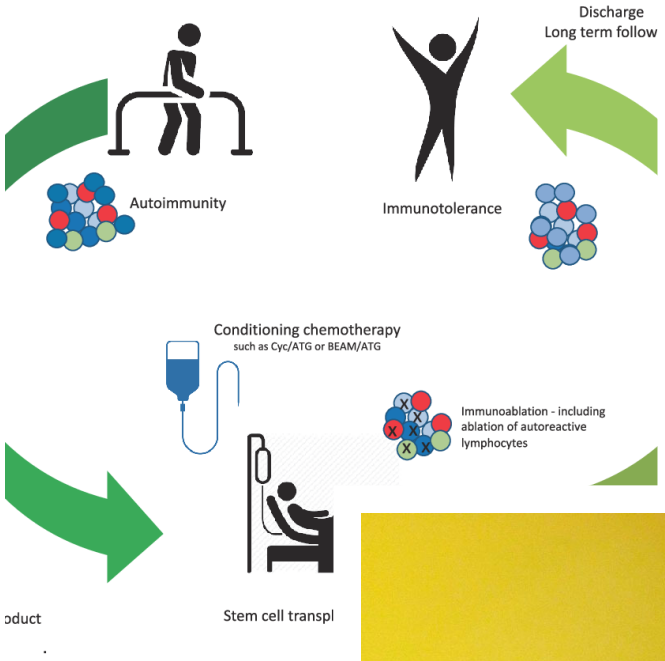
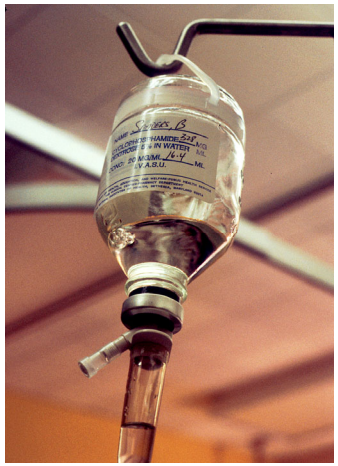
CLINICAL TRAIL FOR IXAZOMIB FOLLOWING ASCT IN MYELOMA PATIENTS

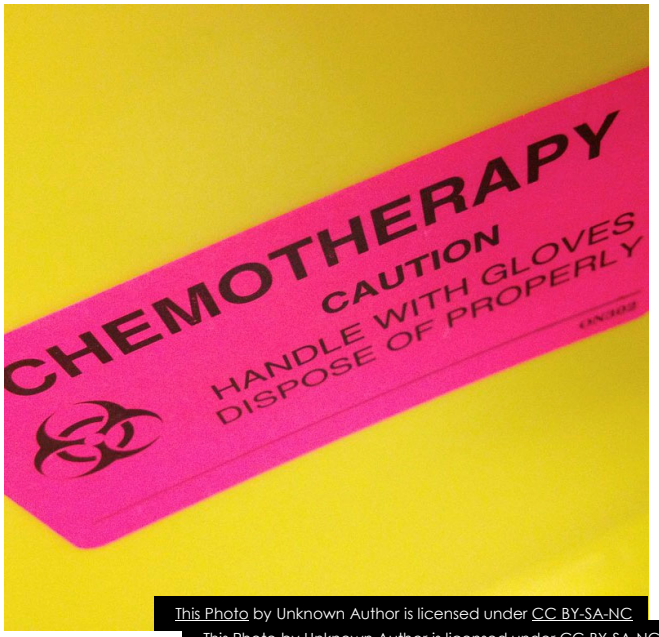
BY: Ms. Sample Student

AUTOLOGOUS STEM CELL TRANSPLANTATION FOR MULTIPLE MYELOMA

- BONE MARROW TRANSPLANT FOLLONG HIGH-DOSE CHEMOTHERAPY
- STANDARD CARE IN TREATING MYELOMA
- AUTOLOGOUS VS ALLOGENIC
- CAN PROVIDE SIGNIFICANT REMISSION AND EXTEND SURVIVAL
- RELAPSE IS ALMOST INEVITABLE







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MAINTENANCE THERAPY

- **PRIMARY PURPOSE:** TO PREVENT RELAPSE AND KEEP PATIENT IN REMISSION
- **TRAGETED THERAPY**: MAIN TYPE OF THERAPY USED TO TREAT MULTIPLE MYELOMA
  - LENALIDOMIDE
  - BORTEZOMIB
  - THALIDOMIDE
- MAY BE USED IN INDUCTION THERAPY BUT USUALLY USED AFTER STEM CELL TRANSPLANT
- THE AIM OF MANY CLINICAL TRIALS IS TO TEST TARGETED THERAPY POST ASCT TO DELAY DISEASE RETREATMENT WITH MINIMAL TOXICITY

TRIAL AND DATASET BACKGROUND

- ORAL IXAZOMIB MAINTENANCE FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION: A DOUBLE – BLIND, RANDOMISED, PLACEBO-CONTROLLED PHASE 3 TRIAL
- 2 YEARS, IN 167 CLINICAL SITES
- PRIMARY ENDPOINT: PROGRESSION FREE SURVIVAL
- SECONDARY ENDPOINTS: OVERALL SURVIVAL, BEST RESPONSE ACHIEVED PRIOR TO PROGRESSIVE DISEASE, TIME TO PROGRESSION, MAINTENANCE OF MRD-NEGATIVE STATUS, ADVERSE EFFECTS, SAFETY
    - MINIMAL RESIDUAL DISEASE-NEGATIVE: LESS THAN ONE MYELOMA CELL PER ONE MILLION BONE MARROW CELLS

TREATMENT: 2 GROUPS

IXAZOMIB

MAINTENANCE THERAPY

ONE CAPSULE WEEKLY FOR APPROX. 24 MONTHS

Median Time From Diagnosis To First Dose: 9.5 Months
After Data Cutoff Median Follow-up: 30.9 Months

PLACEBO

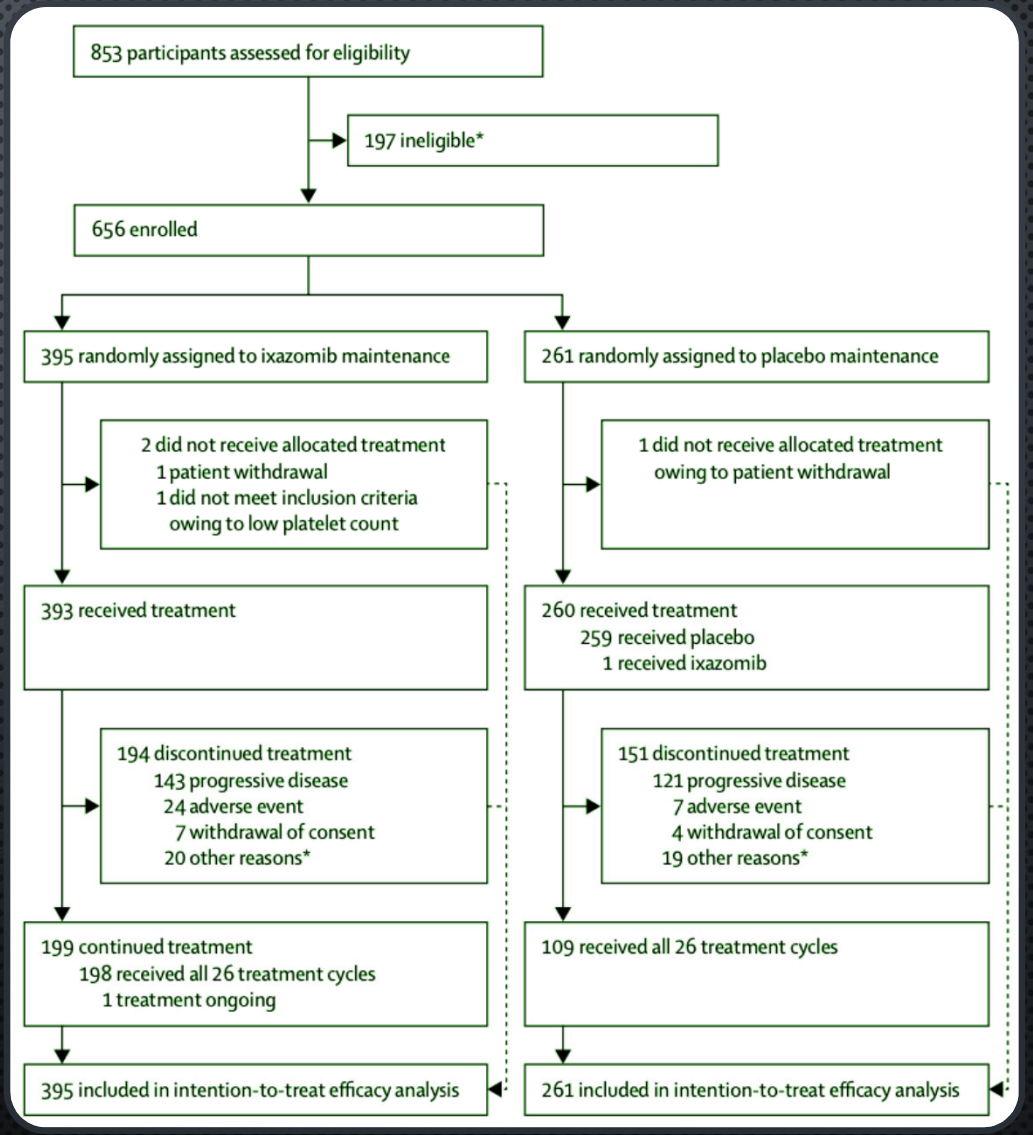
STANDARD MAINTENANCE THERAPY

SIMILAR CAPSULE TAKEN WEEKLY FOR APPROX. 24 MONTHS

Median Time From Diagnosis To First Dose: 9.4 Months
After Data Cutoff Median Follow-up: 31.3 Months

GROUP SIZE

- IXAZOMIB GROUP: N = 395
- PLACEBO GROUP: N = 261
- TOTAL PARTICIPANTS: N = 656
- MEDIAN AGE OF PARTICIPATES AT ENTRY WAS 52 YEARS



STRATIFIED RANDOMIZATION PROCEDURE

- PROGNOSTIC FACTORS: INDUCTION THERAPY, PRE-INDUCTION DISEASE STAGE, RESPONSE AFTER TRANSPLANTATION
- 3:2 RATIO DRUG THERAPY TO PLACEBO
- PATIENTS ARE RANDOMIZED SEQUENTIALLY
- PATIENTS, INVESTIGATORS, AND STUDY STAFF ARE BLINDED TO TREATMENT ALLOCATION

PROTEASOME INHIBITOR	IMMUNOMODULATORY DRUG	DISEASE STAGE	RESPONSE AT SCREENING
WITH	WITH	I	COMPLETE RESPONSE
WITHOUT	WITHOUT	II	GOOD RESPONSE
		III	PARTIAL RESPONSE

TRIAL PROCEDURE

PATIENT RECIEVES ORAL IXAZOMIB OR PLACEBO CAPSULE

ONCE WEEKLY FOR APPROXIMATELY 24 MONTHS
(OR UNTL PROGRESSIVE DISEASE)

STUDY VISITS IN 28 DAY CYCLES

RESPONSE IS MEASURED BY M-PROTEIN RESULTS, BONE MARROW DATA, IMAGING DATA

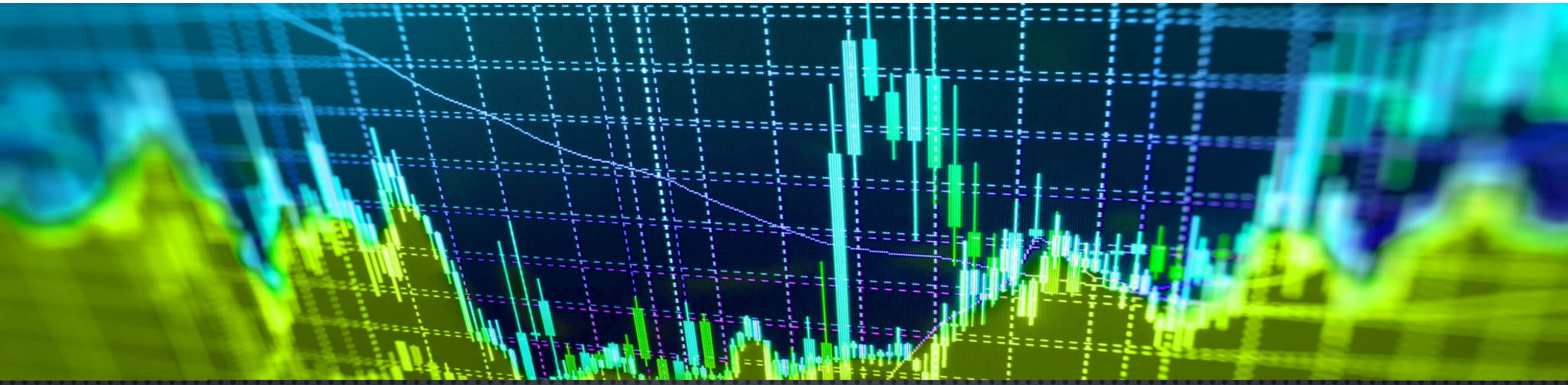
END-OF-TREATMENT VISIT AFTER 30 DAYS, FOLLOWED UNTIL DEATH

STATISTICAL METHODS

INTERIM DATA MONITORING

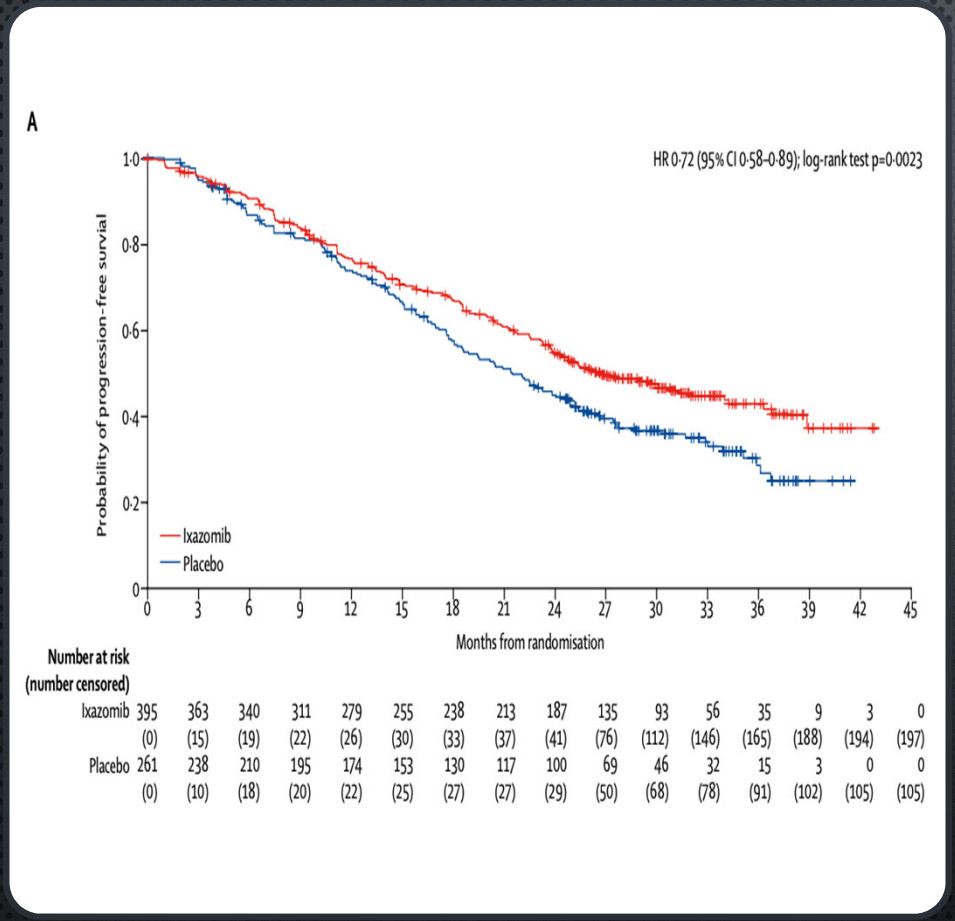
KAPLAN-MEIER ESTIMATION

LOG RANK TEST



INTERIM DATA MONITORING

- CLOSED SEQUENTIAL TESTING
- TWO INTERIM ANALYSES (PLUS ONE FINAL ANALYSIS) TO TEST OVERALL SURVIVAL
- FIRST INTERIM ANALYSIS: WHEN 50% OF PATIENS EXPERIENCE A PFS EVENT OR 2 YEARS AFTER THE LAST PATIENT WAS ENROLLED
- THE SECOND INTERIM ANALYSIS: WHEN 200 DEATHS HAVE OCCURED



COMPARISON OF TWO SURVIVAL FUNCTIONS: LOG-RANK TEST

$$H_0: S_1(t) = S_2(t) \; for \; all \; t$$

$$H_1: S_1(t) \neq S_2(t) \; for \; some \; t$$

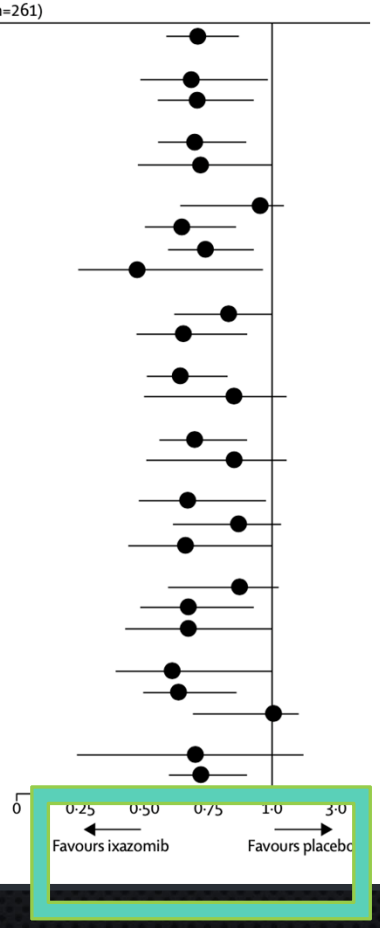
p-value: 0.0023
Tested at alpha = 0.05

KAPLAN-MEIER ANALYSIS OF PROGRESSION FREE SURVIVAL

BY PATIENT SUB-GROUPS

B

	Events/patients	
	Ixazomib (n=395)	Placebo (n=261)
All subjects (n=656)	**198/395**	**156/261**
Pre-induction ISS stage (local)		
I (n=242)*	68/146	56/96
II or III (n=414)	130/249	100/165
Response after transplant		
Complete or very good partial (n=509)	142/305	118/204
Partial (n=147)*	56/90	38/57
Induction regimen		
Immunomodulatory drug and proteasome inhibitor (n=196)	61/118	41/78
Proteasome inhibitor without immunomodulatory drug (n=389)	120/234	97/155
Proteasome inhibitor exposed (n=585)	181/352	138/233
Immunomodulatory drug without proteasome inhibitor (n=71)	17/43	18/28
Age		
<60 years (n=356)	118/229	74/127
≥60 years and <75 years (n=300)	80/166	82/134
Race		
White (n=528)	148/315	126/213
Asian (n=95)	36/59	25/36
Region		
EMEA (n=518)	150/306	129/212
APAC (n=121)	44/76	26/45
Pre-induction ISS stage		
I (n=245)*	69/151	55/94
II (n=221)	76/129	55/92
III (n=190)	53/115	46/75
Response at study entry		
Complete (n=225)	56/132	47/93
Very good partial (n=294)	93/179	73/115
Partial (n=137)*	49/84	36/53
Cytogenetic risk		
High risk (n=115)	38/61	38/54
Corresponding standard risk (n=404)	118/252	90/152
Unclassifiable (n=137)	42/82	28/55
Renal function based on baseline creatinine clearance		
<60 mL/min (n=58)	14/38	10/20
≥60 mL/min (n=595)	184/355	146/240



- OBSERVED BENEFIT FOR PFS IN IXAZOMIB GROUP IN PATIENTS 60 YEARS OR OLDER
- BENEFIT IN PFS IN PATIENS WHO HAS ISS STAGE III BEFORE INDUCTION

	Ixazomib group (n=394)	Placebo group (n=259)
Treatment and follow-up		
Follow-up (months)	30·9 (27·1–35·6)	31·3 (27·4–35·7)
Number of treatment cycles	25 (13–26)	22 (12–26)
Dose escalated to 4 mg at cycle 5	317/368 (86%)	222/242 (92%)
Duration of treatment at a dose of 4 mg (months)	15·2 (4·9–19·6)	16·6 (8·3–19·4)
Adverse events		
Any adverse event	382 (97%)	241 (93%)
Any drug-related adverse event	307 (78%)	149 (58%)
Any grade ≥3 adverse event	166 (42%)	67 (26%)
Any drug-related grade ≥3 adverse event	73 (19%)	13 (5%)
Any serious adverse event	108 (27%)	51 (20%)
Adverse event resulting in discontinuation of the study drug	28 (7%)	12 (5%)
Adverse event resulting in dose reduction of the study drug	73 (19%)	13 (5%)
Death during the treatment period*	1 (<1%)	0

Data are n (%) or median (IQR). *Death during the treatment period was recorded through 30 days after receiving the last dose of study drug.

Table 3: **Overall safety profile in the safety population**

ADVERSE EFFECTS

- HAEMATOLOGICAL: NEUTROPENIA, THROMBOCYTOPENIA, ANEMIA
- NON- HAEMATOLOGICAL: INFECTION, GASTROINTESTINAL DISORDERS, RASH

	Ixazomib group (n=394)			Placebo group (
	Any grade	Grade 3	Grade 4	Any grade
Common haematological adverse events of any cause				
Neutropenia*	36 (9%)	17 (4%)	3 (1%)	20 (8%)
Thrombocytopenia*	53 (13%)	14 (4%)	5 (1%)	8 (3%)
Anaemia	29 (7%)	4 (1%)	0	10 (4%)
Common non-haematological adverse events of any cause				
Infections and infestations (MedDRA SOC)†	292 (74%)	55 (14%)	3 (1%)	166 (64%)
Upper respiratory tract infection	101 (26%)	2 (1%)	0	54 (21%)
Viral upper respiratory tract infection	94 (24%)	0	0	69 (27%)
Pneumonia†	40 (10%)	23 (6%)	1 (<1%)	21 (8%)
Gastrointestinal disorders (MedDRA SOC)	270 (69%)	25 (6%)	0	124 (48%)
Nausea	154 (39%)	1 (<1%)	0	40 (15%)
Diarrhoea	137 (35%)	10 (3%)	0	61 (24%)
Vomiting	106 (27%)	6 (2%)	0	28 (11%)
Rash*	120 (30%)	7 (2%)	0	57 (22%)
Cough	87 (22%)	0	0	55 (21%)
Arthralgia	86 (22%)	3 (1%)	0	30 (12%)
Pyrexia	84 (21%)	1 (<1%)	0	38 (15%)
Fatigue	79 (20%)	5 (1%)	0	43 (17%)
Back pain	77 (20%)	5 (1%)	0	49 (19%)
Peripheral neuropathy*	73 (19%)	1 (<1%)	0	39 (15%)
Headache	43 (11%)	0	0	23 (9%)
Influenza	42 (11%)	3 (1%)	0	30 (12%)
Other adverse events of clinical interest				
Acute renal failure	11 (3%)	1 (<1%)	0	8 (3%)
Cardiac arrhythmias	19 (5%)	7 (2%)	0	7 (3%)
Liver impairment	24 (6%)	9 (2%)	0	11 (4%)
Hypotension or orthostatic hypotension	4 (1%)	1 (<1%)	0	1 (<1%)
New primary malignant tumour‡	12 (3%)	..	..	8 (3%)

RESULTS

- PRIMARY ENDPOINT: PFS

PROGRESSION FREE SURVIVAL (PFS)

28% REDUCTION IN RISK OF PROGRESSION OR DEATH IN TREATMENT GROUP VS. PLACEBO GROUP

PATIENTS WITH HIGH CYTOGENETIC RISK

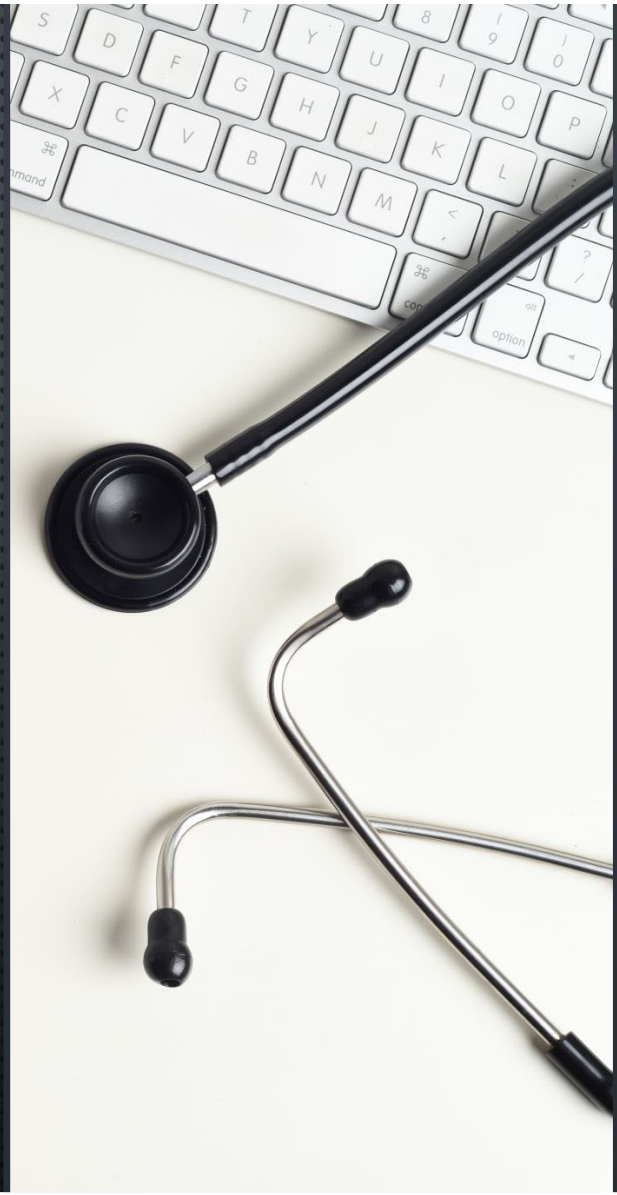
46% OF PATIENTS ACHIEVED PFS VS. 24% IN THE PLACEBO GROUP

IMPROVED RESPONSE DURING MAINTENANCE

46% WITH GOOD OR PARTIAL RESPONSE IN TREATMENT GROUP VS. 32% IN PLACEBO GROUP

MINIMAL RESIDUAL DISEASE (MRD)

12% OF TREATMENT PATIENTS CONVERTED TO MRD-NEGATIVE STATUS VS. 7% IN PLACEBO GROUP



RESULTS CONT.

QUALITY-OF-LIFE ASSESMENT: NO CHANGE

NO INCREASE IN SECOND PRIMARY MALIGNANCIES

PFS IMPROVEMENT IN IXAZOMIB THERAPY PATIENTS

- PROTEASOME INHIBITOR-NAÏVE (P-VALUE: 0.038)
- PROTEASOME INHIBITOR-EXPOSED (P-VALUE: 0.011)

TIME TO PROGRESSION:

- MEDIAN TIME 26.6 MONTHS IN TREATMENT GROUP
- MEDIAN TIME 21.4 MONTHS IN CONTROL GROUP

CONCLUSION

Overall, the treatment was effective and well tolerated with minimal increase in adverse events and low rates of discontinuation. The study provides a lot of additional support for the value of maintenance therapy in multiple myeloma and confirms the efficacy of a fixed duration of Ixazomib in this disease and has a lot of potential in the direction of myeloma treatment and maintenance.

THANK YOU!