Selinexor in combination with carboplatin and paclitaxel in patients with advanced or metastatic solid tumors: Results of an open label, single-center, multi-arm phase 1b study

Kyaw Z. Thein[1,2] , Apostolia M. Tsimberidou[1] , Sarina A. Piha-Paul[1] , Filip Janku[1] , Daniel D. Karp[1] , Siqing Fu[1] , Abdulrazzak Zarifa[1], Jing Gong[1] , Timothy A. Yap[1] , David S. Hong[1] , Vivek Subbiah[1] , Shubham Pant[1] , Funda Meric-Bernstam[1] , Aung Naing[1]

[1]The University of Texas MD Anderson Cancer Center, Texas/USA ; [2]Oregon Health & Science University/ Knight Cancer Institute, Portland/USA.

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Poster- 554P

INTRODUCTION

- Selinexor is a first-in-class novel, oral potent selective inhibitor of nuclear export which blocks the transport protein called Exportin-1.
- Carboplatin+ Taxol (CT) is one of the standard chemotherapy regimens used in various tumor types.
- Preclinical models have suggested that selinexor and CT exerts antitumor activity in multiple malignancies.

METHODS

Patients

- Adult (age ≥18 years) patients with histologically documented, advanced or metastatic solid tumors (excluding brain tumors) who were unresponsive or had relapsed following prior systemic therapy or where the addition of selinexor to standard chemotherapy deemed appropriate and acceptable, were eligible.
- Patients in the study had to have at least one measurable target lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) criteria for solid tumors, except for patients with castrate resistant prostate cancer (CRPC) where prostate cancer working group 2 (PCWG2) criteria was utilized.
- Key exclusions were patients with primary CNS tumor or active CNS tumor involvement, evidence of complete or partial bowel obstruction or needing total parenteral nutrition, prior treatment with an agent targeting the exportin, and unstable cardiovascular functions.

Study design and treatment

- This was an open label, single-center, multi-arm phase 1B of selinexor in combination with standard chemotherapy to determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of selinexor and further explore the safety and tolerability of the MTD in patients with advanced or metastatic solid tumors (ClinicalTrials.gov identifier: NCT02419495).
- The study was conducted in multi-arms utilizing a "3 + 3" design and a "basket type" expansion.
- Selinexor in combination with carboplatin and paclitaxel was employed as one of the 13 parallel arms.
- While carboplatin was dosed at AUC4 along with paclitaxel at 175 mg/m2 intravenously every 3 weeks, selinexor was dosed at 60 mg twice weekly orally on days 1, 3, 8, and 10 of each 21-day cycle as well as 40-60 mg once weekly on days 1, 8, and 15.
- The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at the MD Anderson Cancer Center and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and all local and federal regulatory guidelines.
- All patients signed informed consent prior to enrolling onto the study.

Corresponding Author : theink@ohsu.edu.
Presented at European Society for Medical Oncology (ESMO) 2020 Congress.

METHODS (Cont'd)

- The primary objective was to establish the safety and tolerability of Selinexor when given in combination with standard chemotherapy regimens and to determine the disease control and progression free survival of selinexor administered with standard chemotherapy treatments were the secondary objectives.
- The primary efficacy parameter was the safety according to NCI CTCAE v 4.03 and the secondary parameters were clinical benefit rate (CBR; percentage of complete response, partial response plus stable disease), disease control rate (DCR; percentage of complete response, partial response plus stable disease for at least 4 months, assessed according to RECIST 1.1 criteria), the objective tumor response rate (complete response + partial response), assessed according to RECIST 1.1 criteria and progression-free survival (PFS) defined as the time between the cycle 1 start date and the date of disease progression or death, whichever is reported first.

Table 1. Patients baseline demographics and disease characteristics

Characteristic n (%)	Carboplatin 5AUC and Paclitaxel 175mg/m2 IV Q3W			Carboplatin 4AUC and Paclitaxel 175mg/m2 Intravenous Q3W		Arm E (N= 13)
	Selinexor 40mg PO QW (n=1)	Selinexor 60mg PO BIW (n=1)	Selinexor 60mg PO QW (n=4)	Selinexor 40mg PO QW (n=5)	Selinexor 60mg PO QW (n=2)	
Age at consent (years)						
Median Range	45 (45-45)	57	60 (41-70)	58 (50-71)	55.5 (50-61)	57.6 (41.8 - 71.6)
Gender, n (%)						
Male	0	0	1 (25)	3 (60)	1 (50)	5 (38)
Female	1 (100)	1 (100)	3 (75)	2 (40)	1 (50)	8 (62)
Race, n (%)						
White	1 (100)	0	4 (100)	1 (20)	2 (100)	8 (62)
Hispanic	0	1 (100)	0	2 (40)	0	3 (23)
Black	0	0	0	2 (40)	0	2 (15)
ECOG performance status, n (%)						
0	0	1 (100)	0	0	0	1 (8)
1	1 (100)	0	4 (100)	5 (100)	2 (100)	12 (92)
Primary tumor, n (%)						
Ovarian	0	1 (100)	1 (25)	0	0	2 (15)
Breast	0	0	1 (25)	2 (40)	1 (50)	4 (31)
Endometrial/Fallopian	0	0	1 (25)	0	0	1 (8)
Lung	0	0	1 (25)	1 (20)	0	2 (15)
Neuroendocrine	0	0	0	0	0	0
Pancreas	0	0	0	1 (20)	0	1 (8)
Esophageal	0	0	0	1 (20)	1 (50)	2 (15)
Liver/ cholangiocarcinoma	1 (100)	0	0	0	0	1 (8)
Prior lines of systemic therapies, n (%)						
0 - 1	0	0	0	1 (20)	0	1 (8)
2 - 3	1 (100)	0	2 (50)	2 (40)	2 (100)	7 (53)
4 - 5	0	1 (100)	2 (50)	0	0	3 (23)
> 5	0	0	0	2 (40)	0	2 (15)
Prior exposure to carboplatin and/or paclitaxel, n (%)						
Yes	0	1 (100)	4 (100)	4 (80)	0	11 (85)
No	1 (100)	0	0	1 (20)	0	2 (15)

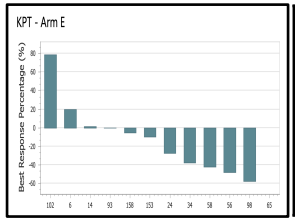
RESULTS

- Of 13 patients treated, 12 patients were evaluable for response. The most common cancers were breast (n=4), esophageal (n=2), ovarian (n=2) and non-small cell lung cancers (n=2). (Table 1)
- All 13 patients had at least one treatment-emergent adverse events (TEAE) and the commonest TEAE were anemia (84%), neutropenia (84%), leukopenia (84%), thrombocytopenia (84%), fatigue (61%), elevated AST or ALT (61%), nausea (53%), hypomagnesemia (53%), and peripheral motor or sensory neuropathy (53%). (Table 2)

RESULTS (Cont'd)

- The most prevalent grade ≥ 3 TEAE were neutropenia (69%), thrombocytopenia (53%), leukopenia (46%), and anemia (15%).
- One patient at 60mg once weekly had experienced DLT with grade 4 neutropenia lasting >7 days.
- Partial response was noted in 4 patients (33.3%) in patients with esophageal (n=2), 1 patient each with breast and ovarian cancer. (Figure 1)
- Five patients (41.7%) achieved stable disease and the clinical benefit rate was 75%. Disease control rate (DCR; percentage of CR+PR+SD ≥4 months) was 41.7%. (Figure 1)
- Majority of patients (84%), including 3 patients who had PR, had prior exposure to carboplatin and/ or paclitaxel.
- Treatment time to failure (TTF) ranged from 6 to 154 weeks.

Figure 1. Waterfall plot of maximum change in tumor measurements (per RECIST v1.1) for evaluable patients and summary of best overall tumor response



Measure	Arm E (N= 13)
Response, n (%)	
CR	0
PR	4 (33)
SD	5 (42)
CBR (CR+PR+SD)	9 (75)
DCR (CR+PR+SD ≥4 months)	5 (41.7)
PD	3 (25)
Not evaluated	1

Table 2. Summary of treatment-emergent and -related adverse events in all grades of severity

N (%)	Treatment emergent adverse events (TEAE)		Treatment related adverse events (TRAE)	
	All grades	Grade 3/4	All grades	Grade 3/4
Anemia	11 (84)	2 (15)	7 (53)	2 (15)
Leukopenia	11 (84)	6 (46)	11 (84)	6 (46)
Neutropenia	11 (84)	9 (69)	11 (84)	9 (69)
Thrombocytopenia	11 (84)	7 (53)	11 (84)	7 (53)
Constipation	6 (46)	0	2 (15)	0
Diarrhea	4 (30)	0	2 (15)	0
Nausea	7 (53)	1 (7)	7 (53)	1 (7)
Vomiting	6 (46)	1 (7)	6 (46)	1 (7)
Elevated AST/ALT	6 (46)	1 (7)	3 (23)	1 (7)
Fever	4 (30)	0	0	0
Fatigue	8 (61)	0	6 (46)	0
Anorexia	4 (30)	0	3 (23)	0
Hyponatremia	3 (23)	1 (7)	3 (23)	1 (7)
Hypomagnesemia	7 (53)	0	2 (15)	0
Peripheral motor/ sensory neuropathy	7 (53)	0	4 (30)	0
Dyspnea	3 (23)	1 (7)	1 (7)	0
Cough	5 (38)	0	0	0
Elevated CPK	2 (15)	1 (7)	1 (7)	1 (7)
Infection or infestation	5 (38)	4 (30)	0	0

CONCLUSION

- One weekly oral selinexor can be safely combined with carboplatin/ paclitaxel and the RP2D was 60 mg once weekly in combination with carboplatin and paclitaxel.
- The combination conferred appreciable clinical activity with durable objective responses which should further be explored in tumor types for which carboplatin + paclitaxel is used as standard of care and supports the evaluation of the combination of selinexor and carboplatin plus paclitaxel in patients with carboplatin and paclitaxel naïve disease.

ACKNOWLEDGEMENTS

- We thank the patients, and their families who participated in this study.
- ClinicalTrials.gov Identifier: NCT02419495
- Sponsor(s): Karyopharm Therapeutics

REFERENCES

1. Fukuda M, Asano S, Nakamura T, Adachi M, Yoshida M, Yanagida M, et al. CRM1 is responsible for intracellular transport mediated by the nuclear export signal. Nature 1997;390(6657):308-11 doi 10.1038/36894.
2. Xu D, Grishin NV, Chook YM. NESdb: a database of NES-containing CRM1 cargoes. Mol Biol Cell 2012;23(18):3673-6 doi 10.1091/mbc.E12-01-0045.
3. Nguyen KT, Holloway MP, Altura RA. The CRM1 nuclear export protein in normal development and disease. Int J Biochem Mol Biol 2012;3(2):137-51.
4. Senapedis WT, Baloglu E, Landesman Y. Clinical translation of nuclear export inhibitors in cancer. Semin Cancer Biol 2014;27:74-86 doi 10.1016/j.semcancer.2014.04.005.
5. Arango NP, Yuca E, Zhao M, Evans KW, Scott S, Kim C, et al. Selinexor (KPT-330) demonstrates anti-tumor efficacy in preclinical models of triple-negative breast cancer. Breast Cancer Res. 2017;19(1):93
6. Kashyap T, Argueta C, Unger T, Klebanov B, Debler S, Senapedis W, et al. Selinexor reduces the expression of DNA damage repair proteins and sensitizes cancer cells to DNA damaging agents. Oncotarget 2018;9(56):30773-86 doi 10.18632/oncotarget.25637.
7. Turner JG, Dawson J, Sullivan DM. Nuclear export of proteins and drug resistance in cancer. Biochem Pharmacol 2012;83(8):1021-32 doi 10.1016/j.bcp.2011.12.016.
8. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England : 1990) 2009;45(2):228-47 doi 10.1016/j.ejca.2008.10.026.
9. Nishino M, Jagannathan JP, Ramaiya NH, Van den Abbeele AD. Revised RECIST guideline version 1.1: What oncologists want to know and what radiologists need to know. AJR American journal of roentgenology 2010;195(2):281-9 doi 10.2214/ajr.09.4110.
10. Sonpavde G, Pond GR, Armstrong AJ, Galsky MD, Leopold L, Wood BA, et al. Radiographic progression by Prostate Cancer Working Group (PCWG)-2 criteria as an intermediate endpoint for drug development in metastatic castration-resistant prostate cancer. BJU Int 2014;114(6b):E25-e31 doi 10.1111/bju.12589.

554P