**Supplementary Tables and Figures:**

Supplementary Table S1. Experience with MET, EGFR, VEGFR Inhibitors in Papillary RCC

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | S1107 | DFC/NCI1 | S03172 | GETUG3 | Astra Zeneca4 |
| Drug | ARQ 197+/-  erlotinib | foretinib | erlotinib | sunitinib | savolitinib |
| Mechanism | MET/EGFR | VEGFR/MET | EGFR | VEGFR | MET |
| N | 50 | 68 (9 HPRC\*) | 52 | 46/15 (type 2/1) | 109 (44 with MET alterations) |
| RR% | 0 | 13.5 (5% if HPRC excluded) | 11 | 11/13 (type 2/1) | 7  (18% in MET driven tumors |
| PFS months | 2.0/3.9 | 9.3 | 5 | 5.5/6.6 (type 2/1) | 6.2 for MET driven  1.4 for MET neg |
| OS months | 10.3/11.3 | NR (1 year-70%) | 27 | 12.4/17.8 (type 2/1) | Not reported |

\*Hereditary Papillary Renal Cell Carcinoma

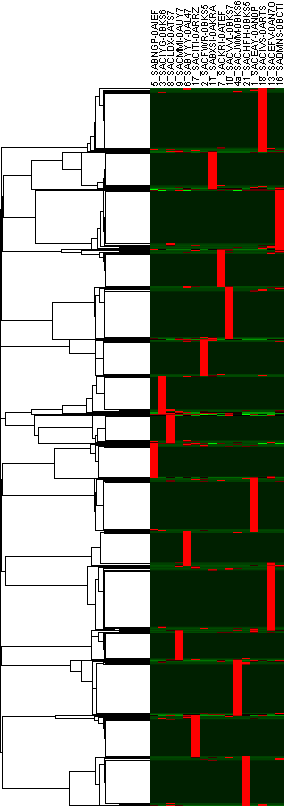
1. Choueri TK et al. Phase II biomarker study of the dual MET/VEGFR2 inhibitor foretinib in patients with papillary renal cell carcinoma J.Clin Oncol.2013 Jan 10;31 (2):181-6.
2. Gordon M. et al. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cancer: SWOG S0317. J.Clin Oncol 2009 Dec;27(34):5788-93.
3. Ravaud A. et al. First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group (GETUG). Ann Oncol.2015 Mar 23.
4. Choueri TK et al. Biomarker-Based Phase II Trial of Savolitinib in Patients with Advanced Papillary Renal Cell Cancer. [J Clin Oncol.](https://www.ncbi.nlm.nih.gov/pubmed/28644771) 2017 Sep 10;35(26):2993-3001.

Supplementary Table S2. Number of Patients with a Reported Grade ≥ 3 Adverse Events Assessed as Being Possibly, Probably or Definitely Related to Treatment, By Treatment Arm

|  | **ARQ 197 (n=25) Grade** | | | | | | **ARQ 197 + Erlotinib (n=25) Grade** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ADVERSE EVENTS** |  | **3** | **4** | **5** |  | **3** | | **4** | **5** |
| ALT increased |  | 0 | 0 | 0 |  | 1 | | 0 | 0 |
| AST increased |  | 0 | 0 | 0 |  | 1 | | 0 | 0 |
| Anemia |  | 2 | 0 | 0 |  | 0 | | 1 | 0 |
| Dyspnea |  | 1 | 0 | 0 |  | 1 | | 0 | 0 |
| Erythema multiforme |  | 0 | 0 | 0 |  | 1 | | 0 | 0 |
| Fatigue |  | 0 | 0 | 0 |  | 1 | | 0 | 0 |
| Febrile neutropenia |  | 0 | 0 | 0 |  | 1 | | 0 | 0 |
| Hypertension |  | 1 | 0 | 0 |  | 0 | | 0 | 0 |
| Hypoxia |  | 0 | 0 | 0 |  | 1 | | 0 | 0 |
| Infections/infestations-Other |  | 0 | 0 | 0 |  | 1 | | 0 | 0 |
| Lung infection |  | 0 | 0 | 0 |  | 1 | | 0 | 0 |
| Lymphocyte count decreased |  | 1 | 0 | 0 |  | 0 | | 0 | 0 |
| Myocardial infarction |  | 0 | 0 | 0 |  | 0 | | 0 | 1 |
| Nausea |  | 1 | 0 | 0 |  | 0 | | 0 | 0 |
| Neutrophil count decreased |  | 1 | 0 | 0 |  | 0 | | 0 | 0 |
| Pain in extremity |  | 1 | 0 | 0 |  | 0 | | 0 | 0 |
| Pneumonitis |  | 0 | 0 | 0 |  | 1 | | 0 | 0 |
| Rash acneiform |  | 0 | 0 | 0 |  | 2 | | 0 | 0 |
| Rash maculo-papular |  | 0 | 0 | 0 |  | 1 | | 0 | 0 |
| Stroke |  | 0 | 1 | 0 |  | 0 | | 0 | 0 |
| Weight loss |  | 1 | 0 | 0 |  | 0 | | 0 | 0 |
| White blood cell decreased |  | 1 | 0 | 0 |  | 1 | | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** |  | 6 | 1 | 0 |  | 7 | | 1 | 1 |
|  |  |  |  |  |  |  | |  |  |
|  |  |  |  |  |  |  | |  |  |

Supplementary Table S3. Pathway analysis of mutated genes

|  |  |  |  |
| --- | --- | --- | --- |
| Pathways | P-value | FDR | Genes |
| Wnt signaling pathway(P) | 1.05E-07 | 1.79E-05 | FAT1,PCDHB8,PCDHB6,CREBBP,PCDHB1,CELSR2,PCDH15,CTNNA2,EP400,CDH11 |
| Cadherin signaling pathway(P) | 1.72E-07 | 1.79E-05 | FAT1,PCDHB8,PCDHB6,PCDHB1,CELSR2,PCDH15,CTNNA2 |
| Mitotic G2-G2/M phases(R) | 3.46E-07 | 2.39E-05 | AKAP9,TUBGCP3,TUBGCP6,CEP131,ALMS1,CENPJ,PLK1 |
| Assembly of the primary cilium(R) | 7.11E-05 | 3.70E-03 | AKAP9,CEP131,ALMS1,CENPJ,PLK1,IFT88 |
| Urokinase-type plasminogen activator (uPA) and uPAR-mediated signaling(N) | 7.08E-04 | 0.029 | NCL,LRP1,PLAU |
| Chromatin modifying enzymes(R) | 1.07E-03 | 0.0363 | KDM6A,KMT2C,CREBBP,SMARCC2,EP400 |
| Activation of anterior HOX genes in hindbrain development during early embryogenesis(R) | 2.57E-03 | 0.0744 | KDM6A,KMT2C,CREBBP |
| Myogenesis(R) | 4.47E-03 | 0.1161 | MEF2A,CTNNA2 |
| the information processing pathway at the ifn beta enhancer(B) | 6.87E-03 | 0.1464 | IRF6,SMARCC2 |
| amb2 Integrin signaling(N) | 7.32E-03 | 0.1464 | LRP1,PLAU |

pt_symbol_by_occurrence_0_or_1_colorbar.pngSupplementary Fig. S1. Clustering genes with variants by sample