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Introduction:
The PD-1/PD-L1 immune checkpoint pathway is involved in sepsis-associated immunopathy. We assessed the safety of anti-PD-L1 (BMS-936559, Bristol-Myers Squibb) and its effect on immune biomarkers and exploratory clinical outcomes in participants with sepsis-associated immunopathy.

Methods:
Participants with sepsis/septic shock and absolute lymphocyte count ≤1100 cells/μL received BMS-936559 i.v. (10–900mg; n=20) or placebo (PBO; n=4) + standard of care and were followed for 90d. Primary endpoints were death and adverse events (AEs); secondary endpoints were monocyte (m)HLA-DR levels and clinical outcomes.

Results:
Apart from the treated group being older (median 62y treated pooled vs 46y PBO) and sicker (≥3 organ dysfunctions: 55% treated pooled vs 25% PBO), baseline characteristics were comparable. 6/24 (25%) participants died (10mg: 2/4 [50%]; 30mg: 2/4 [50%]; 100mg: 1/4 [25%]; 300mg: 1/4 [25%] 900mg: 0/4; PBO: 0/4). All participants had AEs (grade 1–2: 75%), with one participant (30mg) having potentially drug-related AEs (grade 1–2 increases in amylase, lipase and LDH). 3/20 (15%) treated pooled and 1/4 (25%) PBO had a serious AE, with none deemed drug-related. AEs of special interest (AEOSI, i.e. potentially immune-related) occurred in ≥1 participant per group, with diarrhea (33%) the most common. All but 3 AEOSI (1 lung infiltration, 2 diarrhea) were grade 1–2. At the two highest doses there was a trend toward an increase in mHLA-DR expression (>5000 mAb/cell) that persisted beyond 30d. No clear dose-relationship or between-group difference in clinical outcomes (duration of organ support, viral reactivation, ICU/hospital length of stay) was seen.

Conclusion:
In this sick population, BMS-936559 was well tolerated. There were no AEs indicative of an excessive drug-induced pro-inflammatory state. At higher doses, a trend toward sustained restoration of mHLA-DR expression was seen. These findings justify further study of PD-1/PD-L1 inhibitors in sepsis.