**Supplemental Table 1**. Baseline characteristics of mesothelioma and frequently associated genomic aberrations (N=42)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Genomic aberrations | All mesothelioma  N=42, No. (%) | Pleural mesothelioma  N=23, No. (%) | Peritoneal mesothelioma  N=11, No. (%) | Pericardial mesothelioma  N=2, No. (%) | Subtype unknown  N=6, No. (%) |
| *BAP1* aberration \* | 20 (47.6%) | 14 (60.9%) | 3 (27.3%) | 2 (100%) | 1 (16.7%) |
| *NF2* aberration # | 16 (38.1%) | 8 (34.8%) | 4 (36.4%) | 0 (0%) | 4 (66.7%) |
| *CDKN2A/B* loss | 15 (35.7%) | 12 (52.2%) | 1 (9.1%) | 0 (0%) | 2 (33.3%) |
| *TP53* mutation | 7 (16.7%) | 4 (17.4%) | 1 (9.1%) | 0 (0%) | 2 (33.3%) |
| *CDKN2A* mutation | 3 (7.1%) | 2 (8.7%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *CTNNB1* mutation | 3 (7.1%) | 2 (8.7%) | 0 (0) | 1 (50%) | 0 (0%) |
| *DNMT3A* mutation | 3 (7.1%) | 2 (8.7%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *EPHA3* amplification | 3 (7.1%) | 2 (8.7%) | 0 (0) | 0 (0%) | 1 (16.7%) |
| *BRCA2* mutation | 2 (4.8%) | 1 (4.3%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *FBXW7* mutation | 2 (4.8%) | 1 (4.3%) | 0 (0) | 0 (0%) | 1 (16.7%) |
| *MCL1* amplification | 2 (4.8%) | 0 (0) | 1 (9.1%) | 1 (50%) | 0 (0%) |
| *MYC* amplification | 2 (4.8%) | 2 (8.7%) | 0 (0) | 0 (0%) | 0 (0%) |
| *PTCH1* mutation | 2 (4.8%) | 2 (8.7%) | 0 (0) | 0 (0%) | 0 (0%) |
| *RICTOR* amplification | 2 (4.8%) | 1 (4.3%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *TSC2* aberration§ | 2 (4.8%) | 1 (4.3%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *VHL* mutation | 2 (4.8%) | 2 (8.7%) | 0 (0) | 0 (0%) | 0 (0%) |
| *ABL1* mutation | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *AKT2* amplification | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *ARID1A* mutation | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *ARID2* mutation | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *ALK* fusion | 1 (2.4%) | 0 (0%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *ATM* mutation | 1 (2.4%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (16.7%) |
| *BCL2* mutation | 1 (2.4%) | 0 (0%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *CBL* mutation | 1 (2.4%) | 0 (0%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *CCNE1* amplification | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *CDH1* mutation | 1 (2.4%) | 0 (0%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *EMSY* amplification | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *FGFR3* amplification | 1 (2.4%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (16.7%) |
| *IGF1R* amplification | 1 (2.4%) | 0 (0%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *KDR* mutation | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *KRAS* mutation | 1 (2.4%) | 0 (0%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *KMT2A* mutation | 1 (2.4%) | 0 (0%) | 1 (9.1%) | 0 (0%) | 0 (0%) |
| *MAP2K1* mutation | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *MDM2* amplification | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *NF1* mutation | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *NRAS* mutation | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *PIK3R2* mutation | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *SOX2* amplification | 1 (2.4%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (16.7%) |
| *STK11* mutation | 1 (2.4%) | 1 (4.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| *SUFU* mutation | 1 (2.4%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (16.7%) |

\* *BAP1* aberrations (N=20) include mutation (N=10), loss (N=5), multiple alterations (N=4) and rearrangement (N=1).

# *NF2* aberrations (N=16) include mutation (N=13), loss (N=2) and multiple alterations (N=1).

§ *TSC2* aberrations (N=2) include mutation (N=1) and loss (N=1).

**Supplemental Table 2**. Patient characteristics and molecular profiling of 42 mesothelioma and examples of cognate targeted therapies.

|  |  |
| --- | --- |
| Histology | Molecular aberration |
| Pleural mesothelioma | *BAP1* Y129\*  *BAP1* R512fs\*59  *TP53* A86fs\*55  *PIK3R2* R218fs\*121 |
| Pleural mesothelioma | *BAP1* rearrangement, intron 4  *CDKN2A/B* loss |
| Pleural mesothelioma | *CDKN2A* truncation  *CDKN2A/B* loss  *NF2* Y177fs\*26 |
| Pleural mesothelioma | *MYC* amplification  *ABL1* A75T |
| Pleural mesothelioma | *CDKN2A/B* loss  *NF2* R516fs\*23  *BAP1* T517fs\*51  *DNMT3A* F909C |
| Pleural mesothelioma | *CDKN2A/B* loss  *RICTOR* amplification  *MYC* amplification  *EPHA3* amplification  *TP53* R282W |
| Pleural mesothelioma | *BAP1* R610fs\*7  *BAP1* truncation, exon 3/4  *CDKN2A/B* loss |
| Pleural mesothelioma | *CDKN2A/B* loss  *MDM2* amplification  *EMSY* amplification  *BAP1* loss |
| Pleural mesothelioma | *BAP1* loss  *CTNNB1* Q280\* |
| Pleural mesothelioma | *CDKN2A/B* loss  *NF2* loss  *KDR* N793S |
| Pleural mesothelioma | *AKT2* amplification  *CDKN2A/B* loss  *ARID2* deletion, exon 10-20  *CCNE1* amplification |
| Pleural mesothelioma | *BRCA2* K3326\*  *BAP1* H169fs\*18  *NF2* W184\* |
| Pleural mesothelioma | *NF2* S287fs\*9 |
| Pleural mesothelioma | *CDKN2A/B* loss  *VHL* P25L |
| Pleural mesothelioma | *PTCH1* deletion, exons 6-14  *NF2* E427\*  *BAP1* S460\* |
| Pleural mesothelioma | *EPHA3* amplification  *BAP1* S63C  *ARID1A* E602\* |
| Pleural mesothelioma | *BAP1* splice site 784-2A>C  *DNMT3A* R882S  *CTNNB1* Y432\* |
| Pleural mesothelioma | *NF2* V24fs\*25  *TP53* S314F  *MAP2K1* E203K |
| Pleural mesothelioma | *TP53* K132N  *NRAS* Q61L  *NF1* R416\*  *CDKN2A* P114L |
| Pleural mesothelioma | *BAP1* splice site 659+1G>T  *CDKN2A/B* loss  *STK11* T24fs\*138 |
| Pleural mesothelioma | *BAP1* loss  *FBXW7* R479Q |
| Pleural mesothelioma | *CDKN2A/B* loss  *NF2* Y266\*  *BAP1* splice site 362\_375+10del  GTTTCAGCCCTGAGGTAGGCTGCA  *VHL* P81S |
| Pleural mesothelioma | *TSC2* Q432\*  *PTCH1* P25fs\*54  *BAP1* N349fs\*13  *BAP1* splice site 784-1G>T  *CDKN2A/B* loss |
| Peritoneal mesothelioma | *BRCA2* K1872\*  *NF2* M484fs\*1 |
| Peritoneal mesothelioma | *CDKN2A/B* loss  *NF2* Q320\*  *KRAS* G13C |
| Peritoneal mesothelioma | *MCL1* amplification  *CDH1* T379M  *ALK-STRN* fusion |
| Peritoneal mesothelioma | *DNMT3A* Y735C |
| Peritoneal mesothelioma | *CBL* R420Q  *BAP1* Q40\* |
| Peritoneal mesothelioma | *BAP1* splice site 1730-2A>G |
| Peritoneal mesothelioma | *TSC2* loss |
| Peritoneal mesothelioma | *BCL2* H20Q |
| Peritoneal mesothelioma | *IGF1R* amplification  *NF2* L14fs\*34 |
| Peritoneal mesothelioma | *BAP1* loss  *KMT2A* L3614P |
| Peritoneal mesothelioma | *RICTOR* amplification  *CDKN2A* L16fs\*23  *TP53* N268I  *NF2* Q147fs\*27 |
| Pericardial mesothelioma | *BAP1* S113fs\*3  *BAP1* M80fs\*45  *BAP1* Y44\*  *MCL1* amplification |
| Pericardial mesothelioma | *BAP1* loss  *CTNNB1* splice site 1955-2\_1955-1ins16 |
| Subtype unknown | *NF2* loss  *BAP1* deletion of int1-ex2 splice site |
| Subtype unknown | *ATM* splice site 2921+1G>C  *NF2* Q165\* |
| Subtype unknown | *TP53* R175H  *NF2* R262\*  *FBXW7* R658\* |
| Subtype unknown | *CDKN2A/B* loss  *NF2* Q115fs\*14  *NF2* E527\* |
| Subtype unknown | *EPHA3* amplification  *SOX2* amplification |
| Subtype unknown | *SUFU* T13fs\*83  *FGFR3* amplification  *TP53* R248Q  *CDKN2A/B* loss |

**Supplemental Table 3.** Association between *BAP1* aberrations, subtypes of mesothelioma and co-existing molecular alterations (N=42)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Aberrant *BAP1*  N=20 (%) | Wild-type *BAP1*  N=22 (%) | Odds ratio  (95% CI) | *p*-value Univariate \* |
| Histology § |  |  |  |  |
| Pleural |  |  | 3.4 (0.94 to 12.0) | 0.059 |
| Yes (N=23) | 14 (60.9) | 9 (39.1) |  |  |
| No (N=19) | 6 (31.6) | 13 (68.4) |  |  |
| Peritoneal |  |  | 0.31 (0.07 to 1.40) | 0.12 |
| Yes (N=11) | 3 (27.3) | 8 (72.7) |  |  |
| No (N=31) | 17 (54.8) | 14 (45.2) |  |  |
| Co-existing aberrations § |  |  |  |  |
| *NF2* |  |  | 0.33 (0.09 to 1.20) | 0.12 |
| Aberrant (N=16) | 5 (31.3) | 11 (68.7) |  |  |
| Wild-type (N=26) | 15 (57.7) | 11 (42.3) |  |  |
| *CDKN2A/B* |  |  | 0.94 (0.27 to 3.34) | 1.0 |
| Loss (N=15) | 7 (46.7) | 8 (53.3) |  |  |
| Wild-type (N=27) | 13 (48.1) | 14 (51.9) |  |  |
| *TP53* |  |  | 0.14 (0.02 to 1.30) | 0.096 |
| Aberrant (N=7) | 1 (14.3) | 6 (85.7) |  |  |
| Wild-type (N=35) | 19 (54.3) | 16 (45.7) |  |  |

\* *p*-values are from Fisher's exact test.

§ Included characteristics with N≥7.

**Supplemental Table 4.** Association between *NF2* aberration, subtypes of mesothelioma and co-existing molecular alterations (N=42)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Aberrant *NF2*  N=16 (%) | Wild-type *NF2*  N=26 (%) | Odds ratio  (95% CI) | *p*-value Univariate \* |
| Histology § |  |  |  |  |
| Pleural |  |  | 0.73 (0.21 to 2.6) | 0.63 |
| Yes (N=23) | 8 (34.8) | 15 (65.2) |  |  |
| No (N=19) | 8 (42.1) | 11 (57.9) |  |  |
| Peritoneal |  |  | 0.90 (0.22 to 3.8) | 0.89 |
| Yes (N=11) | 4 (36.4) | 7 (63.6) |  |  |
| No (N=31) | 12 (38.7) | 19 (61.3) |  |  |
| Co-existing aberrations § |  |  |  |  |
| *BAP1* |  |  | 0.33 (0.09 to 1.20) | 0.12 |
| Aberrant (N=20) | 5 (25.0) | 15 (75.0) |  |  |
| Wild-type (N=22) | 11 (50.0) | 11 (50.0) |  |  |
| *CDKN2A/B* |  |  | 1.1 (0.31 to 4.1) | 1 |
| Loss (N=15) | 6 (40.0) | 9 (60.0) |  |  |
| Wild-type (N=27) | 10 (37.0) | 17 (63.0) |  |  |
| *TP53* |  |  | 1.3 (0.24 to 6.6) | 1 |
| Aberrant (N=7) | 3 (42.9) | 4 (57.1) |  |  |
| Wild-type (N=35) | 13 (37.1) | 22 (62.9) |  |  |

\* *p*-values are from Fisher's exact test.

§ Included characteristics with N≥7.

**Supplemental Table 5.** Association between *CDKN2A/B* loss, subtypes of mesothelioma and co-existing molecular alterations (N=42)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Loss of *CDKN2A/B*  N=15 (%) | Wild-type *CDKN2A/B*  N=27 (%) | Odds ratio  (95% CI) | *p*-value Univariate \* |
| Histology § |  |  |  |  |
| Pleural |  |  | 5.8 (1.3 to 26) | **0.01** |
| Yes (N=23) | 12 (52.2) | 11 (47.8) |  |  |
| No (N=19) | 3 (15.8) | 16 (84.2) |  |  |
| Peritoneal |  |  | 0.12 (0.014 to 1.1) | **0.032** |
| Yes (N=11) | 1 (9.1) | 10 (90.9) |  |  |
| No (N=31) | 14 (45.2) | 17 (54.8) |  |  |
| Co-existing aberrations § |  |  |  |  |
| *BAP1* |  |  | 0.94 (0.27 to 3.3) | 1 |
| Aberrant (N=20) | 7 (35.0) | 13 (65.0) |  |  |
| Wild-type (N=22) | 8 (36.4) | 14 (63.6) |  |  |
| *NF2* |  |  | 1.1 (0.31 to 4.1) | 1 |
| Aberrant (N=16) | 6 (37.5) | 10 (62.5) |  |  |
| Wild-type (N=26) | 9 (34.6) | 17 (65.4) |  |  |
| *TP53* |  |  | 0.68 (0.11 to 4.0) | 1 |
| Aberrant (N=7) | 2 (28.6) | 5 (71.4) |  |  |
| Wild-type (N=35) | 13 (37.1) | 22 (62.9) |  |  |

\* *p*-values are from Fisher's exact test.

§ Included characteristics with N≥7.

**Supplemental Table 6: Explanations for the examples of theoretical therapies on Table 1.**

|  |  |
| --- | --- |
| Gene aberration | Comment for examples of theoretical therapies |
| *ABL1* mutation | *ABL1* aberration is potentially targetable with imatinib, nilotinib or dasatinib (S1). |
| *AKT2* amplification | AKT is targetable with mTOR inhibitors such as everolimus (S2, 3). |
| *ALK* fusion | Ligand-independent activation of ALK is associated with dependency of the cancer on continued signaling from the oncogenic kinase for cell growth and survival (S4). *ALK* fusion is targetable with crizotinib (S4, 5). |
| *ARID1A* mutation | Inhibition of EZH2 methyltransferase was shown to act in a synthetic lethal manner in *ARID1A*-mutated cancer in preclinical model (S64). Clinical trial with EZH2 inhibitor (EPZ-6438) is ongoing (NCT01897571). |
| *ARID2* mutation | To our knowledge, there is no targeted therapy for *ARID2* aberration. |
| *ATM* mutation | Aberration in *ATM* leads to defects in DNA double strand break repair. PARP inhibitor selectively inhibited *ATM* mutant leukemia cell lines in vivo and in vitro by synthetic lethality (S8). Thus *ATM* mutation is potentially targetable with PARP inhibitor such as olaparib. |
| *BAP1* aberration | BAP1 binds to the BRCA1 and regulates key cellular pathway including DNA damage response (S9).  Renal cancer cell line with BAP1 loss was sensitive to PARP inhibitors (S10). However in mesothelioma cell lines, no difference was observed between BAP-1 mutant and wild-type cells in sensitivity to PARP inhibitors (S65) and requires further investigation.  Since BAP1 is BRCA1 associated protein-1, platinum such as cisplatin or carboplatin can be considered (S11, 12).  Vorinostat (histone deacetylase [HDAC] inhibitor): Phase III randomized study failed to demonstrate improve overall survival in patients with malignant pleural mesothelioma (S66). However, this trial did not stratify patients based on *BAP1* aberration status and thus further subset analysis is required.  In a preclinical study, mesothelioma cells that lack BAP1 were sensitive to EZH2 pharmacologic inhibition. EPZ011989 is an EZH2 inhibitor (S13). |
| *BCL2* mutation | *BCL2* mutation was associated with increased risk of transformation and shortened survival in follicular lymphoma patients. BCL2 is potentially targetable with Bcl-2 inhibitors (S67). |
| *BRCA2* mutation | *BRCA1/2* mutations are sensitive to inhibition of PARP enzymatic activity, resulting in chromosomal instability and apoptosis (S16).  Patients with *BRCA1/2* mutations are more sensitive to platinum such as cisplatin or carboplatin (S11, 12). |
| *CBL* mutation | CBL is involved in cell signaling and protein ubiquitination. To our knowledge, there is no targeted therapy for *CBL* aberration. |
| *CCNE1* amplification | *CCNE1* amplification promotes unscheduled S-Phase entry, disrupted DNA replication, and genomic instability (S18). Since Cyclin E1 forms a complex with CDK2, it is potentially targetable with CDK inhibitor such as dinaciclib (CDK1/2/5/9 inhibitor) (S19).  shRNA synthetic lethal screen showed members of the ubiquitin pathway were selectively required in cancers that harbor *CCNE1* amplification. Subsequently, it was shown there was specific sensitivity of *CCNE1* amplified tumor cells to the proteasome inhibitor, bortezomib (S20). |
| *CDH1* mutation | *CDH1* aberration has been associated with cancer disorders such as hereditary diffuse gastric cancer and poor clinical outcome in patients with cancer(S21). However, to our knowledge, there is no targeted therapy for *CDH1* aberration. |
| *CDKN2A/B* loss and mutation | *CDKN2A/B* loss leads to activation of cyclin D-CDK 4/6 complex. Thus it is potentially targetable with CDK4/6 inhibitor such as palbociclib (S22, 68). However, some publications suggest that patients with these alterations may not respond (S69). |
| *CTNNB1* mutation | Beta-catenin antagonist is currently in early phase clinical trials (CT02413853, NCT01764477). |
| *DNMT3A* mutation | *DNMT3A* mutations predicted response to decitabine in patients with acute myeloid leukemia (S70). |
| *EMSY* amplification | Since EMSY is capable of silencing the activity of BRCA2, its amplification is potentially targetable with PARP inhibitor or platinum (S71, 72). |
| *EPHA3* amplification | Clinical trial with anti-EphA3 antibody is currently in early phase clinical trial (NCT 01211691). |
| *FBXW7* mutation | *FBXW7* is key regulator of the cell cycle and involved in cell division, growth and differentiation (S29).  mTOR is target for ubiquitination and degradation by binding to Fbxw7. Thus *Fbxw7* mutation may lead to increase level of mTOR protein which may be targeted with mTOR inhibitors (S30). |
| *FGFR3* amplification | FGFR3 is involved in cell survival, migration, angiogenesis and carcinogenesis (S31).  FGFR3 is targetable with tyrosine kinase inhibitors such as dovitinib and ponatinib (S4). |
| *IGF-1R* amplification | *IGF-1R* amplification is targetable with IGF-1R inhibitor (S32, 33). |
| *KDR* mutation | *KDR* aberration is potentially targetable with VEGFR-2 inhibitor such as cabozantinib (S34). |
| *KMT2A* mutation | KMT2 family protenin is involved in modulating chromatin structures, DNA accessibility and tumorigenesis (S35).  Potentially targetable with small molecules that targets KMT2A associated proteins that includes DOT1L and CDK9 (DOT1L targeted with EPZ-5676, CDK9 targeted with flavopiridol) (S35). |
| *MAP2K1* mutation | MAP2K1 is involved in cell proliferation, differentiation and development.  *MAP2K1* aberration is targetable with MEK inhibitor trametinib (S50). |
| *MCL1* amplification | MCL1 maintains cell survival and also associated with therapeutic resistance (S36).  In preclinical model, sorafenib downregulated phospho-STAT3 and subsequently reduced the expression of MCL-1 leading to decrease cell viability (S37). |
| *MDM2* amplification | *MDM2* amplification leads to inactivation of p53 (S38).  *MDM2* amplification is targetable with MDM2 inhibitors that are currently in early phase clinical trials (DS-3032b: NCT01877382, RO6839921: NCT02098967). |
| *MYC* amplification | MYC affects cell cycle entry, proliferation, differentiation and metabolism (S39).  To date, although there is no successful therapy targeting MYC, rapid progress is being made by utilizing genomics to identify MYC-dependent synthetic genetic interaction to identify druggable targets (S39).  Aurora kinase has been shown to demonstrate synthetic lethal interaction with MYC. Aurora kinase is targetable with aurora kinase inhibitor (e.g. MLN8237) (S40).  In preclinical model, MYC overexpressed cells were sensitive to CDK1 inhibitor. Thus *MYC* amplification is potentially actionable with dinaciclib (CDK1/2/5/9 inhibitor) (S41). |
| *NF1* mutation | *NF1* encodes protein neurofibromin(S42) that function as a RAS-GTPase activating protein (GAP) which is a negative regulator of RAS proto-oncogene. Thus aberration of *NF1* leads to increased activation of downstream signaling, especially mTOR pathway (S42).  *NF1* aberration is targetable with mTOR inhibitors such as everolimus or temsirolimus (S42, 43).  *NF1* aberration is associated with RAS activation and leads to MEK dependency. Thus it is targetable with MEK inhibitor such as trametinib (S44). |
| *NF2* aberration | Since NF2 is negative regulator of mTOR, it is potentially targetable with mTOR inhibitor. Of interest, one patient with metaplastic breast cancer with *NF2* aberration achieved complete response (3+ years) with temsirolimus containing regimen (S73). It is also reported one patient with neurofibromatosis type 2 with brain tumor had partial response with temsirolimus containing regimen (S74).  In preclinical model, lack of NF2/merlin was associated with increase sensitivity to FAK inhibitor. There are ongoing trial with FAK inhibitors, VS-6063 (defactinib) (NCT02004028) and GSK2256098 (NCT01938443) in patients with mesothelioma. |
| *PIK3R2* mutation | *PIK3R2* aberration is targetable with mTOR inhibitors such as with everolimus (S47). |
| *PTCH1* mutation | PTCH1 is receptor for Hedgehog signaling pathway that regulates cell growth and differentiation. Mutation of *PTCH1* can lead to decreased inhibition of smoothened (SMO) which results in activation of *GLI* transcription factors and consequent induction of target genes.  *PTCH1* mutation is targetable with SMO inhibitor vismodegib (S48). |
| *RAS* mutations | *RAS* mutations leads to constitutive activation of RAS which results in persistent stimulation of it multitude of downstream signaling pathways. This results in increased proliferation, suppression of apoptosis, altered metabolism and metastasis (S49).  Although targeting *RAS* mutation has been challenging (S49), it is potentially targetable with MEK inhibitor, trametinib (S50). |
| *RICTOR* amplification | Since selective mTORC1 (mTOR/RAPTOR) inhibition such as with everolimus will lead to increase AKT phosphorylation through mTORC2 complex activation, dual inhibition of both mTORC1/2 is necessary to target RICTOR amplification (S75). |
| *SOX2* amplification | *SOX-2* is associated with tumor initiation and progression (S52).  *SOX2* is a transcription factor and to our knowledge, there is no targeted therapy for *SOX2* aberration. |
| *STK11* mutation | *STK11* aberration contributes to mTORC1 activation and thus it is targetable with mTORC1 inhibitor such as everolimus or temsirolimus (S53, 55).  STK11 also functions as inhibitor of focal adhesion kinase (FAK). Thus its aberration can lead to increase in FAK signaling (S54). FAK signaling is targetable with dasatinib (S56) or bosutinib (S57). |
| *SUFU* mutation | *SUFU* aberration can lead to activation of Hedgehog pathway and associated with Gorlin syndrome (nevoid basal cell carcinoma syndrome) (S58). *SUFU* aberration has been associated with vismodegib (smoothened receptor antagonist) resistance (S58). However, targeting the downstream of SUFU with arsenic trioxide or bromo and extra C-terminal (BET) inhibitors that regulates glial transcriptional activity can be considered. |
| *TP53* mutation | TP53 is involved in wide range of functions including regulation of gene expression, genetic stability and cell cycle (S59).  Retrospective data suggest patients with *TP53* mutation had longer progression-free survival with bevacizumab containing regimen when compared to non-bevacizumab containing regimen (medialn 11.0 vs. 4.0 months (p<0.0001) (S60). Interestingly, multiple regression analysis of transcriptomic data revealed *TP53* mutations are associated with higher *VEGF-A* expression (p = 0.0006) suggesting the *TP53* as a marker to predict bevacizumab response (S76). |
| *TSC2* aberration | Since TSC2 is negative regulator of mTOR, it is targetable with mTOR inhibitor such as everolimus or temsirolimus (S61). |
| *VHL* mutation | In setting of non-functional VHL, HIF accumulates leading to increase vascular endothelial growth factor (VEGF) or platelet derived growth factor (PDGF) (S62).  *VHL* mutation is targetable with VEGF or PDGF receptor inhibitors (S63). |

**SUPPLEMENTAL FIGURE LEGEND**

**Supplemental Figure 1**.

(A) Number of genetic aberrations per patient (N=42). Median number of molecular aberrations per patient was 3 (range, 1 to 5)

(B) Number of actionable genetic aberrations per patient either with FDA approved therapies or with therapies that are in clinical trial. Median number of potentially actionable aberrations per patient was 3 (range, 1 to 5) (**Supplemental Table 1**) (N=42).

**Supplemental Figure 1**. Number of genetic aberrations per patient (**A**) and number of potentially actionable genetic aberrations per patient (**B**) (N=42)

**A**.

**B**.

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