Title: Extended follow-up and the feasibility of Panobinostat maintenance for patients with Relapsed Multiple Myeloma treated with Bortezomib, Thalidomide, Dexamethasone plus Panobinostat (MUK six open label, multi-centre phase I/II Clinical Trial)

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Panobinostat, a potent oral pan-deacetylase inhibitor is indicated for patients with relapsed multiple myeloma (MM) in combination with bortezomib and dexamethasone. This was based upon the sub-group analysis of the PANORAMA 1 phase 3 clinical trial demonstrating an improvement in progression free survival (PFS) of 12.5 vs 4.5 months (Richardson*, et al* 2016). MUK-six (ISRCTN59395590, NCT02145715) was a multi-centre phase I/II clinical trial for patients with relapsed MM (1-4 prior lines), designed to improve the efficacy, tolerability by adding low dose thalidomide and incorporating low intensity subcutaneous bortezomib followed by panobinostat maintenance. The epigenetic mechanism of action, role in aggressome disruption and evidence of immunomodulation (Govindaraj*, et al* 2014, Hideshima*, et al* 2005, Mitsiades*, et al* 2003) provided a hypothesis that continuing panobinostat monotherapy may prolong response. We previously reported primary and secondary endpoints for the trial interpreting that the regimen was efficacious and well tolerated (Popat*, et al* 2016). Here with extended follow-up, we report updated secondary endpoint of PFS, overall survival (OS) and feasibility of panobinostat maintenance.

Patients received bortezomib (V) 1.3mg/m^2 days 1, 8 with thalidomide (T) 100mg daily (50 mg if peripheral neuropathy) dexamethasone (D) 20mg days 1, 2, 8, 9 and panobinostat (P) days 1, 3, 5, 8, 10 and 12 of a 21 day cycle for 16 cycles followed by 1 year of panobinostat maintenance (current dosing level or maximum tolerated dose (MTD)) for patients completing 16 cycles of therapy only. The primary objectives were to determine the MTD of panobinostat and the overall response rate at the recommended dose within 16 cycles. The trial was funded by Myeloma UK, Novartis and approved by the UK national ethics committee and the Medicines and Healthcare Products Regulatory Agency (MHRA).

Following a median follow-up of 28 months, 46 patients received at least one dose of the recommended 20mg panobinostat dose and are reported for PFS overall; censoring patients coming off study for an autologous stem cell transplant (ASCT) at point of ASCT (see original paper for definitions and supplementary Figure for CONSORT diagram). The median overall PFS was 16.1 months (95%CI: 13.40, 21.55) and appeared similar for those with standard and adverse cytogenetic risk (standard (n=23) 16.10 months (95% CI: 13.40, 24.80), adverse (n=21) 17.90 months (95% CI: 9.40, Not calculable [>26.8]) 2, results not available, figure 1). 24 patients came off study to proceed to ASCT (median PFS 29.40 months (95% CI: 18.73, 37.65)) and 22 continued therapy (median PFS of 15.11 months (95% CI: 7.00, 20.47)). The median OS was not reached, for patients that did not come off to proceed to ASCT (n=22), the estimated 2 year OS was 71.4% (95% CI: 47.2%, 86.0%) (Figure 1).

15 of the 20 patients that completed 16 cycles of VTD-P went on to receive panobinostat maintenance (demographics in supplementary materials, table 1). Of the 5 that did not, 3 were eligible for ASCT and

2 had prior toxicity to panobinostat. Patients were predominantly at first relapse (11, 73.3%). 12 (80.0%) patients started maintenance at panobinostat 20mg and 3 at 15mg due to dose reductions during initial therapy. Clinic visits were six weekly for trial safety and response assessments (2 cycles of maintenance). Patients remained on maintenance for a median of 7.5 cycles (range 3-18). 5 completed the full 1 year, 9 stopped early due to disease progression and 1 withdrew consent for due to toxicity. 3 patients maintained their response during maintenance, 2 had disease progression at the end of the 1 year maintenance and 9 had disease progression on therapy with 1 patient beginning to lose the response (but not fulfilling criteria for disease progression) during maintenance before withdrawing after 4 cycles. No patients deepened their response on treatment (Figure 2). Median PFS for patients that received maintenance was 17.9 months (95% CI 13.4, 21.5). No serious adverse events were reported during maintenance. The commonest change in reported AEs from initial therapy (all grades) were diarrhoea (grade 1: 3/15, 20%; grade 3: 2/15, 13.3%), anorexia (grade 1: 4/15, 26.7%), infection (grade 1: 3/15, 20%; grade 2: 1/15, 6.7%). Overall treatment compliance was maintained with a median overall dose taken of 20mg (range 10-20mg). Four patients (26.7%) required at least 1 dose reduction for toxicity during maintenance, all requiring a reduction due to diarrhoea. Five patients (33.3%) required at least 1 dose omission of which 2 were due to nausea and diarrhoea.

In comparison, the phase 3 PANORAMA 1 trial which investigated VD-P (8 x 3 weekly cycles followed by 4 x 6 weekly cycles, with no maintenance) in patients with 1-3 prior lines of therapy (51% 1 prior line) reported a median PFS of 11.99 months (95% CI 10·33, 12·94, n=387) and OS of 40.3 months (95% CI, 35.0-44.8 months)(San-Miguel*, et al* 2014, San-Miguel*, et al* 2016). Here we report an overall median PFS of 16.1 months, and 15.11 months for those that did not proceed to ASCT in a smaller phase I/II study (1-4 prior lines, 80% 1 prior line).

There is limited data to the efficacy of panobinostat monotherapy in MM. In a phase 2 trial of 38 patients, only 2 derived clinical benefit (1 PR, 1 MR). However both patients had long responses of 19 and 28 months (Wolf*, et al* 2012). A case report from a phase 1b trial of VD-P described 2 patients that gained long term benefit from ongoing panobinostat monotherapy (at least 65 months and 75 months) (Ocio*, et al* 2015). There are also ongoing trials investigating panobinostat post ASCT (Sengsayadeth*, et al* 2017). The MUK-six trial demonstrated that 1 year of panobinostat maintenance was feasible, with dose intensity maintained. The predominant AEs were gastrointestinal, mainly grade 1-2. Some maintained their response during maintenance; however 11 of the 15 patients developed disease progression on panobinostat. As a result, the clinical benefit of panobinostat

monotherapy maintenance appeared minimal. However the conclusions are limited due to a small selected group without comparative data.

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Figure Legends:

Figure 1: Progression free and overall survival of patients treated with VTD-P. A: PFS of all patients; B: PFS split for those that received ASCT and those that continued on therapy; C: PFS split by standard and adverse cytogenetic risk ; D: OS split for those that received ASCT and those that continued on therapy.

Figure 2: Swim lane plot of each individual patient that received panobinostat maintenance following 16 cycles of VTD-P showing response at end of initial therapy and response over maintenance period.