Supplemental box 1 | Reported studies with Pan-CDK inhibitors

Flavopiridol
Targets: CDK1, CDK2, CDK4, CDK6, CDK7 and CDK9

Phase 1 clinical trials:

2014:
A phase I trial of flavopiridol in relapsed multiple myeloma[1]
Flavopiridol can be safely administered using a pharmacologically derived schedule and demonstrates activity in relapsed and refractory non-Hodgkin's lymphoma[2]

2013:
Cyclophosphamide, alvocidib (flavopiridol), and rituximab (CAR), a novel feasible chemoimmunotherapy regimen for patients with high-risk chronic lymphocytic leukemia[3]
A phase I trial of vorinostat and alvocidib in patients with relapsed, refractory, or poor prognosis acute leukemia, or refractory anemia with excess blasts-2[4]

2012:
A dose-finding, pharmacokinetic and pharmacodynamic study of a novel schedule of flavopiridol in patients with advanced solid tumors[5]
Phase I trial of the combination of flavopiridol and imatinib mesylate in patients with Bcr-Abl+ hematological malignancies[6]
The cyclin-dependent kinase inhibitor flavopiridol potentiates doxorubicin efficacy in advanced sarcomas: preclinical investigations and results of a phase I dose-escalation clinical trial[7]

2011:
A phase I pharmacokinetic study of pulse-dose vorinostat with flavopiridol in solid tumors[8]
Phase 1 and pharmacokinetic study of bolus-infusion flavopiridol followed by cytosine arabinoside and mitoxantrone for acute leukemias[9]
Phase I trial of bortezomib (PS-341; NSC 681239) and alvocidib (flavopiridol; NSC 649890) in patients with recurrent or refractory B-cell neoplasms[10]

2010:
A phase I study of flavopiridol in combination with gemcitabine and irinotecan in patients with metastatic cancer[11]
Flavopiridol, fludarabine, and rituximab in mantle cell lymphoma and indolent B-cell lymphoproliferative disorders[12]
Phase I clinical and pharmacokinetic study of a novel schedule of flavopiridol in relapsed or refractory acute leukemias[13]
A phase I clinical trial of FOLFIRI in combination with the pan-cyclin-dependent kinase (CDK) inhibitor flavopiridol[14]

2009:
Clinical response and pharmacokinetics from a phase 1 study of an active dosing schedule of flavopiridol in relapsed chronic lymphocytic leukemia[15]
Phase I study of flavopiridol with oxaliplatin and fluorouracil/leucovorin in advanced solid tumors[16]

2008:
Phase I study of flavopiridol in combination with Paclitaxel and Carboplatin in patients with non-small-cell lung cancer[17]

2007:
Phase I dose-finding study of weekly docetaxel followed by flavopiridol for patients with advanced solid tumors[18]

2006:
Flavopiridol administered using a pharmacologically derived schedule is associated with marked clinical efficacy in refractory, genetically high-risk chronic lymphocytic leukemia[19]
Flavopiridol in patients with relapsed or refractory multiple myeloma: a phase 2 trial with clinical and pharmacodynamic end-points[20]
A phase I study of flavopiridol and docetaxel[21]

2005:
Flavopiridol administered as a 24-hour continuous infusion in chronic lymphocytic leukemia lacks clinical activity[22]
A phase I clinical trial of the sequential combination of irinotecan followed by flavopiridol[23]
Phase 1 trial of flavopiridol combined with cisplatin or carboplatin in patients with advanced malignancies with the assessment of pharmacokinetic and pharmacodynamic end points[24]
Phase I and pharmacokinetic study of flavopiridol followed by 1-beta-D-arabinofuranosylcytosine and mitoxantrone in relapsed and refractory adult acute leukemias[25]
Phase I clinical and pharmacokinetic study of flavopiridol in children with refractory solid tumors: a Children's Oncology Group Study[26]

2004:
Phase I trial of the cyclin-dependent kinase inhibitor flavopiridol in combination with docetaxel in patients with metastatic breast cancer[27]

2003:
Clinical pharmacology and pharmacogenetics of flavopiridol 1-h i.v. infusion in patients with refractory neoplasms[28].
Flavopiridol-related proinflammatory syndrome is associated with induction of interleukin-6[29]

2002:
Phase I clinical and pharmacokinetic trial of the cyclin-dependent kinase inhibitor flavopiridol[30]
Phase I clinical and pharmacokinetic study of flavopiridol administered as a daily 1-hour infusion in patients with advanced neoplasms[31].
Phase I study of the cyclin-dependent kinase inhibitor flavopiridol in combination with paclitaxel in patients with advanced solid tumors[32]

2000:
Flavopiridol, a novel cyclin-dependent kinase inhibitor, in metastatic renal cancer: a University of Chicago Phase II Consortium study[33].

1998:
Phase I trial of continuous infusion flavopiridol, a novel cyclin-dependent kinase inhibitor, in patients with refractory neoplasms[34].

Phase 2 clinical trials:

2012:
A phase 2 trial of flavopiridol (Alvocidib) and cisplatin in platin-resistant ovarian and primary peritoneal carcinoma: MC0261[35]
Randomized phase II study of two schedules of flavopiridol given as timed sequential therapy with cytosine arabinoside and mitoxantrone for adults with newly diagnosed, poor-risk acute myelogenous leukemia[36]

2010:
Clinical activity of sequential flavopiridol, cytosine arabinoside, and mitoxantrone for adults with newly diagnosed, poor-risk acute myelogenous leukemia[37]

2009:
A phase II study of flavopiridol (Alvocidib) in combination with docetaxel in refractory, metastatic pancreatic cancer[38]
Phase II study of flavopiridol in relapsed chronic lymphocytic leukemia demonstrating high response rates in genetically high-risk disease[39]

2007:
Sequential flavopiridol, cytosine arabinoside, and mitoxantrone: a phase II trial in adults with poor-risk acute myelogenous leukemia[40]

2005:
Treatment of relapsed chronic lymphocytic leukemia by 72-hour continuous infusion or 1-hour bolus infusion of flavopiridol: results from Cancer and Leukemia Group B study 19805 [41]
A phase II study of flavopiridol in patients with advanced renal cell carcinoma: results of Southwest Oncology Group Trial 0109[42]
A phase II evaluation of flavopiridol as second-line chemotherapy of endometrial carcinoma: a Gynecologic Oncology Group study[43]

2004:
A Phase II trial of flavopiridol (NSC #649890) in patients with previously untreated metastatic androgen-independent prostate cancer[44]
Phase II trial of flavopiridol, a cyclin dependent kinase inhibitor, in untreated metastatic malignant melanoma[45]

2003:
Flavopiridol in untreated or relapsed mantle-cell lymphoma: results of a phase II study of the National Cancer Institute of Canada Clinical Trials Group[46]
Phase II study of flavopiridol in patients with advanced colorectal cancer[47]
2001: A phase II trial of the cyclin-dependent kinase inhibitor flavopiridol in patients with previously untreated stage IV non-small cell lung cancer[48]

2001: Phase II study of the cyclin-dependent kinase inhibitor flavopiridol administered to patients with advanced gastric carcinoma[49]

Dinaciclib
Targets: CDK1, CDK2, CDK4, CDK5, CDK6, CDK7 and CDK9

Phase 1 clinical trials:

2013:
Clinical and laboratory studies of the novel cyclin-dependent kinase inhibitor dinaciclib (SCH 727965) in acute leukemias[50]
No remissions were achieved. Common AE: gastrointestinal, fatigue, transaminitis, and clinical and laboratory manifestations of tumor lysis syndrome, including one patient who died of acute renal failure. While dinaciclib given as a 2-h bolus did not exhibit durable clinical activity, pharmacokinetic and pharmacodynamic data support the exploration of prolonged infusion schedules in future trials in patients with acute leukemias.

A first-in-human, phase 1, dose-escalation study of dinaciclib, a novel cyclin-dependent kinase inhibitor, administered weekly in subjects with advanced malignancies [51].
N= 48. MAD was 14 mg/m2 and the RP2D: 12 mg/m2. DLTs at the MAD included orthostatic hypotension and elevated uric acid. Common AEs: nausea, anemia, decreased appetite, and fatigue. 10 patients achieved prolonged SD for 4 ≥ cycles.

2010:
Phase 1/2 trial of a novel CDK inhibitor dinaciclib (SCH727965) in patients with relapsed multiple myeloma demonstrates encouraging single agent activity [52].
MTD: 50 mg/m^2 for the Phase II portion. Overall confirmed response rate was 3 of 27 (11%).

Phase 2 clinical trials:

2014:
Randomized phase 2 study of the cyclin-dependent kinase inhibitor dinaciclib (MK-7965) versus erlotinib in patients with non-small cell lung cancer[53].
Median TTP was 1.49 months (95% CI: 1.31, 2.63) following initial treatment with dinaciclib vs. 1.58 months (95% CI: 1.38, 2.83) with erlotinib. Conclusion: No single agent activity demonstrated in previously treated NSCLC.

Randomized Phase II Trial of the Cyclin-Dependent Kinase Inhibitor Dinaciclib (MK-7965) Versus Capecitabine in Patients With Advanced Breast Cancer[54]
N=30. Unplanned interim analysis showed that TTP was inferior with dinaciclib treatment compared with capecitabine treatment. Dinaciclib monotherapy demonstrated some antitumor activity, was well tolerated, efficacy was not superior to capecitabine hence study terminated early

2010:
Phase II study of the cyclin-dependent kinase (CDK) inhibitor dinaciclib (SCH727965) in patients with advanced acute leukemias[55].
N= 26 (20 AML, 6 ALL) AML patients were randomized between dinaciclib and gemtuzumab ozogamicin (GO) with cross-over to dinaciclib if no response to GO was seen, while ALL patients only received dinaciclib. Dinaciclib showed anti-leukemia activity in this heavily pre-treated patient population

AT7519

TARGETS: CDK2, CDK4, CDK5, CDK9, CDK1, CDK6 and GSK3β

Phase 1 clinical trials:

2013: A Phase I/II Open-Label Multicenter Study Of The Cyclin Kinase Inhibitor AT7519M Alone and In Combination With Bortezomib In Patients With Previously Treated Multiple Myeloma (MM)[56]
No DLTs with 2 AE ≥ Grade 3 in severity (neutropenia, and dyspnea) possibly related to treatment. MTD: 21 mg/m^2 AT7519M and 1.3 mg/m^2 Bortezomib. Combination tolerated well with significant (33% ≥ PR) responses in heavily pre-treated/refractory to Bortezomib.

2011:
A phase I pharmacokinetic and pharmacodynamic study of AT7519, a cyclin-dependent kinase inhibitor in patients with refractory solid tumors[57]**.**
N=28 treated. Study terminated early. DLTs at 34 mg/m(2)/day QTc prolongation with one death (grade 5), fatigue (grade 4) and mucositis (grade 3). ECG review suggested a dose-dependent increase in QTc and recruitment was discontinued without establishing a maximum tolerated dose.

A Phase I study of AT7519M given as short infusion twice weekly[58]
Refractory solid tumours, N=28 Schedule: AT7519 was administered escalating doses on days 1,4,8,11 every 3 weeks. RP2D was 27mg/m2.
DLTs: mucositis, rash, fatigue and muscle weakness, renal dysfunction and febrile neutropenia. No evidence of QTc prolongation. 9 patients with SD (2.5-11.1 months). Short AT7519M infusions are tolerable with no QTc prolongation.

Seliciclib (Cyclacel) also known as R-roscovitine, CYC202

Targets: CDK1, CDK2, CDK5, CDK7 and CDK9

Phase 1 clinical trials:

2012: Phase I study of sequential sapacitabine and seliciclib in patients with advanced solid tumors[59]**.**
N=27. MTD and RP2D is sapacitabine 50 mg bid./seliciclib 1200 mg bid. DLTs were reversible transaminase elevations and neutropenia. Common AE: anorexia, fatigue, abdominal pain, dizziness, nausea, anemia, neutropenia, creatinine elevation, hyperglycemia, hyperbilirubinemia, hypophosphatemia, hypokalemia and hypomagnesemia

2010: Phase I evaluation of seliciclib (R-roscovitine), a novel oral cyclin-dependent kinase inhibitor, in patients with advanced malignancies[60]**.**
N=56. DLTs: nausea, vomiting, asthenia and hypokalaemia at 1600 mg bid for schedule A and in schedule C, DLT of hypokalaemia and asthenia occurred at 1800 mg bid. Arm B was discontinued due to toxicity. 1 PR in a patient with hepatocellular carcinoma. MTD:1250 mg bid for 5d every 3 weeks. RP2D: 1600 mg bid for 3d every 2 weeks.

2007: A phase I trial of the selective oral cyclin-dependent kinase inhibitor seliciclib (CYC202; R-Roscovitine), administered twice daily for 7 days every 21 days[61]**.**
N=21 DLTs were seen at 800 mg bid: G3 fatigue, G3 skin rash, G3 hyponatraemia and G4 hypokalaemia. No objective tumour responses, but disease stabilisation was recorded in eight patients.

Phase 2 clinical trials:

2010: APPRAISE Phase 2b study of seliciclib[62] NSCLC cancer, study terminated early
Study terminated after interim analyses suggested no difference between seliciclib arm and placebo.

2009: A phase II randomized study of oral seliciclib in patients with previously treated nasopharyngeal carcinoma.[63]
DLTs: G3 increase in ALT or AST (n=3), and treatment delay > 2 weeks for grade 1 creatinine (n=1). Common AE: fatigue, nausea/vomiting, constipation, cough, fever, hypokalemia, hyponatremia, and elevation in ALT/AST, most of which were mild to moderate in intensity. Interim data confirms that both dosing schedules are tolerable for proceeding to the randomized phase with SD in NPC patients.

R547 also known as R0-4584820 (Hoffmann-La-Roche)

Targets: CDK1, CDK2, CDK4 AND CDK7

Phase 1 clinical trials:

2007: A phase I study of R547, a novel, selective inhibitor of cell cycle and transcriptional cyclin dependent kinases (CDKs)[64]
N=41. AE: nausea (54%), fatigue (34%), emesis (34%), headache (34%), and hypotension (32%). DLTs for 90mins infusion: G3 somnolence, G3 confusion, G3 fatigue, 1 pt each, all at 195 mg/m^2. DLTs for 180mins infusion: G3 pruritis at 195 mg/m^2. R547 is tolerable at a dose of 155 mg/m^2 on D1, D8 (21 day cycle) for both 90 and 180 min schedules with manageable side effects.

SNS-032, also known as BMS-387032 (Sunesis)

Targets: CDK2, CDK7 and CDK9

Phase 1 clinical trials:

2010: Phase I and pharmacologic study of SNS-032, a potent and selective Cdk2, 7, and 9 inhibitor, in patients with advanced chronic lymphocytic leukemia and multiple myeloma[65]**.**
CLL cohort: N=9 DLT: Tumor lysis syndrome, MTD: 75 mg/m(2) G3/4 toxicity: myelosuppression. 1 patient had >50% reduction in measurable disease without improvement in hematologic parameters. Another patient with low tumor burden had SD for 4 courses. Multiple myeloma cohort: no DLT and MTD was not identified at up to 75 mg/m(2), owing to early study closure. 2 patients had SD, 1 had normalization of spleen size with treatment.

2008: A phase 1 study of SNS-032 (formerly BMS-387032), a potent inhibitor of cyclin-dependent kinases 2, 7 and 9 administered as a single oral dose and weekly infusion in patients with metastatic refractory solid tumors[66]**.**
Starting dose of 4 mg/m^2 intravenously administered over 1-h with a cycle defined as 3 weekly doses of SNS-032 every 21 days. N=21. Commonest AE (>20%): Fatigue (25%) and nausea (20%). 3 (15%) patients experienced a best response of SD. Study enrollment was terminated during dose-escalation due to a change in the development strategy for the study drug.

PR=partial response; CR=complete response SD=stable disease; PD= progressive disease; MAD=maximum administered dose; RP2D=recommended phase 2 dose; AE=adverse events; TTP=time to progression; IV= intravenous infusion, CIV=continuous intravenous, B.I.D= twice daily; OS=overall survival; DLT=drug limiting toxicity; G3= grade 3; ALT=alanine transaminase; AST= aspartate transaminase; NPC= nasopharyngeal cancer.

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