**Supplementary Table 1: prior treatments**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Overall** | **control** | **monoallelic** | **biallelic** | **p** |
| **N** | 180 | 144 | 8 | 28 |  |
| **Docetaxel = Yes (%)** | 173 (96.1) | 138 (95.8) | 8 (100.0) | 27 (96.4) | **1.000\*** |
| **Docetaxel in HSPC** |  | 13/138 (13.1) | 3/8 (37.5) | 8/27 (29.6) | **0.020\*** |
| **Abi\_Enza (as first line) = Yes (%)** | 171 (95%) | 138 (95.8) | 8 (100.0) | 25 (89.2) | **0.340\*** |
| **Cabazitaxel = Yes (%)** | 101 (56.1) | 88 (61.1) | 4 ( 50.0) | 9 (32.1) | **0.014\*** |

**Supplementary Table 2**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Number** | **Targeted Sequencing – Diagnostic (A)** | **Targeted Sequencing – mCRPC (F)** | **Tumour Content - A** | **Tumour Content - F** | **Concomitant Relevant Mutations** | **CDK12 Loss** |
| Pat.1B | S440\*, 43% |  | 60% |  | PIK3CA E545K 39%, SPOP F133V 44% | Biallelic |
| Pat.2B |  | Y319fs, 98% |  | 90% | CTNNB1 D32V 59%, FANCA and RB1 deep del | Biallelic |
| Pat.3B | H194fs, 30%; K354fs, 25% |  | Microdissected |  |  | Biallelic |
| Pat.4B | R344fs\*9, 25%; P903T, 16% | R344fs\*9, 44%; P903T, 31% | 70% | 70% | PALB2 I265Tfs\*12 12% (A), PALB2 I265Tfs\*12 34%, SPOP G148I 26% (F) | Biallelic |
| Pat.5B | S131Kfs\*21, 41%; S142\*, 23% |  | microdissected |  | BRCA2 S744\* 49%, CHEK2 L464fs\*16 50% | Biallelic |
| Pat.6B |  | Q1088fs\*13, 28% |  | 15% |  | Biallelic |
| Pat.7B |  | M816fs\*5, 24%; splice\_site donor EX10, 57% |  | 90% | AR L702H 66% | Biallelic |
| Pat.8B | Q602\*, 23%; R858Gln, 20% (kinase domain) |  | 80% |  |  | Biallelic |
| Pat.9B | R308\*, 41%; T460\_INS\_TELNW\*, 33%; V463G 34% |  | 70% |  |  | Biallelic |
| Pat.10B | Y285\*, 29%; Q944\*, 44% |  | 80% |  |  | Biallelic |
| Pat.11B |  | S583fs\*55, 44%; R882W, 38% |  | 80% | PTEN E40\*, SPOP F133L (math dom), AR and PIK3CA ampl | Biallelic |
| Pat.12B | Y319\*, 66%; F969S, 23% |  | 50% |  |  | Biallelic |
| Pat.13B | T289Pfs\*49, 72% |  | 75% |  |  | Biallelic |
| Pat.14B |  | deep deletion on CNVkit |  | 65% | ATM 21% subc | Biallelic |
| Pat.15B | G64fs\*28, 38%; K796Nfs\*25, 36% |  | 80% |  |  | Biallelic |
| Pat.16B |  | R979\*, 22%; G1399\_D1400insProLeu, 1% |  | 80% | MSH6 Y214\* 28%, ERCC3 Q677\* 16%, APC R1450\* 22% (F). | MMR |
| Pat.17B | D748Glu, 59%; F1019fs, 41% | D748Glu, 57%; F1019fs, 28% | 70% | microdissected |  | Biallelic |
| Pat.18B | S651Fs\*4, 23%; F986V, 20% | S651Fs\*4, 38%; F986V, 33% | 80% | 90% |  | Biallelic |
| Pat.19B | T914fs\*16, 23%; Splice site donor Ex5, 20% |  | 70% |  |  | Biallelic |
| Pat.20B | E72fs\*1, 30%; A881Gfs\*5, 29% |  | 90% |  |  | Biallelic |
| Pat.21B | L632fs\*, 32%, P961fs\*1, 32% |  | 50% |  |  | Biallelic |
| Pat.22B | T893R, 15%; I935F, 17%; Q937\*, 17% |  | 60% |  |  | Biallelic |
| Pat.23B | V492Cfs\*2, 67%; K523Tfs\*48 ,37% |  | 70% |  |  | Biallelic |
| Pat.24B | Q937Kfs\*9, 34%; S1215N, 8% |  | 60% |  |  | Biallelic |
| Pat.25B | E182\*, 15%; P424fs\*12, 29% |  | 50% |  |  | Biallelic |
| Pat.26B | Y279\*, 53% |  | 50% |  | ALK P1260Qfs\*102 27% | Biallelic |
| Pat.27B | Y319\*, 34%; G739V, 32% (ATP pocket) |  | microdissected |  |  | Biallelic |
| Pat.28B | Q602\*, 55%; P682fs\*71 48% |  | 80% |  |  | Biallelic |
| Pat.29B | S171fs\*16, 28%; S119fs\*5, 22% |  | microdissected |  | FANCL T372Ifs\*2 37% | Biallelic |
| Pat.30B | F83fs\*3, 45%; K339Fs\*11, 13% |  | microdissected |  |  | Biallelic |
| Pat.31B | L179fs\*21, 41%, D235fs\*, 48% |  | 80% |  |  | Biallelic |
| Pat.32B | K699\*, 28%, S681fs\*, 45% |  | 80% |  |  | Biallelic |

**Supplementary Table 3**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Beta (SE)** | **HR (95% CI)** | **P** |
| **CDK12 status** |  |  |  |
| control (ref) | - | - | **-** |
| mono/biallelic | -0.06 (0.26) | 0.94 (0.57, 1.56) | **0.81** |
| **T status** (1/2 vs 3/4) | 0.59 (0.34) | 1.80 (0.92, 3.51) | **0.09** |
| **N status** (0 vs 1) | 0.83 (0.24) | 2.29 (1.42, 3.71) | **<0.001** |
| **M status** ( 0 vs 1) | 0.91 (0.23) | 2.49 (1.60, 3.88) | **<0.001** |
| **Gleason score** (≤7 vs >8) | 0.47 (0.27) | 1.60 (0.94, 2.73) | **0.08** |

**Supplementary Table 4**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Bone marrow** | **Lympnode** | **Soft tissue/liver** | **Prostate** |
| CDK12 loss n=17  (13 bi-, 4 monoallelic) | 3 (17.6%) | 4 (23.5%) | 1 (5.9%) | 9 (53%) |
| Controls n=35 | 7 (20%) | 27 (77.1%) | 1 (2.9%) | 0 |