Supplementary Materials

eMethods

SUBJECT ELIGIBILITY

Study Population

Diagnosis/Condition for Entry into the Trial

Male and female subjects with or without PD-L1 positive advanced tumor of at least 18 years will be enrolled in this trial.

Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Have measurable disease based on RECIST 1.1 or irRECIST. Only Cohort 9 and Cohort 10 can have evaluable disease (non-measureable lesions). Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Patients may have bone metastatic disease evaluable according to tumor evaluation criteria best suitable and accepted for the tumor type evaluated.

4. Have one of the following advanced (unresectable and/or metastatic) solid tumor indications, that has progressed following standard therapies, where standard therapies are available:

    1) Squamous cell carcinoma of the skin
    2) Small cell malignancies of non-pulmonary origin
    3) Adrenocortical carcinoma
    4) Medullary renal cell carcinoma
    5) Carcinoma of unknown primary
    6) Penile carcinoma
    7) Vascular sarcoma
    8) Germ Cell Tumor
    9) Paraganglioma-pheochromocytoma
    10) Other rare tumor histologies (except those tumor types listed in 5.1.3.)

5. Have failed prior treatment within 6 months of consent date.

6. Have biopsiable disease. Subjects must have at least one lesion amenable to biopsy. Tumor lesions used for biopsy should not be lesions used as target lesions for response evaluation. In Cohort 9: Paraganglioma-pheochromocytoma or Cohort 10, where there is prominent bony disease, biopsies may not be possible due to the nature of the disease.

7. Be willing to provide archival tissue. If archival tissue is not available, a newly obtained core or excisional biopsy of a tumor lesion will be obtained. Newly-obtained is defined

as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. In Cohort 9: Paraganglioma-pheochromocytoma or Cohort 10, where there is prominent bony disease, biopsies may not be possible due to the nature of the disease.

8. Have a performance status of 0 or 1 on the ECOG Performance Scale.

9. Demonstrate adequate organ function as defined in **Error! Reference source not found.**, all screening labs should be performed within 28 days of treatment initiation.

Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Platelets	≥75,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

10. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

11. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the

study through 120 days after the last dose of study medication (Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

12. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

13. For subjects in Cohort 2 (Small cell malignancies of non-pulmonary origin), confirmation of no brain metastases via imaging.

Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment at the time of administration of first dose of trial treatment. Continuation of hormone replacement therapy is permitted. Stable regimens of hormonal therapy i.e. for prostate cancer (e.g. leuprolide, a GnRH agonist), ovarian, or breast cancer are not exclusionary.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3. Has a known history of active TB (Bacillus Tuberculosis).

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer, and diseases for which the treatment could reasonably include Pembrolizumab and are not part of the excluded tumor type list or not eligible for the phase I trial.

7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

8. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of Pembrolizumab. Note: corticosteroids given within 24 hours of an imaging study for purposes of pre-medication in patients with hypersensitivity to radiologic contrast agents are allowed.

9. Has known history of, or any evidence of active, non-infectious pneumonitis.

10. Has an active infection requiring systemic therapy.

11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

16. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

17. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

18. Is participating in Cohort 10 and has melanoma; non-small cell lung cancer; hepatocellular carcinoma; Merkel cell carcinoma; colon or rectal adenocarcinoma; anal canal squamous cell carcinoma; pancreas adenocarcinoma; esophageal squamous cell carcinoma or adenocarcinoma (including GE junction); biliary tract adenocarcinoma (gallbladder and biliary tree but excluding ampulla of vater cancers); carcinoid tumors; neuroendocrine carcinomas (well or moderately differentiated pancreatic neuroendocrine tumor); ER-positive HER2-negative breast cancer; triple negative breast cancer; ovarian epithelial, fallopian tube or primary peritoneal carcinoma; endometrial carcinoma; cervical squamous cell cancer; vulvar squamous cell carcinoma; small cell lung cancer; mesothelioma (malignant pleural mesothelioma); thyroid cancer (papillary or follicular subtype); salivary gland carcinoma; nasopharyngeal carcinoma; glioblastoma multiforme; leiomyosarcoma; prostate adenocarcinoma; gastric adenocarcinoma; or small bowel malignancy.

Supplemental Table 1. Treatment-emergent adverse events in 127 patients with advanced rare cancer treated with pembrolizumab

	Grade					
Adverse Event	**G1**	**G2**	**G3**	**G4**	**G5**	**Notes (grade)**
Blood and lymphatic system disorders						
Anemia	16	13	11			
Leukocytosis	1	1				
Cardiac disorders						
Atrial fibrillation		1				
Cardiac disorders - Other, specify	1					Systolic murmur
Chest pain - cardiac	1	1	1			
Palpitations	1					
Sinus bradycardia	1					
Sinus tachycardia	2	1	1			
Ear and labyrinth disorders						
Ear and labyrinth disorders - Other, specify	1					Ramsay Hunt syndrome (G1)
Hearing impaired	1	1				
Tinnitus	1					
Endocrine disorders						
Endocrine disorders - Other, specify	1					Low testosterone (G1)
Hyperthyroidism	4	1				
Hypothyroidism	5	16				
Eye disorders						
Blurred vision	1	1				
Eye disorders - Other, specify		2				1) Vision loss (G2) 2) Swelling of upper eyelid (G2)
Watering eyes	1					
Gastrointestinal disorders						
Abdominal distension		2				
Abdominal pain	5		6		1[a]	
Colitis			1			
Constipation	24	9				
Diarrhea	17	3	2			
Dry mouth	1					
Dyspepsia	1					
Dysphagia	3		1			
Gastritis			1			
Gastroesophageal reflux disease	1					
	Grade					

Adverse Event	**G1**	**G2**	**G3**	**G4**	**G5**	**Notes (grade)**
Gastrointestinal disorders - Other, specify	3	2	1			1) GI bleeding (G1) 2) Blood in stool (G1) 3) Swelling of the tongue (G1) 4) Fallen tooth (G2) 5) Xerostomia (G2) 6) Uncomplicated diverticulitis (G3)
Gingival pain	1					
Hemorrhoidal hemorrhage	1					
Hemorrhoids	1					
Mucositis, oral	4					
Nausea	16	6	2			
Periodontal disease	1					
Small intestinal obstruction			1			
Tooth development disorder		1				
Vomiting	5	1	3			
General disorders and administration site conditions						
Chills	2					
Death NOS					2	
Edema, face			1			
Edema, limbs	6	4				
Fatigue	32	12	2			
Fever	7	4				
Gait disturbance			2			
General disorders and administration site conditions - Other, specify	2		1			1) Increased number of facial moles (G1) 2) Dry nose (G1) 3) Dehydration, weakness, fatigue, and loss of appetite (G3)
Localized edema	1					
Noncardiac chest pain		1	1			
Pain	6	4	1			
Hepatobiliary disorders						
Hepatic hemorrhage	1					
Immune system disorders						
Allergic reaction	1					
Infections and infestations						
Lung infection	2	1	4			
	Grade					
Adverse Event	**G1**	**G2**	**G3**	**G4**	**G5**	**Notes (grade)**
Mucosal infection		1				

Otitis media	1					
Peripheral nerve infection		1				
Pharyngitis	2					
Sepsis		1				
Sinusitis	1	1				
Skin infection	3		1			
Tooth infection		1				
Upper respiratory infection	1	4				
Urinary tract infection	1	4	1			
Vaginal infection		2				
Wound infection	1					
Injury, poisoning, and procedural complications						
Burn		1				
Fall	2		1			
Intestinal stoma site bleeding			1			
Injury, poisoning, and procedural complications - Other, specify	1					1) Left hand injury (G1)
Investigations						
Activated partial thromboplastin time prolonged	1	3				
Alanine aminotransferase increased	17	2	2			
Alkaline phosphatase increased	12	4	4			
Aspartate aminotransferase increased	22	1	2			
Blood bilirubin increased	2	3	2			
Cholesterol high	1					
Creatinine increased	17	3				
INR increased	3	1				
Investigations - Other, specify	5					1) Increased BUN increased (G1) (n=2) 2) Hyperphosphatemia (G1) 3) Elevated total protein (G1) 4) Elevated HCG (G1)
Lymphocyte count decreased	1	1		1		
Neutrophil count decreased		1	1			
Platelet count decreased	8	1				
White blood cell decreased	7	1				
Metabolism and nutrition disorders						
Anorexia	19	2				
Hypercalcemia	12	1		1		
	Grade					
Adverse Event	**G1**	**G2**	**G3**	**G4**	**G5**	**Notes (grade)**
Hyperglycemia	18	4		1		

Hyperkalemia	10	5		1		
Hypernatremia	2		1			
Hyperuricemia	13		1			
Hypoalbuminemia	2					
Hypoglycemia	2					
Hypokalemia	8	1				
Hypomagnesemia	21	1	1			
Hyponatremia	7		2	1		
Hypophosphatemia	1	1				
Metabolism and nutrition disorders - Other, specify	4	1				1) Hypochloremia (G1) 2) Hyperalbuminemia (G1) 3) Increased LDH (G1) 4) Hyperphosphatemia (G1) 5) B12 deficiency (G2)
Musculoskeletal and connective tissue disorders						
Arthralgia	7					
Arthritis	1		1			
Avascular necrosis		1				
Back pain	6		3			
Bone pain	1					
Flank pain	2					
Generalized muscle weakness	1					
Muscle weakness, lower limb	2					
Muscle weakness, upper limb	1					
Musculoskeletal and connective tissue disorder - Other, specify	2	1				1) Cramps (G1) 2) Shoulder pain (G1) 3) Left hip pain (G2)
Myalgia	9					
Neck pain	3					
Pain in extremity	7	1				
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)						
Neoplasms, benign, malignant, and unspecified (incl. cysts and polyps) - Other, specify	2	1	1			1) SCC (G1) 2) New lesion on forehead (G1) 3) New nodules on upper lip (G2) 4) New brain metastasis (G3)
Tumor pain	3	4	4			
	Grade					
Adverse Event	**G1**	**G2**	**G3**	**G4**	**G5**	**Notes (grade)**
Nervous system disorders						

Dizziness	1		1			
Dysgeusia		1				
Headache	6	2	1			
Memory impairment	1					
Nervous system disorders - Other, specify	2		1			1) Spasmodic torticollis (G1) 2) Polyneuropathy (G1) 3) Spinal cord compression (G3)
Neuralgia		1				
Peripheral sensory neuropathy	10	1				
Seizure		1				
Syncope			1			
Transient ischemic attacks	1					
Tremor	1		1			
Psychiatric disorders						
Anxiety	2	2				
Confusion	1		1			
Depression	2					
Insomnia	5	1				
Psychiatric disorders - Other, specify	1					Nightmares (G1)
Renal and urinary disorders						
Acute kidney injury	3				1	
Bladder spasm		1				
Hematuria	2					
Renal and urinary disorders - Other, specify	3	2	1			1) Dysuria (G1), n=2 2) Elevated urine WBC (G1) 3) Purulent discharge in Foley catheter (G2) 4) Hydroureteronephrosis (G2) 5) Acute renal failure (G3)
Renal calculi			1			
Urinary retention		1				
Urinary tract obstruction			1			
Urinary urgency		1				
Reproductive system and breast disorders						
Genital edema	1					
Prostatic obstruction	1					
	Grade					
Adverse Event	**G1**	**G2**	**G3**	**G4**	**G5**	**Notes (grade)**

Reproductive system and breast disorders - Other, specify	1		1			1) Genital warts (G1) 2) Prolapsed uterus (G3)
Testicular disorder		1				
Testicular pain		1				
Respiratory, thoracic, and mediastinal disorders						
Cough	10	4				
Dyspnea	21	3	4		1[a]	
Hiccups		1				
Hypoxia		1				
Laryngeal hemorrhage			1			
Pleural effusion	2	2	2			
Pneumonitis		1	3			
Productive cough	1	1				
Sinus disorder	1					
Stridor			1			
Wheezing		1				
Skin and subcutaneous tissue disorders						
Alopecia	2					
Dry skin	3					
Hyperhidrosis	1					
Nail loss	1					
Pruritus	3					
Rash, acneiform	1					
Rash, maculopapular	18	5				
Skin and subcutaneous tissue disorders - Other, specify	7		1			1) Skin abrasion (G1) 2) Rash, eczematous (G1) 3) Raised lesion on left forearm (G1) 4) Nail bed changes (G1) 5) Wound (G1) 6) Rash, erythematous (G1) (n=2) 7) Bleeding from right chest wall tumor (G3)
Skin ulceration		1				
Surgical and medical procedures						
Surgical and medical procedures - Other, specify	1	1	1			1) Endoscopy for *C. difficile* infection (G1) 2) Cataract surgery (G2) 3) Total left hip replacement (G3)
Vascular disorders						
	Grade					
Adverse Event	**G1**	**G2**	**G3**	**G4**	**G5**	**Notes (grade)**

Hematoma			1			
Hot flashes	1					
Hypertension	3	1	3			
Hypotension	5	1	2		1[a]	
Lymphedema	1					
Superficial thrombophlebitis			1			
Superior vena cava syndrome		1				
Thromboembolic event		1				
Vascular disorders - Other, specify	1					Vascular thrombus in pulmonary artery (G1)

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

[a]Adverse event attributed to progressive disease by the investigator.

Supplemental Table 2. Treatment-related immune-related adverse events in 127 patients treated with pembrolizumab.

Adverse Event	**Any grade n (%)**	**Grade 3-4 n (%)**
Hypothyroidism	14 (11)	
Pneumonitis	4 (3)	3 (2)
Hyperthyroidism	4 (3)	
Aspartate aminotransferase increased	3 (2)	
Alanine aminotransferase increased	2 (2)	1 (1)
Alkaline phosphatase increased	2 (2)	1 (1)
Rash, maculopapular	2 (2)	
Dyspnea	2 (2)	
Arthralgia	2 (2)	
Colitis	1 (1)	1 (1)
Anemia	1 (1)	1 (1)
Diarrhea	1 (1)	1 (1)
Hyperglycemia	1 (1)	1 (1)
Arthritis	1 (1)	1 (1)
Tremor due to subacute progressive cerebellar dysfunction	1 (1)	1 (1)
Myalgia	1 (1)	
Thyroiditis	1 (1)	

Supplemental Table 3. PD-L1 and TIL scores in 91 patients with advanced rare cancer treated with pembrolizumab[a]

Cohort	Alive and progression-free at 27 weeks (n)	PD-L1 H score >42.5	PD-L1 H score ≤42.5	TIL score 0	TIL score 1	TIL score 2	TIL score 3
1) Squamous cell carcinoma of the skin	Yes (5)	4	1	0	2	1	2
	No (7)	5	2	0	3	2	2
2) Small cell malignancies of nonpulmonary origin	Yes (0)	0	0	0	0	0	0
	No (9)	0	9	0	7	1	1
3) Adrenocortical carcinoma	Yes (3)	0	3	1	1	1	0
	No (9)	0	9	0	3	5	1
4) Medullary renal cell carcinoma	Yes (0)	0	0	0	0	0	0
	No (4)	1	3	0	1	1	2
5) Carcinoma of unknown primary	Yes (4)	2	2	0	2	0	2
	No (8)	0	8	0	5	1	2
6) Penile carcinoma	Yes (0)	0	0	0	0	0	0
	No (2)	1	1	0	1	1	0
7) Vascular sarcoma	Yes (1)	0	1	0	0	0	1
	No (3)	0	3	0	0	2	1
8) Germ cell tumor	Yes (1)	0	1	1	0	0	0
	No (7)	2	5	1	5	0	1
9) Paraganglioma-pheochromocytoma	Yes (2)	1	1	1	1	0	0
	No (4)	0	4	0	2	2	0
10) Other rare tumors	Yes (7)	1	6	0	2	3	2
	No (15)	0	15	0	7	2	6

Abbreviations: TIL, tumor infiltrating lymphocyte

[a]91 patients who had results from biomarker (PD-L1 membrane expression and presence of TILs) assessment in tumor samples and were evaluable for primary endpoint (alive and progression-free at 27 weeks) were included.