Molecular Treatment Stratification for Newly Diagnosed High Risk Myeloma, including Plasma Cell Leukemia

Feasibility Results of the UKMRA OPTIMUM: MUKnine trial

Matthew Jenner[1], Amy Sherborne[2], Andrew Hall[3], Vallari Shah[2], Katrina Walker[3], Sidra Ellis[2], Kim Sharp[2], Amy Price[2], James Croft[2], Graham Jackson[4], Louise Flanagan[3], Mark Drayson[5], Ruth deTute[6], Roger Owen[6], Guy Pratt[7], Gordon Cook[8,9], Sarah Brown[3], Martin Kaiser[10,11]

1University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom; 2The Institute of Cancer Research, London, United Kingdom; 3Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, Leeds, United Kingdom; 4Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, United Kingdom; 5University of Birmingham, Birmingham, United Kingdom; 6Haematological Malignancy Diagnostic Service, St. James's University Hospital, Leeds, United Kingdom; 7Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom; 8Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, United Kingdom; 9Department of Haematology, Clinical Trials Research Unit, NIHR (Leeds) IVD Cooperative, Leeds Teaching Hospital, Leeds, United Kingdom; 10Myeloma Molecular Therapy Group, The Institute of Cancer Research, London, United Kingdom; 11The Royal Marsden Hospital, London, United Kingdom

Background

- Newly diagnosed **High Risk Myeloma** and **primary Plasma Cell Leukemia** (PCL) have a **high unmet need** and novel approaches for these groups are urgently needed.
- Standard therapies lead to very short PFS and OS in patients with molecular High Risk MM, specifically:
  - **Double-hit tumors** (any ≥2 lesions of t(4;14), t(14;16), t(14;20), del(1p), gain(1q), del(17p)) [1,2]
  - **GEP High Risk signature** tumors, such as SKY92 [2]
- We designed and conducted a prospective, multi-center risk-stratified trial for NDMM High Risk and PCL patients, using an innovative and novel treatment approach.

Design

- The OPTIMUM MUK9 trial consists of the central **OPTIMUM*screen* protocol (MUK9A)** and the **OPTIMUM*treat* protocol (MUK9B)** offered to patients found to have High Risk MM on central results (**Figure 1**).
- Central molecular profiling of CD138-selected tumour material consisted of **IGH translocation** (RT-qPCR), **copy number aberration** (CNA) (MLPA; MRC Holland) and **GEP SKY92** risk profiling (MMProfiler; SkylineDx/AffymetrixDX2).
- A maximum of 2 cycles of VTD standard of care induction could be given whilst central results were pending. Patients with newly diagnosed primary PCL were offered direct enrolment into MUK9B.
- **OPTIMUM*treat*** MUK9B therapy consisted of daratumumab, cyclophosphamide, bortezomib, lenalidomide, dexamethasone induction (**Dara-CVRd**), bortezomib-augmented single HDMEL+ASCT, Dara-VRd consolidation 1, Dara-VR consolidation 2 and Dara-R maintenance until progression of lack of tolerability (**Figure 1**).
- Non-High Risk **OPTIMUM*screen*** MUK9A patients are a **Molecularly Characterized Real-World** cohort and are followed up through NHS SOC 1st and 2nd line therapies.

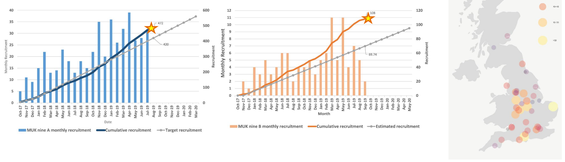


Figure 2: Recruitment graphs of OPTIMUM*screen* (MUK9A; left) and OPTIMUM*treat* (MUK9B; middle) and geographical distribution (right). Note increasing recruitment speed throughout trial and completion 9 months ahead of projections. Star = recruitment target met.

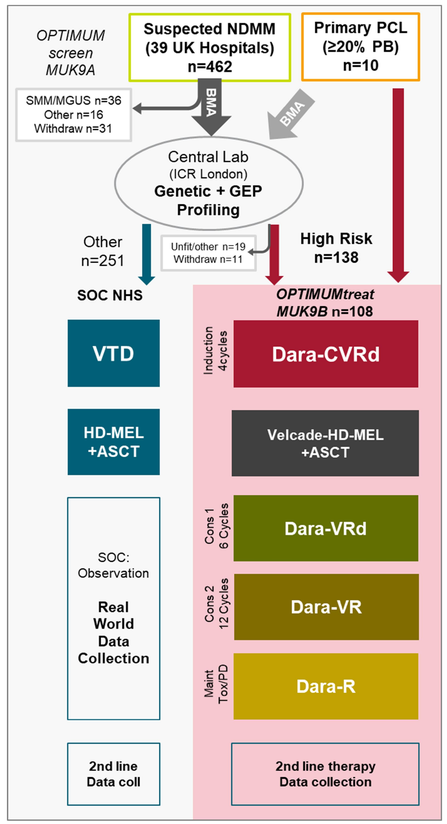


Figure 1: Trial flow diagram and final numbers of patients enrolled into OPTIMUM*screen* (MUK9A) and OPTIMUM*treat* (MUK9B) protocols.

Results

- OPTIMUM recruited between Sept 2017 – July 2019 when it reached recruitment **target of 108 High Risk/PCL** OPTIMUM*treat* patients **(Figures 1&2).**
- Recruitment speed accelerated throughout the trial and recruitment completed 9 months ahead of schedule, demonstrating the unmet need for risk adapted treatment protocols for fit NDMM patients.

Feasibility Outcomes

- OPTIMUM demonstrates **feasibility of central risk profiling** in a time-sensitive setting like NDMM, using an intelligent design:
  - Suspected NDMM were allowed to enrol pre-BM biopsy to avoid repeat biopsy: **89% were confirmed as symptomatic MM**.
  - Median **Risk Status turnaround time was 18 days (IQR 13-22)**, well below protocol defined maximum limit of 8 weeks.
  - Central results were **successfully generated for 93%** of patients, the majority of technical failures were caused by aspirate quality.
  - Patients could receive VTD SOC whilst central BM results were generated, none progressed during this phase.
- OPTIMUM is one of the first trials to prospectively enroll PCL in the era of modern therapies (**Table 1**)

PCL	IGH TL	HiR CNA	SKY92 GEP
1	None	del(1p) & gain(1q)	High Risk
2	t(11;14)	del(1p) & del(17p)	High Risk
3	t(14;16)	none	High Risk
4	t(11;14)	none	High Risk
5	None	del(17p)	High Risk
6	t(6;14)	del(17p)	High Risk
7	t(11;14)	gain(1q)	High Risk
8	t(11;14)	del(17p)	Other
9	t(11;14)	none	Other

Table 1: PCL characteristics defined by ≥20% PBPCs prospectively enrolled in OPTIMUM*treat* protocol. Note enrichment of t(11;14) group and presence of high risk markers in majority of patient tumor cells. (1 patient not shown due to insufficient material sent at enrolment).

Virtual / Digital / Synthetic Comparator Design

- OPTIMUM*treat* is, to our knowledge, the first trial for NDMM that is based on a **Bayesian Design** using a Virtual, or Digital, comparator.
- This is enabled by availability of **molecularly matched patient data** from the near-concurrent Myeloma XI trial (**Figure 3**)**.**
- Molecular data was generated by the same laboratory using the same methods (RT-qPCR; MLPA; MMProfiler), maximizing comparability.
- **Recruitment** (**Figure 2**) supports attractivity of this approach for **patients and physicians/care teams**.

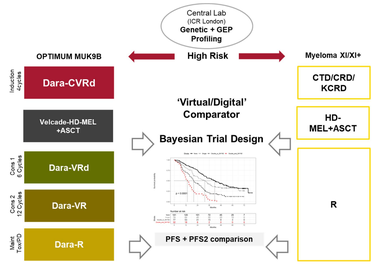
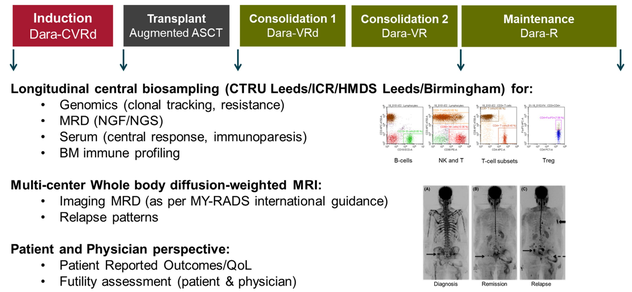


Figure 3: Efficacy of therapy in OPTIMUM*treat* will be compared against molecularly and clinically matched Virtual / Digital priors using a pre-defined Bayesian Design.

Translational / Longitudinal Studies

- There is a program of translational studies accompanying OPTIMUM*treat* primary PFS/PFS2 investigations (**Figure 4**).
- Translational studies aim at gaining a **deeper understanding** of High Risk MM.
- In parallel, OPTIMUM aims to **reflect Patient and Physician perspective** on this novel approach, which will provide **benchmark comparator datasets** for the community.

Figure 4: Longitudinal translational studies



Conclusions

- OPTIMUM demonstrates feasibility of centrally stratified Risk Adapted clinical trials in NDMM, both addressing unmet patient need and opening potential of accelerated clinical development of innovative therapies.
- OPTIMUM is generating important benchmark data for several dimensions of Risk Adapted therapy.
- OPTIMUM is the first trial in NDMM to use a Virtual / Digital Comparator in a Bayesian Design.
- The OPTIMUM trial is now in active follow-up.

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Contacts: Martin.Kaiser@icr.ac.uk S.Brown@leeds.ac.uk

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References: [1] Shah V, Leukemia 2017.; [2] Boyd et al, Leukemia 2012; [3] Kuiper R, Leukemia 2012.