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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| \* docetaxel stopped due to infusion reaction\*\* withdrawn due to non-compliance with oral regimen |

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| **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) |

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| **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)**

