EARLY THERAPEUTICS AND RARE CANCERS COMMITTEE

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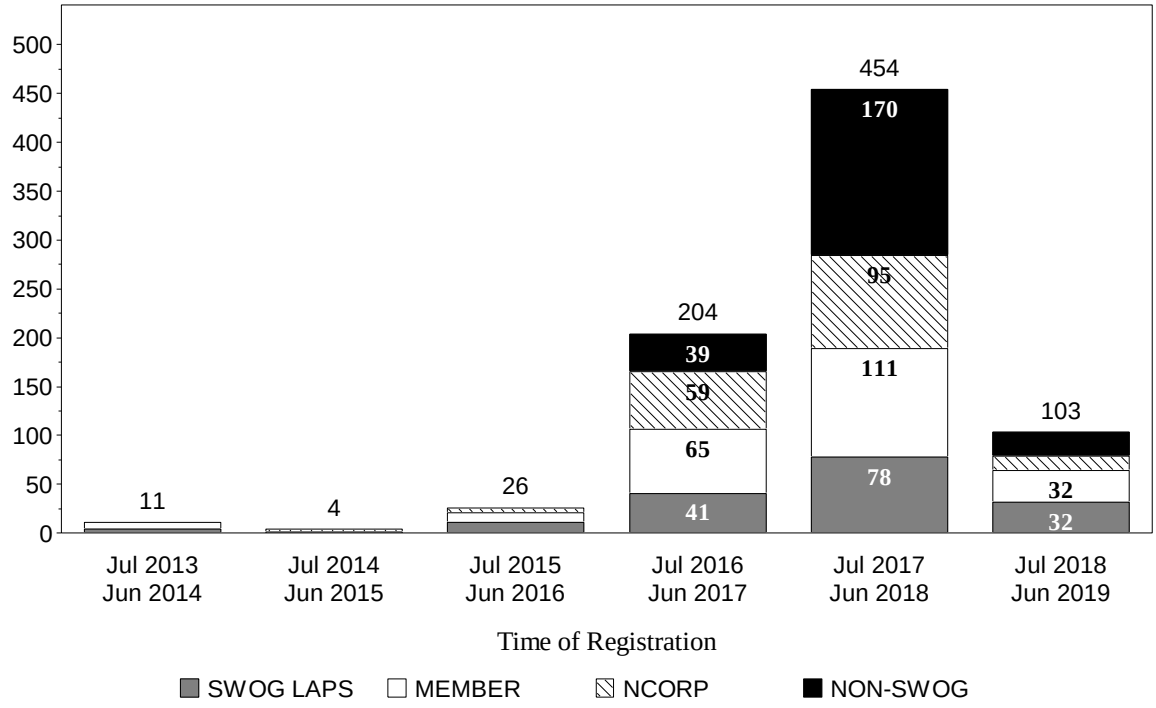
Patient Registrations to Studies

by 12 Month Intervals
EARLY THERAPEUTICS AND RARE CANCERS COMMITTEE



Screening registrations and registrations to Biologic only studies are excluded.

Patient Registrations by Study and Arm

EARLY THERAPEUTICS AND RARE CANCERS COMMITTEE

	Jan 2019 Jun 2019	Jul 2018 Dec 2018	Jan 2018 Jun 2018	All Patients
S1609 Rare Tumor, Comb Nivo/Ipi				
Registration				
Nivolumab + Ipilimumab	28	27	280	574

Non-SWOG Studies with SWOG-Credited Registrations

EARLY THERAPEUTICS AND RARE CANCERS COMMITTEE

Studies with Accrual from January 2018 - June 2019

	SWOG Champion	SWOG Accrual Jan 2019 Jun 2019	SWOG Accrual Jul 2018 Dec 2018	SWOG Accrual Jan 2018 Jun 2018	SWOG Total	Total Accrued
A071102 GBM, adj TMZ +/- Veliparib Date Activated: 09/19/14 Date Closed: 10/15/18 *Most Recent Progress Report*	D Piccioni	0	5	6	49	447
A071401 Prog Meningiomas,SMO/AKT/NF2 Inhib Date Activated: 08/06/15 *Most Recent Progress Report*	D Piccioni	0	0	0	5	40
ARST1321 NonRhabdo STS,Pazopanib (PAZNTIS) Date Activated: 05/16/14 Date Closed: 01/22/19 *Most Recent Progress Report*	V Villalobos	0	0	4	9	140
EAY131 MATCH Date Activated: 08/12/15 *Most Recent Progress Report*	V Villalobos	20	23	9	154	1015

S1609 Phase II

Coordinating Group: SWOG

DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors

Participants:
SWOG, CTSU

Date Activated:
01/13/2017

Study Chairs:
S Patel, Y Chae

Statisticians:
M Othus, M Plets, E Mayerson

Data Coordinators:
C Magner, S Gurung

Objectives

To evaluate the RECIST 1.1 overall response rate (ORR) in subsets of patients with advanced rare cancers treated with ipilimumab plus nivolumab combination immunotherapy.

To evaluate the overall response rate (ORR) in patients with gestational trophoblastic tumors treated with ipilimumab plus nivolumab combination immunotherapy.

To evaluate the RECIST 1.1 overall response rate (ORR) in patients PD-L1 amplified cancers treated with nivolumab immunotherapy.

To evaluate toxicities in each cohort.

To estimate overall survival (OS), progression-free survival (PFS), clinical benefit rate; and to estimate immune-related ORR (irORR), and immune-related PFS (irPFS) by unidimensional immune-related response criteria.

To collect specimens for banking for use in future correlative biomarker research studies.

Patient Population

Patients must have histologically confirmed rare cancer and/or cancer of unknown primary specified on the list of eligible rare cancer histologic cohorts in the S1609 protocol or with PD-L1 amplification only. As of September 11, 2017, patients are no longer required to have been enrolled in EAY131 (NCI-MATCH) to be eligible for this study.

Patients must have measurable disease and have progressed following at least one line of standard systemic therapy and there must not be other approved/standard therapy available that has been shown to prolong overall survival. Patients are also eligible if no standard treatment exists that has been shown to prolong overall survival. Patients in one of the histologically defined rare cancer cohorts maybe have received either prior anti-CTLA-4 or other prior anti-PD-1/anti-PD-L1 therapy, but not both, provided that it is completed at least 4 weeks prior to registration. Patients in the PD-L1 amplification cohort must not have received anti-PD-1/anti-PD-L1 therapy; prior anti-CTLA-4 is allowed provided that it is completed at least 4 weeks prior to registration. Patients who had a prior immune-related adverse event with prior immunotherapy are not eligible. Patients with brain metastases or primary brain tumors must have completed treatment, surgery or radiation therapy at least 28 days prior to registration and have stable disease at time of registration. Patients with metastatic brain parenchymal disease must have been treated and off steroids for seven days prior to registration. Patients must have been off all other systemic anti-cancer therapy at least seven

days prior to registration and any therapy-induced toxicity must have recovered to Grade 1 or less.

Patients must have a Zubrod performance status of 0-2 and have adequate hematologic, hepatic, renal, thyroid, and adrenal axis function. Patients must not have active autoimmune disease that has required systemic treatment in the past two years or any uncontrolled intercurrent illness. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection at time of registration. Patients with HBV or HCV that have an undetectable viral load, or in the opinion of the treating investigator is well controlled, are eligible. Patients who are known to be HIV-positive at registration are eligible if they meet the conditions outlined in the protocol.

Stratification/Descriptive Factors

Patients will be described by histologic cohorts, with the exception of PD-L1 amplification patients.

Accrual Goals

The accrual goal for this study is 707 patients to achieve 636 eligible patients. A two-stage design will be used for all cohorts, with the exception of the NOC and "Cancer of Unknown Primary" (CuP) cohorts. Initially, six eligible patients will be registered to each histologic cohort. If at least one response is observed within a cohort, an additional 10 eligible patients will be registered to that cohort. Up to 16 eligible patients will be registered to the CuP cohort with no formal first stage response assessment. Up to 60 eligible patients will be enrolled to the NOC cohort, and data may be used to open additional cohorts.

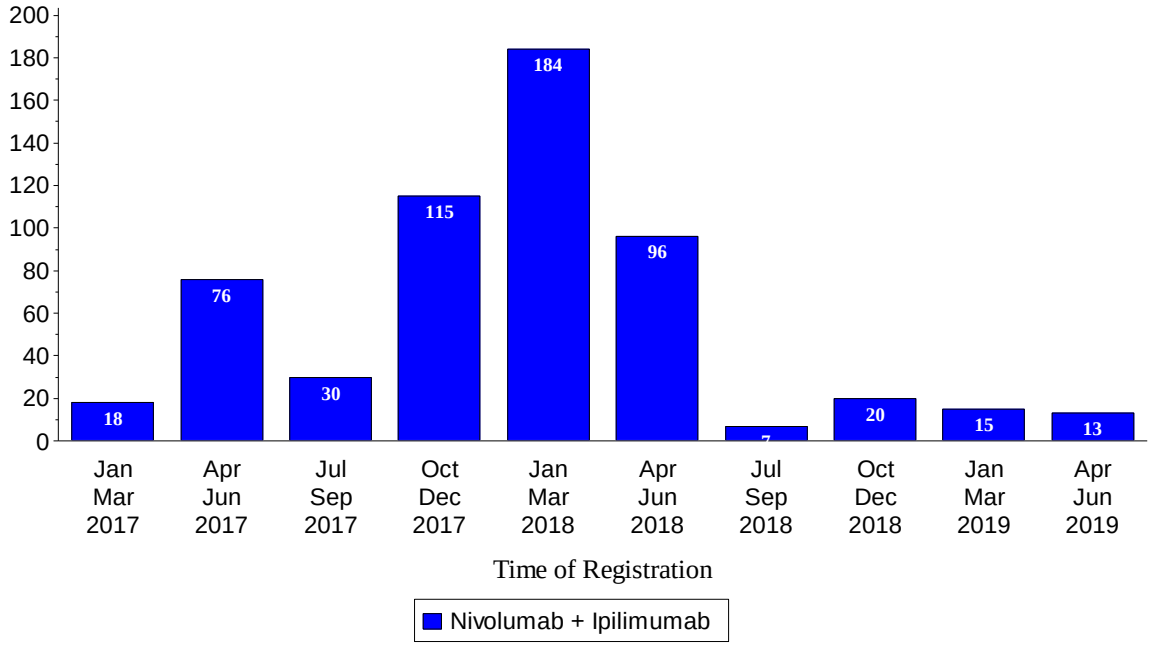
Summary Statement

As of June 30, 2019, 574 patients had been registered to this study. Forty-nine patients are currently ineligible, primarily due to insufficient baseline documentation deemed irreversible (22), laboratory value of out range (11), and disease histology not deemed rare (6). Eleven patients did not receive any protocol therapy, either due to refusal of treatment after registration (5 patients), patient death prior to treatment start (4), or elevated lab values that required removal from therapy (2). These 11 patients are not analyzable for any endpoint. One major deviation is coded for a patient who remained on protocol treatment beyond second disease progression. Of the 19 patients going off treatment with reason coded as "Other - not protocol specified", the most common reason is physician's decision.

Five hundred seven have been assessed for adverse events. Seventeen patients have experienced Grade 5 toxicities, including death not otherwise specified (4, including one also coded as sudden death NOS), respiratory failure (2), multi-organ failure (2), neoplasms, all (2), pneumonitis (2), sepsis (2); and duodenal hemorrhage, enterocolitis, "Musculoskeletal and connective tissue disorders-Other, spec" noted as rhabdomyalysis, and "Nervous system disorders-Other, spec" noted as paraneoplastic syndrome (1 patient each). Forty-five patients experienced Grade 4 adverse events as maximum grade, including increased lipase (12 patients), increased AST (8), increased ALT (6), hyperglycemia (4), sepsis (4), respiratory failure (4), "Heptobiliary disorders-Other,spec" noted as jaundice (1), "Heptobiliary disorders-Other,spec" noted as immune-related hepatitis (1), "Metabolic and nutrition disorders-Other,spec" noted as diabetic ketoacidosis (1), and "Endocrine disorders-Other,spec" noted as diabetes with ketoacidosis (1) . The most common adverse events were fatigue, diarrhea, and nausea.

Initial Registrations by 3 Month Intervals

Divisions by ARM



Registration by Institution

Registrations ending June 30, 2019

Institutions	Total Reg	Institutions	Total Reg
Kansas, U of	27	CORA NCORP	5
Michigan, U of	25	San Antonio, U of TX	5
Kaiser Perm NCORP	24	Yale University	5
MD Anderson CC	17	Georgia NCORP	4
H Lee Moffitt CC	16	MUSC MU-NCORP	4
Nevada CRF NCORP	16	Southeast COR NCORP	4
San Diego, U of CA	16	Arizona CC, Univ of	3
Michigan CRC NCORP	15	Columbus NCORP	3
Heartland NCORP	14	Essentia Hlth NCORP	3
New Mexico MU-NCORP	14	Hawaii MU-NCORP	3
Henry Ford Hospital	12	MAVERIC	3
Montana NCORP	10	Mississippi, Univ of	3
Northwestern Univ	9	Oregon Hlth Sci Univ	3
PCRC NCORP	9	Utah, U of	3
Davis, U of CA	8	All Other SWOG Institutions	26
Irvine, U of CA	8	NRG	93
Wisconsin NCORP	8	ALLIANCE	72
Fred Hutchinson CRC	6	ECOG-ACRIN	68
Cedars-Sinai Med Ctr	5	**Total (53 Institutions)**	**574**
Colorado, U of	5		

Registration, Eligibility, and Evaluability

Registrations ending June 30, 2019; Data as of July 3, 2019

	Nivolumab + Ipilimumab
NUMBER REGISTERED	574
INELIGIBLE	49
Insufficient Documentation	22
Irreversible	22
ELIGIBLE	525
Analyzable, Pend. Elig.	12
Not Analyzable	11
ADVERSE EVENT ASSESSMENT	
Evaluable	507
Too Early	7

Histologic Cohorts

Enrollment as of July 18, 2019; Closure Status as of July 18, 2019

* Denotes Temporary Closure

For most up to date study accrual, visit www.swogstat.org/accrual/dart.htm

Cohort Number	Histology	Patients Enrolled	Percent of Total N	Open Status
1	Epithelial tumors of nasal cavity, sinuses, nasopharynx	7	1.2	Closed
2	Epithelial tumors of major salivary glands	30	5.1	Closed
3	Salivary gland type tumors of head and neck, lip, esophagus, stomach, trachea and lung, breast and other location	6	1.0	Closed
4	Undifferentiated carcinoma of gastrointestinal (GI) tract	6	1.0	Closed*
5	Adenocarcinoma with variants of small intestine	25	4.3	Closed
6	Squamous cell carcinoma with variants of GI tract (stomach small intestine, colon, rectum, pancreas)	6	1.0	Closed
7	Fibromixoma and low grade mucinous adenocarcinoma (pseudomixoma peritonei) of the appendix and ovary	10	1.7	Closed
8	Pancreatic tumor including acinar cell carcinoma, mucinous or serous cystadenocarcinoma	11	1.9	Closed*
9	Intrahepatic cholangiocarcinoma	9	1.5	Closed
10	Cholangiocarcinoma and extrahepatic bile duct tumors	10	1.7	Closed
11	Sarcomatoid carcinoma of lung	7	1.2	Open
12	Bronchoalveolar carcinoma lung (a.k.a. adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma, or invasive mucinous adenocarcinoma)	7	1.2	Open
13	Non-epithelial tumors of the ovary	25	4.3	Closed
14	Trophoblastic tumor	3	0.5	Closed
15	Transitional cell carcinoma other than renal pelvis ureteral or bladder	1	0.2	Closed
16	Cell tumor of the testes and extragonadal germ tumors	17	2.9	Closed
17	Epithelial tumors of penis - squamous adenocarcinoma cell carcinoma with variants of penis	22	3.8	Closed*
18	Squamous cell carcinoma variants of the genitourinary (GU) system	5	0.9	Open
19	Spindle cell carcinoma of kidney, pelvis, ureter	4	0.7	Open
20	Adenocarcinoma with variants of GU system (excluding prostate cancer)	9	1.5	Closed
21	Odontogenic malignant tumors	4	0.7	Open
22	Endocrine carcinoma of pancreas and digestive tract	13	2.2	Open
23	Neuroendocrine carcinoma including carcinoid of the lung	35	6.0	Closed
24	Pheochromocytoma, malignant	7	1.2	Closed*
25	Paraganglioma	6	1.0	Closed
26	Carcinomas of pituitary gland, thyroid gland parathyroid gland and adrenal cortex	17	2.9	Open
27	Desmoid tumors	12	2.1	Open
28	Peripheral nerve sheath tumors and NF1-related tumors	9	1.5	Closed
29	Malignant giant cell tumors	3	0.5	Open
30	Chordoma	11	1.9	Closed
31	Adrenal cortical tumors	21	3.6	Closed
32	Tumor of unknown primary (Cancer of Unknown Primary; CuP)	21	3.6	Closed
33	Not Otherwise Categorized (NOC) Rare Tumors, after discussion with Study Chairs	56	9.6	Closed
34	Adenoid cyctic carcinoma	29	5.0	Closed
35	Vulvar cancer	10	1.7	Open
36	MetaPLASTIC carcinoma (of the breast)	19	3.3	Closed*
37	Gastrointestinal stromal tumor (GIST)	12	2.1	Closed
38	Perivascular epithelioid cell tumor (PEComa)	3	0.5	Open
39	Apocrine tumors/Extramammary Paget's Disease	9	1.5	Closed*

Cohort Number	Histology	Patients Enrolled	Percent of Total N	Open Status
40	Peritoneal mesothelioma	3	0.5	Open
41	Basal cell carcinoma	3	0.5	Open
42	Clear cell cervical cancer	5	0.9	Open
43	Esthenioneuroblastoma	7	1.2	Closed*
44	Endometrial carcinosarcoma (malignant mixed Mullerian tumors)	22	3.8	Closed*
45	Clear cell endometrial cancer	5	0.9	Open
46	Clear cell ovarian cancer	8	1.4	Open
47	Gestational trophoblastic disease (GTD)	0	0.0	Open
48	Gallbladder cancer	6	1.0	Open
49	Small cell carcinoma of the ovary, hypercalcemic type	1	0.2	Open
50	PD-L1 amplified tumors	2	0.3	Open
51	Angiosarcoma	0	0.0	Open
52	High-grade neuroendocrine carcinoma	3	0.5	Open
53	Treatment-emergent small-cell neuroendocrine prostate cancer (t-SCNC)	2	0.3	Open

Patient Characteristics

Registrations ending June 30, 2019; Data as of July 3, 2019

	Nivolumab + Ipilimumab (n=514)	
AGE		
Median	60.9	
Minimum	19.4	
Maximum	88.7	
SEX		
Males	245	48%
Females	269	52%
HISPANIC		
Yes	45	9%
No	463	90%
Unknown	6	1%
RACE		
White	412	80%
Black	51	10%
Asian	19	4%
Pacific Islander	2	0%
Native American	4	1%
Unknown	26	5%

Treatment Summary

Registrations ending June 30, 2019; Data as of July 3, 2019

	Nivolumab + Ipilimumab
NUMBER ON PROTOCOL TREATMENT	50
NUMBER OFF PROTOCOL TREATMENT	464
REASON OFF TREATMENT	
Treatment completed as planned	0
Adverse Event or side effects	74
Refusal unrelated to adverse event	33
Death	18
Other - not protocol specified	19
Reason under review	4
MAJOR PROTOCOL DEVIATIONS	1
LOST TO FOLLOW-UP	0
CONSENT WITHDRAWAL AFTER TREATMENT INITIATION	15

Number of Patients with a Given Type and Grade of Adverse Event

Adverse Events Unlikely or Not Related to Treatment Excluded

Adverse Events with No Entries for Grades 3 to 5 Have Been Suppressed

Registrations ending June 30, 2019; Data as of July 3, 2019

	Nivolumab + Ipilimumab (n=507) Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**
ALT increased	444	37	8	12	6	0
AST increased	434	41	7	17	8	0
AV block complete	506	0	0	0	1	0
Abdominal pain	478	13	15	1	0	0
Acidosis	505	1	0	0	1	0
Acute kidney injury	493	6	4	2	2	0
Adrenal insufficiency	476	10	11	9	1	0
Alkaline phosphatase increased	458	29	12	8	0	0
Anaphylaxis	506	0	0	1	0	0
Anemia	434	35	23	15	0	0
Anorexia	437	32	37	1	0	0
Arthralgia	470	21	12	4	0	0
Ascites	506	0	0	1	0	0
Atrial fibrillation	503	0	1	3	0	0
Autoimmune disorder	501	0	2	4	0	0
Back pain	495	4	4	4	0	0
Blood bilirubin increased	485	10	4	6	2	0
Blood/lymph disorder-Other	503	2	1	1	0	0
Bronchial infection	506	0	0	1	0	0
CPK increased	504	1	0	0	2	0
Cardiac disorder-Other, spec	505	1	0	1	0	0

	Nivolumab + Ipilimumab (n=507) Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**
Cardiac troponin T increased	504	2	0	1	0	0
Colitis	487	1	13	5	1	0
Confusion	504	0	2	1	0	0
Death NOS	503	0	0	0	0	4
Dehydration	491	3	9	4	0	0
Diarrhea	409	49	27	20	2	0
Dizziness	492	14	0	1	0	0
Duodenal hemorrhage	506	0	0	0	0	1
Dysphagia	504	0	2	1	0	0
Dyspnea	463	16	13	14	1	0
Encephalopathy	501	0	1	5	0	0
Endocrine disorders-Other	495	6	3	2	1	0
Enterocolitis	505	0	1	0	0	1
Enterocolitis infectious	505	0	1	1	0	0
Fatigue	327	76	81	23	0	0
GGT increased	505	0	0	2	0	0
GI disorders-Other, specify	503	1	2	1	0	0
Gastric hemorrhage	506	0	0	1	0	0
Gastritis	505	0	1	1	0	0
Generalized muscle weakness	478	13	9	7	0	0
Headache	474	24	7	2	0	0
Heart failure	505	1	0	1	0	0
Hematuria	503	3	0	1	0	0
Hepatic failure	505	0	0	1	1	0
Hepatitis viral	506	0	0	1	0	0
Hepatobil disorders-Other	503	0	0	2	2	0
Hypercalcemia	497	6	1	2	1	0
Hyperglycemia	477	14	9	3	4	0
Hyperkalemia	504	2	0	1	0	0
Hypertension	498	1	7	1	0	0
Hyperthyroidism	474	20	11	2	0	0
Hypoalbuminemia	477	16	13	1	0	0
Hypocalcemia	486	16	4	1	0	0
Hypokalemia	493	9	1	3	1	0
Hyponatremia	481	19	0	6	1	0
Hypophosphatemia	503	1	2	1	0	0
Hypotension	494	5	5	3	0	0
Hypothyroidism	426	34	45	2	0	0
Hypoxia	501	0	1	5	0	0
INR increased	506	0	0	1	0	0
Infections/infestations-Other	495	3	3	6	0	0
Kidney infection	506	0	0	1	0	0
Leukocytosis	506	0	0	1	0	0
Lipase increased	467	9	10	9	12	0
Localized edema	502	2	2	1	0	0
Lower GI hemorrhage	506	0	0	1	0	0
Lung infection	502	0	1	4	0	0
Lymphedema	505	0	0	2	0	0
Lymphocyte count decreased	457	18	14	17	1	0
MS/connective tissue disorder	502	1	3	0	0	1
Meningitis	506	0	0	1	0	0

	Nivolumab + Ipilimumab (n=507) Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**
Metab/nutrition disorders-Oth	500	4	1	1	1	0
Mucositis oral	496	6	4	1	0	0
Multi-organ failure	505	0	0	0	0	2
Myocarditis	499	0	2	3	3	0
Myositis	503	1	0	3	0	0
Nausea	422	49	29	7	0	0
Neck pain	499	3	4	1	0	0
Neoplasms, all	505	0	0	0	0	2
Nervous sys disorders-Other	503	0	2	1	0	1
Neutrophil count decreased	493	7	6	1	0	0
Non-cardiac chest pain	502	2	2	1	0	0
Pain in extremity	489	10	7	1	0	0
Pancreatitis	503	0	1	3	0	0
Pericardial effusion	505	0	0	0	2	0
Pericarditis	506	0	0	1	0	0
Peripheral motor neuropathy	505	0	0	2	0	0
Peripheral sensory neuropathy	494	9	3	1	0	0
Platelet count decreased	480	22	2	2	1	0
Pleural effusion	501	3	2	1	0	0
Pneumonitis	485	1	12	5	2	2
Portal vein thrombosis	505	0	0	2	0	0
Pruritus	426	56	21	4	0	0
Psychosis	506	0	0	1	0	0
ROM decreased	505	1	0	1	0	0
Rash maculo-papular	421	55	25	6	0	0
Resp/thoracic/mediastinal ds	503	1	1	1	1	0
Respiratory failure	501	0	0	0	4	2
Retinopathy	506	0	0	0	1	0
Sepsis	501	0	0	0	4	2
Serum amylase increased	481	15	4	6	1	0
Sinusitis	503	0	3	1	0	0
Sudden death NOS	506	0	0	0	0	1
Syncope	504	0	0	3	0	0
Thromboembolic event	503	0	2	1	1	0
Tumor lysis syndrome	506	0	0	1	0	0
Tumor pain	504	1	0	2	0	0
Upper GI hemorrhage	506	0	0	1	0	0
Urinary tract infection	502	0	2	3	0	0
Urinary tract obstruction	506	0	0	1	0	0
Ventricular arrhythmia	506	0	0	0	1	0
Vomiting	464	30	9	4	0	0
White blood cell decreased	489	12	5	1	0	0
MAX. GRADE ANY ADVERSE EVENT	91	72	147	135	45	17