PREVENTION AND EPIDEMIOLOGY COMMITTEE

CONTENTS

Patient Registrations to Studies

By 12 Month Intervals
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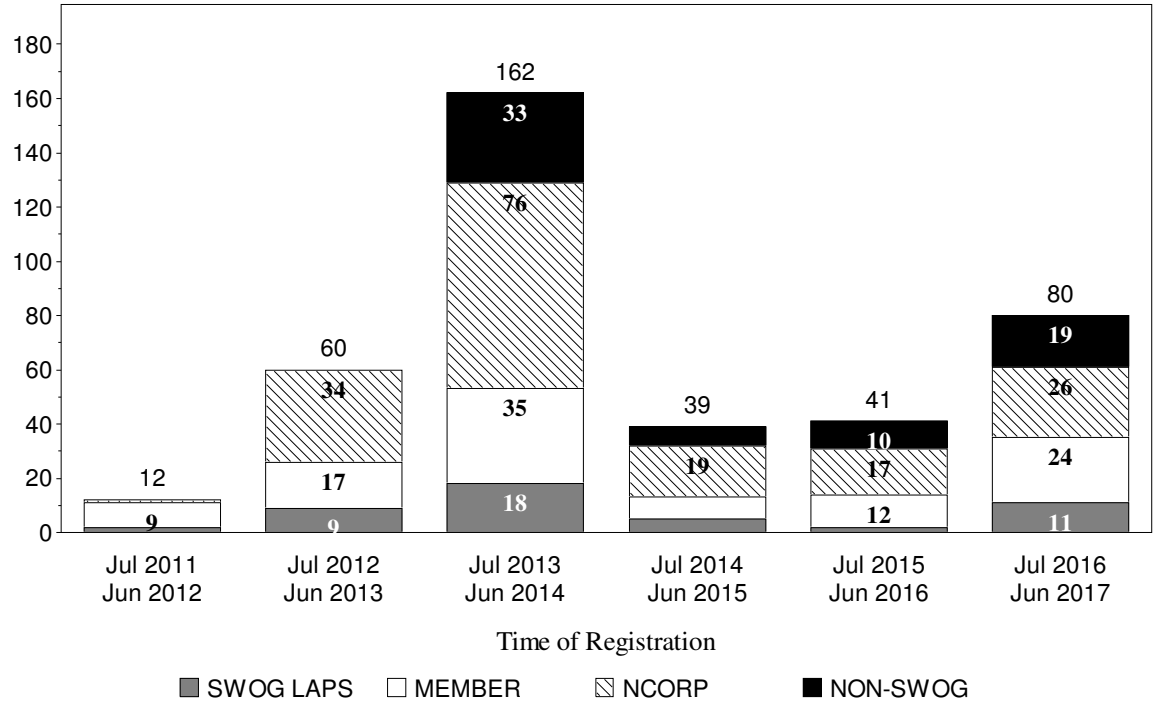

Screening registrations and registrations to Biologic only studies are excluded.

Patient Registrations by Study and Arm

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	Jan 2017 Jun 2017	Jul 2016 Dec 2016	Jan 2016 Jun 2016	All Patients
S0820 PACES: ColrecStg0-3 Blind DFMO/Sulindac				
Pre-Registration				
Pre-Registration	52	71	162	360
Randomization				
Blinded drug	34	28	24	153
A011502 Brst, Adj, Nodal+&HER2-, Aspirin vs. Placebo*				
Total Registrations	6	0	0	6
A211102 Breast, Atypia via RPFNA, Metformin v Placebo*				
Total Registrations	1	1	1	3
A211201 Breast Density, MA.32 companion*				
Total Registrations	0	0	2	14
EA1141 Breast, Abbrev. MRI vs Digital Tomosynthesis*				
Total Registrations	6	0	0	6
NHLBIMDS LEUK, National MDS Study*				
Total Registrations	3	1	0	4

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

Non-SWOG Studies with SWOG-Credited Registrations

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Studies with Accrual from January 2016 - June 2017

	SWOG Champion	Date Activated	Date Closed	Total Accrued
A011502 Brst, Adj, Nodal+&HER2-, Aspirin vs. Placebo *No Progress Report Available*		12/08/16		113
A211102 Breast, Atypia via RPFNA, Metformin v Placebo *Most Recent Progress Report*		02/01/15		125
A211201 Breast Density, MA.32 companion *Most Recent Progress Report*		08/22/12		177
EA1141 Breast, Abbrev. MRI vs Digital Tomosynthesis *Most Recent Progress Report*		09/02/16		448
NHLBIMDS LEUK, National MDS Study *No Progress Report Available*	D Hill	04/05/16		216

S0820 Phase III

Coordinating Group: SWOG

A Double Blind Placebo-Controlled Trial of Eflornithine and Sulindac to Prevent Recurrence of High Risk Adenomas and Second Primary Colorectal Cancers in Patients with Stage 0-III Colon or Rectal Cancer, Phase III - Preventing Adenomas of the Colon with Eflornithine and Sulindac (PACES)

Participants:
SWOG, CTSU (Supported by ECOG-ACRIN, NRG, Alliance)

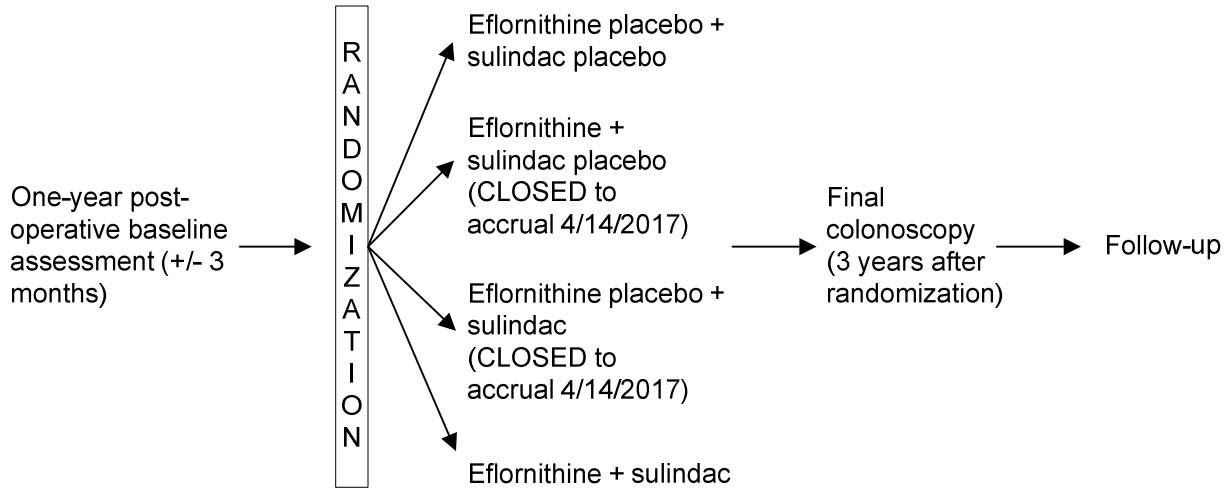
Date Activated:
03/01/2013

Study Chairs:
J Zell, P Brown, R Bergan (ECOG-ACRIN), J Dorth (NRG), Y You (Alliance)

Statisticians:
J Unger, G Anderson, K Arnold

Data Coordinator:
M Yee

SCHEMA



Objectives

To assess whether the combination of eflornithine and sulindac is effective in reducing the three-year event rate (high-risk adenomas and second primary colorectal cancers) in patients with previously treated Stage 0-III colon or rectal cancer.

To assess whether the combination of eflornithine and sulindac (compared to corresponding placebos)

has efficacy against colorectal lesions with respect to high-grade dysplasia, adenomas with villous features, adenomas 1 cm or greater, multiple adenomas, any adenomas ≥ 0.3 cm, total advanced colorectal events, or total colorectal events.

To assess quantitative and qualitative toxicities of patients when treated with the combination of eflornithine and sulindac compared to corresponding placebos.

To evaluate a minimal set of tagging single nucleotide polymorphisms across multiple genes relevant to eflornithine and sulindac, in order to characterize associations with decreased adenoma/second primary colorectal (CRC) risk and adverse events.

To evaluate biomarker responses of treatment effect using novel microfluidics-based digital droplet detection system.

To explore the interaction of intervention arm and baseline statin use with respect to the 3-year event rate.

To explore the interaction of the intervention arm and patient-reported meat consumption with respect to the 3-year event rate.

To perform population pharmacokinetic (PK) analysis of eflornithine and sulindac in patients with previously treated Stage 0-III colon or rectal cancer. (Sites participating in PK sampling are listed on page 1a of the protocol.)

Patient Population

Patients must have a history of Stage 0, I, II or III colon or rectal adenocarcinoma that has been treated per standard care with resection alone or in combination with radiation or chemotherapy. Adjuvant chemotherapy and/or radiation treatment must have been completed at least 30 days prior to registration.

Patients must be registered between 180 days and 456 days (inclusive) of primary resection. Patients must show no evidence of disease based on post-operative colonoscopy (performed at least 180 days after the colon resection date or at least 120 days after the rectal resection date and prior to registration) and CT or MRI scans (at the discretion of the treating physician for high risk patients, per NCCN guidelines) of chest, abdomen and pelvis (performed at least 180 days after the colon resection date or at least 120 days after the rectal resection date and prior to registration). Patients with adenomas detected at the one-year postoperative colonoscopy are eligible if all adenomas have been completely removed.

Patients must be at least 18 years of age and must not have cardiovascular risk factors as outlined in the protocol. Patients must have Zubrod performance status of 0-1 and adequate hematologic, hepatic and renal function. Patients must not have a known history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or inflammatory bowel disease. Patients must have a pure tone audiometry evaluation within 30 days prior to registration: patients with at least 40 dB hearing loss of any of the tested frequencies are not eligible. Patients must not be hypersensitive to selective inhibitors of cyclooxygenase-2, non-steroidal anti-inflammatory drugs, salicylates, or sulfonamides. Patients must not have documented history of gastric/duodenal ulcer within the last 12 months.

Stratification/Descriptive Factors

At randomization, patients will be stratified by risk of recurrence: Stage 0/I vs Stage II with no prior chemotherapy vs Stage II with prior chemotherapy vs Stage III.

Accrual Goals

A total of 420 eligible patients will be enrolled, 210 to each study arm. An additional 71 patients were enrolled to Arms 2 and 3 prior to their closure under Amendment #2 on April 14, 2017.

Summary Statement

This study activated on March 1, 2013. As of June 30, 2017, 153 patients have been randomized.

In Amendment #2, distributed March 15, 2017, the two single-agent arms of the study (eflornithine + sulindac placebo and eflornithine placebo + sulindac) were closed, effective April 14, 2017. This design change was made because full accrual was determined not be achievable under the original design. The revised primary objective is to compare the combination of eflornithine + sulindac to eflornithine placebo + sulindac placebo in a two-arm, phase III trial. The sample size was modified accordingly. The two arms with active drug and placebo combinations (eflornithine plus sulindac placebo and eflornithine placebo plus sulindac) were closed to further accrual. Patients currently enrolled on those combination arms will continue to be treated

and followed per protocol, and sites will continue to order study drugs per protocol. Surgical eligibility for rectal patients has been modified.

Study status will be presented by currently open arms versus closed arms for this report only. Reports thereafter will present data only on the two open arms, as these are the arms that contribute to the revised study objectives.

For patients on the currently open arms:

As of June 30, 2017, 82 patients have been randomized to the currently open arms. Six patients are ineligible due to: baseline hearing loss (3), baseline lab values out of range (1), high cardiovascular risk (1), and primary resection done too late (1). Two patients who never started treatment are coded as major deviations; these patients are also not evaluable for adverse events. One additional patient is not evaluable for adverse events due to site error. Twenty-five patients are off treatment, including four patients coded as "Other – not protocol specified", two of whom did not take study medication for more than 90 days, one of whom the site was unable to contact, and one who stopped medication.

Among 60 patients who have had adverse events evaluated, one patient reported Grade 3 anemia, duodenal ulcer, and upper GI hemorrhage.

For patients on the closed arms:

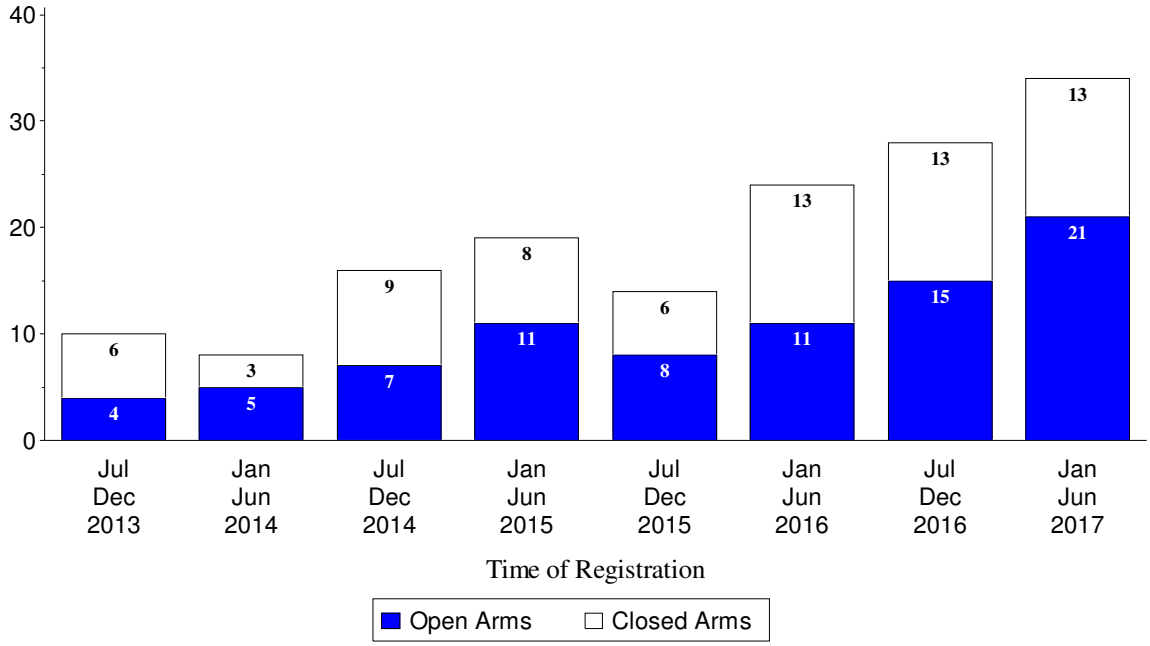
Seventy-one patients were randomized to the closed arms. Three patients are ineligible due to: baseline hearing loss (1) and baseline lab values out of range (2). Four patients who never started treatment are coded as major deviations; these patients are also not evaluable for adverse events. Thirty patients are off treatment, including two patients coded as "Other – not protocol specified", one of whom did not take study medication for more than 90 days and one the site removed in error.

Among 62 patients who have had adverse events evaluated, three Grade 3 events were reported for three patients: two patients reported hypertension and one patient reported diarrhea.

A tool for tracking patients from the time of their initial resection to their registration window was made available in Revision #4. As of June 30, 2017, 360 patients have been logged into the tracking tool, of whom 25 were subsequently randomized, 10 to the open arms and 15 to the closed arms. Two hundred and thirty-six logged patients have passed the eligibility window and will never be randomized.

Initial Registrations By 6 Month Intervals

Divisions by Study Arm Status



Registration by Institution

Registrations ending June 30, 2017

Institutions	Total Reg	Institutions	Total Reg
Kaiser Perm NCORP	18	Baptist MU-NCORP	1
Irvine, U of CA	15	Bridgeport Hospital/Yale University	1
Wichita NCORP	9	Brooke Army Med Ctr	1
Hawaii MU-NCORP	6	City of Hope Med Ctr	1
San Antonio, U of TX	6	Columbia MU-NCORP	1
Yale University	5	Dayton NCORP	1
Banner MD Anderson/MD Anderson CC	4	Eisenhower Army MC/Brooke Army Med Ctr	1
MD Anderson CC	4	Georgia NCORP	1
Michigan CRC NCORP	4	Loma Linda Univ	1
So Calif, U of	4	NE Georgia Med Ctr/Georgia NCORP	1
Columbus NCORP	3	Oklahoma, Univ of	1
Essentia Hlth NCORP	3	Providence Hosp	1
KaiserPermanenteSCAL/Kaiser Perm NCORP	3	Southeast COR NCORP	1
Kansas, U of	3	St Joseph Hospital/Mississippi, Univ of	1
MAVERIC	3	Weiss Memorial Hosp/Loyola University	1
Northwest NCORP	3	ALLIANCE	14
Colorado, U of	2	NRG	14
CORA NCORP	2	ECOG-ACRIN	9
Heartland NCORP	2	**Total (38 Institutions)**	**153**
McLaren Cancer Inst/Wayne State Univ	2		

Registration, Eligibility, and Evaluability

Registrations ending June 30, 2017; Data as of August 2, 2017

	TOTAL	Open Arms	Closed Arms
NUMBER REGISTERED	153	82	71
INELIGIBLE	9	6	3
ELIGIBLE	144	76	68
Analyzable, Pend. Elig.	4	4	0
RESPONSE ASSESSMENT			
Not Applicable	144	76	68
ADVERSE EVENT ASSESSMENT			
Evaluable	122	60	62
Not Evaluable	7	3	4
Too Early	15	13	2

Patient Characteristics

Registrations ending June 30, 2017; Data as of August 2, 2017

	Open Arms (n=76)		Closed Arms (n=68)	
AGE				
Median	52.5		53.0	
Minimum	30.6		29.2	
Maximum	78.2		78.2	
SEX				
Males	33	43%	25	37%
Females	43	57%	43	63%
HISPANIC				
Yes	11	14%	6	9%
No	62	82%	62	91%
Unknown	3	4%	0	0%
RACE				
White	57	75%	45	66%
Black	3	4%	5	7%
Asian	8	11%	11	16%
Pacific Islander	1	1%	1	1%
Native American	1	1%	0	0%
Multi-Racial	0	0%	1	1%
Unknown	6	8%	5	7%
RISK OF RECURRENCE				
Stage 0 or I	15	20%	12	18%
Stage II with no prior chemotherapy or radiation therapy	13	17%	13	19%
Stage II with prior chemotherapy or radiation therapy	8	11%	9	13%
Stage III	40	53%	34	50%

Treatment Summary

Registrations ending June 30, 2017; Data as of August 2, 2017

	TOTAL	Open Arms	Closed Arms
NUMBER ON PROTOCOL TREATMENT	89	51	38
NUMBER OFF PROTOCOL TREATMENT	55	25	30
REASON OFF TREATMENT			
Treatment completed as planned	8	4	4
Adverse Event or side effects	16	7	9
Refusal unrelated to adverse event	13	4	9
Progression/relapse	7	4	3
Death	1	0	1
Other - not protocol specified	6	4	2
Reason under review	4	2	2
MAJOR PROTOCOL DEVIATIONS	6	2	4

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

Adverse Events Unlikely or Not Related to Treatment Excluded

Registrations ending June 30, 2017; Data as of August 2, 2017

	Open Arms (n=60) Grade						Closed Arms (n=62) Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
ALT increased	57	3	0	0	0	0	60	2	0	0	0	0
AST increased	58	2	0	0	0	0	62	0	0	0	0	0
Abdominal pain	58	2	0	0	0	0	59	0	3	0	0	0
Alkaline phosphatase increased	59	1	0	0	0	0	62	0	0	0	0	0
Allergic reaction	59	0	1	0	0	0	62	0	0	0	0	0
Alopecia	59	1	0	0	0	0	62	0	0	0	0	0
Anemia	59	0	0	1	0	0	61	1	0	0	0	0
Anorexia	60	0	0	0	0	0	61	1	0	0	0	0
Anxiety	59	1	0	0	0	0	62	0	0	0	0	0
Arthralgia	59	1	0	0	0	0	60	2	0	0	0	0
Bloating	59	1	0	0	0	0	61	0	1	0	0	0
Blood bilirubin increased	58	1	1	0	0	0	58	2	2	0	0	0
Blurred vision	60	0	0	0	0	0	61	1	0	0	0	0
Bruising	59	1	0	0	0	0	62	0	0	0	0	0
Cardiac disorder-Other, spec	60	0	0	0	0	0	61	1	0	0	0	0
Chest pain - cardiac	59	1	0	0	0	0	62	0	0	0	0	0
Constipation	56	4	0	0	0	0	54	6	2	0	0	0
Creatinine increased	60	0	0	0	0	0	61	1	0	0	0	0
Diarrhea	55	4	1	0	0	0	53	4	4	1	0	0
Dizziness	58	2	0	0	0	0	57	5	0	0	0	0
Dry mouth	59	1	0	0	0	0	61	1	0	0	0	0
Duodenal ulcer	59	0	0	1	0	0	62	0	0	0	0	0
Dyspepsia	59	1	0	0	0	0	59	3	0	0	0	0
Dysphagia	59	1	0	0	0	0	62	0	0	0	0	0

Number of Patients with a Given Type and Grade of Adverse Event (continued)

Adverse Events Unlikely or Not Related to Treatment Excluded

Registrations ending June 30, 2017; Data as of August 2, 2017

	Open Arms (n=60) Grade						Closed Arms (n=62) Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Dyspnea	59	1	0	0	0	0	61	1	0	0	0	0
Edema limbs	58	2	0	0	0	0	61	1	0	0	0	0
Fatigue	51	8	1	0	0	0	59	3	0	0	0	0
Flatulence	60	0	0	0	0	0	61	1	0	0	0	0
Flu like symptoms	59	1	0	0	0	0	62	0	0	0	0	0
Flushing	59	0	1	0	0	0	62	0	0	0	0	0
GERD	60	0	0	0	0	0	60	1	1	0	0	0
GI disorders-Other, specify	60	0	0	0	0	0	61	1	0	0	0	0
Gastritis	60	0	0	0	0	0	61	0	1	0	0	0
Gastrointestinal pain	59	1	0	0	0	0	60	2	0	0	0	0
Generalized muscle weakness	59	1	0	0	0	0	62	0	0	0	0	0
Headache	55	5	0	0	0	0	57	3	2	0	0	0
Hematuria	58	2	0	0	0	0	62	0	0	0	0	0
Hot flashes	59	1	0	0	0	0	61	1	0	0	0	0
Hyperglycemia	60	0	0	0	0	0	61	0	1	0	0	0
Hyperhidrosis	59	1	0	0	0	0	62	0	0	0	0	0
Hypertension	56	1	3	0	0	0	57	2	1	2	0	0
Insomnia	59	0	1	0	0	0	62	0	0	0	0	0
Investigations-Other, specify	59	1	0	0	0	0	62	0	0	0	0	0
Irregular menstruation	60	0	0	0	0	0	61	1	0	0	0	0
Muscle weakness upper limb	59	1	0	0	0	0	62	0	0	0	0	0
Myalgia	60	0	0	0	0	0	61	1	0	0	0	0
Nausea	54	6	0	0	0	0	56	6	0	0	0	0
Pain	59	1	0	0	0	0	62	0	0	0	0	0
Pain in extremity	58	2	0	0	0	0	62	0	0	0	0	0
Peripheral sensory neuropathy	59	1	0	0	0	0	62	0	0	0	0	0
Platelet count decreased	59	1	0	0	0	0	62	0	0	0	0	0
Pleuritic pain	59	1	0	0	0	0	62	0	0	0	0	0
Pruritus	59	0	1	0	0	0	62	0	0	0	0	0
Rash maculo-papular	59	1	0	0	0	0	62	0	0	0	0	0
Rectal hemorrhage	60	0	0	0	0	0	61	1	0	0	0	0
Renal/urinary disorders-Other	59	1	0	0	0	0	62	0	0	0	0	0
Skin/subq tissue ds-Other	59	1	0	0	0	0	61	0	1	0	0	0
Somnolence	59	1	0	0	0	0	62	0	0	0	0	0
Stomach pain	60	0	0	0	0	0	61	1	0	0	0	0
Tinnitus	58	1	1	0	0	0	59	2	1	0	0	0
Transient ischemic attacks	59	0	1	0	0	0	62	0	0	0	0	0
Upper GI hemorrhage	59	0	0	1	0	0	62	0	0	0	0	0
Vaginal dryness	59	1	0	0	0	0	62	0	0	0	0	0
Vomiting	58	2	0	0	0	0	62	0	0	0	0	0
Weight loss	60	0	0	0	0	0	61	1	0	0	0	0
White blood cell decreased	59	1	0	0	0	0	62	0	0	0	0	0
MAX. GRADE ANY ADVERSE EVENT	26	23	10	1	0	0	31	16	12	3	0	0