First report on OS and improved PFS in a completed Phase 2a Study of melflufen in advanced RRMM

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Background:
Melflufen is a next generation alkylator, designed for efficient targeting of tumor cells with a unique mechanism of action. Melflufen provides a peptidase potentiated therapy with an alkylating payload and triggers fast, robust and irreversible DNA damage. The lipophilicity of melflufen leads to rapid and extensive distribution into cells where it is readily metabolized by intracellular peptidases (often over-expressed in malignant cells) into hydrophilic alkylating metabolites leading to 50-fold enrichment of these metabolites in MM cells. In addition, melflufen has potent anti-angiogenic properties.

Methods:
40 mg melflufen was given i.v. on Day 1 of each 28-day cycle, with 40 mg dexamethasone weekly, in RRMM patients with measurable disease and ≥2 prior lines of therapy including lenalidomide and bortezomib (NCT01897714).

Response was investigator assessed at each cycle by IMWG criteria. After disease progression (PD) or start of subsequent therapy, patients were followed for survival every 3 months for up to 24 months.

Results:
Enrollment was closed in Dec 2016. 45 patients were included with data cut-off on 19 July 2017. Patient characteristics included median age 66 years (47–78), 73% ISS stage 1 or 2, 20% stage 3, 27% high-risk cytogenetics [del(17p), t(14;16) or t(4;14)]. The median time since initial diagnosis was 5.0 years (1-15). The median number of prior therapies was 4 (2-14). 100% of patients were exposed to immunomodulatory drugs (IMiDs), 98% to proteasome inhibitors (PIs), 93% to alkylators (any dose of melphalan, cyclophosphamide or bendamustine) and 82% to melphalan. 62% were double refractory (IMiD + PI) and 36% were triple refractory (2 PIs+1 IMiD or 1 PI + 2 IMiDs). Patients were treated with a median of 5 cycles (1-14), median treatment duration was 17 weeks. At time of data cut-off, 2 patients were ongoing, 17 discontinued due to AEs, 14 due to PD, 2 died, and 9 completed treatment as planned (8 cycles). One patient was discontinued due to physician's discretion.

The overall response rate (ORR) was 41% among 34 treatment evaluable patients (≥2 doses of melflufen with baseline and follow-up assessments) including Very Good Partial Response

in 4 (12%) and partial response (PR) in 10 (29%). Seven (21%) additional patients achieved minimal response (MR) for a clinical benefit rate (CBR) of 62%. ORR in all treated patients was 31%.

The median progression free survival (PFS) in all treated patients was 5.1 months (95% CI: 3.7 – 8.5) based on 40 events in 45 patients. In patients with ≥PR the PFS, was 11.0 months (95% CI: 8.0 – ∞, event rate 86%).

The median overall survival (OS) in all treated patients was 20.7 months (95% CI: 11.8 - ∞) based on 24 events in 45 patients. Of note is that in the 13 patients that achieved stable disease (SD), the median OS was 27.2 months (95% CI: 10.0 – ∞, event rate 54%), and in patients with high cytogenetic risk the OS was 14.9 months (10.0 - ∞, event rate 75%).

The most frequent adverse events (AEs), all grades, were mainly hematologic; with thrombocytopenia (76%), anemia (62%) and neutropenia (60%) as the most common. Additional AEs occurring in >10% included pyrexia (40%), asthenia (31%), fatigue (29%), nausea (27%), diarrhoea (24%), pneumonia (18%), cough (18%), constipation (16%), mucosal inflammation (13%), back pain (13%), bone pain (13%), dyspnoea (13%), epistaxis (13%), headache (13%), insomnia (13%), vomiting (11%), upper respiratory tract infection (11%), arthralgia (11%) and muscle spasms (11%).

Treatment related hematologic grade 3/4 events were reported in 37 patients (82%), with those occurring in >10% included thrombocytopenia (60%), neutropenia (53%) and anemia (42%).

Conclusion:
Treatment with melflufen, a peptidase-potentiated alkylator, shows long-term benefit in late-stage RRMM patients where conventional therapies have failed. The median PFS and OS in this heavily pretreated population, with limited treatment options, are both encouraging at 5.1 months and 20.7 months, respectively. The long median OS of 27.2 months in patients that only achieved SD as best response will be further studied in the ongoing studies OCEAN (phase 3) and HORIZON (phase 2). Treatment-related hematologic toxicity was common, but non-hematologic AEs were infrequent. Detailed and updated results will be presented at the meeting.

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