Poster #38

Eniluracil + 5-fluorouracil + leucovorin (EFL) vs. capecitabine Phase 2 trial for metastatic breast cancer (AHX-03-202)

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CTRC–AACR SAN ANTONIO BREAST CANCER SYMPOSIUM

December 4–8, 2012

Abstract

Based on a modified dosing protocol designed to optimize efficacy, an open-label EFL vs. capecitabine (4:3 randomization) Phase 2 trial for metastatic breast cancer is in progress. Eniluracil inactivates dihydropyrimidine dehydrogenase, thereby preventing the formation of α-fluoro-β-alanine, and conferring 100% oral bioavailability and a 5 hr half-life on 5-fluorouracil (5-FU). Study drugs are administered orally for 1st- or 2nd-line treatment for metastatic disease in patients previously treated with an anthracycline and a taxane. Arm 1: eniluracil (40 mg) taken 11-16 hr before 5-FU (30 mg/m^2); leucovorin (30 mg) taken with 5-FU and the next day. The regimen is administered once/week for 3 weeks/4 weeks. Arm 2: capecitabine (1000 mg/m^2) taken bid for 14 days/21 days. Arm 2 patients with disease progression could crossover to take EFL in Arm X. Two sites in the USA and 19 in Russia are enrolling. Currently, 115 patients (21% are 1st-line, 70% had previous 5-FU treatment) are enrolled and 83 have had tumor assessments. EFL was well tolerated with no unexpected toxicities. As of May 2012, there were 11, 7, & 1 partial responses in Arms 1, 2, & X, respectively. The primary endpoint, progression-free survival, will be determined approximately 7.5 months after the trial is enrolled with 140 evaluable patients.

Background

5-Fluorouracil (5-FU) is rapidly inactivated by dihydropyrimidine dehydrogenase (DPD) and then converted to α-fluoro β-alanine (F-Bal). F-Bal is neurotoxic, may contribute to hand-foot syndrome and may interfere with antitumor activity of 5-FU. Levels of DPD are highly variable causing markedly variable 5-FU pharmacokinetics that significantly affect 5-FU efficacy and safety. Eniluracil (EU) irreversibly inactivates DPD, thereby eliminating the problems associated with 5-FU variability and the formation of F-Bal. EU confers linear, consistent pharmacokinetics, 100% oral bioavailability and a 5-hr half-life on 5-FU[1,2], and markedly reduces the incidence of hand-foot syndrome[3]. In the year 2000, oral EU/5-FU failed to achieve non-inferiority in overall survival vs. intravenous 5-FU/leucovorin (Lv) for colorectal cancer[3]. Subsequently, a study in laboratory animals revealed that the high EU:5-FU ratio in those Phase 3 studies could have decreased antitumor activity[4].

The current study is based on a promising Phase 1 trial with weekly dosed oral EU, 5-FU, and Lv that produced durable tumor responses in patients with advanced colorectal cancer that was refractory to intravenous 5-FU/Lv[5]. The regimen was modified to:

- Administer a high EU dose to eliminate all DPD, including DPD in nervous tissue to minimize neurotoxicity
- Allow excess EU to be cleared before dosing with 5-FU
- Administer 5-FU when the EU:5-FU ratio is very low to optimize efficacy
- Administer Lv with 5-FU and 24 hr afterwards to potentiate 5-FU efficacy.

The study compares the efficacy and safety of this regimen to capecitabine (Xeloda®), an oral prodrug of 5-FU, for treatment of metastatic breast cancer. Patients with disease progression on capecitabine may crossover to take EU/5-FU/Lv. Capecitabine would not be effective in patients who have deficiencies in one or more of the three enzymes required to convert it to 5-FU, and/or have elevated DPD. EU/5-FU/Lv circumvents and/or eliminates these problems and the others described above. EU/5-FU/Lv would also avoid the rare, but severe toxicity caused by DPD deficiency in capecitabine treated patients.

Objectives

1. Primary Objective
   Progression-free survival
2. Secondary Objectives
   Safety, antitumor response rate, disease control rate, duration of response, and time to treatment response.

Study Design

Design
(Enroll 140 evaluable Patients)

Arm 1: Oral EU/5-FU/Lv vs. **Arm 2**: Oral Capecitabine (4:3 Randomization)

Arm X: Subjects in Arm 2 (capecitabine) who have radiologically documented disease progression may crossover to receive EU/5-FU/Lv.

Key Inclusion Criteria

- Women needing 1st- or 2nd-line treatment for metastatic breast cancer
- Previous treatment with an anthracycline and a taxane
- Measurable disease by RECIST 1.1
- EGOG = 0 or 1
- No prior capecitabine treatment

Study Drug Administration
(All drugs are self-administered oral tablets)

Arm 1 & Arm X: EU/5-FU/Lv: (28-day cycle):
Taken weekly for 3 consecutive weeks followed by 7 days off treatment

1st Day: EU (40 mg)
2nd Day: 5-FU (30 mg/m^2) and Lv (30 mg) taken 11-16 hr after Eniluracil
3rd Day: Lv (30 mg)

Arm 2: Capecitabine: (21-day cycle)
Capecitabine (1000 mg/m^2) twice daily for 14 days followed by 7 days off treatment

Assessments

- Tumor evaluations by CT or MRI every 6 weeks using RECIST 1.1
- Routine safety and hand-foot syndrome assessments every clinic visit

Statistics

The sample size of 140 patients (80 Arm 1, 60 Arm 2), has at least 68% power (1-sided, 5% significance level) to detect a difference of 15% more patients in Arm 1 (43%) achieving progression-free survival (PFS) than patients in Arm 2 (28%) after 7.5 months follow-up. The Kaplan-Meier method will be used to estimate PFS at 6 and 7.5 months.

Preliminary Interim Results

Efficacy
(as of Oct. 29, 2012)

Table 1. Arm 1 vs. Arm 2

Arm	Evaluated patients	CR n (%)	PR n (%)	SD n (%)	CR + PR + SD* n (%)
Arm 1	68	1 (1)	16 (24)	35 (51)	52 (76)
Arm 2	54	0 (0)	14 (26)	26 (48)	40 (74)

* Clinical benefit. CR = Complete Response, PR = Partial Response, SD = Stable Disease

Table 2. Arm X: Arm 2 Patients with PD Who Crossed Over to Take EU/5-FU/Lv

Arm	Evaluated patients	CR n (%)	PR n (%)	SD n (%)	CR + PR + SD* n (%)
Arm X (All Subjects)	18	0 (0)	3 (17)	8 (44)	11 (61)
Arm X (Rapid Capecitabine Failures)#	9	0 (0)	3 (33)	5 (56)	8 (89)

* Clinical benefit. # Subjects who progressed (PD) on Arm 2 within 70 days (one scan)

Table 3. Rapid Capecitabine Failures Subsequently Treated in Arm X

Patient	Arm X		Arm 2		Adjuvant/Neoadjuvant 5-FU Treatment(s)
	PFS# (Days)	Best Response	PFS (Days)	Best Response	
1	**232***	SD	38	PD	No
2	212	SD	41	PD	Yes
3	124	**PR**	41	PD	Yes
4	28	PD	41	PD	Yes
5	335	**PR**	42	PD	Yes
6	**117***	**PR**	43	PD	No
7	82	SD	43	PD	Yes
8	84	SD	57	SD	No
9	63	SD	42	PD	Yes
Median PFS	**117**		**42**		
Mean PFS	**143**		**43**		

PFS was calculated starting from the first EU/5-FU/Lv dose (a conservative estimate)
* Ongoing EU/5-FU/Lv treatment

Safety

Both EU/5-FU/Lv (Arm 1) and capecitabine (Arm 2) were generally well-tolerated and produced the historically-expected 5-FU side effects. Arm 1 had three drug-related SAEs. One of these, metrorrhagia, was unexpected and possibly related. To date, no drug-related SAEs have occurred in Arm 2 and Arm X.

Conclusions

As of Oct. 29, 2012, 122 patients had tumor assessments. Approximately 20% of patients were treated as 1st-line for metastatic disease (80% as 2nd-line) and 70% had previous 5-FU treatment(s).

- Preliminary tumor response rate was 25%, 26%, and 17% in Arms 1, 2, & X, respectively. One CR occurred in Arm 1.
- Preliminary clinical benefit was 76%, 74%, and 61% in Arms 1, 2, & X, respectively.
- **Eight of the 9 (89%) crossover patients in Arm X who had rapidly failed capecitabine experienced clinical benefit on EU/5-FU/Lv. Three of these patients (33%) had PRs and two patients are still being treated with EU/5-FU/Lv.**
- EU/5-FU/Lv could potentially allow patients who rapidly fail capecitabine to continue with another oral 5-FU therapy rather than switching to the less well-tolerated intravenous microtubule-interfering agents, ixabepilone (Ixempra®) and eribulin mesylate (Halaven®).
- **A small clinical trial in patients with metastatic breast cancer who failed capecitabine within 70 days (one scan) may be an attractive path to rapidly demonstrate the clinical usefulness of EU/5-FU/Lv.**

References

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