Real world, multi-centre experience of daratumumab monotherapy and response to subsequent treatments in relapsed/refractory myeloma

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Introduction

- Daratumumab (DARA) is the first anti-CD38 human monoclonal antibody against CD38.
- It acts via direct cytotoxicity to malignant plasma cells, as well as triggering complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis. It also improves host anti-tumour immune response, by eliminating immune-suppressing cells that also express CD38[(1)].
- In the UK, DARA has been NICE-approved as a 4th line monotherapy for the treatment of relapsed/refractory multiple myeloma (RRMM) since January 2018 and has been reimbursed through the Cancer Drugs Fund (CDF)[(2)]. Patients may continue on DARA until progression.
- There is as yet no consensus about the preferred 5th line regime following progression on DARA
- Here we present real world, multi-centre data on the effectiveness of DARA monotherapy and patients' response to subsequent therapies.

Methods

- This was a retrospective observational study with an aim to assess patients' responses to DARA monotherapy and subsequent lines of therapy.

Patient Selection

- Using electronic patient records, we identified a cohort of patients at University College London Hospital, Leeds Teaching Hospitals and Huddersfield Royal Infirmary who had commenced at least 1 cycle of DARA monotherapy between April 2016 and October 2019.
- Patients were included if DARA monotherapy was received through the CDF, enrolment in clinical trials, compassionate access schemes or via private prescription.
- Patients received at least a single dose of DARA according to the licensed regimen (16 mg/kg IV weekly (8 weeks (w)), fortnightly (16w), monthly thereafter) for inclusion. We excluded patients with amyloidosis or lymphoplasmacytic lymphoma or those who received DARA as part of CAR-T trial.

Data collection

- Data regarding patient and disease characteristics, prior lines of therapy, response to DARA monotherapy and subsequent therapies, progression-free survival and adverse events were collected from electronic case note review. Death and cause of death were recorded where applicable.
- Response was assessed according to the International Myeloma Working Group (IMWG) criteria[(3)].
- High risk cytogenetics (CG) were defined as t(4;14), t(14;16) and del 17p only. Extramedullary disease (EMD) was defined as a clonal plasmacytic infiltrate at anatomic sites distant from the bone marrow. Performance status was determined using the Eastern Cooperative Oncology Group standards[(4)].
- Information on adverse events was only available from the UCLH site. Adverse events were graded in accordance with the NCI Common Terminology Criteria for Adverse Events version 5.0[(5)].

Statistical analysis

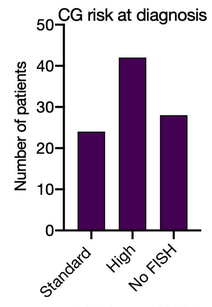
- Kaplan-Meier analysis was used to assess survival, with the logrank test used to compare survival curves.

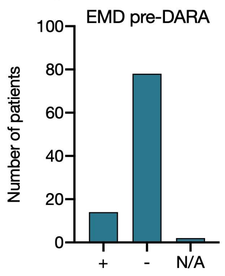
Results

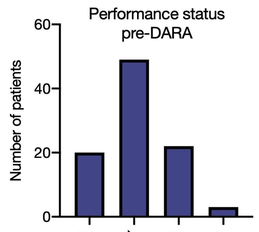
Figure 1. Characteristics pre-DARA monotherapy

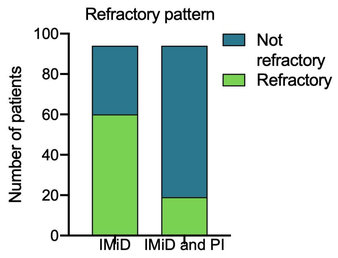
Baseline characteristics	Total (n=94)
Median age at Diagnosis	59.5 (37-90)
Isotype	
IgA	19 (20.2%)
IgG	54 (57.4%)
Light chain	18 (19.1%)
Non-secretory	3 (3.2%)
ISS at diagnosis	
1	21 (22.3%)
2	24 (25.5%)
3	14 (14.9%)
Missing	35 (37.2%)

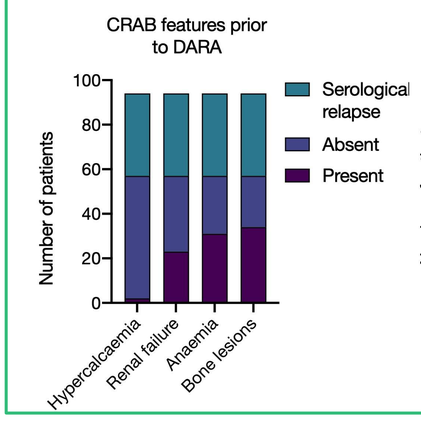
Characteristics prior to DARA	Total (n=94)
Median age at DARA	66.5 (40-91)
Median years from diagnosis to DARA	5.2 (0.9-15.9)
Relapse type	
Serological	38 (40.4%)
Clinical	56 (59.6%)
Treatment provider	
CDF	82 (87.2%)
Private patient	3 (3.2%)
MM3010 trial	8 (8.5%)
MM3003 compassionate access	1 (1.1%)
Number of prior regimen	
2	6 (6.4%)
3	81 (86.2%)
4	5 (5.3%)
5	2 (2.1%)
Autologous stem cell transplant?	
0	33 (35.1%)
1	51 (54.3%)
2	10 (10.6%)
Allogenic stem cell transplant?	
0	89 (94.7%)
1	5 (5.3%)











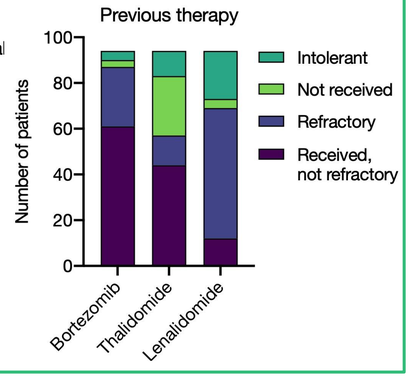
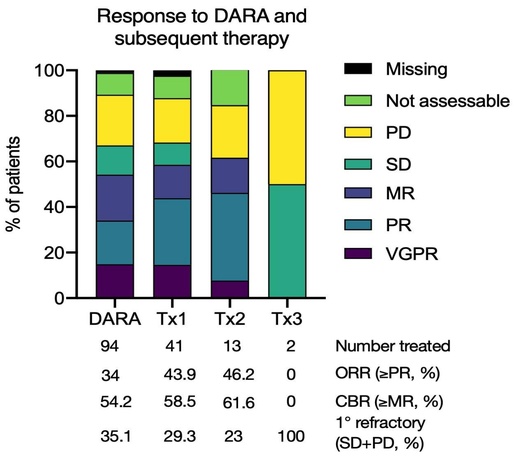
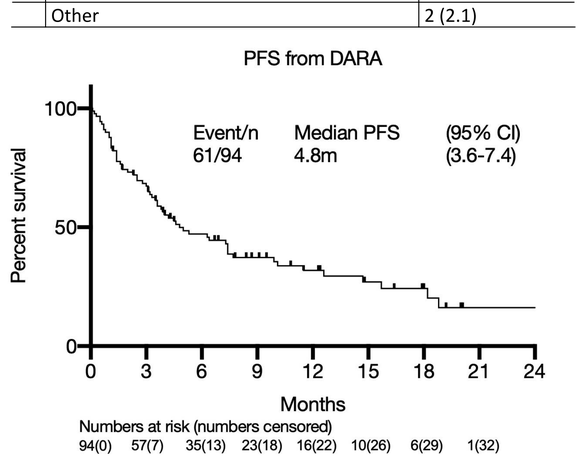
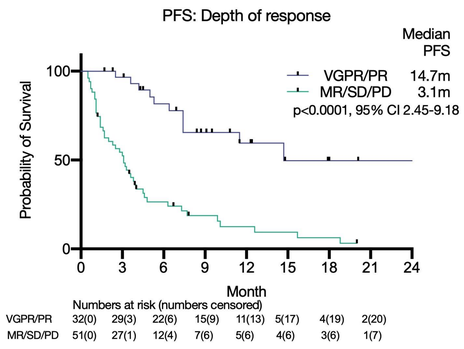


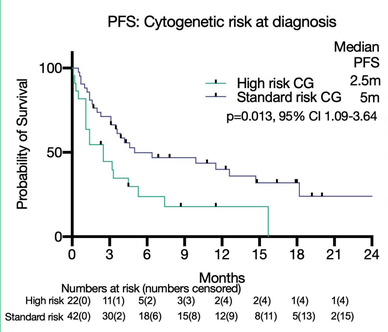
Figure 2. Response and survival on DARA monotherapy

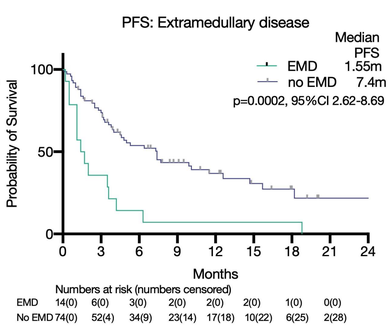
Outcomes on DARA monotherapy	Total (n=94)
Median number of DARA cycles received	5 (1-36)
Median follow-up (IQR)	13.6 m (8.4-18.5)
Median progression-free survival (PFS)(IQR)	4.8 m (1.7-15.7)
Median overall survival (IQR)	23.7 m (8.7-NR)
Median time to treatment discontinuation (IQR)	5.7 m (2.5-14.3)
Median time to next treatment (IQR)	8.3 m (3.4-20.0)
Number died (%)	30 (31.9)
Progressive disease	26 (27.7)
Sepsis	4 (4.2)
Other	2 (2.1)

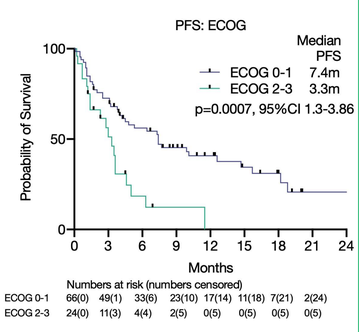










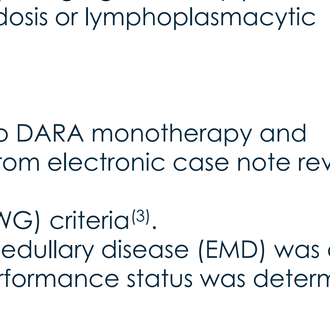


Adverse Events with DARA monotherapy	Total (n=59)
AE reported (n(%))	55 (93%)
Median number of AEs per pt (range)	4 (0-11)
Median grade of AEs (range)	1 (1-3)
Cessation of DARA	0
Infusion reactions (median grade)	1 (2)
Bronchospasm reactions (median grade)	1 (1)
Common reported AEs (n,(%, median grade))	
Fatigue	45 (76%, 1)
Pain	21 (36%, 1)
Infection	19 (32%, 1)
Peripheral neuropathy	18 (31%, 1)
Breathlessness	17 (29%, 1)
Constipation	16 (27%, 1)
Nausea	15 (25%, 1)
Anorexia	13 (22%, 1)
Hearing loss	11 (19%, 1)
Glucose intolerance	1 (2%, 3)

Figure 3. Subsequent therapies and outcomes

Subsequent therapy	
Number who stopped DARA	64 (100%)
Number who received subsequent Tx	41 (64.1%)
Number receiving 1st subsequent line	41
Median number of cycles (range)	4 (1-24)
Number receiving 2nd subsequent line	13
Median number of cycles (range)	4 (1-21)
Number receiving 3rd subsequent line	2
Median number of cycles (range)	2.5 (1-4)

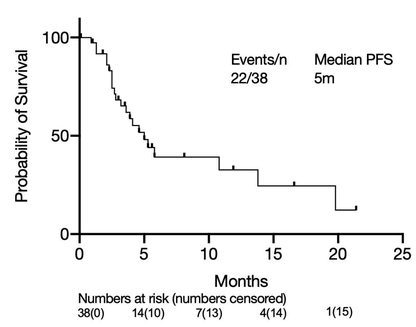
Regime at 1st subsequent treatment



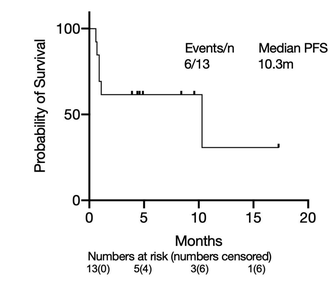
Pomalidomide-containing	30 (73.2%)
Protease inhibitor-containing	3 (7.3%)
Chemotherapy	2 (4.9%)
Supportive (including CTD, CD)	2 (4.9%)
CAR-T trial	1 (2.4%)
Antibody drug conjugate trial	2 (4.9%)
Melphalan autograft	1 (2.4%)

Total=41

PFS 1st subsequent therapy



PFS 2nd subsequent therapy



Conclusions

- DARA monotherapy shows clinical benefit in a heavily pre-treated population, the majority of whom are IMiD-refractory, with an overall response rate (≥ PR) of 34% and a clinical benefit rate (≥MR) of 54.2%.
- Response rates align with those reported in clinical trials. Combined analysis of GEN501 and SIRIUS demonstrated an ORR of 31.1% and CBR of 37.2%[(6)].
- Adverse event monitoring was available from 1 site, which demonstrated good tolerability and no need to halt treatment due to toxicity. This is especially important in this frail, heavily pre-treated population.
- PFS is comparable to the combined analysis of GEN501 and SIRIUS: 4.8 months in our cohort, compared to 4 months, albeit with a shorter median follow up (13.6 months vs 20.7 months).
- High risk CG, EMD and poor performance status prior to DARA-monotherapy was associated with a poorer PFS, while a deeper response to DARA conferred an improved PFS.
- Most patients who relapse can receive further effective therapies (the majority of whom receive a pomalidomide-containing regime), with the median PFS for the next line of therapy being 5 months.

References

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Myeloma

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