**Table S1: Therapeutic trials targeting cell cycle regulators for cancer treatment**

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| --- | --- | --- | --- | --- |
| **Drug** | **Target** | **Phase of clinical trials and type of cancer** | **Status** | **References** |
| **Palbociclib, Ribociclib, Abemaciclib** | CDK4/6 | **1. III** ER-positive, Advanced Breast Cancer Within the HER2-Enriched Intrinsic Subtype (HARMONIA) **NCT05207709**  **2.** **III** HR+/HER2- metastatic breast cancer PALOMA-3 **NCT01942135**  **3. III** Advanced breast cancer MONALEESA–2 **NCT01958021**  **4. III** Advanced breast cancer MONARCH–3 **NCT02246621** | **1. Recruiting:** Ribociclib showed higher efficacy and overall survival in patients with HR+/HER2- breast cancer patients by changing tumor biology. The study is still ongoing.  **2. Completed:** Palbociclib in combination with fulvestrant improved the progression-free survival of HR+/HER2- metastatic breast cancer patients. Some adverse effects included neutropenia, febrile neutropenia, and leukopenia.  **3. Completed:** Ribociclib in combination with letrozole resulted in 12 months longer overall survival in advanced breast cancer patients as compared to placebo in combination with letrozole.  **4. Active, not recruiting:** Abemaciclib treated patients had prolonged overall survival as compared to placebo (28.18 versus 14.76 months). The adverse events included neutropenia, diarrhea and leucopenia. | [1–4] |
| **Samuraciclib (ICEC0942/CT7001)** | CDK7 | **1. II** ER+ Breast cancer **NCT03363893** | **1. Completed:** The drug showed promising effects in patients with a maximum tolerant dose of 360 mg. The common adverse events included low-grade nausea, vomiting, and diarrhea. Further studies are required to validate combination therapies for warranted therapeutic effects. | [5] |
| **Adavosertib (AZD1775)** | WEE1 kinase | **1. II** Small cell lung cancer (SCLC), ovarian cancer, non-small cell lung cancer (NSCLC), acute myeloid leukemia (AML), gastric adenocarcinoma, advanced solid tumors **NCT03253679** | **1.** **Completed:** The drug demonstrated promising clinical activity, especially in epithelial ovarian cancer with a median overall survival of 14.9 months and a manageable toxicity profile including gastrointestinal tract infection, hematological toxicities, and fatigue. Further studies experimenting with treatment alone or in combination with other drugs needs to be validated. | [6] |
| **M6620 (VX970/Berzosertib)** | ATR | **1. II** recurrent ovarian, primary peritoneal, and fallopian tube carcinoma **NCT02595892**  **2. I** recurrent ovarian, primary peritoneal, and fallopian tube carcinoma **NCT02627443**  **3. II** metastatic urothelial carcinoma **NCT02567409** | **1.** **Active, not recruiting:** The drug was provided to the patients in combination with gemcitabine which resulted in median progression-free survival of 22.9 weeks as compared to gemcitabine alone (14.7 weeks). It also had some adverse effects like neutropenia and decreased platelet count.  **2.** **Active, not recruiting:** The maximum tolerant dose included a combination of berzosertib with carboplatin and gemcitabine resulting in dose-limiting cytotoxicity of grade 4 thrombocytopenia  **3. Active, not recruiting:** The combination of berzosertib with cisplatin and gemcitabine showed less progression-free survival as compared to cisplatin and gemcitabine alone and resulted in significantly high hematological toxicities. | [7–9] |
| **LY2606368 (Prexasertib), MK-8776 (SCH 900776)** | CHK1 | **1. II** SCLC **NCT02735980**  **2.** Breast, ovarian, TNBC, prostate cancer **NCT02203513**  **3. I** Leukemia **NCT00907517**  **4. I** Lymphoma **NCT00779584** | **1. Completed:** Prexasertib did not prove to be effective as a monotherapy in ED-SCLC due to adverse events like decreased platelet count, febrile neutropenia, and anemia.  **2. Terminated:** Transcriptomic analysis revealed high levels of DNA-replication related genes (POLA1, POLE, GINS3) and progression-free survival of less than 6 months in high-grade serous ovarian cancer patients upon treatment with prexasertib. POLA1 expression was found to be toxic to HGSOC cell lines hence it proved to be predictive for CHK1i resistance.  **3. Terminated:** The study was terminated due to dose-limiting toxicities including corrected QT interval prolongation, grade 3 palmar-plantar erythrodysesthesia, and remission in 33% of cases when SCH 900776 was administered in patients in combination with cytarabine (cytosine arabinoside). An increase in phosphorylation of H2Ax in marrow blasts obtained during pretreatment and ongoing therapy showed consistent unrepairable DNA damage.  **4. Completed:** The drug MK-8776 was well tolerated in lymphoma patients with adverse effects of QTc prolongation, nausea, fatigue, and constipation. A higher frequency of adverse effects was observed in combination treatment of drug. | [10–13] |
| **Taxanes (Paclitaxel, Docetaxel, nanoparticle albumin bound paclitaxel)** | Mitotic Spindle | **1. I/II** Metastatic appendiceal adenocarcinoma **NCT06207305**  **2. III** Solid tumors **NCT04889599**  **3.** Ovarian, breast, lung, bladder, prostate cancer, melanoma, and esophageal cancer **NCT00499291** | **1. Recruiting:** The phase I of this study will include determination of maximum tolerable dose and phase II will rely on determining the response determined by change in PCI (Peritoneal cancer index) score.  **2. Completed:** The treatment of BH009 and Docetaxel in patients with solid tumors was well tolerated. No serious adverse events or death occurred during the course of study.  **3. Withdrawn:** No reason reported. | [14,15] |
| **Vinca alkaloids (Vinblastine, vincristine, and vinorelbine)** | Mitotic Spindle | **1. II** Acute lymphoblastic leukemia **NCT02143414**  **2. III** Acute myeloid leukemia **NCT00136084**  **3. II** Hodgkin’s lymphoma (HL) **NCT00147875**  **4. I** Neuroblastoma **NCT02163356**  **5. II** NSCLC **NCT04208854** | **1. Active, not recruiting:** Phase II study of combination of Blinatumomab followed by POMP (prednisone, vincristine sulfate, methotrexate, and mercaptopurine) showed very limited toxicity with improved overall survival as compared to historical controls. Further, improvements are required as a large proportion of patients experienced relapse.  **2. Completed:** A combination of drugs Etoposide, Cytarabine, Gemtuzumab, L-asparaginase, Mercaptopurine, methotrexate, Mitoxantrone, Prednisone and Vincristine was administered into patients in the low dose cytarabine (LDAC) arm. Complete remission was observed in 80% and 94% population in induction 1 and 2 groups respectively. The cumulative incidence of 6-month grade 3 or higher infections was 75.5% with overall survival of 71.1% suggesting efficacy and improved outcomes of targeted chemotherapy followed by hematopoietic stem cell therapy in patients with childhood AML.  **3. Completed:** The combination of drugs prednisone, vinblastine, doxorubicin, and gemcitabine (PVAG) resulted in overall survival of 66% and progression-free survival of 58%, proving the safety and feasibility of PVAG combination in elderly Hodgkin’s lymphoma patients.  **4. Terminated:** Fenretinide Lym-X-Sorb oral powder, ketoconazole, and vincristine were administered in patients with recurrent or resistant neuroblastoma. The study was terminated due to insufficient drug supply. | [16–19] |
| **5. Unknown status:** The study approved the activity and safety of metronomic oral vinorelbine in patients with wild-type local/advanced and metastatic NSCLC with 32% overall survival and mild toxicity. |
| **BAY 1161909, BAY 1217389** | Spindle Assembly Checkpoint | **1. I** Neuroblastoma, medulloblastoma, and Advanced solid malignancies **NCT02138812**  **2. I** Breast cancer **NCT02366949** | **1. Terminated:** The study of BAY 1161909 oral drug in combination with intravenous paclitaxel for patients with advanced solid malignancie**s** showed good tolerability with manageable adverse events such as fatigue, anemia, alopecia, diarrhea, and nausea. The study was terminated as the company developed another Mps1 inhibitor BAY 1217389.  **2. Completed:** The study of BAY 1217389 in combination with paclitaxel showed hematological toxicities, nausea, fatigue and diarrhea. Dose determined by randomized continuous reassessment method (rCRM) outperformed traditional designs in determining the true MTD. Bone marrow toxicity limited the therapeutic window of this drug combination**.** | [20,21] |
| **GSK1070916, AMG 900, AZD1152, AZD 2811, PHA-739358, AT9283** | Spindle Assembly Checkpoint | **1. I** Advanced solid malignancies **NCT01118611**  **2. I** AML **NCT01380756**, **NCT00530699**  **3. II** Lymphoma **NCT01354392**  **4. I** Advanced solid malignancies **NCT00497679**  **5. II** SCLC **NCT03366675**  **6. II** Multiple myeloma **NCT00872300**  **7. II** Hormone refractory prostate cancer **NCT00766324**  **8. II** Multiple myeloma **NCT01145989**, | **1. Completed:** The drug GSK1070916 treatment showed predictable and manageable neutropenia with tolerable doses in patients with advanced solid tumors.  **2. Completed:** AMG 900 reported manageable extra-hematological toxicity and modest response in AML patients, although prolonged cytopenias hindered further dose-escalation. Hence, further studies administering low doses of AMG 900 in combination with other anticancer agents need to be explored; **Completed:** AZD1152 displayed a manageable tolerability profile in leukemia patients, but study was terminated due to frequently observed adverse effects like neutropenia and febrile neutropenia.  **3. Completed:** AZD1152 treatments in DLBCL showed reductions in tumor, and consistent tolerability but the responses were short-lived. Due to inconvenient administration and modest responses, the treatment was unlikely to be further investigated.  **4. Terminated:** AZD1152 treatment in patients with advanced solid malignancies was terminated due to technical difficulties with administration of drug in patient population with the planned schedule.  **5. Terminated:** The study of AZD 2811 in relapsed SCLC patients was terminated due to limited clinical efficacy. Altered administration or combination therapy needs to be developed.  **6.**  **Terminated:** The study of multiple myeloma patients with PHA-739358 **(**Danusertib) was terminated due to low recruitment rate.  **7. Completed:** The monotherapy with PHA-739358 **(**Danusertib) in hormone-refractory prostate cancer was well tolerated but it showed less efficacy in treatment of patients. For establishment of specific biomarkers predictive for either response or prolonged disease stabilization, further studies are required.  **8. Completed:** AT9283 treatment in multiple myeloma patients resulted in myelosuppression hence, the dose and schedule were not prescribed for further studies. | [22–28] |
| **PROTACs (Indisulam/E7070)** | CDK4/6 | **1. II** Malignant melanoma **NCT00014625** | **1. Completed:** The treatment of the patient with indisulam resulted in a progression-free interval of 105 months and 9 years of survival. | [29] |

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