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| --- | --- | --- | --- | --- | --- | --- | --- |
| eTable 1. Selected patient characteristics | | | | | | | |
| Patient # | **Age** | **Gender** | **“T”** | **“N”** | **“M”** | **p16 status** | **Site** |
| 1 | 46 | Female | T4 | N1 | M0 | NA | Buccal/Alveolar |
| 2 | 72 | Male | T2 | N2a | M0 | Positive | Tonsil |
| 3 | 59 | Male | T2 | N3 | M0 | Positive | Tonsil |
| 4 | 46 | Female | T4 | N2c | M0 | NA | Buccal/Alveolar |
| 5 | 52 | Male | T4 | N2b | M0 | NA | Tongue |
| 6 | 46 | Female | T4 | N2c | M0 | NA | Tongue |
| 7 | 64 | Female | T3 | N2b | M0 | Positive | Base of Tongue |
| 8 | 76 | Female | T4 | N2c | M0 | NA | Tongue |
| 9 | 53 | Male | T4 | N2b | M0 | NA | Buccal/Alveolar |
| 10 | 61 | Male | T4 | N1 | M0 | Negative | Retromolar Trigone/Tonsil |
| 11 | 52 | Male | T4 | N2a | M0 | Positive | Tonsil |
| 12 | 45 | Male | T4 | N2b | M0 | NA | Buccal/Hard Palate |
| NA: not applicable  “T”; “N”, “M” based on to 7th edition AJCC staging | | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- |
| eTable 2. Dosing schedules and duration of treatment | | | | | | |
| PATIENT # | **Dose** | **# Cycles** | **Days on TX** | **Total doses AZD1775** | **Total doses of Cisplatin** | **Total doses of docetaxel** |
| 1\* | 125mg | 1 | 7 | 8 | 1 | 1 |
| 2 | 125mg | 1 | 24 | 18 | 3 | 3 |
| 3 | 125mg | 1 | 22 | 18 | 3 | 3 |
| 4 | 125mg | 2 | 64 | 32 | 6 | 6 |
| 5\*\* | 175mg | 1 | 8 | 8 | 1 | 1 |
| 6 | 175mg | 1 | 30 | 18 | 3 | 3 |
| 7 | 175mg | 1 | 22 | 18 | 3 | 3 |
| 8 | 175mg | 2 | 51 | 27 | 5 | 5 |
| 9 | 150mg | 1 | 23 | 18 | 3 | 3 |
| 10 | 150mg | 1 | 30 | 18 | 3 | 3 |
| 11 | 150mg | 2 | 50 | 32 | 6 | 6 |
| 12 | 150mg | 2 | 53 | 34 | 6 | 6 |
| \* docetaxel stopped due to infusion reaction  \*\* withdrawn due to non-compliance with oral regimen | | | | | | |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **eTable 3. Pharmacokinetic parameters of AZD1775 in patients following twice a day doses for 2.5 days in combination with cisplatin and docetaxel** | | | | | | | |
| **Cycle 1, Day 2 Cycle 1, Day 4** | | | | | | | |
| **Dose**  **(mg)** | **Cmax**  **(nM)** | **AUC**  **(nM/hr)** | **Tmax**  **(hr)** | **Cmax**  **(nM)** | **AUC**  **(nM/hr)** | | **Tmax**  **(hr)** |
| 125 mg (n=3) | 317 (192%) | 2151 (183%) | 4  (2-4) | 715 (90%) | 4887  (121%) | 2  (1-4) | |
| 150 mg (n=4) | 472 (25%) | 3011  (11%) | 2  (2-6) | 1027 (35%) | 7541  (30%) | 2  (2-4) | |
| 175 mg (n=3) | 549 (18%) | 3368 (33%) | 2  (2-6) | 939 (55%) | 7840  (33%) | 4  (4-4) | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **eTable 4. Selected somatic mutations and copy number aberrations** | | | | | |
| **PATIENT #** | **Selected Somatic Mutations** | | | **CNAs** | **p16/HPV\* Status** |
| **1** | **TP53** V272Sfs\*73, V272M | | | **EGFR** Amplification | NA |
| **2** | **TP53** E258K  **EGFR** V769dupV  **ARAF** H121Y  **HIF1A** Q730E, Q43X  **FBXW7** S92X | **VHL** E42Q  **MAPK1** H125R  **MDM2** R187T  **PDGFRB** E471K  **TSC2** E1413K, S1730C | **DPYD** Q860H  **DOCK7** E367X  **KMT2A** D184N  **NOTCH1** I133M | **PIK3CA** Amplification | Positive (HPV 16) |
| **3** | **MAPK1** R135K **NOTCH1** A1850T | **RAF1** E278K  **RUNX1** M418L | | **PIK3CA** Amplification | Positive (HPV 16) |
| **4** | **TP53** V197M  **FGFR3-TACC3** Fusion  **CDKN2A** W110X | **EPHA3** R684X, N493S  **MPL** P106L | | - | NA |
| **5** | **TP53** R280S **PBRM1** Y600X **EZH2** E341G | **GRM3** E78K  **H3F3A** P67T  **GRIN2A** K1078M | | - | NA |
| **6** | **TP53** Y220C  **PIK3CA** E545K | **CDKN2A** R58X | | - | NA |
| **7** | **IKZF1** E345K  **NOTCH1** W1474C | **KIT** N945T | | **CCND1** Amplification **EGFR** Amplification  **PIK3CA** Copy gain | Positive (HPV 16) |
| **8** | **CDKN2A** R80X  **ATM** Splice site | **TP53** Splice site | | - | NA |
| **9** | **TP53** R248W LOH **HRAS** G12S | **CALR** D390Y  **GRM3** A320T | | **HRAS** Copy gain | NA |
| **10** | **TP53** R213\*, Q317\* **CDKN2A** A20Gfs\*19 | **BCORL1** L1114Afs\*14 LOH | | **Chr 7** Amplification | Negative |
| **11** | **ARID1A** N1849Tfs\*69  **AKT3** D219H | **PIK3CA** E726K, R88Q, D891H | | **Chr** **9** Amplification  **PIK3CA** Copy gain | Positive (HPV 16) |
| **12** | **TP53** Exon3 – Intron3 del | | | **EGFR** Amplification  **CCND1** Copy gain | NA |
| **LOH:** loss of heterozygosity  **NA:** not applicable  **del:** deletion  **CNV:** copy number aberrations  \*HPV type was determine using the UWOncoPlex test as described in Materials and Methods | | | | | |

**eFigure 1.**

Title: Clinical trial overview and schematic.

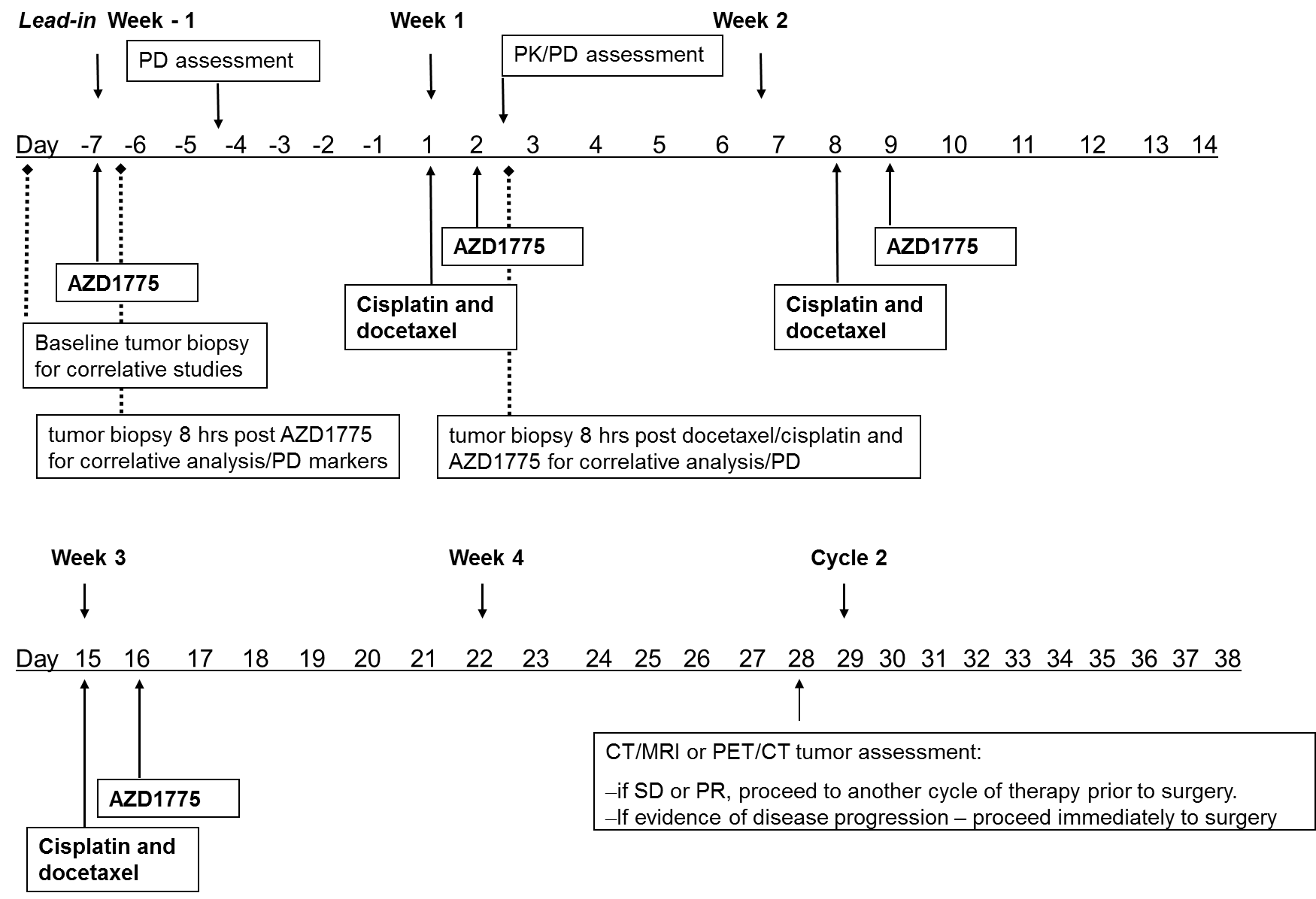
Legend: Treatment was administered in 28 days cycles, with AZD1775 given orally twice a day on the first week for 5 doses, followed by AZD1775 at the same dose and frequency but in combination with cisplatin (25mg/m2) and docetaxel (35 mg/m2) every 7 days for three additional weeks. Patients were re-assessed for response and either received a second cycle of AZD1775/chemotherapy for three weeks or definitive therapy.

**eFigure 2.**

Title: Biomarker response and clinical correlation after neoadjuvant therapy with AZD1775.

Legend: Scatterplot correlation of clinical response with quantified IHC biomarkers of response for **(A)** percent pCDC2 loss and **(B)** percent CC3 gain. Biomarker response as demonstrated by IF (left panels) and quantified IHC data as % cells stained (right panels) for **(C)** H2AX and **(D)** pHH3 in biopsies pre-treatment (sample “A”), post-AZD alone (sample “B”), and post-AZD plus cisplatin plus docetaxel (sample “C”).

**eFigure1 (see powerpoint for true figure)**



**eFigure2 (see powerpoint for true figure)**

