Prognostic Molecular Stratification in Relapsed/Refractory Multiple Myeloma

Results of the UKMRA MUKSeven Pomalidomide Biomarker Trial

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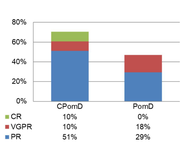
Background

- 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.

Design

- MUKseven was a phase 2 randomised multi-center trial designed to
  - **Compare efficacy** of cyclophosphamide 500 mg po D1, 8, 15 /pomalidomide 4 mg po D1-21/dexamethasone 40 mg (20 if ≥75yo) (**CPomD**) vs. pomalidomide/dexamethasone (**PomD**). **Primary endpoint was PFS**, secondary included OS, response rate, safety. Trial entry criteria were designed to include a real-world RRMM population, permitting transfusions and growth factor support. Original planned sample size was 250 patientsto detect 2 month improvement in PFS; due to a change in UK SOC 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, C1D14, C4D14 and progression. Tumour cells were immunomagnetically CD138 purified and processed for RNA/DNA and protein analysis.

Results: Efficacy analysis



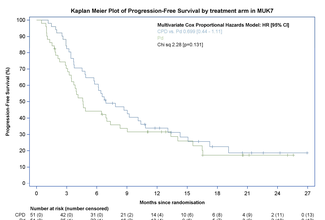


Figure 1: ORR (above) for CPomD and PomD treatment arms; PFS Kaplan-Meier curves (right) for both treatment arms

- 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').

Genetic predictors of outcome

- High-risk genetic aberrations were tested by RT-qPCR (translocations) and MLPA (CNA) and found at following frequencies for patients with available information: t(4;14): 6%, t(14;16)/t(14;20): 2%, gain(1q): 45%, del(17p): 13%.
- Of note, gain(1q) was significantly associated with shorter PFS (Figure 2) in RRMM (*P*=0.0013).

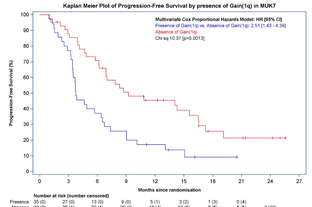


Figure 2: Presence of gain(1q) is associated with significantly shorter PFS in the MUKseven RRMM population

- 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 (≥2 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: 6.9–17.3) (P=0.005; Figure 3).

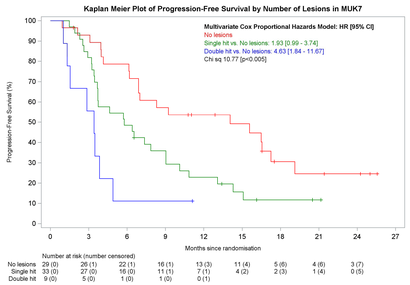


Figure 3: PFS Kaplan-Meier curve showing outcome by number of genetic risk markers: Double-hit (≥2 risk markers; blue curve); single-hit (1 risk marker; green curve); no risk marker (red curve)

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

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.
- EMC92 high risk MM had short median PFS of 3.4 months (CI: 2.0–5.7) vs. 7.4 (CI: 3.9–15.1) for standard risk (*P*=0.037) (Figure 4).

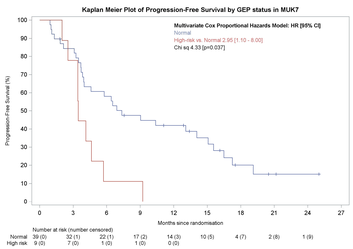


Figure 4: PFS Kaplan curves for EMC92 high risk (red curve) and standard risk (blue curve) MM tumours.

Immune biomarkers

- T-cell subsets in peripheral blood were measured by multi-parametric flow cytometry at baseline and longitudinally on therapy at C1D14, C4D14, progression.
- We reported on dynamic changes in T-cell populations, such as (HLA-DR+) CD4+ T-cells, including their differential increase between CPomD and PomD, previously
- We did not find these dynamic changes to be predictive of treatment outcome.

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

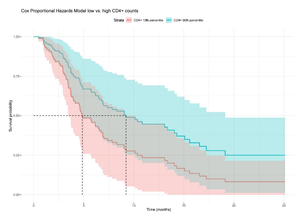


Figure 5: PFS Kaplan-Meier curves for 10th percentile (red curve) and 90th percentile (blue curve) of PB CD4 T-cell %. Lower CD4 % at baseline/prior to pomalidomide therapy is associated with shorter PFS.

Pharmacodynamic profiling

- $CRL4^{CRBN}$ 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.
- Aiolos and ZFP91 H-scores decrease in most cases, but some show little change. Clinical correlation is currently ongoing.

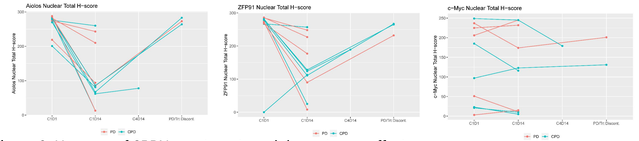


Figure 6: H-scores of CRBN neo-targets and downstream effectors.

Conclusions

- We demonstrate that gain(1q) is associated with short 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.

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