

SUPPLEMENTARY INFORMATION

In format provided by Otto, T. & Sicinski, P. (doi:10.1038/nrc.2016.138)

Supplementary information S5 | Clinical trial results of selected inhibitors of other cell cycle proteins

| Tumour type | Study characteristics, ClinicalTrials.gov Identifier | Drug dosage and combination | Efficacy | Major grade 3/4 adverse effects ($\geq 10\%$) |
|---|--|--|---|--|
| MK-8776 (SCH 900776) | | | | |
| Acute leukaemias (relapsed or refractory) ¹ | <ul style="list-style-type: none"> Phase I N=24 (AML: N=21) NCT00907517 | <ul style="list-style-type: none"> • 10-80 mg/m² IV OD (days 2, 3, 11 and 12), RP2D: 56 mg/m² • Combination with cytarabine (2 g/m² IV over 72 hours, days 1-3 and 10-12) | <ul style="list-style-type: none"> • CR/CRI: 33% (8/24) | <ul style="list-style-type: none"> • Hepatic dysfunction (17%) |
| LY2606368 (prexasertib) | | | | |
| Anal squamous cell carcinoma (metastatic) ² | <ul style="list-style-type: none"> Phase I N=26 (subgroup expansion) NCT01115790 | <ul style="list-style-type: none"> • 105 mg/m² IV every 14 days • Monotherapy | <ul style="list-style-type: none"> • CR: 4% (1/26) • PR: 12% (3/26) • SD: 42% (11/26) | <ul style="list-style-type: none"> • Neutropaenia (grade 4: 77%) |
| AZD1775 (MK-1775) | | | | |
| Ovarian cancer (refractory or resistant, p53-mutant) ³ | <ul style="list-style-type: none"> Phase II N=24 NCT01164995 | <ul style="list-style-type: none"> • 225 mg PO BD (for 2.5 days in a 21-day cycle) • Combination with carboplatin (IV, day 1) | <ul style="list-style-type: none"> • PR: 27% (6/22) • SD: 41% (9/22) | <ul style="list-style-type: none"> • NA |
| Ovarian cancer (platinum-sensitive, p53-mutant) ⁴ | <ul style="list-style-type: none"> Phase II N=121 AZD1775 + "P/C" (N=59) vs placebo + "P/C" (N=62) NCT01357161 | <ul style="list-style-type: none"> • 225 mg PO BD (for 2.5 days in a 21-day cycle) • Combination with "P/C": paclitaxel (175 mg/m² IV, day 1) and carboplatin (IV, day 1) | <ul style="list-style-type: none"> • Median PFS: 42 weeks vs 35 weeks (HR=0.55, p=0.03) • RR: 81% vs 76% (p=0.459) | <ul style="list-style-type: none"> • Various (overall: 78% vs 65%) |
| Rigosertib (ON 01910.Na) | | | | |
| MDS (primary HMA failure) ⁵ | <ul style="list-style-type: none"> Phase III N=169 (subgroup) Rigosertib (N=117) vs best supportive care (N=52) NCT01241500 (ONTIME) | <ul style="list-style-type: none"> • 1800 mg IV OD (for 3 days; every 2 weeks for 16 weeks, then every 4 weeks) | <ul style="list-style-type: none"> • Median OS: 8.6 months vs 4.5 months (HR=0.63, p=0.011) | <ul style="list-style-type: none"> • Anaemia (16% vs 10%), thrombocytopaenia (15% vs 6%), neutropaenia (15% vs 8%), febrile neutropaenia (13% vs 10%), pneumonia (12% vs 12%) |
| MDS (very high risk) ⁶ | <ul style="list-style-type: none"> Phase III N=134 (subgroup) Rigosertib (N=93) vs best supportive care (N=41) NCT01241500 (ONTIME) | <ul style="list-style-type: none"> • 1800 mg IV OD (for 3 days; every 2 weeks for 16 weeks, then every 4 weeks) | <ul style="list-style-type: none"> • Median OS: 7.6 months vs 3.2 months (HR=0.56, p=0.005) | <ul style="list-style-type: none"> • Anaemia (24% vs 11%), thrombocytopaenia (21% vs 11%), febrile neutropaenia (17% vs 11%), neutropaenia (15% vs 13%), pneumonia (12% vs 13%) |
| Pancreatic cancer (metastatic, first-line treatment) ⁷ | <ul style="list-style-type: none"> Phase II/III N=160 (subgroup) Rigosertib + gemcitabine (N=106) vs gemcitabine alone (N=54) NCT01360853 (ONTRAC) | <ul style="list-style-type: none"> • 1800 mg/m² IV twice per week (3 weeks on, 1 week off) • Combination with gemcitabine (1000 mg/m² weekly, 3 weeks on, 1 week off) | <ul style="list-style-type: none"> • Median PFS: 3.4 months vs 3.4 months (HR=0.96) • Median OS: 6.1 months vs 6.4 months (HR=1.24) • PR: 19% vs 13% • SD: 50% vs 56% | <ul style="list-style-type: none"> • Hyponatremia (17% vs 4%) |
| Volasertib (BI 6727) | | | | |
| AML (patients ineligible for intensive treatment) ⁸ | <ul style="list-style-type: none"> Phase II N=87 Volasertib + cytarabine (N=42) versus cytarabine alone (N=45) NCT00804856 | <ul style="list-style-type: none"> • 350 mg IV OD (on days 1 and 15 of 28-day cycle) • Combination with cytarabine (20 mg s.c. BD, days 1-10) | <ul style="list-style-type: none"> • Median EFS: 5.6 months vs 2.3 months (HR=0.57, p=0.021) • Median OS: 8.0 months vs 5.2 months (HR=0.63, p=0.047) • CR/CRI: 31% vs 13% | <ul style="list-style-type: none"> • Febrile neutropaenia (55% vs 16%), infections (48% vs 22%), gastrointestinal (24% vs 7%) |

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| Alisertib (MLN8237) | | | | |
|---|--|--|---|--|
| Peripheral T-cell lymphoma and transformed Mycosis Fungoïdes (relapsed or refractory) ⁹ | <ul style="list-style-type: none"> Phase II N=37 NCT01466881 | <ul style="list-style-type: none"> • 50 mg PO BD (1 week on, 2 weeks off) • Monotherapy | <ul style="list-style-type: none"> Peripheral T-cell lymphoma: • CR: 7% (2/30) • PR: 23% (9/30) • SD: 17% (5/30) Transformed Mycosis Fungoïdes: • RR: 0% (0/7) • SD: 28% (0/7) | <ul style="list-style-type: none"> • Neutropaenia (32%), anaemia (30%), thrombocytopaenia (24%), lymphopaenia (22%), febrile neutropaenia (14%) |
| B-cell and T-cell non-Hodgkin lymphoma (relapsed or refractory) ¹⁰ | <ul style="list-style-type: none"> Phase II N=48 NCT00807495 | <ul style="list-style-type: none"> • 50 mg PO BD (1 week on, 2 weeks off) • Monotherapy | <ul style="list-style-type: none"> • CR: 10% (5/48) • PR: 17% (8/48) • SD: 33% (16/48) | <ul style="list-style-type: none"> • Neutropaenia (63%), anaemia (35%), thrombocytopaenia (33%), stomatitis (15%), febrile neutropaenia (13%) |
| Ovarian, fallopian tube, primary peritoneal and breast cancer (recurrent) ^{11, 12} | <ul style="list-style-type: none"> Phase I N=28 (ovarian: N=20) NCT01091428 | <ul style="list-style-type: none"> • 10-50 mg PO BD (days 1-3, 8-10, 15-17 in 28-day cycle), RP2D: 40 mg • Combination with paclitaxel (60-80 mg/m² IV BD, days 1+8+15, RP2D: 60 mg/m²) | <ul style="list-style-type: none"> • PR: 29% (8/28) • SD: 11% (3/28) | <ul style="list-style-type: none"> • Neutropaenia (54%) |
| Breast, small-cell lung, non-small-cell lung, head and neck squamous cell, gastro-oesophageal cancer (advanced, relapsed or refractory) ¹³ | <ul style="list-style-type: none"> Phase II N=249 NCT01045421 | <ul style="list-style-type: none"> • 50 mg PO BD (1 week on, 2 weeks off) • Monotherapy | <ul style="list-style-type: none"> Breast cancer: • PR: 18% (9/49) • SD: 51% (25/49) Small-cell lung cancer: • PR: 21% (10/48) • SD: 33% (16/48) | <ul style="list-style-type: none"> Breast cancer: • Neutropaenia (57%), stomatitis (15%), fatigue (11%) Small-cell lung cancer: • Neutropaenia (37%), anaemia (17%), thrombocytopaenia (10%) |
| Solid tumours (advanced) including prostate cancer (castration-resistant) ¹⁴ | <ul style="list-style-type: none"> Phase I N=35 NCT01094288 | <ul style="list-style-type: none"> • 10-50 mg PO BD (1 week on, 2 weeks off); RP2D: 20 mg • Combination with docetaxel (60-75 mg/m² IV OD, on day 1, RP2D: 75 mg/m²) | <ul style="list-style-type: none"> For castration-resistant prostate cancer: • PR: 35% (6/17) • SD: 35% (6/17) | <ul style="list-style-type: none"> • Neutropaenia (86%), febrile neutropaenia (23%), stomatitis (14%) |
| Multiple myeloma ¹⁵ | <ul style="list-style-type: none"> Phase Ib N=26 NCT01034553 | <ul style="list-style-type: none"> • 20-50 mg PO BD (1 week on, 3 weeks off) • Combination with bortezomib (1.5 mg/m² IV weekly) | <ul style="list-style-type: none"> • CR: 4% (1/26) • PR: 23% (6/26) • SD: 38% (10/26) • Median PFS: 5.9 months • Median OS: 23.6 months | <ul style="list-style-type: none"> • Neutropaenia (38%), thrombocytopaenia (31%), lymphopaenia (19%), infection (15%), muscle weakness (12%) |
| Neuroblastoma (relapsed or refractory) ¹⁶ | <ul style="list-style-type: none"> Phase I N=22 NCT01601535 | <ul style="list-style-type: none"> • 45-80 mg/m² PO OD (days 1-7 in 21-day cycle) • Combination with irinotecan (50 mg/m² IV OD, on days 1-5) and temozolamide (100 mg/m² PO OD, on days 1-5) | <ul style="list-style-type: none"> • CR: 23% (5/22) • PR: 9% (2/22) • SD: 50% (11/22) | <ul style="list-style-type: none"> • NA |
| ENMD-2076 | | | | |
| Ovarian cancer (recurrent, platinum-resistant) ¹⁷ | <ul style="list-style-type: none"> Phase II N=64 NCT01104675 | <ul style="list-style-type: none"> • 250-325 mg PO OD (continuous) • Monotherapy | <ul style="list-style-type: none"> • PR: 8% (5/64) • SD: 50% (32/64) • PFS at 6 months: 22% • Median OS: ≈12 months | <ul style="list-style-type: none"> • Hypertension (27%), fatigue (19%) |
| Soft tissue sarcoma (advanced) ¹⁸ | <ul style="list-style-type: none"> Phase II N=10 NCT01719744 | <ul style="list-style-type: none"> • 275 mg PO OD (continuous) • Monotherapy | <ul style="list-style-type: none"> • PR: 20% (2/10) • SD ≥ 6 months: 10% (1/10) • Median PFS: 1.8 months | <ul style="list-style-type: none"> • Hypertension (20%), elevated transaminases (10%), leukopaenia (10%), diarrhoea (10%) |

⁹ meeting abstract data. AML, acute myeloid leukaemia. BD, twice daily. CR, complete response. CRI, complete response with incomplete recovery. EFS, event-free survival. HMA, hypomethylating agents (azacitidine or decitabine). HR, hazard ratio. IV, intravenous administration. MDS, myelodysplastic syndromes. N, number of patients. NA, not available. OD, once daily. OS, overall survival. p, p value of two-sided statistical test. PFS, progression-free survival. PO, oral administration. PR, partial response. RP2D, recommended phase II dose. RR, overall response rate (complete + partial responses). s.c., subcutaneously. SD, stable disease. vs, versus.

REFERENCES

1. Karp, J.E. et al. Phase I and pharmacologic trial of cytosine arabinoside with the selective checkpoint 1 inhibitor Sch 900776 in refractory acute leukemias. *Clin Cancer Res* **18**, 6723-31 (2012).
2. Bendell, J.C. et al. Checkpoint kinase (CHK) 1/2 inhibitor LY2606368 in a phase I, dose-expansion study in patients (pts) with metastatic squamous cell carcinoma (mSCC) of the anus. *J Clin Oncol* **33**, suppl; abstr 3520 (2015).
3. Leijen, S. et al. Phase II study with Wee1 inhibitor AZD1775 plus carboplatin in patients with p53 mutated ovarian cancer refractory or resistant (<3 months) to standard first line therapy. *J Clin Oncol* **33**, suppl; abstr 2507 (2015).
4. Oza, A.M. et al. An international, biomarker-directed, randomized, phase II trial of AZD1775 plus paclitaxel and carboplatin (P/C) for the treatment of women with platinum-sensitive, TP53-mutant ovarian cancer. *J Clin Oncol* **33**, suppl; abstr 5506 (2015).
5. Fenaux, P. et al. Overall survival (OS) and baseline disease characteristics in MDS patients with primary HMA failure in a randomized, controlled, phase III study of rigosertib. *J Clin Oncol* **33**, suppl; abstr e18079 (2015).
6. Silverman, L.R. et al. Prognostic and predictive value of IPSS-R in assessing overall survival (OS) in a phase III study of rigosertib in second-line higher-risk (HR) MDS patients. *J Clin Oncol* **33**, suppl; abstr 7092 (2015).
7. O'Neil, B.H. et al. A phase II/III randomized study to compare the efficacy and safety of rigosertib plus gemcitabine versus gemcitabine alone in patients with previously untreated metastatic pancreatic cancer. *Ann Oncol* **26**, 1923-9 (2015).
8. Döhner, H. et al. Randomized, phase 2 trial of low-dose cytarabine with or without volasertib in AML patients not suitable for induction therapy. *Blood* **124**, 1426-33 (2014).
9. Barr, P.M. et al. Phase II Intergroup Trial of Alisertib in Relapsed and Refractory Peripheral T-Cell Lymphoma and Transformed Mycosis Fungoides: SWOG 1108. *J Clin Oncol* **33**, 2399-404 (2015).
10. Friedberg, J.W. et al. Phase II study of alisertib, a selective Aurora A kinase inhibitor, in relapsed and refractory aggressive B- and T-cell non-Hodgkin lymphomas. *J Clin Oncol* **32**, 44-50 (2014).
11. Falchook, G.S. et al. Phase I/II study of weekly paclitaxel with or without MLN8237 (alisertib), an investigational aurora A kinase inhibitor, in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (OC), or breast cancer (BrC): Phase I results. *J Clin Oncol* **30**, suppl; abstr 5021 (2012).
12. Venkatakrishnan, K. et al. Recommended phase (Ph) II dose (RP2D) selection for investigational Aurora A kinase (AAK) inhibitor MLN8237 (Alisertib; A) combined with paclitaxel (P): Clinical pharmacokinetics (PK), drug-drug interaction (DDI) assessment, and translational exposure-efficacy modeling. *J Clin Oncol* **31**, suppl; abstr 2598 (2013).
13. Melichar, B. et al. Safety and activity of alisertib, an investigational aurora kinase A inhibitor, in patients with breast cancer, small-cell lung cancer, non-small-cell lung cancer, head and neck squamous-cell carcinoma, and gastro-oesophageal adenocarcinoma: a five-arm phase 2 study. *Lancet Oncol* **16**, 395-405 (2015).
14. Sarantopoulos, J. et al. Phase I trial of the investigational aurora A kinase (AAK) inhibitor MLN8237 (alisertib) in combination with docetaxel (DTX) in patients (pts) with advanced solid tumors, including castration-resistant prostate cancer (CRPC). *J Clin Oncol* **32**, suppl 4; abstr 217 (2014).
15. Rosenthal, A. et al. A Phase Ib Study of the combination of the Aurora Kinase Inhibitor Alisertib (MLN8237) and Bortezomib in Relapsed Multiple Myeloma. *Br J Haematol* (2015).
16. DuBois, S.G. et al. Phase I Study of the Aurora A Kinase Inhibitor Alisertib in Combination With Irinotecan and Temozolomide for Patients With Relapsed or Refractory Neuroblastoma: A NANT (New Approaches to Neuroblastoma Therapy) Trial. *J Clin Oncol* (2016).
17. Matulonis, U.A. et al. ENMD-2076, an oral inhibitor of angiogenic and proliferation kinases, has activity in recurrent, platinum resistant ovarian cancer. *Eur J Cancer* **49**, 121-31 (2013).

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18. Loong, H.H. et al. A phase II study of oral ENMD-2076 administered to patients (pts) with advanced soft tissue sarcoma (STS). *J Clin Oncol* **31**, suppl; abstr TPS10593 (2013).