**Supplemental Table 1:** Genomics and survival data for the entire cohort of squamous cell carcinomas

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patient number | Diagnosis | Sex | Age (years) | Genomic alterations | MSI status | TMB (mutations/mb) | Treatment | Best response | TTF (months) | OS (months) |
| 1 | Cutaneous | Male | 71.4 | *NOTCH1 R365C NOTCH1 splice site 2467\_2467+1GG>AA TP53 R273H TP53 S241F ASXL1 G646fs\*12 CTCF T89fs\*6 FAT1 L4137fs\*69 FAT1 Q3524\* LRP1B Q3874\* LRP1B splice site 13248-1G>C NOTCH2 E1259\* NOTCH2 Q1872\* SLIT2 D704N TERT promoter -146C>T* | N/A | 66 | Pembrolizumab | SD | 9.9 | 11.2 |
| 2 | Cutaneous | Male | 65.3 | N/A | N/A | N/A | Nivolumab | PR | 24.2+ | 24.2+ |
| 3 | Cutaneous | Male | 70.4 | *EGFR amplification TSC1 S673F CDKN2A p16INK4a E69\* and p14ARF G83V TP53 F270L, H179Y ARID2 Q1318\*, R1272\* CREBBP P760S SPTA1 Q92\** | N/A | 45 | Pembrolizumab | SD | 5.5 | 6.2+ |
| 4 | Cutaneous | Male | 79.6 | *CDK6 R87Q CDKN2A p16INK4a W110\* CDKN2A p14ARF G125R NOTCH1 P391S NOTCH1 R353C TP53 P152L TP53 P98L TP53 R282W ASXL1 I490fs\*213 CHEK2 splice site 1095+1G>A* | MS-Stable | 41 | Pembrolizumab | PR | 27.3+ | 27.3+ |
| 5 | Cutaneous | Male | 65.9 | *BRCA1 E1375\* FLT3 L939F CTNNB1 S37F NOTCH1 P1770S, Q1810\*, T1997M TP53 R342\* ASXL1 Q748\* ATRX splice site 6327-1G>A BRD4 rearrangement intron 11 CHD2 S521\* CREBBP Q1245\* EPHA3 T215M FAT1 I659M KDM6A S1400\* LRP1B loss exons 12-15 MAGI2 R766\* RB1 S474N SETD2 R1592\* SLIT2 R1454\*, splice site 611+2T>A TERT promoter -146C>T* | MS-Stable | 347 | Pembrolizumab | PR | 24.6+ | 24.6+ |
| 6 | Cutaneous | Male | 75.0 | *ABL2 R359P ERBB2 S310F FGFR1 S790\* PDGFRA E556K ATM Q2433\* ATM R717W GRM3 D280N TP53 Q331\* CSF1R splice site 1511-1G>A FAT1 R1070\* LRP1B G1055R NOTCH1 A1967fs\*14 RB1 R579\* SPTA1 R1277H TERT promoter -124C>T* | MS-Stable | 182 | Pembrolizumab | CR | 21.4+ | 21.4+ |
| 7 | Cutaneous | Male | 63.0 | N/A | N/A | N/A | Pembrolizumab | CR | 10.5+ | 10.5+ |
| 8 | Cutaneous | Male | 77.4 | *CCND1 amplification FGF19 amplification FGF3 amplification FGF4 amplification LRP1B splice site 13561-1G>A PBRM1 W1365\* TET2 Q654\* TP53 R282W* | MS-high | 26 | Pembrolizumab | PD | 3.6 | 17.4 |
| 9 | Cutaneous | Male | 60.5 | *ATR splice site 4642-1G>A CDKN2A/B loss MLL2 R2635Q NOTCH1 P391S NOTCH2 Q831\* RAC1 P29S SF3B1 R831Q TERT promoter -146C>T* | MS-Stable | 12 | Pembrolizumab | SD | 20.5+ | 20.5+ |
| 10 | Cutaneous | Male | 66.7 | *TSC2 P670S ARID2 L1790\* CDKN2A p16INK4a P114L CREBBP Q1777\* EP300 Q447\* LRP1B W3570\* NOTCH1 Q1214\* NOTCH2 splice site 2027-1G>A TERT promoter -124C>T TP53 H179R TP53 R196\** | MS-stable | 11 | Pembrolizumab | PD | 3.0 | 7.4+ |
| 11 | Cutaneous | Male | 71.6 | *ARID2 P994fs\*16 DNMT3A R736H – subclonal⧺ FOXP1 Q17\* MSH2 E580fs\*10 SMAD4 W99\* TP53 R282W – subclonal⧺ , splice site 783-2A>T* | MS-stabl | 8 | Pembrolizumab | SD | 16.3+ | 16.3+ |
| 12 | Cutaneous | Male | 44.8 | *CDK12 Y279 CDKN2A p16INK4aD74V FAT1 W4175 SETD2 R2077 TP53 R196* | N/A | 5 | Pembrolizumab | PR | 8.3 | 8.7 |
| 13 | Cutaneous | Male | 64.4 | *NF2 L360fs\*4 CDKN2A p16INK4a Q50\* FAT1 W1345\* LRP1B W2722\* NOTCH1 Q1957\* NOTCH2 Q2452\* PREX2 M1298I TAF1 E1774\* TERT promoter -124C>T TP53 R248Q TP53 splice site 376-11\_380>CCT* | N/A | 11 | Pembrolizumab | PR | 10.1+ | 10.1+ |
| 14 | Cutaneous | Female | 63.8 | N/A | N/A | N/A | Pembrolizumab | PR | 7.9+ | 7.9+ |
| 15 | Cutaneous | Male | 67.0 | *MLH1 E594fs\*23*  *MSH6 R248fs\*8*  *ARID1A P1326fs\*155*  *ARID1A Q1519fs\*8*  *BLM N515fs\*16*  *CDC73 E303Q*  *CDKN2A p16INK4a A102fs\*18*  *CDKN2A p14ARF A117fs\*18+*  *CHD2 K337fs\*2*  *CREBBP L524fs\*6*  *GRM3 S154F*  *LRP1B loss exons 15-25*  *MLL2 G5182fs\*61*  *MLL2 Q791fs\*139*  *NOTCH1 P422S*  *PBRM1 N258fs\*25*  *PBRM1 R534\**  *RB1 loss exons 1-9*  *SPEN A2105fs\*33*  *STAT4 splice site 129-2delA – subclonal*  *TP53 P153\_R156>G* | N/A | 107 | Pembrolizumab | PD | 0.0 | 0.3 |
| 16 | Head & neck | Male | 80.7 | Insufficient tissue | not performed | not performed | Nivolumab | PD | 1.4 | 4.2 |
| 17 | NSCLC | Female | 45.9 | not performed | not performed | not performed | Nivolumab | PR | 28.9+ | 28.9+ |
| 18 | Head & neck | Male | 60.3 | not performed | not performed | not performed | Pembrolizumab | PD | 0.1 | 0.1 |
| 19 | NSCLC | Male | 81.8 | not performed | not performed | not performed | Nivolumab | PD | 4.5 | 12.8 |
| 20 | Head & neck | Male | 72.3 | *PIK3CA amplification – equivocal*  *PTEN Q298\**  *CDKN2A p16INK4a D84Y*  *CDKN2A p14ARF R98L*  *PRKCI D396E*  *SOX2 amplification – equivocal*  *TP53 Q144\**  *NFE2L2 W8C* | MS-Stable | 2 | Pembrolizumab | SD | 7.6 | 9.8 |
| 21 | Head & neck | Male | 87.6 | not performed | not performed | not performed | Pembrolizumab | SD | 11.7+ | 11.7+ |
| 22 | Head & neck | Male | 59.2 | *SRC amplification – equivocal*  *NOTCH1 T2466fs\*11* | MS-Stable | 6 | Pembrolizumab | PR | 7.3 | 21.0 |
| 23 | Head & neck | Female | 69.2 | not performed | not performed | not performed | Nivolumab+Carboplatin | CR | 32.1+ | 32.1+ |
| 24 | NSCLC | Male | 66.8 | not performed | not performed | not performed | Nivolumab | PD | 1.9 | 2.3 |
| 25 | Head & neck | Male | 74.1 | *CDKN2A/B loss RNF43 G659fs\*41 FAT1 R1096\* – subclonal⧺ TP53 splice site 375G>T* | MS-Stable | 3 | Pembrolizumab | PD | 1.4 | 2.8 |
| 26 | Head & neck | Male | 78.5 | *TERT promoter -124C>T TP53 R282W* | MS-Stable | 4 | Pembrolizumab | PD | 1.2 | 2.1 |
| 27 | NSCLC | Female | 63.5 | not performed | not performed | not performed | Nivolumab | PD | 0.9 | 1.6 |
| 28 | NSCLC | Male | 72.3 | *PIK3CA amplification SOX2 amplification CDKN2A/B loss KDM6A deletion exons 5-20 LRP1B G783V MCL1 amplification TP53 V274L* | MS-Stable | 12 | Nivolumab | SD | 5.8 | 17.6 |
| 29 | Urethral | Male | 39.8 | *BRAF G606R EGFR amplification FGFR2 amplification – equivocal⧺ NF1 loss exons 36-57 C17orf39 amplification – equivocal⧺ FAT1 loss MLL3 S2860\* SPTA1 R2211H STAT4 splice site 1571-10\_1578del18* | MS-Stable | 10 | Pembrolizumab | SD | 2.8 | 23.3 |
| 30 | Head & neck | Male | 44.3 | not performed | not performed | not performed | Pembrolizumab | SD | 14.4 | 17.9 |
| 31 | Esophageal and hypopharyngeal | Female | 69.5 | *BRCA2 M965fs\*13 BRCA2 S884\* ERBB2 I767M – subclonal FGFR3 S249C CDKN2A/B loss TP53 R175H BCORL1 Q851\* MLL3 Q2197\* – subclonal SMAD4 D351H* | MS-Stable | 20 | Nivolumab | PR | 6.4 | 17.4 |
| 32 | Head & neck | Male | 76.9 | *MYC amplification* | not performed | 6 | Nivolumab | SD | 16.1 | 27.5 |
| 33 | Esophageal | Male | 73.8 | *CDKN2A/B loss TP53 C176F TP53 D61fs\*62 EP300 P925T* | not performed | 6 | Nivolumab+Palbociclib | SD | 4.0 | 4.7 |
| 34 | Head & neck | Male | 60.9 | *CDKN2A p16INK4a W110\* TERT promoter -124C>T TP53 K305fs\*40* | MS-Stable | 3.19 | Avelumab | PD | 1.3 | 9.6 |
| 35 | Head & neck | Male | 58.7 | *ASXL1 Q575\* – subclonal BCORL1 I790fs\*64 CREBBP R1103\* DNMT3A R771\* – subclonal* | MS-Stable | 4 | Nivolumab | SD | 5.8 | 19 |
| 36 | NSCLC | Female | 71.0 | not performed | not performed | not performed | Nivolumab | SD | 21.9 | 26.8 |
| 37 | NSCLC and renal cell carcinoma | Male | 75.8 | *ARID1A Q1519fs\*13 CDK8 A155V MAGI2 E1315fs\*159 MLH1 H289fs\*17 NOTCH1 R1962S SETD2 K1969fs\*2 TERT promoter -124C>T TP53 R175H VHL L135fs\*9* | MS-Stable | 4 | Nivolumab | SD | 5.1 | 8.9 |
| 38 | Cervical | Female | 68.8 | *FBXW7 R465H CTNNB1 S37C BCOR Q224\* BCOR Q990\* RB1 E31\* RB1 S230\** | MS-Stable | 1 | Pembrolizumab | SD | 4.4 | 5.7 |
| 39 | Head & neck | Female | 79.1 | *PIK3CA V344G SOX9 E75K – subclonal* | MS-Stable | 7 | Pembrolizumab | SD | 4.8 | 6.9 |
| 40 | Head & neck | Male | 56.4 | not performed | not performed | not performed | Pembrolizumab | SD | 3.2 | 3.8 |
| 41 | Head & neck | Male | 57.6 | none | not performed | 3 | Nivolumab | PD | 3.5 | 12.5 |
| 42 | Cervical | Female | 59.8 | not performed | not performed | not performed | Nivolumab | PR | 12.6 | 13.1 |
| 43 | Head & neck | Male | 57.7 | *CTNNB1 loss MYB rearrangement intron 14 PARK2 P113fs\*51 PIK3R2 R89fs\*43 SOX9 S414\** | MS-Stable | 3 | Pembrolizumab | SD | 6.4 | 9.0 |
| 44 | Esophageal | Male | 77.6 | *BCL2L2 amplification – equivocal FAT1 R937\* ROS1 S1810F SMARCA4 Q1236fs\*51 TP53 L252P TP53 R196\* VHL L188fs\*28+* | MS-Stable | 17 | Nivolumab | PR | 16.1+ | 16.1+ |
| 45 | NSCLC | Female | 62.2 | not performed | not performed | not performed | Durvalumab | CR | 12.9 | 29.6 |
| 46 | NSCLC | Female | 70.0 | not performed | not performed | not performed | Nivolumab | PR | 19.4 | 19.7 |
| 47 | Head & neck | Female | 69.2 | not performed | not performed | not performed | Nivolumab | PD | 0.8 | 0.8 |
| 48 | NSCLC | Male | 63.4 | not performed | not performed | not performed | Nivolumab | PD | 3.4 | 3.7 |
| 49 | Head & neck | Male | 62.9 | not performed | not performed | not performed | Avelumab+Utomilumab | PD | 2.6 | 3.7 |
| 50 | NSCLC | Male | 72.0 | not performed | not performed | not performed | Nivolumab | CR | 25.2+ | 25.2+ |
| 51 | Head & neck | Female | 86.2 | *HRAS Q61L CDKN2A p16INK4a loss CDKN2A p14ARF loss exons 2-3 ARID2 Q1027\* ASXL1 G710fs\*15 BCORL1 Q1664\* FAT1 Q1244\* FAT1 S869\* NOTCH2 Q1392\* PMS2 V415M TERT promoter -124C>T* | MS-Stable | 9 | Pembrolizumab | PD | 4.0 | 12.2 |
| 52 | Head & neck | Male | 50.7 | *CDKN2A/B loss CYLD S371\** | MS-Stable | 3 | Pembrolizumab | PD | 1.9 | 11.4 |
| 53 | Head & neck | Female | 89.5 | *FAT1 S2682 FAT1 S3830 MPL S505N NOTCH1 loss exons3-15 TP53 G266R* | MS-Stable | 14 | Pembrolizumab | PR | 16.5+ | 16.5+ |
| 54 | NSCLC and mantle cell lymphoma | Female | 80.9 | not performed | not performed | not performed | Pembrolizumab | PD | 3.1 | 3.9 |
| 55 | Head & neck | Female | 44.8 | not performed | not performed | not performed | Pembrolizumab | PD | 1.2 | 1.6 |
| 56 | NSCLC | Female | 70.9 | not performed | not performed | not performed | Nivolumab | PD | 1.3 | 4.7 |
| 57 | Head & neck | Male | 69.7 | *PIK3CA E542K ARID2 splice site 1023+1G>A LRP1B Q3874\* TERT promoter -146C>T* | MS-Stable | 8 | Nivolumab+Cabiralizumab | PR | 9.5+ | 9.5+ |
| 58 | Head & neck | Male | 61.8 | not performed | not performed | not performed | Pembrolizumab | PD | 2.9 | 4.8 |
| 59 | Head & neck | Male | 70.9 | not performed | not performed | not performed | Nivolumab | PR | 7.7 | 8.3 |
| 60 | Head & neck | Male | 58.9 | *CD274 amplification PDCD1LG2 amplification FAT1 E4156* | MS-Stable | 7.19 | Avelumab+Utomilumab | SD | 4.3 | 9.9 |
| 61 | Head & neck | Male | 79.3 | *CDKN2A p16INK4a R58\* CDKN2A p14ARF P72L EP300 D1399N FAT1 R2726\* MLL2 E233\* MUTYH G382D NOTCH2 Q2006\* TERT promoter -146C>T TP53 P301Q – subclonal⧺ TP53 R196P TP53 R280T – subclonal⧺ WT1 C350R* | MS-Stable | 25 | Pembrolizumab | PD | 2.1 | 4.4 |
| 62 | Head & neck | Female | 52.4 | not performed | not performed | not performed | Pembrolizumab | PD | 1.8 | 4.5 |
| 63 | NSCLC | Male | 66.7 | not performed | not performed | not performed | Nivolumab+Cabiralizumab | SD | 2.9 | 7.9 |
| 64 | Head & neck | Male | 74.2 | not performed | not performed | not performed | Avelumab+Utomilumab | SD | 4.8 | 5.3 |
| 65 | Head & neck | Female | 65.6 | not performed | not performed | not performed | Pembrolizumab | PD | 2.3 | 3.9 |
| 66 | Head & neck | Male | 53.9 | not performed | not performed | not performed | Pembrolizumab | PD | 1.9 | 6.4 |
| 67 | Head & neck | Male | 90.4 | *CD274 (PD-L1) amplification PDCD1LG2 (PD-L2) amplification CDKN2A p16INK4a R58\* CDKN2A p14ARF P72L APC I1307K FAT1 S1357\* JAK2 amplification TERT promoter -124C>T TP53 H193N TP53 R248W* | MS-Stable | 5 | Pembrolizumab | PR | 10.1+ | 10.1+ |
| 68 | NSCLC | Female | 71.3 | *MYC amplification TP53 R280I BCORL1 splice site 4306-2A>G NOTCH2 Q1634\** | MS-Stable | 19 | Nivolumab | PD | 0.4 | 1.3 |
| 69 | NSCLC | Male | 82.7 | not performed | not performed | not performed | Nivolumab | PD | 1.4 | 2.2 |
| 70 | NSCLC | Male | 63.1 | *STK11 V236fs\*51 CDK6 amplification IDH2 R140Q MLL2 A3051fs\*20 RUNX1T1 A491T SMARCA4 I382fs\*28 TP53 P151R* | MS-Stable | 19 | Nivolumab | PD | 1.7 | 7.5 |
| 71 | Head & neck | Male | 57.4 | not performed | not performed | not performed | Pembrolizumab | PD | 0.6 | 0.7 |
| 72 | Head & neck | Male | 56.8 | not performed | not performed | not performed | Pembrolizumab | PD | 6.3 | 24.4 |
| 73 | Head & neck | Male | 76.2 | *CD274 (PD-L1) amplification JAK2 amplification PIK3CA E545K PTCH1 M1fs\*81 PDCD1LG2 (PD-L2) amplification SOX2 amplification SUFU S79fs\*5 BCL2L2 amplification – equivocal KEAP1 R320Q MLL3 C310S – subclonal* | MS-Stable | 9 | Pembrolizumab | PD | 4.7 | 22.4 |
| 74 | Anal | Male | 33.0 | *STK11 loss exons 1-6 CHD2 truncation exon 31* | MS-Stable | 6 | Pembrolizumab | PD | 1.3 | 2.9 |
| 75 | Rectal | Female | 62.9 | *AKT1 E17K CYLD Q26\* – subclonal⧺ LRP1B T2117fs\*5 SPTA1 R374\* STAG2 Q167\** | MS-Stable | 18 | Pembrolizumab | SD | 8.5+ | 8.5+ |

**Abbreviations**: CR = complete response; mb= megabase; MSI = microsatellite instability; N/A = not available; NSCLC = non-small cell lung cancer; OS = overall survival; PD = progressive disease; PR = partial response; SD = stable disease; TMB = tumor mutational burden; TTF = time to treatment fail

**Supplemental Table 2**: Total alterations seen in all SCCs segregated by cutaneous vs. other SCC

|  |  |  |  |
| --- | --- | --- | --- |
| Alteration | Total (N) | Other SCC (N) | Cutaneous SCC (N) |
| Total alterations | 298 | 157 | 141 |
| TP53 | 37 | 19 | 18 |
| CDKN2A/B | 23 | 14 | 9 |
| FAT1 | 16 | 10 | 6 |
| TERT | 13 | 7 | 6 |
| PIK3CA | 5 | 5 | 0 |
| BCORL1 | 4 | 4 | 0 |
| CD274 | 3 | 3 | 0 |
| LRP1B | 11 | 3 | 8 |
| MLL3 | 3 | 3 | 0 |
| NOTCH1 | 15 | 3 | 12 |
| NOTCH2 | 8 | 3 | 5 |
| PDCD1LG2 | 3 | 3 | 0 |
| SOX2 | 3 | 3 | 0 |
| ARID2 | 6 | 2 | 4 |
| ASXL1 | 5 | 2 | 3 |
| BCL2L2 | 2 | 2 | 0 |
| BCOR | 2 | 2 | 0 |
| BRCA2 | 2 | 2 | 0 |
| CTNNB1 | 3 | 2 | 1 |
| CYLD | 2 | 2 | 0 |
| EP300 | 3 | 2 | 1 |
| JAK2 | 2 | 2 | 0 |
| MLL2 | 5 | 2 | 3 |
| MYC | 2 | 2 | 0 |
| RB1 | 5 | 2 | 3 |
| SMARCA4 | 2 | 2 | 0 |
| SOX9 | 2 | 2 | 0 |
| SPTA1 | 4 | 2 | 2 |
| STK11 | 2 | 2 | 0 |
| VHL | 2 | 2 | 0 |
| AKT1 | 1 | 1 | 0 |
| APC | 1 | 1 | 0 |
| ARID1A | 3 | 1 | 2 |
| BRAF | 1 | 1 | 0 |
| C17orf39 | 1 | 1 | 0 |
| CDK6 | 2 | 1 | 1 |
| CDK8 | 1 | 1 | 0 |
| CHD2 | 3 | 1 | 2 |
| CREBBP | 5 | 1 | 4 |
| DNMT3A | 2 | 1 | 1 |
| EGFR | 2 | 1 | 1 |
| ERBB2 | 2 | 1 | 1 |
| FBXW7 | 1 | 1 | 0 |
| FGFR2 | 1 | 1 | 0 |
| FGFR3 | 1 | 1 | 0 |
| HRAS | 1 | 1 | 0 |
| IDH2 | 1 | 1 | 0 |
| KDM6A | 2 | 1 | 1 |
| KEAP1 | 1 | 1 | 0 |
| MAGI2 | 2 | 1 | 1 |
| MCL1 | 1 | 1 | 0 |
| MLH1 | 2 | 1 | 1 |
| MPL | 1 | 1 | 0 |
| MUTYH | 1 | 1 | 0 |
| MYB | 1 | 1 | 0 |
| NF1 | 1 | 1 | 0 |
| NFE2L2 | 1 | 1 | 0 |
| PARK2 | 1 | 1 | 0 |
| PIK3R2 | 1 | 1 | 0 |
| PMS2 | 1 | 1 | 0 |
| PRKCI | 1 | 1 | 0 |
| PTCH1 | 1 | 1 | 0 |
| PTEN | 1 | 1 | 0 |
| RNF43 | 1 | 1 | 0 |
| ROS1 | 1 | 1 | 0 |
| RUNX1T1 | 1 | 1 | 0 |
| SETD2 | 3 | 1 | 2 |
| SMAD4 | 2 | 1 | 1 |
| SRC | 1 | 1 | 0 |
| STAG2 | 1 | 1 | 0 |
| STAT4 | 2 | 1 | 1 |
| SUFU | 1 | 1 | 0 |
| WT1 | 1 | 1 | 0 |
| ABL2 | 1 | 0 | 1 |
| ATM | 2 | 0 | 2 |
| ATR | 1 | 0 | 1 |
| ATRX | 1 | 0 | 1 |
| BLM | 1 | 0 | 1 |
| BRCA1 | 1 | 0 | 1 |
| BRD4 | 1 | 0 | 1 |
| CCND1 | 1 | 0 | 1 |
| CDC73 | 1 | 0 | 1 |
| CDK12 | 1 | 0 | 1 |
| CHEK2 | 1 | 0 | 1 |
| CSF1R | 1 | 0 | 1 |
| CTCF | 1 | 0 | 1 |
| EPHA3 | 1 | 0 | 1 |
| FGF19 | 1 | 0 | 1 |
| FGF3 | 1 | 0 | 1 |
| FGF4 | 1 | 0 | 1 |
| FGFR1 | 1 | 0 | 1 |
| FLT3 | 1 | 0 | 1 |
| FOXP1 | 1 | 0 | 1 |
| GRM3 | 2 | 0 | 2 |
| MSH2 | 1 | 0 | 1 |
| MSH6 | 1 | 0 | 1 |
| NF2 | 1 | 0 | 1 |
| PBRM1 | 3 | 0 | 3 |
| PDGFRA | 1 | 0 | 1 |
| PREX2 | 1 | 0 | 1 |
| RAC1 | 1 | 0 | 1 |
| SFS3B1 | 1 | 0 | 1 |
| SLIT2 | 3 | 0 | 3 |
| SPEN | 1 | 0 | 1 |
| TAF1 | 1 | 0 | 1 |
| TET2 | 1 | 0 | 1 |
| TSC1 | 1 | 0 | 1 |
| TSC2 | 1 | 0 | 1 |

Abbreviations: SCC = squamous cell carcinoma

**Supplemental Table 3**: Univariate and multivariate analysis of factors affecting outcome for patients with squamous cell carcinoma treated with PD-1/PD-L1 blockade. TMB stratified as low, intermediate or high. (See **Table 2** for TMB stratified as <12 versus >12 mutations/megabase)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | Group (N) | SD ≥ 6 months plus PR/CR 1 N = 31 (%) | OR2 (95% CI) | P univariate\* | Median TTF (mos) | HR2 (95% CI) | P univariate | P multivariate\* | Median OS | HR3 (95% CI) | P univariate |
| Age (years) | <60 (N = 18) | 6 (33%) | 0.6 [0.2-1.8] | 0.5844 | 3.9 | 1.8 [0.9-3.4] | 0.0848 |  | 11.4 | 1.6 [0.8-3.4] | 0.1724 |
|  | ≥60 (N = 57) | 25 (44%) | 1.6 [0.5-5.0] | 5.0 | 0.6 [0.3-1.2] |  | 19.7 | 0.6 [0.3-1.3] |
| Sex | Male (N = 54) | 21 (39%) | 0.7 [0.3-1.8] | 0.6032 | 4.8 | 1.0 [0.5-1.7] | 0.9261 |  | 17.4 | 1.0 [0.5-2.0] | 0.9157 |
|  | Female (N = 21) | 10 (48%) | 1.4 [0.5-3.7] | 4.8 | 1.0 [0.6-1.8] |  | 17.4 | 1.0 [0.5-2.2] |
| Ethnicity | White (N = 61) | 25 (41%) | 0.9 [0.3-3.2] | >0.9999 | 5.0 | 0.8 [0.4-1.5] | 0.4328 |  | 17.4 | 1.0 [0.4-2.5] | 0.9361 |
|  | Other (N = 14) | 6 (43%) | 1.1 [0.3-3.2] | 2.9 | 1.3 [0.6-2.6] |  | 11.4 | 1.0 [0.4-2.3] |
| Disease status | Locally advanced (N = 23) | 10 (43%) | 1.1 [0.4-3.2] | 0.8052 | 5.5 | [0.9 [0.5-1.6] | 0.8419 |  | 17.4 | 0.7 [0.3-1.4] | 0.3422 |
|  | Metastatic (N = 52) | 21 (40%) | 0.9 [0.3-2.2] | 4.7 | 1.1 [0.6-1.8] |  | 13.1 | 1.4 [0.7-2.9] |
| TMB | Low (N = 11) | 3 (26%) | 1 [reference] |  | 4.4 | 1 [reference] |  |  | 11.4 | 1 [reference] |  |
|  | Intermediate (N = 18) | 8 (44%) | 2.1 [0.5-9.1] | 0.4486 | 5.3 | 0.6 [0.2-1.4] | 0.1518 |  | 21.0 | 0.6 [0.2-1.9] | 0.8352 |
|  | High (N = 12) | 7 (58%) | 3.7 [0.6-17.3] | 0.2138 | 9.9 | 0.4 [0.1-1.0] | **0.0339** | 0.570 | 17.4 | 0.5 [0.1-1.6] | 0.1650 |
| Treatment | ≤1 prior therapy (N = 46) | 20 (44%) | 1.3 [0.5-3.4] | 0.8101 | 4.8 | 0.9 [0.5-1.6] | 0.7385 |  | 19.7 | 0.8 [0.4-1.5] | 0.4657 |
|  | 2 or more prior therapies (N = 29) | 11 (38%) | 0.8 [0.3-2.0] | 5.2 | 1.1 [0.6-1.9] |  | 12.2 | 1.2 [0.7-2.5] |
|  | PD-1/PD-L1 blockade monotherapy (N = 68) | 29 (43%) | 1.9 [0.3-9.8] | 0.6926 | 5.1 | 1.1 [0.4-2.6] | 0.8822 |  | 17.4 | 0.7 [0.2-2.3] | 0.5067 |
|  | PD-1/PD-L1 blockade + other (N = 7) | 2 (29%) | 0.5 [0.1-2.9] | 4.3 | 0.9 [0.4-2.3] |  | 8.9 | 1.4 [0.4-4.7 |
| Histology | Cutaneous SCC (N = 15) | 11 (73%) | 5.5 [1.6-16.9] | **0.008** | Not reached | 0.3 [0.2-0.5] | **0.0015** | 0.065 | Not reached | 0.5 [0.2-1.0] | 0.0593 |
|  | Non cutaneous SCC (N = 60) | 20 (33%) | 0.2 [0.1-0.6] | 4.2 | 3.5 [2.0-6.2] | 12.5 | 2.1 [1.0-4.5] |

\*41 patients were included in the multivariate analysis (since only 41 patients had TMB performed). P values ≤ 0.10 were included in the multivariate analysis.

1Response included patients with stable disease ≥ 6 months, partial responders, and complete responders

2Calculated using Fischer’s exact test

3Calculated using long-rank (Mantel-Cox)

Other therapy: chemotherapy (N = 1), targeted therapy (N = 1), and investigational agent (N = 5)

**Abbreviations**: HR = hazard ratio; mb = megabase; MSI = microsatellite instability; OR = odds ration; OS = overall survival; SCC = squamous cell carcinoma; TMB = tumor mutational burden; TTF= Time to treatment failure

**Supplemental Figure 1:** CONSORT Diagram (UCSD cohort)

Not treated with immunotherapy (N = 2323)

Patients with any cancer histology

eligible for analysis (N = 2651)

Patients with squamous cell carcinomas treated with immunotherapy

(N = 75)

Patients with cutaneous squamous cell carcinoma

(N = 15)

Non-squamous cell carcinoma (N = 253)

Head and neck (N = 35)

Patients with non-cutaneous squamous cell carcinoma

(N = 60)

NSCLC (N = 17)

Esophageal (N = 3)

Cervical (N = 2)

Anal (N = 1)

Rectal (N = 1)

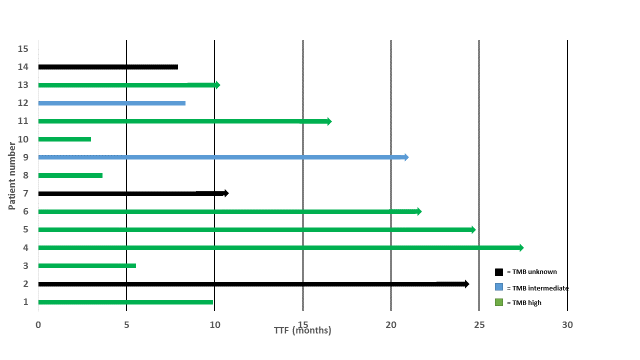
Urothelial (N = 1)

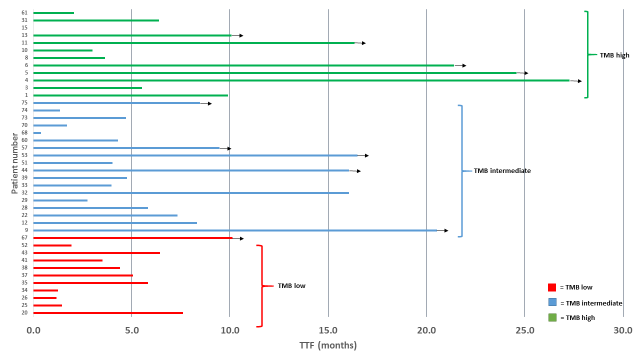
Patients treated with immunotherapy (N = 328)

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**Supplemental Figure 2: Molecular alterations in 12 patients with available data (cutaneous SCC)**

**Top panel**: Genomic alterations identified in 12 patients with locally advanced/metastatic cutaneous squamous cell carcinoma.



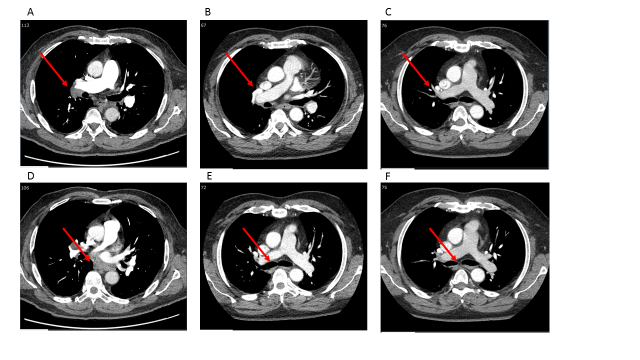
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**Supplemental Figure 3**:

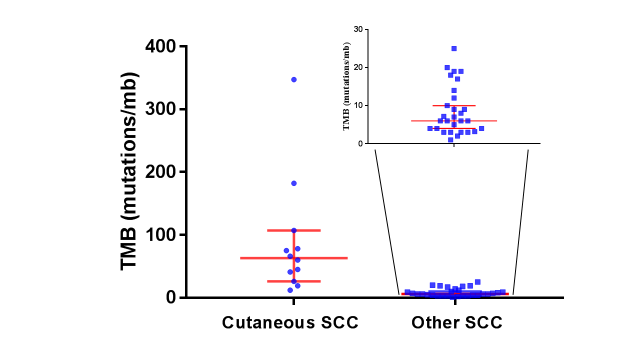
Top panel: TTF for patients (N = 15) with cutaneous SCC treated with PD-1 blockade. Arrows indicate ongoing response. Patient #15 died after receiving one dose of PD-1 blockade.

Bottom panel: TTF for patients with SCC (N = 41 patients with available TMB) treated with PD-1 blockade categorized by TMB level. Arrows indicate ongoing response. Patient # 67 had *PD-L1* amplification in addition to high TMB (22).

**Abbreviation**s: TMB = tumor mutational burden; TTF = time to treatment failure



**Supplemental Figure 4**: 64 year old male with metastatic cutaneous squamous cell carcinoma. Panels A and D are pre-treatment computerized tomographic scans of the chest demonstrating right hilar and subcarinal lymphadenopathy. Panels B and E, and C and F were taken approximately 3 and 7 months after starting pembrolizumab and demonstrate resolution of previous intrathoracic lymphadenopathy.



**Supplemental Figure 5**: Median TMB in mutations per megabase of cutaneous SCC (N = 12) vs. other SCC (N = 29) was 63 (range 12-347) versus 6 (range 1-25) mutations megabase.(p **<0.0001)** (UCSD cohort)

Red brackets represent 95% CI.

**Abbreviations:** mg = megabase; SCC = squamous cell carcinoma; TMB = tumor mutational burden