Documentation for NCT00070564-D2 (SWOG S0221)
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There are 2 datasets associated with this publication: NCT00070564-D1 and NCT00070564-D2. The first dataset contains patient-level efficacy data. The second dataset includes toxicity data with one record per event. This documentation describes the toxicity data. However, it is necessary to merge these data with the efficacy data for these data to be useful.

NCT00070564-D2 documentation (toxicity)
Toxicity (one record per event) - Uses standard CTCAE 3.0 descriptions

Variable Name	Description	Format	Coding
Patid	Unique patient identifier	Numeric (9 digits)	Patient identifier
Studyid	Trial being reported	Character (8)	S0221 for all
Regtype	Registration type	Character (1)	1 for all in this trial
Toxno	Ordinal toxicity reported for that patient	Numeric (3 digits)	1 = First toxicity 2 = Second etc
Toxdeg	Degree reported for toxicity (only grades 3-5 were required to be reported)	Character (40)	1-5 May also have a P as in 3P if degree is still pending
Toxtype	CTCAE version	Character (8)	CTC3.0 for all
Toxcode	CTCAE version 3.0 codes	Character (8)	CTC toxcodes (e.g. HE00)
Toxcyc	Tox segment (AC; paclitaxel)	Numeric (1 digit)	1= AC cycle 2= Paclitaxel cycle . = Not recorded
Toxlabel	Label corresponding to toxcode	Character (30)	e.g. Leukocytes
Txatt	Attribution of toxicity to treatment	Character (40)	1 = unrelated 2 = unlikely 3 = possible 4 = probable 5 = definite
Toxcat	Overarching tox category	Character (70)	
CTC_cat	Alternative overall classification (less granular)	Character (70)	
Cycle	Tox segment (AC; paclitaxel) Some inference has been performed to classify missing values based on other info	Numeric (1 digit)	1= AC cycle 2= Paclitaxel cycle . = Not recorded

Publication Abstract

Budd GT, Barlow WE, Moore HC, Hobday TJ, Stewart JA, Isaacs C, Salim M, Cho JK, Rinn KJ, Albain KS, Chew HK, Burton GV, Moore TD, Srkalovic G, McGregor BA, Flaherty LE, Livingston RB, Lew DL, Gralow JR, Hortobagyi GN.

SWOG S0221: a phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer.

J Clin Oncol. 2015 Jan 1; 33(1):58-64. Epub 2014 Nov 24.

PURPOSE: To determine the optimal dose and schedule of anthracycline and taxane administration as adjuvant therapy for early-stage breast cancer.
PATIENTS AND METHODS: A 2 × 2 factorial design was used to test two hypotheses: (1) that a novel continuous schedule of doxorubicin-cyclophosphamide was superior to six cycles of doxorubicin-cyclophosphamide once every 2 weeks and (2) that paclitaxel once per week was superior to six cycles of paclitaxel once every 2 weeks in patients with node-positive or high-risk node-negative early-stage breast cancer. With 3,250 patients, a disease-free survival (DFS) hazard ratio of 0.82 for each randomization could be detected with 90% power with two-sided α = .05. Overall survival (OS) was a secondary outcome.
RESULTS: Interim analyses crossed the futility boundaries for demonstrating superiority of both once-per-week regimens and once-every-2-weeks regimens. After a median follow-up of 6 years, a significant interaction developed between the two randomization factors (DFS P = .024; OS P = .010) in the 2,716 patients randomly assigned in the original design, which precluded interpretation of the two factors separately. Comparing all four arms showed a significant difference in OS (P = .040) but not in DFS (P = .11), with all treatments given once every 2 weeks associated with the highest OS. This difference in OS seemed confined to patients with hormone receptor-negative/human epidermal growth factor receptor 2 (HER2) –negative tumors (P = .067), with no differences seen with hormone receptor-positive/HER2-negative (P = .90) or HER2-positive tumors (P = .40).
CONCLUSION: Patients achieved a similar DFS with any of these regimens. Subset analysis suggests the hypothesis that once-every-2-weeks dosing may be best for patients with hormone receptor-negative/HER2-negative tumors.

PMCID: PMC4268253
PMID: 25422488 [PubMed – indexed for MEDLINE]

```
/* There are 2 datasets associated with this publication: NCT00070564-
D1 and NCT00070564-D2.
 The following is the program for the toxicity data in NCT00070564-D2.
The efficacy data are in NCT00070564-D1
 To use the toxicity data you need to use both datasets.
*/;

/* Toxicity Manuscript Tables 2 and 3
Toxicities have been updated to include revision and additions since
original publication.  For the most part the numerators for grades 3,
4 , and 5
are the same or very similar to those in the publication.  We have
increased the denominator for the paclitaxel segment since we are now
less stringent on who
was included for the toxixity assessment on the paclitaxel treatment.
We still attempt to filter out those who did not appear to start
paclitaxel therpy.

Some of the deaths have been reevalauted as well.  The tables below
reflect these changes.
*/;


options ls=100 ps=6000 nodate;


data s0221archive;
infile
'I:\groups\SWOGSTAT\Analyses\Breast\S0221\Manuscript_JCO_2014\s0221.tx
t';
input patid  regyear  trno  weeklyt weeklyac  use  excludereason  age
gender  menop blackrace   posnodesclass  her2  posrecep  subtype
dfstim  dfsind  surtim  surind includetox includetox2 ;
run;


proc format;
                value $toxdeg
                '0' = '0-2'
                '1' = '0-2'
                '2' = '0-2'
                '3' = '3'
                '4' = '4'
                '5' = '5'
                ;
            value weekly
                0='Q2 week'
                1='Weekly'
                ;
run;
```

```
data ts0221;
infile
'I:\groups\SWOGSTAT\Analyses\Breast\S0221\Manuscript_JCO_2014\ts0221.t
xt'   LRECL=340 ;
input @1 PATID @12 STUDYID $8. @22 REGTYPE $1. @24 toxno @28 TOXDEG
$40. @71 TOXTYPE $8. @81 TOXCODE $8. @91 TOXCYC @94 TOXLABEL $30. @127
TXATT $40.
  @171 TOXCAT  $70. @250 CTC_CAT $70. @325 cycle ;
  cards;
run;

data ts; set ts0221;
/* Eliminate 602 toxicities with attribution unrelated to treatment
*/;
if ((txatt='1')|(txatt='2')|(txatt='2P')) then delete;
/* Eliminate 2 additional toxicities with unknown degree coded as 9
*/;
if toxdeg^='9';
/* There are 443 toxicities with tox degree coded as 1-2 ; these were
not required to be reported and may reflect biased recording
   These will be collapsed into the 0-2 grade toxicity */;
drop regtype studyid toxtype;
format toxdeg $toxdeg. ;
run;

data ts1; set ts;
/* toxicities that occurred during AC treatment or unspecified time
*/;
if ((cycle=1)|(cycle=.));
run;
data ts2; set ts;
/* toxicities that occurred during paclitaxel treatment  */;
if (cycle=2);
run;

data rstox; set s0221archive; if use=1;
format weeklyac weeklyt weekly. ;
keep patid trno weeklyac weeklyt includetox includetox2;
run;

data rs1; set rstox;
if (includetox=1);
keep patid trno weeklyac;
run;
proc sort data=rs1; by patid; run;

data rs2; set rstox;
if (includetox2=1);
keep patid trno weeklyt;
run;
proc sort data=rs2; by patid; run;
```

```
proc sort data=ts1 out=ts1tox ; by patid descending toxdeg ;
run;
data tsmax; set ts1tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts1max; merge tsmax(in=in2) rs1(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'All adverse events - AC Segment';
proc freq data=ts1max; tables weeklyac*toxdeg/missing nocol nopercent
;
run;

/* Hemoglobin */;

proc sort data=ts1 out=ts1tox ; by patid descending toxdeg ;
where (toxcode='HE20'); run;
data tsmax; set ts1tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts1max; merge tsmax(in=in2) rs1(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Hemoglobin - AC Segment';
proc freq data=ts1max; tables weeklyac*toxdeg/missing nocol nopercent
;
run;

/* Leukocytes */;

proc sort data=ts1 out=ts1tox ; by patid descending toxdeg ;
where (toxcode='HE00'); run;
data tsmax; set ts1tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts1max; merge tsmax(in=in2) rs1(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Leukocytes - AC Segment';
proc freq data=ts1max; tables weeklyac*toxdeg/missing nocol nopercent
;
run;


/* Neutrophils */;

proc sort data=ts1 out=ts1tox ; by patid descending toxdeg ;
where (toxcode='HE30'); run;
data tsmax; set ts1tox; by patid; if first.patid;
```

```
run;
proc sort data=tsmax; by patid; run;
data ts1max; merge tsmax(in=in2) rs1(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Neutrophils - AC Segment';
proc freq data=ts1max; tables weeklyac*toxdeg/missing nocol nopercent
;
run;


/* Platelets */;

proc sort data=ts1 out=ts1tox ; by patid descending toxdeg ;
where (toxcode='HE10'); run;
data tsmax; set ts1tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts1max; merge tsmax(in=in2) rs1(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Platelets - AC Segment';
proc freq data=ts1max; tables weeklyac*toxdeg/missing nocol nopercent
;
run;

/* Cardiac */;

proc sort data=ts1 out=ts1tox ; by patid descending toxdeg ;
where (substr(toxcode,1,2)='CA'); run;
data tsmax; set ts1tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts1max; merge tsmax(in=in2) rs1(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Cardiac general - AC Segment';
proc freq data=ts1max; tables weeklyac*toxdeg/missing nocol nopercent
;
run;


/* Mucositis clinical */;

proc sort data=ts1 out=ts1tox ; by patid descending toxdeg ;
where (substr(toxcode,1,3)='GIC'); run;
data tsmax; set ts1tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
```

```
data ts1max; merge tsmax(in=in2) rs1(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Mucositis clinical - AC Segment';
proc freq data=ts1max; tables weeklyac*toxdeg/missing nocol nopercent
;
run;

/* Dermatologic/skin */;

proc sort data=ts1 out=ts1tox ; by patid descending toxdeg ;
where (substr(toxcode,1,2)='SK'); run;
data tsmax; set ts1tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts1max; merge tsmax(in=in2) rs1(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Dermatologic/skin - AC Segment';
proc freq data=ts1max; tables weeklyac*toxdeg/missing nocol nopercent
;
run;

/* Infection */;

proc sort data=ts1 out=ts1tox ; by patid descending toxdeg ;
where ((ctc_cat='Infection')); run;
data tsmax; set ts1tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts1max; merge tsmax(in=in2) rs1(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Infection - AC Segment';
proc freq data=ts1max; tables weeklyac*toxdeg/missing nocol nopercent
;
run;

/* Febrile Neutropenia */;

proc sort data=ts1 out=ts1tox ; by patid descending toxdeg ;
where ((ctc_cat='Infection')&(toxcode='IN30'));  run;

data tsmax; set ts1tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts1max; merge tsmax(in=in2) rs1(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;
```

```
title 'Febrile Neutropenia - AC Segment';
proc freq data=ts1max; tables weeklyac*toxdeg/missing nocol nopercent
;
run;

/* Flu-like symptoms */;

proc sort data=ts1 out=ts1tox ; by patid descending toxdeg ;
where (substr(toxcode,1,2)='FL');  run;

data tsmax; set ts1tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts1max; merge tsmax(in=in2) rs1(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Flu-like Symptoms - AC Segment';
proc freq data=ts1max; tables weeklyac*toxdeg/missing nocol nopercent
;
run;

/* All deaths possibly due to toxicity  */;

proc sort data=ts1 out=ts1death; by patid;
where toxdeg='5'; run;

data rstox1; merge rs1(in=in) ts1death(in=in2); by patid;
if in;
if in2;
run;

proc sort data=rstox1; by patid descending weeklyac ; run;

title 'All deaths possibly due to toxicity - AC Segment - Q2 week';
proc print data=rstox1;
var patid weeklyac toxdeg toxcode toxlabel txatt toxcat ctc_cat;
where weeklyac=0;
run;

title 'All deaths possibly due to toxicity - AC Segment - Weekly';
proc print data=rstox1;
var patid weeklyac toxdeg toxcode toxlabel txatt toxcat ctc_cat;
where weeklyac=1;
run;

/* Paclitaxel segment */;

proc sort data=ts2 out=ts2tox ; by patid descending toxdeg ;
run;
data tsmax; set ts2tox; by patid; if first.patid;
```

```
run;
proc sort data=tsmax; by patid; run;
data ts2max; merge tsmax(in=in2) rs2(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'All adverse events - Paclitaxel Segment';
proc freq data=ts2max; tables weeklyt*toxdeg/missing nocol nopercent ;
run;

/* Hemoglobin */;

proc sort data=ts2 out=ts2tox ; by patid descending toxdeg ;
where (toxcode='HE20'); run;
data tsmax; set ts2tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts2max; merge tsmax(in=in2) rs2(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Hemoglobin - Paclitaxel Segment';
proc freq data=ts2max; tables weeklyt*toxdeg/missing nocol nopercent ;
run;

/* Leukocytes */;

proc sort data=ts2 out=ts2tox ; by patid descending toxdeg ;
where (toxcode='HE00'); run;
data tsmax; set ts2tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts2max; merge tsmax(in=in2) rs2(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Leukocytes - Paclitaxel Segment';
proc freq data=ts2max; tables weeklyt*toxdeg/missing nocol nopercent ;
run;


/* Neutrophils */;

proc sort data=ts2 out=ts2tox ; by patid descending toxdeg ;
where (toxcode='HE30'); run;
data tsmax; set ts2tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts2max; merge tsmax(in=in2) rs2(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;
```

```
title 'Neutrophils - Paclitaxel Segment';
proc freq data=ts2max; tables weeklyt*toxdeg/missing nocol nopercent ;
run;


/* Neurologic */;

proc sort data=ts2 out=ts2tox ; by patid descending toxdeg ;
where (toxcat='Neurologic'); run;

data tsmax; set ts2tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts2max; merge tsmax(in=in2) rs2(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Neurologic - Paclitaxel Segment';
proc freq data=ts2max; tables weeklyt*toxdeg/missing nocol nopercent ;
run;


/* Dermatologic/skin */;

proc sort data=ts2 out=ts2tox ; by patid descending toxdeg ;
where (substr(toxcode,1,2)='SK'); run;

data tsmax; set ts2tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts2max; merge tsmax(in=in2) rs2(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Dermatologic/skin - Paclitaxel Segment';
proc freq data=ts2max; tables weeklyt*toxdeg/missing nocol nopercent ;
run;

/* Allergy */;

proc sort data=ts2 out=ts2tox ; by patid descending toxdeg ;
where toxcode='IM00'; run;

data tsmax; set ts2tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts2max; merge tsmax(in=in2) rs2(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Allergy - Paclitaxel Segment';
proc freq data=ts2max; tables weeklyt*toxdeg/missing nocol nopercent ;
```

```
run;

/* Febrile Neutropenia */;

proc sort data=ts2 out=ts2tox ; by patid descending toxdeg ;
where ((ctc_cat='Infection')&(toxcode='IN30'));  run;

data tsmax; set ts2tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts2max; merge tsmax(in=in2) rs2(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Febrile Neutropenia - Paclitaxel Segment';
proc freq data=ts2max; tables weeklyt*toxdeg/missing nocol nopercent ;
run;

/* Musculoskeletal Pain */;

proc sort data=ts2 out=ts2tox ; by patid descending toxdeg ;
where (toxcat='Musculoskeletal Pain');  run;

data tsmax; set ts2tox; by patid; if first.patid;
run;
proc sort data=tsmax; by patid; run;
data ts2max; merge tsmax(in=in2) rs2(in=in); by patid; if in;
if in2=0 then toxdeg='0';
run;

title 'Musculoskeletal Pain - Paclitaxel Segment';
proc freq data=ts2max; tables weeklyt*toxdeg/missing nocol nopercent ;
run;

/* All deaths possibly due to toxicity  */;

proc sort data=ts2 out=ts2death; by patid;
where toxdeg='5'; run;

data rstox2; merge rs2(in=in) ts2death(in=in2); by patid;
if in;
if in2;
run;

proc sort data=rstox2; by patid descending weeklyt ; run;

title 'All deaths possibly due to toxicity - Paclitaxel Segment - Q2
week';
proc print data=rstox2;
var patid weeklyt toxdeg toxcode toxlabel txatt toxcat ctc_cat;
where weeklyt=0;
run;
```

```
title 'All deaths possibly due to toxicity - Paclitaxel Segment -
Weekly';
proc print data=rstox2;
var patid weeklyt toxdeg toxcode toxlabel txatt toxcat ctc_cat;
where weeklyt=1;
run;
```