ctDNA Monitoring of FGFR3-Altered Metastatic Urothelial Cancer Treated With Dabogratinib (TYRA-300) in the SURF301 Trial

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BACKGROUND

- Fibroblast growth factor receptor-3 (*FGFR3*) alterations occur in approximately 10%-25% of mUC[1,2]
- A pan-FGFR inhibitor has been approved for *FGFR3*-altered metastatic urothelial cancer (mUC)[3]
  - However, inhibition of FGFR1/2/4 isoforms results in significant side effects, particularly hyperphosphatemia, skin disorders, and ocular toxicity[2,4-6]
- Dabogratinib is a novel, potent, and highly selective inhibitor of FGFR3 with potentially less off-target toxicity relative to pan-FGFR inhibitors and has shown preclinical activity against acquired resistance *FGFR3* gatekeeper mutations[7,8]
- SURF301 (NCT05544552) is a phase 1/2 study evaluating oral dabogratinib in solid tumors including mUC expressing altered FGFR3[9]
  - Encouraging anti-tumor activity and safety were observed in initial results[8]
- Here we report phase 1 results on early circulating tumor DNA (ctDNA) dynamics in *FGFR3*-altered patients with mUC enrolled in SURF301

METHODS

SURF301 Study Design

- Eligible adults with advanced malignancies with any FGF/FGFR alterations received oral dabogratinib in continuous 28-day cycles.[9] Dose escalation (10 mg to 120 mg QD); allowed any *FGF/FGFR* pathway alteration. Dose expansion (40 mg to 90 mg QD): required *FGFR3* alterations
- Key primary and secondary/exploratory outcomes[9]
  - Primary outcomes: determine maximum tolerated dose and recommended phase 2 dose, and evaluate preliminary antitumor activity
  - Secondary/Exploratory: characterize safety and tolerability, pharmacokinetics, overall response rate, duration of response, disease control rate, time to response, and progression-free survival and identify markers of FGFR engagement and inhibition
- SURF301 is not actively recruiting patients

Exploratory ctDNA Analysis[10]

- Blood was collected at baseline, cycle (C) 1 day (D) 15 (C1D15), C2D1, and at each disease assessment visit. In patients without a C2D1 collection, C3D1 was used instead
- Plasma cell-free DNA (cfDNA) was sequenced using a custom targeted panel of 78 mUC genes
- Somatic variants were called via an established bioinformatic pipeline, leveraging same-patient serial samples to boost detection sensitivity. ctDNA variant allele frequency (VAF) is a surrogate for ctDNA quantity defined as the highest VAF of an on-target somatic coding mutation on an unamplified gene
- On-treatment ctDNA changes from baseline were calculated and statistical significance assessed using Fisher's exact test and Bayesian posterior estimates derived from Beta-binomial models with Jeffreys priors

RESULTS

Patient and Disease Characteristics

Characteristic	40 - 60 mg QD dose n = 10	≥90 mg QD dose n = 12	Overall n = 22
Mean age, years	69.6 ± 8.9	66.1 ± 9.0	66.7 ± 8.9
Male sex, n (%)	10 (100)	9 (75)	19 (86.4)
FGFR3 mutations, n (%)	6 (60)	8 (66.7)	14 (63.6)
FGFR3 fusions, n (%)	5 (50)	4 (33.3)	9 (40.9)
≥2 prior systemic therapies	10 (100)	8 (66.7)	18 (81.8)

Table 1. Twenty-two heavily pretreated patients with *FGFR3*+ mUC from the Phase 1 QD cohorts with available ctDNA were included in this analysis; 82% had ≥2 prior lines of therapy. Data cut off date: December 15, 2025.

Baseline Genomic Features, *FGFR3* Alterations, and Early On-Treatment ctDNA Change

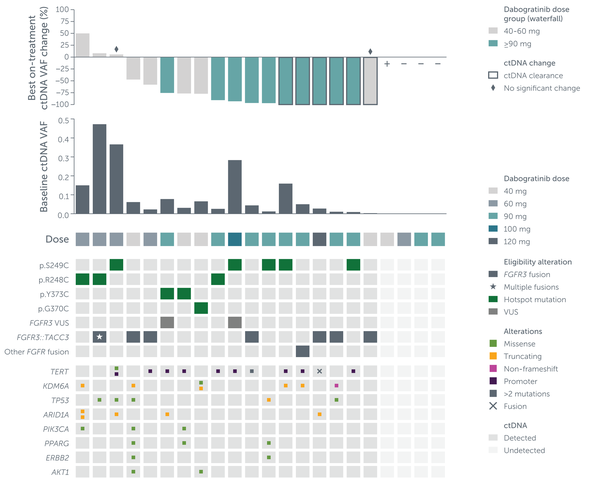


Figure 1. Top, Best % change from baseline in patients with *FGFR3*-altered mUC. Upon treatment with dabogratinib, ctDNA remained stable or decreased in the majority of patients with mUC. Bottom, OncoPrint visualization of somatic alterations detected in baseline ctDNA. 18 of 22 patients have ctDNA detected with 10 mutations, 7 TACC3 fusions, and 1 both. On-treatment changes for baseline undetected ctDNA denoted with + (increase, n = 1) or – (maintained undetected, n = 3).

Dabogratinib Induces Early Molecular Responses Across Dose Groups

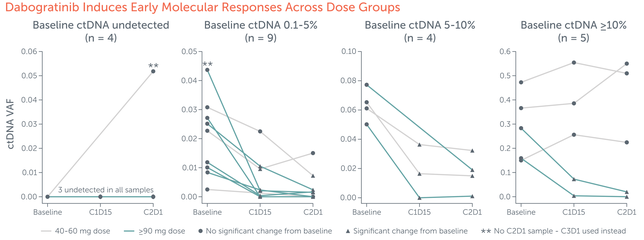
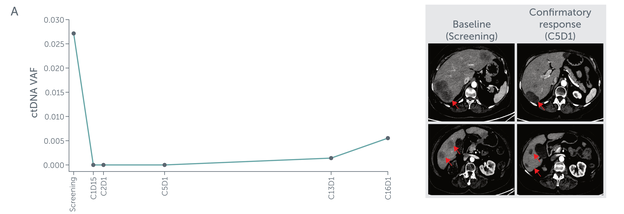
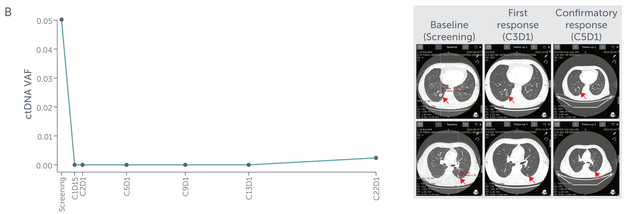


Figure 2. Dabogratinib treatment resulted in significant decreases in ctDNA fraction as early as C1D15 across all dose groups. All patients with 0.1%-10% baseline ctDNA had decreases in ctDNA, independent of dose group. Patients with ≥10% ctDNA tended to have poorer ctDNA responses, consistent with high ctDNA being a poor prognostic indicator.

Extended ctDNA Decreases Correspond With Durable Partial Responses



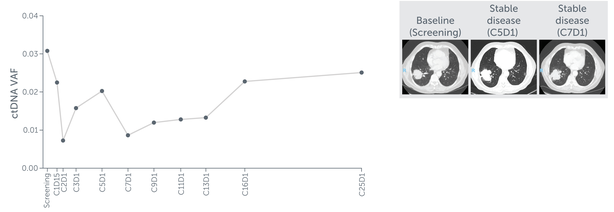
Age/Sex	67-year old female
FGFR3 alteration	*FGFR3::TACC3* fusion
Prior lines therapy, n	2 prior lines in metastatic setting
Target lesions (n)	Liver (2), peritoneum (2), lymph node (1)
Best overall response	PR
Treatment	Dabogratinib 120 mg QD through C3; decreased to 90 mg QD at C4 and discontinued at C21



Age/Sex	64-year old male
FGFR3 alteration	*FGFR3::JAKMIP1* fusion
Prior lines therapy, n	2 prior lines in metastatic setting
Target lesions (n)	Lung (2), lymph node (2)
Best overall response	PR
Treatment	Dabogratinib 90 mg QD; still on treatment as of C29

Figure 3. Reduction in ctDNA after dabogratinib ≥90 mg was associated with durable partial responses.[11] Images copyright © 2025, American Association for Cancer Research. Starrett JH, et al. *Mol Cancer Ther.* 2025; doi: 10.1158/1535-7163.MCT-25-0652.

Increasing Dabogratinib Dose Resulted in Additional ctDNA Reduction and Stable Disease



Age/Sex	73-year old male
FGFR3 alteration	*FGFR3* p.Y373C
Prior lines therapy, n	4 prior lines in metastatic setting
Target lesions (n)	Lung (3)
Best overall response	SD
Treatment	40 mg QD through C6; 60mg QD to C20; 40mg BID at C20 (discontinued at C28)

Figure 4. Initial dabogratinib dose was 40 mg, increased to 60 mg, resulting in a second molecular response at C7D1.

SURF301 CONCLUSIONS

1. In the SURF301 trial, oral dabogratinib resulted in rapid decreases of ctDNA in patients with *FGFR3*-altered mUC at all doses
2. At 40 mg and above, 14 of 18 (78%) participants had molecular responses and 6 (33.3%) had ctDNA clearance
3. Sustained decreases in ctDNA occurred with dabogratinib doses ≥90 mg in patients with durable PR's per Response Evaluation Criteria in Solid Tumours v1.1

Sponsor Contact Information

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Abbreviations

BID, twice daily; C, cycle; cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; D, day; FGFR, fibroblast growth factor receptor; mUC, metastatic urothelial cancer; PR, partial response; QD, once daily; SD, stable disease; VAF, variant allele frequency; VUS, variant of unknown significance.

References, author affiliations, and acknowledgments