

## Brief Report

# Selinexor in Combination with Carboplatin and Pemetrexed in Patients with Advanced or Metastatic Solid Tumors: Results of an Open-Label, Single-Center, Multi-Arm Phase 1b Study

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Selinexor is a first-in-class, oral, potent selective inhibitor of exportin-1 (XPO-1), which is overexpressed in various malignancies. Previous phase I and II studies demonstrated the modest activity of the single-agent selinexor in patients with solid tumors.<sup>[1–3]</sup> Carboplatin plus pemetrexed (CP) is used in many solid cancers. In vivo studies of selinexor in combination with different chemotherapeutics demonstrated synergistic activity.<sup>[4–6]</sup> To further investigate the safety, tolerability, and clinical activity of selinexor in combination with standard therapies, we conducted an open-label, single-center, multi-arm phase 1b trial (ClinicalTrials.gov Identifier: NCT02419495) of selinexor in combination with standard chemotherapy in patients with advanced or

metastatic solid tumors. Herein, we report the use of selinexor in combination with CP in patients with advanced or metastatic solid tumors.

The study was conducted in multiple arms using a standard 3 + 3 design and a basket-type expansion. Adult patients (age ≥ 18 years) with histologically documented relapsed or metastatic refractory solid tumors following standard therapy or after adding selinexor to systemic therapy as appropriate were eligible. The primary objective was to establish the safety and tolerability of selinexor when given in combination with standard chemotherapy regimens, and the secondary objective was to determine the preliminary antitumor activity (disease control rate [DCR] and progression-free survival

**Table 1.** Baseline demographics and disease characteristics of included patients

Characteristic	Carboplatin AUC6 and Pemetrexed 500 mg/m <sup>2</sup> Q3W			All Patients (N = 6)
	Selinexor 40 mg PO QW (n = 2)	Selinexor 60 mg PO BIW (n = 1)	Selinexor 60 mg PO QW (n = 3)	
Age at consent, y				
Median	53.8	52.7	50.5	51.6
Range	37.8–69.9	52.7–52.7	42.3–53.4	37.8–69.9
Sex, n (%)				
Male	1 (50)	0	1 (33)	2 (33)
Female	1 (50)	1 (100)	2 (67)	4 (67)
Race, n (%)				
White	2 (100)	1 (100)	1 (33)	4 (67)
Hispanic	0	0	2 (67)	2 (33)
Black	0	0	0	0
Asian	0	0	0	0
ECOG performance status, n (%)				
0	0	0	0	0
1	2 (100)	1 (100)	3 (100)	6 (100)
Primary tumor, n (%)				
Ovarian or peritoneal	1 (50)	0	1 (33)	2 (33)
Breast	0	0	0	0
Colorectal	0	0	1 (33)	1 (17)
Endometrial or fallopian	0	0	0	0
Lung	0	1 (100)	0	1 (17)
Neuroendocrine	0	0	0	0
Pancreatic	0	0	0	0
Esophageal	0	0	0	0
Head and neck or salivary gland	0	0	0	0
Liver or cholangiocarcinoma	0	0	0	0
Sarcoma	0	0	0	0
Prostate	0	0	0	0
Other	1 (50)*	0	1 (33)†	2 (33)
Prior lines of systemic therapies, n (%)				
0-1	0	0	0	0
2-3	0	1 (100)	1 (33)	2 (33)
4-5	2 (100)	0	2 (67)	4 (67)
> 5	0	0	0	0

\*: includes thymoma; †: includes cervical squamous cell carcinoma (moderate to poorly differentiated).

AUC6: area under the curve 6; BIW: twice weekly; ECOG: Eastern Cooperative Oncology Group; PO: orally; QW: once weekly; Q3W: every 3 weeks.

[PFS]). Selinexor was dosed orally at 40–60 mg once weekly (QW) as well as 60 mg twice weekly (BIW) on each 21-day cycle, whereas carboplatin was dosed at area under the curve 6 (AUC6) along with pemetrexed at 500 mg/m<sup>2</sup> intravenously every 3 weeks (Q3W). The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at MD Anderson Cancer Center and was conducted in accordance with the U.S. Common Rule, Declaration of Helsinki, Good Clinical Practices, and all local and federal regulatory guidelines. Informed consent was obtained from all participants included in the study.

A total of six patients with advanced metastatic malignancies were enrolled between July 2015 and June 2016. The demographic and clinical characteristics are summarized in Table 1. The median age was 52 (range, 38–70 years), with 67% women and 33% men. The cancer types included were ovarian (*n* = 2) and one patient each with thymoma, cervical, rectal, and non-small cell lung cancers. All six patients were no longer in the study. Progression of disease and clinically unacceptable treatment-emergent adverse events (TEAEs) contrib-

uted to withdrawal of three patients from the study. All patients had at least one treatment-related adverse event (TRAE). The overall summary of TEAE and TRAE is depicted in Supplemental Table S3 (available online). The most common TEAEs were thrombocytopenia (100%), neutropenia (83%), fatigue (83%), anemia (67%), leukopenia (67%), elevated liver function tests (50%), nausea (50%), and vomiting (50%). The most prevalent TEAEs of grade 3 or greater were thrombocytopenia (67%), anemia (50%), and neutropenia (50%). The most common TRAEs were thrombocytopenia (100%), neutropenia (83%), leukopenia (67%), nausea (50%), fatigue (50%), anemia (33%), vomiting (33%), and anorexia (33%). The most common high-grade TRAEs were thrombocytopenia (67%), neutropenia (50%), anemia (33%), leukopenia (33%), and fatigue (33%). One patient dosed with 40 mg QW selinexor experienced dose-limiting toxicities (DLTs) with grade 3 fatigue despite medical supportive care for 5 or more days. Two patients dosed with 60 mg QW selinexor experienced a serious adverse event of special interest, and both instances were considered unrelated to the

study drug. One patient had grade 4 elevated bilirubin, and the other patient experienced grade 3 acute kidney injury from hydronephrosis; both were attributed to disease. No patient died during the study.

Best overall tumor response is shown in Supplemental Table S1 and S2 and Supplemental Figure S1 (available online). Six patients enrolled in the study had measurable disease, but two patients had not completed their first restaging scans due to early withdrawal of consent due to toxicity. Four patients completed their first restaging scans per protocol and were therefore evaluable for efficacy. Per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors version 1.1), a patient with lung adenocarcinoma obtained unconfirmed partial response (uPR), whereas two patients, one with ovarian cancer and one with cervical cancer, achieved stable disease (SD). There was no complete response (CR), and the DCR (CR + PR + SD  $\geq$  6 months) was 0%. The patient who obtained uPR had previously progressed on two prior lines of treatment including carboplatin and paclitaxel (CT). The time-to-treatment failure (TTF) was 20 weeks. A patient with ovarian cancer who had progressed on five prior lines of therapies, including platinum, paclitaxel, liposomal doxorubicin, and bevacizumab (poly-ADP ribose polymerase inhibitor naive), achieved SD with TTF of 19 weeks, and another patient with cervical cancer who had received two prior lines of treatment (including CT) also achieved SD (TTF of 13 weeks). Lastly, one patient with rectal adenocarcinoma who had received four prior lines of therapies (including oxaliplatin) had progressive disease as the best response, and TTF was 7 weeks. The median PFS was 2.3 months (95% CI, 0.5–4.6 months), and the median overall survival was 7.7 months (95% CI, 2.1–17.2 months) (Supplemental Fig. S2).

To our knowledge, this is the first study reporting selinexor in combination with CP, which is one of the most commonly used regimens in solid tumors. Previous single-agent selinexor studies showed that fatigue and hematologic laboratory abnormalities were the most common high-grade TRAE (range, 6–21%).<sup>[1–3,7,8]</sup> Despite a small cohort, greater incidence of high-grade hematologic laboratory abnormalities was observed with this combination strategy with the standard dose of CP. Regarding selinexor dosing, most participants (83%) received QW selinexor dosing regimen in this study, whereas selinexor was given BIW in prior selinexor monotherapy studies. The initial dosing schedule of selinexor in our study was 60 mg BIW. After the first patient had prolonged grade 2 hematologic toxicities despite not meeting the DLT criteria, the selinexor dose was reduced to 60 mg QW. Three patients were enrolled, and none had DLT. As they also experienced prolonged adverse events, the dosing was further de-escalated to dose level –1 (40 mg QW). All patients experienced at least one TRAE, and the most common TRAEs were hematologic laboratory abnormalities, nausea, and fatigue. The addition of standard chemotherapy to selinex-

or heightened the risk of high-grade toxicities despite using a lower selinexor dosing regimen and reducing standard of care doses of different chemotherapies.

Though the number of patients in this arm was small, oral selinexor in combination with CP showed limited clinical activity, albeit at the expense of toxicity. Although the recommended phase 2 dose of selinexor was 40 mg QW in combination with CP, the study arm was not pursued for dose expansion due to toxicities and lack of efficacy. Proper utility of growth factors and optimizing supportive care is crucial in this combination strategy.

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## Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Supplemental Material

Supplemental materials are available online with the article.

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