## Supplementary information S3 | Clinical trial results of selected CDK inhibitors

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Study characteristics, ClinicalTrials.gov Identifier</th>
<th>Drug dosage and combination</th>
<th>Efficacy</th>
<th>Major grade 3/4 adverse effects (≥10%)</th>
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<tbody>
<tr>
<td><strong>Flavopiridol (alvocidib)</strong></td>
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</tbody>
</table>
| AML (poor prognosis)¹ | - Phase II  
- N=62  
- NCT00407966 | - 50 mg/m² IV OD (days 1-3)  
- Combination with cytarabine (2 g/m² IV over 72 hours, days 6-8) and mitoxantrone (40 mg/m² IV on day 9) (“FLAM”) | - CR: 52% (32/62)  
- PR: 12% (7/62)  
- Median OS: 8 months | - Tumour lysis syndrome (53%) |
| AML (newly diagnosed)² | - Phase II  
- N=165  
- “FLAM” (N=112) vs “7+3” (N=56)  
- NCT01349972 | - “FLAM” (see study above)  
- “7+3”: cytarabine (100 mg/m² IV daily, days 1-7) with daunorubicin (90 mg/m² IV daily, days 1-3), for residual leukaemia after 14 days: cytarabine (100 mg/m² IV daily, days 1-5) with daunorubicin (45 mg/m² IV daily, days 1-2) | - Median EFS: 9.7 months vs 3.4 months (HR=0.74, p=0.15)  
- Median OS: 17.5 months vs 22.2 months (HR=1.2, p=0.39)  
- CR: 70% (73/109) vs 57% (32/56) (p=0.08) | - Febrile neutropaenia (48% vs 45%), infection (35% vs 38%), hepatic dysfunction (21% vs 23%), gastrointestinal dysfunction (11% vs 9%) |
| CLL (relapsed)³ | - Phase II  
- N=64  
- NCT00098371 | - 60-80 mg/m² IV over 4 hours (days 1, 8, 15 of 28-day cycle)  
- Monotherapy | - CR: 2% (1/64)  
- PR: 52% (33/64)  
- Median PFS: 8.6 months | - Neutropaenia (88%), diarrhoea (64%), tumour lysis syndrome (42%), elevated transaminases (34%), infection (31%), thrombocytopenia (27%) |
| CLL (fiudarabine-refractory)⁴ | - Phase II  
- N=159  
- NCT00464633 | - 60-80 mg/m² IV over 4 hours (days 1, 8, 15 of 28-day cycle)  
- Monotherapy | - CR: 2% (3/159)  
- PR: 24% (38/159)  
- SD: 33% (53/159)  
- Median PFS: 7.6 months  
- Median OS: 14.6 months | - Neutropaenia (34%), infections (30%), gastrointestinal (25%), tumour lysis syndrome (21%) and other |
| **Dinaciclib (SCH 727965, MK-7965)** | | | | |
| CLL (relapsed or refractory)⁵ | - Phase I  
- N=52  
- NCT00871663 | - 5-17 mg/m² IV weekly (3 weeks on, 1 week off), RP2D: 14 mg/m²  
- Monotherapy | - PR: 54% (28/52)  
- SD: NA  
- Median PFS: 15.8 months | - Neutropaenia (75%), thrombocytopenia (40%), increased AST (29%), anaemia (25%), hyperglycaemia (21%) and other |
| Multiple myeloma (advanced prior therapy)⁶ | - Phase I/II  
- N=27  
- NCT01096342 | - 30-50 mg/m² IV every 3 weeks, MTD: 50 mg/m²  
- Monotherapy | - PR: 11% (3/27)  
- SD: 56% (15/27) | - Neutropaenia (12%), diarrhoea (12%), blurred vision (12%) |
| **Palbociclib (PD0332991)** | | | | |
| Breast cancer (advanced, ER⁺ HER2⁻, first-line treatment, post-menopausal)⁷ | - Phase II  
- N=165  
- Palbociclib + letrozole (N=84) vs letrozole alone (N=81)  
- NCT00721409 (PALOMA-1) | - 125 mg PO OD (3 weeks on, 1 week off)  
- Combination with letrozole (2.5 mg PO OD, continuous) | - Median PFS: 20.2 months vs 10.2 months (HR=0.488, p=0.0008)  
- Median OS: 37.5 months vs 33.3 months (HR=0.813, p=0.42)  
- CR: 1% vs 1%  
- PR: 42% vs 32%  
- SD: 44% vs 37%  
- SD ≥ 24 weeks: 38% vs 25% | - Neutropaenia (54% vs 1%) |
| Breast cancer (advanced, ER⁺ HER2⁻, relapsed or progressed during prior hormone therapy)⁸ | - Phase III  
- N=512  
- Palbociclib + fulvestrant (N=347) vs placebo + fulvestrant (N=174)  
- NCT01942135 | - 125 mg PO OD (3 weeks on, 1 week off)  
- Combination with fulvestrant (500 mg IM every 2-4 weeks)  
- Additional goserelin for pre/perimenopausal women | - Median PFS: 9.5 months vs 4.6 months (HR=0.46, p=0.001)  
- Effect on OS yet unknown | - Neutropaenia (65% vs 1%) |
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>(PALOMA-3)</th>
<th>Breast cancer (metastatic, RB+)</th>
<th>Breast cancer (metastatic, RB+)</th>
<th>Non-small cell lung cancer (previously-treated, recurrent or metastatic, RB+, with p16 deletion/loss)</th>
<th>Head and neck squamous cell carcinoma (incurable)</th>
<th>Mantle cell lymphoma (relapsed, with cyclin D1 overexpression)</th>
<th>Liposarcoma (advanced, well-differentiated or dedifferentiated, RB+, with CDK4 amplification)</th>
<th>Germ cell tumours (incurable, refractory, RB+)</th>
<th>Ribociclib (LEE011)</th>
<th>Breast cancer (metastatic, ER+ HER2-, post-menopausal)</th>
<th>Breast cancer (metastatic, ER+ HER2+)</th>
<th>Non-small cell lung cancer (advanced, relapsed/progressed)</th>
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</thead>
<tbody>
<tr>
<td>Breast cancer (metastatic, RB+)</td>
<td>• Phase II</td>
<td>• N=37 (84% ER+HER2+)</td>
<td>• NCT01394016</td>
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<td>Breast cancer (metastatic, RB+)</td>
<td>• Phase II</td>
<td>• N=15</td>
<td>• NCT01320592</td>
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<tr>
<td>Non-small cell lung cancer (previously-treated, recurrent or metastatic, RB+, with p16 deletion/loss)</td>
<td>• Phase II</td>
<td>• N=19</td>
<td>• NCT01291017</td>
<td>[21]</td>
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<tr>
<td>Head and neck squamous cell carcinoma (incurable)</td>
<td>• Phase I</td>
<td>• N=9</td>
<td>• NCT02101034</td>
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<td>Mantle cell lymphoma (relapsed, with cyclin D1 overexpression)</td>
<td>• Phase Ib</td>
<td>• N=17</td>
<td>• NCT00420056</td>
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<td>Liposarcoma (advanced, well-differentiated or dedifferentiated, RB+, with CDK4 amplification)</td>
<td>• Phase II</td>
<td>• N=30</td>
<td>• NCT01209598</td>
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<td>Germ cell tumours (incurable, refractory, RB+)</td>
<td>• Phase II</td>
<td>• N=29 (arm 4)</td>
<td>• NCT01037790</td>
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<td>Ribociclib (LEE011)</td>
<td>Breast cancer (advanced, ER+, HER2-, post-menopausal)</td>
<td>• Phase Ib</td>
<td>• N=10 (arm 1)</td>
<td>• NCT01872260</td>
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<td>Melanoma (NRAS mutant)</td>
<td>• Phase Ib/II</td>
<td>• N=14</td>
<td>• NCT01781572</td>
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<tr>
<td>Abemaciclib (LY2835219)</td>
<td>Breast cancer (metastatic)</td>
<td>• Phase I</td>
<td>• N=47 (arm 1)</td>
<td>• NCT01394016</td>
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<tr>
<td>Breast cancer (metastatic, ER+ HER2+)</td>
<td>• Phase Ib</td>
<td>• N=36 (parts A+B)</td>
<td>• N=16 (part C)</td>
<td>• NCT02057133</td>
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<tr>
<td>Non-small cell lung cancer (advanced, relapsed/progressed)</td>
<td>• Phase I</td>
<td>• N=49</td>
<td>• NCT01394016</td>
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- **PR**: partial response
- **SD**: stable disease
- **RR**: overall response rate
- **PFS**: progression-free survival
- **OS**: overall survival
- **17p**: a deletion in chromosome 17
- **RB** protein
- **HER2**
- **ERBB2**
- **PALOMA-3**
- **NCT01394016**
- **NCT01037790**
- **NCT01209598**
- **NCT01037790**
- **NCT01291017**
- **NCT02101034**
- **NCT01291017**
- **NCT01037790**
- **NCT01872260**
- **NCT01781572**
- **NCT01394016**
- **NCT01037790**

References and notes are provided in the original text.
REFERENCES