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Multicenter, open-label, phase I study of DSP-7888 Dosing Emulsion in patients with advanced malignancies

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Supplementary Data

Supplementary Methods S1

Inclusion criteria

Adults aged ≥18 years with histologically or cytologically confirmed advanced malignancies and an Eastern Cooperative Oncology Group performance status of ≤2 were eligible for enrollment. Additionally, patients had to have experienced disease progression or recurrence despite receiving appropriate standard therapy, or have a malignancy with no standard therapy, or be intolerant to or not be a candidate for standard therapy, and additional or alternative standard therapies either did not exist or had been exhausted, and not be a candidate for allogeneic hematopoietic stem cell transplantation (acute myeloid leukemia [AML] and myelodysplastic syndrome [MDS] only). Patients also had to test positive for human leukocyte antigen (HLA)-A*02:01, HLA-A*02:06, and/or HLA-A*24:02. Patients with solid tumors had to have measurable disease per immune-related response criteria (or Gynecologic Cancer Intergroup criteria for those with ovarian cancer evaluable by CA-125 only) [1-3] and hemoglobin ≥9.0 g/dL, absolute lymphocyte count ≥1.0 × 10^9/L, absolute neutrophil count ≥1.5 × 10^9/L, and platelets ≥100.0 × 10^9/L. Patients with MDS had to have been diagnosed per the World Health Organization (fourth edition) or French-American-British classification system and an International Prognostic Scoring System (IPSS) score ≥1.5 or an IPSS score <1.5 with evidence of transfusion dependency (disease requiring ≥2 units of red blood cells or ≥10 units of platelets in the 8 weeks prior to enrollment). Patients with AML or MDS also had to have a white blood cell count ≤50,000 cells/μL.

Exclusion criteria

Exclusion criteria included left ventricular ejection fraction ≤40%; total bilirubin >2.0 mg/dL (>3.0 mg/dL for patients with Gilbert's syndrome); aspartate transaminase >3.0 × the upper limit of normal (ULN) (or ≥5 × ULN in the presence of liver metastases); alanine transaminase >3.0 × ULN (or ≥5 × ULN in the presence of liver metastases); creatinine >2.0 × ULN; extensively disseminated primary glioblastoma; acute promyelocytic leukemia; symptomatic brain metastases; use of systemic, pharmacologic doses of corticosteroids equivalent to >10 mg prednisone/day; surgery, radiotherapy, or chemotherapy (including molecular-targeted drugs) or use of immunosuppressants or cytokine formulations (excluding granulocyte colony stimulating factor) in the 4 weeks

prior to enrollment; and use of endocrine therapy or immunotherapy (including biological response modifier therapy) in the 2 weeks prior to enrollment.

Supplementary Methods S2

Dose-limiting toxicities (DLTs)

DLTs were evaluated over days 1–29. A DLT was defined as the occurrence of any grade ≥3 treatment-emergent adverse event (TEAE) that was at least possibly related to study treatment, except for grade 3 injection site reactions that were anticipated and adequately controlled by medical treatment (e.g. topical steroid administration). Other TEAEs not considered DLTs were inadequately treated nausea, vomiting, diarrhea, or fever, as these events were not commonly considered to be dose-limiting. For patients with MDS, grade 3–4 hematologic toxicities were not considered DLTs, since these were considered part of the disease process.

Supplementary Methods S3

Cytotoxic T lymphocyte (CTL) induction assessment

Peripheral blood samples were obtained for the evaluation of Wilms' tumor (WT1)-specific CTL induction activity by tetramer assay, which contained three WT1 tetramer types. Activity was assessed by tetramer-positive $CD8^+$ T-cell event number and the ratio of post/pretreatment tetramer-positive $CD8^+$ T-cell events. A result was considered positive if the posttreatment sample had ≥10 events and the post/pretreatment ratio was ≥2. If tetramer-positive $CD8^+$ T-cell events were not detected in the pretreatment sample, a result was considered positive if the posttreatment sample had ≥10 events. If any of the three tetramer reagents were positive, then the blood sample was considered positive for WT1-specific CTL induction activity.

Supplementary Methods S4

HLA immunohistochemistry (IHC)

To determine HLA expression in patients with solid tumors (exploratory endpoint), tumor samples were obtained before the first and after the last dose of study drug in consenting patients. Archived tissue could have been provided for the pretreatment tumor sample, and provision of a biopsy after the last dose of study drug was not mandatory.

HLA class I membrane expression was determined by IHC using monoclonal mouse antihuman HLA-ABC (EMR8-5, Abcam, Cambridge, UK), and HLA class II membrane expression was determined by IHC using monoclonal mouse antihuman HLA-DR, alpha-chain (Dako Carpinteria, CA). Staining was evaluated independently by three pathologists, and graded based on staining intensity and/or the percentage of stained cells. For evaluation of HLA class I staining: grade 0 = <10% of tumor cells; grade 1+ = moderate or greater stain in 10%–<50% of tumor cells, or weak stain in ≥10% of tumor cells; grade 2+ = moderate or greater stain in 50%–<90% of tumor cells; and grade 3+ = moderate or greater stain in ≥90% of tumor cells. For evaluation of HLA class II staining: grade 0 = <1% of tumor cells; grade 1+ = 1%–<10%; grade 2+ = 10%–<50%; and grade 3+ = ≥50%.

Supplementary References

1. Hoos A, Eggermont AM, Janetzki S, Hodi FS, Ibrahim R, Anderson A, et al. Improved endpoints for cancer immunotherapy trials. J Natl Cancer Inst. 2010;102:1388–97.
2. Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011;21:419–23.
3. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412–20.

Supplementary Table S1. DSP-7888 Dosing Emulsion dose levels

Dose level	Dose	Number of injection sites
	ID	
I	3.5 mg (2.0 mg killer peptide + 1.5 mg helper peptide)	2
II	10.5 mg (6.0 mg killer peptide + 4.5 mg helper peptide)	6
III	17.5 mg (10.0 mg killer peptide + 7.5 mg helper peptide)	10
	SC	
I	3.5 mg (2.0 mg killer peptide + 1.5 mg helper peptide)	2
II	10.5 mg (6.0 mg killer peptide + 4.5 mg helper peptide)	2

ID, intradermal; SC, subcutaneous.

Supplementary Table S2. Overall assessment of CTL induction activity in evaluable patients

Parameter, n (%)	ID DSP-7888				SC DSP-7888		
	3.5 mg (n=4)	10.5 mg (n=3)	17.5 mg (n=2)	Overall (N=9)	3.5 mg (n=7)	10.5 mg (n=5)	Overall (N=12)
CTL induction activity							
Positive	3 (75.0)	2 (66.7)	1 (50.0)	6 (66.7)	3 (42.9)	2 (40.0)	5 (41.7)
Negative	1 (25.0)	1 (33.3)	1 (50.0)	3 (33.3)	4 (57.1)	3 (60.0)	7 (58.3)

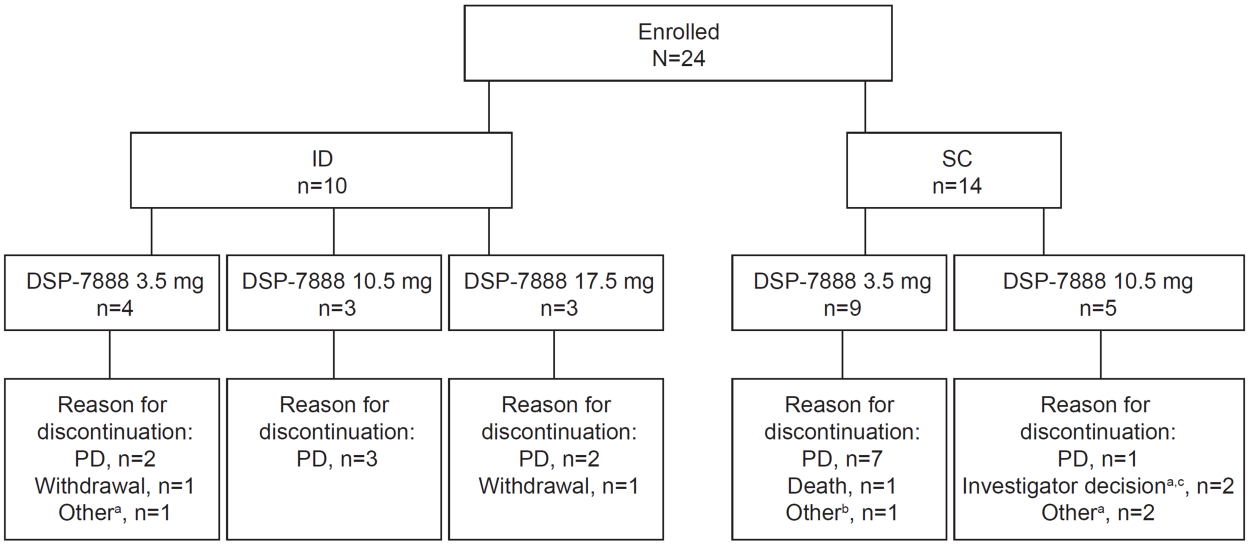
CTL, cytotoxic T-lymphocyte; ID, intradermal; SC, subcutaneous.

Supplementary Table S3. Safety and pharmacodynamic parameters by route of administration

Parameter	ID DSP-7888 (n=10)	SC DSP-7888 (n=14)
Any TEAE, n (%)	10 (100)	10 (100)
Grade ≥3	4 (40)	5 (35.7)
Any ISR, n (%)	10 (100)	5 (35.7)
Grade ≥3	0	0
Dose interruption or discontinuation, %	0	0
DLT, %	0	0
CTL induction, %	n=9 6 (66.7)	n=12 5 (41.7)

CTL, cytotoxic T-lymphocyte; DLT, dose-limiting toxicity; ISR, injection site reaction; TEAE, treatment-emergent adverse event.

Supplementary Figure S1. Patient disposition



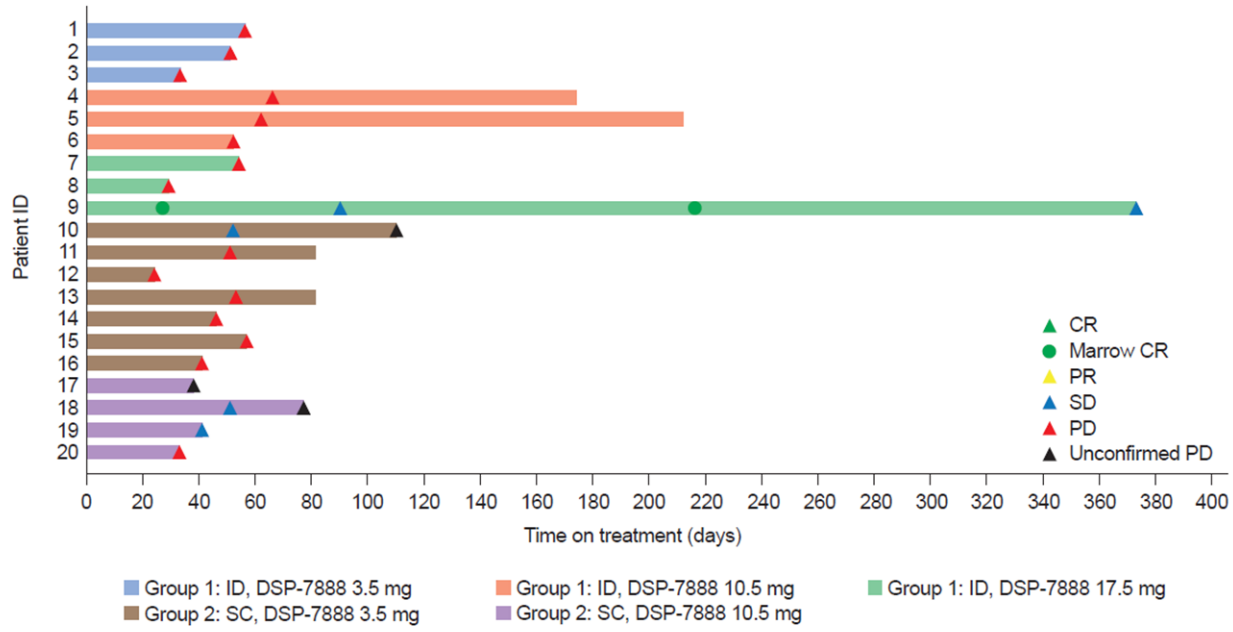
[a]Clinical progression.

[b]Withdrew consent because the study had been placed on clinical hold.

[c]Computed tomography performed at the local hospital. Investigator determined the scan to show PD (pending confirmation).

ID, intradermal; PD, progressive disease; SC, subcutaneous.

Supplementary Figure S2. Time on treatment by responder status



CR, complete response; ID, intradermal; PD, progressive disease; PR, partial response; SC, subcutaneous; SD, stable disease.