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Immune checkpoint inhibition in sepsis: a Phase 1b randomized study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of nivolumab

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Compliance with ethical standards

Conflicts of interest

EC, JY, IMC, IGG, and DMG are Bristol-Myers Squibb employees; EC, IMC, and DMG are Bristol-Myers Squibb shareholders. RSH receives research grant support and serves on advisory boards for Bristol-Myers Squibb. SY received grant support from Bristol-Myers Squibb for the design of this study. GSM reports grant support provided to Emory University from Bristol Myers Squibb for the conduct of the study. PKP's institution received funding from the National Institutes of Health (NIH) and other support from the U.S. Food and Drug Administration/Biomedical Advanced Research and Development Authority, Atox Bio, and the Marcus Foundation. MWD receives funding from the NIH, American Heart Association, Open Philanthropy Project, General Electric, and Kaneka. DCA received consulting fees from Bristol-Myers Squibb for advice on study design. The remaining authors (LLM, EDC, TA, CMC, SCB, MT, FBM, RRB, and MJD) declare that they have no conflict of interest.

Data sharing

BMS policy on data sharing may be found at: https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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Abstract

Purpose: Sepsis-associated immunosuppression increases hospital-acquired infection and viral reactivation risk. A key underlying mechanism is programmed cell death protein-1 (PD-1)-mediated T-cell function impairment. This is one of the first clinical safety and pharmacokinetics (PK) assessments of the anti-PD-1 antibody nivolumab and its effect on immune biomarkers in sepsis.

Methods: Randomized, double-blind, parallel-group, Phase 1b study in 31 adults at 10 US hospital ICUs with sepsis diagnosed ≥ 24 h before study treatment, ≥ 1 organ dysfunction, and absolute lymphocyte count ≤ 1.1×10^3 cells/μL. Participants received one nivolumab dose [480 mg ($n = 15$) or 960 mg ($n = 16$)]; follow-up was 90 days. Primary endpoints were safety and PK parameters.

Results: Twelve deaths occurred [$n = 6$ per study arm; 40% (480 mg) and 37.5% (960 mg)]. Serious AEs occurred in eight participants [$n = 1$, 6.7% (480 mg); $n = 7$, 43.8% (960 mg)]. AEs considered by the investigator to be possibly drug-related and immune-mediated occurred in five participants [$n = 2$, 13.3% (480 mg); $n = 3$, 18.8% (960 mg)]. Mean ± SD terminal half-life was 14.7 ± 5.3 (480 mg) and 15.8 ± 7.9 (960 mg) days. All participants maintained > 90% receptor occupancy (RO) 28 days post-infusion. Median (Q1, Q3) mHLA-DR levels increased to 11,531 (6528, 19,495) and 11,449 (6225, 16,698) mAbs/cell in the 480- and 960-mg arms by day 14, respectively. Pro-inflammatory cytokine levels did not increase.

Conclusions: In this sepsis population, nivolumab administration did not result in unexpected safety findings or indicate any ‘cytokine storm’. The PK profile maintained RO > 90% for ≥ 28 days. Further efficacy and safety studies are warranted.

Keywords

Sepsis; Anti-PD-1; Immunosuppression; Phase 1; Immune checkpoint inhibition; Nivolumab

Introduction

Sepsis continues to be a highly lethal condition, contributing to as many as one in every two-to-three hospital deaths [1–3]. Treatment in the acute setting involves a multi-pronged approach, including rapid administration of antibiotics, volume resuscitation, hemodynamic support of the circulation, and source control of the site of infection by drainage or excision. Most patients with sepsis survive the initial acute phase of the disease, but die following

subsequent complications days or weeks later [4]. New therapeutic approaches are needed to address these life-threatening complications.

It is likely that almost all patients with protracted sepsis who survive the initial hyper-inflammatory phase progress to a protracted phase of immunosuppression, characterized by reactivation of latent viruses, development of secondary hospital-acquired infections, organ failure, and death [5–10]. One of the features of sepsis-induced immunosuppression is upregulation of the T-cell exhaustion marker programmed cell death protein (PD-1) and its corresponding ligand (PD-L1) [5, 9, 11–13]. Upregulation of PD-1 leads to the suppression of T-cell function, with decreased production of key cytokines such as interferon (IFN)-γ and increased apoptotic cell death. This upregulation of PD-1/PD-L1 is associated with an increased risk of mortality or morbidity in animal sepsis models and in patients with sepsis [5, 11, 12, 14, 15]. This PD-1/PD-L1 upregulation is also seen in certain cancers [16]. Preclinical sepsis models and analyses of blood samples from patients with sepsis suggest that immunomodulation via blockade of this pathway with anti-PD-1/PD-L1 antibodies might restore immune cell function and improve survival [13–15, 17–20]. A recent case report in which nivolumab was used in combination with IFN-γ on a compassionate basis in a patient with intractable disseminated mucormycosis led to clearance of the mucormycosis and survival [21]. Collectively, these studies provide a strong rationale for clinical trials of checkpoint inhibitors in sepsis.

Nivolumab (Bristol-Myers Squibb, Princeton, NJ, USA, and ONO Pharmaceutical Co., Ltd., Osaka, Japan) is a fully human immunoglobulin G4 (IgG4) anti-PD-1 antibody that binds to PD-1 on T cells and other PD-1-expressing cells, blocking its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response [22]. It is currently approved for the treatment of multiple cancer types as repeat doses once every 2–4 weeks [22, 23]. In patients with cancer treated with nivolumab monotherapy, immune-mediated adverse events (AEs) such as pneumonitis, colitis, and hepatitis are reported in ≤ 3% of patients; hypothyroidism and rash are typically reported in ≤ 9% of patients with cancer [22, 24].

This is the one of the first studies to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of a single dose of nivolumab (480 mg or 960 mg) in participants with sepsis and low absolute lymphocyte count (ALC) [25]. This is also one of the first studies of immuno-adjuvant therapies targeting defects in adaptive immunity in patients with sepsis, and joins a recently completed single-dose Phase 1b evaluation of the fully human IgG4 anti-PD-L1 monoclonal antibody, BMS-936559 (Bristol-Myers Squibb), conducted in patients with sepsis (NCT02576457) [26].

Materials and methods

Ethics statement

This study (NCT02960854) was conducted in accordance with Good Clinical Practice, defined by the International Conference on Harmonization, the ethical principles underlying European Union Directive 2001/20/EC, and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50), and all applicable local requirements. Written informed

consent was gained for all participants. Institutional Review Boards and Independent Ethics Com mittees approved the study protocol and amendments.

Study design and population

This was a randomized, double-blind, multicenter, Phase 1b study of a single dose of nivolumab (480 mg or 960 mg) in participants with sepsis and low ALC to evaluate safety, PK, and PD (Supplementary Fig. S1). The doses selected were based on population-based PK modeling and simulation, and were projected to provide exposures comparable to steady-state levels of the approved 3 mg/kg every 2 weeks (Q2W) regimen in oncology (see Supplementary Information). A low ALC was specified as an inclusion criterion, because patients with low ALC and/or low CD4+ T-cell counts have increased incidence of infection consistent with impaired immunity due to lymphopenia; furthermore, studies show that patients with sepsis and persistently low ALC have a higher mortality [8, 27–31]. The study was conducted at 10 US sites (January 2017–January 2018) (see Supplementary Information). All participants also received standard-of-care therapy based on established sepsis management protocols [32].

Eligible participants were 18 years or older with documented or suspected infection and organ dysfunction. A period of ≥ 24 h from the onset of sepsis was required for each participant before nivolumab infusion; this was to account for resolution of the peak pro-inflammatory response associated with sepsis [33]. Participants also met at least one of the following organ dysfunction criteria: hypotension requiring treatment with any vasopressor(s) for ≥ 6 h to maintain systolic pressure ≥ 90 mmHg or mean arterial pressure ≥ 70 mmHg; acute respiratory failure requiring mechanical ventilation for ≥ 24 h; 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 h despite adequate fluid resuscitation). Participants with pre-existing renal impairment had to meet another organ dysfunction criterion. Participants were required to have at least one ALC ≤ 1.1×10^3 cells/μL within 96 h before study treatment infusion [27, 28]. They needed to be receiving treatment in an ICU with no plan for discharge in the next 24 h.

Participants were excluded if they had a previous episode of sepsis during the current hospitalization, had autoimmune disease, or a history of transplant. Prior exposure to nivolumab or any anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody was exclusionary (see Supplementary Information).

Treatment assignment and study procedures

Participants were centrally randomized using computerized Interactive Response Technology (IRT), which was designed to assign treatments in a random allocation, in a 1:1 ratio to receive a single 90-min intravenous infusion of nivolumab 480 mg or 960 mg (Supplementary Fig. S1). Infusions were prepared by an unblinded pharmacist at the site, who was the only person authorized to receive the description of the treatment based on his/her role in the IRT system. All other staff remained blinded. Participants were monitored during the infusion and for 90 days unless they died, withdrew consent for contact, or were lost to follow-up. Analysts were unblinded to the study treatments, but no unblinded data

were communicated to the investigators. The PK endpoints were objective assessments that should not have been affected by unblinding.

Study endpoints and assessments

The primary objective was to assess the safety, tolerability, and PK of a single dose of nivolumab (480 mg or 960 mg) over a 90-day period. Additional objectives were to assess receptor occupancy (RO) and the effect of nivolumab on markers of immune system status, including human leukocyte antigen-DR expression on monocytes (mHLA-DR), ALC, and cytokine levels.

Safety monitoring and physical/laboratory assessments—Participants were monitored for AEs throughout the study. Physical examinations, vital signs, electrocardiograms, and clinical safety laboratory assessments were conducted at selected timepoints. Immune-mediated AEs were a subcategory of AEs consistent with an immune-mediated mechanism or an immune-mediated component, for which non-inflammatory etiologies (e.g., infection or tumor progression) had been ruled out. Immune-mediated AEs noted in patients with cancer include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine dysfunction. The causal relationship of AEs to study drug was determined by the individual site investigators. Potential causes/contributing factors to the AEs/serious adverse events (SAEs) reported [e.g., elevated aspartate aminotransferase (AST) levels prior to dosing, necrotizing fasciitis] were subsequently proposed by the investigators following review of the individual case details. The study did not have an independent safety monitoring committee.

Serial blood samples were taken for PK, RO, mHLA-DR, ALC, and other biomarkers.

Pharmacokinetics—Serum nivolumab was measured by an electrochemiluminescent assay validated in serum from healthy humans and patients with selected cancers to a lower limit of quantitation of 0.2 μg/mL [Bristol-Myers Squibb. Method validation report: quantitative determination of BMS-936558 in human serum by electrochemiluminescent assay. 2011 (document control number 930057755)]. PK parameters derived from concentration versus time data were: maximum serum concentration (C_{max}), area under the serum concentration–time curve (AUC) from time 0 to the time of last quantifiable concentration, AUC from time 0 to infinity ($AUC_{(INF)}$), total clearance (CLT), volume of distribution at steady state (V_{ss}), time of maximum concentration (T_{max}), and terminal half-life ($T_{1/2}$).

Nivolumab receptor occupancy and immune system biomarkers—PD-1 RO on CD3+ T cells and mHLA-DR expression over 90 days were determined using flow cytometry-based assays [34]. The PD-1 RO and mHLA-DR gating strategies are described in Supplementary Figs. S2a and S2b. As previously reported [26], an RO level of ≥ 80% was expected to restore or enhance T-cell function, and was considered a relevant threshold. An RO of 90% was the level of RO measured in this study. mHLA-DR levels above 5000 monoclonal antibodies (mAb)/cell were considered to reflect improvement in immune status based on previous studies [35]. ALC was determined using a standard hematology analyzer.

Levels of pro- and anti-inflammatory cytokines [interleukin (IL)-6, IL-8, IL-10, IL-18, and tumor necrosis factor (TNF)-α] were measured using Luminex bead assays (Myriad-Rules Based Medicine, Austin, TX) in samples at specified timepoints up to 90 days post-infusion. The selection of cytokines was based on review of the literature and previous studies. A 'cytokine storm' was broadly defined as the severe clinical syndrome of fever, shock, and organ failure that can occur during life-threatening infection and is associated with a burst of pro-inflammatory cytokines [36, 37].

Statistical methods

The study was designed to assess safety and tolerability. The number of participants was selected to have sufficient probability of observing AEs that were common in this population. Simulations showed that the administration of nivolumab to approximately 15 participants in each arm provided an 80% probability of observing at least one occurrence of any AE that would occur with ≥ 10% incidence in the population.

AEs were summarized by system organ class and preferred term (Medical Dictionary for Regulatory Activities Version 20.0). Individual participant PK parameter values were derived by non-compartmental methods using actual sampling times [Phoenix™ WinNonlin®, v6.3 or higher (Pharsight Corporation, Phoenix, Mountain View, CA, USA)], and summary statistics by treatment were tabulated as geometric mean [% coefficient of variation (% CV)], arithmetic mean [± standard deviation (SD)] or median (min, max). PD-1 RO levels were reported as percentages by treatment and time. All other endpoints were assessed by summary statistics by time and treatment, and as changes from baseline.

Results

Participant disposition and baseline characteristics

Of 38 participants enrolled, 31 patients at 10 sites were randomized to receive nivolumab 480 mg (n = 15) or 960 mg (n = 16) (Fig. 1). There were two sites where a single participant enrolled. Baseline disease characteristics were consistent with an ICU-bound sepsis population at high risk for mortality (Table 1). At baseline, median (Q1, Q3) ALC was 0.7 (0.5, 0.9) × 10^3 cells/μL, median (Q1, Q3) mHLA-DR was 2950 (1518, 6534) mAb/cell, and the median (Q1, Q3) sequential organ failure assessment (SOFA) score was 9 (7, 13) (Table 1).

Safety

Participants were followed for 90 days post-nivolumab infusion. During this time, 12 deaths occurred (six per group) between 1 and 39 days after nivolumab infusion (the median time was 9.5 days) (Table 2; Supplementary Table S1), none of which were considered by the investigator to be related to study treatment. Three of the deaths occurred outside of the index hospitalization (at days 9, 35, and 39 post-dose, with all three occurring in the 480-mg treatment group) and were recorded as being of "unknown" cause. The investigators attempted to ascertain the cause of death in these participants, but it was not possible to do so (Supplementary Table S1). The most frequently reported (≥ 20%) AEs for the pooled nivolumab dose groups were anemia (n = 16; 51.6%), pyrexia (n = 11; 35.5%), worsening

hypotension (n = 10; 32.3%), pleural effusion (n = 8; 25.8%), diarrhea (n = 7; 22.6%), and hypernatremia (n = 7; 22.6%) (Table 2). The total number of any-Grade events was 476; of these, 174 (36.6%) were Grades 3–4 and two (0.4%) were Grade 5. Therefore, most AEs were Grades 1–2. There were 15 any-Grade SAEs; 13 (86.7%) were Grades 3–4; and two (13.3%) were Grade 5. SAEs occurred in eight participants [n = 1 (6.7%) in the 480-mg nivolumab group and n = 7 (43.8%) in the 960-mg nivolumab group] (Table 2; Supplementary Table S2). No AEs resulted in discontinuation from the study.

AEs, including one SAE, considered by the investigator to be possibly drug-related and immune-mediated occurred in five participants (16.1%): one participant (female, 29 years) in the nivolumab 480-mg group had increased bilirubin (Grade 1), starting approximately 6 h after dosing and resolving after 3 days. The same participant had hepatitis (Grade 2), elevated alanine aminotransferase (ALT; 105 U/L), and elevated AST (162 U/L) starting 9 days after nivolumab dosing. Potential contributing factors to this event included elevated AST levels prior to dosing (93 U/L) and acetaminophen treatment. ALT and AST values normalized within 11 days, although hepatitis was reported for 79 days. No specific treatment was required. One participant (male, 57 years) in the nivolumab 480-mg group had a maculopapular rash (Grade 1) starting 5 days after dosing and resolving within 15 days without requiring treatment. One participant (male, 47 years) in the nivolumab 960-mg group had hypothyroidism (Grade 2) starting 23 days after dosing and continuing at study end. Levels of thyroid-stimulating hormone were within normal limits at baseline and were at 28.0 mU/L at day 64 (upper limit of normal: 4.2 mU/L). This participant received levothyroxine for the hypothyroidism. A potential cause of this patient's hypothyroidism was necrotizing fasciitis that required extensive debridement and removal of tissues in the anterior mediastinum (likely containing part of the thyroid gland) and part of the thyroid cartilage. One participant (male, 63 years) in the nivolumab 960-mg group had a rash (Grade 3) starting 5 days after dosing and resolving after 14 days. Potential contributing factors included concomitant treatment with piperacillin/tazobactam (day − 3 to day 1), vancomycin (day − 3 to day 4), tobramycin (day 2), linezolid (days 2–32), meropenem (day 4), and cefuroxime (days 4–7). One participant (male, 65 years) in the nivolumab 960-mg group had acute kidney injury (Grade 3; SAE) starting 8 days after dosing, peaking 14 days after dosing, and declining by 22 days after dosing; no treatment was required (Table 2; Supplementary Table S2). A potential contributing factor was sepsis-associated disseminated intravascular coagulation, which occurred 3 days prior to the event.

Pharmacokinetics

Mean serum concentration–time profiles for nivolumab 480 mg and 960 mg are presented in Fig. 2. At day 30, approximately 50% of participants receiving the 960-mg dose achieved exposures equal to or higher than the predicted fifth percentile of steady-state trough concentrations (20.1 μg/mL) predicted in participants with melanoma receiving nivolumab 3 mg/kg Q2W. The mean $T_{1/2}$ ranged from 353 to 378 h (14.7–15.8 days). C_{max} values for the 480-mg and 960-mg doses were 82 and 196 μg/mL, respectively, and $AUC_{(INF)}$ was 18,961 and 36,190 μg•h/mL respectively (Supplementary Table S3). Mean CLT values for nivolumab 480 mg and 960 mg were 0.025 and 0.027 L/h, respectively; mean apparent V_{ss} values were 10.9 L and 10.4 L, respectively. The variability in values was high for the $T_{1/2}$

(SD: 127–190 h), moderate for the $AUC_{(INF)}$ and CLT (50–85%), and modest for the C_{max} and V_{ss} parameters (20–38%). A previously conducted population PK analysis from seven Phase 1–3 nivolumab studies in patients with solid tumors reported the following geometric mean (% CV) model-based estimates: $T_{1/2}$ 26.7 days (101%), CLT 0.0095 L/h (50%), and V_{ss} 8.0 L (30%) [Bristol-Myers Squibb. Nivolumab (BMS-936558) Module 2.7.2, Summary of Clinical Pharmacology. 2014 (document control number 930081739)].

Pharmacodynamics and biomarkers

All participants had > 90% RO at 28 days post-infusion, with the majority having > 90% RO at day 90 post-infusion (Fig. 3a).

Levels of mHLA-DR expression increased over time with both doses (Fig. 3b and Supplementary Fig. S3). By day 14, median mHLA-DR levels were > 5000 mAb/cell in both dose groups, with median (Q1, Q3) levels at day 90 of 17,852 (14,400, 23,867) and 13,699 (7263, 17,908) mAb/cell for nivolumab 480 mg and 960 mg, respectively.

Median ALCs did not change substantially over time (Supplementary Figs. S4a and S4b).

IL-6 levels in individual participants were variable; however, there was a consistent trend towards decreasing levels of IL-6 following nivolumab administration (Supplementary Fig. S5). Levels of IL-8, IL-10, IL-18, and TNF-α were also variable between participants (Supplementary Figs. S6–S9). There was no evidence of an overall increase in the levels of these cytokines over time in either dose group.

Discussion

This is one of the first evaluations of a checkpoint inhibitor in patients with sepsis. Within the limits imposed by a study of this size, nivolumab administration did not result in any unexpected safety findings (i.e., that were not consistent with the current label) in this ICU-bound sepsis population [22, 23], with baseline characteristics predictive of a high risk for mortality. Most AEs were mild to moderate and were not unexpected for this population. AEs considered by the investigator to be possibly drug-related and immune-mediated (increased bilirubin/hepatitis, rash, hypothyroidism, acute kidney injury) occurred in this study. Although these AEs were considered by the investigator to be possibly drug-related, the assessment of causality was confounded by the participants' underlying sepsis and concurrently administered medicines. Cytokine analyses found no evidence of a 'cytokine storm'. This finding may be affected by other factors (e.g., sampling times that do not allow for detection of sudden or transient changes in cytokine levels, localized versus systemic cytokine changes, and sample size) [26]. However, these results are consistent with those from the clinical study of anti-PD-L1 (BMS-936559) in sepsis [26].

The causes of mortality and overall mortality rate (39%) were not unexpected given the participants' baseline disease profile. Based on the literature and the authors' own clinical experience, a 90-day mortality of ~ 40–50% might be expected [8, 27, 28, 38–40].

Both nivolumab doses displayed a predictable PK profile and dose-related increases in exposure. Exposure to nivolumab 960 mg was comparable with nivolumab 3 mg/kg Q2W

in oncology at approximately day 30. Based on a previously obtained population PK analysis of patients with solid tumors, elimination was faster in these participants with sepsis than in patients with cancer (CLT ~ 0.03 L/h versus ~ 0.01 L/h, respectively; $T_{1/2}$ ~ 15–16 days versus ~ 27 days, respectively) and V_{ss} was higher (~ 10.5 L versus 8.0 L, respectively) [Bristol-Myers Squibb. Nivolumab (BMS-936558) Module 2.7.2, Summary of Clinical Pharmacology. 2014 (document control number 930081739)]. These differences were also seen in the study of anti-PD-L1 (BMS-936559) in patients with sepsis [26]. Sepsis-associated pathophysiological disturbances affect drug distribution, metabolism, and elimination, and so PK differences in the sepsis and oncology settings may be expected. However, these results should be interpreted carefully due to low participant numbers and high variability, and because of different medical interventions that could influence PK (e.g., fluid resuscitation, renal replacement therapy, and infusion of blood products). The RO data showed a persistently high level of target engagement with both doses.

There was also a progressive increase in mHLA-DR expression over time with both doses, consistent with an improvement in immune status. However, the absence of a placebo arm prevents ascertaining a direct effect of nivolumab.

There are several novel aspects to the present study. This study of nivolumab stands in contrast to many previous clinical trials in sepsis that used therapies to dampen inflammation and suppress the host immune response [41, 42]. The study is based on a new paradigm of sepsis which recognizes that as sepsis persists, it progresses to a state of immune suppression and T-cell exhaustion [5–9]. Another novel aspect is that it represents a new application of checkpoint inhibitors. Although they are widely used and have revolutionized cancer treatment, this is one of the first evaluations of a checkpoint inhibitor in patients with sepsis. Anti-PD-1 antibodies have improved survival in multiple clinically relevant animal models of sepsis, and ex vivo treatment of immune effector cells from septic patients with anti-PD-1/L1 has restored T-cell function and decreased cell death [13–15, 17–20]. Thus, there is a sound scientific rationale for clinical trials of checkpoint inhibitors in sepsis. A final distinctive aspect of this study is that it represents one of the first clinical trials focused on reversing sepsis-induced defects in adaptive immunity, i.e., CD4+ and CD8+ T cells. The few previous immuno-adjuvant therapy trials that sought to enhance immunity in patients with sepsis utilized cytokines and growth factors (e.g., G-CSF, GM-CSF, IL-7, IL-15, and IFN-γ) to increase the number and function of monocytes, macrophages, and neutrophils, which are key cellular components of the innate immune system [43]. Based on the results of both this study and the Phase 1b evaluation of the anti-PD-L1 antibody BMS-936559 [26], additional clinical studies of the efficacy and safety of checkpoint inhibitors in sepsis are warranted.

This study was intended to be a feasibility study, and it was not the intention to conduct a between-dose safety comparison. Nevertheless, this study has several limitations, most notably the lack of a placebo group, which makes it difficult to make too many inferences. Further-more, the sample size was small and there was a limited dose range tested. The assessment of biomarkers was also restricted to a limited number. Lymphopenia was chosen as an inclusion criterion, although this is not predictive of response to checkpoint

inhibitors in oncologic patients [44]. However, individuals with sepsis who have persistent lymphopenia are more likely to be in the immunosuppressive phase of the disorder [7, 28].

Future trials would include a wider range of doses in a larger number of patients. Additional biomarkers, which may correlate with outcomes, would be included, such as soluble PD-1, soluble PD-L1, and lymphocyte and monocyte expression of PD-1 and PD-L1. In addition to using lymphopenia to identify immunosuppressed patients, other sepsis patient groups would be considered, such as those who present with hypothermia, the elderly, those on chronic hemodialysis, with fungal sepsis, or sepsis due to multiple drug-resistant bacteria.

Conclusions

This was one of the first studies of the PD-1 inhibitor nivolumab in patients with sepsis and low ALC. Although this was a study involving a small number of participants, nivolumab administration did not result in any unexpected safety findings; specifically, there was no evidence of worsening fever, shock, or other signs or symptoms of ‘cytokine storm’. The PK profile of nivolumab resulted in RO of > 90% for at least 28 days. Findings were consistent with those in an earlier study of anti-PD-L1 (BMS-936559) in sepsis [26]. Further study of immunotherapies targeting the PD-1/PD-L1 pathway is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Take-home message

There were no safety concerns reported with nivolumab in an ICU-bound sepsis population at high risk for mortality and no indication of a ‘cytokine storm’; findings were consistent with those of the anti-PD-L1, BMS-936559, in participants with sepsis-induced immuno-suppression. Further efficacy and safety studies are needed to assess the potential of checkpoint inhibitors as a treatment for sepsis.

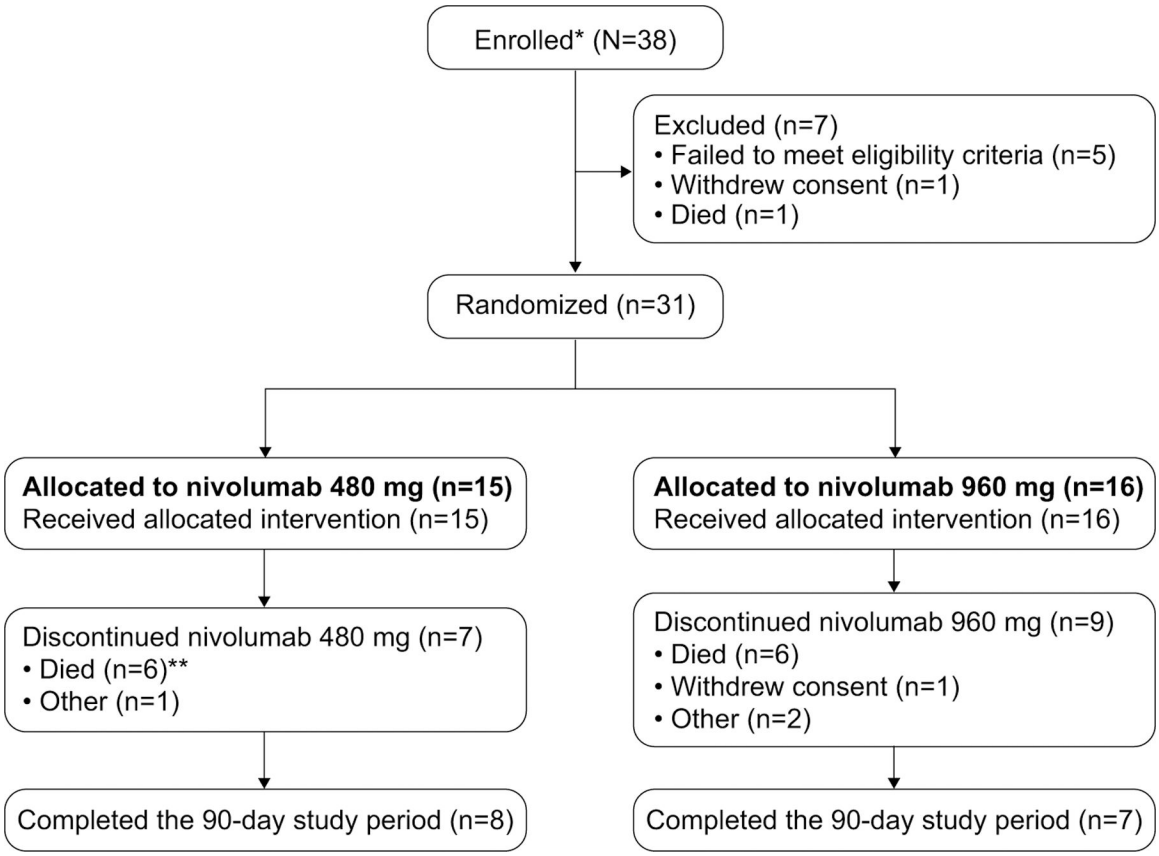

Fig. 1.

Study participant flow chart. Single asterisk: individuals were enrolled for whom consent to participate in the study was provided. Double asterisk: one participant met study criteria pre-dose but subsequently transitioned to ‘do not resuscitate’ post-dose and died. Another participant who discontinued for a reason classified as ‘other’ died after discontinuation

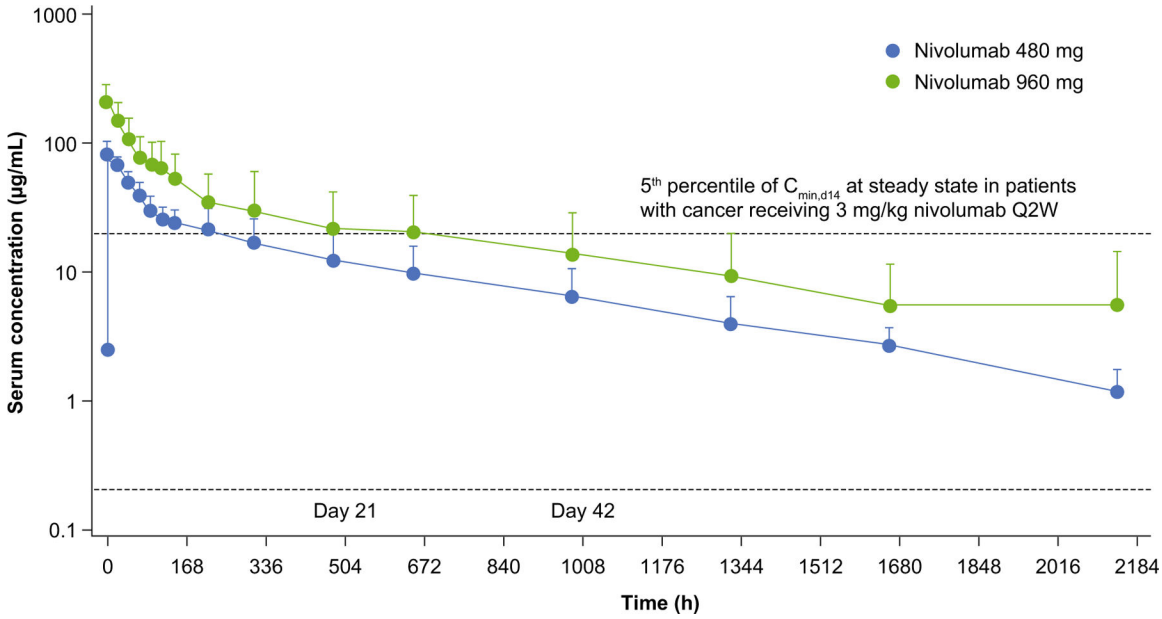

Fig. 2.

Mean (standard deviation) plot of serum nivolumab concentration versus time after single intravenous infusion (semi-log scale). The lower dashed line represents the lower limit of quantitation (0.2 µg/mL). $C_{min,d14}$ minimum concentration at 14 days, *Q2W* every 2 weeks

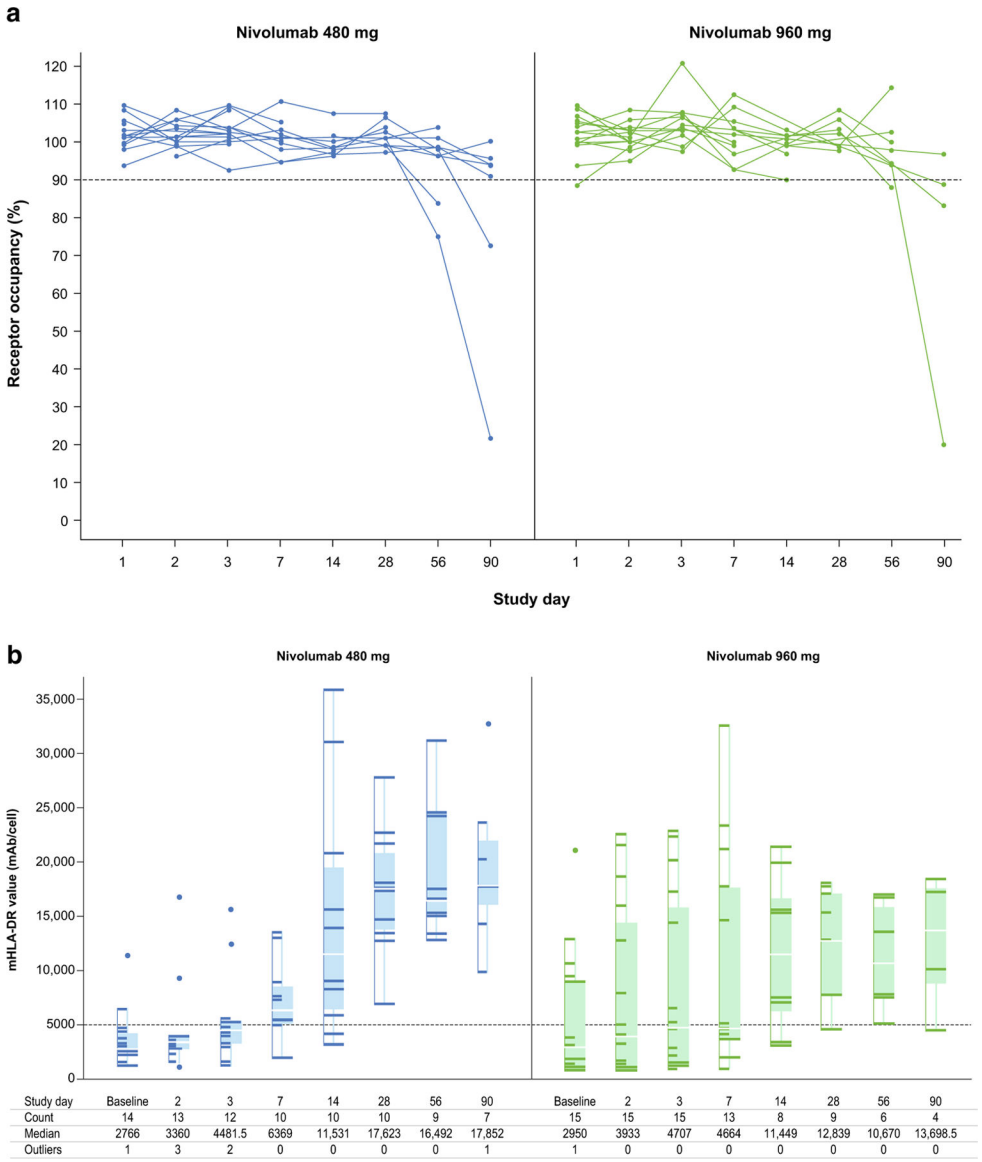

Fig. 3.

Receptor occupancy and monocyte human leukocyte antigen-DR expression with nivolumab over time. **a** PD-1 receptor occupancy with nivolumab on CD3 ± T cells over the 90-day study period. Dashed line represents 90% receptor occupancy. **b** mHLA-DR expression with nivolumab over the 90-day study period. For **b**, horizontal colored lines represent individual participants; if two participants have the same value, the pair are represented by one full-length line and a half-length line represents one participant; colored circles represent outliers, horizontal pale lines represent median mHLA-DR values, vertical shaded boxes show the interquartile range, and vertical lines show the min–max range (excluding the outliers). Dashed line represents mHLA-DR 5000 mAb per cell. Timepoints with visit windows (**a**, **b**): day 14 ± 1, day 28 ± 3, day 56 ± 5, and day 90 ± 9. *CD* cluster of

differentiation, *mAb* monoclonal antibody, *mHLA-DR* monocyte human leukocyte antigen-DR, *PD-1* programmed cell death protein-1

Table 1

Baseline demographics and disease parameters

Parameter	Nivolumab treatment		
	480 mg (*n* = 15)	**960 mg (*n* = 16)**	**Total (*n* = 31)**
Age, years; median (min, max)	58 (29, 77)	64 (25, 78)	60 (25, 78)
Age categorization, *n* (%)			
< 65 years	10 (66.7)	8 (50.0)	18 (58.1)
≥ 65 years	5 (33.3)	8 (50.0)	13 (41.9)
Sex, n (%)			
Male	11 (73.3)	10 (62.5)	21 (67.7)
Female	4 (26.7)	6 (37.5)	10 (32.3)
Race, *n* (%)			
White	12 (80.0)	11 (68.8)	23 (74.2)
Black/African American	2 (13.3)	4 (25.0)	6 (19.4)
Other	1 (6.7)	1 (6.3)	2 (6.5)
ALC[a], × 10^3 cells/μL			
Mean (SD)	0.73 (0.30)	0.67 (0.24)	0.70 (0.27)
Median (Q1, Q3)	0.80 (0.50, 1.00)	0.68 (0.54, 0.82)	0.70 (0.50, 0.90)
mHLA-DR[b], mAb/cell			
Mean (SD)	3610 (2712)	5860 (5983)	4774 (4756)
Median (Q1, Q3)	2766 (2209, 4334)	2950 (1136, 9341)	2950 (1518, 6534)
Site of infection, *n* (%)			
Abdominal cavity	5 (33.3)	–	5 (16.1)
Bone/joint	–	4 (25.0)	4 (12.9)
CNS	1 (6.7)	–	1 (3.2)
Lung	6 (40.0)	7 (43.8)	13 (41.9)
Other	–	2 (12.5)	2 (6.5)
Reproductive tract	1 (6.7)	–	1 (3.2)
Skin/soft tissue	2 (13.3)	2 (12.5)	4 (12.9)
Urinary tract	–	1 (6.3)	1 (3.2)

Parameter	Nivolumab treatment		
	480 mg (*n* = 15)	960 mg (*n* = 16)	Total (*n* = 31)
Number of organ dysfunctions[c], *n* (%)			
1	2 (13.3)	2 (12.5)	4 (12.9)
2	6 (40.0)	4 (25.0)	10 (32.3)
3	7 (46.7)	10 (62.5)	17 (54.8)
SOFA score (continuous)			
Mean (SD)	10.6 (4.0)	9.5 (4.2)	10.0 (4.1)
Median (Q1, Q3)	10.0 (8.0, 13.0)	9.0 (6.5, 11.5)	9.0 (7.0, 13.0)

ALC absolute lymphocyte count, *CNS* central nervous system, *mAb* monoclonal antibody, *mHLA-DR* monocyte human leukocyte antigen-DR, *n* number of participants, *Q* quartile, *SD* standard deviation, *SOFA* sequential organ failure assessment

[a] ALC values shown represent the lowest recorded in the 96 h prior to dosing

[b] Baseline data available for *n* = 14 (480 mg) and *n* = 15 (960 mg)

[c] Organ dysfunction refers to the one of three organ dysfunctions that participants were required to have to be eligible for the study and is not inclusive of all organ dysfunctions that they may have been experiencing

Table 2

Safety results for all treated participants

System organ class Preferred term	Nivolumab 480 mg (*n* = 15)		Nivolumab 960 mg (*n* = 16)		Total (*n* = 31)	
	Any Grade	Grades 3–4	Any Grade	Grades 3–4	Any Grade	Grades 3–4
Deaths, *n* (%)	6 (40.0)		6 (37.5)		12 (38.7)	
Drug-related SAEs						
Total participants with a drug-related SAE, *n* (%)	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
Renal and urinary disorders, *n* (%)	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
Acute kidney injury	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
SAEs						
Total participants with an SAE, *n* (%)	1 (6.7)	1 (6.7)	7 (43.8)	5 (31.3)	8 (25.8)	6 (19.4)
Gastrointestinal disorders, *n* (%)	1 (6.7)	1 (6.7)	2 (12.5)	2 (12.5)	3 (9.7)	3 (9.7)
Gastrointestinal hemorrhage	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
Intra-abdominal hemorrhage	1 (6.7)	1 (6.7)	–	–	1 (3.2)	1 (3.2)
Megacolon	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
Blood and lymphatic system disorders, *n* (%)	–	–	2 (12.5)	2 (12.5)	2 (6.5)	2 (6.5)
Anemia	–	–	2 (12.5)	2 (12.5)	2 (6.5)	2 (6.5)
Disseminated intravascular coagulation	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
Thrombocytopenia	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
Infections and infestations, *n* (%)	1 (6.7)	1 (6.7)	1 (6.3)	1 (6.3)	2 (6.5)	2 (6.5)
Abdominal abscess	1 (6.7)	1 (6.7)	–	–	1 (3.2)	1 (3.2)
Urosepsis	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
Renal and urinary disorders, *n* (%)	–	–	2 (12.5)	2 (12.5)	2 (6.5)	2 (6.5)
Acute kidney injury	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
Ureterolithiasis	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
Cardiac disorders, *n* (%)	–	–	1 (6.3)	–	1 (3.2)	–
Cardiac arrest	–	–	1 (6.3)	–	1 (3.2)	–
General disorders and administration site conditions, *n* (%)	–	–	1 (6.3)	–	1 (3.2)	–
Multiple organ dysfunction syndrome	–	–	1 (6.3)	–	1 (3.2)	–
Investigations, *n* (%)	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
Electrocardiogram ST segment elevation	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)

System organ class Preferred term	Nivolumab 480 mg (*n* = 15)		Nivolumab 960 mg (*n* = 16)		Total (*n* = 31)	
	Any Grade	Grades 3–4	Any Grade	Grades 3–4	Any Grade	Grades 3–4
Metabolism and nutrition disorders, *n* (%)	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
Acidosis	–	–	1 (6.3)	1 (6.3)	1 (3.2)	1 (3.2)
AEs with incidence ≥ 20%						
Total participants with an AE with incidence ≥ 20%, *n* (%)	14 (93.3)	10 (66.7)	14 (87.5)	12 (75.0)	28 (90.3)	22 (71.0)
Gastrointestinal disorders, *n* (%)	11 (73.3)	6 (40.0)	5 (31.3)	4 (25.0)	16 (51.6)	0 (32.3)
Diarrhea	5 (33.3)	–	2 (12.5)	1 (6.3)	7 (22.6)	1 (3.2)
Nausea	4 (26.7)	–	2 (12.5)	1 (6.3)	6 (19.4)	1 (3.2)
Vomiting	3 (20.0)	–	2 (12.5)	1 (6.3)	5 (16.1)	1 (3.2)
Metabolism and nutrition disorders, *n* (%)	7 (46.7)	3 (20.0)	11 (68.8)	7 (43.8)	18 (58.1)	10 (32.3)
Hypernatremia	3 (20.0)	–	4 (25.0)	1 (6.3)	7 (22.6)	1 (3.2)
Malnutrition	1 (6.7)	–	4 (25.0)	1 (6.3)	5 (16.1)	1 (3.2)
Respiratory, thoracic, and mediastinal disorders, *n* (%)	7 (46.7)	3 (20.0)	10 (62.5)	7 (43.8)	17 (54.8)	10 (32.3)
Pleural effusion	3 (20.0)	1 (6.7)	5 (31.3)	2 (12.5)	8 (25.8)	3 (9.7)
Atelectasis	–	–	4 (25.0)	–	4 (12.9)	–
Vascular disorders, *n* (%)	7 (46.7)	4 (26.7)	7 (43.8)	6 (37.5)	14 (45.2)	10 (32.3)
Hypotension	6 (40.0)	4 (26.7)	4 (25.0)	4 (25.0)	10 (32.3)	8 (25.8)
General disorders and administration site conditions, *n* (%)	6 (40.0)	1 (6.7)	7 (43.8)	2 (12.5)	13 (41.9)	3 (9.7)
Pyrexia	5 (33.3)	–	6 (37.5)	–	11 (35.5)	–
Blood and lymphatic system disorders, *n* (%)	6 (40.0)	6 (40.0)	13 (81.3)	9 (56.3)	19 (61.3)	15 (48.4)
Anemia	6 (40.0)	6 (40.0)	10 (62.5)	7 (43.8)	16 (51.6)	13 (41.9)
Leukocytosis	2 (13.3)	2 (13.3)	4 (25.0)	1 (6.3)	6 (19.4)	3 (9.7)
Skin and subcutaneous tissue disorders, *n* (%)	3 (20.0)	–	5 (31.3)	2 (12.5)	8 (25.8)	2 (6.5)
Decubitus ulcer	1 (6.7)	–	4 (25.0)	2 (12.5)	5 (16.1)	2 (6.5)

All recorded AEs were summarized by system organ class and preferred term using MedDRA Version 20.0. Participants could have experienced more than one AE/SAE

AEs were graded according to the National Cancer Institute CTCAE Version 4.03

AE adverse event, *CTCAE* Common Terminology Criteria for Adverse Events, *MedDRA* Medical Dictionary for Regulatory Activities, *n* number of participants, *SAE* serious adverse event