

Safety and Activity of Sorafenib in Addition to Vinflunine in Post-Platinum Metastatic Urothelial Carcinoma (Vinsor): Phase I Trial

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT01844947
- **Sponsor(s):** Anders Ullén
- **Principal Investigator:** Anders Ullén
- **IRB Approved:** Yes

LESSONS LEARNED

- First trial to report safety and activity of the microtubule inhibitor vinflunine plus the tyrosine kinase inhibitor sorafenib in post-platinum metastatic urothelial cancer (mUC) patients.
- A recommended phase II dose was identified for the treatment combination of vinflunine plus sorafenib, with main adverse events including fatigue, febrile neutropenia, neutropenia, hypertension, and hyponatremia.
- An overall response rate of 41% to second-line vinflunine plus sorafenib treatment in patients with platinum-resistant mUC was confirmed.

ABSTRACT

Background. Platinum-progressive metastatic urothelial carcinoma (mUC) is a clinical challenge. The tyrosine kinase inhibitor sorafenib has demonstrated varied activity in mUC. This trial was designed to examine safety and activity of vinflunine plus sorafenib in mUC.

Methods. In addition to standard dose of vinflunine (320 or 280 mg/m²), patients received sorafenib (400, 600, or 800 mg/day), in a 3 + 3 dose-escalation phase I design.

Results. Twenty-two patients (median age 62.5 years) were included. Five patients received vinflunine 320 mg/m² and 17 received 280 mg/m². The maximum tolerated dose (MTD) of sorafenib with vinflunine 280 mg/m² was 600 mg, and with vinflunine 320 mg/m² it was not determined, owing to toxicity. Adverse events (AEs) grades 3 + 4 consisted of neutropenia (6 patients), febrile neutropenia (5), and hyponatremia (5). The overall response rate (ORR) in the efficacy-evaluable patients was 41% (7 of 17), all partial responses evaluated by RECIST version 1.1. Median overall survival (OS) was 7.0 months (1.8–41.7).

Conclusion. The defined recommended phase II dose (RPTD) was vinflunine 280 mg/m² plus sorafenib 400 mg. Sorafenib was too toxic in combination with vinflunine 320 mg/m². The ORR of 41% to this second-line combination treatment of mUC is noteworthy and supports further trials. *The Oncologist* 2019;24:745–e213

DISCUSSION

For mUC patients with rapidly progressive platinum-resistant disease, development of effective treatment options remains a challenge and an unmet medical need. The combination of vinflunine in standard dose plus dose-escalated sorafenib was evaluated for safety and toxicity in this phase I trial in second-line treatment of mUC. All subjects had disease progression or relapse ≤6 months following previous platinum-based chemotherapy, reflecting a cohort of patients with platinum-resistant disease.

The observed high rate of toxicity for patients treated with vinflunine of 320 mg/m² is in line with previously reported

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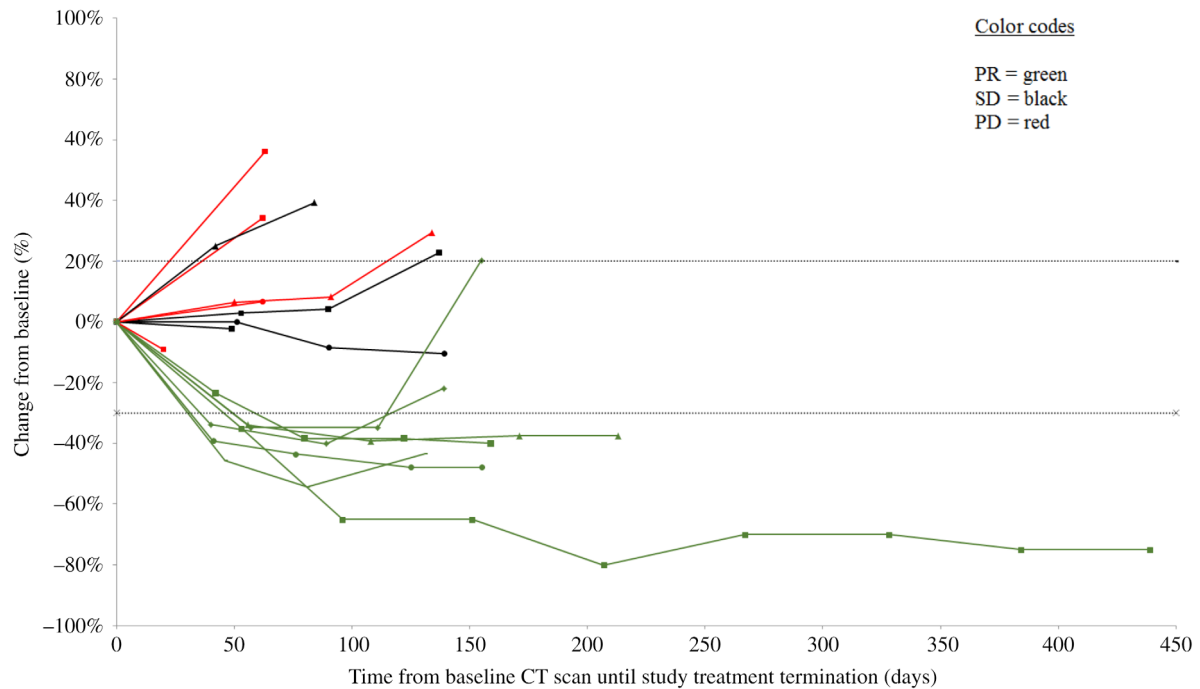


Figure 1. Tumor response by RECIST version 1.1. Percentage change in sum of the diameters of tumor lesions from baseline. Abbreviations: CT, computed tomography; PD, progressive disease; PR, partial response; SD, stable disease.

phase I vinflunine combination studies, including doublets with pazopanib and pemetrexed [1, 2]. It appears as if full-dose vinflunine doublets for patients with platinum-progressive disease require combination with compounds with low bone marrow toxicity. Hence, the combination with sorafenib in this trial proved only to be safe and tolerable with a vinflunine starting dose of 280 mg/m² [3–6]. The most frequent AE grades 3 + 4 in this study included neutropenia, hypertension, and hyponatremia. These side effects are potentially caused by both vinflunine and sorafenib, but more frequently reported in the former except for hypertension [7, 8].

The addition of sorafenib to vinflunine did not significantly improve median OS as compared with the vinflunine registration trial (7.0 vs. 6.9 months). For patients administered vinflunine 280 mg/m² (e.g., Eastern Cooperative Oncology Group performance status [ECOG PS] 1, creatinine clearance 40–60 mL/minute) in this study, the prognosis was most likely even worse than for the average second-line patient treated within the vinflunine registration trial. Considering this fact, the observed ORR of 41% and disease control rate (DCR) of 71% in this study is notable, especially compared with the ORR and DCR of 8.6% and 55.1% in the vinflunine registration trial [3]. The higher response rates

are plausibly attributable to the addition of sorafenib, possibly resulting in an additive effect of this specific drug combination. Further, the results of the present study are in line with the RANGE study, reporting an advantage of combining docetaxel with another vascular endothelial growth factor receptor 2 active compound, ramucirumab, thus adding evidence that selected platinum-refractory mUC patients may benefit from concomitant standard chemotherapy plus antiangiogenic targeted therapy [9].

Within the context of this phase I trial, an RPTD for the treatment combination of vinflunine and sorafenib was identified for mUC patients with platinum-resistant and progressive disease. The observed side effects were expected but with a higher incidence of grade 3 + 4 hyponatremia than previously reported for vinflunine and sorafenib each administered as monotherapy. Clinically meaningful disease stabilization and objective responses were observed but with large differences in OS (Figs. 1 and 3). Future trials should aim to evaluate this treatment combination in a randomized setting, define biomarkers for treatment benefit, and explore the effects in patients with both platinum- and immunotherapy-resistant disease.

TRIAL INFORMATION

Disease	Bladder cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	One prior regimen
Type of Study – 1	Phase I
Type of Study – 2	3 + 3
Primary Endpoint	Maximum tolerated dose
Primary Endpoint	Recommended phase II dose

Secondary Endpoints

Efficacy; response and survival outcomes

Additional Details of Endpoints or Study Design

The Vinsor study was a phase I trial evaluating the treatment combination of standard-dose vinflunine and sorafenib, in dose escalation. Patients with progressive locally advanced mUC following platinum combination-chemotherapy were screened for inclusion at three cancer centers within the Nordic Urothelial Cancer Oncology Group collaboration, one center in Stockholm, Sweden, and two centers in Denmark, Copenhagen and Aarhus. The study was investigator-initiated and conducted as an academic clinical trial. The trial was monitored independently at the respective sites in Sweden and Denmark. The study was approved by the regional Ethical Review Board in Stockholm (October 12, 2011, ref 2011/1398-31/1) and by the Scientific Research Council Komité E, Region Hovedstaden, Hillerød, Denmark (August 28, 2012, ref H-1-2012-079). The study was approved by the Swedish Medical Products Agency (151:2012/12127) and by the Danish Health and Medicines Authority (2012053960). Study participation was compliant with the Declaration of Helsinki. Prior to screening procedures and treatment, signed informed consent was obtained from all patients. This trial is registered with ClinicalTrials.gov, number NCT01844947.

Eligibility Criteria: Eligible patients, aged 18–80 years, with ECOG PS 0 or 1, had a histologically confirmed diagnosis of UC (pure or mixed) of the urothelial tract. The major inclusion criteria stipulated that UC patients had a confirmed disease relapse or progression no later than at the 6-month follow-up visit after completion of previous platinum-based chemotherapy. Patients were not allowed to have received more than one previous line of chemotherapy treatment for locally advanced or mUC. Alternatively, patients with mUC and contraindication to platinum-containing chemotherapy were eligible. Any prior systemic chemotherapy needed to be permanently terminated 14 days prior to inclusion and recovery from treatment-related toxicity (grade 1 or less). Patients needed to have measurable or nonmeasurable disease using RECIST version 1.1. Patients with predominantly adenocarcinoma, squamous cell carcinoma, or any other nontransitional cell carcinoma were excluded. Prior treatment with vinflunine was not allowed. Patients with brain metastasis or leptomeningeal involvement were not eligible. Patients with congestive heart failure (New York Heart Association class \geq III), angina pectoris, poorly controlled hypertension $>150/90$ mmHg, hypercalcemia, hypokalemia, or QTc time >450 ms at baseline were excluded. ECG controls were performed to exclude patients at high risk for developing arrhythmias. Included patients were required to have an acceptable hematologic function: hemoglobin ≥ 10 g/dL, absolute neutrophil count $\geq 1.0 \times$ lower limit of normal, and platelets $\geq 100\,000$ per μL ; adequate hepatic function: bilirubin $<1.5 \times$ upper limit of normal (ULN), and transaminases $<2.5 \times$ ULN; renal function: creatinine clearance ≥ 40 mL/minute (measured by iohexol or ^{51}Cr -EDTA techniques).

Procedures: The study subjects were treated with standard doses of vinflunine, 320 or 280 mg/m^2 , depending on their condition (see details below). In addition, patients were prescribed a fixed start dose of sorafenib (400, 600, or 800 mg). Patients with ECOG PS 0, age ≤ 74 years, presenting adequate hepatic and renal function (defined as creatinine clearance >60 mL/minute) were treated with vinflunine 320 mg/m^2 intravenous (IV) on day 1, and sorafenib in 200 mg dose steps from 200 to 400 mg b.i.d. on days 2–21 every 3 weeks (Q3W). For patients with PS 1, or age 75–80 years, or previous exposure to radiation of the lower pelvic region, or with impaired renal function (creatinine clearance 40–60 mL/minute) but adequate hepatic function, the dose of vinflunine was 280 mg/m^2 IV on day 1 and sorafenib as per above days 2–21, repeated every 21 days. Treatment continued until progression, unacceptable toxicity, or any other medical event requiring a stop. Pause in treatment was allowed for up to 14 days. Dose reductions were permitted as described in the protocol. Toxicity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Adverse events were evaluated during all treatment cycles for all patients. Study drug-related adverse events recorded during cycle 1 and 2 served to define dose-limiting toxicity (DLT) as hematological toxicity: grade ≥ 4 neutropenia (absolute neutrophil count $<0.5 \times 10^9$ for ≥ 7 days or $<0.1 \times 10^9$ for ≥ 3 days), or febrile neutropenia of grade ≥ 3 (absolute neutrophil count $<1.0 \times 10^9$ and temperature $\geq 38.5^\circ\text{C}$), or platelet count $<25 \times 10^9/\text{L}$ or thrombocytopenia with bleeding or requiring platelet transfusion; and nonhematological toxicity: liver toxicity (alanine aminotransferase or aspartate aminotransferase) of grade ≥ 3 for >7 days, or any other grade ≥ 3 major organ toxicity according to CTCAE v 4.0. Any AE had to resolve to grade ≤ 2 within 14 days to continue study treatment. Tumor response was radiologically evaluated by computer tomography after completing every two treatment cycles. Evaluation of response to treatment was performed on measurable and/or nonmeasurable tumor lesions using RECIST v 1.1.

Safety Assessment: Examination by physician (including performance status [World Health Organization ECOG scale] and body weight) weekly during cycle one and thereafter prior to every new treatment cycle (i.e., every 3rd week). Complete blood counts, electrolytes, and renal and hepatic function prior to and at day 8 in every treatment cycle. All patients were followed-up by a oncology nurse at day 8 and 15 during all treatment cycles. Blood pressure was monitored weekly during the first two cycles and thereafter every 3rd week as long as the active treatment remained.

Investigator's Analysis

Active and should be pursued further

DRUG INFORMATION**Drug 1**

Generic/Working Name	Vinflunine
Trade Name	Javlor
Company Name	Pierre Fabre
Drug Type	Small molecule
Drug Class	Tubulin/Microtubules targeting agent
Dose	280 and 320 mg/m^2
Route	IV
Schedule of Administration	Day 1, Q3W

Drug 2	
Generic/Working Name	Sorafenib
Trade Name	Nexavar
Company Name	Bayer Healthcare AG
Drug Type	Small molecule
Drug Class	Raf - BRAF
Dose	400, 600, or 800 per day (200 + 200, 200 + 400, or 400 + 400) mg per flat dose
Route	p.o.
Schedule of Administration	Morning and evening (b.i.d.) on days 2–21, Q3W

DOSE ESCALATION TABLE

Dose level	Dose of drug: vinflunine, mg/m ²	Dose of drug: sorafenib, mg	Number enrolled	Number evaluable for toxicity
IA	320	400	5	5
IB	280	400	5	3
IIB	280	600	6	6
IIIB	280	800	6	5

PATIENT CHARACTERISTICS

Number of Patients, Male	13
Number of Patients, Female	9
Stage	Metastatic urothelial cancer (all patients)
Age	Median (range): 62.5 years, range 44–71 years
Number of Prior Systemic Therapies	Median (range): 1, range 1–1
Performance Status: ECOG	0 — 9 1 — 13 2 — 0 3 — 0 Unknown — 0

Other

Previous treatments included cystectomy (10 patients) and nephrectomy/ureterectomy (3). No previous surgery (9). No patient had received radiation to the pelvic region prior to study inclusion. All patients had received one line of platinum (cisplatin or carboplatin)-containing systemic chemotherapy treatment (median 5 cycles [range 1–11]).

Cancer Types or Histologic Subtypes

Urothelial tract cancer (urothelial histology) ICD-10: C66.9-C68.9

PRIMARY ASSESSMENT METHOD

Title	Efficacy assessment
Number of Patients Screened	69
Number of Patients Enrolled	22
Number of Patients Evaluable for Toxicity	19
Number of Patients Evaluated for Efficacy	17
Evaluation Method	RECIST 1.1
Response Assessment CR	<i>n</i> = 0 (0%)
Response Assessment PR	<i>n</i> = 7 (41%)
Response Assessment SD	<i>n</i> = 5 (29%)
Response Assessment PD	<i>n</i> = 5 (29%)
Response Assessment OTHER	<i>n</i> = 0 (0%)
(Median) Duration Assessments PFS	4.5 months
(Median) Duration Assessments TTP	4.2 months
(Median) Duration assessments OS	7.0 months
(Median) Duration Assessments Duration of Treatment	2.3 months

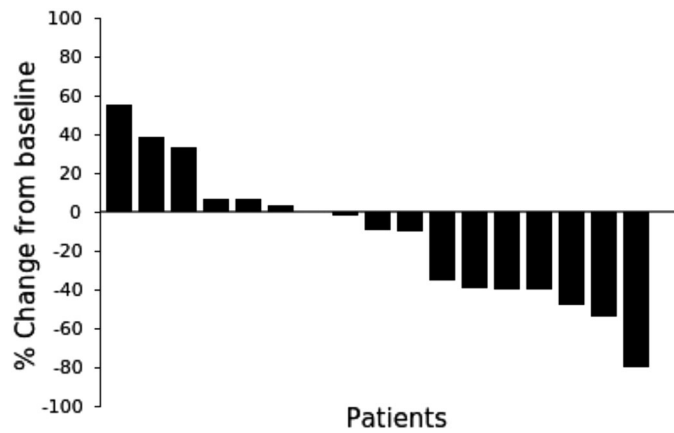


Figure 2. Waterfall plot of individual patient’s tumor response by RECIST version 1.1. Best percentage change in the sum of size (diameters) of tumor lesions from baseline until the end of study treatment. One patient (number 17) developed brain metastases (new nontarget tumor lesions) during cycle 2. No formal treatment evaluation of this patient’s target lesions was performed.

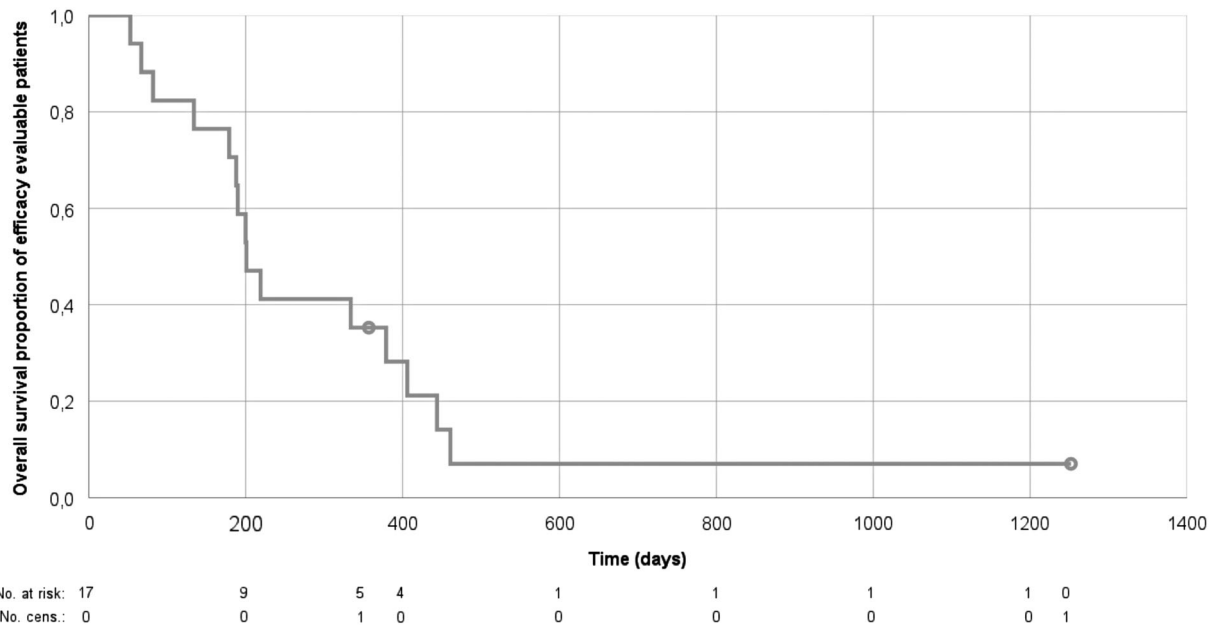


Figure 3. Kaplan-Meier plot of overall survival outcome. Overall survival in days from date of study assignment until recorded death among the efficacy-evaluable patients (*n* = 17).

KAPLAN-MEIER TIME UNITS					
Days					
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	17
53	1	0	100.00	94.12	16
67	1	0	94.12	88.24	15
82	1	0	88.24	82.35	14
134	1	0	82.35	76.47	13
179	1	0	76.47	70.59	12
188	1	0	70.59	64.71	11

190	1	0	64.71	58.82	10
200	1	0	58.82	52.94	9
201	1	0	52.94	47.06	8
219	1	0	47.06	41.18	7
334	1	0	41.18	35.29	6
357	0	1	35.29	35.29	5
379	1	0	35.29	28.24	4
406	1	0	28.24	21.18	3
444	1	0	21.18	14.12	2
461	1	0	14.12	7.06	1
1,252	0	1	7.06	0.00	0

Outcome Notes:

Sixty-nine patients were screened for inclusion between April 2012 and September 2017. Screening failures included no progression on platinum within 6 months, comorbidity or insufficient PS, second-line treatment previously administered, history of other malignancy, and prolonged QTc interval. Twenty-two patients at three sites in two countries were included. The primary tumor was located in the bladder (18 patients), renal pelvis (2 patients), and ureter (2 patients). All included patients had confirmed histology of pure urothelial carcinoma at inclusion and disease progression within 6 months following treatment with platinum and gemcitabine. Previous surgical treatment included cystectomy in 10 patients and nephrectomy/ureterectomy in 3 patients. The median number of cycles administered was 4 (range 1–16). Median duration of study treatment was 4.1 months (0.1–14.5) among the DLT-evaluable patients. The MTD of vinflunine 320 mg/m² day 1 with sorafenib days 2–21 Q3W was not defined (<400 mg) because three out of five patients had a DLT in the first dose cohort. For patients treated with vinflunine 320 mg/m², adding sorafenib, even at a dose of 400 mg daily, resulted in unacceptable toxicity. The MTD of vinflunine 280 mg/m² day 1 with sorafenib was 600 mg (200 + 400 mg) days 2–21 Q3W. Five of eight patients with treatment-induced hypertension received at least six cycles of treatment, and three partial responses were reported. Two of the six efficacy-evaluable patients with skin rash had a partial response and three had stable disease on study treatment. Two patients continued with vinflunine monotherapy after study completion. Three patients received experimental treatment within clinical trial protocols and two patients received immunotherapy. At data cutoff date, October 1, 2018, two patients remained alive.

ADVERSE EVENTS**All Cycles**

Name	NC/NA	1	2	3	4	5	All grades
Febrile neutropenia	73%	0%	0%	16%	11%	0%	27%
Neutrophil count decreased	63%	0%	5%	16%	16%	0%	37%
Platelet count decreased	90%	0%	5%	5%	0%	0%	10%
Anemia	70%	10%	20%	0%	0%	0%	30%
Palpitations	95%	5%	0%	0%	0%	0%	5%
Hypertension	53%	0%	26%	21%	0%	0%	47%
Gum infection	68%	16%	16%	0%	0%	0%	32%
Diarrhea	58%	37%	5%	0%	0%	0%	42%
Oral pain	89%	11%	0%	0%	0%	0%	11%
Dysgeusia	95%	5%	0%	0%	0%	0%	5%
Dyspepsia	95%	5%	0%	0%	0%	0%	5%
Constipation	40%	5%	55%	0%	0%	0%	60%
Vomiting	68%	16%	16%	0%	0%	0%	32%
Nausea	57%	32%	11%	0%	0%	0%	43%
Dizziness	84%	11%	5%	0%	0%	0%	16%
Weight gain	95%	5%	0%	0%	0%	0%	5%
Anorexia	95%	5%	0%	0%	0%	0%	5%
Weight loss	90%	5%	5%	0%	0%	0%	10%
Blood bilirubin increased	95%	5%	0%	0%	0%	0%	5%
Hyponatremia	74%	0%	0%	21%	5%	0%	26%

Hypokalemia	90%	5%	5%	0%	0%	0%	10%
Headache	90%	5%	5%	0%	0%	0%	10%
Fatigue	20%	35%	35%	10%	0%	0%	80%
Peripheral sensory neuropathy	78%	11%	11%	0%	0%	0%	22%
Dry skin	84%	16%	0%	0%	0%	0%	16%
Alopecia	84%	11%	5%	0%	0%	0%	16%
Palmar-plantar erythrodysesthesia syndrome	79%	16%	5%	0%	0%	0%	21%
Skin and subcutaneous tissue disorders - rash/desquamation	65%	15%	20%	0%	0%	0%	35%
Urinary tract infection	95%	0%	5%	0%	0%	0%	5%
Urinary frequency	95%	5%	0%	0%	0%	0%	5%
Myalgia	80%	15%	5%	0%	0%	0%	20%
Abdominal pain	95%	0%	5%	0%	0%	0%	5%
Pelvic pain	95%	5%	0%	0%	0%	0%	5%
Injection site reaction	95%	5%	0%	0%	0%	0%	5%
Dyspnea	85%	5%	5%	5%	0%	0%	15%
Ileus	90%	0%	5%	5%	0%	0%	10%
Edema limbs	95%	5%	0%	0%	0%	0%	5%
Thromboembolic event	84%	0%	11%	0%	0%	5%	16%
Abdominal infection	95%	0%	0%	5%	0%	0%	5%
Urinary tract obstruction	95%	0%	5%	0%	0%	0%	5%
Back pain	95%	0%	5%	0%	0%	0%	5%
Nervous system disorders - Dysesthesia	95%	0%	5%	0%	0%	0%	5%
Palmar-plantar erythrodysesthesia syndrome	95%	0%	5%	0%	0%	0%	5%
Hypothyroidism	100%	0%	0%	0%	0%	0%	0%

Number of cases that reported adverse events and grade of adversity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Three patients did not complete the initial two treatment cycles and were not diagnosed with a dose-limiting toxicity, hence the variation in *n*.

Abbreviation: NC/NA, no change from baseline/no adverse event.

SERIOUS ADVERSE EVENTS		
Name	Grade	Attribution
Subileus	3	Unlikely
Malnutrition	2	Unlikely
Febrile neutropenia (DLT)	4	Definite
Pain	2	Probable
Ileus	3	Unrelated
Deep vein thrombosis	2	Unrelated
Dyspnea	3	Unrelated
Dyspnea	2	Unrelated
Constipation	2	Probable
Urinary obstruction (nephrostomy)	2	Unrelated
Febrile neutropenia (DLT)	3	Definite
Hypertension (DLT)	3	Definite
Fever	1	Probable
Febrile neutropenia (DLT)	3	Definite
Constipation	2	Probable
Fever	3	Unrelated
Deep vein thrombosis	2	Unlikely
Ileus	2	Unlikely
Abdominal pain	2	Unlikely

Pulmonary embolism	5	Unlikely
Abdominal abscess	3	Unrelated
Febrile neutropenia (DLT)	4	Definite
Febrile neutropenia (DLT)	3	Definite
Neutropenia (DLT)	4	Definite

Attribution (if not identical relation to sorafenib and vinflunine): febrile neutropenia (DLT) G4 - definite vinflunine (sorafenib: unlikely), pain G2 - probable vinflunine (sorafenib: not related), constipation G2 - probable vinflunine (sorafenib: unlikely) × 2, febrile neutropenia (DLT) G3 - definite vinflunine (sorafenib: probable) × 2, neutropenia (DLT) G4 - definite vinflunine (sorafenib: unlikely), hypertension (DLT) G3 - definite sorafenib (vinflunine: not related). Abbreviation: DLT, dose-limiting toxicity.

DOSE-LIMITING TOXICITIES				
Dose level	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity	Dose-limiting toxicity information
IA	5	5	3	Febrile neutropenia ×2, hypertension
IB	5	3	0	
IIB	6	6	1	Febrile neutropenia
IIIB	6	5	3	Febrile neutropenia ×2, neutropenia

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion

Study completed

Investigator's Assessment

Active and should be pursued further

Although the recently approved immunotherapies can induce impressive and durable responses, the majority of patients with metastatic urothelial cancer (mUC) do not have major responses. In the randomized second-line phase III trial of pembrolizumab, the overall response rate (ORR) was limited to 21.1%, and the response rates reported for atezolizumab, durvalumab, avelumab, and nivolumab are in the same range [10–14]. For these postimmunotherapy patients, as well as for patients with rapidly progressive platinum-resistant disease, further development of effective treatment options remains a challenge and an unmet medical need.

The combination of vinflunine in standard dose with dose-escalated sorafenib was evaluated for safety and toxicity in this phase I trial for patients with mUC. All included patients in this study had disease progression or relapse within 6 months following previous platinum-based chemotherapy, reflecting a cohort of typically platinum-resistant patients with aggressive disease.

The observed high rate of toxicity for patients treated with a start dose of vinflunine of 320 mg/m² is in line with previously reported phase I vinflunine combination studies, including doublets with pazopanib and pemetrexed [1, 2]. It appears as if full-dose vinflunine doublets for patients with progressive disease after cisplatin requires combination compounds with low bone marrow toxicity. Hence, the combination with sorafenib proved only to be safe and tolerable with a vinflunine start dose of 280 mg/m². Side effects of grade 1 and 2 were mainly gastrointestinal (constipation and diarrhea), fatigue, nausea/vomiting, and skin rash. Constipation and pain have more commonly been reported with vinflunine, whereas diarrhea is frequently seen with tyrosine kinase inhibitor therapies and fatigue with either [3–6]. The top three reported adverse events (AEs) of grade ≥3 in this study

included neutropenia (31.6%), hyponatremia (26.3%), and febrile neutropenia (26.3%). These side effects are potentially caused by both vinflunine and sorafenib, but are more frequent in the former except for hypertension [7, 8]. No definite treatment-related death was recorded, but one patient had fatal pulmonary embolism (unlikely relation to study treatment). Overall, the AEs are in line with previous studies combining vinflunine and other cytotoxic agents [1, 2, 15].

The addition of sorafenib to vinflunine did not improve median overall survival (OS) as compared with the registration trial by Bellmunt et al. evaluating monotherapy with vinflunine with best supportive care (BSC) versus BSC alone (7.0 vs. 6.9 months). For the cohort of patients receiving the vinflunine start dose of 280 mg/m² (e.g., Eastern Cooperative Oncology Group performance status 1, creatinine clearance 40–60 mL/minute), and in which the recommended phase II dose (RPTD) was defined, the prognosis is, however, most likely even worse than for the average second-line patient treated within the vinflunine registration trial [3]. In this view, the observed ORR of 41% and DCR of 71% in this study of platinum-refractory mUC is notable, especially compared with the ORR and DCR of 8.6% and 55.1% in the vinflunine phase III trial, and 16%–18% and 57%–67%, respectively, in previous phase II trials [3, 16, 17]. It can be speculated that the reduction of metastatic tumor burden and stabilization of disease could translate into clinical meaningful palliation and increased quality of life for some mUC patients with otherwise aggressive disease and few treatment options. Interestingly, both rash and hypertension, two side effects correlated with treatment benefit in renal cell carcinoma, were common in patients with partial response or disease stabilization. The favorable overall response rates in this study are plausibly attributable to the addition of sorafenib to

vinflunine, possibly resulting in an additive effect of this specific drug combination. Further, the results of the present study are in line with the recently reported outcome of the RANGE study, reporting an advantage of combining docetaxel with another vascular endothelial growth factor receptor 2 active compound, ramucirumab, thus adding evidence that patients with platinum-refractory mUC may benefit from combined treatment with standard chemotherapy and antiangiogenic targeted therapy [9]. Nevertheless, the overall positive response rate of this trial could still be at random considering the limited size and phase I design. In comparison, a phase II randomized study of gemcitabine and cisplatin plus sorafenib or placebo in first-line mUC resulted in an ORR of 52.5% and DCR of 75% versus 50% and 79%, showing no additional response effect of sorafenib [18]. If this trial could be repeated, eligible patients would include those with relapse within 12 months of platinum-containing systemic treatment, thus increasing inclusion rate. Future trials should aim to evaluate this treatment combination in a randomized setting, define biomarkers for treatment benefit, and explore the effects in patients with both platinum- and immunotherapy-resistant disease.

Within the context of this phase I trial, a RPTD for the treatment combination of vinflunine and sorafenib was identified for mUC patients with platinum-resistant and progressive disease. The observed side effects were as

expected and reversible but with a higher incidence of grade 3 and 4 hyponatremia than previously reported for vinflunine and sorafenib administered as monotherapy. Clinically meaningful disease stabilization and objective responses were observed in a number of patients with poor prognosis along with interindividual variation in OS.

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DISCLOSURES

Carl-Henrik Shah: Pierre Fabre Pharma Norden AB, Bayer Healthcare AG (RF); **Helle Pappot:** Merck Sharpe & Dohme, Roche (RF); **Karin Holmsten:** Pierre Fabre Pharma (RF, study/meeting expenses); **Anders Ullén:** Pierre Fabre Pharma (C/A), Pierre Fabre Pharma, Bayer (RF, study/meeting expenses). 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

REFERENCES

- Gerullis H, Eimer C, Ecke TH et al. Combined treatment with pazopanib and vinflunine in patients with advanced urothelial carcinoma refractory after first-line therapy. *Anticancer Drugs* 2013;24:422–425.
- Pappot H, von der Maase H, Ullen A et al. Combined treatment with pemetrexed and vinflunine in patients with metastatic urothelial cell carcinoma after prior platinum-containing chemotherapy - results of an exploratory phase I study. *Invest New Drugs* 2018;36:615–618.
- Bellmunt J, Theodore C, Demkov T et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009;27:4454–4461.
- Escudier B, Szczylik C, Hutson TE et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:1280–1289.
- Brose MS, Nutting CM, Jarzab B et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: A randomised, double-blind, phase 3 trial. *Lancet* 2014;384:319–328.
- Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–390.
- Summary of Product Characteristics - Javlor dated 30/07/2014. Available at ema.europa.eu. Accessed October 2, 2018.
- Summary of Product Characteristics - Nexavar dated 30/09/2016. Available at ema.europa.eu. Accessed October 2, 2018.
- Petrylak DP, de Wit R, Chi KN et al. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): A randomised, double-blind, phase 3 trial. *Lancet* 2017;390:2266–2277.
- Bellmunt J, de Wit R, Vaughn DJ et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017;376:1015–1026.
- Patel MR, Ellerton J, Infante JR et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): Pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol* 2018;19:51–64.
- Powles T, O'Donnell PH, Massard C et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: Updated results from a phase 1/2 open-label study. *JAMA Oncol* 2017;3:e172411.
- Rosenberg JE, Hoffman-Censits J, Powles T et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. *Lancet* 2016;387:1909–1920.
- Sharma P, Retz M, Siefker-Radtke A et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017;18:312–322.
- De Santis M, Wiechno PJ, Bellmunt J et al. Vinflunine-gemcitabine versus vinflunine-carboplatin as first-line chemotherapy in cisplatin-unfit patients with advanced urothelial carcinoma: results of an international randomized phase II trial (JASINT1). *Ann Oncol* 2016;27:449–454.
- Culine S, Theodore C, De Santis M et al. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. *Br J Cancer* 2006;94:1395–1401.
- Vaughn DJ, Srinivas S, Stadler WM et al. Vinflunine in platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma: Results of a large phase 2 study. *Cancer* 2009;115:4110–4117.
- Krege S, Rexer H, vom Dorp F et al. Prospective randomized double-blind multicentre phase II study comparing gemcitabine and cisplatin plus sorafenib chemotherapy with gemcitabine and cisplatin plus placebo in locally advanced and/or metastasized urothelial cancer: SUSE (AUO-AB 31/05). *BJU Int* 2014;113:429–436.

TABLE

Table 1. Baseline characteristics, including previous treatment and prognostic factors

Characteristic	All patients (n = 22), n (%)
Median age, years (range)	62.5 (44–71)
Sex	
Men	13 (59)
Women	9 (41)
ECOG PS	
0	9 (41)
1	13 (59)
Previous treatments	
Cystectomy	10 (45)
Nephrectomy/ureterectomy	3 (14)
No surgery	9 (41)
Radiation to pelvic region	0 (0)
No radiation to pelvic region	22 (100)
Neoadjuvant cisplatin and gemcitabine	6 (27)
Adjuvant cisplatin and gemcitabine ^a	2 (9)
Palliative cisplatin and gemcitabine ^a	13 (59)
Palliative carboplatin and gemcitabine	3 (14)
Previous platinum and gemcitabine treatment cycles	
≥6	9 (41)
2–5	12 (55)
1	1 (5)
Hemoglobin, g/L	
≥120	9 (41)
100–119	12 (55)
<100	1 (5)
Liver metastasis	
Yes	6 (27)
No	16 (73)

^aTwo patients received both adjuvant and palliative cisplatin and gemcitabine.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.

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