Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2025, Volume 5, Issue 1, Page No: 208-220

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Galaxy Publication

Lurbinectedin and Capecitabine Combination Therapy in Relapsed Metastatic Breast Cancer: Phase I Evaluation of Safety and Efficacy

Yuki Hassan[1], Carlos L. Brown[1], Lina W. Smith[1], Hiroshi Smith[1], Omar Wilson[1], Laura Sharma[1]*

[1]Department of Hematology and Oncology, School of Medicine, Medical University of Warsaw, Warsaw, Poland.

***E-mail** ✉ lsharma@gmail.com

Received: 28 February 2025; **Revised:** 15 May 2025; **Accepted:** 15 May 2025

ABSTRACT

Studies in preclinical models have suggested that combining lurbinectedin with 5-fluorouracil enhances antitumor effects against solid tumors. This phase I clinical trial aimed to assess the safety, efficacy, and pharmacokinetics of combining capecitabine and lurbinectedin in patients with advanced solid tumors, with a particular focus on those with relapsed metastatic breast cancer (MBC). Patients in the trial were given capecitabine orally from day (D)1 to D14, alongside lurbinectedin administered intravenously either on D1 and D8, or every 3 weeks on D1 alone, following a traditional 3 + 3 dose escalation approach. Once the recommended dose (RD) was identified, the study continued to explore its efficacy and safety. Among the 81 patients enrolled, 28 had relapsed MBC, including 20 with hormone receptor (HR)-positive and 8 with triple-negative breast cancer. Three patients followed the D1, D8 schedule, and 25 followed the D1-only regimen. The recommended dose for this combination was capecitabine 1650 mg/m² daily from D1 to D14, with lurbinectedin 2.2 mg/m² administered on D1 every three weeks. At all dose levels, 16 patients achieved confirmed responses and 2 showed prolonged disease stabilization lasting more than 6 months, leading to an overall response rate (ORR) of 57% and a clinical benefit rate (CBR) of 64%. At the RD, ORR and CBR were 47% and 60%, respectively. Notably, patients with HR-positive tumors demonstrated a higher response rate (ORR of 60%, CBR of 70% across all doses; ORR of 56%, CBR of 78% at the RD). Among the triple-negative cohort, 4 patients showed responses (ORR and CBR of 50% at all doses, dropping to 33% at the RD). The treatment was generally well tolerated, with reversible myelotoxicity at the RD and mostly mild-to-moderate non-hematologic side effects. No serious cases of febrile neutropenia or severe palmar-plantar erythrodysesthesia syndrome were reported, and there were no major pharmacokinetic interactions between capecitabine, its metabolites, and lurbinectedin. The combination of capecitabine and lurbinectedin exhibited promising antitumor activity in relapsed MBC, particularly in HR-positive cases. The toxicity profile was manageable, and further investigation into this combination therapy for relapsed MBC is warranted.

Keywords: Capecitabine, Lurbinectedin, Breast cancer, Phase I study

How to Cite This Article: Hassan Y, Brown CL, Smith LW, Smith H, Wilson O, Sharma L. Lurbinectedin and Capecitabine Combination Therapy in Relapsed Metastatic Breast Cancer: Phase I Evaluation of Safety and Efficacy. Asian J Curr Res Clin Cancer. 2025;5(1):208-20. https://doi.org/10.51847/lt2GZ44ZUV

Introduction

Lurbinectedin is a synthetic alkaloid related to trabectedin, known for its ability to interfere with oncogenic transcription. It works by binding to guanine-rich DNA regions, particularly around the promoters of protein-coding genes. This binding alters the DNA's structure, causing the displacement of transcription factors that promote cancer, ultimately halting their abnormal activity [1-3]. Furthermore, lurbinectedin can interfere with RNA polymerase II by preventing its phosphorylation, reducing mRNA production and triggering the breakdown of RNA polymerase II itself [4]. The formation of DNA double-strand breaks induced by lurbinectedin also contributes to programmed cell death (apoptosis) in cancer cells [5].

In previous phase I trials, the recommended doses (RDs) for lurbinectedin as a single-agent therapy were identified for two treatment schedules. One involved a 7.0 mg flat dose (FD) given on Day 1 of a 3-week cycle (1-hour intravenous infusion every 3 weeks), while the other used a 5.0 mg FD administered on Days 1 and 8 of the same cycle. The most common side effects at these doses included transient neutropenia, mild gastrointestinal symptoms, and fatigue [6, 7].

Preclinical data indicated that lurbinectedin had a synergistic effect when combined with 5-fluorouracil (5-FU), showing enhanced activity in vitro against gastric and colon cancer cells, and in vivo in mouse models with xenografted gastric, colon, or pancreatic tumors [8]. Notably, lurbinectedin's toxicity profile differs from that of capecitabine, an oral form of 5-FU used in treating metastatic colorectal cancer (mCRC) and metastatic breast cancer (MBC).

This phase I study aimed to explore the safety, pharmacokinetics, and antitumor activity of lurbinectedin when combined with capecitabine in patients with advanced solid tumors. The results, particularly for those with metastatic breast cancer (MBC), are highlighted here, as the combination showed promising anticancer effects during the dose escalation phase.

Materials and Methods

Patients and methods

The clinical trial was conducted across sites in Spain and Belgium, adhering to the International Conference on Harmonisation (ICH) Good Clinical Practice standards. The study protocol received approval from the respective research ethics committees at each center. Before undergoing any study-related procedures, all participants provided written informed consent. The trial is registered with the identifier NCT02210364 on clinicaltrials.gov.

Eligibility criteria

Patients eligible for the study were between 18 and 75 years of age, with unresectable metastatic colorectal cancer (mCRC), metastatic breast cancer (MBC), or pancreatic cancer (PC). To qualify, patients also needed to have a life expectancy of at least 3 months, an ECOG performance status score of 1 or less, and adequate bone marrow, liver, kidney, and metabolic function. Additionally, patients were required to have a normal left ventricular ejection fraction and must have recovered from any prior treatment-related toxicities. For those enrolled in the expansion cohort at the recommended dose (RD), the disease had to be measurable based on RECIST v.1.1, with documented disease progression.

Exclusion criteria included prior treatment with lurbinectedin or capecitabine for advanced disease, having received three or more chemotherapy regimens for advanced disease, undergoing bone marrow or stem cell transplantation, or receiving extensive radiotherapy. Also excluded were lactating women or individuals not using reliable contraception, those with symptomatic brain metastases or leptomeningeal disease, chronic liver disease, active infections, serious cardiac conditions, external drainage devices, oxygen-dependent dyspnea, dihydropyrimidine dehydrogenase deficiency, or other diseases that could interfere with study outcomes.

Study treatment

Treatment initially involved dose-escalation with oral capecitabine taken twice daily from Day 1 to Day 14, followed by lurbinectedin administered as a 1-hour intravenous infusion on Days 1 and 8 of each 21-day cycle. If at least half of the assessable patients at any dose level were unable to receive the Day 8 lurbinectedin infusion during the first or second cycle, or if the combination's starting dose was found to be unfeasible, the lurbinectedin schedule was adjusted to be administered only on Day 1 of each 21-day cycle, while keeping the original capecitabine regimen intact.

Lurbinectedin was supplied as a lyophilized powder concentrate, which was then reconstituted and diluted with either a 5% glucose solution or 0.9% sodium chloride solution. Capecitabine was provided in its commercially available form. Antiemetic treatment was given with intravenous dexamethasone and ondansetron before each lurbinectedin infusion. If needed, oral metoclopramide and other antiemetics could be used (excluding aprepitant, which was prohibited). Treatment continued until disease progression, intolerable side effects, a medical condition that prevented continuation, patient withdrawal, non-compliance, a treatment delay exceeding 15 days (unless there was evident clinical benefit), or the need for more than two dose reductions.

Dose-limiting and dose escalation toxicities

The study employed a classic 3 + 3 dose-escalation scheme. The initial dose of capecitabine (1650 mg/m² per day, given in two divided doses separated by at least 12 hours) equated to about 66% of its established single-agent recommended dose of 2510 mg/m² per day on the same intermittent regimen,9 whereas the starting lurbinectedin dose (2.0 mg as a flat dose) was 40% of the single-agent recommended flat dose of 5.0 mg, previously determined for 1-hour intravenous administration on days 1 and 8 every 3 weeks.7

Dose-limiting toxicities (DLTs) included the following criteria: grade 4 neutropenia persisting beyond 3 days; febrile neutropenia or infection associated with neutropenia; grade 4 thrombocytopenia (or grade 3 requiring platelet transfusion); grade 4 hepatic transaminase elevation (or grade 3 lasting more than 7 days); grade ≥2 transaminase elevation concurrent with total bilirubin ≥2× the upper limit of normal and normal alkaline phosphatase levels; any other clinically significant grade ≥3 non-hematologic adverse event; and treatment-related delays or interruptions, such as cycle postponement exceeding 15 days, capecitabine omission for more than 5 consecutive days or 7 days total in a cycle, or skipping the day 8 lurbinectedin dose followed by cycle delay.

Determination of the recommended dose

The main goal of the trial was to establish the recommended dose (RD) for lurbinectedin when administered with capecitabine. This was identified as the maximum dose level at which fewer than one-third of evaluable patients encountered a DLT during the first treatment cycle in the escalation phase. The candidate dose was then subjected to cohort expansion and validated as the RD provided that fewer than one-third of the initial nine evaluable patients experienced cycle 1 DLTs.

Safety assessments

Blood counts and clinical chemistry parameters were monitored at study entry, weekly during the first cycle (with hematology continued weekly in cycle 2), and on days 1 and 8 of later cycles. Electrocardiograms were performed at screening and repeated only when clinically warranted.

Treatment-emergent adverse events and abnormal laboratory values were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4,10 and encoded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

Efficacy assessments

Tumor response was measured using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.111 at 6-week intervals through cycle 6, then every 9 weeks thereafter. The overall response rate (ORR) represented the proportion of patients who achieved a complete or partial response. The clinical benefit rate (CBR) encompassed patients with complete response, partial response, or durable stable disease. Key time-dependent endpoints were progression-free survival (PFS) and duration of response (DoR).

Pharmacokinetic evaluations

From each participant, twelve blood samples were drawn to determine plasma levels of lurbinectedin, capecitabine, and its key metabolites—including 5′-deoxy-5-fluorouridine (5′-DFUR), 5-fluorouracil (5-FU), and α-fluoro-β-alanine (FBAL). Samples were taken before treatment and at various intervals over a 3-week period following the initial dose. Drug levels were quantified using validated liquid-liquid extraction procedures combined with ultra-performance liquid chromatography coupled to tandem mass spectrometry (performed by Dynakin, Derio, Spain). Established calibration curves covered ranges of 0.1–50 ng/ml for lurbinectedin, 100–10 000 ng/ml for capecitabine, 500–10 000 ng/ml for 5′-DFUR, 5–1000 ng/ml for 5-FU, and 200–10 000 ng/ml for FBAL. Lurbinectedin's individual pharmacokinetic parameters were derived via non-compartmental methods. In contrast, parameters for capecitabine and its metabolites were estimated through a population pharmacokinetic (PopPK) modeling strategy, building on the framework described by Urien *et al.* [9] and integrating data from every patient across all tumor types. To achieve more robust conclusions, assessments of dose-proportionality and possible drug–drug interactions similarly drew on the full dataset from the trial.

Statistical methods

Descriptive summaries (means, medians, ranges) were reported for continuous data, whereas counts and percentages were used for categorical data. Survival and time-to-event outcomes were analyzed with Kaplan–

Meier estimates. Ninety-five percent confidence intervals (95% CIs) for proportions were calculated using the exact binomial method. Plasma concentration-time curves were examined with conventional non-compartmental techniques. All individual pharmacokinetic values were compiled in tables and presented with summary measures.

Results and Discussion

Dose escalation phase

The trial enrolled 81 patients from April 2013 to October 2016, comprising 31 with metastatic colorectal cancer (mCRC), 28 with metastatic breast cancer (MBC), and 22 with pancreatic cancer. Investigators explored seven distinct dose levels: two employing capecitabine days 1–14 with lurbinectedin on days 1 and 8 every 3 weeks, and five using capecitabine days 1–14 with lurbinectedin solely on day 1 every 3 weeks. The single-day lurbinectedin schedule was adopted after observations that monotherapy on day 1 every 3 weeks resulted in briefer periods of blood count nadirs compared with the days 1 and 8 regimen.6,7 Furthermore, lurbinectedin administration transitioned from flat dosing (FD) to dosing normalized by body surface area (BSA; derived by dividing the FD by a standard BSA of 1.8 m²), based on pooled phase II analyses revealing increased risk of severe thrombocytopenia in patients with smaller BSA values. The majority of dose-limiting toxicities across schedules involved bone marrow suppression and arose at levels higher than the recommended doses. Recommended doses were set at capecitabine 1650 mg/m² days 1–14 combined with either lurbinectedin 2.0 mg FD on days 1 and 8 every 3 weeks or lurbinectedin 2.2 mg/m² on day 1 every 3 weeks; the day 1 regimen was ultimately selected for advancement to phase II testing.

Patient characteristics and prior treatments in metastatic breast cancer

Demographic and clinical features at baseline for the 28 MBC patients treated with the combination are detailed in **Table 1**. The cohort consisted entirely of women with a median age of 51.5 years (range 29–71). Disease subtypes included HR-positive/HER2-negative in 19 patients (68%), HR-positive/HER2-positive in one patient (4%), and triple-negative in eight patients (29%). Among 11 patients tested for BRCA alterations, five harbored pathogenic BRCA1 or BRCA2 variants. Visceral involvement was present in 27 patients (96%), with liver metastases in 22 (79%). Patients had received a median of one prior systemic line for advanced disease (range 0–3). Common previous exposures included taxanes (89%), anthracyclines (86%), and cyclophosphamide (82%). Endocrine treatments were administered to 19 patients (68%), most frequently tamoxifen (16 patients; 57%), letrozole (11; 39%), fulvestrant (8; 29%), exemestane or goserelin (5 each; 18%), and anastrozole (2; 7%). Two patients (7%) had prior exposure to CDK4/6 inhibitors (one to abemaciclib and one to ribociclib, both investigational during the study period). The sole patient with HR-positive/HER2-positive disease had been treated with trastuzumab for about 12 months before study entry.

Table 1. Baseline characteristics of patients with metastatic breast cancer

Characteristic	All Dose Levels (n = 28)	Recommended Dose* (capecitabine 1650 mg/m² days 1–14 + lurbinectedin 2.2 mg/m² day 1) (n = 15)
ECOG performance status		
0	18 (64%)	11 (73%)
1	10 (36%)	4 (27%)
Median BSA, m² (range)	1.7 (1.3–2.2)	1.7 (1.5–2.1)
Age, years		
Median (range)	51.5 (29–71)	46.0 (29–71)
≤40	3 (11%)	2 (13%)
41–60	17 (61%)	8 (53%)
>60	8 (29%)	5 (33%)
BRCA mutation status		
BRCA2 mutation	—	1 (4%)
BRCA1 mutation	4 (14%)	4 (27%)
BRCA1/2 wild-type	6 (21%)	4 (27%)

Unknown	17 (61%)	7 (47%)
HR and HER2/neu status		
HR-positive	20 (71%)	9 (60%)
HR-positive/HER2-positive	1 (4%)	1 (7%)
HR-positive/HER2-negative	19 (68%)	8 (53%)
Triple-negative	8 (29%)	6 (40%)
Bulky disease (any target lesion ≥50 mm)	7 (25%)	5 (33%)
Sites of disease		
Bone	18 (64%)	10 (67%)
CNS	1 (4%)	—
Visceral*a*	27 (96%)	15 (100%)
Liver	22 (79%)	12 (80%)
Number of metastatic sites		
Median (range)	3.0 (1–6)	3.0 (2–6)
1	1 (4%)	—
2	7 (25%)	6 (40%)
≥3	20 (71%)	9 (60%)
Prior lines of therapy for advanced disease		
Median (range)	1.0 (0–3)	1.0 (0–3)
0*b*	8 (29%)	3 (20%)
1	9 (32%)	5 (33%)
2	10 (36%)	6 (40%)
3	1 (4%)*c*	1 (7%)*c*
Prior anticancer agents		
Nitrogen mustard analogues	23 (82%)	13 (87%)
Pyrimidine analogues	11 (39%)	5 (33%)
Taxanes	25 (89%)	14 (93%)
Anthracyclines and related	24 (86%)	12 (80%)
Platinum compounds	4 (14%)	4 (27%)
Prior hormone therapy	19 (68%)	8 (53%)
Prior CDK4/6 inhibitor therapy	2 (7%)	—

Data are reported as number (%) of patients unless indicated as median (range).

D, day; HR, hormone receptor; MBC, metastatic breast cancer; RD, recommended dose; ECOG, Eastern Cooperative Oncology Group; ECOG; FOLFIRI, leucovorin, 5-fluorouracil plus irinotecan; BEV, bevacizumab; BSA, body surface area; CDK4/6, cyclin-dependent kinase 4/6; CNS, central nervous system.

[a] Visceral involvement covers sites such as lung, liver, and adrenal glands.

[b] These cases involved systemic treatment limited to neoadjuvant or adjuvant phases only.

[c] This case involved initial FOLFIRI for 2 months, one locoregional mitomycin cycle, followed by FOLFIRI re-challenge with added BEV.

From the overall group of 28 MBC cases, 15 underwent therapy at the RD regimen (capecitabine 1650 mg/m² on days 1 through 14 with lurbinectedin 2.2 mg/m² on day 1, repeated every 3 weeks). In this RD subset, patients had a median age of 46 years (spanning 29–71 years). HR-positive tumors accounted for nine cases (60%), whereas triple-negative tumors made up six cases (40%). BRCA results were available for eight individuals, including four with confirmed BRCA1 pathogenic variants. Visceral metastatic spread was universal in these 15 cases, with hepatic lesions in 12 (80%). Prior lines of systemic treatment for metastatic spread numbered a median of one (range 0–3). High rates of earlier use included taxanes in 93%, cyclophosphamide in 87%, and anthracyclines in 80% **(Table 1).** Endocrine-based treatments preceded enrollment in eight cases (53%), comprising tamoxifen in six (40%), letrozole in five (33%), fulvestrant or goserelin in three each (20%), exemestane in two (13%), and anastrozole in one (7%). CDK4/6 inhibitor exposure was absent in the RD cohort. Overall, the combination was given in 248 cycles across dose cohorts (median of 7.5 cycles per case). The RD cohort alone accounted for 108 cycles (median of 7 cycles per case). Achieved median weekly dose intensities at the RD stood at 5810 mg/m² for capecitabine and 0.7 mg/m² for lurbinectedin, translating to median delivered fractions of 75.4% for capecitabine and 91.1% for lurbinectedin versus protocol-planned amounts.

Safety profile

Every MBC case who started treatment could be evaluated for tolerability. Details of drug-related clinical adverse effects and lab anomalies noted across the full dose range and particularly at the RD (capecitabine 1650 mg/m² days 1–14 combined with lurbinectedin 2.2 mg/m² day 1 every 3 weeks) appear in **Table 2**.

Table 2. Drug-related clinical adverse effects (affecting more than 10% of cases or reaching grade 3 or higher) together with hematologic and biochemical lab anomalies in MBC cases treated with the capecitabine–lurbinectedin regimen across all tested doses and specifically at the recommended dose

Category / Event or Abnormality	All Dose Levels (n=28)				RD (n=15)			
	Grade 1-2	Grade 3	Grade 4	Total	Grade 1-2	Grade 3	Grade 4	Total
Biochemical laboratory abnormalities								
CPK increased	21	—	—	21	20	—	—	20
Creatinine increased	96	—	—	96	93	—	—	93
AST increased	71	7	—	79	80	7	—	87
Bilirubin increased	29	—	—	29	40	—	—	40
ALT increased	79	11	—	89	87	7	—	93
AP increased	54	—	—	54	47	—	—	47
Hematological laboratory abnormalities								
Neutropenia	25	32	25	82	27	40	7	73
Anemia	82	11	—	93	80	13	—	93
Thrombocytopenia	64	7	—	71	73	—	—	73
Adverse events								
Diarrhea	46	—	—	46	33	—	—	33
Dyspepsia	43	—	—	43	33	—	—	33
Constipation	18	—	—	18	13	—	—	13
Decreased appetite	39	—	—	39	33	—	—	33
Fatigue	50	7	—	57	40	7	—	47
Headache	11	—	—	11	7	—	—	7
Mucositis	32	—	—	32	33	—	—	33
Myalgia	7	—	—	7	13	—	—	13
Hypertriglyceridemia	—	4	—	4	—	—	—	—
Nausea	71	—	—	71	60	—	—	60
Peripheral sensory neuropathy	21	—	—	21	13	—	—	13
Pulmonary embolism	—	4	—	4	—	—	—	—
Palmar-plantar erythrodysesthesia syndrome	43	—	—	43	33	—	—	33
Paronychia	14	—	—	14	20	—	—	20
Xerosis	11	—	—	11	—	—	—	—
Vomiting	29	—	—	29	20	—	—	20
Weight decreased	7	—	—	7	13	—	—	13
Category / Event or Abnormality	**All Dose Levels (n=28)**				**RD (n=15)**			
	Grade 1-2	Grade 3	Grade 4	Total	Grade 1-2	Grade 3	Grade 4	Total

Biochemical laboratory abnormalities								
CPK increased	21	—	—	21	20	—	—	20
Creatinine increased	96	—	—	96	93	—	—	93
AST increased	71	7	—	79	80	7	—	87
Bilirubin increased	29	—	—	29	40	—	—	40
ALT increased	79	11	—	89	87	7	—	93
AP increased	54	—	—	54	47	—	—	47
Hematological laboratory abnormalities								
Neutropenia	25	32	25	82	27	40	7	73
Anemia	82	11	—	93	80	13	—	93
Thrombocytopenia	64	7	—	71	73	—	—	73
Adverse events								
Diarrhea	46	—	—	46	33	—	—	33
Dyspepsia	43	—	—	43	33	—	—	33
Constipation	18	—	—	18	13	—	—	13
Decreased appetite	39	—	—	39	33	—	—	33
Hypertriglyceridemia	—	4	—	4	—	—	—	—
Mucositis	32	—	—	32	33	—	—	33
Fatigue	50	7	—	57	40	7	—	47
Headache	11	—	—	11	7	—	—	7
Palmar-plantar erythrodysesthesia syndrome	43	—	—	43	33	—	—	33
Paronychia	14	—	—	14	20	—	—	20
Myalgia	7	—	—	7	13	—	—	13
Nausea	71	—	—	71	60	—	—	60
Vomiting	29	—	—	29	20	—	—	20
Weight decreased	7	—	—	7	13	—	—	13
Peripheral sensory neuropathy	21	—	—	21	13	—	—	13
Pulmonary embolism	—	4	—	4	—	—	—	—
Xerosis	11	—	—	11	—	—	—	—

The figures presented represent the percentage of patients affected. Irrespective of their association with the treatment, hematological and biochemical abnormalities are reported.

AP, alkaline phosphatase; ALT, alanine aminotransferase; CPK, creatine phosphokinase; AST, aspartate aminotransferase; RD, recommended dose; D, day; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Safety summary for the recommended dose group

All 15 patients receiving the recommended dose experienced at least one adverse event considered either treatment-related or of undetermined causality. Predominantly, these events were mild or moderate (grade 1/2). Frequently occurring ones included nausea (in 60% of cases), fatigue (47%), and several others at 33% each: reduced appetite, diarrhea, dyspepsia, mucositis, and hand-foot syndrome (palmar-plantar erythrodysesthesia). A single case of severe (grade 3) fatigue affected one patient (7%), representing the only high-grade treatment-linked event. No events escalated to grade 4 severity in relation to treatment.

Among hematological findings: anemia occurred in 93% (grade 3: 13%), neutropenia in 73% (grade 3/4 combined: 47%, without any febrile episodes), and thrombocytopenia in 73%. Common biochemical changes featured elevated creatinine (93%), alanine aminotransferase (93%; grade 3: 7%), aspartate aminotransferase (87%; grade 3: 7%), alkaline phosphatase (47%), and bilirubin (40%). Red blood cell transfusions were administered to one patient (6.7%), but no one needed support with granulocyte colony-stimulating factors. Neither treatment discontinuations due to toxicity nor any deaths linked to the regimen were reported.

Efficacy outcomes

Efficacy evaluation included all 28 patients diagnosed with metastatic breast cancer. Confirmed responses totaled 16 across dose levels, among them one complete response, producing an objective response rate of 57% (95% CI: 37.2–75.5%). Furthermore, prolonged disease stabilization (≥6 months) in two additional cases led to a 6-month clinical benefit rate of 64% (95% CI: 44.1–84.1%) **(Table 3).** Median duration of response stood at 6.8 months (95% CI: 3.4–12.5 months), while median progression-free survival reached 7.3 months (95% CI: 3.9–10.2 months). Evidence of tumor reduction was noted in 23 cases (82%) **(Figure 1a).**

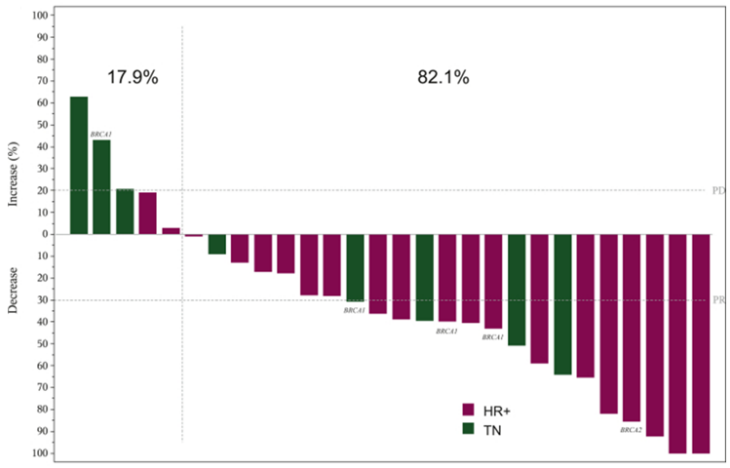
Table 3. Best overall tumor response assessed by RECIST criteria in metastatic breast cancer patients treated with the combination of capecitabine and lurbinectedin.

Parameter	RD: Capecitabine 1650 mg/m² D1–D14 + Lurbinectedin 2.2 mg/m² D1 (n=15)		Capecitabine D1–D14 + Lurbinectedin D1,D8 (All dose levels, n=3)		Capecitabine D1–D14 + Lurbinectedin D1 (All dose levels, n=25)		All patients (All dose levels, n=28)	
	n	%	n	%	n	%	n	%
Stable disease ≥4 months	3	20	—	—	3	12	3	11
Stable disease <4 months	2	13	1	33	4	16	5	18
Median duration of response (months) (95% CI)	6.8 (1.3–NR)		12.5 (—)		6.8 (2.4–12.5)		6.8 (3.4–12.5)	
Median progression-free survival (months) (95% CI)	5.5 (1.1–10.2)		16.9 (1.1–16.9)		7.3 (3.9–10.2)		7.3 (3.9–10.2)	
Complete response (CR)	—	—	—	—	1	4	1	4
Partial response (PR)	7	47	1	33	14	56	15	54
Clinical benefit rate after 4 months* (95% CI)	67% (38.4–88.2%)		33% (0.8–90.6%)		72% (50.6–87.9%)		68% (47.7–84.1%)	
Clinical benefit rate after 6 months (95% CI)**	60% (32.3–83.7%)		33% (0.8–90.6%)		68% (46.5–85.1%)		64% (44.1–84.1%)	
Progressive disease (PD)	3	20	1	33	3	12	4	14
Objective response rate (ORR) (95% CI)	47% (21.3–73.4%)		33% (0.8–90.6%)		60% (38.7–78.9%)		57% (37.2–75.5%)	

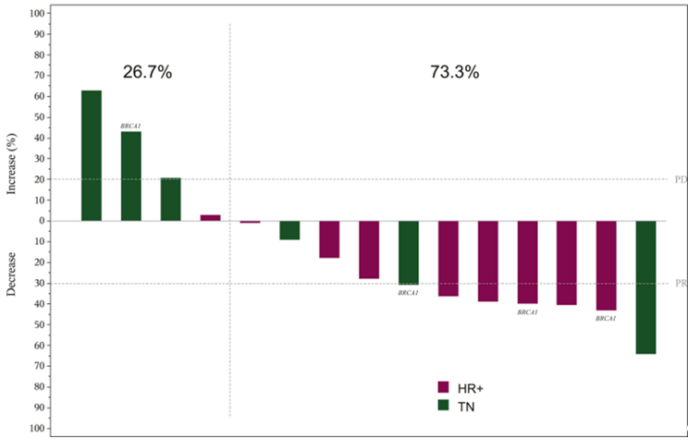
CI, confidence interval; CBR, clinical benefit rate; D, day; DoR, duration of response; CR, complete response; ORR, overall response rate; NR, not reached; PFS, progression-free survival; PD, progressive disease; RD, recommended dose; PR, partial response; SD, stable disease.

[a]Patients with CR + PR + SD ≥4 months.

[b]Patients with CR + PR + SD ≥6 months.



a)



b)

Figure 1. The waterfall plot illustrates the greatest change in target lesion size among patients with metastatic breast cancer who had measurable lesions and underwent at least one follow-up imaging scan during treatment with capecitabine combined with lurbinectedin. Part (a) covers patients across all tested dose levels (n=28), whereas part (b) shows those receiving the recommended dose (RD): capecitabine 1650 mg/m² on days 1–14 plus lurbinectedin 2.2 mg/m² on day 1 (n=15). Individuals with confirmed BRCA mutations are specifically indicated.

Day; HR = hormone receptor; PD = progressive disease; PR = partial response; RD = recommended dose; TN = triple negative.

In the 15 patients treated at the RD (capecitabine 1650 mg/m² days 1–14 and lurbinectedin 2.2 mg/m² day 1, every 3 weeks), there were seven confirmed objective responses and two instances of stable disease lasting at least 6 months. This translated to an objective response rate (ORR) of 47% (95% CI 21.3–73.4%) and a 6-month clinical benefit rate (CBR) of 60% (95% CI 32.3–83.7%) **(Table 3).** The median duration of response was 6.8 months (95% CI 1.3 months–not reached), with median progression-free survival (PFS) reaching 5.5 months (95% CI 1.1–10.2 months). Tumor shrinkage of any degree was achieved in 73% of these patients (11 out of 15); **(Figure 1b).**

Nearly all confirmed responses (12 in total, including one complete response) and both long-term stable diseases occurred in patients whose tumors were hormone receptor (HR)-positive. For this subgroup, the ORR was 60% (95% CI 36.1–80.9%) with a 6-month CBR of 70% (95% CI 45.7–88.1%) when considering all dose levels, and an ORR of 56% (95% CI 21.2–86.3%) with a 6-month CBR of 78% (95% CI 40.0–97.2%) at the RD **(Table 4).** Responses in HR-positive disease proved durable, with median duration of response of 10.9 months (95% CI 2.4 months–not reached) across all doses and 7.0 months (95% CI 1.3 months–not reached) at the RD. Median PFS in this subgroup was 10.2 months both overall (95% CI 3.9–16.9 months) and at the RD (95% CI 2.3–10.2 months). Objective reduction in tumor size was observed in the vast majority of HR-positive cases—90% across all dose levels and 89% at the RD **(Figures 1a and 1b).**

Table 4. Presents the best overall responses by RECIST criteria, stratified by hormone receptor status, for patients with metastatic breast cancer receiving the capecitabine–lurbinectedin combination, both across all dose levels and specifically at the recommended dose.

Outcome	HR-positive all doses (n=20)	HR-positive at RD (n=9)	Triple-negative all doses (n=8)	Triple-negative at RD (n=6)
Stable Disease ≥4 months	3 (15%)	3 (33%)	0 (—)	0 (—)
Stable Disease <4 months	4 (20%)	1 (11%)	1 (13%)	1 (17%)
Complete Response (CR)	1 (5%)	0 (—)	0 (—)	0 (—)
Partial Response (PR)	11 (55%)	5 (56%)	4 (50%)	2 (33%)
Clinical Benefit Rate (CBR) at 4 months* (95% CI)	75% (50.9–91.3%)	89% (51.8–99.7%)	50% (15.7–84.3%)	33% (4.3–77.7%)
Progressive Disease (PD)	1 (5%)	0 (—)	3 (38%)	3 (50%)
Objective Response Rate (ORR) (95% CI)	60% (36.1–80.9%)	56% (21.2–86.3%)	50% (15.7–84.3%)	33% (4.3–77.7%)
Median Progression-Free Survival (PFS) (months, 95% CI)	10.2 (3.9–16.9)	10.2 (2.3–10.2)	3.0 (1.1–8.0)	1.5 (1.1–8.3)
Clinical Benefit Rate (CBR) at 6 months (95% CI)**	70% (45.7–88.1%)	78% (40.0–97.2%)	50% (15.7–84.3%)	33% (4.3–77.7%)
Median Duration of Response (DoR) (months, 95% CI)	10.9 (2.4–NR)	7.0 (1.3–NR)	3.9 (1.6–6.8)	5.6 (4.4–6.8)

CI, confidence interval; SD, stable disease; CBR, clinical benefit rate; D, day; DoR, duration of response; CR, complete response; MBC, metastatic breast cancer; HR, hormone receptor; ORR, overall response rate; NR, not reached; PFS, progression-free survival; PD, progressive disease; RD, recommended dose; PR, partial response.

[a]Patients with CR + PR + SD ≥4 months.

[b]Patients with CR + PR + SD ≥6 months.

Outcomes in triple-negative tumors

In comparison, patients with triple-negative breast cancer experienced four verified responses but no extended periods of disease stabilization [objective response rate (ORR) and clinical benefit rate (CBR) both at 50% (95% CI 15.7%–84.3%) across all dose levels; 33% (95% CI 4.3%–77.7%) at the recommended dose (RD)] **(Table 4).** Time-to-event measures were notably briefer: median duration of response (DoR) reached 3.9 months (95% CI 1.6–6.8 months) overall and 5.6 months (95% CI 4.4–6.8 months) at the RD, while median progression-free survival (PFS) was 3.0 months (95% CI 1.1–8.0 months) across doses and 1.5 months (95% CI 1.1–8.3 months) at the RD. Fewer individuals with triple-negative disease exhibited any degree of tumor reduction: 63% at all dose levels and 50% at the RD **(Figures 1a and b).**

BRCA-mutated subgroup

Among the five patients identified with BRCA mutations, four demonstrated confirmed responses to the capecitabine–lurbinectedin regimen across all doses: three with BRCA1 alterations and one with BRCA2. Notably, all three BRCA1-mutated patients who responded had received treatment at the RD. In total, 80% (4 out of 5) of those with confirmed BRCA1 or BRCA2 mutations achieved partial responses and tumor shrinkage at all dose levels, including 75% (3 out of 4) at the RD **(Figure 1b).**

Comparison to prior therapy

The best responses to capecitabine plus lurbinectedin were evaluated against outcomes from the immediately preceding treatment in the 15 patients dosed at the RD. In total, 40% (6 out of 15) displayed superior anticancer effects with this combination versus their last regimen: 44% (4 out of 9) among those with hormone receptor (HR)-positive tumors and 33% (2 out of 6) in the triple-negative group. Importantly, each of the four HR-positive patients showing enhanced activity had undergone previous chemotherapy for metastatic disease as well as endocrine treatment.

Pharmacokinetics

Pharmacokinetic (PK) profiles were obtained for every one of the 28 metastatic breast cancer patients. At the RD (capecitabine 1650 mg/m² on days 1–14 combined with lurbinectedin 2.2 mg/m² on day 1 every 3 weeks), lurbinectedin exhibited an average half-life of 32.7 hours and an average clearance of 13.5 L/h. Exposure metrics, including the area under the concentration–time curve and peak plasma levels, rose proportionally with increasing doses for lurbinectedin. In contrast, the PK patterns for capecitabine and its breakdown products displayed considerable interpatient variation.

The combination of capecitabine and lurbinectedin exhibited promising anticancer effects in patients with relapsed metastatic breast cancer (MBC). At the recommended dose (RD: capecitabine 1650 mg/m² on days 1–14 plus lurbinectedin 2.2 mg/m² on day 1 every 3 weeks), the objective response rate (ORR) was 47%, with a 6-month clinical benefit rate (CBR) of 60%. Efficacy was substantially stronger in hormone receptor (HR)-positive tumors (ORR 56%; 6-month CBR 78%) than in triple-negative tumors (ORR and CBR both 33%). At the RD, responses were sustained, with a median duration of 7.0 months for HR-positive disease and 5.6 months for triple-negative disease. Overall median progression-free survival (PFS) stood at 5.5 months, reaching 10.2 months in HR-positive cases but only 1.5 months in triple-negative cases.

Despite substantial progress in breast cancer management over the past 20 years, metastatic disease remains incurable, and survival following metastatic diagnosis is limited—typically 4–5 years for HR-positive or HER2-positive subtypes and approximately 1 year for triple-negative subtypes [10]. Key unmet needs in relapsed MBC involve therapeutic options after CDK4/6 inhibitors in HR-positive/HER2-negative disease, following immunotherapy plus chemotherapy in PD-L1-positive cases, and post-PARP inhibitor treatment in BRCA1/2-mutated tumors. First-line metastatic therapy often includes anthracyclines or taxanes, while capecitabine is commonly chosen upon progression. Previous trials of single-agent capecitabine in relapsed MBC (without selection by HR status) have shown ORRs of 12%–29% and median PFS of 3.1–4.9 months [11-16], improving to ORRs of 35%–43% and median PFS of 5.8–6.2 months when paired with agents such as docetaxel or ixabepilone [14, 15, 17]. The ORR achieved here with capecitabine plus lurbinectedin at the RD therefore represents the upper boundary of rates seen with other capecitabine-based regimens in relapsed MBC across HR subtypes. Notably, 75% of patients with confirmed BRCA mutations who received the RD demonstrated objective responses or tumor reduction. In addition, 40% of patients treated at the RD experienced longer PFS with this combination compared to their immediately preceding regimen.

The tolerability of capecitabine combined with lurbinectedin was predictable and controllable. Myelosuppression occurred frequently at the RD but was transient and reversible. Non-blood-related adverse effects were predominantly mild to moderate, with the most common being fatigue, gastrointestinal issues (nausea, diarrhea, dyspepsia), reduced appetite, and hand-foot syndrome. Predictably, rates of severe neutropenia and many of these non-hematologic events at the RD exceeded those observed with monotherapy at approved doses—lurbinectedin 3.2 mg/m² day 1 every 3 weeks [18, 19] or capecitabine 2500 mg/m² days 1–14 every 3 weeks [11, 20, 21]. The increased incidence of diarrhea, mucositis, anorexia, and hand-foot syndrome relative to lurbinectedin alone is likely attributable to capecitabine, as these are well-recognized with capecitabine monotherapy. Pairing capecitabine with other anticancer agents has previously been linked to greater rates of severe gastrointestinal toxicity and severe hand-foot syndrome compared to the partner drug alone [22]. However, in this study, all reported gastrointestinal events and hand-foot syndrome cases at the RD were only mild or moderate in severity. Importantly, certain skin-related toxicities typical of taxanes, such as hair loss or nail changes [23], were absent at this RD. Furthermore, no treatment-related deaths or withdrawals due to adverse events occurred at the RD, reinforcing an acceptable safety profile.

Pharmacokinetic (PK) characteristics of lurbinectedin in this trial closely matched those previously documented for the agent alone [6]. Plasma concentration-time curves for capecitabine and its metabolites displayed marked interpatient variability. A population PK model derived from these data showed comparable absorption rates, but reduced volume of distribution for capecitabine and lower clearance for metabolites relative to models from other phase I studies [9]. Exposure to capecitabine and its metabolites was roughly 2- to 3-fold higher, with a shorter time to peak concentration for capecitabine, than values reported in other sources [24]. No correlation was identified between lurbinectedin dose/exposure and levels of capecitabine or its metabolites, indicating absence of pharmacokinetic drug-drug interactions.

Conclusion

In conclusion, the regimen of oral capecitabine administered daily on days 1–14 together with intravenous lurbinectedin on day 1 every 3 weeks demonstrated a tolerable safety profile alongside encouraging efficacy in relapsed MBC, particularly in HR-positive patients. These findings warrant additional investigation of this combination in this patient population.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Cuevas C, Perez M, Martin MJ, et al. Synthesis of ecteinascidin ET-743 and phthalascidin Pt-650 from cyanosafracin B. Org Lett. 2000;2:2545–8. doi:10.1021/ol0062502
2. Bueren-Calabuig JA, Giraudon C, Galmarini CM, Egly JM, Gago F. Temperature-induced melting of double-stranded DNA in the absence and presence of covalently bonded antitumour drugs: insight from molecular dynamics simulations. Nucleic Acids Res. 2011;39:8248–57. doi:10.1093/nar/gkr512
3. Harlow ML, Maloney N, Roland J, et al. Lurbinectedin inactivates the Ewing sarcoma oncoprotein EWS-FLI1 by redistributing it within the nucleus. Cancer Res. 2016;76:6657–68. doi:10.1158/0008-5472.CAN-16-0568
4. Santamaria Nunez G, Robles CM, Giraudon C, et al. Lurbinectedin specifically triggers the degradation of phosphorylated RNA polymerase II and the formation of DNA breaks in cancer cells. Mol Cancer Ther. 2016;15:1–14. doi:10.1158/1535-7163.MCT-16-0172
5. Leal JF, Martinez-Diez M, Garcia-Hernandez V, et al. PM01183, a new DNA minor groove covalent binder with potent in vitro and in vivo anti-tumour activity. Br J Pharmacol. 2010;161:1099–110. doi:10.1111/j.1476-5381.2010.00945.x
6. Elez ME, Tabernero J, Geary D, et al. First-in-human phase I study of lurbinectedin (PM01183) in patients with advanced solid tumors. Clin Cancer Res. 2014;20:2205–14. doi:10.1158/1078-0432.CCR-13-1880
7. Jimeno A, Sharma MR, Szyldergemajn S, et al. Phase I study of lurbinectedin, a synthetic tetrahydroisoquinoline that inhibits activated transcription, induces DNA single- and double-strand breaks, on a weekly × 2 every-3-week schedule. Invest New Drugs. 2017;35:471–7. doi:10.1007/s10637-017-0427-2
8. Aviles P, Guillen MJ, Galmarini C, et al. Synergism of lurbinectedin (PM01183) combined with 5-fluorouracil (5-FU): in vitro and in vivo studies. Cancer Res. 2013;73:Abstract 5498
9. Urien S, Rezai K, Lokiec F. Pharmacokinetic modelling of 5-FU production from capecitabine – a population study in 40 adult patients with metastatic cancer. J Pharmacokinet Pharmacodyn. 2005;32:817–33. doi:10.1007/s10928-005-0018-2
10. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321:288–300. doi:10.1001/jama.2018.19323
11. Blum JL, Jones SE, Buzdar AU, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol. 1999;17:485–93. doi:10.1200/JCO.1999.17.2.485
12. Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer. 2004;40:536–42. doi:10.1016/j.ejca.2003.11.007
13. Pallis AG, Boukovinas I, Ardavanis A, et al. A multicenter randomized phase III trial of vinorelbine/gemcitabine doublet versus capecitabine monotherapy in anthracycline- and taxane-pretreated women with metastatic breast cancer. Ann Oncol. 2012;23:1164–9. doi:10.1093/annonc/mdr405
14. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol. 2007;25:5210–17. doi:10.1200/JCO.2007.12.6557

15. Sparano JA, Vrdoljak E, Rixe O, et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2010;28:3256–63. doi:10.1200/JCO.2009.24.4244
16. Kaufman PA, Awada A, Twelves C, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015;33:594–601. doi:10.1200/JCO.2013.52.4892
17. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002;20:2812–23. doi:10.1200/JCO.2002.09.002
18. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol. 2020;21:645–54. doi:10.1016/S1470-2045(20)30068-1
19. Gaillard S, Oaknin A, Ray-Coquard I, et al. Lurbinectedin versus pegylated liposomal doxorubicin or topotecan in patients with platinum-resistant ovarian cancer: a multicenter, randomized, controlled, open-label phase 3 study (CORAIL). Gynecol Oncol. 2021;163:237–45. doi:10.1016/j.ygyno.2021.08.032
20. Van Cutsem E, Findlay M, Osterwalder B, et al. Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer: results of a randomized phase II study. J Clin Oncol. 2000;18:1337–45. doi:10.1200/JCO.2000.18.6.1337
21. Nishijima TF, Suzuki M, Muss HB. A comparison of toxicity profiles between the lower and standard dose capecitabine in breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2016;156:227–36. doi:10.1007/s10549-016-3756-5
22. Wang Y, Yang H, Wei JF, Meng L. Efficacy and toxicity of capecitabine-based chemotherapy in patients with metastatic or advanced breast cancer: results from ten randomized trials. Curr Med Res Opin. 2012;28:1911–19. doi:10.1185/03007995.2012.748655
23. Marks DH, Qureshi A, Friedman A. Evaluation of prevention interventions for taxane-induced dermatologic adverse events: a systematic review. JAMA Dermatol. 2018;154:1465–72. doi:10.1001/jamadermatol.2018.3465
24. Reigner B, Blesch K, Weidekamm E. Clinical pharmacokinetics of capecitabine. Clin Pharmacokinet. 2001;40:85–104. doi:10.2165/00003088-200140020-00002