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FIERCE-21: Phase 1b/2 Study of Docetaxel + B-701, a Selective Inhibitor of FGFR3, in Relapsed or Refractory Metastatic Urothelial Carcinoma

J. Bellmunt[1], J. Picus[2], M. Kohli[3], Y. E. Arriaga[4], M. I. Milowsky[5], G. Currie[6], E. Abella[6], S. Pal[7]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Washington University School of Medicine, St. Louis, MO; [3]Mayo Clinic, Rochester, MN; [4]University of Texas Southwestern Medical Center, Dallas, TX; [5]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; [6]BioClin Therapeutics, Inc., San Leandro, CA; [7]City of Hope National Medical Center, Duarte, CA

BioClin THERAPEUTICS
1040 Davis St. #202
San Leandro, CA 94577 USA
info@bioclintherapeutics.com
925-413-6140

Introduction

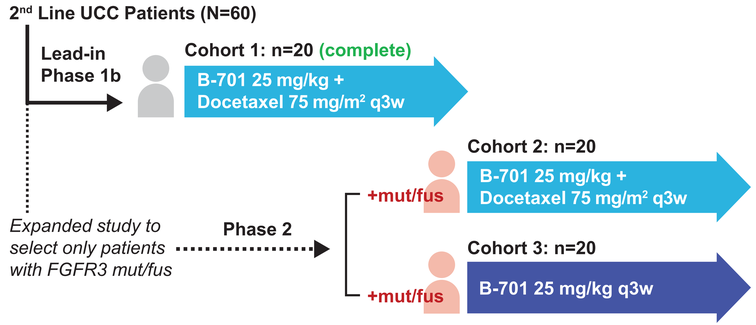
- Patients with locally advanced or metastatic urothelial cell carcinoma (UCC) have a poor prognosis
- Although immune checkpoint inhibitors have demonstrated promise, most patients require additional treatments and there are no other FDA approved therapies in patients who progress after 1st-line chemotherapy and/or checkpoint inhibitors
- Fibroblast growth factor receptor 3 (FGFR3) is frequently overexpressed in UCC and 15–20% of patients with metastatic UCC (mUCC) have FGFR3 gene mutations or fusions (mut/fus)
- B-701 (formerly R3mAb) is a fully human monoclonal antibody that blocks activation of the wild-type and genetically activated receptor
- FIERCE-21(NCT02401542) is a Phase 1b/2 study designed to evaluate the safety and efficacy of B-701 alone or in combination with docetaxel in advanced UCC patients
- Initial results were published at ASCO 2017; this provides an update on trial progress and longterm outcome data

Objective

- To evaluate the safety and efficacy of B-701 with docetaxel in advanced UCC patients

Methods

Study Design (NCT02401542)



- The study consists of a Phase 1b lead-in (n=20 enrolled, 19 treated; reported here) followed by Phase 2 expansion and a separate randomized phase
- **Eligibility:** stage IV mUCC, relapsed or refractory to prior chemotherapy regimens (excluding taxanes); Eastern Cooperative Oncology Group (ECOG) performance status 0–1
- **Primary endpoints:** progression-free survival (PFS; RECIST 1.1) and safety
- **Secondary endpoints:** overall response rate, duration of response, disease control rate (DCR), and overall survival (OS)
- **Exploratory endpoints**: association of FGFR3 status (expression level and mutational status) with efficacy and adverse events (AEs)
- Archival tumor for Foundation Medicine testing and Ventana Medical Systems for immunohistochemical analysis of FGFR3

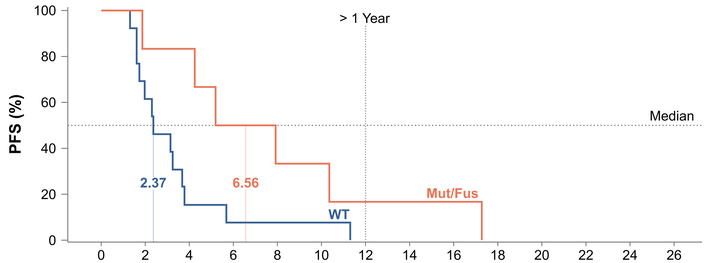
Results

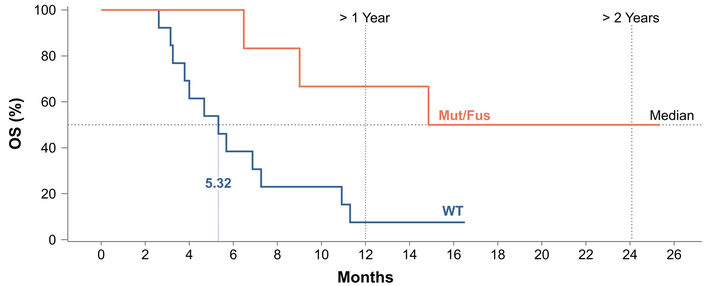
Patient Demographics

	Total N=19*	FGFR3 Mut/Fus n=6
Female/male, n	5/14	1/5
Age, y	66	64
ECOG 1, n (%)	11 (58)	5 (83)
Hemoglobin <10 mm Hg, n (%)	2 (11)	0 (0)
Liver metastases, n (%)	5 (26)	1 (17)
≥2 prior regimens, n (%)	14 (74)	5 (83)

*20 patients enrolled on study; patient 12 progressed prior to treatment and was not included.

Efficacy





	Total N=19	WT n=13	FGFR3 Mut/Fus n=6
Best response	1 CR; 2 PR	1 PR	1 CR, 1 PR
Median DCR % (95% CI)	63.2 (39.2, 74.5)	53.8 (25.1, 80.8)	83.3 (35.9, 99.6)
Median PFS, mo (95% CI)*	3.25 (1.9, 5.2)	2.37 (1.6, 3.7)	6.56 (1.9, 17.3)
Median OS, mo (95% CI)*	6.87 (4.01, 11.30)	5.32 (3.25, 7.3)	NR at 20 mo FU

*Based on data cutoff on April 18, 2018. CI, confidence interval; CR, complete response; FU, follow-up; NR, not reached; PFS, progression-free survival; PR, partial response.

Safety

n (%)

TEAEs in ≥10% of Patients, N=19			
Diarrhea	12 (63)	Anemia	2 (11)
Nausea	7 (37)	Dysgeusia	2 (11)
Fatigue	6 (32)	Epistaxis	2 (11)
Alopecia	5 (26)	Headache	2 (11)
Decreased neutrophil count*	5 (26)	Hypotension	2 (11)
Fever	5 (26)	Neuropathy (peripheral)	2 (11)
Constipation	4 (21)	Neutropenia	2 (11)
Abdominal pain	4 (21)	Upper respiratory tract infection	2 (11)
Insomnia	4 (21)	Edema peripheral	2 (11)
Decreased white blood cells*	3 (16)	Back pain	2 (11)
Pruritis	3 (16)	Cough	2 (11)
Vomiting	3 (16)	Dyspnea exertional	2 (11)
Pain in extremity	3 (16)	Lacrimation increased	2 (11)
Urinary tract infection	3 (16)		
Grade ≥3 AEs Attributed to B-701 Occurring in >10% Patients, N=19			
Decreased neutrophil count	4 (21)		
Decreased white blood cells	2 (11)		
Fatigue	2 (11)		

*Related to study treatment per investigator assessment. TEAE, treatment-emergent AE.

- 5 patients experienced 15 treatment-related AEs which have led to B-701 dose interruption or modification
- 4 patients also had docetaxel dose reductions and 1 patient discontinued treatment due to AE (disseminated intravascular coagulation; DIC)
- 15 deaths occurred on study:
  - 11 due to progressive disease
  - 2 due to AEs (DIC considered possibly related; intracranial hemorrhage considered unrelated)
  - 2 of which cause was unknown

Conclusions

- B-701 combined with docetaxel q3wk in patients with mUCC was well tolerated
- Dose-limiting toxicity was not reached in Phase 1b
- FGFR3 mut/fus patients experienced prolonged PFS (>6 mo) and with 20-month follow-up, the median OS was not reached
- Phase 2 is currently enrolling mut/fus patients
- B-701 is also in Phase 2 in combination with pembrolizumab in a clinical trial (NCT03123055)

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