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Ex Vivo drug sensitivity Testing Assay in urothelial cancer: EVITA trial

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BACKGROUND

Patients with Bladder Cancer (BC) are treated with chemotherapy, either intravesically or systemically. Predictive biomarkers to guide clinical decision-making on chemotherapy, however, are lacking, risking non-responders to undergo ineffective treatment while being exposed to toxicity. We hypothesized that an ex vivo tumor test assay could identify chemoresponsive BC prior to treatment and therefore performed a prospective feasibility trial (OZBS62.21051).

METHODS

- **Collection** of fresh tumor tissue at transurethral resection of bladder tumor (TURBT; N=45) or radical cystectomy (RC; N=3) (Table I).
- **Sample characterization** including histological evaluation of H&E slides, IHC-based basal/luminal subtyping and hotspot mutation analysis of hTERT, FGFR3 and PIK3CA genes.
- **Ex vivo tumor testing**: fresh tumor clusters were isolated, seeded, and exposed to single-agent chemotherapies and the targeted therapy Erdafitinib.
- **Sensitivity evaluation** was performed by extraction of morphological features from high-throughput 3D imaging data, followed by AUC comparison of fitted dose-response curves (see Figure I for complete workflow).

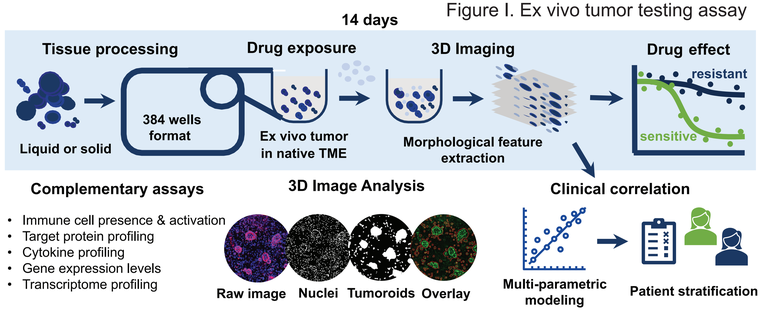
RESULTS

- **Successful ex vivo drug testing** for 28 out of 48 patients (58%). Higher success in non-muscle invasive BC (NMIBC) (17/20 (85%), OR: 3.8, 95% CI: 1.7 – 9.1) than in muscle-invasive BC (MIBC) (11/28 (39%)).
- **Patient-specific response profiles** were observed, and a subgroup of NMIBC samples with exceptional ex vivo response to gemcitabine was identified.
- **Erdafitinib sensitivity** was observed ex vivo in two patients with somatic FGFR3-Y375C mutations but not in FGFR3-WT patients (N=10, P = 0.03).
- **Correlation ex vivo response platinum-based CTx** (Pearson coeff. = 0.93) confirms assay robustness.
- Results were generated <2 weeks after tissue collection.

Table I Patient characteristics

Baseline characteristics (N=48)	
Hospital (%)	
Amphia	15 (31.2)
Erasmus MC	14 (29.2)
Haga	11 (22.9)
Franciscus Gasthuis en Vlietland	8 (16.7)
Age (median & range)	71 (42-96)
Sex (%)	
Male	37 (77.1)
Female	11 (22.9)
Surgery (%)	
TURBT	45 (93.7)
Radical cystectomy	3 (6.3)
Invasion of musculus detrusor (%)	
Yes	28 (58.3)
No	20 (41.7)
Tumor grade WHO 1973/2004 (%)	
G2 (Low grade)	4 (8.3)
G2 (High grade)	11 (22.9)
G3	33 (68.8)
Clinical Tumor stage (%)	
Ta	9 (18.8)
T1	12 (25)
T2	15 (31.3)
T3	10 (20.8)
T4	2 (4.2)
Clinical Nodal stage (%)	
N0	38 (79.2)
N1	3 (6.2)
N2	6 (12.5)
N3	1 (2.1)

Figure I. Ex vivo tumor testing assay



CONCLUSIONS

We report the feasibility of ex vivo 3D tumor testing for BC.

- A correlation with clinical response to chemotherapy could not yet be established due to a lack of successfully screened patients with matching clinical chemotherapy treatment.
- However, differential ex vivo sensitivity to platinum, gemcitabine, and a preliminary correlation for ex vivo sensitivity to erdafitinib and FGFR3 mutation status offers a potential solution to select BC patients for effective (novel) treatment options.

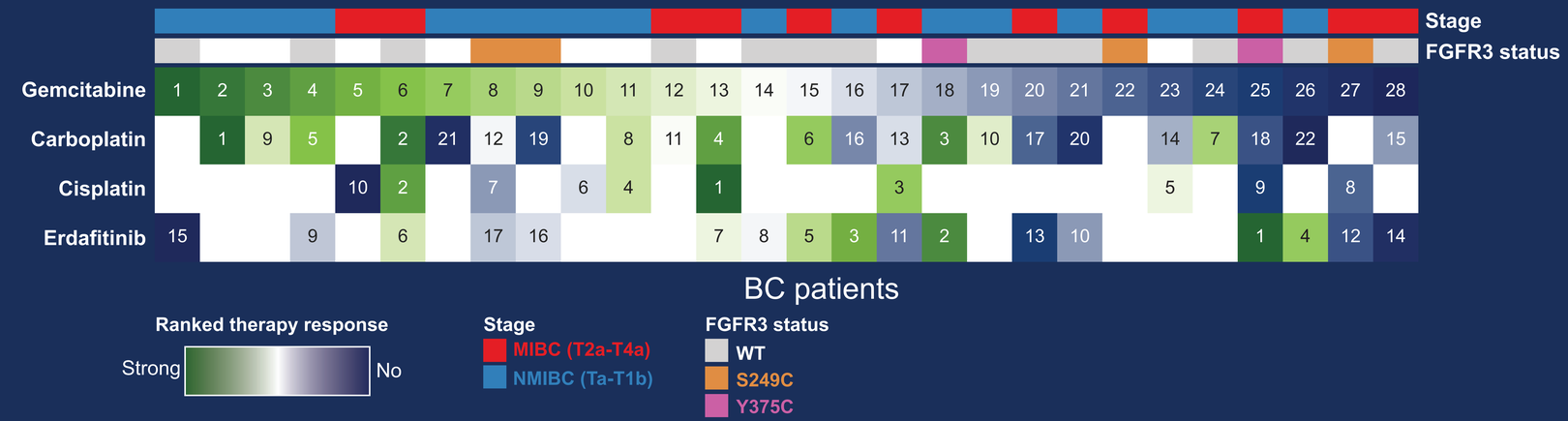
ONLINE POSTER

Erasmus MC

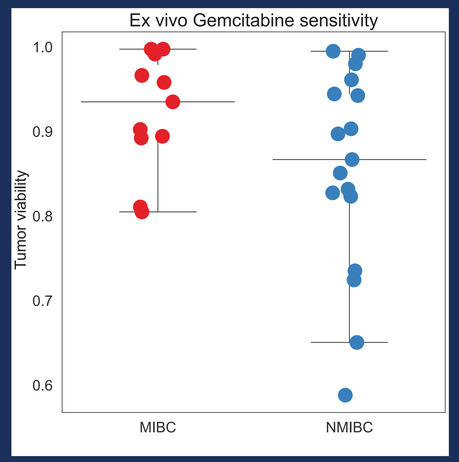
VitroScan PREDICTING TREATMENT OUTCOME

support@vitroscan.nl

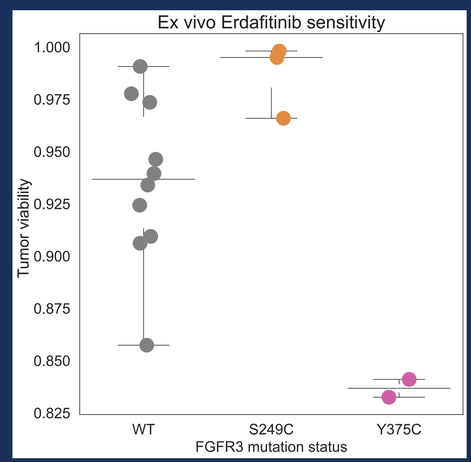
Ex vivo 3D tumor testing to rank the patient's sensitivity to gemcitabine, platinum and targeted therapy



Chemotherapy



Targeted therapy



High ex vivo Erdafitinib sensitivity in FGFR3-Y375C mutated patients