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SWOG S0215: A Phase II study of docetaxel and vinorelbine plus filgrastim with weekly trastuzumab for HER2-positive, stage IV breast cancer

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Abstract

Purpose—SWOG trial S0102 showed significant activity of the combination of docetaxel and vinorelbine in HER2-negative metastatic breast cancer (MBC). For HER2-positive patients, additional benefit may occur with the addition of trastuzumab due to its synergy with docetaxel and vinorelbine.

Design—Patients with HER2-positive MBC, but without prior chemotherapy for MBC or adjuvant taxane, were eligible. Docetaxel (60 mg/m²) was given intravenously on Day 1, vinorelbine (27.5 mg/m²) intravenously on Days 8 and 15, and filgrastim (5 µg/kg) on Days 2–21 of a 21-day cycle. Additionally, patients received weekly infusions of trastuzumab (2 mg/kg) after an initial bolus of 4 mg/kg. The primary outcome was one-year overall survival (OS), with secondary outcomes of progression-free survival (PFS), response rate, and toxicity. Due to slow accrual (February 2003–December 2006), enrollment was stopped after 76 of 90 planned patients.

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Previous presentation

Earlier results from the trial were presented as a poster at the 2008 annual meeting of the American Society of Clinical Oncology [1].

Results—There have been 32 deaths and 51 progressions among the 74 eligible patients who received treatment. The estimated 1-year OS was 93% (95% CI 84%–97%) with a median of 48 months. One-year PFS was 70% (95% CI 58–79%) with a median of 20 months. Response rate for measurable disease was 84%. No deaths were attributed to treatment. Grade 4 toxicities were reported for 19% with neutropenia the most common (15%). The most common grade 3 toxicities (33%) were leucopenia (14%) and fatigue (10%).

Conclusion—The combination of trastuzumab, docetaxel, and vinorelbine is effective as first-line chemotherapy in HER2-positive MBC with minimal toxicity. One-year survival estimates are among the highest reported in this population.

Keywords

Docetaxel; vinorelbine; trastuzumab; HER2-positive metastatic breast cancer

Introduction

Until 2001, HER2 positivity was considered a poor prognostic sign for survival in metastatic breast cancer (MBC). Subsequently, Slamon published the results of a pivotal trial [2], which showed a significant improvement in median time to disease progression (TTP) from 4.6 to 7.4 months, and longer overall survival (median, 25.1 versus 20.3 months) by the addition of trastuzumab to chemotherapy. Among patients who had received prior anthracyclines in the adjuvant setting, the addition of trastuzumab to paclitaxel improved median TTP from 3.0 to 6.9 months, and overall median survival was 18.4 versus 22 months, results comparable to those seen in the other subtypes of metastatic breast cancer.

Since then, it has been well recognized that doublets based on the addition of trastuzumab to taxanes are active. Higher response rates may be achieved with weekly paclitaxel and trastuzumab [3] in HER2-positive patients (67–81%) compared to patients given the same treatment without HER2 overexpression (41–46%), and the response rate with the weekly taxane combination appears higher than was seen in the pivotal trial with paclitaxel on a schedule of every 3 week administration (42%). A randomized trial of docetaxel with or without trastuzumab [4] showed improved efficacy for the doublet in outcomes, including response rate (61%), TTP (11.7 months), and overall survival (31.2 months). Based on these encouraging results, and on preclinical evidence of synergy from the addition of platinum salts to trastuzumab [5], there have been randomized trials of paclitaxel, carboplatin and trastuzumab versus the doublet, and also of docetaxel, carboplatin, and trastuzumab versus the doublet [6, 7]. In the former, there was an improvement in response rate (52 versus 36%) and TTP (10.7 versus 7.1 months), but no significant effect on overall survival (35.7 versus 32.2 months); in the latter, the two treatment arms were not statistically significantly different for TTP or overall survival. Thus, use of platinum-based triplets has not become the standard of care.

Another reproducibly active doublet is that of vinorelbine with trastuzumab. Burstein reported a 68% response rate and median TTP of 5.6 months in a patient population where the majority had received prior adjuvant anthracyclines [8], and Jahanzeb, in a previously untreated cohort, saw a response rate of 78% and median TTP of 16.7 months [9]. De Maio [10] obtained intermediate results (response rate 50%, median TTP 9.6 months, overall survival 22.7 months). There have been no randomized trials to date of vinorelbine-based combinations with trastuzumab.

Both the taxanes and vinorelbine belong to the antitubulin class of drugs, and are felt to have primary cytotoxic effects mediated through effects on the mitotic spindle. Vinorelbine inhibits the polymerization of microtubules, essential to formation of the spindle, and the

taxanes inhibit the “takedown” of polymerized microtubules that is essential for the next wave of mitosis to take place. Schedule-dependent synergism for the cytotoxic effects of this combination has been reported in vitro [11], though the relevance of the schedule dependence in vivo may be questioned [12]. A potential molecular mechanism for complimentary effects has to do with whether p53 function is intact: if p53 is activated, sensitivity to vinorelbine is increased and that to paclitaxel is decreased, via downregulation of microtubule associated protein (MAP 4), which stabilizes polymerized microtubules [13]. These effects on sensitivity to the respective antitubulins are not seen when p53 function is lost, as by mutation. Approximately 50% of human breast cancers are associated with loss of function in p53 [14].

Empiric evidence for the activity of vinorelbine in breast cancers which had progressed after taxane therapy was initially reported by Livingston [15], and the same group went on to test the feasibility and efficacy of combinations with vinorelbine and paclitaxel [16], as well as vinorelbine and docetaxel [17]. Encouraging evidence of activity was observed in these trials, but dose-limiting myelosuppression necessitated the concurrent use of filgrastim. This experience led to the first study of this two-drug combination with filgrastim support, reported by Gralow [18] in patients with HER2-negative metastatic breast cancer (SWOG 0102). Based on its feasibility and efficacy, and on the cited experience with taxane and vinorelbine containing doublets with trastuzumab, the current trial (SWOG 0215; ClinicalTrials.gov Identifier: NCT00041067) was designed, specifically for treatment of patients with HER2-positive metastatic disease in the first-line setting. Docetaxel and vinorelbine were given as in S0102, and trastuzumab was added.

Patients and Methods

The primary objective was to evaluate one-year overall survival in HER2-positive stage IV breast cancer patients treated with a combination of trastuzumab, docetaxel, and vinorelbine with concurrent C-GSF (filgrastim) support. Secondary objectives included assessment of progression-free survival, response rate, and treatment-associated toxicity.

Patient Population

Eligible patients were women aged 18 or greater who had HER2-positive, stage IV, microscopically-confirmed breast carcinoma. HER2 status was determined by local immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). Patients with 3+ IHC stain were considered to have HER2-positive breast cancer without FISH, but otherwise a positive FISH test was required to be eligible. Patients may have had no more than one previous line of chemotherapy for primary disease and must have completed chemotherapy six months prior to study entry. Ongoing hormonal treatment prior to registration needed to be stopped. They may have received prior anthracycline, hormonal, or radiation therapy (completed three weeks prior), but not have been treated with prior docetaxel or vinca alkaloid therapy. Prior cumulative doses of doxorubicin or epirubicin could not have exceeded 360 mg/m² or 720 mg/m², respectively.

All patients had a Zubrod performance status of 0 to 2, normal hematologic values (ANC 1,500/mm³ and platelets 100,000 /mm³), normal renal function, and normal liver function (total bilirubin institutional upper limit of normal (ULN), SGOT (AST) or SGPT (ALT) 1.5 x ULN, and alkaline phosphatase 2.5 x ULN). Exclusions included central nervous system (CNS) metastases, grade 2 or greater motor or sensory peripheral neuropathy not due to cancer, known sensitivity to E. Coli-derived proteins, or history of severe hypersensitivity reaction to drugs formulated with polysorbate 80. All patients completed written informed consent documenting they understood the investigational nature of the study and would

comply with study procedures. Consent for tissues samples was recorded separately at the time of registration.

Study Treatment

On Day 1 of the first cycle, patients received 4mg/kg of trastuzumab by IV over a 90 minute period. Thereafter, patients received weekly subsequent infusions of trastuzumab 2mg/kg by IV over a 30 minute period. On Day 1 of 21-day cycles, patients were administered docetaxel (60 mg/m²) intravenously over a one-hour period. Beginning one day prior to docetaxel administration, patients were medicated with dexamethesone 8 mg bid, PO, for a total of three days to reduce the incidence of acute and delayed allergic manifestations and fluid retention. On Days 2 to 21, G-CSF support (5 µg/kg/day) was given SQ. G-CSF was not given on the day of docetaxel administration. On Days 8 and 15 of the 21-day cycle patients were given vinorelbine (27.5 mg/m²) intravenously over a 6 to 10 minute period. Treatment was terminated if there was disease progression, unacceptable toxicity, treatment delay for more than two weeks due to hematologic toxicity (three weeks due to other toxicity), physician decision, or patient withdrawal from the study. Otherwise patients continued treatment for three years or death whichever was earlier.

Dose Modifications

If the absolute neutrophil count (ANC) was < 1,500/mm³ on the day of chemotherapy, the start of the cycle was delayed for one week but G-CSF was continued. After one week if the ANC was < 1,500/mm³ the dose of both docetaxel and vinorelbine was reduced permanently by 25% and treatment was resumed. If the ANC remained < 1,500/mm³ then treatment was delayed for another week. If the ANC was < 1,500/mm³ after a two week delay, the dose of both docetaxel and vinorelbine was reduced by 25% and treatment resumed. If the ANC continued < 1,500/mm³ at two weeks, the patient was removed from protocol treatment. If the patient experienced neutropenic fever (temperature ≥ 101.5° F/ 38.5° C and ANC < 1,000/mm³), dosage of both docetaxel and vinorelbine was reduced permanently by 25%.

Similarly, patients who had platelet counts < 100,000 /mm³ were suspended from treatment and rechecked at one and two weeks. Patients whose platelet counts returned to ≥ 100,000 /mm³ had treatment resumed with a 25% dose reduction in both docetaxel and vinorelbine for all cycles. If platelet counts continued < 100,000 /mm³ at two weeks, patients were removed from the study drugs.

If the patient had motor or sensory neuropathy (grade 3 or higher) administration of both docetaxel and vinorelbine was delayed until recovery to grade ≤ 2. If the patient had grade 2 stomatitis, chemotherapy was delayed until recovery to grade ≤ 1. If either condition persisted for three weeks, the patient was removed from protocol treatment.

If there was evidence of abnormal liver function (total bilirubin > ULN, or SGOT > 5 x ULN, or alkaline phosphatase > 5 x ULN), treatment with docetaxel was stopped for up to three weeks until recovery on all three measures and then resumed with a 25% dose reduction of docetaxel on all subsequent cycles. Protocol treatment was terminated if no recovery within three weeks. If SGOT was elevated between >1.6 to 5 x ULN, but the total bilirubin was ≤ ULN and alkaline phosphatase was ≤ 5 x ULN, then the docetaxel dose was reduced by 25% but treatment was given on schedule.

If grade 4 docetaxel hypersensitivity to treatment was observed, the patient was removed from protocol treatment. Dose reductions were not made for docetaxel hypersensitivity or fluid retention.

Trastuzumab dose modifications were not allowed. Trastuzumab therapy was withheld if the patient developed signs or symptoms of CHF or if ejection fractions fell below institutional lower limits of normal during treatment. Other treatment was continued if trastuzumab was stopped.

Study Assessments

Prior to study entry, patient clinical information was obtained and tumor assessment completed. CBC/differential/platelets were evaluated at baseline and weekly thereafter. Serum creatinine, bilirubin, SGOT/SGPT, and alkaline phosphatase were assessed at the beginning of each 21-day treatment cycle. Electrolytes (sodium, potassium, chloride, and bicarbonate) were assessed at baseline and after 6 and 15 weeks of treatment.

X-rays and scans were required at baseline and after three cycles (9 weeks) of treatment, but could be performed more often. Toxicity was assessed after each treatment cycle. Response was measured by the RECIST criteria. A patient was considered a responder if there was confirmed or unconfirmed partial or complete response. All others were considered non-responders even if the patient was technically not assessable due to different measurement techniques at the two time points.

Adverse events were recorded and graded using the standardized CTC (NCI Common Toxicity Criteria) Version 2.0 for toxicity and adverse event reporting. Within each toxicity category only the highest grade of toxicity was recorded for each patient.

Statistical Analysis

The primary outcome was one-year overall survival (OS) where OS was defined as time from registration to death by any cause. A secondary outcome was progression-free survival (PFS) defined as time from registration to the earliest of death due to any cause or disease progression. Patients who were known to be alive were censored at the last follow-up visit. The method of Kaplan-Meier was used to compute both OS and PFS and to give a 95% confidence interval (CI) at one year. The accrual goal was 90 which allowed one-year OS to be estimated to within 11% with 95% confidence (2-sided). We did not pre-specify an expected OS that would need to be obtained for the drug combination to be considered as better than standard care. All individuals were included in the analysis unless deemed to be ineligible or did not start study medication as described below.

Results

Patient Population

During the period February 2003 to December 2006, 76 patients were enrolled at 28 institutions. The trial expected to enroll 90 patients with a monthly accrual of 4 to 5 patients. The actual enrollment rate was 1.65 patients per month so the trial was stopped early due to slow accrual. Outcome results were unknown when the decision to terminate the trial was made. Two patients were excluded due to ineligibility. Of the remaining 74 eligible patients analyzed, one patient did not have toxicity assessments performed so only 73 patients are included in the toxicity evaluation. Patient characteristics and current status with respect to treatment are summarized in Table 1. Patients ranged in age from 33 to 78 with a median age of 50 years. Three patients are on protocol treatment at the current time. Reasons for going off treatment include adverse events (n=20); progression or relapse (n=19), refusal unrelated to adverse events (n=12); other (n=17); or unknown (n=3).

Treatment Outcomes

Thirty-two deaths have occurred among the 74 patients. Figure 1 shows the Kaplan-Meier plot of overall survival. Overall survival at 1-year is estimated to be 93% (95% CI 84%–97%), two-year OS is 88% (95% CI 78%–93%), and three-year OS is 69% (95% CI 57%–79%). The median OS is 48 months with a lower bound of the 95% CI at 40 months, but the upper bound is not yet estimable until more follow-up has occurred. No difference in OS was observed between those with hormone receptor positive (n=41) or negative disease (n=32) (log-rank p=0.78; Figure 1).

Of the 74 patients, 51 progressed and another 3 patients died without progression. Progression-free survival (PS) is shown in Figure 2. One year progression-free survival is 70% (95% CI 58–79 %), two-year PFS is 46% (95% CI 34%–57%), and three-year PFS is 33% (95% CI 23%–44%). Median PFS is 20 months (95% CI 15–28 months). PFS was not significantly different for patients with receptor positive or receptor negative disease (log-rank p=0.93; Figure 2).

Overall the response rate was 74% (95% CI 63%–84%). Table 2 shows the distribution of responses for patients with measurable disease; 53 of 63 responded for a response rate of 84% (95% CI 73%–92%). For patients with nonmeasurable disease (n=11), the RECIST criteria show 2 complete responses, 7 with stable disease, and 2 with increasing disease. The response rate is only 18% (95% CI 2%–52%) in those with non-measurable disease.

Safety

Over 135 possible categories of adverse events possibly due to treatment were recorded. The maximum adverse event over all categories was also recorded. Two patients (3%) had no adverse events and one patient had only a Grade 1 adverse event. A total of 32 (44%) and 24 (33%) patients had maximum adverse event grade of 2 and 3, respectively. Fourteen (19%) patients reported grade 4 adverse events and there were no grade 5 toxicities. Table 3 shows the most common adverse events with at least 4 or more patients reporting a Grade 2 or higher toxicity or any patient reporting a Grade 3 or higher toxicity.

Discussion

The overall results of this trial are best seen in the context of results reported by others (see Table 4). Our observed response rate of 74% is comparable to that reported in a number of other trials. The median survival of 48 months is impressive, and appears to be as high as that reported for most other regimens, but there may be an impact of treatment given at progression on survival, especially with the evolving development of more effective second-line regimens for HER 2+ disease [19]. What is most striking, and presumably reflects the treatment effect specific to this regimen, is the time to disease progression, with a median of 20 months achieved in the setting of a cooperative group trial. Survival at one year was our stated primary objective, and is 93%, with 69% still alive at 3 years, which is obviously encouraging, but more difficult to compare to other series, as it was not a commonly reported endpoint.

Infante [20] used the same triplet as our trial using a schedule of docetaxel at 30 mg/m² and vinorelbine at 25 mg/m² on days 1 and 8 of an every 3 week cycle, coupled with weekly administration of trastuzumab. There was no initial use of filgrastim, but 72% of their patients had grade 4 neutropenia, and 13% were hospitalized for febrile neutropenia. Two-thirds required dose modification in the first two cycles for neutropenia. Their observed response rate of 68% was similar to ours, but the median TTP was 12 months. The difference between the two TTP outcomes could be a function of the difference in drug schedule, delivered dose, or a difference in the patient population. Our own tentative

conclusion is that, to administer this antitubulin combination effectively, supportive care with filgrastim is required prophylactic ally.

If we analyze our study for other evidence of serious toxicity, it is modest. There were a total of 4 cases of febrile neutropenia (5.7%), with one documented infection and no treatment-related deaths. In spite of concern about combined neurotoxicity, this was not seen (seven grade 2 and 5 grade 3 sensory neuropathy, a total of 17%), with an overall frequency approximating that expected for weekly paclitaxel alone. Nausea/vomiting reported as grade 3 was seen in only 5 patients (7%).

We did not see a difference in efficacy between those with ER+ disease and those with ER-disease. One factor favoring our patient population may have been the lack of prior adjuvant chemotherapy in the majority, although data from other series are not consistent on this point. Our trial has some limitations including the single-arm design and lack of tissue samples for correlative studies. Since the trial was not randomized, one cannot tell whether the very good survival was due to the drug triplet or to a population with a favorable prognosis anyway. We had difficulty accruing patients, but it may have been due to competition with existing industry trials at the time, rather than a narrow patient population. The sample size leads to wide confidence intervals for the survival estimates so survival equivalent to other combinations cannot be ruled out. Nonetheless, the median time to progression and median survival of HER 2 + patients exceeds what is generally reported for the use of chemotherapy in patients with HER 2 – disease (including our experience from S0102), reflecting the dramatic change in prognosis for this subgroup from the addition of targeted therapy. Current interest in new therapy development for HER 2 positive disease involves the development of other HER 2-targeted therapies, not only as “salvage” in patients after progression on a trastuzumab-based regimen, but in combination (concurrent or sequenced) with trastuzumab. However, it remains clear at this point that such treatments, like trastuzumab, need to be combined with chemotherapy for optimal effects. We believe the regimen reported here should be compared in a randomized trial to “standard” doublet therapy with paclitaxel and trastuzumab, in the first-line setting for HER 2+ metastatic breast cancer.

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Fig. 1. Kaplan-Meier plot of overall survival; overall survival by hormone receptor positivity or negativity

Fig. 2.
Progression free survival; progression free survival by hormone receptor positivity or negativity

Table 1

Descriptive Characteristics of Evaluable Patients Enrolled in S0215 (n=74)

Characteristic	Frequency	Percentage
Age (range 33–78)		
30–39	11	15
40–49	26	35
50–59	19	26
60–69	15	20
70–79	3	4
Race		
White	66	89
Black	5	7
Asian/ Pacific Islander	3	4
Hormone Receptor Status		
Positive	41	55
Negative	32	43
Unknown	1	1
Prior Adjuvant Chemotherapy		
None	51	69
Anthracycline	19	26
Non-anthracycline	4	5
Prior Hormonal Therapy	29	39
Number of Metastatic Sites		
< 3	54	73
3	20	27
Measurable Disease		
Yes	63	85
No	11	15

Table 2

Response to Treatment in Patients with Measurable Disease (N=63)

Response	Classification	Frequency	Percentage
Complete response	Responder	13	21%
Partial response	Responder	40	63%
Stable/No response	Non-Responder	3	5%
Increasing disease	Non-Responder	5	8%
Unable to assess	Non-Responder	2	3%

Table 3

Adverse Events Possibly Related to Treatment (N=73)

	Grade							
ADVERSE EVENT	Unk	0	1	2	3	4	5	
Alkaline phosphatase increase	0	33	37	2	1	0	0	
Alopecia	0	30	18	25	0	0	0	
Anemia	0	14	29	23	6	1	0	
Anorexia	0	61	8	4	0	0	0	
Arthralgia	0	60	9	3	1	0	0	
Bone pain	0	40	16	15	2	0	0	
Catheter related infection	0	72	0	0	1	0	0	
Chest pain, not cardiovascular or pleural	0	68	2	1	2	0	0	
Constipation/bowel obstruction	0	57	12	4	0	0	0	
Dehydration	0	69	2	1	1	0	0	
Depression	0	69	1	2	1	0	0	
Diarrhea without colostomy	0	41	23	7	2	0	0	
Dyspepsia/heartburn	0	65	4	3	1	0	0	
Dyspnea	0	58	0	13	2	0	0	
Dysuria	0	69	0	4	0	0	0	
Edema	0	55	12	6	0	0	0	
Fatigue/malaise/lethargy	0	10	26	29	7	1	0	
Febrile neutropenia	0	69	0	0	4	0	0	
Headache	0	58	12	0	3	0	0	
Hyperglycemia	0	55	5	7	5	1	0	
Hypermagnesemia	0	72	0	0	1	0	0	
Hypokalemia	0	66	5	0	2	0	0	
Hypophosphatemia	0	72	0	0	1	0	0	
Hypotension	0	68	2	2	1	0	0	
Hypoxia	0	72	0	0	1	0	0	
Infection w/o 3-4 neutropenia	0	61	0	8	4	0	0	

ADVERSE EVENT	Grade					
	Unk	0	1	2	3	4 5
Infection with 3–4 neutropenia	0	72	0	0	1	0 0
Insomnia	0	58	11	4	0	0 0
LVEF decrease/CHF	0	70	2	0	1	0 0
Leukopenia	0	51	4	7	10	1 0
Lymphopenia	0	70	0	1	2	0 0
Muscle weakness (not neurologic)	0	65	2	5	0	1 0
Myalgia	0	50	16	7	0	0 0
Nail changes	0	57	5	11	0	0 0
Nausea	0	47	15	8	3	0 0
Neutropenia/granulocytopenia	0	50	3	4	5	11 0
PRBC transfusion	0	72	0	0	1	0 0
Pain-other	0	59	4	7	3	0 0
Pericardial effusion/pericarditis	0	72	0	0	1	0 0
Pneumonitis/infiltrates	0	69	0	1	3	0 0
Rash/desquamation	0	61	8	4	0	0 0
Respiratory infect w/ neutropenia	0	72	0	0	1	0 0
SGPT (ALT) increase	0	59	12	1	1	0 0
Sensory neuropathy	0	39	22	7	5	0 0
Stomatitis/pharyngitis	0	53	10	10	0	0 0
Surgery-wound infection	0	72	0	0	1	0 0
Syncope	0	72	0	0	1	0 0
Taste disturbance	0	61	7	5	0	0 0
Tearing	0	58	11	3	1	0 0
Thrombosis/embolism	0	71	0	1	0	1 0
Transplant-pRBC transfusion	0	72	0	0	1	0 0
Vomiting	0	61	6	4	2	0 0
MAXIMUM GRADE – ANY ADVERSE EVENT						
Number	0	2	1	32	24	14 0

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Table 4

Comparison of Trial Results in Similar Settings

Reference No.	First Author	Regimen(s)	No Pts.	Response Rate(%)	TTP (mo)	Median Survival (mo)
2	Slamon	P	96	17	2.8	18
		P+H	92	49	6.7	25
3	Seidman	p ³ H	76	58	–	–
		p ^w H	88	55	–	–
4	Marty	D	94	34	6.1	22.7
		DH	94	61	11.7	31.2
6	Robert	PH	98	36	7.1	35.7
		PCH	98	52	10.7	32.2
7	Forbes	DH	131	73	11.1	>40
		DCH	132	73	10.4	41.7
8	Burstein	VH	54	68	5.6	–
9	Jahanzeb	VH	37	78	16.7	–
10	De Maio	VH	40	50	9.6	22.7
20	Infante	DVH	60	68	12.0	40.8
21	Burstein	VH	41	51	8.5	–
		“T”H	40	40	6.0	–
22	Seidman	PH	40	75	–	–
23	Leyland-Jones	PH	32	59	12.2	–
		PCH weekly	48	81	13.8	38.4
24	Perez	PCH q 3 weeks	43	65	9.9	27
25	Ruiz	PCH	41	56	12.3	–
26	Tan	VH+Capecitabine	45	67	11.3	27.2
Current study	Livingston	DVH	74	74	20	40