**Supplementary Table 1.**

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| **Patient Number** | **Age (years)**  **at Staging** | **Gender**  **(M:male, F: female)** | **Primary Site** | **IO Agent; Duration (months)** | **TNM**  **(at IO Start/ PDL1 Status Assessment)** | **Chemo/RT Status**  **(at IO Start)** | **TMB (mt/MB)** | **PD-L1 Status Method** | **Outcome Post Pathologic Staging**  **(m:months)** |
| **Amplifications** | | | | | | | | | |
| 1 | 71 | M | Bladder | Atezolizumab;  19 months | pT3N0M0  &  Pelvic Recurrence | s/p NAC (GC)/ RC;  s/p adjuvant  Chemo/ RT | 11.2 | NGS, FISH, IHC (Pre-IO) | Stable;  Met: 9m  AWD: 68m |
| 2 | 75 | F | Upper Tract | Nivolumab;  35 months | pTisN1Mx  (Imaging: TisN1M1) | s/p NU | 9.7 | NGS (Pre-IO) | Near Complete Response;  Met: 7m  AWD: 29m |
| 3 | 80 | M | Bladder | Pembrolizumab;  4 months | pT2  (Imaging: T4N1M1) | s/p GC | - | FISH, IHC (Pre-IO) | Progression  DOD: 3m |
| 4 | 57 | M | Bladder | Atezolizumab;  16 months | pT3N0M0 | s/p RC;  s/p adjuvant GC | 7.9 | NGS, FISH, IHC (Post-IO) | Progression;  Met: 29m;  DOD: 38m |
| 5 | 60 | F | Upper Tract | Atezolizumab;  1 month | pT3N0M1 | s/p NU;  s/p adjuvant  EP, EC | 20.7 | NGS, FISH, IHC (Pre-IO) | Progression;  Met: 20m;  DOD: 30m |
| 6 | 68 | M | Bladder | **No IO** | pT3N0M1 | s/p NAC/ RC | - | FISH, IHC (**No IO)** | Progression;  Met: 6m  DUK: 8m |
| 7 | 50 | F | Bladder | Pembrolizumab;  9 months | pT3N2Mx (Imaging: T3N2M1) | - | 2.6 | NGS, IHC (Pre-IO) | NED: 3m |
| 8 | 86 | M | Bladder | **No IO** | NA  (Imaging: M0) | - | 38.6 | NGS, IHC (No IO) | NED: 1m |
| 9 | 68 | M | Bladder | **No IO** | pT1NxMx | s/p adjuvant GC, paclitaxel; s/p cystoprostatectomy | 10.5 | NGS, IHC (No IO) | Progression;  Met: 8m;  NED: 21m |
| **Deletions** | | | | | | | | | |
| 10 | 52 | M | Bladder | Atezolizumab;  24 months | pT2 (Imaging: T4N1M1) | s/p GC | 5.3 | NGS (Pre-IO) | Clinical Benefit;  DOD: 32m |
| 11 | 65 | M | Bladder | Nivolumab; Subsequently Ipilimumab/ Nivolumab;  5 months | pT1N1 | s/p RC; GC and paclitaxel | 15.8 | NGS, IHC (Post IO) | Progression; Met: 3m;  DOD: 25m |
| 12 | 58 | F | Bladder | Durvalumab;  3 months | pT1 (TURBT)  N1 (FNA) | s/p GC; IO concurrent with AZD4547 (anti-FGFR, due to presence of FGFR3 *S249C* mutation) | 6.9 | NGS (Pre-IO) | Progression;  Met: 7m,  POD: 40m |
| 13 | 52 | M | Bladder | **No IO** | pT3N0M0 | Subsequent therapy:  TC | 21.2 | NGS (No IO) | Progression;  Met: 1m;  DOD: 21m |
| 14 | 87 | F | Bladder | **No IO** | pT1 | - | 7.9 | NGS (No IO) | DUK: 53m |
| 15 | 53 | M | Bladder | **No IO** | pT2 | Subsequent therapy:  NAC (GC);  Chemo/ RT | 4.4 | NGS, IHC (No IO) | Recurrence: 4m;  AWD: 20m |
| 16 | 66 | M | Bladder | Pembrolizumab; 1 month | pT2 (Imaging: N1) | Subsequent therapy: NAC (GC) & RC (ypTisN2) | 25.5 | NGS, IHC (Pre-IO) | Progression;  Met: 6m;  AWD: 20m |
| 17 | 48 | M | Bladder | **No IO** | pTa | Subsequent therapy: BCG, Mitomycin, TURBT | 7 | NGS, IHC (No IO) | Recurrence: 4m; AWoD: 64m |
| 18 | 57 | M | **Bladder** | **No IO** | pT2 | s/p GC | 16.7 | NGS, IHC (No IO) | AWD: 3m |

**Supplementary Table 1.**

RC: radical cystectomy; NU: nephroureterectomy; TURBT: transurethral resection of bladder tumor; FNA: fine needle aspiration; IO: immunotherapy; NAC: neoadjuvant chemotherapy; Chemo/RT: chemotherapy/ radiation therapy; GC: gemcitabine and cisplatin; EP: etoposide and cisplatin; EC: etoposide and carboplatin; TC: paclitaxel and carboplatin; TMB: tumor mutation burden; mt/MB: mutations/megabase; NGS: next generation sequencing; FISH: fluorescent in situ hybridization; IHC: immunohistochemistry; Met: metastasis; AWD: alive with disease; NED: no evidence of disease; DOD: dead of disease; DUK: dead of unknown causes.

**Supplementary Table 2.**

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| **Patient Number** | **Primary/ Metastasis/ Recurrence** | **Specimen Type** | **Divergent Differentiation** | **Molecular Co-Alterations Include** |
| **Amplifications (7 of 1050, 0.66%)** | | | | |
| 1 | Primary | Radical Cystectomy | Neuroendocrine and Lymphoepithelioma-like | Somatic: *TP53*, *RB1* |
| 2 | Metastasis | Biopsy, Lymph Node | None | Germline: *APC*, *BLM*; Somatic: *TP53*, *TERT*, *AKT2* (Amplification) |
| 3 | Primary | Transurethral Resection of Bladder Tumor | Lymphoepithelioma-like and sarcomatoid | - |
| 4 | Recurrence | Biopsy, Neobladder | None | Somatic: *TP53*, *TERT*, *CDKN1A*,  *FGFR3* (Amplification) |
| 5 | Primary | Nephroureterectomy, Renal Pelvis | Neuroendocrine, Glandular and Micropapillary | Somatic: *TP53*, *RB1*, *TERT*, *CDKN1B* |
| 6 | Primary | Radical Cystectomy | Neuroendocrine | - |
| 7 | Primary | Radical Cystectomy | Poorly Differentiated Carcinoma with Clear Cell Adenocarcinoma Features | Somatic: *SETD2*, *KMT2C*, *CDKN2A/CDKN2B* (Loss) |
| 8 | Primary | Transurethral Resection of Bladder Tumor | None | Somatic: *TP53, RB1*, *ERCC2* (Amplification) |
| 9 | Primary | Transurethral Resection, Prostate | None | Germline: *MUTYH*; Somatic: *TP53, TERT* |
| **Deletions (9 of 1050, 0.86%)** | | | | |
| 10 | Primary | Biopsy, Bladder | Squamous, associated with high-risk HPV | *TP53* |
| 11 | Metastasis | Biopsy, Skin | None | *TP53*, *TERT* |
| 12 | Primary | Transurethral Resection of Bladder Tumor | None | *FGFR3*, *TERT* |
| 13 | Primary | Transurethral Resection of Bladder Tumor | None | *JAK2, TP53*, *TERT* |
| 14 | Primary | Transurethral Resection of Bladder Tumor | None | *FGFR3*, *TERT* |
| 15 | Primary | Transurethral Resection of Bladder Tumor | None | *FGFR3*, *TERT* |
| 16 | Primary | Transurethral Resection of Bladder Tumor | None | *TP53*, *TERT* |
| 17 | Primary | Transurethral Resection of Bladder Tumor | None | *FGFR3*, *TERT* |
| 18 | Primary | Transurethral Resection of Bladder Tumor | None | *TP53, ERBB2* (Amplification), *TERT* |

**Supplementary Table 3.**

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| --- | --- | --- | --- | --- |
| **Case No.** | **TCGA ID,**  **Age, Gender, TNM** | ***JAK2***  **copy number,**  **& mRNA percentile** | ***CD274***  **copy number,**  **& mRNA percentile** | ***PDCD1LG2***  **copy number,**  **& mRNA percentile** |
| **Amplifications (8 of 406, 2%)** | | | | |
| **1** | TCGA-BT-A3PJ,  76, Male, T3N0M0 | Amplified (94) | Amplified (95) | Amplified (93) |
| **2** | TCGA-E7-A85H,  64, Male, T3N0M0 | Amplified (40) | Amplified (70) | Amplified (53) |
| **3** | TCGA-FD-A3B6,  75, Male, T2N0MX | Amplified (69) | Amplified (100) | Amplified (98) |
| **4** | TCGA-FD-A6TF,  80, Female, T3N2M0 | Amplified (84) | Amplified (87) | Amplified (77) |
| **5** | TCGA-FJ-A3Z7,  76, Male, T4N2MX | Amplified (98) | Amplified (88) | Amplified (42) |
| **6** | TCGA-GC-A4ZW,  71, Male, T3N0M0 | Amplified (75) | Amplified (89) | Amplified (23) |
| **7** | TCGA-GU-A764,  66, Male, T2N0MX | Amplified (100) | Amplified (96) | Amplified (100) |
| **8** | TCGA-GV-A3JZ,  55, Male, T4N3MX | Amplified (97) | Amplified (93) | Amplified (58) |
| **9** | TCGA-XF-AAN4,  77, Female, T3N0MX | Amplified (95) | Amplified (89) | Amplified (95) |
| **10** | TCGA-XF-A9T4,  48, Male, T2N1MX | - | Amplified (98) | Amplified (97) |
| **Deletions (5 of 406, 1.2%)** | | | | |
| **11** | TCGA-FD-A62S,  60, Female, T3N0MX | Deletion (59) | Deletion (58) | Deletion (79) |
| **12** | TCGA-KQ-A41O,  84, Male, T3N1M0 | Deletion (13) | Deletion (3) | Deletion (5) |
| **13** | TCGA-XF-A9SV,  82, Male, T4N2M1 | Deletion (2) | Deletion (1) | Deletion (36) |
| **14** | TCGA-BT-A0YX,  70, Female, T3N0M0 | Deletion (12) | - | - |
| **15** | TCGA-G2-A2EO,  69, Male, T3N0M0 | Deletion (33) | - | - |