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Clinical Trial Results

A Phase I/II Study of the Investigational Drug Alisertib in Combination With Abiraterone and Prednisone for Patients With Metastatic Castration-Resistant Prostate Cancer Progressing on Abiraterone

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT01848067
- **Sponsor:** Thomas Jefferson University
- **Principal Investigator:** Jianqing Lin
- **IRB Approved:** Yes

Lessons Learned

- Patients with metastatic castration-resistant prostate cancer did not tolerate the combination of alisertib with abiraterone and prednisone.
- There was no clear signal indicating that adding alisertib might be beneficial for those patients progressing on abiraterone.

Abstract

Background. We hypothesized that Aurora A kinase (AK) contributes to castrate resistance in prostate cancer (PCa) and that inhibiting AK with alisertib can resensitize PCa cells to androgen receptor (AR) inhibitor abiraterone.

Methods. This was a phase I/II trial to determine the safety and efficacy of alisertib when given in combination with abiraterone plus prednisone (AP). Metastatic castration-resistant prostate cancer (mCRPC) patients were treated with dose escalation (alisertib at 30, 40, and 50 mg orally b.i.d., days 1–7 every 21 days) per standard 3+3 design.

Results. Nine of 43 planned subjects were enrolled. The maximum tolerated dose (MTD) was not reached, and the dose-limiting toxicities (DLTs) included neutropenic fever (1 of 9), neutropenia (1 of 9), fatigue with memory impairment (1 of 9), and diarrhea/mucositis (1 of 9). No prostate-specific antigen (PSA) decrease or circulating tumor cell (CTC) changes were observed during the study. Pharmacodynamically, adding alisertib did not affect total testosterone or dehydroepiandrosterone (DHEA) levels. There was some change in neuroendocrine markers after therapy. Mean duration on study was 2.5 months. The trial was terminated early.

Conclusion. A tolerable dose of alisertib in combination with AP in mCRPC was not established in this study. There was no clear signal indicating that alisertib might be beneficial for patients with mCRPC progressing on abiraterone. ***The Oncologist*** 2016; 21:1296–1297e

Discussion

Abiraterone acetate is active and approved for use in patients with metastatic castration-resistant prostate cancer [1, 2], but resistance does develop, and the mechanism of drug resistance is under active investigation [3]. Preclinical studies have shown AK as a potential target for advanced PCa, especially for PCa with neuroendocrine differentiation. We investigated whether the addition of alisertib, an AK inhibitor, to an AP regimen was tolerable and effective to reverse resistance to abiraterone.

The trial was terminated early because of toxicity and lack of clinical benefit. The first three patients in cohort 1 (30 mg b.i.d., days 1–7 every 21 days) did not experience a DLT. Two patients experienced DLTs in cohort 2 (40 mg level) (fatigue with memory impairment or neutropenic fever), resulting in dose de-escalation Three additional patients were treated at 30 mg b.i.d., and two developed DLTs (neutropenia and diarrhea/mucositis). Evaluation of side-effect profile among the nine patients demonstrated poor tolerability of alisertib and abiraterone/prednisone combination. Bone marrow suppression is a known side effect from alisertib [4, 5], but the rate of grade 3/4 toxicities was higher in our study compared with others. It is important to note that previous studies used alisertib as monotherapy in solid tumors. To improve patient tolerance, it might be reasonable to use a

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Dose-limiting toxicities

Dose level	Dose of drug: MLN 8237	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity	Dose-limiting toxicity information
−1	20 mg p.o. b.i.d., days 1–7 every 21 days	0	0	0	None
0	30 mg p.o. b.i.d., days 1–7 every 21 days	3	3	0	None
1	40 mg p.o. b.i.d., days 1–7 every 21 days	3	3	2	Grade 3 fatigue; grade 4 white blood cell decrease
0*	30 mg p.o. b.i.d., days 1–7 every 21 days	3	3	3	Grade 4 febrile neutropenia; grade 3 mucositis

*First cohort treated at level 0 with no dose-limiting toxicities. Second cohort treated at level 1 with two dose-limiting toxicities. Per protocol, dose de-escalation to level zero with three additional subjects.

different dose and schedule for patients with relatively slow-growing tumors such as prostate cancer.

The efficacy is difficult to assess in this phase I trial. Three patients were taken off the study because of disease progression. Seven (of 9) patients had an increase in PSA during the study. Four (of 9) patients in the trials had ≥5 CTCs at baseline, but no conversion was observed at the end of therapy. Mean duration on the study was 2.5 months. These results suggest an unfavorable efficacy-to-toxicity ratio for this combination. The trial was prematurely terminated, and the phase II portion was not performed.

From measuring the total testosterone and DHEA levels during the study, we believe alisertib does not interfere with the ability of abiraterone to inhibit biosynthesis of androgens. For neuroendocrine biomarkers, we observed three (of nine) patients who had a sustained decreased in chromogranin A levels and four (of nine) patients who had a decrease in neuron-specific enolase levels. The significance of these changes is not clear, given the small sample size of the study. Fluorescence in situ hybridization analysis of collected CTCs did not demonstrate AK amplification. Further study is certainly needed to make any conclusions.

In summary, adding alisertib to abiraterone regimen seems intolerable in mCRPC. The optimal dose and schedule of alisertib could not be determined. There was no clear signal indicating that alisertib might be beneficial for patients with mCRPC progressing on abiraterone, and further development of this treatment combination is not warranted.

Trial Information	
Disease	Prostate cancer
Stage of disease / treatment	Metastatic/advanced
Prior Therapy	1 prior regimen
Type of study - 1	Phase I
Type of study - 2	3+3 dose escalation
Primary Endpoint	Safety
Primary Endpoint	Maximum tolerated dose
Secondary Endpoint	PSA kinetics after alisertib is added to abiraterone and prednisone regimen
Secondary Endpoint	Baseline and post-therapy CTCs enumeration
Secondary Endpoint	Baseline and post-therapy chromogranin A and neuron-specific enolase levels
Additional Details of Endpoints or Study Design	1. DHEA and testosterone kinetics after alisertib 2. Aurora kinase A gene amplification status
Investigator's Analysis	Poorly tolerated/not feasible

Drug Information	
Drug 1	
Generic/working name	MLN 8237
Trade name	Alisertib
Company name	Millennium: The Takeda Oncology Company
Drug type	Small molecule
Drug class	Mitotic - Aurora kinase
Dose	milligrams (mg) per flat dose
Route	oral (p.o.)

Schedule of administration	Dose Level −1: Alisertib, 20 mg p.o. b.i.d., days 1–7 every 21 days Dose Level 0 (starting): Alisertib, 30 mg p.o. b.i.d., days 1–7 every 21 days Dose Level 1: Alisertib, 40 mg p.o. b.i.d., days 1–7 every 21 days Dose Level 2: Alisertib, 50 mg p.o. b.i.d., days 1–7 every 21 days The first cohort was treated at dose level 0 with no DLTs. The second cohort was treated at dose level 1 with two DLTs. Per protocol, dose de-escalation was to level 0 with three additional subjects.

Patient Characteristics

Number of patients, male	9
Number of patients, female	0
Stage	Stage IV, Metastatic
Age	Median (range): 68 (62–82)
Number of prior systemic therapies	Median (range): 1 (1–2)
Performance Status: ECOG	0 — 7 1 — 2 2 — 0 3 — 0 Unknown — 0
Other	Not collected
Cancer types or histologic subtypes	Adenocarcinoma of prostate: 9

Primary Assessment Method

Number of patients screened	9
Number of patients enrolled	9
Number of patients evaluable for toxicity	9
Number of patients evaluated for efficacy	9
Evaluation method	Clinic visit at 12 weeks or progression: CT\MRI Abd and Pelvis; CT of chest or CXR; Bone Scan; PSA; Androgen Panel
Response assessment CR	0
Response assessment PR	0
Response assessment SD	0
Response assessment PD	$n = 3$
Response assessment OTHER	$n = 6$

Adverse Events

All Dose Levels, All Cycles

Name	*NC/NA	1	2	3	4	5	All Grades
Fatigue	22%	67%	0%	11%	0%	0%	78%
Mucositis oral	56%	11%	22%	11%	0%	0%	44%
Alopecia	56%	44%	0%	0%	0%	0%	44%
Dizziness	78%	11%	11%	0%	0%	0%	22%
Memory impairment	56%	11%	22%	11%	0%	0%	44%
Diarrhea	78%	11%	0%	11%	0%	0%	22%
Nausea	78%	22%	0%	0%	0%	0%	22%
Dyspepsia	89%	0%	11%	0%	0%	0%	11%
Anorexia	78%	22%	0%	0%	0%	0%	22%
Constipation	89%	11%	0%	0%	0%	0%	11%
Rectal pain	89%	11%	0%	0%	0%	0%	11%
Confusion	89%	11%	0%	0%	0%	0%	11%
Headache	89%	11%	0%	0%	0%	0%	11%
Personality change	89%	11%	0%	0%	0%	0%	11%

Dyspnea	89%	11%	0%	0%	0%	0%	11%
Electrocardiogram QT corrected interval prolonged	89%	11%	0%	0%	0%	0%	11%
Hypertension	89%	11%	0%	0%	0%	0%	11%
Pharyngitis	89%	11%	0%	0%	0%	0%	11%
Skin hyperpigmentation	89%	11%	0%	0%	0%	0%	11%
Palmar-plantar erythrodysesthesia syndrome	89%	11%	0%	0%	0%	0%	11%
Rash maculo-papular	89%	11%	0%	0%	0%	0%	11%
Pruritus	89%	11%	0%	0%	0%	0%	11%
Urinary tract infection	89%	11%	0%	0%	0%	0%	11%
Hypocalcemia	67%	33%	0%	0%	0%	0%	33%
Hypokalemia	78%	22%	0%	0%	0%	0%	22%
Hyponatremia	89%	11%	0%	0%	0%	0%	11%
Hyperglycemia	67%	0%	11%	11%	11%	0%	33%
White blood cell decreased	45%	0%	44%	0%	11%	0%	55%
Anemia	56%	0%	44%	0%	0%	0%	44%
Neutrophil count decreased	67%	0%	22%	11%	0%	0%	33%
Platelet count decreased	78%	11%	0%	11%	0%	0%	22%
Febrile neutropenia	89%	0%	0%	0%	11%	0%	11%

Adverse Events Legend
Adverse Events occurring in any patient during any cycle are shown in the table
*No Change From Baseline/No Adverse Event

Serious Adverse Events

Name	Grade	Attribution
Neutropenic Fever	4	Probable

Dose-Limiting Toxicities

Dose level	Dose of drug: MLN 8237	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity	Dose-limiting toxicity information
−1	20 mg p.o. b.i.d., days 1–7 every 21 days	0	0	0	No data
0	30 mg p.o. b.i.d., days 1–7 every 21 days	3	3	0	No dose-limiting toxicity
1	40 mg p.o. b.i.d., days 1–7 every 21 days	3	3	2	Grade 3 fatigue; grade 4 white blood cell decrease
0*	30 mg p.o. b.i.d., days 1–7 every 21 days	3	3	3	Grade 4 febrile neutropenia; grade 3 mucositis

*First cohort treated at dose level 0 with no dose-limiting toxicities. Second cohort treated at dose level 1 with two dose-limiting toxicities. Per protocol, dose de-escalation to level 0 with three additional subjects.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated reason	Toxicity
Investigator's assessment	Poorly tolerated/not feasible

Abiraterone acetate is active and approved for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) [1, 2]. Unfortunately, disease progression inevitably occurs, and patients require additional therapy, which remains an unmet medical need. The mechanism of resistance to abiraterone is not clear and is still under active investigation [3]. It is widely accepted that prostate cancer (PCa) is composed of heterogeneously distinct cell subtypes, including neuroendocrine prostate cancer (NEPC). NEPC is generally considered an aggressive and lethal variant of PCa that most commonly arises from existing PCa [6]. Clinically, NEPC often has high serum levels of chromogranin A (CgA) and neuron-specific enolase (NSE) [7]. The presence of the neuroendocrine (NE) tumor subpopulation can be gauged noninvasively by measuring circulating levels of secretory products, primarily CgA [8]. Increased plasma CgA was observed in 64.3% of patients with CRPC [9]. Increased NSE was seen in 35% of patients [10]. These NEPC can be considered to be castration-resistant and androgen receptor (AR)-independent because AR signaling is not a key player for survival of these cells [11, 12]. The development of the NE features (transformation) in androgen-deprived conditions may contribute to castrate resistance and/or abiraterone resistance. Molecularly, Aurora Kinase (AK) (and concurrent *MYCN* oncogene) amplification was identified by

fluorescence in situ hybridization (FISH) in 75% of primary PCa of patients with NEPC (>95% cells) [11]. By using tissue biopsies from metastatic sites, up to 53% metastatic PCa were found to harbor AK amplification [11].

In vitro studies support the fact that there is a functional relationship between AK and PCa: (a) AK is overexpressed in PCa, especially in anti-androgen-resistant PCa [13, 14]; (b) AK phosphorylates and interacts with AR, enhancing AR DNA binding [15]; (c) AK induces cell growth in the presence and absence of androgen; (d) AK induces/enhances AR activity and potentiates androgen action in AR; and (e) targeting AK reverses the androgen-independent phenotype in vitro [15]. Features of mCRPC likely include AK (and concurrent MYCN) amplification/overexpression with NE phenotype. AK is potentially an important drugable target for CRPC with or without neuroendocrine differentiation. Therefore, we investigated whether mCRPC is sensitive to AK suppression by alisertib, especially in the subgroup of patients with neuroendocrine phenotype. We hypothesized that adding alisertib to the existing androgen-deprivation therapy regimen may reverse the resistance to abiraterone.

We designed a phase I/II, open-label, single-institution trial to determine the safety and efficacy of the AK inhibitor alisertib when given in combination with abiraterone plus prednisone (AP). In the phase I portion, we evaluated the maximum tolerated dose of alisertib. In the phase II study, we planned to evaluate the proportion of patients who had no disease progression after alisertib is added to abiraterone and prednisone.

The trial was terminated early because of toxicity and lack of clinical benefit. The first three patients in cohort 1 (30 mg b.i.d., days 1–7 every 21 days) did not experience a dose-limiting toxicity (DLT). Two patients experienced DLTs in cohort 2 (fatigue with memory impairment and neutropenic fever), resulting in dose de-escalation. Three additional patients were treated at 30 mg b.i.d., and two developed DLTs (neutropenia and diarrhea/mucositis). Evaluation of the side-effect profile among the nine patients demonstrated poor tolerability of the alisertib and abiraterone/prednisone combination. Five (of 9) patients required a treatment delay. Bone marrow suppression is a known side effect from alisertib [4, 5], and although the rate of grade 3/4 toxicities was higher in our study compared with others, it is important to note that previous studies used alisertib as monotherapy. To improve patient tolerance, it might be reasonable to use a different dose and schedule for patients with relatively slow-growing tumors such as prostate cancer.

The efficacy of alisertib and abiraterone is difficult to assess in this phase I trial. Three patients were taken off the study because of disease progression. Seven (of 9) patients had an increase in prostate-specific antigen (PSA) during the study. The effect of alisertib on circulating tumor cell (CTC) enumeration before and after treatment was also measured. Four (of 9) patients in the trials had ≥5 CTCs at baseline, but no conversion was observed at the end of therapy. These results suggest an unfavorable efficacy to toxicity ratio of alisertib with abiraterone and prednisone. Therefore, the trial was terminated earlier, and the phase II portion was not performed.

We looked at the possible pharmacodynamic interactions between alisertib and abiraterone. The addition of alisertib did not significantly affect the total testosterone and dehydroepiandrosterone (DHEA) levels. This suggests that alisertib does not interfere with the ability of abiraterone to inhibit the biosynthesis of androgens.

For neuroendocrine biomarkers, we observed 3 (of 9) patients who had a sustained decreased in chromogranin A levels and 4 (of 9) patients who had a decrease in neuron-specific enolase levels. The significance of these changes is not clear, given the small sample size of the study. FISH analysis of collected CTCs did not demonstrate AK amplification. Further study is certainly needed to make any conclusions.

In summary, adding alisertib to an abiraterone regimen seems intolerable in mCRPC. The optimal dose and schedule of alisertib could not be determined. There was no clear signal indicating that alisertib might be beneficial for patients with mCRPC progressing on abiraterone, and further development of this treatment combination is not warranted.

Disclosures

Nancy Lewis: Novartis (E); **Massimo Cristofanilli:** Dompe, Vorlex, Agendia (C/A), Pfizer (H). The other authors indicated no financial relationships.

(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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Figure and Tables

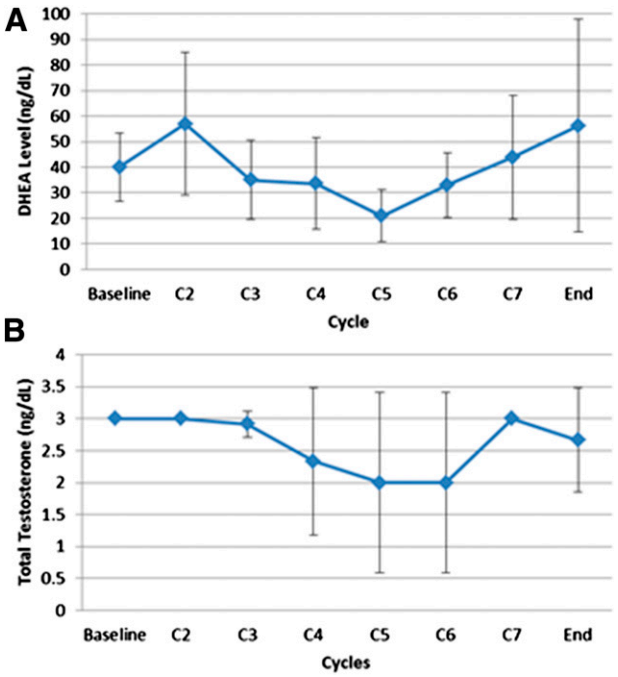

Figure 1. Effects of alisertib on androgen synthesis. **(A)**: DHEA levels during the study treatment. **(B)**: Total testosterone levels during the study treatment.

Abbreviations: C2, cycle 2; DHEA, dehydroepiandrosterone.

Table 1. Summary of the phase I safety data

Pt	Age	Prior systemic treatment	Dose level (mg)	No. of cycles received	AE > G2	DLT (yes/no)	Reason off Tx
1	67	Docetaxel Abiraterone	30	1	None	N	Family obligations (left USA)
2	76	Abiraterone	30	7	None	N	Disease progression
3	65	Abiraterone	30	3	None	N	Patient compliance
4	68	Abiraterone	40	1	Grade 3 fatigue, short-term memory loss	Y	DLT
5	82	Abiraterone	40	7	None	N	Disease progression
6	73	Abiraterone	40	2	Neutropenia, dysphagia	Y	DLT
7	66	Abiraterone	30	5	Neutropenia	Y	DLT
8	74	Docetaxel Abiraterone	30	1	Neutropenic fever, mucositis, thrombocytopenia	Y	DLT
9	62	Docetaxel Abiraterone	30	6	Diarrhea, mucositis	N	Disease progression

Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; G2, grade 2; N, no; Pt, patient; Tx, treatment; Y, yes.

Table 2. Changes of CgA and NSE levels after treatment with alisertib

	Chromogranin A		Neuron-specific enolase	
Patient	**Initial**	**End**	**Initial**	**End**
1	7	6.4	6.5	7.9
2	2.5	92	13.2	22.5
3	5.8	1.4	7.2	5.6
4	4	3.8	8.1	5.4
5	3.6	2.14	9.1	<5
6	<1	<1	5.5	7.6
7	6.2	9.2	5.1	8.7
8	6	6	7.3	<5
9	4.2	4.2	29.7	30.8

Abbreviations: CgA, chromogranin A; NSE, neuron-specific enolase.