# CLINICAL GRADE COMPREHENSIVE GENOMIC PROFILING (CGP) OF UROTHELIAL CARCINOMA (UC)

Authors: P. Bose[1], A. Gibson[1], M. Dean[1], T. Xu [1], M. Murali[1], M. Kolinsky[2], S. North[2], D. Heng[3], J.D. Ruether[3], S. Karim[3], V. Navani[3], R. Lee-Ying[3], B. Osborne[4], T. Bismar[5], R. Fahidi[6], S. Sharma[7], S. Alam[6], F. Khan[6], N. Alimohamed[3 *], S. Yip[1 *] (* denotes co-senior authors)

***Institutional Affiliations***: 1: Precision Oncology and Experimental Therapeutics (POET) program, Cumming School of Medicine, University of Calgary, Calgary, Canada. 2: Cross Cancer Institute, Alberta Health Services, Edmonton, Canada. 3: Arthur JE Child Comprehensive Cancer Centre, Calgary, Canada. 4: Medical Science, Jassen Inc., Toronto, Canada. 5: Pathology and Lab Medicine, Faculty of Medicine, University of Calgary, Calgary, Canada. 6: OncoHelix, Calgary, Canada. 7: Hematology Translational Lab, Alberta Precision Laboratory, Calgary, Canada. * Denotes co-senior authors

UNIVERSITY OF CALGARY

## Background

Urothelial carcinoma is among the top ten causes of cancer- related death in Canada and represents significant clinical challenges due to extensive genomic heterogeneity. The recent identification of actionable genomic alterations (i.e. FGFR1–4 fusions and mutations) has initiated a shift towards the use of precision medicine in the management of UC. While this represents meaningful progress, further characterization of UC's genomic and molecular landscape and associated clinical outcomes in real-world patients remains a critical unmet need, as is equitable access to CGP which is currently unfunded in our jurisdiction (Alberta, Canada).

This study combines CGP data with clinical outcomes to reveal insights into UC biology and identify potential therapeutic targets and prognostic markers.

## Methods

Patients with a pathological diagnosis of UC in the bladder or upper tract were prospectively consented to allow collection of clinical data and outcomes (treatment type and sequence, overall survival), and use of standard-of-care tissue samples. CGP using the Illumina TST 170 panel which captures small variants (SV), copy number variations, and gene fusions, was performed on standard-of care UC tissue samples, and matched to clinical information derived from the academic POET Clinical Database

## Results: Clinical

**67 patients received CGP and were included in this study.**

Median age at diagnosis was 68 years, and 85% (57/67) were male. Primary tumour site was bladder (81%; 54/67) or upper tract in (19%; 13/67). 85% (57/67) have locally advanced or metastatic disease (LA/mUC)

79% (45/57) of those with LA/mUC have received a first-line palliative intent systemic therapy comprised of cytotoxic chemotherapy (80%; 36/45) with 47% (17/36) transitioning to maintenance avelumab. 18% (8/45) received enfortumab vedotin + pembrolizumab, and 2% (1/45) received concurrent chemoimmunotherapy. This study facilitated the use of an FGFR-inhibitor (erdafitinib) in the 3rd line setting for one patient with an *FGFR3–FGFR1* fusion identified with CGP.

Median overall survival after palliative systemic therapy initiation was 20.8 months.

POET
PRECISION ONCOLOGY
EXPERIMENTAL THERAPEUTICS

## Results: CGP & Outcomes

**Genomic Alterations Identified in CGP of UC tissue samples:**

A median of 13 (range: 0-19) small variants (SV) per sample were identified.

Table 1: Most Prevalent SV

| SV | Count & Frequency |
|---|---|
| TP53 | 43% (29/67) |
| TSC2 | 13% (9/67) |
| TET2 | 13% (9/67) |
| ARID1A | 12% |
| BRCA2 | 10% |

Table 2: Most Prevalent Amplifications

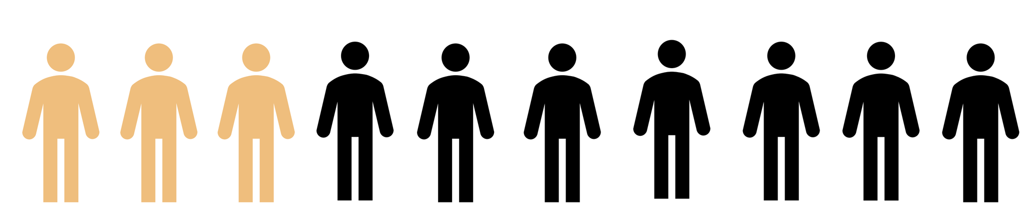
| Amplification | Frequency |
|---|---|
| MDM2 | 15% (3/20) |
| CCND1 | 6% |
| ERBB2 | 5% (1/20) |

Amplifications were identified in 15% of samples.

Table 3: Most Prevalent Fusions

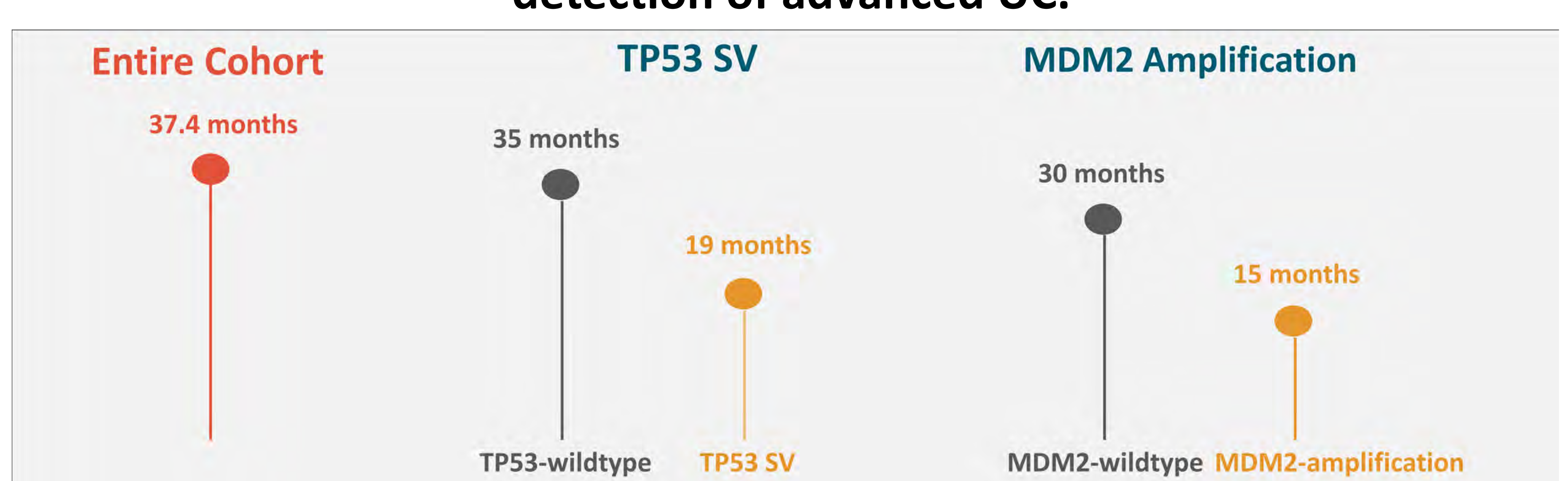
| Fusion | Frequency |
|---|---|
| PLEKHF2-MROH1 | 18% |
| KIFB5-ARHGAP12 | 2% |
| ETS1-FEV | 10% |

Gene fusions were identified in 25% of samples.



One out of every three CGP tested patients (30%; 20/67) possessed an actionable genomic alteration in *FGFR2/3*, of which 7 were fusion events.

**Genomic pattern significantly influenced median overall survival after the detection of advanced UC.**




**Survival Post-Locally Advanced or Metastatic (Unresectable) Disease Detection**

Compared to wildtype, significantly poorer outcome ($p<0.05$) was observed in association with TP53 (SV) and MDM2 (amplification).

## Conclusions

**An integrated analysis combining CGP with clinical data in a real-world cohort, reveals:**

- Substantial variability in the genomic profiles of real-world UC diagnoses.
- Distinct genomic profiles are associated with significantly different outcomes.
- Erdafitinib use for FGFR2/3 alterations was limited, possibly due to testing at earlier-stage disease or pending clinical suitability.

**This study reinforces the importance of comprehensive genomic profiling in precision oncology and highlights a current unmet need for a precision medicine informed approach to the management of UC**

## Future Directions

- The study is ongoing, with a **target enrollment of 200 patients over 24 months.**
- Genomic testing in patients with advanced urothelial carcinoma is currently not funded in Alberta. This project facilitates ongoing access to CGP and subsequent targeted therapy for eligible patients.
- This will be a comprehensive real-world analysis of treatment sequencing, outcomes, uptake, and safety of novel therapies in patients with advanced urothelial carcinoma. Serum and urine biomarkers are being evaluated to develop and validate minimally-invasive tests.

*This research received financial support from the Johnson & Johnson Alberta Health Innovation Partnership (JAHIP), a collaboration between the Janssen Pharmaceutical Companies of Johnson & Johnson, University Hospitals Foundation and the Government of Alberta.*

Corresponding Author: Dr. Pinaki Bose

pinaki.bose@ucalgary.ca

Dr. Bose declares no conflicts of interest for this study

POET Program: poetoncology.ca

**Final Publication Number: 76eP**