Online supplementary material

Prevention and Management of Adverse Events of Novel Agents in Multiple Myeloma: A Consensus of the European Myeloma Network

Table S1. Novel agents EMA and/or FDA approved in multiple myeloma and overview of pivotal trials [as per 10/2017]

		NDMM – eligible for ASCT		NDMM – not eligible for ASCT	RRMM
		Induction	**Maintenance**	**Primary therapy**	**Salvage therapy**
IMiDs	Thalidomide[1, 2]	✓ **(EMA: age ≥65, MPT; FDA: TD)** IFM 99-06[3], ECOG E1A00[4]		✓ **(EMA: MPT; FDA: TD)** IFM 99-06[3], ECOG E1A00[4]	
	Lenalidomide[5, 6]	✓ **(FDA approval only; Rd)** ECOG E4A03[7]	✓ **(EMA: R mono; FDA: Rd)**	✓**(EMA: Rd, MPR-R; FDA: Rd)** MM-020[8], MM-015[9]	✓*** (Rd)** MM-009/MM-010[10-12]
	Pomalidomide[13, 14]				✓**** (Pom-D)** NIMBUS[15]
PIs	Bortezomib[16, 17]	✓ **(EMA: VD; VDT; FDA: VMP)** IFM-2005-01[18]	✓	✓ **(VMP)** VISTA[19]	✓ **(EMA: V mono, V-PLD; FDA: V mono, Vd)** APEX[20, 21], SUMMIT[22], MMY-2045[21], DOXIL-MMY-3001[21, 23], RETRIEVE[24]
	Carfilzomib[25, 26]				✓*** (KRd, Kd; K mono FDA approved only)** ASPIRE[27], ENDEAVOR[28], FOCUS[29], FX-171-003-A1[30]
	Ixazomib[31, 32]				✓*** (Ixa-Rd)** TOURMALINE-MM1[33]
HDACis	Panobinostat[34, 35]				✓**** (Pan-Vd)** PANORAMA-1[36], PANORAMA-2[37]
mABs	Elotuzumab[38, 39]				✓*** (Elo-Rd)** ELOQUENT-2[40-42]

	Daratumumab[43, 44]				✓ **(Dara mono; ** EMA; *** FDA)** SIRIUS[45], GEN501[46] ✓ **(Dara-Vd, Dara-Rd; * EMA; * FDA)** CASTOR[47], POLLUX[48] ✓ **(Dara-Pom-Dex; ** FDA)** EQUULEUS[49]

ASCT, autologous stem cell transplantation; d, dexamethasone; HDACis, histone deacetylase inhibitors; IMiDs, immunomodulatory agents; Ixa-Ixazomib; K, carfilzomib; M, melphalan; mABs, monoclonal antibodies; NDMM, newly diagnosed multiple myeloma; P, prednisone; PIs, proteasome inhibitors; PLD, pegylated liposomal doxorubicin; R, lenalidomide; RRMM, relapsed and/or refractory multiple myeloma; V, bortezomib, * at least 1 prior therapy; ** at least 2 prior therapies; *** at least 3 prior therapies; Sources: www.ema.europa.eu, www.accessdata.fda.gov

Table S2A. Immunomodulatory agents: Grade ≥3 adverse events reported in pivotal trials

IMiDs	Thalidomide		Lenalidomide			Pomalidomide
	MP-T[3]	TD[4]	Rd[7, 8, 10-12]	MPR†[9]	MPR-R†[9]	Pom-d[15]
Hematological disorders						
Anemia	14%		3-18%	27%	29%	33%
Neutropenia	48%		7-41%	100%	96%	48%
Febrile neutropenia			2%	7%	3%	10%
Thrombocytopenia	14%		2-15%	47%	51%	22%
Leukopenia			5-6%	27%	31%	9%
Lymphopenia			3-6%			
Infection	13%	2%	2-29%	10%	15%	34%
Herpes zoster	3%					
Pneumonia	7%	5%	8-12%			14%
Septicemia	3%					
Meningitis	2%					
Gastrointestinal disorders						
Nausea	1%	4%	1-3%			1%

IMiDs	**Thalidomide**		**Lenalidomide**			**Pomalidomide**
Constipation	10%	8%	2-3%			2%
Diarrhea			3-4%	3%	1%	1%
Musculoskeletal disorders and pain						
Non-neuropathic weakness			4-11%			
Muscle weakness		6%	6-7%			1%
Back pain			2-7%			7%
Bone pain			1-5%			7%
Mineral imbalances						
Hypokalemia			4-7%			
Hypercalcemia		8%				4%
Hyponatremia		4%				
Cardiac disorders	2%		6-12%	5%	5%	
Arrhythmia	2%					
Cardiac ischemia			<1-3%			
Atrial fibrillation or flutter			<1-3%			
Hypotension		4%				

IMiDs	Thalidomide		Lenalidomide			Pomalidomide
Others						
Peripheral neuropathy	6%	4% (sensory); 7% (motor)	<1%-2%			
Thrombosis or embolism	12%	20%	2-26%	1%	5%	
Fatigue	8%‡	15%	3-15%	5%	2%	5%
Asthenia			3-8%			3%
Hyperglycemia		15%	4-11%			
Rash		4%	6%	5%	5%	
Cataracts			3-6%			
Dyspnea		11%	3-6%			5%
Edema		6%				
Hypoxia		3%				
Seizure		3%				
Syncope		3%				

D, dexamethasone; IMiD, immunomodulatory agent; M, melphalan; n.r., not reported; P, prednisone; Pom, pomalidomide; R, lenalidomide; T, thalidomide

Note: Adverse events with a reported incidence >2% in the original publication are listed; if an adverse event was reported to have an incidence >2% in one given regimen, the incidence of that adverse event is listed for all regimens. †Induction phase only; ‡Is listed as combined event of somnolence/fatigue/dizziness in the original publication[3], but listed in the fatigue category in this table.

Table S2B. Proteasome inhibitors: Grade ≥3 adverse events reported in pivotal trials

PIs	Bortezomib				Carfilzomib			Ixazomib
	V mono[19-23]	Vd[18, 21, 24]	V-PLD[23]	KRd[50, 51]	K mono[29, 30]	Kd[28]	KRd[27]	IRd[33]
Hematological disorders								
Anemia	9-19%	4-5%	9%	13%	24-25%	14%		9%
Neutropenia	14- 40%	4-7%	29%	19%	8-11%			23%
Thrombocytopenia	16-37%	3-35%	22%	18%	24-39%	9%		19%
Leukopenia	23%			14%	3%			
Lymphopenia	19%			23%	23%			
Neurologic disorders								
Peripheral neuropathy	8-13%	7-18%		24%	1%	1%		2%
Neuralgia	8-9%		3%			<1%		
Infection	13-16%	9-17%						
Herpes zoster	3-13%							
Pneumonia	7%	6%			6-9%			
Upper respiratory tract infection					5%	2%	2%	<1%
Cardiac disorders	3%		2%					

PIs	Bortezomib				Carfilzomib			Ixazomib
Arrhythmia								5%
Hypertension					3%	9%	4.3%	2%
Cardiac failure					2%		4%	
Ischemic heart disease							3%	
Gastrointestinal disorders								
Nausea	<1-6%		2%		1-2%	1%		2%
Vomiting	1-8%		4%		<1%	1%		1%
Diarrhea	4-8%	7%	7%	8%	<1%	3%	4%	6%
Pain								
Back pain	3%					<1%		<1%
Bone pain	4%							
Pain in extremity	2-7%					<1%		
Mineral imbalances								
Hypokalemia	7%			9%			9%	
Hypercalcemia					4%			
Hypophosphatemia					6%			

PIs	Bortezomib				Carfilzomib			Ixazomib
Hyponatremia					8%			
Renal function								
Acute renal failure					3-10%		3%	
Renal impairment					2-7%			
Others								
Thrombosis or embolism	1%	2%		8%				2%
Fatigue	2-12%		6%	16%	8%	5%	8%	4%
Asthenia	3-6%		6%			3%		
Rash	<1-1%							7%
Dyspnea	4-5%				1-3%	5%	3%	
Myopathy				7%				
Hyperglycemia				7%				
Dehydration				3%				
Second primary malignancy				8%				

D, dexamethasone; I, ixazomib; K, carfilzomib; mono, monotherapy; PI, proteasome inhibitor; PLD, pegylated liposomal doxorubicin; R, lenalidomide; V, bortezomib

Note: Adverse events with a reported incidence >2% in the original publication are listed; if an adverse event was reported to have an incidence >2% in one given regimen, the incidence of that adverse event is listed for all regimens. In RETRIEVE[24], 28% of patients received bortezomib monotherapy (V mono) and 72% received a combination of bortezomib and dexamethasone (V-dex). For this study, adverse events were not reported separately for these treatment groups. Since the majority of patients received V-dex, adverse events for this study have been reported in the V-dex column. In SUMMIT[22], patients received bortezomib monotherapy; in those with suboptimal response, dexamethasone was added. Only bortezomib-related adverse

events were reported. Therefore, the adverse events are shown in the V mono column. The FX-171-003-A1 study[30] reports all grade and grade 3 or 4 adverse events irrespective of cause and carfilzomib-related adverse events of all grades. In this table grade, 3 or 4 adverse events irrespective of cause are reported.

Note: VRd is not a regimen tested in pivotal trials. VRd has, however, been well researched in the phase III SWOG S0777 trial and is widely used and thus included in this table for completeness. Adverse event incidence was taken from the publication at ASH 2015[51]; newer data is available as full publication,[50] but shows CTCAE categories only, which do not match categories used within this table.

Table S2C. Histone deacetylase inhibitors: Grade ≥3 adverse events reported in pivotal trials

HDACis	Panobinostat	HDACis	Panobinostat
	Pan-Vd[36, 37]		Pan-Vd[36, 37]
Hematological disorders		**Gastrointestinal disorders**	
Anemia	15-58%	Nausea	5-6%
Neutropenia	15-35%	Vomiting	7%
Thrombocytopenia	64-68%	Diarrhea	20-25%
Leukopenia	62%	Decreased appetite	3%
Lymphopenia	68%	Flatulence	6-7%
Neurologic disorders		**Others**	
Peripheral neuropathy	17%	Peripheral edema	2%
Headache	3%	Hypotension	2-9%
Dizziness	3%	Fatigue or Asthenia	24-29%
Infection		Abdominal pain	2-6%
Pneumonia	13-15%	Dehydration	5%
Sepsis/septic shock	6-9%	Syncope	9%
Mineral imbalances			

HDACis	Panobinostat	HDACis	Panobinostat
Hypokalemia	7%		
Hypophosphatemia	6%		

D, dexamethasone; HDACi, histone deacetylase inhibitor; Pan, panobinostat; V, bortezomib
Note: Adverse events with a reported incidence >2% in the original publication are listed; if an adverse event was reported to have an incidence >2% in one given regimen, the incidence of that adverse event is listed for all regimens.

Table S2D. Monoclonal antibodies: Grade ≥3 adverse events reported in pivotal trials

MAbs	Elotuzumab	Daratumumab			
	Elo-Rd[40]	Dara mono[45, 46]	Dara-Rd[48]	Dara-Vd[47]	Dara-Pom-d[52]
Hematological disorders					
Anemia		24%	12%	14%	28%
Neutropenia	34%	12%	52%	13%	77%
Febrile neutropenia			6%		8%
Thrombocytopenia	19%	19%	13%	45%	19%
Leukopenia					24%
Lymphopenia	19%		5%	10%	
Neurologic disorders					
Peripheral neuropathy				5%	
Infection					32%
Pneumonia			8%	8%	
Upper respiratory tract infection					3%
Others					
Fatigue	8%	1-3%	6%	5%	12%

Pyrexia	3%	1%			2%
Diarrhea	5%		5%	4%	4%
Back pain	5%	3%			6%
Dyspnea			3%	4%	8%
Hypertension				7%	
Hyperglycemia					8%
Fall					6%
Infusion-related reactions					4%

D, dexamethasone; Dara, daratumumab; Elo, elotuzumab; R, lenalidomide

Note: Adverse events with a reported incidence >2% in the original publication are listed; if an adverse event was reported to have an incidence >2% in one given regimen, the incidence of that adverse event is listed for all regimens

Table S3. Special warnings and precautions with regards to toxicities of chemotherapy and corticosteroid backbone as per USPI / EU SmPC

		Teratogenicity	Cardiac disorders	Neuromuscular effects	Thrombocytopenia	Leukopenia	Neutropenia	Anemia	Infections	Viral/bacterial reactivation	Hypertension	GI perforation	SPM	Allergic/hypersensitivity reactions	Infusion reaction	Hepatic impairment	Renal impairment	Electrolyte imbalances	Cataracts/ophthalmic effects	Pulmonary disorders	Mood/behavior disturbances	Endocrine disorders	Bone density decrease	Hand-foot syndrome
Glucocorticosteroids	Dexamethasone		●	●					●		●	●					●	●	●		●	●	●	
	Prednisone	●	●	●					●	●	●	●	●[a]				●		●		●	●	●	
Alkylating agent	Cyclophosphamide	●	●		●[b]	●[b]	●[b]	●[b]	●[c]				●			●	●	●		●				
	Melphalan	●			●	●	●	●					●	●										
Anthracycline	Doxorubicin (liposomal)	●	●										●		●									●

a. Kaposi's sarcoma; b. hematological toxicities include bone marrow failure; c. includes sepsis and septic shock
GI, gastrointestinal

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