

## A Phase II Study of Irinotecan and Etoposide as Treatment for Refractory Metastatic Breast Cancer

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### TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT00693719
- **Sponsor:** University of Arizona Cancer Center
- **Principal Investigator:** Robert B. Livingston
- **IRB Approved:** Yes

### LESSONS LEARNED

- The combination of irinotecan and etoposide showed modest efficacy in terms of response rate in the refractory setting for patients with metastatic breast cancer.
- The studied dose and schedule of irinotecan and etoposide is very toxic, with >70% grade 3 or 4 treatment-related adverse events.

### ABSTRACT

**Background.** As single agents, both irinotecan and etoposide have documented activity against breast cancer among patients who have received multiple lines of prior chemotherapy. Irinotecan interacts with topoisomerase I (Topo I) to stabilize its cleavable complex, and etoposide has an analogous interaction with topoisomerase II (Topo II). This stabilization without rapid resealing of the cleavage point results in apoptotic cell death and accounts for the antitumor activity of these agents. Topo II levels may increase after administration of a Topo I inhibitor, thus providing a rationale for combining these agents in practice. Based on preclinical data, we conducted a phase II trial of the Topo I inhibitor irinotecan combined with the Topo II inhibitor etoposide in patients with metastatic breast cancer (MBC).

**Methods.** This was a single-arm phase II clinical trial in patients with MBC refractory to prior anthracycline, taxane, and capecitabine therapy. All patients were treated with oral etoposide at 50 mg/day on days 1–14 and intravenous irinotecan at 100mg/m<sup>2</sup> on days 1 and 15. Treatment cycles were repeated every 28 days. The primary endpoint was median time to progression. Secondary end points included overall clinical response rate using RECIST criteria and

assessing the toxicity and safety profile associated with this combination regimen.

**Results.** We enrolled 31 women with refractory MBC to our trial. Median age was 54 (range, 36–84), with the majority (64%) having hormone receptor positive (HR+) human epidermal growth factor receptor 2 negative (HER2 neg) MBC. Median number of prior therapies was five (range, 3–14). Efficacy was evaluated in 24 patients. Seventeen percent had a partial response, and 38% had stable disease as best response. Median progression-free survival was 9 weeks (range, 3–59). All 31 patients were evaluable for toxicity assessment, and 22 patients (71 %) experienced treatment-related grade 3 or 4 adverse events (AEs; Table 1). The most common grade 3–4 AE was neutropenia. The study was terminated early based on interim analysis assessment that suggested toxicities outweighed the efficacy.

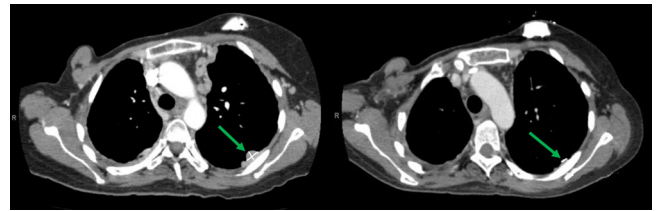
**Conclusion.** Irinotecan and etoposide demonstrated only modest clinical activity and poor tolerability in patients with MBC refractory to anthracycline, taxane, and capecitabine therapy. Further studies testing a lower dose and/or different schedule could be considered given ease of administration and responses seen. *The Oncologist* 2019;24:1512–e1267

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**Table 1.** Treatment-related adverse events

Adverse event	Number of patients (%)
Patients who experienced any grade 3/4 AE	22 (71)
Grade 3 only	9 (29)
Grade 4	13 (42)
Patients who experienced >1 grade 3/4 AE	8 (26)
Patients who experienced >2 grade 3/4 AE	4 (13)
Neutropenia	19 (61)
Grade 3	7 (23)
Grade 4	12 (39)
Anemia	4 (13)
Fatigue	3 (10)
Dehydration	2 (6)
Diarrhea	2 (6)
Abdominal cramps/pain/bloating	1 (3)
Grade 4	1 (3)
Bone pain	1 (3)
Elevated AST/ALT	1 (3)
Flu-like syndrome	1 (3)
Hypokalemia	1 (3)
Leukopenia	1 (3)
Nausea/vomiting	1 (3)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.



**Figure 1.** Computed tomography chest showing decrease in left pleural nodule after three cycles of therapy.

## DISCUSSION

Combinations of Topo I and Topo II inhibitors have been suggested based on the preclinical data that Topo II levels may be upregulated after administration of a Topo I inhibitor. We enrolled women with MBC who were heavily pretreated on this trial evaluating combination of irinotecan and etoposide. Although the regimen was found to have modest clinical activity in terms of response rates and progression-free survival (PFS), it had significant side effects, with a majority of patients experiencing a grade 3 or 4 treatment-related adverse event, and the study was terminated early. Based on our experience, the studied combination regimen dose and schedule is not optimal for patients.

## TRIAL INFORMATION

<b>Disease</b>	Breast cancer
<b>Stage of Disease/Treatment</b>	Metastatic / Advanced
<b>Prior Therapy</b>	More than 2 prior regimens
<b>Type of Study – 1</b>	Phase II
<b>Type of Study – 2</b>	Single arm
<b>Primary Endpoint</b>	Time to progression
<b>Secondary Endpoint</b>	Overall response rate
<b>Secondary Endpoint</b>	Safety
<b>Secondary Endpoint</b>	Overall survival
<b>Investigator's Analysis</b>	Active but too toxic as administered in this study

**DRUG INFORMATION****Drug 1**

<b>Generic/Working Name</b>	Irinotecan
<b>Trade Name</b>	Camptosar
<b>Company Name</b>	Pfizer Oncology
<b>Drug Type</b>	Biological
<b>Drug Class</b>	Topoisomerase I
<b>Dose</b>	100 mg/m <sup>2</sup>
<b>Route</b>	IV
<b>Schedule of Administration</b>	100 mg/m <sup>2</sup> every 2 weeks in a 28-day cycle

**Drug 2**

<b>Generic/Working Name</b>	Etoposide
<b>Trade Name</b>	VePesid
<b>Drug Class</b>	Topoisomerase II
<b>Dose</b>	50 mg per flat dose
<b>Route</b>	p.o.
<b>Schedule of Administration</b>	50 mg per day for 14 days, then off 2 weeks for a 28-day cycle

**PATIENT CHARACTERISTICS**

<b>Number of Patients, Male</b>	0
<b>Number of Patients, Female</b>	31
<b>Stage</b>	Metastatic breast cancer, prior exposure to anthracycline, taxane, and capecitabine therapy
<b>Age</b>	Median (range): 54 (36–84)
<b>Number of Prior Systemic Therapies</b>	Median (range): 5 (3–14)
<b>Performance Status: ECOG</b>	0 — 16 1 — 14 2 — 1 0 0

**Other**

<b>Tumor Biology (Number)</b>	Triple-negative breast cancer = 5 HR+/HER2 neg = 20 HER2 pos = 3 Unknown = 3
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<b>Cancer Types or Histologic Subtypes</b>	Invasive ductal carcinoma, 24 Invasive lobular carcinoma, 3 Inflammatory, 2 Unknown, 2
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**PRIMARY ASSESSMENT METHOD**

<b>Title</b>	Time to progression
<b>Number of Patients Enrolled</b>	31
<b>Number of Patients Evaluable for Toxicity</b>	31
<b>Number of Patients Evaluated for Efficacy</b>	24
<b>Evaluation Method</b>	RECIST 1.0
<b>Response Assessment PR</b>	<i>n</i> = 4 (17%)
<b>Response Assessment SD</b>	<i>n</i> = 7 (38%)
<b>Response Assessment PD</b>	<i>n</i> = 11 (45%)

<b>(Median) Duration Assessments PFS</b>	9 weeks
<b>(Median) Duration Assessments TTP</b>	63 days
<b>(Median) Duration Assessments OS</b>	29 weeks

### ASSESSMENT, ANALYSIS, AND DISCUSSION

<b>Completion</b>	Study terminated before completion
<b>Terminated Reason</b>	Toxicity
<b>Investigator's Assessment</b>	Active but too toxic as administered in this study

As single agents, both irinotecan and etoposide have documented activity against breast cancer among patients who have received multiple forms of prior chemotherapy [1, 2].

Combinations of Topo I and Topo II inhibitors have been suggested based on the observation that Topo II levels may be upregulated after administration of a Topo I inhibitor [3]. In addition, Topo II may be able to partially compensate for Topo I, as has been seen in *Saccharomyces cerevisiae* [5, 6], permitting maintenance of critical transcriptional functions. This concept has been difficult to realize in the clinic when topotecan and etoposide were administered sequentially [4]. One explanation may be the lapsed time between administration of the Topo I and Topo II inhibitors in the clinical trial, whereas the preclinical data showed maximal synergy when the Topo II inhibitor was administered immediately after the Topo I inhibitor [3].

In our trial, the majority of patients had refractory disease with an extensive prior treatment history (see Patient Characteristics for demographics). The combination of irinotecan and etoposide was found to have modest clinical activity, with a 55% response rate by RECIST criteria (Fig. 1) and median PFS of 9 weeks (range, 3–59). However, there were significant side effects, with >70% of patients experiencing grade 3 or 4 treatment-related adverse events, primarily neutropenia. See attached table 1 for details on AEs. All patients on study received maximal symptomatic management, transfusions for cytopenias, growth colony-stimulating factor when indicated, dose reductions, and drug holidays. Growth colony-stimulating factor support was needed in 85% of patients who had grade 3 or

4 neutropenia requiring dose reduction. Transfusion support for anemia was needed in 13% of patients.

The study protocol originally planned to accrue a total of 54 patients and specified early stopping if the response rate was 2 or fewer of the first 21 evaluable patients (9.5%) according to Simon's optimal design criteria. At the time of interim analysis, despite a promising response rate, the regimen was determined to be too toxic, and the study was terminated early by the data safety monitoring board and study principal investigator.

The current treatment armamentarium for MBC is expanding with newer targeted therapies that improve PFS and quality of life. As the tumor becomes refractory to more treatments, the current treatment landscape includes evaluating for mutations in driver pathways, assessing the microenvironment, and testing novel targeted therapies. As MBC tumor biology and pathways are better understood, allowing for exploitation with novel targeted therapies, the field is moving away from combination chemotherapy regimens. Although combination chemotherapy does have some role in MBC (e.g., in visceral crisis), it is not ideal for long-term therapy. Based on our experience, we do not expect the combination of irinotecan and etoposide to be used routinely because of an unacceptable toxicity profile.

#### DISCLOSURES

**Alison Stoepck:** Novartis, AstrzZeneca, Biothera (C/A), Genomic Health, Amgen (H), Amgen, Eli Lilly & Co. (RF); **Pavani Chalasani:** Pfizer (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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