Daratumamab in High Risk Relapse/Refractory Myeloma Patients; Effect of 1q21 Duplication and GEP70 Status

Mohan, MD[1], Niels Weinhold[1], Frits van Rhee, MD[1], Carolina Schinke, MD[1], Sharmilian Thanedrarajan, MD[1], Leo Rasche, MD[1], Jeffrey Sawyer, MD[1], Erming Tian, PhD[1], Faith Davies, MD[1], Gareth Morgan, MD[1], Maurizio Zangari, MD[1]

1UAMS Myeloma Institute, University of Arkansas for Medical Sciences, Little Rock, AR, USA.

BACKGROUND AND OBJECTIVES

In the last twenty years, the outcome of multiple myeloma (MM) has markedly improved. However MM remains an incurable cancer and patients with refractory disease to both immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs) have a dismal prognosis with a median overall survival (OS) of only 9 months.

Daratumumab is the first anti-CD38 monoclonal antibody (mAb) recently approved for the treatment of relapsed refractory multiple myeloma (RRMM) and is also active in high risk disease.

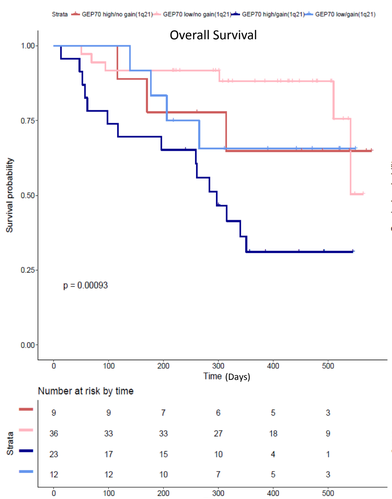
Gains of the long of chromosome 1 are one of the most common genetic abnormalities in myeloma. There is data to suggest that 1q gain or amplification may confer an adverse outcome in MM, however it is yet to be part of routine FISH in MM.

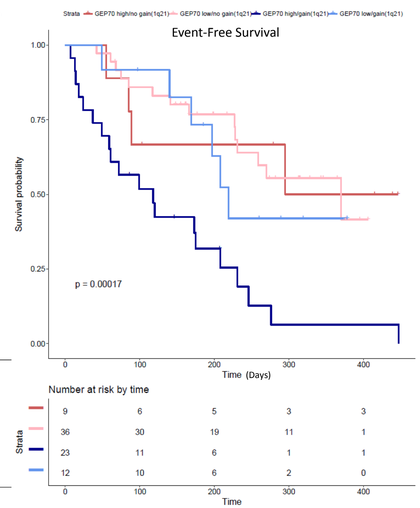
DESIGN AND METHODS

After IRB approval UAMS Myeloma data base was interrogated to identify patients with relapsed refractory multiple myeloma who received daratumumab either a monotherapy or in combination with other agents between November 2015 and December 2016. Patient were risk stratified to high and low risk MM using GEP studies on bone marrow specimens collected within one year from the time of relapse. Patients were further risk stratified based on interphase FISH on bone marrow specimens collected at the time of diagnosis or first visit to our institution. The patients were followed with serum Immunoglobin levels, Serum and urine M component, serum free light chains MRI T1, STIR, MRI DWIBS. PET CT and bone marrow examinations as indicated. Response rates were determined as per the IMWG criteria. Interphase FISH probes were generated for *CKS1B* (1q21), *AHCYL1* (1p13), *TP53* (17p13), and *ERBB2* (17q11). Myeloma cells were identified post hybridization by cIg Kappa or Lambda light chain. A 20% cutoff point was used for detection of significant abnormalities. Gene expression profiling was performed on the U133 plus 2.0 microarrays. High risk was defined by ≥ 0.66 GEP-70 score.

RESULTS

87 MM patients were identified with a median age of 61 years, 57% were male. Median time from diagnosis to daratumumab treatment was 5 years. All patients were previously exposed to proteasoame inhibitors IMiDs. Ninety-five percent progressed after autologous transplant. About 95% of the patient in this analysis received three or more lines of chemotherapy prior to starting daratumumab .Patients were treated using a dose of daratumumab at 16 mg/kg administered weekly for weeks 1 to 8; every two weeks for weeks 9 to 24; and then every four weeks until progression. In 35 patients interphase FISH at baseline identified 1q21 duplication and 32 were high risk by GEP 70 score. Seven patients had deletion of 17p13. Seventeen patients received daratumumab as single agent 70 in combination therapy. Daratumumab and immunomodulatory drug combination (mostly pomalidomide) was used in 80% of treated patients, in the remaining 20% daratumumab was used in combination with proteasome inhibitors. Fourteen percent of patients received daratumumab in combination with both IMID and PI drugs. The median event free survival in patients with high risk GEP 70 and 1q21 amplification was 120 days.





RESULTS

Baseline characteristics	Results
Median Age (Yrs)	61.5 (N=86)
Min Age (Yrs)	33.5 (N=86)
Max Age (Yrs)	85.9 (N=86)
Age >= 60 yr	46/86 (53.5%)
Age >= 65 yr	31/86 (36.0%)
Female	37/86 (43.0%)
IgA Isotype	15/81 (18.5%)
IgD Isotype	1/81 (1.2%)
IgG Isotype	46/81 (56.8%)
Nonsecretory	1/81 (1.2%)
LC Isotype	14/81 (17.3%)
at least 1 cycle of prior therapy	44/86 (51.2%)
Albumin < 3.5 g/dL	21/86 (24.4%)
B2M >= 3.5 mg/L	28/48 (58.3%)
B2M > 5.5 mg/L	15/48 (31.3%)
ISS Stage 1	13/47 (27.7%)
ISS Stage 2	19/47 (40.4%)
ISS Stage 3	15/47 (31.9%)
Creatinine >= 2 mg/dL	5/86 (5.8%)
CRP >= 8 mg/L	13/86 (15.1%)
Hb < 10 g/dL	30/86 (34.9%)
LDH >= 190 U/L	12/54 (22.2%)
Cytogenetic Abnormalities	21/43 (48.8%)
- Abnormal	21/43 (48.8%)
- Any CA13 (not including hypo)	5/43 (11.6%)
- Hypodiploidy	8/43 (18.6%)
- Hyperdiploidy	11/43 (25.6%)
Creatinine >= 2 mg/dL	5/86 (5.8%)
CRP >= 8 mg/L	13/86 (15.1%)
Hb < 10 g/dL	30/86 (34.9%)
LDH >= 190 U/L	12/54 (22.2%)
Excess Kappa Free Light Chains	54/81 (66.7%)
Excess Kappa Free Light Chains __ Labs	33/50 (66.0%)
Excess Lambda Free Light Chains	23/81 (28.4%)
Excess Lambda Free Light Chains __Labs	16/51 (31.4%)
Normal FLC Ratio	0/86 (0.0%)
GEP 70 High Risk	16/86 (18.6%)
GEP CD-1 subgroup	2/86 (2.3%)
GEP CD-2 subgroup	7/86 (8.1%)
GEP HY subgroup	10/86 (11.6%)
GEP LB subgroup	4/86 (4.7%)
GEP MF subgroup	3/86 (3.5%)
GEP MS subgroup	3/86 (3.5%)
GEP PR subgroup	4/86 (4.7%)
At least One Treat After Enrolled	84/85 (98.8%)
Tx1 Auto	71/86 (82.6%)
Tx2 Auto	52/86 (60.5%)

CONCLUSIONS

Patients with high risk relapse/refractory myeloma defined by interphase FISH 1q21 duplication and or GEP 70 high risk disease do not have a satisfactory response to daratumumab even in combination with IMID or PI drugs. This data suggest that in this high risk patient population the use of such treatment approach should be applied at early stage of disease.

Myeloma Institute
University of Arkansas for Medical Sciences

Authors declare no relevant conflicts of interest