The Oncologist®

Clinical Trial Results

A Multicenter Randomized Three-Arm Phase II Study of (1) Everolimus, (2) Estrogen Deprivation Therapy (EDT) with Leuprolide + Letrozole, and (3) Everolimus + EDT in Patients with Unresectable Fibrolamellar Carcinoma

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT01642186
- **Sponsor:** Memorial Sloan Kettering Cancer Center
- **Principal Investigator:** Ghassan K. Abou-Alfa
- **IRB Approved:** Yes

Lessons Learned

- FLC is a complex cancer with many implicated oncogenic pathways. Single or dual targeting does not appear to alter the natural history of the cancer, and novel therapeutics are needed.
- Estrogen deprivation therapy with letrozole and leuprolide, alone or in combination with the mTOR inhibitor, everolimus, did not demonstrate clinical activity in advanced fibrolamellar carcinoma.
- The study drugs were well tolerated when administered as single agents or in combination in this patient population.
- This study demonstrates that, despite the rarity of FLC, multicenter therapeutic clinical trials are feasible and support the value of this consortium.

Abstract

Background. Fibrolamellar carcinoma (FLC) is an uncommon malignancy in young people and is sometimes associated with pregnancy and oral contraceptive use. Immunohistochemical staining and genetic profiling of FLC tumor specimens have revealed aromatase overexpression. The overexpression of mTOR and S6 kinase has been noted in 25% of FLC. On the basis of interaction between estrogen and the PI3K/Akt/mTOR pathway, we hypothesized that suppression of estrogen and mTOR signaling could have antineoplastic activity in FLC.

Methods. Patients were randomized to arm A (everolimus), arm B (letrozole/leuprolide; estrogen deprivation therapy [EDT]), or arm C (everolimus/letrozole/leuprolide). Upon disease progression, patients in arm A or B could proceed to part 2 (everolimus/letrozole/leuprolide). The primary endpoint was progression-free survival (PFS) at 6 months (PFS6) assessed using a Simon's minimax two-stage design, hypothesizing an improvement in PFS6 from 40% to 64% with the study regimen.

Results. Twenty-eight patients were enrolled. An unplanned analysis was performed because of perceived concern for lack of efficacy. Stable disease was observed in 9 of 26 evaluable patients (35%). PFS6 was 0%. Median overall survival (OS) was 12.4 months (95% confidence interval [CI], 7.4–20.9) for the whole study cohort. Grade 3 adverse events in ≥10% of patients were nausea (11%), vomiting (11%), anemia (11%), elevated aspartate transaminase (AST; 32%), alanine transaminase (ALT; 36%), and alkaline phosphatase (14%). All 28 patients experienced an event for PFS outcome, and four deaths were due to disease progression.

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Table 1. Outcomes by study cohort

Outcome	Arm A (*n* = 9)	Arm B (*n* = 8)	Arm C (*n* = 9)	Part 2 (*n* = 15)
PFS, months	2.6 (0.9–5.5)	2.7 (1.7–5.2)	2.4 (1.0–2.9)	2.7 (1.8–4.4)
OS, months	12.5 (2.7–41.9)	14.0 (3.2–22.4)	10.6 (2.3–5.5)	NE[a]
SD, %	55	37	11	NE[a]

[a]Endpoint was PFS only for part 2 (calculated from time of switch).
Abbreviations: NE, not evaluable; OS, overall survival; PFS, progression-free survival; SD, stable disease.

Conclusion. Neither EDT nor mTOR inhibition improved outcomes in FLC. Other treatment strategies are needed. ***The Oncologist*** 2020;25:925–e1603

Discussion

FLC is a rare primary liver malignancy affecting adolescents and young adults and occurs in the absence of underlying chronic liver disease [1].

Estrogen and mTOR pathway signaling have been described in FLC. Several clinical series have reported expression of mTOR and its downstream kinase in FLC [2]. Recently, a case report described clinical and radiologic response in a patient with FLC treated with everolimus [3]. Expression of aromatase in FLC and cases of estrogenic phenotype have been reported [4, 5]. Herein, we conducted a multicenter randomized phase II clinical trial to evaluate the role of antiestrogen therapy with or without mTOR inhibition in patients with advanced FLC.

We hypothesized an improvement in PFS6 from a presumed historical estimate of 40% [6] to 64% for any study arm independently. Secondary endpoints included OS, response rate by RECIST version 1.1, and safety. Twenty-eight patients were screened and enrolled. Twenty-six patients were evaluable for response. All patients were evaluable for safety endpoints.

In view of concern for lack of clinical activity an unplanned interim analysis was undertaken. No patient was free of progression at 6 months, and the low probability of extending PFS6 by adding more participants led to the study being halted. Median OS for the entire study population was 12.4 months (7.4–20.9 months), and median PFS was 2.7 months (1.9–2.7 months). There was no difference in median OS or PFS among study cohorts. Of 18 patients randomized to arms A and B, 15 patients subsequently received the combination (EDT and everolimus) on part 2 of the study. Median PFS was 2.7 months (range, 1.8–4.4 months). The response was stable disease at 35%. There were no complete or partial responses reported. The most common adverse events were nausea (11%), vomiting (11%), anemia (11%), elevated AST (32%), ALT (36%), and alkaline phosphatase (14%). No grade 5 adverse events were attributed to study drugs.

Estrogen deprivation therapy and mTOR inhibition did not improve outcomes in FLC.

Trial Information	
Disease	Advanced cancer/solid tumor only
Disease	Fibrolamellar carcinoma
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	No designated number of regimens
Type of Study	Phase II, randomized
Primary Endpoint	Progression-free survival at 6 months
Secondary Endpoints	Overall response rate, safety, overall survival, progression-free survival
Additional Details of Endpoints or Study Design	
The primary endpoint PFS6 was to be assessed using a Simon's minimax two-stage design, hypothesizing an improvement in PFS6 from 40% to 64% with the study regimen. Sixteen patients were to be enrolled onto each of arms A, B, and C for a total of 48 patients in the first stage. If six or fewer patients in one arm were progression free at 6 months, this arm would be terminated. If seven or more patients were alive and progression-free at 6 months, enrollment would be extended in that arm to 28 patients (maximum total of 84 patients). At the end of stage 2, the regimens were to be considered promising if 15 or more of the 28 patients in each arm were alive and progression free at 6 months. Type I and type II error were both set to 10%.	
Investigator's Analysis	Inactive because results did not meet primary endpoint

Drug Information	
Arm A	
Generic/Working Name	Everolimus
Drug Type	Small molecule
Drug Class	AKT
Dose	7.5 milligrams (mg) per flat dose
Route	Oral (p.o.)
Arm B	
Generic/Working Name	Letrozole and leuprolide
Drug Class	Estrogen receptor
Dose	Letrozole 2.5 mg + leuprolide 7.5 mg milligrams (mg) per flat dose
Route	Oral (p.o.)
Arm C	
Generic/Working Name: Drug 1	Everolimus
Drug Type	Small molecule
Drug Class	AKT
Dose	7.5 milligrams (mg) per flat dose
Route	Oral (p.o.)
Generic/Working Name: Drug 2	Letrozole and leuprolide
Drug Type	Small molecule
Drug Class	Estrogen receptor
Dose	Letrozole 2.5 mg + leuprolide 7.5 mg per flat dose
Route	Oral (p.o.)

Drug Information for Part 2	
Drug 1	
Generic/Working Name	Everolimus
Drug Type	Small molecule
Drug Class	AKT
Dose	7.5 mg milligrams (mg) per flat dose
Route	Oral (p.o.)
Drug 2	
Generic/Working Name	Letrozole and leuprolide
Dose	Letrozole 2.5 mg + leuprolide 7.5 mg milligrams (mg) per flat dose
Route	Oral (p.o.)

Patient Characteristics: All Arms	
Number of Patients, Male	14
Number of Patients, Female	14
Age	Median (range): 22 (14–41)
Performance Status: ECOG	0 — 8 1 — 20 2 — 3 — Unknown —
Cancer Types or Histologic Subtypes	Fibrolamellar carcinoma

Patient Characteristics: Arm A	
Number of Patients, Male	5
Number of Patients, Female	4
Patient Characteristics: Arm B	
Number of Patients, Male	4
Number of Patients, Female	5
Patient Characteristics: Arm C	
Number of Patients, Male	5
Number of Patients, Female	5
Patient Characteristics for Part 2	
Number of Patients, Male	9
Number of Patients, Female	6

Primary Assessment Method	
Title	All Arms Parts 1 and 2
Number of Patients Screened	28
Number of Patients Enrolled	28
Number of Patients Evaluable for Toxicity	28
Number of Patients Evaluated for Efficacy	26
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 0 (0%)
Response Assessment SD	*n* = 9 (35%)
Response Assessment PD	*n* = 17 (65%)
(Median) Duration Assessments PFS	2.7 months; CI, 1.9–2.7
(Median) Duration Assessments OS	12.5 months; CI, 7.4–20.9

Adverse Events: Treatment Related

All Cycles Name	NC/ NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
Alanine aminotransferase increased	0	55	27	18	0	0	100
Aspartate aminotransferase increased	0	70	20	10	0	0	100
Alkaline phosphatase increased	0	86	14	0	0	0	100
Anemia	0	57	29	14	0	0	100
Cholesterol high	0	100	0	0	0	0	100
Fatigue	0	78	11	11	0	0	100
Mucositis oral	0	100	0	0	0	0	100
Nausea	0	75	0	25	0	0	100
Platelet count decreased	0	100	0	0	0	0	100
Vomiting	0	67	0	33	0	0	100
White blood cell decreased	0	100	0	0	0	0	100
Hypertriglyceridemia	0	100	0	0	0	0	100
Hypoalbuminemia	0	80	20	0	0	0	100
Hypoglycemia	0	100	0	0	0	0	100
Hyperglycemia	0	90	10	0	0	0	100
Hyponatremia	0	100	0	0	0	0	100

Abbreviation: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion	
Completion	Study terminated before completion
Investigator's Assessment	Inactive because results did not meet primary endpoint

Fibrolamellar carcinoma (FLC) is an exceedingly rare form of primary liver cancer, with only a few hundred cases having been identified during the past two decades in the U.S., based on Surveillance, Epidemiology, and End Results database analysis [7]. The median age at diagnosis is around 22 years, and more than 50% of patients have metastatic disease at presentation [8]. Although surgical resection offers the possibility of long-term disease control and prolonged survival for some patients with FLC, there are no effective systemic therapies for patients with unresectable or metastatic disease who have a median survival of 12 months or less [9]. Clinical experience with cytotoxic chemotherapy has been disappointing in FLC [6]. Anecdotal reports of FLC with prolonged complete response and another case of successful downstaging with gemcitabine and oxaliplatin leading to surgical resection have been reported [10, 11]. Similarly, limited reports of response to 5-fluorouracil (5-FU) and interferon (IFN) showed some degree of success. A phase II study of 3-week continuous 5-FU infusion and subcutaneous injections of IFN reported radiologic response and median overall survival (OS) of 23.1 months [12] but was limited by a small patient sample size, inclusion of patients with both hepatocellular carcinoma (n = 34) and FLC (n = 9), and frequent treatment toxicities. The paucity of patients with this disease [1] has made it extremely challenging to conduct clinical trials exclusively in FLC.

Recently, a fusion transcript in FLC, resulting from a deletion on chromosome 19 and a break between exon 1 of *DNAJB1* and exon 2 of *PRKACA* genes, has stimulated additional studies in this disease [13]. Several efforts to understand the fusion transcript were performed, suggesting a role for the molecular aberrancy in the carcinogenesis of FLC [14, 15].

Until this latest advance, the pathogenesis of FLC was largely unknown, although several potential drivers have been previously described [16–18]. FLC tumor overexpression of aromatase, in association with a hyperestrogenic clinical phenotype and PI3K/Akt/mTOR pathway signaling, have been reported by both immunohistochemistry and gene expression profiling [18]. Case reports have described young male patients who presented with elevated serum estrogen levels and gynecomastia that subsequently regressed following tumor resection [4, 5]. Among women, FLC has been associated with pregnancy and oral contraceptive use [19, 20]. In a small series examining mTOR activity in primary liver tumors including 13 FLC specimens, approximately 25% of FLC tumors exhibited overexpression of total and phosphorylated mTOR [2]. Another series examined the gene expression profile of two primary and two metastatic FLC tumors, showing that the PI3K signaling cascade was found to be consistently upregulated in both primary and metastatic lesions. The clinical relevance of these findings is unclear, and it is unknown whether positive immunohistochemical staining for mTOR activity translates into sensitivity to therapeutic mTOR inhibition. The estrogen receptor and PI3K/Akt/mTOR pathways cross-communicate, with the former capable of activating the latter [21]. In breast cancer, selective downregulation of the PI3K/Akt/mTOR pathway is one of several mechanisms by which antiestrogens exert an antitumor effect [22].

Based on these data, we conducted this multicenter, randomized, open-label, phase II study of estrogen deprivation therapy [EDT]) and mTOR inhibition, alone or in combination with EDT, in patients with unresectable or metastatic FLC. In the first part, patients were randomized to one of three arms: arm A (everolimus 7.5 mg), arm B (EDT: letrozole 2.5 mg + leuprolide 7.5 mg), or arm C (everolimus + EDT). Upon disease progression, patients initially randomized to arm A or B could proceed to part 2 of the study in which they would receive the combination therapy of everolimus and EDT.

An unplanned analysis was conducted 28 months after the start of enrollment because of perceived concern regarding lack of efficacy. With a median follow-up period among survivors (n = 3) of 30.6 months (range, 20.3–32), no patient was progression free at 6 months, the primary endpoint of the study. Median progression-free survival (PFS) for the whole study cohort was 2.8 months (1.9–2.7), and the median OS was 12.5 months (7.4–20.9). There was no difference in median OS or PFS among the three study cohorts. The best response as determined by RECIST version 1.1 was stable disease at 55%, 37%, and 11%, on arms A, B, and C, respectively. There were no partial or complete responses.

Our study did not demonstrate any signal of efficacy for inhibition of estrogen and or mTOR pathway signaling. There was no difference in outcome between single or dual pathway blockade. Tissue and serum biomarkers were collected for clinical correlation and will be reported separately. Examining these data might provide some additional insights into the clinical signal observed.

Since the completion of this study, several compounds have been evaluated in FLC [23]; however, no significant improvement in outcomes has been observed. The most recent breakthrough in FLC was the discovery of the universal *DNAJB1-PRKACA* fusion transcript [13, 14]. This fusion is currently an area of active therapeutic research. Targeting *AURKA* was evaluated in a recent study evaluating ENMD-2076 with selective activities against Aurora kinases (ClinicalTrials.gov identifier NCT02234986). Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, was evaluated as single agent in patients with FLC in an open-label, multinational, phase II study (ClinicalTrials.gov identifier NCT01953926), which was recently discontinued in view of lack of efficacy. Current efforts are directed toward exploring efficacy of addressing different oncologic targets resulting from the chimeric transcript of the fusion protein that retains kinase activity. Other ongoing studies are evaluating checkpoint inhibitors as a single agent or in combination with other targeted therapies [24]. Chimeric antigen receptor–engineered T-cell therapy is starting to be evaluated in primary liver cancer and might be explored in FLC soon. As a very rare cancer and an area of unmet need, FLC

needs a multidisciplinary and collaborative approach to improve outcomes.

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Disclosures

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(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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Tables and Figures

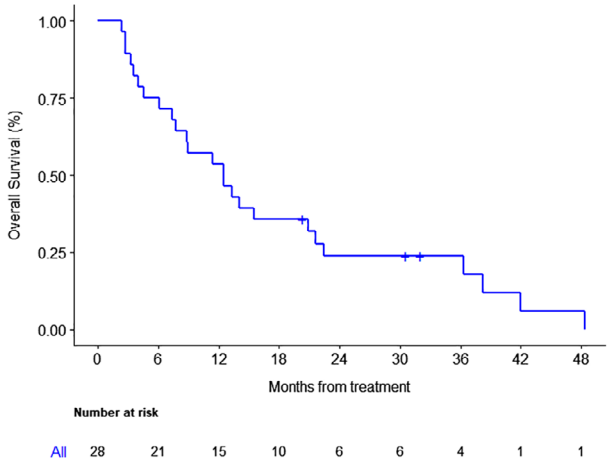

Figure 1. Overall survival for all study arms.

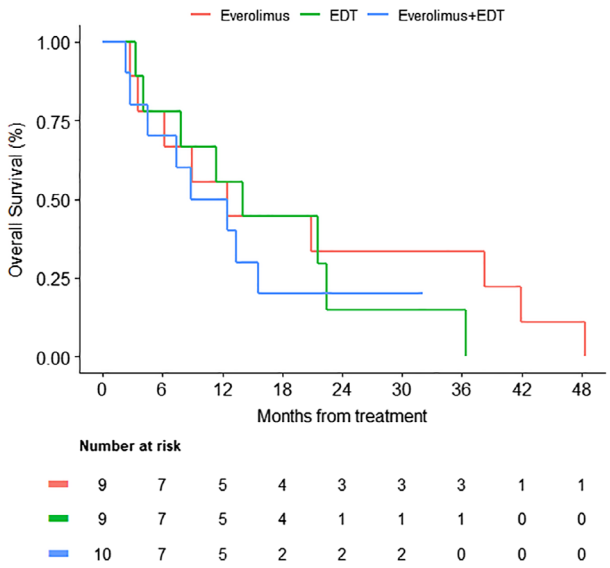

Figure 2. Overall survival by each study arm.
Abbreviation: EDT, estrogen deprivation therapy.

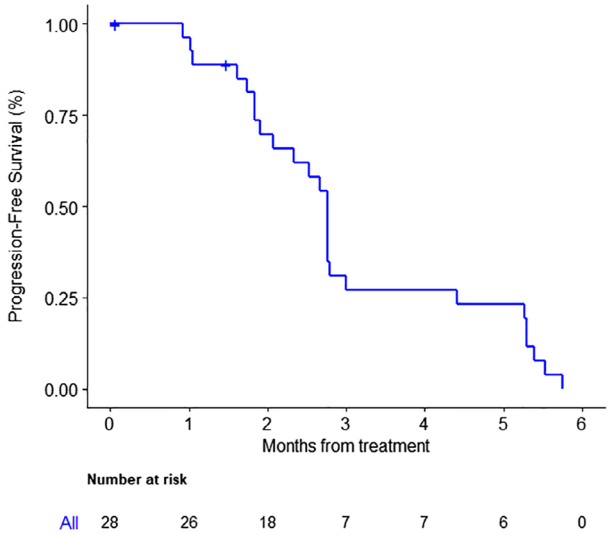

Figure 3. Progression-free survival for all study arms.

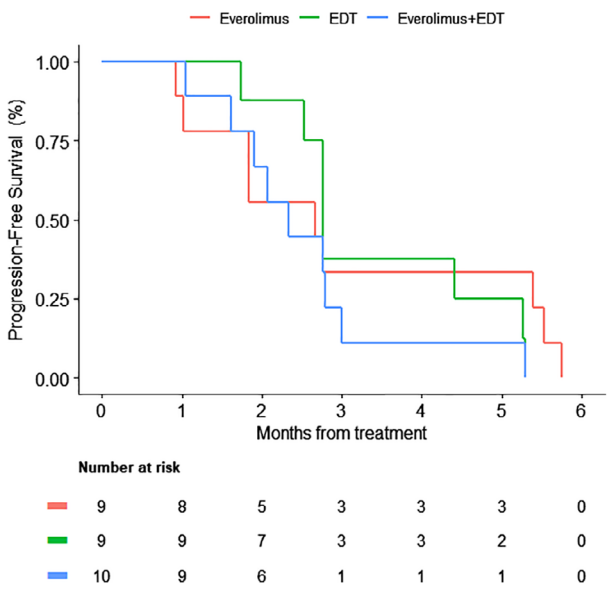

Figure 4. Progression-free survival by each study arm.
Abbreviation: EDT, estrogen deprivation therapy.

Table 2. Patient demographics

Characteristic	Part 1, *n*				Part 2, *n*
	All patients (*n* = 28)	Everolimus (*n* = 9)	EDT (*n* = 9)	Everolimus + EDT (*n* = 10)	Everolimus + EDT (*n* = 15)
Age, median (range)	22 (14–41)	22 (18–41)	24 (14–31)	23 (15–39)	22 (14–41)
Gender					
Male	14	5	4	5	9
Female	14	4	5	5	6
Race					
White	23	8	8	7	13
Black	2	1	0	2	0
Asian	2	0	1	0	2
Other	1	0	0	1	0
ECOG					
0	8	2	2	4	4
1	20	7	7	6	11

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EDT, estrogen deprivation therapy.

Table 3. Adverse events

Toxicity	Part 1, *n* (%)					Part 2, *n* (%)	
	Everolimus (*n* = 9) Any grade	EDT (*n* = 9) Any grade	Everolimus + EDT (*n* = 10) Any grade	Total (*n* = 28) Any grade	Total (*n* = 28) Grade > 3	Everolimus + EDT (*n* = 15) Any grade	Everolimus + EDT (*n* = 15) Grade > 3
Patients with any TRAE	9 (100)	9 (100)	9 (90)	27 (96)	12 (43)	11 (73)	4 (27)
ALT increased	7 (78)	7 (78)	8 (80)	23 (82)	7 (25)	10 (67)	3 (20)
Alkaline phosphatase increased	7 (78)	8 (89)	9 (90)	22 (79)	1 (4)	7 (47)	3 (20)
Anemia	4 (44)	8(89)	8 (80)	22 (79)	2 (7)	8 (53)	2 (13)
AST increased	8 (89)	8 (89)	8 (80)	23 (82)	6 (21)	11 (73)	3 (20)
Blood bilirubin increased	0 (0)	3 (33)	3 (30)	8 (29)	1 (4)	3 (20)	1 (7)
Cholesterol high	5 (56)	3 (33)	3 (30)	13 (46)	0 (0)	7 (47)	0 (0)
Epistaxis	0 (0)	1 (11)	2 (20)	3 (11)	0 (0)	2 (13)	0 (0)
Fatigue	8 (89)	8 (89)	6 (60)	22 (79)	2 (7)	10 (67)	0 (0)
Lipase increased	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	1 (7)	1 (7)
Mucositis oral	3 (33)	1 (11)	3 (30)	7 (25)	0 (0)	2 (13)	0 (0)
Nausea	3 (33)	4 (44)	5 (50)	12 (43)	3 (11)	3 (20)	0 (0)
Neutrophil count decreased	0 (0)	1 (11)	3 (30)	6 (21)	0 (0)	2 (13)	0 (0)
Platelet count decreased	3 (33)	2 (22)	6 (60)	10 (36)	0 (0)	4 (27)	0 (0)
Vomiting	3 (33)	5 (56)	4 (40)	11 (39)	3 (11)	3 (20)	1 (7)
White blood cell decreased	3 (33)	3 (33)	7 (70)	13 (46)	0 (0)	3 (20)	0 (0)
Hypertriglyceridemia	6 (67)	3 (33)	4 (40)	14 (50)	0 (0)	6 (40)	0 (0)
Hypoalbuminemia	4 (44)	5 (56)	8 (80)	19 (68)	0 (0)	6 (40)	0 (0)
Hypoglycemia	1 (11)	1 (11)	0 (0)	2 (7)	0 (0)	0 (0)	0 (0)
Hyperglycemia	9 (100)	6 (67)	9 (90)	23 (82)	0 (0)	9 (60)	0 (0)
Hyponatremia	3 (33)	4 (44)	5 (50)	12 (43)	0 (0)	3 (20)	0 (0)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; EDT, estrogen deprivation therapy; TRAE, treatment-related adverse event.