Squamous-cell carcinoma variant histology (SCC-VH) in muscle-invasive bladder cancer (MIBC): a comprehensive clinical, genomic and therapeutic assessment from multiple datasets

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Abstract: 258997

BACKGROUND

Pure or predominant SCC-VH is observed in MIBC. Nevertheless, limited data is available about the efficacy of neoadjuvant chemotherapy (NAC) or novel agents for this entity. We undertook this study which combined multiple clinical and genomic datasets to assess the genomic landscape of SCC, and to examine the efficacy of NAC in this disease, and present results for SCC-VH cases from PURE-01, a trial of pembrolizumab in the neoadjuvant setting.

PATIENTS AND METHODS

The combined databases of the Urological Research Institute (URI, n=2,209) of San Raffaele Hospital and the Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC, n=2,598) were queried for patients with non-metastatic MIBC treated with RC between January 1990 and September 2017 (Figure 1). The criteria for initial patient selection included: any histology, clinical $T_{any}N_{any}M0$ stage, and radical cystectomy performance with or without perioperative chemotherapy[1].
An external cohort was also analysed including 1,984 pts with UC 97 patients with SCC who had their tumor assessed with an hybrid capture-based comprehensive genomic profiling (CGP) as routine clinical practice. CGP was performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified, College of American Pathologists (CAP)-accredited laboratory (Foundation Medicine, Inc., Cambridge, MA). The samples were assayed by CGP using adaptor-ligation and hybrid capture performed for all coding exons of from 287 (version 1) to 315 (version 2) cancer related genes plus select introns from 19 (version 1) to 28 (version 2) genes frequently rearranged in cancer. Sequencing of captured libraries was performed using the Illumina HiSeq technology to a mean exon coverage depth of >500X, and resultant sequences were analyzed for all classes of genomic alterations (GA) including short variant (SV) alterations (base substitutions, insertions and deletions), copy number alterations (focal amplifications [<20 Mb], non-focal amplifications [≥20 Mb], and homozygous deletions), and select gene fusions or rearrangements. TMB was determined on 0.8 Mb (version 1) or 1.1 Mb (version 2) of sequenced DNA for each sample based on the number of somatic base substitution or indel alterations per Mb after filtering to remove known functionally oncogenic somatic mutations[2].
Finally, the interim results of the PURE-01 study[3] (NCT02736266) were recently published, reporting a pathologic complete response rate (pT0) of 42% among the first 50 patients enrolled (Necchi A, et al. *J Clin Oncol* 2018). Since then, the study was amended to increase the sample size, allow the inclusion of cT4 patients, and allow the inclusion of non-urothelial histologies. Here, we report the interim results of pembrolizumab use in patients with pure or predominant SCC histology.

STATISTICAL ANALYSIS

Analyses on the URI/RISC database were performed by grouping variant histologies into 6 categories, where pure and mixed cases of each histological variant were respectively combined. Furthermore, we analysed data by separating pure from mixed cases of each variant histology. Here, 11 histological subgroups were tested as independent predictors. For example, SCC was analysed combining pure and mixed cases, and also as pure SCC and UC with SCC component, separately. The primary study endpoint was the cancer-specific survival (CSS), which was analysed across all different histological variants and according to treatment delivered. Here, UC was used as reference category while all others histological variants were compared with (Figure 2).

The secondary endpoint was the clinical-to-pathological downstaging, which was defined as a pathologic nodal stage (N stage) that was at least one stage lower than the pre-NAC clinical N stage. When no variation of the N stage occurred, we used the above-mentioned criteria using the tumour stage (pre-NAC cT and pT). Kaplan-Meier method was used for estimation of CSS, both defined as the period of survival from RC. Logistic regression and Cox regression models were used to analyse the effect of NAC, and supportive subgroup analyses were run.

Within the FMI data, hybrid-capture based CGP of 97 patients with squamous-cell carcinoma patients were examined (Figure 3). Tile plot was generated for SCC patients (Figure 4). Finally, clinical-relevant gene frequency were reported according to UC and SCC histologies with associated p values (Figure 5). All statistical tests were two-sided with a level of significance set at p<0.05. Analyses were performed using the R software environment for statistical computing and graphics.

CONCLUSIONS

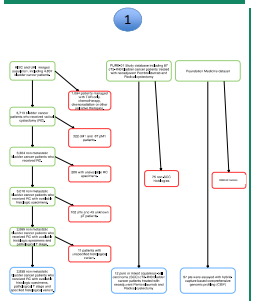
- SCC was the variant histology exhibited the lowest effect of neoadjuvant chemotherapy in terms of activity and CSS.
- Genomic profiling revealed opportunities for targeted immunotherapy.
- Genomic correlates of SCC chemotherapy resistance warrant further investigation
- Finally, data coming from the PURE-01 study show un unprecedented benefit of neoadjuvant immunotherapy on SCC.

PRESENTED AT: 2019 ASCO ANNUAL MEETING

References
1 Bandini M, Briganti A, Plimack ER, Niegisch G, Yu EY, Bamias A, et al. Modeling 1-year Relapse-free Survival After Neoadjuvant Chemotherapy and Radical Cystectomy in Patients with Clinical T2–4N0M0 Urothelial Bladder Carcinoma: Endpoints for Phase 2 Trials. Eur Urol Oncol 2018.
2 Chalmers ZR, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 2017.
3 Necchi A, Anichini A, Raggi D, Briganti A, Massa S, Lucianò R, et al. Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma (PURE-01): An Open-Label, Single-Arm, Phase II Study. J Clin Oncol Off J Am Soc Clin Oncol 2018.

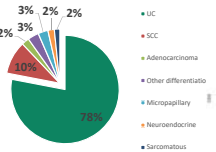
RESULTS

STUDY FLOW-CHART



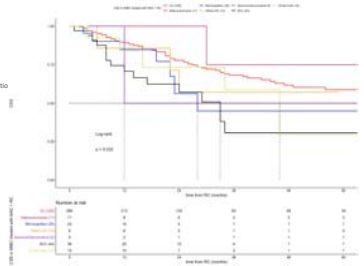
RETROSPECTIVE DATA FROM URI/RISC DATABASES

Frequencies of histological variants in the URI/RISC dataset



UC	2223 (78)
Adenocarcinoma	65 (2.3)
Pure	38 (58.5)
UC with Glandular component	27 (41.5)
Micropapillary	85 (3)
Others DF	95 (3.3)
Pure other/mixed non TCC	63 (66.3)
UC with others component	32 (33.7)
Sarcoma	47 (1.6)
Pure	17 (36.2)
UC with sarcomatoid component	30 (63.8)
SCC	283 (9.9)
Pure	127 (44.9)
UC with squamous component	156 (55.1)
Small-Cells	54 (1.9)
Pure	41 (75.9)
UC with small-cell component	13 (24.1)

Kaplan-Meier curve: CSS rates according to variant histologies in NAC treated patients



After NAC-regimen stratification, SCC patients still exhibited worse CSS rates compared to UC both in cisplatin-based (33 vs. NA months, p=0.009) and other regimens-based (5 vs. 49 months, p<0.0001) groups. Differently, no CSS rate difference (29 vs. 76 months, p=0.7) was found between SCC and UC patients who received a carboplatin-based chemotherapy, likely due to sample size

Cancer-specific survival (CSS) rates according to different histologies (pure and predominant were combined) and perioperative treatment. Comparison was made with UC. *** **significant also in MVA**

Histological variants	Overall (2858)	NAC +RC (458)	RC alone (1244)	RC + AC (500)	RC + perioperative Cht? (913)
UC	116 (103-133), Ref. ****	116 (64-NA), Ref.	127 (115-179), Ref.	103 (88-145), Ref.	112 (98-145), Ref.
Adenocarcinoma	76 (30-NA), p<0.8	107 (30-NA), p=0.64	NA (NA-NA), p<0.16	74 (23-NA), p<0.23	76 (30-NA), p<0.17
Micropapillary	65 (31-NA), p<0.056	28 (22-NA), p<0.23	65 (33-NA), p<0.2	31 (23-NA), p<0.091	31 (23-NA), p<0.056
Small-cells	41 (30-NA), p<0.15	46 (34-NA), p<0.4	33 (30-NA), p<0.073	NA (NA-NA), p<0.35	46 (34-NA), p<0.61
Other/mixed	74 (33-NA), p<0.11	NA (22-NA), p<0.48	33 (10-NA), p<0.012	132 (42-NA), p<0.77	132 (42-NA), p<0.64
Sarcoma	14 (9-NA), p<0.0001***	12 (12-NA), p<0.98	9 (8-NA), p<0.0001*	9 (4-NA), p<0.0001***	12 (9-NA), p<0.015**
SCC	47 (33-NA), p<0.00016 ****	32 (17-NA), p<0.0056***	268 (47-NA), p<0.16	28 (23-NA), p<0.093*	34 (25-NA), p<0.0016**

SCC was the only histological variant associated with worse CSS compared to UC, when only NAC-treated patients were considered, even after multivariable adjustment (HR: 2.1, 95%CI: 1.1-4.2, p=0.03). We obtained virtually the same results in the subgroup of patients who showed a bladder-confined tumour (pN0) on final pathological examination, as well as including cN0 and cisplatin-only treated patients.

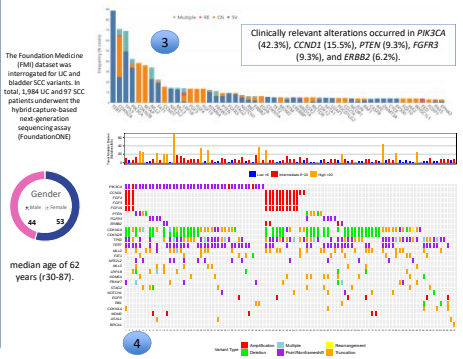
Uni- and multivariable logistic regression models examining the odds of clinic-pathological downstaging within all MIBC variants. *** adjusted for NAC and CCI.

Histological variants (n= 2,458)	Univariable	Multivariable
(Ref. UC)	Ref.	Ref.
SCC (288)	0.37 (0.16-0.75), p=0.012	0.38 (0.14-0.83), p=0.028
Adenocarcinoma (65)	1.05 (0.36-2.47), p=0.9	/
Micropapillary (85)	0.30 (0.04-0.98), p<0.1	/
Small-cells (54)	0.40 (0.09-2.01), p=0.49	/
Sarcoma (47)	0.24 (0.01-1.34), p=0.21	/
Other differentiations (96)	0.61 (0.19-1.60)	/

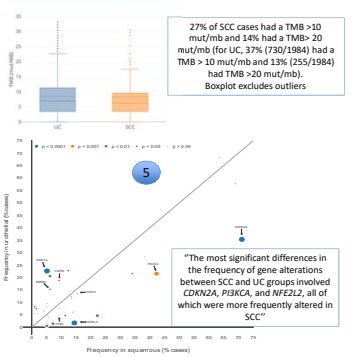
After either univariable or adjustment for NAC administration and Charlson comorbidity index, SCC was the only histological variant associated with statistically significant lower odds of clinical-to-pathological downstaging compared to UC

GENOMIC FEATURES OF BLADDER SQUAMOUS-CELL CARCINOMA

The Foundation Medicine (FMI) dataset was interrogated for UC and bladder SCC variants. In total, 1,984 UC and 97 SCC patients underwent the hybrid capture-based next-generation sequencing assay (FoundationONE)



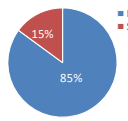
median age of 62 years (r30-87).



PURE-01 DATA

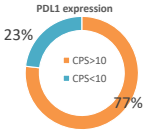
PURE-01 study: neoadjuvant Pembrolizumab (3 courses of pembrolizumab 200 mg intravenously every 3 weeks, followed by RC) in cT2-3bN0M0 BCa patients with UC predominant histology.

The PURE-01 has been recently amended with the inclusion of divergent histologies, such as SCC (n=12), which represents the focus of the third part of our study



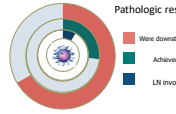
TURB and RC specimens were used to analyse biomarkers and match pre and post-therapy results. PD-L1 expression was determined by immunohistochemistry

PDL1 expression



Within patients with SCC, 4 pT0 (33.3%) and 10 pT≤1 (83.3%) were obtained, and no SCC pts died after a median follow-up of 10.4 months. TURB samples from all patients were retrospectively analysed. Tumors of all pts which underwent IHC demonstrated PD-LI expression.

Pathologic response



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