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Clinical Trial Results

A Phase II Trial of Selinexor (KPT-330) for Metastatic Triple-Negative Breast Cancer

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT02402764
- **Sponsor:** Karyopharm
- **Principal Investigator:** Hyo S. Han
- **IRB Approved:** Yes

Lessons Learned

- Single-agent selinexor has limited activity in heavily pretreated patients with metastatic triple-negative breast cancer.
- Selinexor 60 mg by mouth twice weekly was generally well tolerated with a side-effect profile consistent with previous clinical trials.
- Future studies of selinexor in this population should focus on combination approaches and a biomarker-driven strategy to identify patients most likely to benefit.

Abstract

Background. This phase II trial evaluated the safety, pharmacodynamics, and efficacy of selinexor (KPT-330), an oral selective inhibitor of nuclear export (SINE) in patients with advanced triple-negative breast cancer (TNBC).

Methods. This phase II trial was designed to enroll 30 patients with metastatic TNBC. Selinexor was given at 60 mg orally twice weekly on days 1 and 3 of each week, three of each 4-week cycle. The primary objective of this study was to determine the clinical benefit rate (CBR), defined as complete response + partial response + stable disease (SD) ≥12 weeks.

Results. Ten patients with a median age of 60 years (range 44–71 years) were enrolled between July 2015 and January 2016. The median number of prior chemotherapy lines was 2 (range 1–5). A planned interim analysis for the first stage per protocol was performed. Three patients had SD and seven had progressive disease. On the basis of these results and predefined stoppage rules, the study was halted.

Conclusion. Selinexor was fairly well tolerated in patients with advanced TNBC but did not result in objective responses. However, clinical benefit rate was 30%, and further investigation of selinexor in this patient population should focus on combination therapies. ***The Oncologist*** 2019;24:887–e416

Discussion

Selinexor (KPT-330) is an oral SINE targeting Exportin 1 (XPO1). XPO1 functions as a nuclear exporter of major tumor suppressor proteins (TSPs), including p53, p21, BRCA1, BRCA2, and retinoblastoma protein [1]. TSPs require nuclear localization to regulate cell cycle progression and trigger apoptosis. XPO1 is overexpressed in many cancer cells, including TNBC, and can bypass normal TSP function. By binding to XPO1, selinexor prevents nuclear export of XPO1 cargo proteins [1]. Although not directly cytotoxic, treatment with selinexor retains tumor suppressor proteins in the nucleus where they can carry out their normal functions. Increased XPO1 mRNA production is a compensatory mechanism for selinexor-induced loss of XPO1 function, and comparison of XPO1 mRNA levels predose and after administration of selinexor is a validated pharmacodynamic marker of appropriate drug engagement and inhibition of the target. Selinexor has single-agent activity in diffuse large B-cell lymphoma, multiple myeloma, and acute myeloid leukemia [2–5]. It is currently under priority review for refractory multiple myeloma.

This study investigated the clinical benefit rate of selinexor in heavily pretreated patients with metastatic TNBC. Among

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the first 10 patients who were enrolled, we did not observe any objective responses; therefore, the study was terminated early for lack of efficacy per preplanned interim analysis. Three patients had a best response of stable disease, with two of the three patients having stable disease for ≥3 treatment cycles; however, this was not sufficient to warrant continuation of the study. The median PFS was 0.92 months (95% confidence interval [CI]: 0.62–3.58 months). The median overall survival (OS) was 5.98 months (95% CI: 1.68–10.39 months). Furthermore, we did not observe a correlation between XPO1 mRNA induction after treatment or p53 mutational status in patients who experienced clinical benefit.

The side-effect profile is consistent with that observed in the first-in-class, first-in-human study of selinexor in solid tumors, including nausea, fatigue, anorexia, and vomiting as the most common treatment-related adverse events. Complete details of adverse events are available online. Thrombocytopenia was the most common hematologic toxicity; however, only one patient experienced grade ≥3 thrombocytopenia while on study. Although constitutional adverse events led to dose reductions in three patients in this study, there were no discontinuations due to selinexor treatment. In addition, there were no grade 4 or 5 adverse events observed in this study population.

Despite early termination of this trial for lack of efficacy as a single agent, interest remains in developing a niche for selinexor as a combination therapy in TNBC. A phase Ib clinical trial investigating the safety of combination selinexor and olaparib in patients with advanced solid tumors is currently ongoing (NCT02419495). Given the recent approval of olaparib for patients with metastatic breast cancer harboring *BRCA1* or *BRCA2* mutations, such a combination is intriguing [6].

Trial Information	
Disease	Breast cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	No designated number of regimens
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Clinical benefit rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival
Secondary Endpoint	Overall response rate
Secondary Endpoint	Safety
Secondary Endpoint	Tolerability
Additional Details of Endpoints or Study Design	This study used a Simon two-stage design to test the null hypothesis of the CBR P = 5% versus the alternative P = 20%. Up to 30 patients could potentially be accrued during this trial with 10 patients for stage I and 20 patients for stage II. The alpha level of the design was set at 0.05 and the statistical power at 0.8. If one or more patients achieved objective response (complete or partial response) in the first 10 eligible patients (stage I), another 20 patients would be enrolled in stage II. If three or fewer clinical benefits are observed by the end of stage II, then no further investigation of the regimen is warranted. Therefore, under this design, there would be an 80% chance of detecting a tumor response rate of at least 20%. An objective response rate of 5% or less would lead to the conclusion that the regimen lacks antitumor activity at a .05 significance level in this design. Given that the "true" response probability was equal to or less than 5%, there was a 59.9% probability of ending the trial during stage I.
Investigator's Analysis	Level of activity did not meet planned endpoint

Drug Information	
Drug 1	
Generic/Working Name	Selinexor
Drug Type	Small molecule
Drug Class	SINE
Dose	60 mg per flat dose
Route	p.o.
Schedule of Administration	Two times weekly

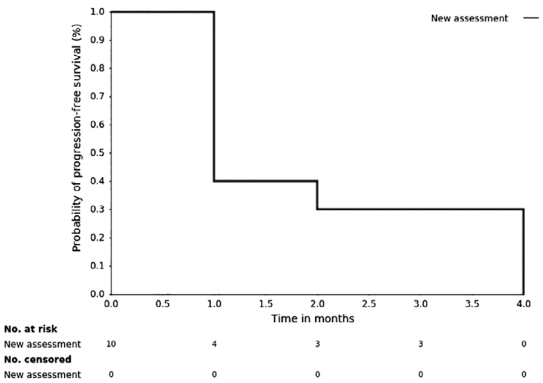
Patient Characteristics	
Number of Patients, Female	10
Stage	4
Age	Median (range): 61 (44–71)
Number of Prior Systemic Therapies	Median (range): 2 (1–5)

Performance Status: ECOG	0 — 7 1 — 3 2 — 0 3 — 0 Unknown — 0
Cancer Types or Histologic Subtypes	Triple-negative breast cancer, 10

Primary Assessment Method	
Number of Patients Screened	13
Number of Patients Enrolled	10
Number of Patients Evaluable for Toxicity	10
Number of Patients Evaluated for Efficacy	10
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 0 (0%)
Response Assessment SD	*n* = 3 (30%)
Response Assessment PD	*n* = 7 (70%)
(Median) Duration Assessments PFS	0.92 months, CI: 0.62–3.58
(Median) Duration Assessments OS	5.98 months, CI: 1.68–10.39

Kaplan-Meier, Time Units, Months

Time of scheduled assessment and/or time of event	No. progressed (or deaths)	No. censored	Percent at start of evaluation period	Kaplan-Meier %	No. at next evaluation/No. at risk
0	0	0	100.00	100.00	10
1	6	0	100.00	40.00	4
2	1	0	40.00	30.00	3
3	0	0	30.00	30.00	3
4	3	0	30.00	0.00	0



Kaplan-Meier plot: Progression-free survival for all treated patients.

Adverse Events

All Cycles

Name	NC/NA	1	2	3	4	5	All grades
Blurred vision	60%	20%	20%	0%	0%	0%	40%
Constipation	50%	40%	10%	0%	0%	0%	50%

Diarrhea	80%	10%	10%	0%	0%	0%	20%
Nausea	70%	30%	0%	0%	0%	0%	30%
Vomiting	50%	40%	10%	0%	0%	0%	50%
Fatigue	50%	20%	20%	10%	0%	0%	50%
Blood bilirubin increased	80%	10%	10%	0%	0%	0%	20%
Platelet count decreased	50%	10%	30%	10%	0%	0%	50%
Anorexia	60%	30%	10%	0%	0%	0%	40%
Hypocalcemia	80%	0%	20%	0%	0%	0%	20%
Arthralgia	80%	20%	0%	0%	0%	0%	20%
Dysgeusia	80%	20%	0%	0%	0%	0%	20%
Cough	80%	20%	0%	0%	0%	0%	20%
Dyspnea	60%	20%	10%	10%	0%	0%	40%
Hot flashes	80%	20%	0%	0%	0%	0%	20%
Arthralgia	80%	20%	0%	0%	0%	0%	20%

Summary of adverse events observed in ≥20% of the study population.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Name	Grade	Attribution
Encephalopathy	3	Possible
Dyspnea	3	Unrelated

Summary and attribution of serious adverse events.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Level of activity did not meet planned endpoint

This study investigated the clinical benefit rate of selinexor in heavily pretreated patients with metastatic triple-negative breast cancer (TNBC). Among the first 10 patients enrolled, we did not observe any objective responses; therefore, the study was terminated early for lack of efficacy per preplanned interim analysis. Three patients had a best response of stable disease with two of the three patients having stable disease for ≥3 treatment cycles; however, this was not sufficient to warrant continuation of study. Furthermore, we did not observe a correlation between XPO1 mRNA induction after treatment or p53 mutational status in patients who experienced clinical benefit.

Although responses to single-agent selinexor were not seen in this study, combination approaches may provide therapeutic benefit to patients with TNBC. Chemotherapy resistance in TNBC is at least partly mediated by survivin, a pro-survival molecule that plays a critical role in resistance to taxanes [7–9]. In pancreatic cell lines, the combination of selinexor and gemcitabine was synergistic and led to depletion of survivin and apoptosis, which was greater than either agent alone. Additionally, the combination demonstrated greater reduction in nuclear localization of DNA repair enzymes, leading to the accumulation of DNA damage. Because increased DNA repair enzymes CHK1 and RAD51 were seen in pretreatment tissue samples in biopsies from two patients, this suggests that a combination approach with cytotoxic chemotherapy could be investigated as a way to augment responses to chemotherapy in patients with TNBC. Preclinical data also suggest that single-agent selinexor can lead to some level of poly ADP ribose polymerase (PARP) cleavage, which is associated with responses [10, 11]. The combination of a PARP inhibitor and selinexor appears to act synergistically in TNBC cell lines [12]. A phase Ib clinical trial investigating the safety of combination selinexor and olaparib in patients with advanced solid tumors is currently ongoing (NCT02419495). Given the recent approval of olaparib for patients with metastatic breast cancer harboring BRCA1 or BRCA2 mutations, such a combination is intriguing [6].

The side-effect profile is consistent with that observed in the first-in-class, first-in-human study of selinexor in solid tumors including nausea, fatigue, anorexia, and vomiting as the most common treatment-related adverse events [13]. Thrombocytopenia was the most common hematologic toxicity; however, only one patient experienced grade ≥3 thrombocytopenia while on study. This result is not unexpected, as a recent study showed that selinexor inhibits the maturation of hematopoietic stem cells to megakaryocytes, without affecting other aspects of platelet production. Although constitutional adverse events led to dose reductions in three patients in this study, there were no discontinuations due to selinexor treatment. In addition, there were no grade 4 or 5 adverse events observed in this study population. Patients were treated with antiemetics and oral dexamethasone in the first cycles to mitigate nausea, vomiting, and anorexia. If tolerated, these

supportive medications could be tapered off during subsequent cycles. Side effects are a function of the dose and schedule.

This trial demonstrated that administration of selinexor 60 mg twice weekly with supportive care is well tolerated. In addition to the dose and schedule chosen, the supportive care measures implemented may have led to the relatively low incidence of observed nausea and anorexia compared with the first-in-human study. Serious adverse events occurred in three patients and included grade 3 dyspnea in two patients and grade 3 reversible encephalopathy, described as memory impairment. The first case of grade 3 dyspnea was unrelated to the study drug. Grade 2 sinus tachycardia and grade 2 blurry vision were associated with this serious adverse event, and whereas sinus tachycardia was unrelated to the study drug, blurry vision was possibly related. The second case of grade 3 dyspnea was also unrelated to study drug and definitely disease related, whereas the case of grade 3 reversible encephalopathy was possibly related to selinexor. No treatment-emergent adverse event of grade 4 or 5 was observed. Dose reductions were required in two patients for fatigue and mood irritability, both related to the study drug. Treatment was temporarily interrupted in one patient for grade 2 thrombocytopenia related to selinexor. No treatment-related events led to discontinuation of selinexor.

Despite early termination of this trial for lack of efficacy as a single agent, interest remains in developing a niche for selinexor as a combination therapy in TNBC. A recent publication demonstrated the ability of selinexor to inhibit proliferative and migratory processes in TNBC cells by restoring arrestin-related domain-containing protein 3 [14]. The preclinical evidence for an effective role of selinexor in TNBC remains intriguing, and our study highlights several areas for further exploration with selinexor in this disease. Outcomes seen in this trial are not generalizable, and patients with TNBC who are treatment naïve may show increased responsiveness to treatment as a single agent or in combination. Efforts are under way to develop a biomarker strategy to identify responsive subsets of patients upfront [3, 15].

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Disclosures

Michael Shafique: GlaxoSmithKline (C/A); **Roohi Ismail-Khan:** Karyopharm (RF-institutional); **Dan Sullivan:** Karyopharm (RF-institutional); **Hatem Soliman:** Pfizer, Eli Lilly, Novartis, PUMA, Astrazeneca (C/A); **Hyo S. Han:** Karyopharm (RF-institutional). The other authors indicated no financial relationships.

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