to-moderate intensity, consistent with BMS-936559 mechanism of action, and generally similar to those reported in patients with cancer (rash, hypothyroidism, and diarrhea) (35). No cases of pneumonitis (a potentially life-threatening condition that has been recorded with anti-PD-1/PD-L1 monoclonal antibodies in the oncology setting (14–18)) were reported. As documented in the AE profile and cytokine measurements, there was no clinical or biomarker evidence of a drug-induced cytokine release syndrome. Specifically, there was no indication that administration of anti-PD-L1 was temporally associated with worsening fever or hemodynamic instability, and no observed clinically significant changes in cytokine concentrations. This is important because, although PD-1/PD-L1 pathway inhibition is effective (14–18), studies of therapies to boost immune activity in sepsis have not been performed, partly because of the theoretical risk of an excessive pro-inflammatory response (see introduction).

In BMS-936559 multiple-dose, 3-month primate toxicology studies, focal retinal lesions were reported, and monitoring was performed in the current clinical study. No focal retinal lesions were detected in any participant. This is consistent with the Phase 1 BMS-936559 HIV-1 study, which did not reveal focal retinal findings similar to those seen in monkeys (36).

The PK findings of this study are interesting because the faster elimination rates and higher volumes of distribution seen compared with patients with cancer suggest that higher doses or more frequent dosing might be warranted for patients with sepsis.

The duration of full RO increased dose-dependently, and the prolonged (28-day) RO at the 900-mg dose level could be advantageous in preventing new secondary infections that cause additional morbidity and mortality.

The mHLA-DR expression also appeared to increase over time, consistent with a restoration of immune function. The post hoc analysis highlighted the sustained, high degree of PD-L1 target engagement (RO) and implied a more rapid recovery of immune function (mHLA-DR expression) at the two higher doses than at the three lower doses. Due to small participant numbers, these data should be interpreted with caution. However, similar associations between immunotherapy and increased mHLA-DR expression (and improved outcome) have
been reported elsewhere. Two IFN-γ (multiple-dose) studies in patients with sepsis/trauma and immunoparalysis reported improved mHLA-DR expression and associated clinical improvements (43,44). A study of granulocyte–macrophage colonystimulating factor (multiple doses) versus placebo in patients with sepsis-associated immunosuppression reported mHLA-DR normalization, along with improved patient outcomes (45).

There was no clear trend in ALC levels after dosing with BMS-936559. Reduced ALC is a frequent and easily measured feature of sepsis-associated immunosuppression (8,21), but may not be the optimal pharmacodynamic marker to assess the effect of PD-1/PD-L1 pathway inhibition in a short-term study. Lymphocyte counts may increase through homeostatic proliferation or de novo lymphocyte production; however, both processes would be expected to take a significant amount of time (46,47). Thus, ALC may not fully recover over 90 days.

There were also no clear or dose-related trends in IL-6, IL-8 or IL-10 levels observed. While animal studies have shown some changes in cytokine levels (24–26,31,33), there may be several reasons for a lack of a detectable change in markers in the current study. For example, the sampling times chosen may not have detected a rapid or transient change in cytokine level. Another reason may have been that any substantial cytokine change may have been highly localized and not detectable systemically. The small sample size may also be a factor. However, there was an absence of any systemic change in cytokine levels indicative of a cytokine storm, which is an important ‘goal’ from a first-in-human study perspective. For comparison, it is worth noting from the literature one study where 39 human cytokines and chemokines (including IL-6, IL-8, and IL-10) were simultaneously quantified in pre- and post-dose plasma samples from 24 patients with cancer who were undergoing antiPD-1 therapy. Only significant increases in IL-1 alpha and CXCL10 plasma levels were reported with anti-PD-1 alone post- versus pre-dose (48).

There are some limitations to the study that should be discussed. As already alluded to, the small sample size results in a lack of power to detect issues associated with a pro-inflammatory response. Larger studies may reveal other AEs not reported here; however, the broad similarity between the AEs reported here and those in the larger study in patients with cancer (35) is encouraging. There is also the question of the definition of immunosuppression used in the study; for practical purposes, an ALC of ≤1100 cells/μL within 96 hours before study treatment administration was employed. Reduced ALC correlates with worse outcomes in patients with sepsis (8,11). However, it is not a definitive marker of sepsis-associated immunosuppression. It is important to note that, in the current study, pre-dose mHLA-DR levels were very low (<5000 mAb/cell) (Figure 2B), which would indicate that these participants were immunosuppressed and at increased risk of mortality (42,49). Recently, an integrated genomics study of patients with sepsis admitted to the ICU also identified two distinct sepsis phenotypes, SRS1 and SRS2, with SRS1 being an immunosuppressive phenotype (50). This immunosuppressed phenotype had lower ALC levels compared with the SRS2 phenotype (Dr. J.C. Knight, personal communication). Together, these findings provide a strong indication that lower ALC levels are indeed associated with immunosuppression in patients with sepsis.
These data suggest that PD-1/PD-L1 pathway inhibition in patients with sepsis-associated immunosuppression is well tolerated. BMS-936559, particularly with the higher doses studied, results in an apparent increase in mHLA-DR expression; further studies are needed to determine whether it safely restores immune functional status and protects against secondary infections and related clinical consequences (readmissions, morbidity, and mortality).

**Conclusions**

This was the first clinical evaluation of an anti-PD-L1 (BMS-936559) in patients with sepsis-associated immunosuppression.

PD-1/PD-L1 pathway inhibition represents an evolution in conceptual understanding of approaches to sepsis treatment. Rather than seeking to inhibit the host response, checkpoint inhibitor therapies that enhance host immunity may represent a new way forward against this highly lethal syndrome. Further study of PD-1/PD-L1 pathway inhibition is warranted.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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Conflicts of interest and source of funding:

EC, JY, IMC, IGG, and DMG are Bristol-Myers Squibb employees; EC and DMG are Bristol-Myers Squibb shareholders. RSH receives research grant support and serves on advisory boards to Bristol-Myers Squibb. SY received grant support from Bristol-Myers Squibb for the design of this study. DCA received consulting fees from Bristol-Myers Squibb for advice on study design.

The remaining authors (LLM, EDC, GSM, CMC, SB, FBM, and PKP) have disclosed that they do not have any relevant conflicts of interest.

**References**


Brief summary of work

**Describe the work reported**

This Phase 1b single ascending dose study is the first clinical evaluation of anti-PD-L1 (BMS-936559) in patients with sepsis-associated immunosuppression. The study was undertaken to evaluate the safety, pharmacokinetics, and pharmacodynamics of anti-PD-L1 in sepsis; the study also explored biologic activity by examining effects on immune-system biomarkers.

**Summarize the major findings**

BMS-936559 appeared to be well tolerated. Adverse events (AEs) of special interest (i.e., potentially immune-related) were consistent with the mechanism of action of BMS-963559 and were generally similar to those previously reported in patients with cancer. Most AEs of special interest were mild to moderate in intensity. There were also no major changes in cytokines observed, indicating that there was no clinical or biomarker evidence of a drug-induced cytokine release syndrome. Nonlinear PK and target-mediated drug disposition kinetics were exhibited for BMS-936559 in patients with sepsis, with faster elimination rates and higher volumes of distribution in these patients than in patients with cancer. The duration of anti-PD-L1 target engagement increased in a dose-dependent manner and, at the highest dose of anti-PD-L1 tested, target engagement was maintained for 28 days. Additionally, monocyte human leukocyte antigen-DR (mHLA-DR) expression appeared to increase over time, especially at the highest doses tested.

**Indicate the significance of the findings**

In this first clinical evaluation in sepsis, anti-PD-L1 appeared to be well tolerated, with no clinical or biomarker evidence of inducing a cytokine release syndrome; this is an important finding because, although PD-1/PD-L1 inhibition is effective in cancer, studies of PD-1/PD-L1 inhibition in sepsis have been lacking, partly because of safety concerns in patients with sepsis. Additionally, mHLA-DR expression appeared to increase over time, particularly at the two higher doses, suggesting potential for restoration of immune competence. In summary, PD-1/PD-L1 inhibition in sepsis represents an evolution in conceptual understanding of approaches to treatment, and results from this study support further study of PD-1/PD-L1 inhibition in sepsis.
Figure 1. Study design

*A total of 5 participants were planned, but only 4 were dosed (all received BMS-936559). There was no intra-participant dose escalation.

ALC, absolute lymphocyte count; EOS, end of study; IV, intravenous; R, randomization.
A. % Receptor Occupancy

--- 80% receptor occupancy.

Study Day
Figure 2. Changes in receptor occupancy and monocyte human leukocyte antigen-DR expression with BMS-936559

A. Change in PD-L1 RO with BMS-936559 (10–900 mg) on CD3+ T cells over the 90-day study treatment period.

B. Change in mHLA-DR expression with BMS-936559 (10–900 mg) on Day 15, Day 29, Day 57, and Day 90.

C. Change in mHLA-DR expression with BMS-936559 Low-Dose and High-Dose on Day 15, Day 29, and Day 57.

Green dashed line represents 80% RO; blue dashed line represents mHLA-DR 5000 mAb per cell.
mg) over the 90-day study period (box-plots are shown for greater clarity and distinction).

C. Changes in RO and mHLA-DR expression in participants receiving placebo, or 10, 30, and 100 mg dose combined (‘low-dose group’), or 300 and 900 mg dose combined (‘high-dose group’) up to Day 29 post-infusion.

CD, cluster of differentiation; mAb, monoclonal antibody; mHLA-DR, monocyte human leukocyte antigen-DR; RO, receptor occupancy.
Table 1.

Baseline demographics and disease parameters

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<tr>
<th>Parameter</th>
<th>BMS-936559 treatment</th>
<th>Placebo (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg (n=4)</td>
<td>30 mg (n=4)</td>
</tr>
<tr>
<td>Age, y; median (min, max)</td>
<td>57 (55, 61)</td>
<td>68 (59, 76)</td>
</tr>
<tr>
<td>Age categorization, n (%)</td>
<td>&lt;65y</td>
<td>4 (100)</td>
</tr>
<tr>
<td></td>
<td>≥65y</td>
<td>0</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male</td>
<td>2 (50)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White</td>
<td>2 (50)</td>
</tr>
<tr>
<td></td>
<td>Black/African American</td>
<td>2 (50)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>0</td>
</tr>
<tr>
<td>ALC, ×10⁹ cells/L; mean (± SD)</td>
<td>1.50 (1.05)</td>
<td>1.04 (0.63)</td>
</tr>
<tr>
<td>Site of infection, n (%)</td>
<td>Abdomen</td>
<td>1 (25)</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>1 (25)</td>
</tr>
<tr>
<td></td>
<td>Skin/soft tissue</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Urinary tract</td>
<td>2 (50)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td>SIRS criteria; number of participants (%)</td>
<td>≤1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2 (50)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Parameter</td>
<td>10 mg (n=4)</td>
<td>30 mg (n=4)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Organ dysfunctions; number of participants (%)</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2 (50)</td>
<td>2 (50)</td>
</tr>
<tr>
<td></td>
<td>1 (25)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>SOFA score; mean (± SD)</td>
<td>7.5 (2.7)</td>
<td>7.8 (4.6)</td>
</tr>
</tbody>
</table>

*aALC values shown represent the lowest recorded in the 48 hours prior to dosing.*

Organ dysfunctions: hypotension, acute respiratory failure, acute kidney injury.

SIRS: hyperthermia/hypothermia, tachycardia, tachypnea, leukocytosis/leukopenia/immature neutrophils increased.

ALC, absolute lymphocyte count; n, number of participants; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMS-936559 treatment</th>
<th>10 mg (n=4)</th>
<th>30 mg (n=4)</th>
<th>100 mg (n=4)</th>
<th>300 mg (n=4)</th>
<th>900 mg (n=4)</th>
<th>Pooled (n=20)</th>
<th>Placebo (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n (%)</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>0</td>
<td>6 (30)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>On-treatment SAE; number of participants (%)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>0</td>
<td>0</td>
<td>1 (25)</td>
<td>3 (15)</td>
<td>1 (25)</td>
<td></td>
</tr>
<tr>
<td>On-treatment Grade 3–4 AE, incidence ≥20%; number of participants (%)</td>
<td>1 (25)</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>7 (35)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>On-treatment AE of any Grade, incidence ≥20%; number of participants (%)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>3 (75)</td>
<td>19 (95)</td>
<td>4 (100)</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (25)</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>4 (100)</td>
<td>2 (50)</td>
<td>11 (55)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
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<td></td>
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<tr>
<td>Lipase increased</td>
<td>0</td>
<td>1 (25)</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>0</td>
<td>5 (25)</td>
<td>2 (50)</td>
<td></td>
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<tr>
<td>Weight decreased</td>
<td>2 (50)</td>
<td>0</td>
<td>2 (50)</td>
<td>0</td>
<td>0</td>
<td>4 (20)</td>
<td>2 (50)</td>
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</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
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<tr>
<td>Hypokalemia</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>0</td>
<td>4 (20)</td>
<td>1 (25)</td>
<td></td>
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<tr>
<td>Malnutrition</td>
<td>1 (25)</td>
<td>0</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>0</td>
<td>4 (20)</td>
<td>1 (25)</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>0</td>
<td>1 (25)</td>
<td>2 (50)</td>
<td>3 (75)</td>
<td>6 (30)</td>
<td>2 (50)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (50)</td>
<td>0</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>7 (35)</td>
<td>1 (25)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>7 (35)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (25)</td>
<td>0</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>0</td>
<td>5 (25)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

All recorded AEs were summarized by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.
The on-treatment phase of the study represents the 90-day period following single-dose administration of study treatment.

AE, adverse event; n, number of participants; SAE, serious adverse event.
### Table 3.

Adverse events of special interest – all treated participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMS-936559 treatment</th>
<th>Placebo (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg (n=4)</td>
<td>30 mg (n=4)</td>
</tr>
<tr>
<td>AEs of special interest, Grade 3–4; number of participants (%)</td>
<td>0</td>
<td>1 (25)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung infiltration</td>
<td>0</td>
<td>1 (25)</td>
</tr>
<tr>
<td><strong>AE of special interest, any Grade; number of participants (%)</strong></td>
<td>3 (75)</td>
<td>1 (25)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (50)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Endocrine disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung infiltration</td>
<td>0</td>
<td>1 (25)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

All recorded AEs of special interest were summarized by preferred term using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. AEs of special interest were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

AEs of special interest are AEs with potential immune-related causes as identified in the anti-PD-L1 study in patients with cancer (35).

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; n, number of participants.