EARLY THERAPEUTICS AND RARE CANCERS COMMITTEE

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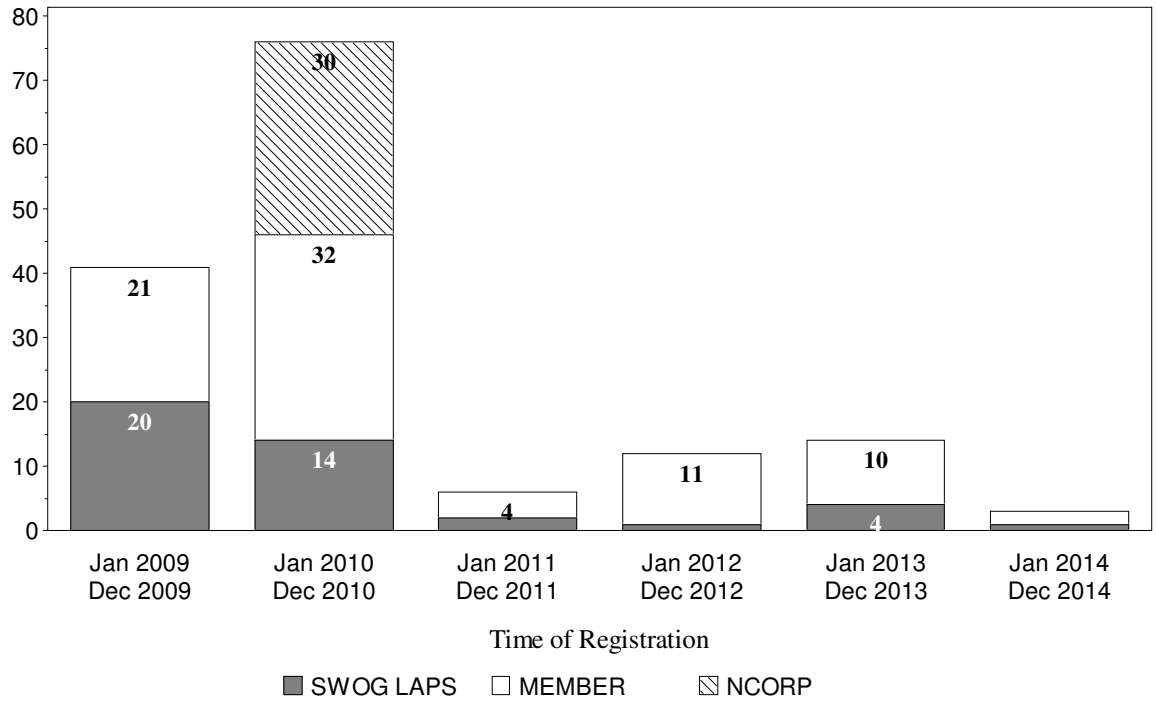
Patient Registrations to Studies

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

	Jul 2014 Dec 2014	Jan 2014 Jun 2014	Jul 2013 Dec 2013	All Patients
S0711 Liver dysfunction PK,Dasatinib				
Grp1, Normal LFT, 140mg	0	0	0	17
Grp2, C-P Class A (Mild), 100mg	0	0	0	3
Grp2, C-P Class A (Mild), 140mg	0	0	0	20
Grp3, C-P Class B (Mod), 70mg	0	0	0	4
Grp3, C-P Class B (Mod), 100mg	0	0	3	19
Grp4, C-P Class C (Severe), 50mg	0	0	0	1
Grp3b, C-P Class B (Mod), 100mg	0	2	2	10
Grp4b, C-P Class C (Severe), 50mg	0	1	3	9
	0	3	8	83

* For non-SWOG coordinated studies only SWOG registrations are shown.

S0711 Phase I

Phase I Pharmacokinetic Study of Dasatinib (BMS-354825; NSC-732517; IND-73969) in Patients with Advanced Malignancies and Varying Levels of Liver Dysfunction

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Study Chair:
J Sarantopoulos

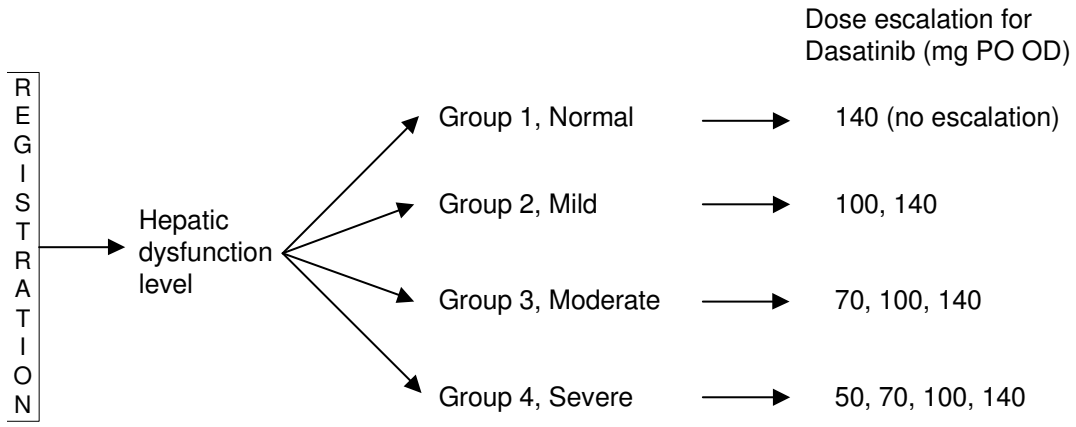
Statisticians:
A Hoering, R Sexton

Data Coordinator:
C McLeod

Date Activated:
10/15/2008

Date Closed:
06/01/2014

SCHEMA



Objectives
To estimate the maximum tolerated dose (MTD) of dasatinib in patients with varying degrees of hepatic impairment.

To estimate the pharmacokinetic (PK) profile of dasatinib in patients with varying degrees of hepatic impairment.

To assess the safety profile and dose limiting toxicities (DLTs, if any) of dasatinib in patients with varying degrees of hepatic impairment.

To describe any antitumor efficacy associated with dasatinib administration in patients with varying degrees of hepatic impairment.

To examine whether the pharmacokinetic clearance of dasatinib correlates with hepatic function as assessed by Child-Pugh Criteria, the NCI Organ Dysfunction Working Group Criteria, or other assessments of liver function such as total bilirubin level.

Patient Population
Patients must have histologically or cytologically confirmed solid tumor or lymphoma that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective. All solid tumor types and lymphoma are eligible. Patients with a liver mass, elevated alpha-fetoprotein level and positive serology for viral hepatitis, consistent with a diagnosis of hepatocellular carcinoma will be eligible without the need for pathologic confirmation of the diagnosis. Patients with evidence of biliary sepsis are not eligible. Patients with unstable or untreated (non-irradiated) brain metastases are not eligible.

Patients must not have had anticancer therapy including chemotherapy, radiotherapy, immunotherapy, or investigational agent within four weeks prior to study registration, except for targeted agents with half-life known to be < 24 hours. Patients must not have had targeted agents with half-life < 24 hours within two weeks prior to registration. Patients must not have received prior therapy with dasatinib.

Patients must have adequate hematologic, renal, and cardiac function and a Zubrod performance status of 0-2. Patients must not have clinically significant pleural or pericardial effusion, active gastrointestinal bleeding, or inability to take oral medications. Patients who are known to be HIV-positive are not eligible for this study.

Patients must also agree to undergo pharmacokinetic sampling.

Refer to the protocol for additional restricted and prohibited concurrent medications.

Stratification/Descriptive Factors
At the time of registration, patients will be stratified into four hepatic function groups per protocol definitions (Group 1: normal, Group 2: mild dysfunction, Group 3: moderate dysfunction, Group 4: severe dysfunction).

Following an amendment approved February 1, 2012, patients with ascites were eligible for the mild, moderate and severe hepatic function groups and these groups were further stratified by presence of ascites.

Accrual Goals
Patient enrollment to each dysfunction group will follow the traditional "3+3" algorithm until the MTD is reached or the highest dose tested is judged tolerable. The dose finding will be carried out separately for each of the liver impairment groups and for each subgroup as determined by presence of ascites. However, if dose escalation is halted in any organ impairment group due to DLTs, escalation cannot proceed to a higher dose level for patients in a worse organ impairment group. Up to 12 patients could be enrolled to the MTD for each dysfunction subgroup.

Summary Statement
The study was permanently closed to accrual on June 1, 2014 with 83 patients registered. For all treatment groups, the tables indicate whether or not a patient was assessable for adverse events; this status does not necessarily coincide with DLT evaluability.

Normal group (no ascites), 140 mg: Seventeen patients had been enrolled to this cohort. Three patients were ineligible for the following reasons: insufficient documentation, having pleural effusion at baseline, and receiving therapeutic doses of Lovenox (1 patient each). Although DLTs will not be evaluated for this group, five patients received less than 21 days of treatment and were replaced in order to enroll 12 patients evaluable for the pharmacokinetic portion of this trial. One of the 14

patients assessed for adverse events in this cohort has experienced a Grade 4 adverse event, GI pain.

Class A (Mild) group (no ascites), 100 mg: Three patients were registered to this dose cohort and were evaluable for DLTs; no DLTs were observed.

Class A (Mild) group (no ascites), 140 mg: Twenty patients were enrolled to this cohort. The first three patients successfully completed 21 days of treatment with no DLTs observed. Sixteen more patients were registered in order to accrue an additional nine DLT evaluable patients to the potential MTD level for the Mild group. One patient was ineligible due to baseline ascites and six patients were removed from treatment after less than 21 days of treatment without DLTs and were replaced. One of these patients was removed from study prior to receiving treatment (a major protocol deviation) and is not assessable for adverse events or response. The twentieth patient was registered after the study had expanded to accrue patients with ascites and was initially indicated as having had ascites. One patient has experienced a DLT (Grade 4 hemoglobin); this patient also experienced Grade 4 myocarditis. Another patient experienced Grade 4 aspartate aminotransferase. There were a total of 13 DLT evaluable patients in this cohort.

Class B (Moderate) group (no ascites), 70 mg: Four patients had been registered to this cohort. One of the first three patients was removed from treatment after only 10 days of treatment with no DLTs, and was thus not evaluable for DLT assessment. A fourth patient was enrolled to replace this patient for a total of three DLT evaluable patients. No DLTs were observed. One patient experienced Grade 4 infection (sepsis).

Class B (Moderate) group (no ascites), 100 mg: Nineteen patients were registered to this dose cohort. One patient was ineligible and did not begin treatment. Fourteen of the remaining 18 were removed after less than 21 days of treatment but did not experience DLTs. Four patients were evaluable for DLTs in this cohort, of whom, one experienced a DLT (Grade 4 creatinine phosphokinase).

Class C (Severe) group (no ascites), 50 mg: One patient was registered to this dose cohort but was removed after only seven days of treatment due to disease progression. Following the amendment to enroll patients with ascites, this arm was permanently closed due to poor accrual.

Class B (Moderate) group (with ascites), 100 mg: Ten patients were enrolled to this cohort. One patient was ineligible due to having received therapy within 28 days of registrations. Six patients were removed from treatment after less than 21 days of therapy with no DLTs observed and were thus inevaluable for DLTs. Three patients were DLT evaluable and one patient is pending DLT evaluability. No Grade 4 adverse events have been reported.

Class C (Severe) group (with ascites), 50 mg: Nine patients had been enrolled to this cohort. Eight patients were removed from treatment after less than 21 days of therapy with no DLTs observed. One patient was DLT evaluable. One patient experienced Grade 4 lymphopenia.

Registration by Institution

Institutions	Total Reg
San Antonio, U of TX	51
Henry Ford Hosp	12
So Calif, U of	11
Davis, U of CA	3
Kansas, U of	3
Scott & White CCOP	2
City of Hope Med Ctr	1
Total (7 Institutions)	**83**

Registration, Eligibility, and Evaluability

Data as of March 12, 2015

	TOTAL	Grp1, Normal LFT, 140mg	Grp2, C-P Class A (Mild), 100mg	Grp2, C-P Class A (Mild), 140mg	Grp3, C-P Class B (Mod), 70mg
NUMBER REGISTERED	83	17	3	20	4
INELIGIBLE	6	3	0	1	0
Insufficient Documentation	1	1	0	0	0
Irreversible	1	1	0	0	0
ELIGIBLE	77	14	3	19	4
RESPONSE ASSESSMENT					
Determinable	61	13	1	12	4
Not Determinable	11	1	2	4	0
Too Early	4	0	0	2	0
Not Applicable	1	0	0	1	0
ADVERSE EVENT ASSESSMENT					
Evaluable	76	14	3	18	4
Not Evaluable	1	0	0	1	0

	Grp3, C-P Class B (Mod), 100mg	Grp4, C-P Class C (Severe), 50mg	Grp3b, C-P Class B (Mod), 100mg	Grp4b,C-P Class C (Severe), 50mg
NUMBER REGISTERED	19	1	10	9
INELIGIBLE	1	0	1	0
Insufficient Documentation	0	0	0	0
Irreversible	0	0	0	0
ELIGIBLE	18	1	9	9
RESPONSE ASSESSMENT				
Determinable	14	1	8	8
Not Determinable	3	0	1	0
Too Early	1	0	0	1
Not Applicable	0	0	0	0
ADVERSE EVENT ASSESSMENT				
Evaluable	18	1	9	9
Not Evaluable	0	0	0	0

Patient Characteristics

Data as of March 12, 2015

	Total (n=77)	
AGE		
Median	59.1	
Minimum	30.1	
Maximum	79.2	
SEX		
Males	42	55%
Females	35	45%
HISPANIC		
Yes	18	23%
No	52	68%
Unknown	7	9%
RACE		
White	59	77%
Black	9	12%
Asian	7	9%
Unknown	2	3%
GROUP		
Normal	14	18%
Child-Pugh Class A (Mild)	22	29%
Child-Pugh Class B (Moderate)	31	40%
Child-Pugh Class C (Severe)	10	13%
PRIMARY SITE		
Bladder	2	3%
Breast	3	4%
Colorectal	21	27%
Esophageal	1	1%
Larynx	1	1%
Lip	1	1%
Melanoma	1	1%
Non small cell lung	4	5%
Other GI	23	30%
Other GU	3	4%
Other GYN	2	3%
Other sarcoma	1	1%
Ovarian	1	1%
Pancreas	5	6%
Prostate	2	3%
Small cell lung	3	4%
Soft tissue sarcoma	2	3%

Treatment Summary

Data as of March 12, 2015

	TOTAL	Grp1, Normal LFT, 140mg	Grp2, C-P Class A (Mild), 100mg	Grp2, C-P Class A (Mild), 140mg	Grp3, C-P Class B (Mod), 70mg
NUMBER ON PROTOCOL TREATMENT	0	0	0	0	0
NUMBER OFF PROTOCOL TREATMENT	77	14	3	19	4
REASON OFF TREATMENT					
Treatment completed as planned	0	0	0	0	0
Adverse Event or side effects	21	2	1	6	0
Refusal unrelated to adverse event	7	1	1	1	0
Progression/relapse	40	11	1	10	2
Death	8	0	0	1	2
Other - not protocol specified	1	0	0	1	0
Reason under review	0	0	0	0	0
MAJOR PROTOCOL DEVIATIONS	1	0	0	1	0

	Grp3, C-P Class B (Mod), 100mg	Grp4, C-P Class C (Severe), 50mg	Grp3b, C-P Class B (Mod), 100mg	Grp4b, C-P Class C (Severe), 50mg
NUMBER ON PROTOCOL TREATMENT	0	0	0	0
NUMBER OFF PROTOCOL TREATMENT	18	1	9	9
REASON OFF TREATMENT				
Treatment completed as planned	0	0	0	0
Adverse Event or side effects	6	0	2	4
Refusal unrelated to adverse event	0	0	2	2
Progression/relapse	9	1	3	3
Death	3	0	2	0
Other - not protocol specified	0	0	0	0
Reason under review	0	0	0	0
MAJOR PROTOCOL DEVIATIONS	0	0	0	0

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

Cycle 1 only

Adverse Events Unlikely or Not Related to Treatment Excluded

Data as of March 12, 2015

	Total (n=76)	Grade				
ADVERSE EVENT	**0**	**1**	**2**	**3**	**4**	**5**
ALT	71	4	0	1	0	0
AST	72	2	0	1	1	0
Alkaline phosphatase	73	2	1	0	0	0
Allergic reaction	74	0	2	0	0	0
Anorexia	67	7	2	0	0	0
CPK	75	0	0	0	1	0
Constipation	75	0	1	0	0	0
Constitutional Symptoms-other	73	3	0	0	0	0
Cough	75	1	0	0	0	0
Creatinine	73	0	3	0	0	0
Diarrhea	63	9	3	1	0	0
Distension	75	0	1	0	0	0
Dysphagia	75	1	0	0	0	0
Dyspnea	73	0	1	2	0	0
Edema-head and neck	75	1	0	0	0	0
Edema-limb	75	0	1	0	0	0
Edema-trunk/genital	75	1	0	0	0	0
Eye Inf, Unk ANC: conjunct.	75	0	0	1	0	0
Fatigue	59	6	8	3	0	0
Fever	71	5	0	0	0	0
Flushing	75	1	0	0	0	0
GGT	75	1	0	0	0	0
GI Hemorrhage: upper GI	75	0	1	0	0	0
GI Pain: abdomen	72	2	1	0	1	0
GI Pain: oral cavity	75	1	0	0	0	0
GI-other	75	0	1	0	0	0
GU Inf, Unk ANC: kidney	75	0	0	1	0	0
Hemoglobin	65	2	7	1	1	0
Hot flashes	75	1	0	0	0	0
Hyperglycemia	72	3	1	0	0	0
Hypermagnesemia	74	1	0	1	0	0
Hypertension	74	2	0	0	0	0
Hypoalbuminemia	73	1	1	1	0	0
Hypoglycemia	75	0	1	0	0	0
Hypokalemia	75	1	0	0	0	0
Hyponatremia	71	4	0	1	0	0
Hypophosphatemia	75	1	0	0	0	0
Hypotension	75	0	0	1	0	0
Insomnia	75	1	0	0	0	0
Joint-function	75	0	1	0	0	0
Left vent. systolic dysfunct.	75	0	1	0	0	0
Leukocytes	72	3	0	1	0	0
Lung Pain: chest wall	75	1	0	0	0	0
Lung Pain: throat/phar/lar	75	1	0	0	0	0

	Total (n=76)					
	Grade					
ADVERSE EVENT	**0**	**1**	**2**	**3**	**4**	**5**
Lymphatics-other	75	1	0	0	0	0
Lymphopenia	68	1	2	4	1	0
Mucositis, clin: oral cavity	73	3	0	0	0	0
Mucositis, funct: oral cav.	75	1	0	0	0	0
Muscle weakness: low. extrem.	75	0	0	1	0	0
Muscle weakness: right-sided	75	1	0	0	0	0
Muscle weakness: whole body	75	1	0	0	0	0
Musculo. Pain: back	75	1	0	0	0	0
Musculo. Pain: bone	75	0	1	0	0	0
Musculo. Pain: muscle	74	2	0	0	0	0
Musculo. Pain: neck	74	1	1	0	0	0
Myocarditis	75	0	0	0	1	0
Nausea	60	9	5	2	0	0
Neuro Pain: head/headache	71	4	0	1	0	0
Neurology-other	75	1	0	0	0	0
Neutrophils	75	0	1	0	0	0
Ocular-other	75	1	0	0	0	0
PTT	75	1	0	0	0	0
Pain-other	75	1	0	0	0	0
Platelets	73	3	0	0	0	0
Pleural effusion	73	0	3	0	0	0
Pruritus	74	1	1	0	0	0
Pulmonary-other	75	0	1	0	0	0
Rash	69	5	2	0	0	0
Renal failure	72	0	0	4	0	0
Rigors/chills	73	3	0	0	0	0
Skin Pain: scalp	75	1	0	0	0	0
Sweating	75	0	1	0	0	0
Taste alteration	74	2	0	0	0	0
Vomiting	63	8	2	3	0	0
Weight gain	75	1	0	0	0	0
MAX. GRADE ANY ADVERSE EVENT	18	20	15	18	5	0

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

Adverse Events Unlikely or Not Related to Treatment Excluded

Data as of March 12, 2015

	Total (n=76)	Grade				
ADVERSE EVENT	**0**	**1**	**2**	**3**	**4**	**5**
ALT	71	4	0	1	0	0
AST	70	3	0	2	1	0
Acne	75	1	0	0	0	0
Alkaline phosphatase	72	2	1	1	0	0
Allergic reaction	74	0	2	0	0	0
Anorexia	65	8	3	0	0	0
Blurred vision	75	1	0	0	0	0
CPK	75	0	0	0	1	0
Constipation	74	0	2	0	0	0
Constitutional Symptoms-other	73	3	0	0	0	0
Cough	74	2	0	0	0	0
Creatinine	72	0	4	0	0	0
Diarrhea	61	11	3	1	0	0
Distension	75	0	1	0	0	0
Dysphagia	75	1	0	0	0	0
Dyspnea	72	1	1	2	0	0
Edema-head and neck	74	2	0	0	0	0
Edema-limb	74	1	1	0	0	0
Edema-trunk/genital	75	1	0	0	0	0
Eye Inf, Unk ANC: conjunct.	75	0	0	1	0	0
Fatigue	56	5	10	5	0	0
Fever	71	5	0	0	0	0
Flushing	75	1	0	0	0	0
GGT	75	1	0	0	0	0
GI Hemorrhage: stoma	75	1	0	0	0	0
GI Hemorrhage: upper GI	75	0	1	0	0	0
GI Pain: abdomen	72	2	1	0	1	0
GI Pain: oral cavity	75	1	0	0	0	0
GI-other	75	0	1	0	0	0
GU Inf, Unk ANC: kidney	75	0	0	1	0	0
Hemoglobin	62	2	7	4	1	0
Hot flashes	75	1	0	0	0	0
Hyperglycemia	71	3	2	0	0	0
Hypermagnesemia	73	2	0	1	0	0
Hypertension	74	2	0	0	0	0
Hypoalbuminemia	72	1	1	2	0	0
Hypocalcemia	75	1	0	0	0	0
Hypoglycemia	74	1	1	0	0	0
Hypokalemia	75	1	0	0	0	0
Hypomagnesemia	75	1	0	0	0	0
Hyponatremia	70	5	0	1	0	0
Hypophosphatemia	74	1	0	1	0	0
Hypotension	75	0	0	1	0	0
INR	74	2	0	0	0	0
Infection-other	75	0	0	0	1	0
Insomnia	75	1	0	0	0	0

	Total (n=76)	Grade				
ADVERSE EVENT	**0**	**1**	**2**	**3**	**4**	**5**
Joint-function	75	0	1	0	0	0
Left vent. systolic dysfunct.	75	0	1	0	0	0
Leukocytes	71	4	0	1	0	0
Lung Pain: chest wall	75	1	0	0	0	0
Lung Pain: throat/phar/lar	75	1	0	0	0	0
Lymphatics-other	75	1	0	0	0	0
Lymphopenia	68	1	2	4	1	0
Mucositis, clin: oral cavity	73	3	0	0	0	0
Mucositis, funct: oral cav.	75	1	0	0	0	0
Muscle weakness: low. extrem.	75	0	0	1	0	0
Muscle weakness: right-sided	75	1	0	0	0	0
Muscle weakness: whole body	75	1	0	0	0	0
Musculo. Pain: back	75	1	0	0	0	0
Musculo. Pain: bone	75	0	1	0	0	0
Musculo. Pain: muscle	74	2	0	0	0	0
Musculo. Pain: neck	74	1	1	0	0	0
Myocarditis	75	0	0	0	1	0
Nausea	58	11	5	2	0	0
Neuro Pain: head/headache	71	4	0	1	0	0
Neurology-other	75	1	0	0	0	0
Neutrophils	75	0	1	0	0	0
Ocular-other	75	1	0	0	0	0
PTT	75	1	0	0	0	0
Pain-other	75	1	0	0	0	0
Platelets	73	3	0	0	0	0
Pleural effusion	72	0	4	0	0	0
Pruritus	74	1	1	0	0	0
Pulmonary-other	75	0	1	0	0	0
Rash	69	5	2	0	0	0
Renal failure	72	0	0	4	0	0
Rigors/chills	73	3	0	0	0	0
Skin Pain: scalp	75	1	0	0	0	0
Sweating	75	0	1	0	0	0
Taste alteration	73	3	0	0	0	0
Vomiting	62	8	3	3	0	0
Weight gain	75	1	0	0	0	0
MAX. GRADE ANY ADVERSE EVENT	17	17	15	21	6	0