5 Minute Journal Club

Key SABCS Presentations

Issue 6, 2011

For more visit ResearchToPractice.com/5MJCSABCS2011

Research To Practice®

CME Information

LEARNING OBJECTIVES

- Recognize the effect of round-robin adjudication and standardized assays on the resolution of discordant HER2 testing results between laboratories.
- Counsel elderly patients with early HER2-positive breast cancer about the known benefits and risks of adjuvant trastuzumab in the population age 65 or older.
- Describe the emerging body of evidence for continued anti-HER2 treatment beyond disease progression for patients with HER2-positive breast cancer.
- Explain the preliminary efficacy and safety of dual HER2-directed treatment with pertuzumab and trastuzumab-DM1 in patients with advanced breast cancer.
- Recall the benefits of using HER2-directed therapy as subsequent treatment for patients who experienced disease progression on prior trastuzumab-DM1.
- Cite the rates of response and toxicity seen with the combination of lapatinib and a novel schedule of capecitabine in patients with HER2-positive metastatic breast cancer refractory to trastuzumab.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CME Information (Continued)

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

FACULTY DISCLOSURES

The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

William J Gradishar, MD
Director, Breast Medical Oncology
Professor of Medicine
Robert H Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Advisory Committee: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Eisai Inc, EMD Serono Inc, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Roche Laboratories Inc, Sanofi-Aventis.

Round-Robin Review of HER2 Testing in the Context of Adjuvant Therapy for Breast Cancer (NCCTG N9831/ BCIRG006/BCIRG005)[1]

Concordance of HER2 Central Assessment by Two International Central Laboratories: A Ring Study within the Framework of the Adjuvant HER2-Positive ALTTO Trial (BIG2-06/N063D/EGF106708)[2]

[1]Perez E et al.
Proc SABCS 2010;Abstract PD10-02.

[2]McCullough AE et al.
Proc SABCS 2010;Abstract P3-10-36.

Round-Robin Review of HER2 Testing in the Context of Adjuvant Therapy for Breast Cancer (NCCTG N9831/ BCIRG006/BCIRG005)

Perez E et al.

Proc SABCS 2010;Abstract PD10-02.

Introduction

- HER2 is an important biomarker in the biology and treatment of breast cancer (BC), and reliable HER2 testing methodology is critical to BC care.
- Controversy exists regarding the definition of HER2 positivity (HER2+) and the type of test that may best predict the efficacy of anti-HER2 therapy.
- Interestingly, similar benefit of adjuvant trastuzumab has been observed in patients whose tumors were HER2+ by local laboratory and *either* positive *or* normal (negative) by central laboratory (*NEJM* 2008;358:1409; *JCO* 2010;28:4307).

Perez E et al. *Proc SABCS* 2010;Abstract PD10-02.

Study Objectives

- **Primary objectives:**
  - Determine the concordance between HER2 results by three central laboratories (NCCTG, BCIRG and NSABP)
  - Determine the impact of round-robin review on discordant cases
  - Determine the intratumor heterogeneity of HER2 status
- **Secondary objective:**
  - Determine the impact of trastuzumab therapy for patients determined to have HER2-normal tumors after round-robin review

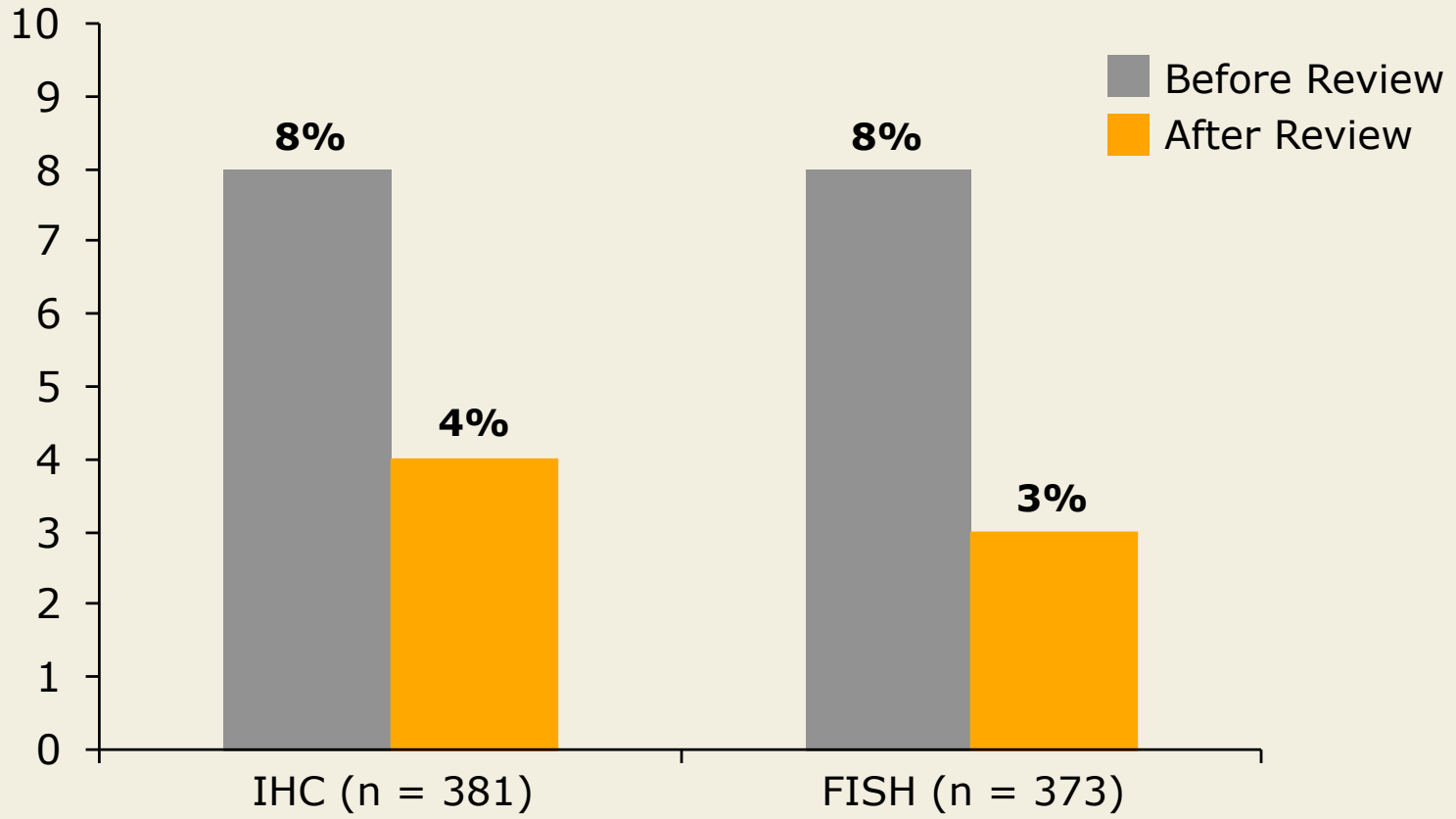
Perez E et al. *Proc SABCS* 2010;Abstract PD10-02.

Materials and Methods

- **Materials**
  - Used specimens from three adjuvant trials (NCCTG N9831, BCIRG005, BCIRG006) for which HER2 testing for study enrollment was performed by both local and central labs:
    - Total number of IHC cases: 381
    - Total number of FISH cases: 373
- **Methods**
  - Blinded "round-robin" exchange of breast tumors among three central labs for confirmatory HER2 testing
  - FDA-approved definitions of HER2 positivity employed for both IHC and FISH testing
  - HER2 status independently determined at each central lab, and centrally discordant IHC and FISH cases were reviewed at a face-to-face meeting

Perez E et al. *Proc SABCS* 2010;Abstract PD10-02.

HER2 Central Discordance Rates Pre- and Post-Round Robin Review



Adjudication led to reaching a consensus in 96% of IHC cases and in 97% of FISH cases

Perez E et al. *Proc SABCS* 2010;Abstract PD10-02.

Author Conclusions

- Initial 8% discordance for each IHC and FISH among expert pathologists across three central laboratories was decreased to ≤4% after round robin review.
- Excellent agreement (≥96%) observed among the pathologists at review suggests that interpretation issues and tumor heterogeneity still play a role in discordant results.
- HER2 heterogeneity across blocks from the same tumor was observed more at the protein level than at the gene level (10% versus 5%, data not shown).
- Trastuzumab benefit was observed in the small subset of 53 N9831 patients **centrally** read as HER2-normal (although these were all initially read as HER2-positive **locally**, data not shown).
  - Disease-free survival HR = 0.34, $p = 0.06$

Perez E et al. *Proc SABCS* 2010;Abstract PD10-02.

Concordance of HER2 Central Assessment by Two International Central Laboratories: A Ring Study within the Framework of the Adjuvant HER2-Positive ALTTO Trial (BIG2-06/N063D/EGF106708)

McCullough AE et al.

Proc SABCS 2010;Abstract P3-10-36.

Background

- Ongoing Phase III ALTTO (**A**djuvant **L**apatinib and/or **T**rastuzumab **T**reatment **O**ptimization) trial for HER2+ BC
- Two central laboratories (European Institute of Oncology [IEO] and Mayo Clinic) confirming local HER2, ER and PR status prior to study entry
- Discordance between local and central laboratories identified:

Central Laboratory	HER2 % local false-positive	ER % discordant
IEO	**14.5%** of 8,037	**12.1%** of 9,021
Mayo Clinic	**5.8%** of 412	**11.7%** of 419

- **Current Study Goal:** Ring study to assess whether the central lab results of a subset of local/central discordant ALTTO cases could be confirmed in the other central lab

McCullough AE et al. *Proc SABCS* 2010;Abstract P3-10-36.

Results and Author Conclusions

- 25 false-positive HER2 cases = **100% concordant** across central pathology review in HER2 IHC status (3+ vs 0-2+) and in HER2 FISH status (amplified vs not)
- 34 discordant ER cases = **85% concordant** across central pathology review when each used own IHC assay methodology
  - Increased to 100% concordance when a dual ER antibody cocktail utilized at both laboratories
- ALLTO enrollment ineligibility did not change when HER2 testing was performed by either IEO or Mayo Clinic central laboratories
- Standardized assays increase proficiency between laboratories (same test on same tissue = same result)

McCullough AE et al. *Proc SABCS* 2010;Abstract P3-10-36.

Investigator Commentary: HER2 Testing in the Intergroup and ALTTO Adjuvant Trials

The study by Perez and colleagues was a follow-up to previously reported data from the NSABP, in which there was a suggestion that some patients with HER2-normal breast cancer may benefit from adjuvant trastuzumab. The investigators went back and evaluated the tissue samples from the Intergroup study and found a small percent of patients in whom there was discordance between IHC and FISH testing, even among experts. In almost every case they could find resolution to the issues causing discordance, but in the end there was still a small group of patients who appeared to have HER2-normal disease and benefited from trastuzumab. So in some troubling cases there is still a problem with HER2 testing, which is likely amplified in the community, with institutions doing fewer cases of HER2 testing than in larger referral centers.

In the BIG and NCCTG co-led ALTTO trial, expert pathologists from central laboratories were able to demonstrate 100 percent concordance for IHC and FISH testing of HER2 status, which suggests that using standardized tests and methodologies increases the likelihood of finding similar results.

Interview with William J Gradishar, MD, January 4, 2011

The Use of Trastuzumab in the Elderly in the Adjuvant Setting and After Disease Progression in Patients with HER2-Positive Advanced Breast Cancer

Dall P et al.
Proc SABCS 2010;Abstract P5-12-01.

Waddell T et al.
Proc SABCS 2010;Abstract P6-11-11.

von Minckwitz G et al.
Proc SABCS 2010;Abstract P6-14-05.

Gruschkus SK et al.
Proc SABCS 2010;Abstract P3-11-15.

Elderly Patients in a Prospective Observation Study on Trastuzumab (Herceptin®) in the Adjuvant Treatment of Breast Cancer

Dall P et al.

Proc SABCS 2010;Abstract P5-12-01.

Methods and Results (n=2,427)

Interim analysis of elderly patients from a prospective, observational German study of early breast cancer treated with adjuvant trastuzumab alone or in combination.

	<65 yrs (n=1,802)	≥65 yrs (n=625)	*p*-value
ECOG PS, 0	65%	52%	<0.0001
Chemotherapy	94%	90%	0.0025
Adjuvant chemotherapy	76%	82%	—
Neoadjuvant chemotherapy	18%	8%	<0.0001
Adjuvant endocrine therapy	56%	53%	—
Median LVEF*	64%	62%	0.037
Cardiac pathology*	6%	13%	<0.0001

*At the end of therapy

Dall P et al. *Proc SABCS* 2010;Abstract P5-12-01.

Author Conclusions

- Trastuzumab is well tolerated and can be effectively used in patients with HER2-positive breast cancer without age restriction.
- Elderly patients with early HER2-positive breast cancer are more often treated with less aggressive treatment in combination with trastuzumab.
- Some differences were evident in cardiac safety and premature withdrawal from treatment among elderly patients treated with trastuzumab, but this did not affect disease-free survival (DFS) rates.
- The DFS rates after two and three years are 96% and 91%, respectively, and are in agreement with results of large randomized studies.
- Elderly patients with breast cancer appear to derive the same benefit from adjuvant trastuzumab treatment as younger patients.

Dall P et al. *Proc SABCS* 2010;Abstract P5-12-01.

Trastuzumab Beyond Progression in HER2-Positive Advanced Breast Cancer: The Royal Marsden Experience

Waddell T et al.

Proc SABCS 2010;Abstract P6-11-11.

Methods

- **Study design**
  - Retrospective, single-center study
- **Objective**
  - To evaluate the clinical efficacy and safety of continuing treatment with trastuzumab beyond progression and to compare those data to recently published literature.
- **Eligibility**
  - Metastatic or locally advanced HER-2 positive breast cancer (IHC3+ or FISH+)
  - Treated at Royal Marsden Hospital between January 2001 and December 2008
  - Continued receiving trastuzumab despite disease progression or relapsed within 12 weeks of completing adjuvant trastuzumab

Waddell T et al. *Proc SABCS* 2010;Abstract P6-11-11.

Results

Outcome	Patients (%)
Radiological response	77 (68%)
Clinical response	16 (14%)
	Median (95% CI)
Time to progression	24 weeks (21-28 weeks)
Overall survival†	19 months (12-24 months)
Time to progression in subgroup*	25 weeks (18-33 weeks)
Overall survival in subgroup*†	22 months (17-27 months)

*Subgroup (n=81) selected to be comparable to German Study Group (*JCO* 2009;27:1999); †Measured from the continuation of trastuzumab at initial progression

Waddell T et al. *Proc SABCS* 2010;Abstract P6-11-11.

Author Conclusions

- Continuing trastuzumab/HER2-directed therapy beyond disease progression had clinically meaningful benefit in this group of unselected patients.
- These data support the positive results and safety data from prior studies.

Waddell T et al. *Proc SABCS* 2010;Abstract P6-11-11.

Final Overall Survival Analysis of the TBP Phase III Study (GBG 26/BIG 3-05): Capecitabine vs Capecitabine + Trastuzumab in Patients with HER2-Positive Metastatic Breast Cancer Progressing During Trastuzumab Treatment

von Minckwitz G et al.

Proc SABCS 2010;Abstract P6-14-05.

GBG 26/BIG 3-05 Study Design

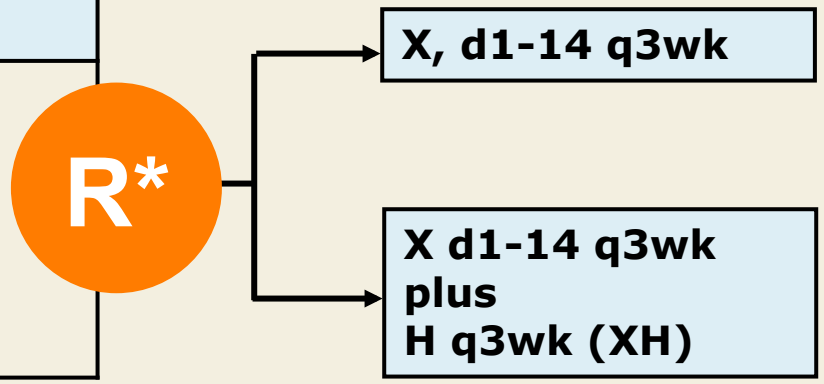
Accrual: 156 (Closed)

Eligibility

HER2-positive

Locally advanced or metastatic breast cancer

Disease progression during treatment with trastuzumab



X=capecitabine 2,500 mg/m^2
H=trastuzumab 6 mg/kg

*Patients were stratified according to previous therapy

Primary objective: Time to progression

Secondary objectives: Overall response rate, duration of response, clinical benefit and overall survival

von Minckwitz G et al. *Proc SABCS* 2010;Abstract P6-14-05.

Results

	X (n=74)	XH (n=77)	*p*-value
Overall survival (OS)	20.6 mos	24.9 mos	0.73
	X (n=53)	**XH (n=31)**	***p*-value**
OS in patients without crossover	20.4 mos	26.7 mos	0.2
	X (n=88)	**XH (n=52)**	***p*-value**
OS in the 3rd-line setting (includes crossovers)	13.3 mos	18.8 mos	0.02

von Minckwitz G et al. *Proc SABCS* 2010;Abstract P6-14-05.

Author Conclusions

- Final OS analysis of the GBG 26/BIG 3-05 study could not demonstrate a statistically significant survival benefit for treatment beyond progression with trastuzumab.
  - OS=20.6 vs 24.9 months (p=0.73)
- A post-hoc analysis of patients receiving trastuzumab in the 3rd-line setting reported an improved OS compared to those who did not continue with trastuzumab therapy.
  - OS=13.3 vs 18.8 months (p=0.02).
- Overall it seems important for patients with HER2-positive breast cancer to continue anti-HER2 treatment despite disease progression.

von Minckwitz G et al. *Proc SABCS* 2010;Abstract P6-14-05.

Patterns of Care and Outcomes of HER2-Positive Metastatic Breast Cancer Patients Receiving 3rd Line Therapy in an Outpatient Community Setting

Gruschkus SK et al.

Proc SABCS 2010;Abstract P3-11-15.

Methods and Results N=139 (from Abstract)

Retrospective study of data from US Oncology's iKnowMed record system of patients with HER2+ metastatic breast cancer treated with 1st-line trastuzumab between 1/1/2006 and 7/31/2007 to identify outcomes and patterns of care in patients receiving 3rd-line treatments.

	1st-line therapy n=139	2nd-line therapy n=139	3rd-line therapy n=48
Progressive disease during follow-up period	66% (n=92)	35% (n=48)	56% (n=27)
Median time to progression from 1st- to 3rd-line therapy (95% CI)	35 months (30.7-39.3 months)		
Deaths prior to progression to 3rd line (n)	17% (23)		
Patients alive without progression to 3rd-line therapy at end of follow-up (n)	49% (68)		

Gruschkus SK et al. *Proc SABCS* 2010;Abstract P3-11-15.

Author Conclusions

- In this retrospective analysis, 35% of patients received 3rd-line therapy and 49% were alive without progression to the 3rd line during the observation period.
- Utilization of 3rd- and 4th-line therapy varied widely (data not shown).
  - Suggests a standard of care has not emerged in this community-based setting.
- Continued active therapy past the 3rd line appears common in this setting. However, its usefulness may decrease in the 4th-line setting (data not shown).

Gruschkus SK et al. *Proc SABCS* 2010;Abstract P3-11-15.

Investigator Commentary: Trastuzumab in the Elderly; Treatment After Disease Progression

In this European registry study of patients with HER2-positive early breast cancer, there did not appear to be a significant difference between older and younger patients in terms of the benefits derived from adjuvant trastuzumab, which has been seen in other studies also. The investigators observed a small but limited increase in cardiac issues, which may be the result of the older age group of patients and other comorbidities.

In the poster by Waddell and colleagues, they report on the Royal Marsden single-institution study, which appeared to corroborate the von Minckwitz German group data that suggested a benefit for continuing trastuzumab beyond disease progression for patients with HER2-positive advanced breast cancer.

In previous reports, von Minckwitz demonstrated an improvement in progression-free survival with the continuation of trastuzumab beyond disease progression. In this final analysis, no improvement in overall survival was demonstrated. In the subset of patients who received anti-HER2 therapy in the 3rd-line setting a survival benefit was observed, but that was a subset analysis in a small number of patients.

Interview with William J Gradishar, MD, January 4, 2011

Patterns of Care and Outcomes of HER2-Positive Metastatic Breast Cancer Patients Receiving 3rd Line Therapy in an Outpatient Community Setting

Gruschkus SK et al.

Proc SABCS 2010;Abstract P3-11-15.

Responses to Subsequent Anti-HER2 Therapy After Treatment with Trastuzumab-DM1 in Women with HER2-Positive Metastatic Breast Cancer[1]

A Phase Ib/II Trial of Trastuzumab-DM1 with Pertuzumab for Patients with HER2-Positive, Locally Advanced or Metastatic Breast Cancer: Interim Efficacy and Safety Results[2]

[1]Olson EM et al.

Proc SABCS 2010;Abstract P3-14-08.

[2]Diéras V et al.

Proc SABCS 2010;Abstract P3-14-01.

Responses to Subsequent Anti-HER2 Therapy After Treatment with Trastuzumab-DM1 in Women with HER2-Positive Metastatic Breast Cancer

Olson EM et al.

Proc SABCS 2010;Abstract P3-14-08.

Methods and Results N=139 (from Abstract)

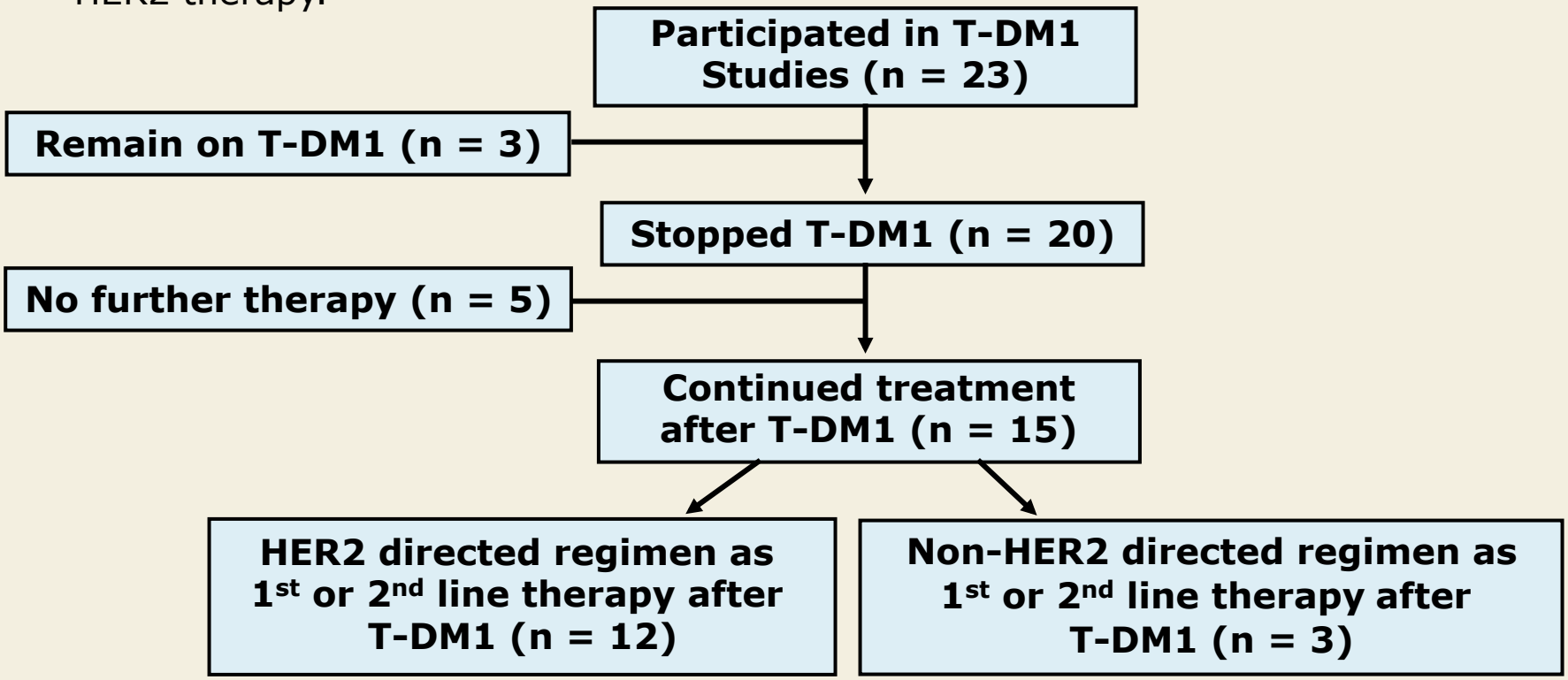
Retrospective study of data from US Oncology's iKnowMed record system of patients with HER2+ metastatic breast cancer treated with 1st-line trastuzumab between 1/1/2006 and 7/31/2007 to identify outcomes and patterns of care in patients receiving 3rd-line treatments.

	1st-line therapy n=139	2nd-line therapy n=139	3rd-line therapy n=48
Progressive disease during follow-up period	66% (n=92)	35% (n=48)	56% (n=27)
Median time to progression from 1st- to 3rd-line therapy (95% CI)	35 months (30.7-39.3 months)		
Deaths prior to progression to 3rd line (n)	17% (23)		
Patients alive without progression to 3rd-line therapy at end of follow-up (n)	49% (68)		

Gruschkus SK et al. *Proc SABCS* 2010;Abstract P3-11-15.

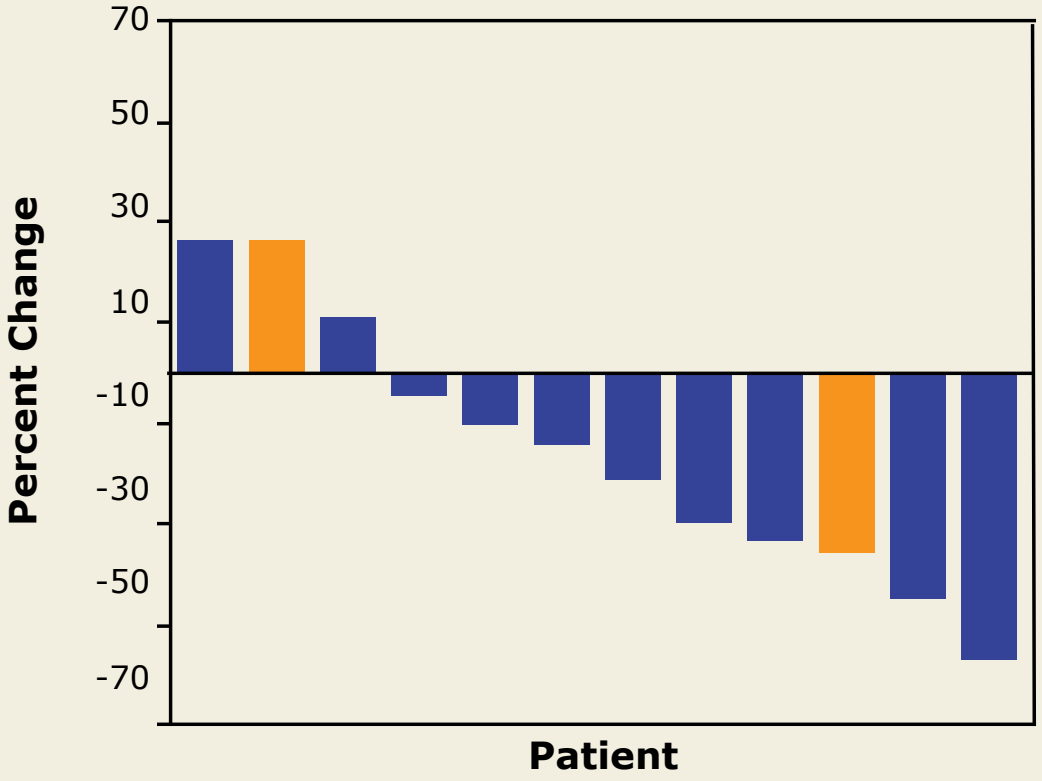
Study Objective and Participant Flow

Primary objective: Retrospective, single-institution study of women with progressive disease following treatment with trastuzumab-DM1 (T-DM1) during clinical trials, conducted to determine outcomes following subsequent lines of anti-HER2 therapy.



Olson EM et al. *Proc SABCS* 2010;Abstract P3-14-08.

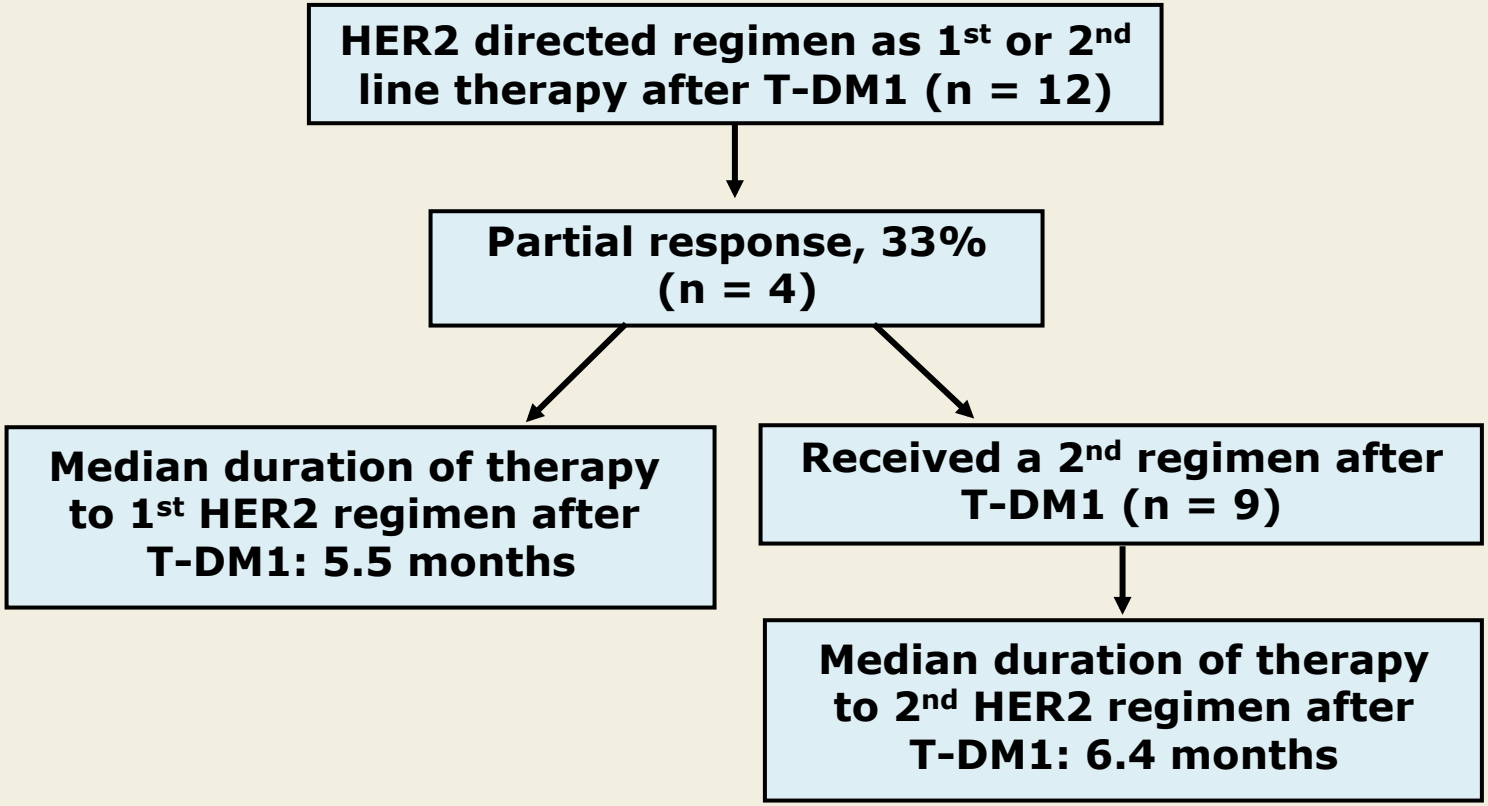
Decreases in Target Lesions



Best response to 1st or 2nd line of subsequent therapy after treatment with T-DM1. Blue bars indicate patients treated with trastuzumab and/or lapatinib-based regimens; orange bars indicate patients treated with non-trastuzumab and non-lapatinib based regimens only.

With permission from Olson EM et al. *Proc SABCS* 2010;Abstract P3-14-08.

Overall Response



Olson EM et al. *Proc SABCS* 2010;Abstract P3-14-08.

Author Conclusions

- Prior exposure to T-DM1 does not exhaust the potential benefit of ongoing anti-HER2 therapy with trastuzumab- and/or lapatinib-based regimens in patients with heavily pretreated HER2-positive metastatic breast cancer.
- This is the first report of outcomes to subsequent treatment after T-DM1.

Olson EM et al. *Proc SABCS* 2010;Abstract P3-14-08.

A Phase Ib/II Trial of Trastuzumab-DM1 with Pertuzumab for Patients with HER2-Positive, Locally Advanced or Metastatic Breast Cancer: Interim Efficacy and Safety Results

Diéras V et al.

Proc SABCS 2010;Abstract P3-14-01.

Background

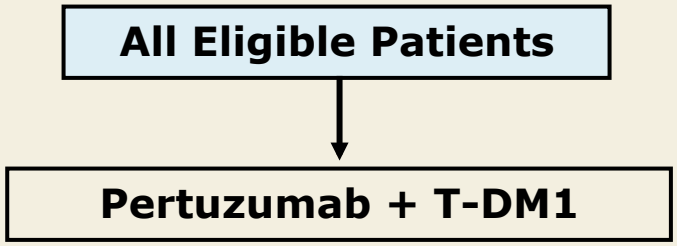
- Trastuzumab-DM1 (T-DM1) contains the cytotoxic maytansine derivative DM1 coupled to trastuzumab using a unique and stable linker.
- The linker allows for the intracellular release of DM1 after trastuzumab binds to HER2-overexpressing tumor cells; therefore, systemic exposure to free DM1 is minimized.
- Pertuzumab is the first HER2-directed dimerization inhibitor for the treatment of metastatic breast cancer (mBC).
- In xenograft models, the combination of T-DM1 and pertuzumab has shown synergistic activity.
- **Objective**
  - To evaluate the safety, tolerability and objective response rates of T-DM1 plus pertuzumab.

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

TDM4373g Study Design

Accrual: 67 (Closed)

Eligibility
Locally advanced or metastatic breast cancer
HER2-positive
Prior treatment with trastuzumab
No prior treatment with T-DM1 or pertuzumab
LVEF ≥55%



Pertuzumab: 840 mg X 1 → 420 mg in subsequent cycles, q3wk
T-DM1: 3.6 mg/kg, q3wk

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

Objective Responses among Patients in 1st-Line and Relapsed Settings

Clinical outcome	1st-line (n = 21)	Relapsed (n = 46)
Confirmed objective response rate	57.1%	34.8%
Clinical benefit rate*	61.9%	45.7%
Best responses		
Complete response	9.5%	2.2%
Partial response	47.6%	32.6%
Stable disease	23.8%	47.8%
Progressive disease	19.0%	15.2%

* Objective response or maintenance of stable disease for at least 6 months from start of study treatment

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

Select Grade ≥3 Adverse Events*

Adverse event (AE)	(n = 67)†
Fatigue	11.9%
Thrombocytopenia	11.9%
Alanine aminotransferase increased	9.0%
Aspartate aminotransferase increased	7.5%
Cellulitis	6.0%
Dyspnea	6.0%
Anemia	4.5%
Pleural effusion	4.5%
Pneumonia	3.0%
Neutropenia	3.0%

* Grade ≥3 AEs occurring in more than one patient. Data reflect number of patients, not number of events; some patients experienced an AE at more than one grade.

† Includes one Grade 5 pneumonia event and four Grade 4 events (three thrombocytopenia and one pain).

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

Safety

- The Phase Ib portion of this study reported that it was safe to combine full doses of T-DM1 and pertuzumab.
- Serious adverse events
  - Pleural effusion (n = 3 - relapsed, 0 - 1st line)
  - Dyspnea (n = 2 - relapsed, 1 - 1st line)
  - Pneumonia (n = 2 - relapsed, 0 - 1st line)
  - Abdominal pain (n = 0 - relapsed, 2 - 1st line)
  - Vomiting (n = 1 - relapsed, 1 - 1st line)
  - Cellulitis (n = 2 - relapsed, 0 - 1st line)
- Grade 5 pneumonia in a relapsed patient who subsequently died due to disease progression.
- No relapsed patients and one 1st-line patient experienced a left ventricular ejection fraction (LVEF) decline of ≥25% from baseline value.
- One relapsed patient discontinued from the study due to Grade 3 LVEF dysfunction.

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

Author Conclusions

- T-DM1 and pertuzumab were well tolerated at full single-agent doses as used in other clinical studies.
- The combination of T-DM1 and pertuzumab provides encouraging efficacy in patients with mBC:
  - Confirmed ORR in 1st-line setting = 57.1%
    - Robust activity reported for patients who received prior trastuzumab and taxane therapy in the early breast cancer setting (data not shown)
  - Confirmed ORR in relapsed setting = 34.8%
- The combination of T-DM1 and pertuzumab has an acceptable safety and tolerability profile.
- The combination of T-DM1 and pertuzumab is being studied as 1st-line treatment for HER2-positive mBC in the ongoing Phase III MARIANNE trial (BO22589/TDM4788g):
  - Randomization: T-DM1 alone or in combination with pertuzumab versus trastuzumab plus taxane

Diéras V et al. *Proc SABCS* 2010;Abstract P3-14-01.

Investigator Commentary: Early Experience with T-DM1

The report by Diéras and colleagues was of a Phase I/II study, so we don't yet have all of the results, but the study clearly demonstrated activity with the combination of trastuzumab-DM1 (T-DM1) and pertuzumab for patients with advanced HER2-positive breast cancer in the 1st-line or relapsed settings, and no significant toxicity was associated with this anti-HER2 combination. This study supports the idea of using anti-HER2 agents that have different mechanisms of action together.

The issue addressed in the study by Olson and colleagues is analogous to the situation with certain hormonal therapies. For instance, when we administer fulvestrant and downregulate the estrogen receptor, we worry about being able to induce a response with other endocrine therapies. In this small study, the investigators demonstrated that some patients with HER2-positive metastatic breast cancer whose disease progressed on T-DM1 would respond to subsequent anti-HER2 therapy with trastuzumab or lapatinib. So treatment with T-DM1 does not preclude future benefit from other anti-HER2 therapies.

Interview with William J Gradishar, MD, January 4, 2011

A Novel Capecitabine Schedule (7 on – 7 off) is Feasible with Lapatinib for Patients with HER2-Positive Metastatic Breast Cancer Refractory to Trastuzumab

Gajria D et al.

Proc SABCS 2010;Abstract P6-11-12.

Objectives

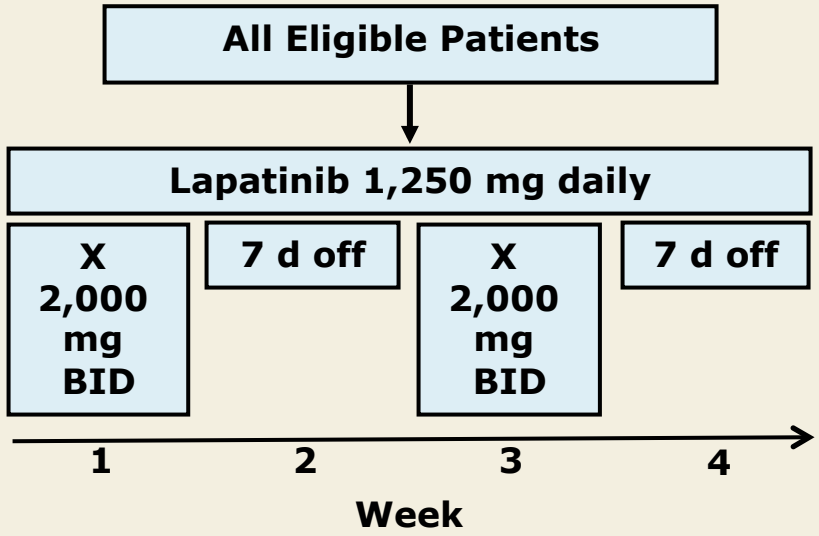
- **Hypothesis**
  - Lapatinib in combination with an optimal schedule of capecitabine 7 days on, 7 days off (7-7) will be feasible and active in patients with HER2-positive metastatic breast cancer refractory to trastuzumab.
- **Primary endpoint**
  - To evaluate complete and partial response rates according to RECIST criteria.
- **Secondary endpoints**
  - Toxicity
  - Stable disease for more than 6 months
  - Progression-free survival at 6 months

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

Study Design

Accrual: 23 (Closed)*

Eligibility
Metastatic breast cancer (mBC)
HER2-positive (IHC3+ or FISH>2)
Disease progression following trastuzumab
No more than 2 prior chemotherapy regimens
No prior use of fluoropyrimidine for metastatic disease
LVEF ≥50% by MUGA scan



X = Capecitabine

* Study closed to further accrual due to slower than expected accrual and an anticipated randomized Phase III trial comparing capecitabine (7–7) to standard capecitabine dose (14 days on, 7 days off)

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

Patient Characteristics

	n = 23
Median age, years (range)	54 (34-72)
Median ECOG PS (range)	0 (0-2)
ER- or PR-positive, n	13
HER2-positive, n	23
Sites of metastases, n	
Visceral metastases	16
Brain metastases	3
Median number of prior regimens for mBC (range)	1 (0-2)

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

Best Response

Outcome	Patients n = 23
Complete response	0
Confirmed partial response	4 (17%)
Stable disease, >6 months	6 (26%)
Stable disease, <6 months	12 (52%)
Progressive disease	1 (4%)

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

Treatment Modifications

Outcome	Patients n = 23
Discontinued treatment due to toxicity*	4
Capecitabine dose reductions or delays	10
Lapatinib dose reductions or delays	3
LVEF declines requiring treatment modification	0

*Grade 2 LFTs, Grade 2 hand-foot-mouth syndrome and Grade 2 rash associated with lapatinib

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

Adverse Events

Toxicity	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	2 (9%)	1 (4%)	1 (4%)
Hand-foot syndrome	9 (39%)	1 (4%)	0
Thrombocytopenia	0	1 (4%)	0
Neutropenia	0	1 (4%)	0
Diarrhea	6 (26%)	0	0
Liver dysfunction	4 (17%)	0	0
Fatigue	2 (9%)	0	0
Nausea	1 (4%)	0	0
Vomiting	0	0	0

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

Author Conclusions

- Capecitabine 7-7 plus lapatinib demonstrates activity and feasibility in patients with HER2-positive, trastuzumab-refractory, metastatic breast cancer.
  - Confirmed partial response rate = 17%
  - Stable disease >6 months = 26%
- The combination of capecitabine 7-7 and lapatinib was associated with mild gastrointestinal toxicity.
  - No reports of ≥Grade 3 nausea, vomiting or diarrhea
- These data have informed the design of a Phase III study that will evaluate capecitabine 7-7 versus standard capecitabine dosing (14 days on/7 days off).

Gajria D et al. *Proc SABCS* 2010;Abstract P6-11-12.

Investigator Commentary: Capecitabine (7 on, 7 off) with Lapatinib in HER2-Positive mBC Refractory to Trastuzumab

This study from Memorial Sloan-Kettering was based on mathematical modeling, which suggested that capecitabine administered on a seven days on, seven days off schedule may be more efficacious and tolerable than the standard 14 days on, seven days off schedule. The investigators evaluated an all-oral regimen with the 7/7 schedule of capecitabine in combination with lapatinib in patients with HER2-positive metastatic breast cancer that was refractory to trastuzumab.

They demonstrated that the combination was feasible, with response rates of approximately 20 percent. Their experience is not large enough to make any definitive conclusions, although much larger studies have evaluated this combination but not with this schedule of capecitabine. The side effects observed in this study were mild, with some hand-foot syndrome but no significant diarrhea or nausea/vomiting. It's a small study, but it suggests that lapatinib can be combined with this novel schedule of capecitabine.

Interview with William J Gradishar, MD, January 4, 2011