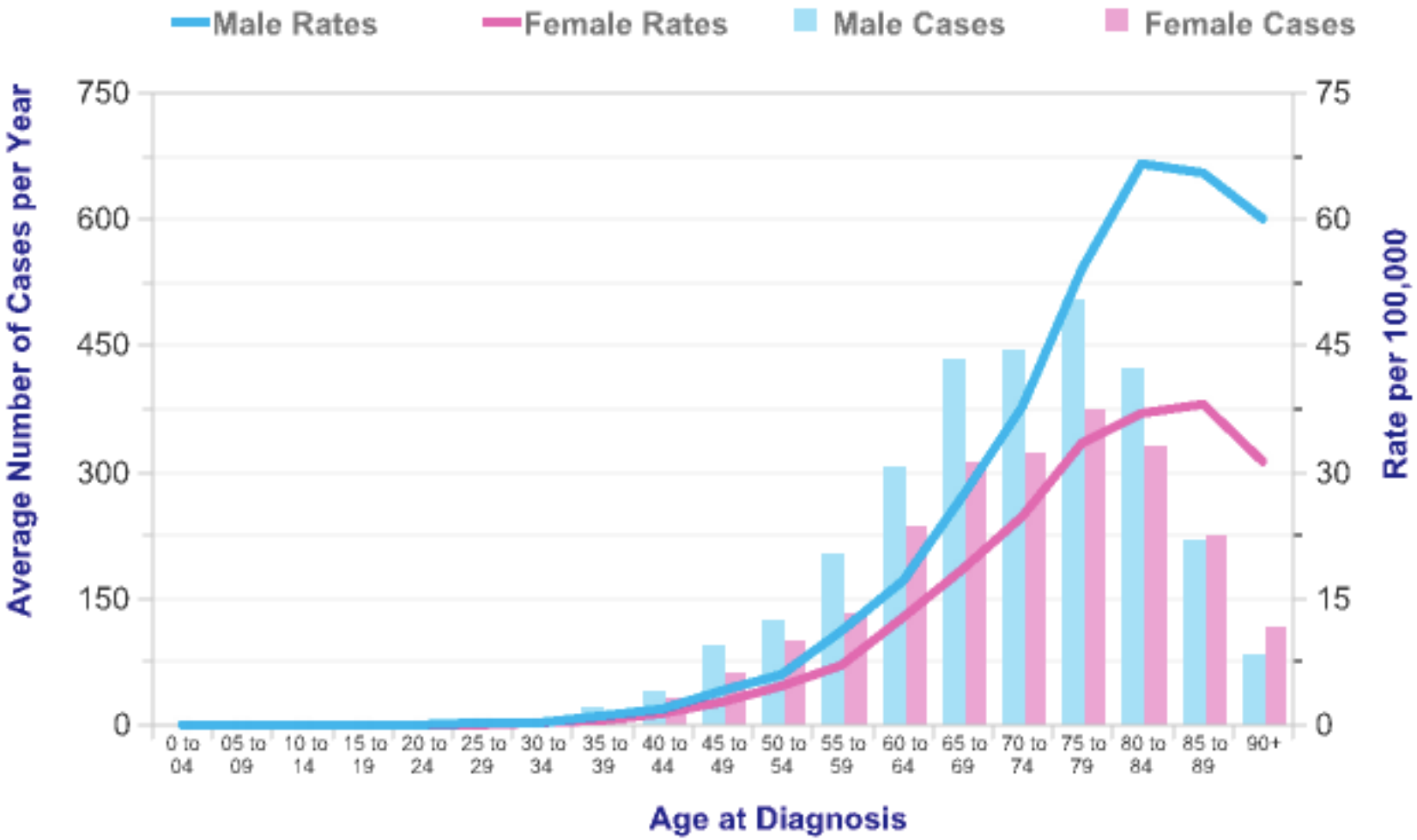
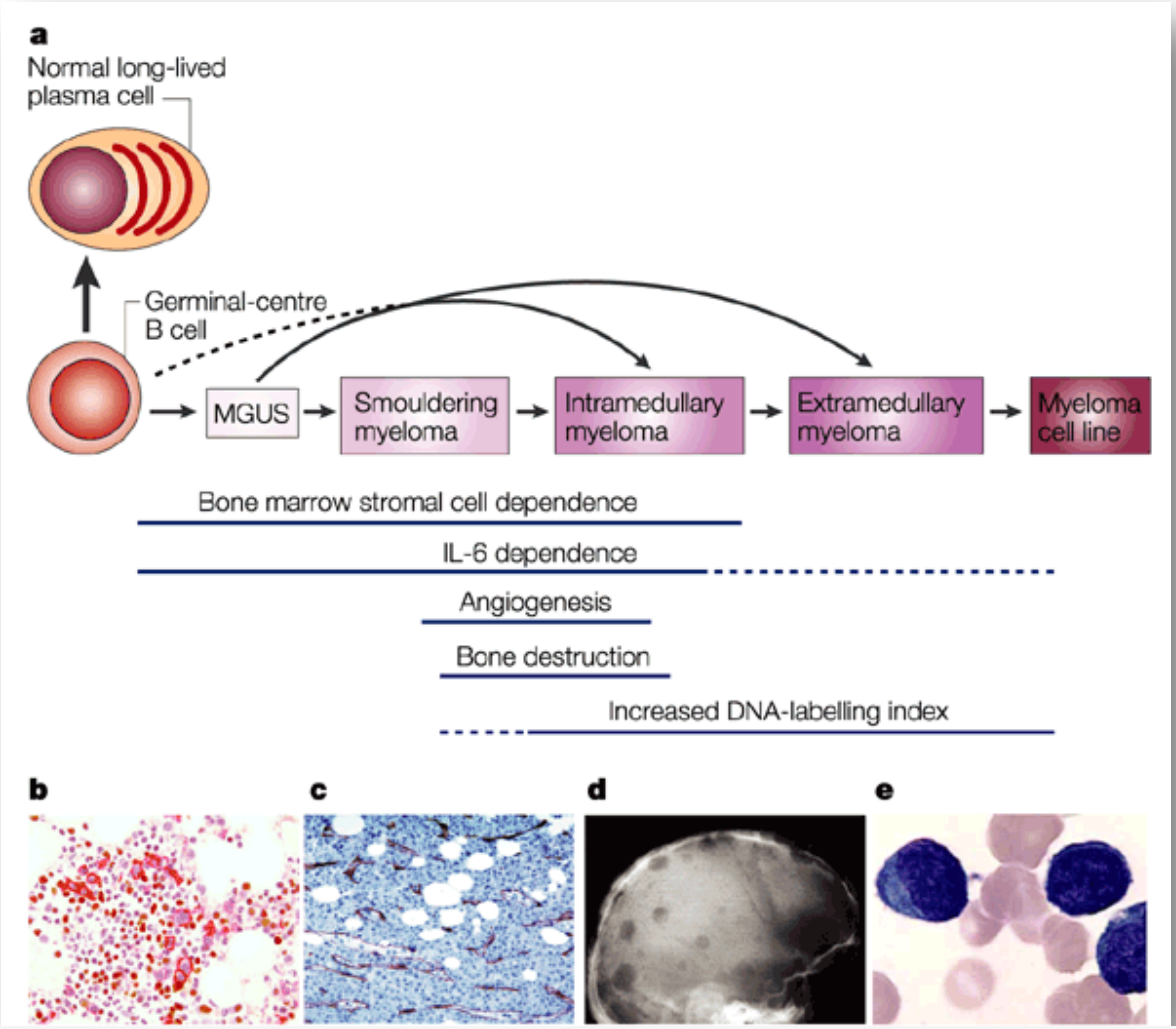
Treatment of Multiple Myeloma Lymphoma Tumor Board
June 24, 2016

Incidence of multiple myeloma by age and gender - UK



http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence



a | Multiple myeloma arises from a normal germinal-centre B cell. At least 30–50% of malignant multiple myeloma seems to arise from the benign plasma-cell neoplasm monoclonal gammopathy of undetermined significance (MGUS)[4]. It does not always pass through a period of smouldering myeloma. Initially, multiple myeloma is confined to the bone marrow (intramedullary), but with time the tumour can acquire the ability to grow in extramedullary locations (such as blood, pleural fluid and skin). Some of these extramedullary multiple myelomas can establish immortalized cell lines *in vitro*. The transition of MGUS to intramedullary multiple myeloma is manifested by increased numbers of multiple myeloma cells at multiple foci, and also associated angiogenesis and osteolytic bone destruction. **b** | The low proliferative index in a patient with MGUS. Bright red surface staining for syndecan identifies the plasma cells (~10%), none of which stain for the brown nuclear proliferation marker Ki67. **c** | A bone-marrow biopsy stained for CD34, identifying the endothelial cells, and emphasizing the increased vascularity in multiple myeloma. **d** | A skull X-ray shows the classic 'punched-out' lytic bone lesions. Although the skull lesions are asymptomatic, extensive vertebral involvement causes compression fractures, resulting in pain and loss of height (5 cm on average by the time of diagnosis). **e** | A peripheral blood smear identifies circulating plasma cells in a patient with plasma-cell leukaemia.

Multiple Myeloma – Differential Diagnosis

Malignant neoplasm that is primarily observed in older adults

- Differential diagnosis:
  - Monoclonal gammopathy of undetermined significance
  - Asymptomatic (smoldering) MM
  - Solitary plasmacytoma
  - Other plasma cell diseases based on the IMWG criteria (Table 1)

Diagnostic Criteria

Table 1.

Diagnostic Criteria for Plasma Cell Diseases

Diagnosis	Diagnostic Criteria
MGUS	All three criteria must be met:
	Serum monoclonal protein (IgG or IgA) < 3 g/100 mL
	Clonal bone marrow plasma cells < 10%
	Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
Smoldering (asymptomatic) MM	Both criteria must be met:
	Serum monoclonal protein (IgG or IgA) ≥ 3 g/100 mL and/or clonal bone marrow plasma cells ≥ 10%
	Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
MM (symptomatic)	All three criteria must be met:
	Clonal bone marrow plasma cells ≥ 10%*
	Presence of serum and/or urinary monoclonal protein (except in patients with true nonsecretory MM)
	Evidence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder, specifically:
	Hypercalcemia: serum calcium ≥ 11.5 mg/100 mL
	Renal insufficiency: serum creatinine > 1.73 mmol/L
	Anemia: normochromic, normocytic with hemoglobin value > 2 g/100 mL below lower limit of normal or hemoglobin value < 10 g/100 mL
	Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures
Solitary plasmacytoma	All four criteria must be met:
	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells
	Normal bone marrow with no evidence of clonal plasma cells
	Normal skeletal survey and MRI of spine and pelvis (except for primary solitary lesion)
	Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
Other plasma-cell diseases	Waldenstrom's macroglobulinemia
	Systemic AL amyloidosis
	Monoclonal Ig deposition disease
	POEMS syndrome

Diagnostic Evaluation

Diagnostic Work-Up for Patients With MM

Work-Up	Description	General Practice	Clinical Trial
First-level investigations to make diagnosis			
History and physical examination		Always	Always
Blood and urine	Complete blood count and differential; chemistry, including creatinine and calcium; serum protein electrophoresis and immunofixation, quantification of immunoglobulin; 24-hour urine collection for proteinuria, electrophoresis, and immunofixation	Always	Always
	Serum free light chains	For oligo and nonsecretory MM and light chain only	Always
Bone marrow	Aspirate and trephine biopsy with plasma cells phenotyping	Always	Always
Imaging	Skeletal survey	Always	Always
Second-level investigations to assess prognosis			
Blood	Albumin, β_2-microglobulin, LDH	Always	Always
	Serum free light chains	Not indicated	Preferred
Cytogenetic	Metaphase karyotype	Preferred	Always
FISH	t(4;14), t(11;14), t(14;16), t(14;20), chromosome 13 deletion, 17p13 deletion, and chromosome 1 abnormalities	Preferred	Always
Third-level investigations required before starting therapy or enrollment onto clinical trials			
Performance status	Karnofsky performance status and WHO scale	Always	Always
Patient status	Assessment of comorbidity, frailty, and disability (cumulative illness rating scale or Charlson score; ADL and IADL score)	Preferred	Always
Organ function	Cardiac, pulmonary, hepatic, GI, and renal function	Always	Always
Infectious disease	Hepatitis B and C, HIV	Always	Always
Additional pretreatment investigations			
Imaging	MRI PET/CT	In selected circumstances	Preferred
Prognostic	GEP	Not indicated	Preferred

Prognostic Factors

Table 2. Summary of cytogenetic risk features

	High-risk	Standard-risk
Cytogenetic abnormality	FISH: t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q) Non-hyperdiploid karyotype Karyotype del(13) GEP: high-risk signature	All others including: FISH: t(11;14), t(6;14)

- Abnormal κ/λ ratio at diagnosis seems to predict poor prognosis.
- Asymptomatic patients should be monitored every 1 to 3 months (grade C/IV).
- Initial therapy is indicated when CRAB symptoms occur (grade C/IV).
- Age is associated with increased frequency of comorbidities, frailty, and disability
  - Negative effect on outcome.

Table 1. Primary and secondary genetic events that can be identified by FISH

Primary Genetic Events			**Secondary Genetic Events**		
IgH translocation	**Gene(s)**	**Frequency (%)**	**Deletion**	**Gene(s)**	**Frequency (%)**
t(4;14)	*FGFR3/MMSET*	15	1p	*CDKN2C, FAF1, FAM46C*	30
t(6;14)	*CCND3*	4	6q		33
t(11;14)	*CCND1*	20	8p		25
t(14;16)	*MAF*	4	13	*RB1,, DIS3*	44
t(14;20)	*MAFB*	1	11q	*BIRC2/BIRC3*	7
			14q	*TRAF3*	38
			16q	*WWOX, CYLD*	35
			17p	*TP53*	7
Hyperdiploidy			**Gain**		
Trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, 21	NA	50	1q	*CKS1B, ANP32E*	40

Genes involved in common myeloma genetic aberrations

TABLE 1: Oncogenes involved in multiple myeloma, and their locations

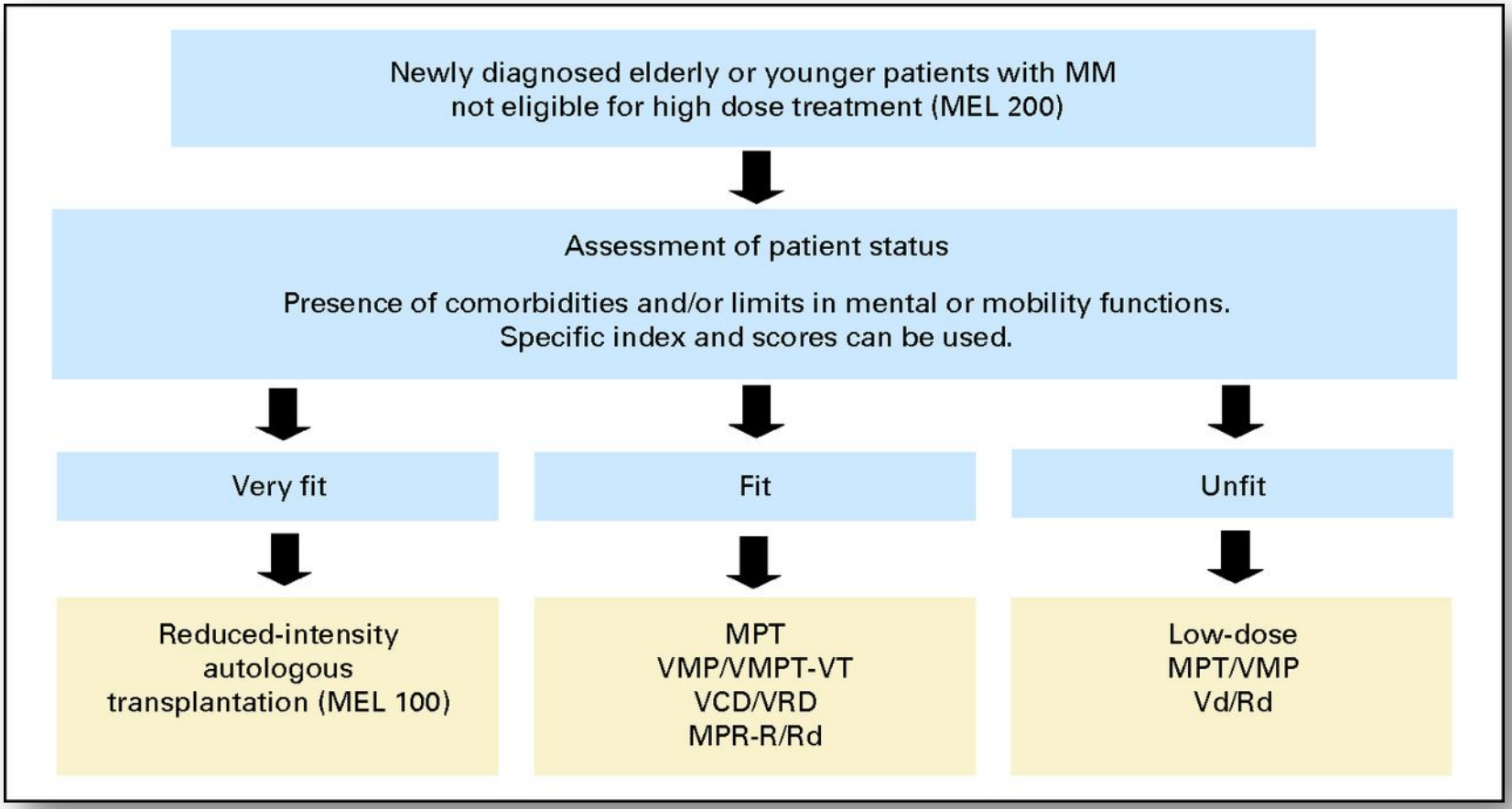
Locus	Oncogene	Incidence
11q13	*CCND1*	15%–20%
6p21	*CCND3*	5%
4p16.3	*FGFR3* and *WHSC1*	12%
16q23	*MAF*	5%–10%
8q24	*MYC*	< 10%
6p25	*MUM1/IRF4*	5%
20q11	*MAFB*	5%
1q21-34	*BCL9, IL6R, MCL1*	Frequent

Table 3. Survival of MM patients with high-risk FISH compared with those without high-risk FISH (Adapted from Bergsagel et al[58])

FISH	Np/Na	End point	Therapy	Present	Absent	Comment	Ref
Conventional Therapy							
t(4;14)	42/290	3-y OS	VBMCP	24%	64%	E9486	13
	100/616	3-y OS	VAD + ASCT x 2	55%	80%	IFM-99	25
	98/414	3-y OS	VAD + ASCT x ½	40%	72%	IFM-2005	68
del17p	37/308	3-y OS	VBMCP	32%	68%	E9486	13
	58/474	3-y OS	VAD + ASCT x 2	50%	78%	IFM-99	25
	119/393	3-y OS	VAD + ASCT x 1	49%	82%	IFM-2005	68
Unfavorable FISH	141/166	3-y OS	CVAD + ASCT x 1	58%	81%	MRC IX intensive	62
	90/125	3-y OS	MP	26%	48%	MRC IX non-intensive	61
	98/129	3-y OS	Placebo maintenance	69%	72%	MRC IX maintenance	39
	18/111	3-y OS	VBMCP/VBAD +Bz x 2 + ASCT x 1	48%	84%	GEM2005 < 65	63
Thalidomide							
t(4;14)	57/181	3-y PFS	TD + ASCT x 2 + TD	20%	48%	GIMEMA	102
	26/156	3-y OS	VAD + ASCT x 1 + Thal maintenance	44%	79%	HOVON65/GMMG-HD4	29
del17p	21/161	3-y OS	VAD + ASCT x 1 + Thal maintenance	17%	79%	HOVON65/GMMG-HD4	29
Unfavorable FISH	43/302	5-y OS	Thal induction, consolidation, maintenance	56%	72%	Total Therapy 2	18
	152/167	3-y OS	CTD + ASCT x 1	59%	82%	MRC IX intensive	62
	96/129	3-y OS	CTDa	58%	78%	MRX IX non-intensive	61
	99/126	3-y OS	Thalidomide maintenance	45%	76%	MRX IX maintenance	39
	17/110	3-y OS	TD + ASCT x 1	56%	86%	GEM2005 < 65	63
Lenalidomide							
t(4;14)	28/102	Median OS	RD in RRMM	18 m	23 m	MM-016	103
	26/158	Median OS	RD in RRMM	9 m	15 m	IFM	83
	152/355	Median PFS	Lenalidomide maintenance	27 m	42 m	IFM-2005	68
del17p	12/118	Median OS	RD in RRMM	4 m	23 m	MM-016	103
	6.6%	Median PFS	Lenalidomide maintenance	29 m	42 m	IFM-2005	68
Unfavorable FISH	16/84	3-y OS	RD	77%	86%	Mayo Clinic	76
	21/105	2-y OS	RD	76%	91%	E4A03	104
Bortezomib							
t(4;14)	106/401	4-y OS	VD + ASCT x 1	63%	85%	IFM-2005	68
	53/183	3-y PFS	VTD + ASCT x 2 + BzTD	65%	61%	GIMEMA	102
	24/148	3-y OS	VAD + ASCT x 1 + Bz	66%	82%	HOVON65/GMMG-HD4	29
del17p	54/453	4-y OS	VD + ASCT x 1	50%	79%	IFM-2005	68
	16/158	3-y OS	VAD + ASCT x 1 + Bz	69%	82%	HOVON65/GMMG-HD4	29
Unfavorable FISH	18/112	3-y OS	VTD + ASCT x 1	60%	88%	GEM2005 < 65	63
	44/188	3-y OS	VMP/BzTP, BzT/BzP	55%	73%	GEM2005 < 65	73
	28/140	3-y OS	VMP	56%	71%	VISTA	72

Treatment

Therapeutic approach should be tailored to patient age and performance status.



Antonio Palumbo et al. J Clin Oncol 2014;32:587-600

A selection of myeloma treatment regimens

Regimen	Schedule	CR (%)	PFS/EFS/TTP	OS
Induction regimens				
MPT	Melphalan: 4 mg/m^2 given orally on days 1-7 every 4 weeks for six cycles[31] or 0.25 mg/kg on days 1-4 every 6 weeks for 12 cycles[32]; prednisone: 40 mg/m^2 given orally on days 1-7 every 4 weeks for six cycles[31] or 2 mg/kg on days 1-4 every 6 weeks for 12 cycles[32]; thalidomide: 100 mg/day given orally continuously until progression or intolerance[31] or 200 mg/day continuously for 12 cycles of 6 weeks[32]	13-16	Median, 20.3 months[33]	Median, 39.3 months[33]
CTDa	Cyclophosphamide: 500 mg/wk for six to nine cycles every 3 weeks; thalidomide: 100 mg/day increased to 200 mg/day for six to nine cycles every 3 weeks; dexamethasone: 20 mg on days 1-4 and 15-18 for six to nine cycles every 3 weeks[34]	13	Median, 13 months	Median, 33 months
VMP	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11, 22, 25, 29, and 32 (cycles one to four) and days 1, 8, 22, and 29 (cycles five to nine) every 6 weeks for nine cycles; melphalan: 9 mg/m^2 given orally on days 1-4 every 6 weeks for nine cycles; prednisone: 60 mg/m^2 given orally on days 1-4 every 6 weeks for nine cycles[35]; as alternative, bortezomib: 1.3 mg/m^2 on days 1, 8, 15, and 22 every 6 weeks for nine cycles[36]	24-30	Median, 22-27 months	At 2 years, 85% to 87%
VMPT	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11, 22, 25, 29, and 32 (cycles one to four) and days 1, 8, 22, and 29 (cycles five to nine) every 6 weeks for nine cycles; melphalan: 9 mg/m^2 given orally on days 1-4 every 6 weeks for nine cycles; prednisone: 60 mg/m^2 given orally on days 1-4 every 6 weeks for nine cycles; thalidomide: 50 mg/day given orally continuously for nine cycles[36]	38	Median, 33 months	At 3 years, 86%[37]
VTP	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, 11, 22, 25, 29, and 32 (cycle one), every 6 weeks, and 1.3 mg/m^2 on days 1, 8, 15, and 22 every 5 weeks (cycles two to six); thalidomide: 100 mg/day given orally for six cycles; prednisone: 60 mg/m^2 given orally on days 1-4 every 6 weeks for six cycles[38]	28	Median, 31 months[*]	At 3 years, 70%[*]
VCD	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, and 11 every 4 weeks for four to 12 cycles; cyclophosphamide: 300 mg/m^2 given orally on days 1, 8, 15, and 22 every 4 weeks for four to 12 cycles; dexamethasone: 40 mg/day given orally on days 1-4, 9-12, and 17-20 every 4 weeks for four to 12 cycles[39]; as alternative, bortezomib: 1.5 mg/m^2 given as bolus intravenous infusion on days 1, 8, 15, and 22[40]	39[†]	—	—

Treatment regimens - continued

	VRd	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, and 11 every 3 weeks for eight cycles; lenalidomide: 25 mg given orally on days 1-14 every 3 weeks for eight cycles; dexamethasone: 20 mg given orally on days 1, 2, 4, 5, 8, 9, 11, and 12 every 3 weeks for eight cycles[41]	37	At 18 months, 75%‡	At 18 months, 97%‡
	Rd	Lenalidomide: 25 mg given orally on days 1-21 every 4 weeks for four cycles§; dexamethasone: 40 mg given orally on days 1, 8, 15, and 22 every 4 weeks for four cycles[42]	4	Median, 25 months	At 2 years, 87%
MPR		Melphalan: 0.18 mg/kg given orally on days 1-4 every 4 weeks for nine cycles; prednisone: 2 mg/kg given orally on days 1-4 every 4 weeks for nine cycles; lenalidomide: 10 mg given orally on days 1-21 every 4 weeks for nine cycles[43]	3	Median, 14 months	Not reached
Maintenance regimens					
	T‖	Thalidomide: 50 mg given orally, increased to 100 mg if tolerated after 4 weeks, until progression[44]	—	Median, 11 months	Median, 38 months
	R	Lenalidomide: 10 mg given orally on days 1-21 every 4 weeks until progression[43]	—	Median, 26 months	—
	VT	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion every 2 weeks for 2 years or until progression; thalidomide: 50 mg given orally for 2 years or until progression[36,37]	45	Median, 27 months	Median, not reached
Salvage regimens					
	V	Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, and 11 every 3 weeks for eight cycles and on days 1, 8, 15, and 22 every 5 weeks for following three cycles[45]	6	Median, 6 months	At 1 year, 80%
V-Peg		Bortezomib: 1.3 mg/m^2 given as bolus intravenous infusion on days 1, 4, 8, and 11 every 3 weeks; peg: 30 mg/m^2 on day 4 of each cycle for eight cycles or until progression[46]	4	Median, 9 months	At 15 months, 76%
	RD	Lenalidomide: 25 mg given orally on days 1-21; D: 40 mg on days 1-4, 9-12, and 17-20 every 4 weeks for four cycles and on days 1-4 for following cycles until progression[47]	14	Median, 11 months	Median, 29.6 months
Carfilzomib		Carfilzomib: 20 mg/m^2 given as 2-10 minute intravenous infusion on days 1, 2, 8, 9, 15, and 16 every 4 weeks (cycle one) and 27 mg/m^2 on days 1,2, 8, 9, 15, and 16 every 4 weeks for up to 12 cycles[48]	0.4	Median, 3.7 months	Median, 15.6 months

Treatment regimens for high-risk disease

Table 4. Survival of high-risk genetic subgroups in randomized controlled clinical trials of newly diagnosed MM: effect of treatment modalities and novel drugs (Adapted from Bergsagel et al[58])

FISH	N1/N2	End point	Arm 1	Arm 2	Arm 1,%	Arm 2,%	Comment	Ref
t(4;14)	26/24	3-y OS	PAD/ASCT/Thal*	VAD/ASCT/Bz*	44	66	HOVON65/GMMG- HD4	15
	98/106	4-y OS	VAD	VD	32	63*	IFM-2005	68
	21/23	2-y OS	Thal*	Placebo*	67	87	TT2	18
	21/29	2-y OS	Thalidomide-TT2	Bortezomib TT3	67	97*	TT2 vs TT3	70
Del(17p)	21/16	3-y OS	VAD/ASCT/ Thalidomide	PAD/ASCT/ Borzezomib*	17	69*	HOVON65/GMMG-HD4	15
	119/54	4-y OS	VAD	V D	36	50	IFM-2005	68
Nonhyperdiploid	92	3-y OS	VTD	VMP	53	72*	PETHEMA	63
Unfavorable FISH	152/141	3-y OS	CTD	VAD-Cyclophosphamide	58	56	MRC IX intensive	62
	96/90	3-y OS	CTD	Placebo MP	34	26	MRC IX non-intensive	61
	99/98	3-y OS	Thalidomide	Placebo	45	69*	MRC IX maintenance	39

Maintenance Therapy

- Long-term maintenance therapy after autologous HCT is standard of care in resource-rich setting.
- Routine use of maintenance in transplantation-ineligible patients is not yet validated.
- Thalidomide is an option for standard-risk patients, although its long-term use is limited by the risk of peripheral neuropathy (grade A/Ib).
- Lenalidomide is well tolerated but associated with a higher risk of SPMs (grade A/Ib).
- Bortezomib can be an effective alternative, with lower risk of peripheral neuropathy than thalidomide (grade B/IIa.)

Treatment for Relapsed/Refractory and Unfit Patients

- Repeating same treatment should be considered after long-lasting remission (20-24 months).
- Alternative regimen is suggested for patients with shorter remission duration (9-12 months; grade C/IV).
- VD or bortezomib-pegylated liposomal doxorubicin and lenalidomide-dexamethasone are the treatments of choice (grade A/Ib).
- Unfit patients should receive reduced-dose MPT or VMP or two-drug combinations with bortezomib or lenalidomide and low-dose dexamethasone.
  - VD or RD; grade C/IV

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