

Documentation for NCT00070564-D1 (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.

NCT00070564-D1 documentation

Variable Name	Description	Coding
Patid	Unique patient identifier	Nine digit identifier
Regyear	Year patient registered for the trial	2003-2012
Trno	Randomized treatment arm	1 = AC+PEG-Gx6 then q2wk T+PEG-Gx6 2 = AC+Gx15wks then q2wk T+PEG-Gx6 3 = AC+PEG-Gx6 then weekly T x 12 4 = AC+Gx15wks then weekly T x 12 5 = AC+PEG-Gx4 then q2wk T+PEG-Gx6 6 = AC+PEG-Gx4 then weekly T x 12
Weeklyt	Taxane given weekly	0 = No (Arms 1,2,5) 1 = Yes (Arms 3,4,6)
Weeklyac	AC given weekly	0 = No (Arms 1,3) 1 = Yes (Arms 2,4) . = NA (Arms 5,6)
Use	Indicator of inclusion in the analysis	0 = Excluded 1 = Included
Excludereason	Reason for exclusion	0 = Included 1 = Ineligible 2 = Withdrew consent 3 = New protocol (Arms 5 and 6)
Age	Age in years at randomization	xx.x
Gender	Gender	0 = Female 1 = Male
Menopause	Menopausal status	0 = Premenopausal 1 = Postmenopausal . = Missing or NA (male)
Blackrace	Black	0 = Not black 1 = Black

Variable Name	Description	Coding
Posnodesclass	Number of positive nodes	0 = Node negative 1 = 1-3 positive nodes 2 = 4 or more positive nodes . = Missing
Her2	HER2 status (locally assessed)	0 = Negative 1 = Positive . = Missing
Posrecep	Hormone receptor status (locally assessed)	0 = Negative 1 = Positive . = Missing
Subtype	Breast cancer subtype (combined from HER2 and receptor status)	1 = Hormone receptor-positive; HER2-negative 2 = Hormone receptor-negative; HER2-negative (TN) 3 = HER2-positive . = Missing
Dfstim	Time from registration to first event (recurrence, new breast primary, death)	Number of days
Dfsind	Event indicator	0 = Censored at time t 1 = Event at time t
Surtim	Time from registration to death due to any cause	Number of days
Surind	Event indicator	0 = Censored at time t 1 = Death at time t
Includetox	Indicator for whether this patient should be included in the toxicity evaluation of AC therapy	. = NA 0 = randomized but ineligible for toxicity assessment due to study ineligibility, failure to start treatment or major protocol deviation 1= include in AC toxicity
Includetox2	Indicator for whether this patient should be included in the toxicity evaluation of paclitaxel therapy	. = NA 0 = randomized but ineligible for toxicity assessment due to study ineligibility, failure to start treatment or major protocol deviation 1= include in paclitaxel toxicity

Note 1: The data are in a column delimited text file. A program is included (S0221analysis.sas) to read the data and to produce the primary and secondary survival analyses as well as the toxicity analyses.

Note 2: Initially patients were randomized in a 2x2 factorial design to Arms 1-4. The protocol was subsequently changed to a single randomization (Arm 5 vs 6) with AC fixed at 4 cycles. Only the first four arms were compared in the publication.

Publication abstract and reference

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 $\alpha = .05$. 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.

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/* SAS program to read the text file and reproduce the results in the
publication; change target directory as appropriate */;

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

/* This shows the DFS and OS analyses for S0221 as published in JCO in 2014
by Budd et al.
It also shows the values for the CONSORT figure and Table 1.
There are a few very minor discrepancies such as one less ineligible in Arm 1
and one more in Arm 2 than in the CONSORT figure
There are also a few very minor differences in Table 1.
However, for the survival analyses all results are identical to those in the
manuscript. */;

options ls=100 ps=6000 nodate;

proc format;
value exclude
    0 = 'Included'
    1 = 'Ineligible'
    2 = 'Consent withdrawn'
    3 = 'New protocol'
    ;
value menop
    0 = 'Premenopausal'
    1 = 'Postmenopausal'
    ;
value gender
    0 = 'Female'
    1 = 'Male'
    ;
value posrecep
    0 = 'HR-negative'
    1 = 'HR-positive'
    ;
value her
    0 = 'HER2-negative'
    1 = 'HER2-positive'
    ;
value black
    0 = 'Not black'
    1 = 'Black'
    ;
value subtype
    1 = 'HR-positive; HER2-negative'
    2 = 'HR-negative; HER2-negative (TN)'
    3 = 'HER2-positive'
    ;
value nodesclass
    0 = 'Node negative'
    1 = '1-3 positive nodes'
    2 = '4+ positive nodes'
    ;
run;

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data s0221archive;
infile
'I:\groups\SWOGSTAT\Analyses\Breast\S0221\Manuscript_JCO_2014\s0221.txt';
input patid regyear trno weeklyt weeklyac use excludereason age gender
menop blackrace posnodesclass her2 posrecep subtype dfstim dfsind
surtim surind includetox includetox2 ;
run;
proc freq data=s0221archive;
tables regyear trno weeklyt weeklyac use excludereason age gender
menop blackrace posnodesclass her2 posrecep subtype dfsind surind
includetox includetox2;
run;

title 'Included and Excluded Data';

proc freq data=s0221archive;
format excludereason exclude. ;
tables excludereason*trno /nopercent norow nocol ;
run;
data allms; set s0221archive; if use=1;
trt2=(trno=2);
trt3=(trno=3);
trt4=(trno=4);
interaction=weeklyac*weeklyt;
futime =(dfstim>0);

run;

title 'Age distribution by Arm and Overall';
proc means data=allms median min max maxdec=1;
var age ;
class trno;
where use=1;
run;
proc means data=allms median min max maxdec=1;
var age ;
run;
title 'Black race';
proc freq data=allms;
format blackrace black. ;
tables blackrace*trno / norow;
run;
title 'Gender';
proc freq data=allms;
format gender gender. ;
tables gender*trno / norow;
run;
title 'Menopausal status';
proc freq data=allms;
format menop menop. ;
tables menop*trno / norow;
where (gender=0);
run;
title 'Number of nodes';
proc freq data=allms;
format posnodesclass nodesclass. ;

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tables posnodesclass*trno / norow;
run;
title 'Hormone receptor status';
proc freq data=allms;
tables posrecep*trno / norow;
format posrecep posrecep. ;
run;
title 'HER2 status';
proc freq data=allms;
tables her2*trno / norow;
format her2 her. ;
run;
title 'Breast cancer subtype';
proc freq data=allms;
format subtype subtype. ;
tables subtype*trno / norow;
run;

title 'DFS events';
proc freq data=allms;
tables dfsind*trno / norow;
where (futime=1);
run;
title ' Cox regression assessing interaction for DFS';
proc phreg data=allms ; model dfstim*dfsind(0) = weeklyt weeklyac
interaction / rl ;
run;
title 'Log rank test over four groups for DFS';
proc lifetest data=allms notable plots=none ; time dfstim*dfsind(0); test
trt2 trt3 trt4 ;
run;
title ' Cox regression comparing each treatment to arm 1 for DFS';
proc phreg data=allms ; model dfstim*dfsind(0) = trt2 trt3 trt4 / rl ;
run;

title 'DFS events - Hormone-receptor positive; HER2-negative';
proc freq data=allms;
tables dfsind*trno / norow;
where ((futime=1)&(subtype=1));
run;
title ' Cox regression assessing interaction for DFS (HR positive; HER2
negative)';
proc phreg data=allms ; model dfstim*dfsind(0) = weeklyt weeklyac
interaction / rl ;
where subtype=1;
run;
title 'Log rank test over four groups for DFS (HR positive; HER2 negative)';
proc lifetest data=allms notable plots=none ; time dfstim*dfsind(0); test
trt2 trt3 trt4 ;
where subtype=1;
run;
title ' Cox regression comparing each treatment to arm 1 for DFS (HR
positive; HER2 negative)';
proc phreg data=allms ; model dfstim*dfsind(0) = trt2 trt3 trt4 / rl ;
where subtype=1;
run;

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title 'DFS events - Hormone-receptor negative; HER2-negative';
proc freq data=allms;
tables dfsind*trno / norow;
where ((futime=1)&(subtype=2));
run;
title ' Cox regression assessing interaction for DFS (HR negative; HER2
negative)';
proc phreg data=allms ; model dfstim*dfsind(0) = weeklyt weeklyac
interaction / rl ;
where subtype=2;
run;
title 'Log rank test over four groups for DFS (HR negative; HER2 negative)';
proc lifetest data=allms notable plots=none ; time dfstim*dfsind(0); test
trt2 trt3 trt4 ;
where subtype=2;
run;
title ' Cox regression comparing each treatment to arm 1 for DFS (HR
negative; HER2 negative)';
proc phreg data=allms ; model dfstim*dfsind(0) = trt2 trt3 trt4 / rl ;
where subtype=2;
run;

title 'DFS events - HER2-positive';
proc freq data=allms;
tables dfsind*trno / norow;
where ((futime=1)&(subtype=3));
run;
title ' Cox regression assessing interaction for DFS (HER2 positive)';
proc phreg data=allms ; model dfstim*dfsind(0) = weeklyt weeklyac
interaction / rl ;
where subtype=3;
run;
title 'Log rank test over four groups for DFS (HER2 positive)';
proc lifetest data=allms notable plots=none ; time dfstim*dfsind(0); test
trt2 trt3 trt4 ;
where subtype=3;
run;
title ' Cox regression comparing each treatment to arm 1 for DFS (HER2
positive)';
proc phreg data=allms ; model dfstim*dfsind(0) = trt2 trt3 trt4 / rl ;
where subtype=3;
run;

title 'Overall survival events';
proc freq data=allms;
tables surind*trno / norow;
where (futime=1);
run;
title ' Cox regression assessing interaction for OS';
proc phreg data=allms ; model surtim*surind(0) = weeklyt weeklyac
interaction / rl ;
run;
title 'Log rank test over four groups for OS';
proc lifetest data=allms notable plots=none ; time surtim*surind(0); test
trt2 trt3 trt4 ;
run;

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title 'Cox regression comparing each treatment to arm 1 for OS';
proc phreg data=allms ;    model surtim*surind(0) = trt2 trt3 trt4 / rl ;
run;

title 'OS events - Hormone-receptor positive; HER2-negative';
proc freq data=allms;
tables surind*trno / norow;
where ((futime=1)&(subtype=1));
run;
title 'Cox regression assessing interaction for OS (HR positive; HER2
negative)';
proc phreg data=allms ;    model surtim*surind(0) = weeklyt weeklyac
interaction / rl ;
where subtype=1;
run;
title 'Log rank test over four groups for OS (HR positive; HER2 negative)';
proc lifetest data=allms notable plots=none ; time surtim*surind(0); test
trt2 trt3 trt4 ;
where subtype=1;
run;
title 'Cox regression comparing each treatment to arm 1 for OS (HR
positive; HER2 negative)';
proc phreg data=allms ;    model surtim*surind(0) = trt2 trt3 trt4 / rl ;
where subtype=1;
run;

title 'OS events - Hormone-receptor negative; HER2-negative';
proc freq data=allms;
tables surind*trno / norow;
where ((futime=1)&(subtype=2));
run;
title 'Cox regression assessing interaction for OS (HR negative; HER2
negative)';
proc phreg data=allms ;    model surtim*surind(0) = weeklyt weeklyac
interaction / rl ;
where subtype=2;
run;
title 'Log rank test over four groups for OS (HR negative; HER2 negative)';
proc lifetest data=allms notable plots=none ; time surtim*surind(0); test
trt2 trt3 trt4 ;
where subtype=2;
run;
title 'Cox regression comparing each treatment to arm 1 for OS (HR
negative; HER2 negative)';
proc phreg data=allms ;    model surtim*surind(0) = trt2 trt3 trt4 / rl ;
where subtype=2;
run;

title 'OS events - HER2-positive';
proc freq data=allms;
tables surind*trno / norow;
where ((futime=1)&(subtype=3));
run;
title 'Cox regression assessing interaction for OS (HER2 positive)';
proc phreg data=allms ;    model surtim*surind(0) = weeklyt weeklyac
interaction / rl ;
where subtype=3;

```



```
run;

title 'Log rank test over four groups for OS (HER2 positive)';
proc lifetest data=allms notable plots=none ; time surtim*surind(0); test
trt2 trt3 trt4 ;
where subtype=3;
run;
title ' Cox regression comparing each treatment to arm 1 for OS (HER2
positive)';
proc phreg data=allms ;    model surtim*surind(0) = trt2 trt3 trt4 / rl ;
where subtype=3;

run;
```