Treatment of relapsed/refractory myeloma (RRMM) remains a challenge as durable responses are often achieved in a sub-group of patients only. Identifying these subgroups by predicting prognosis in RRMM would allow for early risk based treatment stratification. In addition, affordable triplet combination therapies that increase efficacy over doublets in RRMM are highly desirable to enable access for larger patient populations.

Background

Paired whole blood was immunomagnetically isolated for RNA/DNA and protein analysis. A single-hit strategy was designed to include a real-world RRMM population, permitting transusions and growth factor support. Original planned sample size was 250 patients to detect 2 month improvement in PFS; due to a change in UK SOE with pomalidomide becoming widely available, a decision was made to stop recruitment early.

• 102 RRMM patients were randomized 1:1 and received at least 1 dose of trial treatment between March 2016 and February 2018. Median age at randomization: 69 years (range 42-88); median 3 prior lines of therapy (28% ≥5 prior lines of therapy. Median follow-up: 13.4 months (95% CI: 12.0-17.5). 16 patients remained on trial at time of analysis (median number of cycles: 19.5; range 8-28).

• ORR (≥PR) was higher for CPomD 70.6% (95% CI: 56.2-82.5%) compared to PomD 47.1% (CI: 32.9-61.5%) (P=0.006) (Figure 1).

• Median PFS for CPomD was 6.9 months (CI: 5.7-10.4) vs. 4.6 months for PomD (CI: 3.5-7.4), not meeting significance by pre-defined criteria (Figure 1) however study is underpowered given only 40% of target sample size achieved (see ‘Design’).

• This prognostic association was significant independent of treatment arm/randomisation.

Primary endpoint was PFS; secondary included OS, response rate, safety. Trial entry criteria were designed to include a real-world RRMM population, permitting transusions and growth factor support. Original planned sample size was 250 patients to detect 2 month improvement in PFS; due to a change in UK SOE with pomalidomide becoming widely available, a decision was made to stop recruitment early.

• Generate a bio-repository to develop biomarkers for RRMM prognostication and improved treatment response prediction. BM biopsies were taken at baseline, CD14, CD14 and progression. Tumour cells were immunomagnetically purified and processed for RNA/DNA and protein analysis.

Results: Efficacy analysis

Due to high bio-sampling adherence, for 71/102 patients results for all high risk markers were available. Of these, 12.7% had double-hit ultra-high-risk (32 adverse lesions), 46.5% single-hit high-risk and 40.8% no risk marker.

• Double-hit MM had the shortest median PFS: 3.4 months (CI: 1.0-4.9) vs. single-hit: 5.8 months (CI: 3.7-9.0). Of note, MM without risk markers had long median PFS of 14.1 months (CI: 8.9-17.3) (P=0.005; Figure 3).

• Gene expression biomarkers

GEP was performed by Affymetrix HG-U133plus2 array for 48 patients with sufficient material. The EMC92 high-risk signature was detected in 19% of tumors.

• Immune biomarkers

PFS Kaplan-Meier curve showing outcome by number of genetic risk markers: Double-hit ≥2 risk markers; blue curve; single-hit (1 risk marker; green curve); no risk marker (red curve).

• Pharmacodynamic profiling

• CRL4CRBP ubiquitination (neo-)targets, downstream effectors and CRBN were immunohistochemically assessed on bone marrow clots from baseline, C1D14, C4D14, progression. Analysis is ongoing, preliminary results are shown in Figure 6.

• Conclusions

- We demonstrate that gain(1q) is associated with shorter PFS in RRMM. Double-hit tumours as well as GEP high risk constitute ultra-high risk groups. Our results suggest reporting on these features should ideally be included in RRMM trial reports.

- Integration of genetic/GEP markers with immunological and PD markers is currently ongoing.

- However, CD4+ T-cell % at baseline was associated with shorter PFS in a multi-variable Cox regression model (P=0.005; Figure 5).

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