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Clinical Trial Results

Overview

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Title

Clinical activity and safety of cediranib and olaparib combination in patients with metastatic pancreatic ductal adenocarcinoma without BRCA mutation.

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NCT02498613

Sponsor(s)

NCI

Principal Investigator

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IRB Approved

Yes

Author Summary: Abstract and Brief Discussion

Background

Cediranib, a vascular endothelial growth factor receptor inhibitor, suppresses expression of *BRCA1/2* and *RAD51* inducing homologous recombination DNA repair deficiency (HRD) in several cancer cell lines and xenograft models [1]. Olaparib provides a clinical benefit in patients with metastatic pancreatic adenocarcinoma (mPDAC) with germline *BRCA* mutation (gBRCAmt) [2]. We hypothesized that cediranib induces HRD in the absence of gBRCAmt and synergizes with olaparib resulting in an objective response in mPDAC patients.

Methods

Patients with mPDAC with at least one prior systemic chemotherapy were enrolled. Patients with known gBRCAmt were excluded. Patients took cediranib 30mg daily and olaparib 200mg twice daily, orally. The primary endpoint was objective response (OR) rate.

Results

Nineteen patients received the study drugs. Seven patients came off treatment before the first restaging scan: six due to clinical progression and one due to an adverse event. No OR was

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observed**.** Six patients had stable disease (SD) as a best overall response. The median duration of SD was 3.1 months. The median overall survival was 3.4 months. Common treatment-related adverse events were fatigue, hypertension, and diarrhea.

Conclusion

Cediranib and olaparib combination did not result in clinically meaningful activity in patients with mPDAC without gBRCAmt.

Discussion

Clinical efficacy of a poly-(ADP-ribose) polymerase (PARP) inhibitor in patients with homologous recombination DNA repair deficiency (HRD) has been well-documented in pancreatic cancer and other solid tumors [2-4]. Hypoxia induces downregulation of homologous recombination DNA repair (HR) genes in several cancer cell lines and xenograft models including breast, lung, colon, and prostate cancers [5-7]. Cediranib, a vascular endothelial growth factor receptor (VEGFR) inhibitor, suppresses expression of *BRCA1/2* and *RAD51* inducing HR deficiency (HRD) in breast and ovarian cancer cell lines and their xenograft models [1]. The central hypothesis of this study is that cediranib induces tumor hypoxia leading to a HRD phenotype and sensitizes the tumors to a PARP inhibitor resulting in objective responses and disease control in the absence of a deleterious mutation in *BRCA* or other HR related genes. To that end, we accrued patients with metastatic solid tumors in 4 cohorts: pancreatic ductal adenocarcinoma (mPDAC), triple negative breast cancer, small cell lung cancer and non-small cell lung cancer. Patients with known germline *BRCA* mutation were excluded. Patients were treated with cediranib 30mg orally once daily and olaparib 200mg orally twice daily. The primary objective was to determine the objective response rate in each of the disease cohorts.

We found that the combination of cediranib plus olaparib did not result in any objective response in mPDAC patients. Six patients achieved stable disease as best overall response. The median duration of stable disease was only 3.1 months with the range of 1.2 to 6.8 months. This did not translate into durable disease control. Given the lack of clinically meaningful activity of cediranib and olaparib combination in patients with mPDAC, the accrual to the PDAC cohort was terminated early due to futility.

A potential explanation for the lack of activity is that cediranib did not induce HRD phenotype deleterious enough to result in synthetic lethality with olaparib as hypothesized. It should be noted that while the preclinical studies supporting our hypothesis-testing were done in several tumor cell lines and xenograft models including lung, colon, breast, prostate and cervical cancers[5-7], no preclinical studies were performed in pancreatic cancer models.

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This regimen is currently under clinical investigation in other solid tumors with tissue and blood-based correlative studies and will be reported separately.

Lessons Learned

- Cediranib and olaparib combination did not result in clinically meaningful activity in patients with metastatic pancreatic ductal adenocarcinoma without known *BRCA* mutation.

Trial Information

Disease

Pancreatic 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

Overall Response Rate

Secondary Endpoint

Toxicity

Additional Details of Endpoints or Study Design

The primary objective was to assess the objective response rate (ORR) of the combination of cediranib and olaparib in patients with metastatic pancreatic ductal adenocarcinoma. Simon's

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two-stage design was used. The null hypothesis that the true ORR is 5% was tested against a one-sided alternative. In the first stage, 18 response-evaluable patients were accrued. At least one confirmed objective response was required in order to proceed to the second stage accrual for a total of 32 patients. The null hypothesis would be rejected if 4 or more responses are observed in 32 patients. This design yields a type I error rate of 10% and power of 90% when the true ORR is 20%.

Investigator's Analysis

Inactive because results did not meet primary endpoint

Drug Information for Phase Phase II Cediranib/Olaparib

cediranib

Generic/Working name

cediranib

Company Name

AstraZeneca

Drug Type

Small molecule

Drug Class

VEGFR

Dose

30 milligrams (mg) per flat dose

Route

oral (po)

Schedule of Administration

once daily

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olaparib

Generic/Working name

olaparib

Trade Name

Lynparza

Company Name

AstraZeneca

Drug Type

Small molecule

Drug Class

PARP

Dose

200 milligrams (mg) per flat dose

Route

oral (po)

Schedule of Administration

twice daily

Drug Information for Phase Phase II Control

New drug

Generic/Working name

New drug

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Patient Characteristics for Phase Phase II Cediranib/Olaparib

Number of patients, male	11
Number of patients, male	8
Stage	IV
Age	Median (range):68 (45-85)
Number of prior systemic therapies	Median (range):3 (1-5)
Performance Status: ECOG	• 0 — 7 • 1 — 12 • 2 — 0 • 3 — 0 • Unknown — 0
Other	**Number of Patients** N = 19 **Race** White 16 (84%) Black or African American 1 (5%) Asian 2 (11%) **Prior lines of therapy** Median **3**

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1	
3 (16%)	
2	
6 (32%)	
≥ 3	
10 (53%)	
Prior Therapies	
FOLFIRINOX	
14 (74%)	
Gemcitabine-based regimen	
18 (95%)	
BRCA 1/2 mutation status	
known or suspected germline BRCA mutation	
0	
unknown	
19	

Cancer Types or Histologic Subtypes

Patient Characteristics for Phase Phase II Control

Number of patients, male	0
Number of patients, male	0

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Stage

Age

Number of prior systemic therapies

Performance Status: ECOG

- 0 — 0
- 1 — 0
- 2 — 0
- 3 — 0
- Unknown — 0

Other

Cancer Types or Histologic Subtypes

Primary Assessment Method for Phase Phase II Cediranib/Olaparib

Title	Clinical Activity Summary
Number of patients screened	24
Number of patients enrolled	24
Number of patients evaluable for toxicity	19
Number of patients evaluated for efficacy	18
Evaluation Method	RECIST 1.1
Response assessment CR	N = 0 0
Response assessment PR	N = 0 0
Response assessment SD	N = 33 6
Response assessment PD	N = 67 12

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Response assessment OTHER

(Median) duration assessments PFS

(Median) duration assessments TTP

(Median) duration assessments OS 3.4 months , CI:

(Median) duration assessments response duration

(Median) duration assessments duration of treatment 47 Days

Waterfall plot legend

Outcome Notes

Primary Assessment Method for Phase Phase II Control

Phase Phase II Cediranib/Olaparib Adverse Events

All Cycles

Name	*NC/NA	1	2	3	4	5	All Grades
Fatigue	26%	37%	37%	0%	0%	0%	74 %
Hypertension	53%	0%	32%	16%	0%	0%	47 %
Diarrhea	68%	26%	5%	0%	0%	0%	32 %
Platelet count decreased	68%	26%	5%	0%	0%	0%	32 %
Nausea	79%	11%	11%	0%	0%	0%	21 %
Anorexia	79%	21%	0%	0%	0%	0%	21 %
Aspartate aminotransferase increased	79%	11%	11%	0%	0%	0%	21 %
Alkaline phosphatase increased	79%	11%	11%	0%	0%	0%	21 %
Vomiting	84%	11%	5%	0%	0%	0%	16 %
White blood cell decreased	84%	11%	5%	0%	0%	0%	16 %
Lymphocyte count decreased	84%	0%	11%	5%	0%	0%	16 %

Dizziness	84%	16%	0%	0%	0%	0%	16 %
Alanine aminotransferase increased	84%	5%	11%	0%	0%	0%	16 %
Voice alteration	89%	0%	11%	0%	0%	0%	11 %
Anemia	89%	0%	11%	0%	0%	0%	11 %
Constipation	89%	5%	5%	0%	0%	0%	11 %
Hyponatremia	89%	5%	0%	5%	0%	0%	11 %
Peripheral sensory neuropathy	89%	11%	0%	0%	0%	0%	11 %

Adverse Events Legend

Commonly reported treatment-related Adverse Events

Phase Phase II Control Adverse Events

Pharmacokinetics/Pharmacodynamics for Phase Phase II Cediranib/Olaparib

N	Dose of Drug: cediranib	Dose of Drug: olaparib	Cmax	AUC	Half-Life	Volume of distribution	Clearance	Results of Pharmacodynamic analysis

Pharmacokinetics/Pharmacodynamics for Phase Phase II Control

N	Dose of Drug: New drug	Cmax	AUC	Half-Life	Volume of distribution	Clearance	Results of Pharmacodynamic analysis

Assessment, Analysis, and Discussion

Completion

Study completed

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Investigator's Assessment

Inactive because results did not meet primary endpoint

Discussion

Maintenance olaparib prolongs progression-free survival (PFS) in patients with a germline *BRCA* mutation (gBRCAmt) and metastatic pancreatic ductal adenocarcinoma (mPDAC)[2] and has become a standard of care. While there is no question that the approval of olaparib has provided a hope for patients with metastatic PDAC, the scope of the benefit is limited to the 4% to 7% of the pancreatic cancer patients who carry gBRCAmt [8, 9]. Preclinical studies showed that hypoxia and cediranib downregulates the expression of *BRCA1, BRCA2*, and *RAD51*, the key factors of homologous recombination DNA repair (HR), resulting in HR deficiency (HRD) and sensitivity to a PARP inhibitor in several tumor cell lines [1, 5-7, 10]. Consistent with these preclinical data, cediranib and olaparib has demonstrated superior progression-free survival and overall survival in women with platinum-sensitive ovarian cancer compared with olaparib monotherapy regardless of germline *BRCA* mutation status [11, 12]. The question we asked in this study was if homologous recombination DNA repair deficient (HRD) phenotype could be induced in patients without germline *BRCA* mutation with an hypoxia-inducing, vascular endothelial growth factor receptor inhibitor (VEGFRi), cediranib [13], resulting in a synthetic lethality with a poly-(ADP-ribose) polymerase inhibitor (PARPi), olaparib.

We accrued patients without known mutations in *BRCA* genes in 4 disease-specific cohorts: pancreatic ductal adenocarcinoma (PDAC), non-small cell lung cancer, small cell lung cancer and triple-negative breast cancer. Herein, we report the results from the safety and clinical activity analyses of PDAC cohort.

We found that the combination of cediranib 30mg once daily plus olaparib 200mg twice daily did not result in any objective response in patients with metastatic PDAC. While six (32%) of patients achieved stable disease as best overall response including 4 patients with regression in the tumor burden, the median duration of disease control was only 3.1 months. This did not translate into durable disease control. Given the lack of clinically meaningful activity of cediranib and olaparib combination in patients with mPDAC without gBRCAmt, the accrual to the PDAC cohort was terminated early due to futility.

There are a few things to comment about the study populations. First, during enrollment of PDAC cohort, the study intentionally excluded those with known germline *BRCA* mutation to test our hypothesis of cediranib-induced HRD phenotype. While the testing was not required to prove, none of the study patients had known deleterious mutations in *BRCA* genes prior to enrollment. Secondly, the study population was heavily pre-treated. Eighty-five percent of the

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patients had two or more lines of prior systemic therapies. Five (32%) patients had clinical progression prior to the first restaging scan in 2 months. The median overall survival of 3.4 months suggested that the patients were indeed in terminal stage of their disease. Plus, the median duration of drug exposure was less than 2 months, which undermines our confidence in sufficiency of treatment exposure to test the clinical activity of the regimen. While the AE profile was consistent with prior reports, [11, 12, 14] adverse events such as fatigue, anorexia, and diarrhea requiring dose-interruption, and hypertension requiring close blood pressure monitoring and adjustment of antihypertensives made this regimen not so easily tolerated and made it challenging for some patients.

A potential explanation for lack of activity is that cediranib does not induce HRD phenotype in heavily pre-treated pancreatic cancer patients or does not sensitize the tumors to a PARP inhibitor. It should be noted that while the preclinical studies supporting our hypothesis testing were done in several tumor cell lines and xenograft models including lung, colon, breast, prostate and cervical cancers [5-7, 10], it was not tested in pancreatic cancer models.

Olaparib remains a treatment option for metastatic PDAC patients with gBRCAmt as a maintenance therapy after a course of platinum-based chemotherapy without disease progression. We did not find any sign of clinically meaningful activity with the cediranib and olaparib combination in patients with heavily pre-treated mPDAC and without gBRCAmt.

Future studies should focus on the patient population with a limit on prior lines of therapy where patients can receive sufficient treatment exposure. The hypothesis of cediranib-induced HRD phenotype remains to be tested in other tumors. The analyses of clinical activities in other tumor cohorts are ongoing. Biomarkers analyses including circulating tumor DNA and angiogenesis markers in mPDAC patients are underway.

In conclusion, cediranib and olaparib did not result in any clinically meaningful activity in patients with heavily pre-treated metastatic pancreatic ductal adenocarcinoma without *BRCA* mutation.

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Figures and Tables

Print Figures

Table 1. Common (>10%) Treatment Related Adverse Events

AE Terms	Grade 1 (n=15)	Grade 2 (n=13)	Grade 3 (n=8)	Grade 4 (n=0)	Total (n=19)
Fatigue	7 (37%)	7 (37%)			14 (74%)
Hypertension		6 (32%)	3 (16%)		9 (47%)
Diarrhea	5 (26%)	1 (5%)			6 (32%)
Thrombocytopenia	5 (26%)	1 (5%)			6 (32%)
Nausea	2 (11%)	2 (11%)			4 (21%)
Anorexia	4 (21%)				4 (21%)
AST increased	2 (11%)	2 (11%)			4 (21%)
Alkaline phosphatase increased	2 (11%)	2 (11%)			4 (21%)
Vomiting	2 (11%)	1 (5%)			3 (16%)
Leukopenia	2 (11%)	1 (5%)			3 (16%)
Lymphopenia		2 (11%)	1 (5%)		3 (16%)
Dizziness	3 (16%)				3 (16%)
ALT increased	1 (5%)	2 (11%)			3 (16%)
Voice Alteration		2 (11%)			2 (11%)
Anemia		2 (11%)			2 (11%)
Constipation	1 (5%)	1 (5%)			2 (11%)
Hyponatremia	1 (5%)		1 (5%)		2 (11%)
Peripheral sensory neuropathy	2 (11%)				2 (11%)

Figure 1. Duration of Treatment

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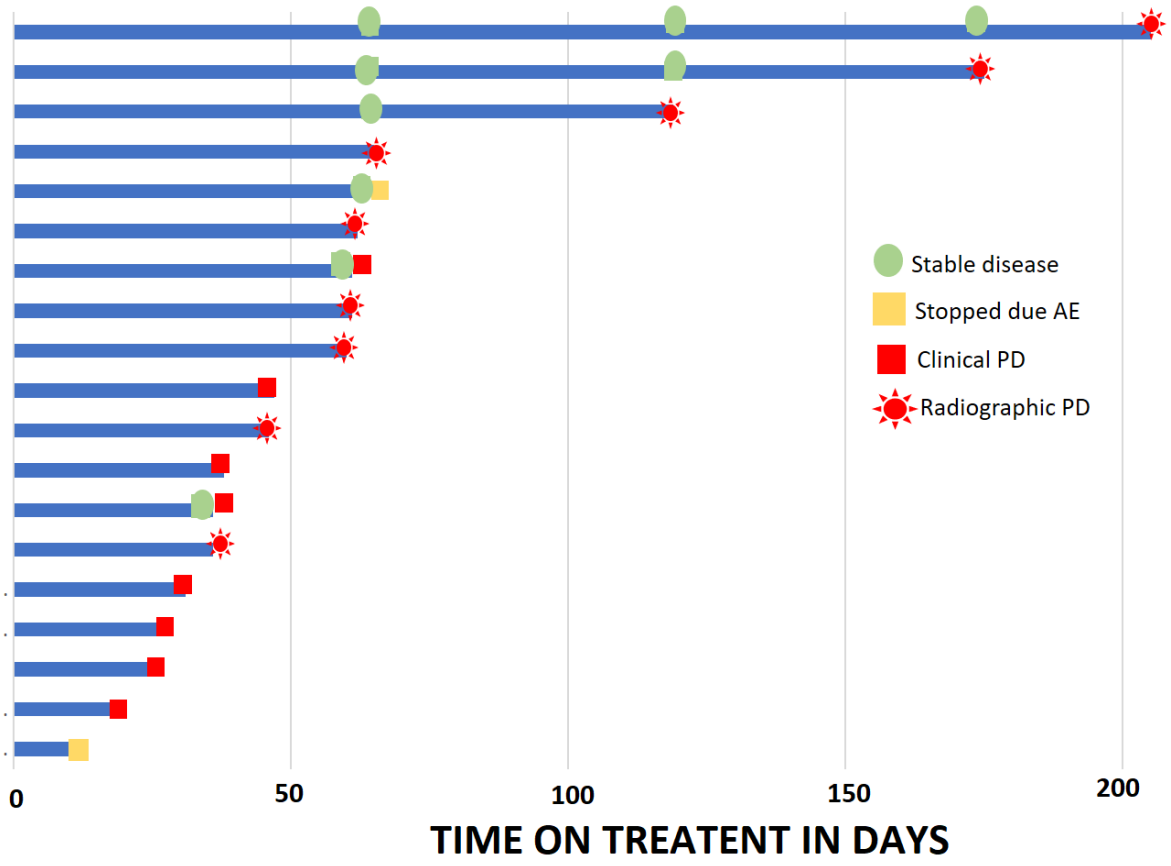

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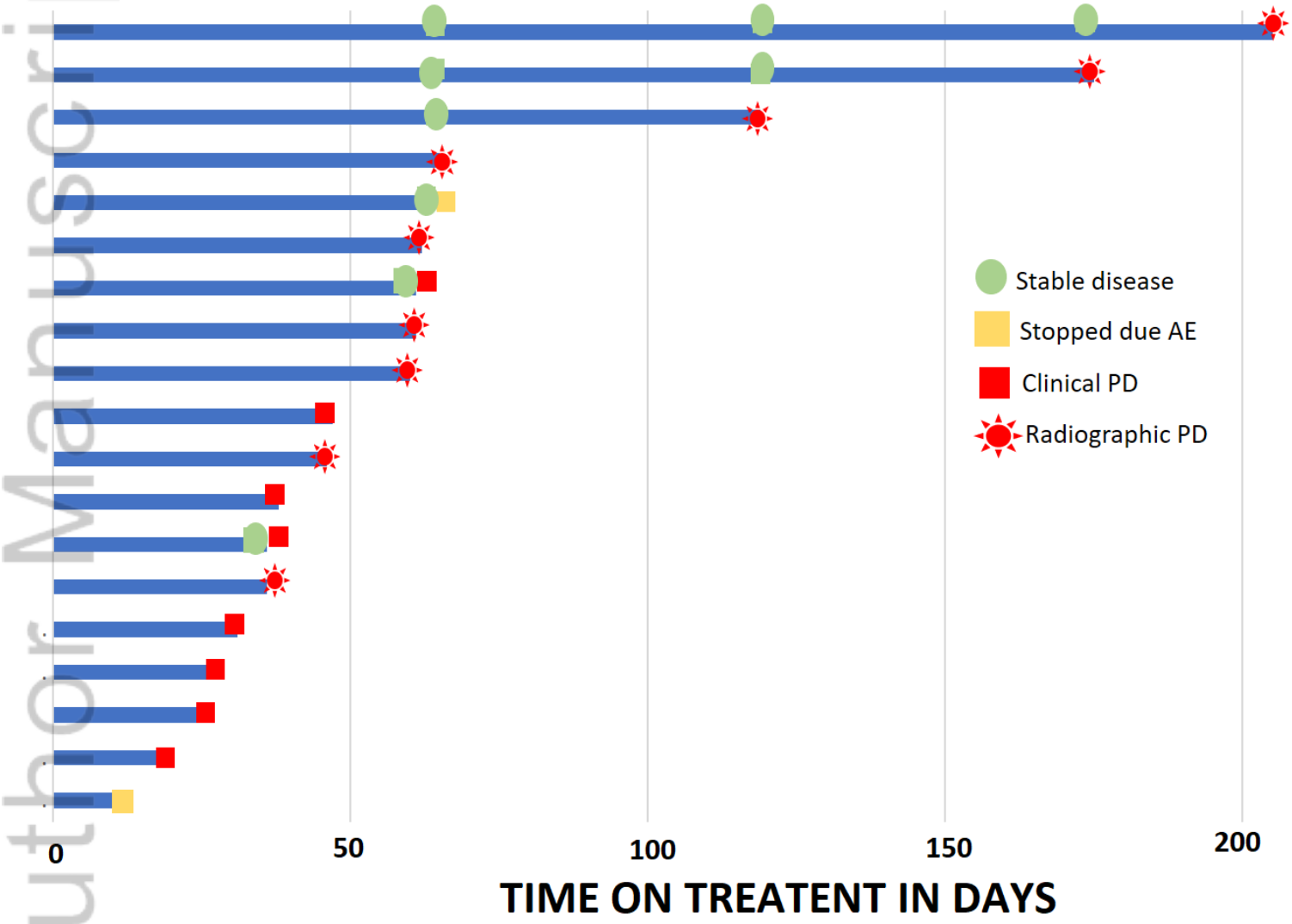

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Constipation	1 (5%)	1 (5%)			2 (11%)
Hyponatremia	1 (5%)		1 (5%)		2 (11%)
Peripheral sensory neuropathy	2 (11%)				2 (11%)

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