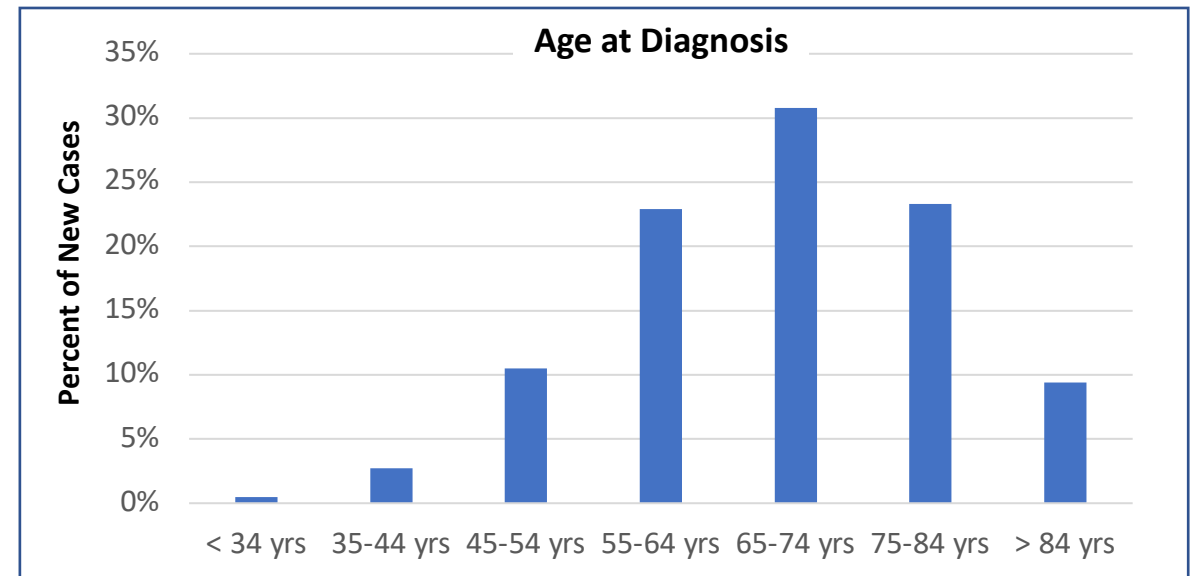


Multiple Myeloma (MM)

- **Multiple Myeloma**

- A severe, generally incurable, haematological malignancy
- The median age at diagnosis is 69 years
- The age-adjusted incidence is about 6-7/100.000/year
- The absolute number of patients increases in key markets due to aging populations

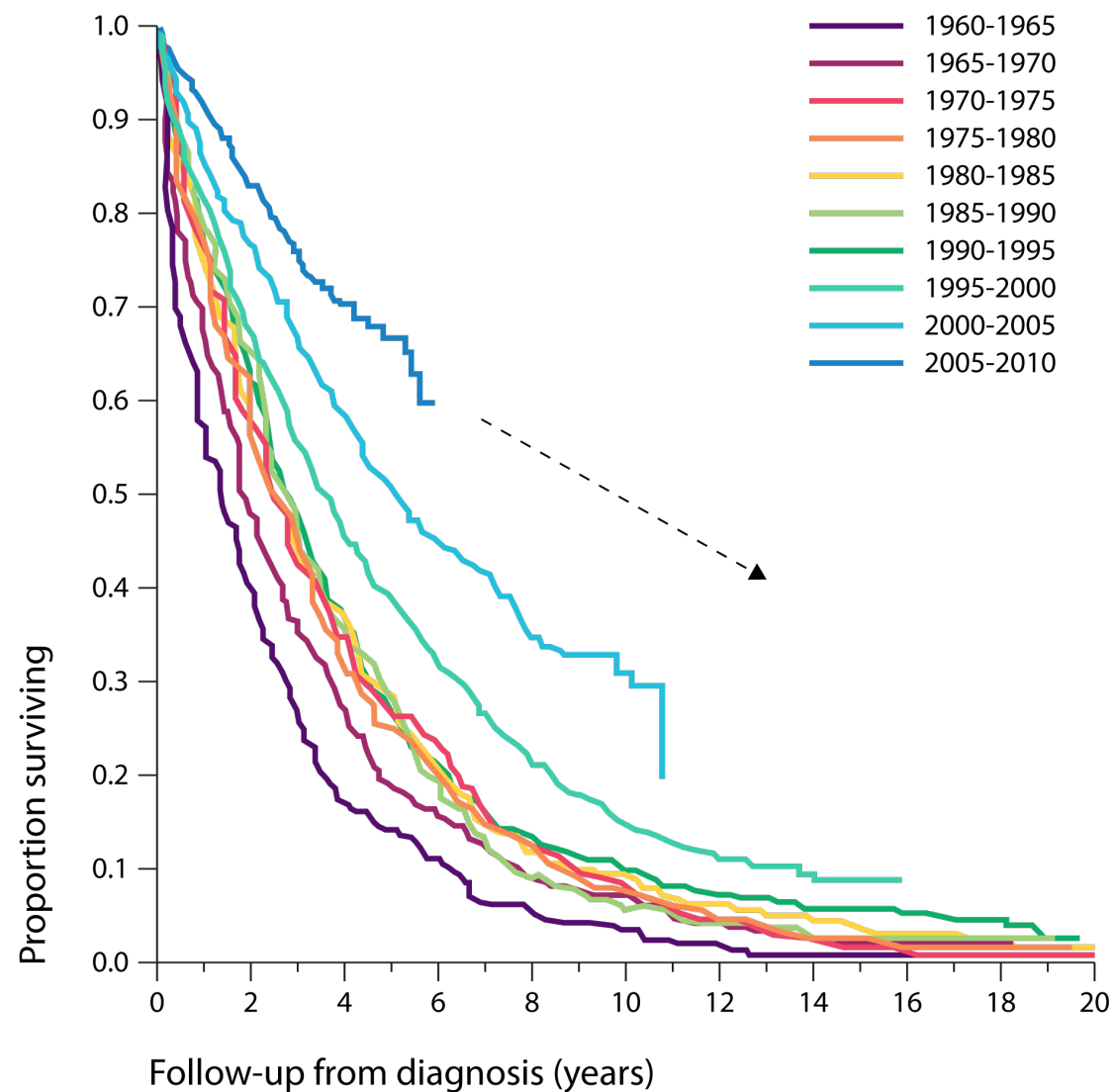
Region	Incidence
USA	29.252
Europe	48.297
Global	159.985



Pharmaceutical market in MM was US\$19.5B in 2018 with an expected 6.0% CAGR in 2019-2026

Improvement of overall survival in Multiple Myeloma

From a median of 2 years to 8-10 years



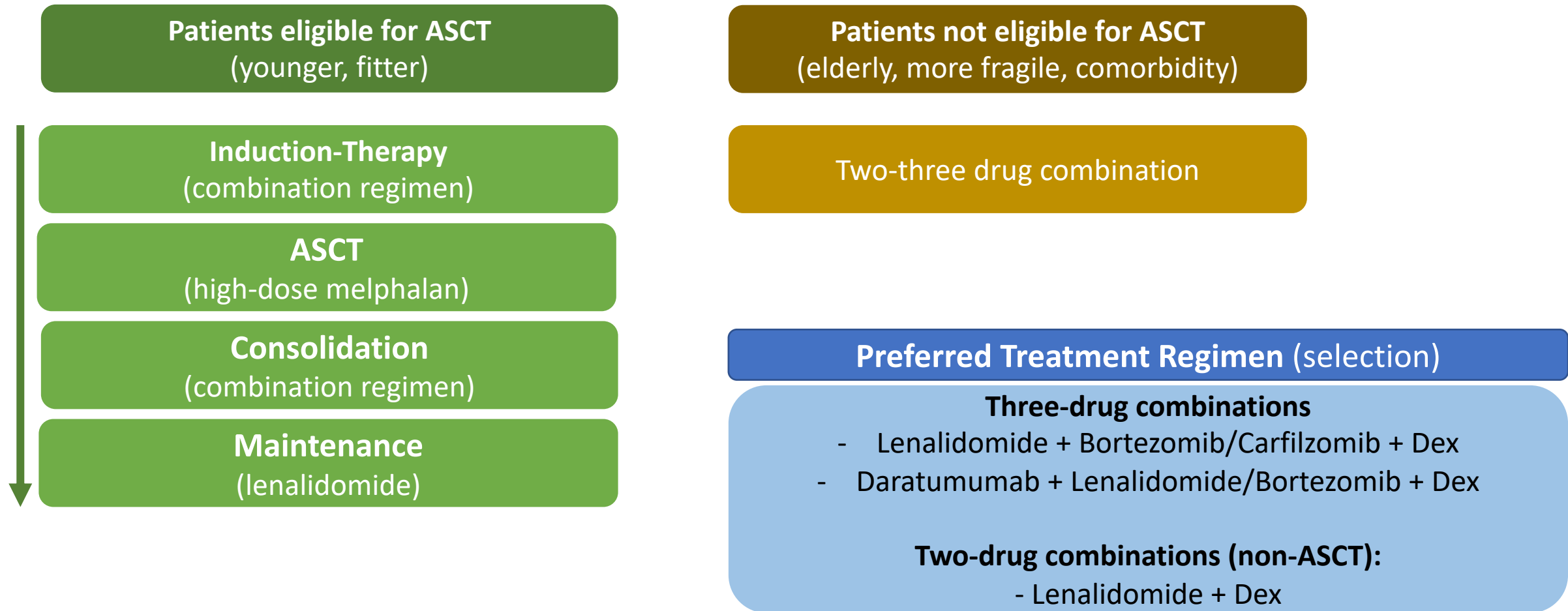
Multiple Myeloma: Approved Therapeutics

Drug Class	Target	Substances (highlighted = most frequently used)	1 st US Approval
Alkylating Agents	DNA Alkyl Groups	Melphalan (generic) Cyclophosphamide (generic) Bendamustine (<i>Treanda</i>)	1960s* 2008
Corticosteroids	Glucocorticoid Receptor	Prednisone (generic) Dexamethasone (generic)	1960s* 1980s*
Proteasome Inhibitors	Proteasome	Bortezomib (<i>Velcade/generic</i>) Carfilzomib (<i>Kyprolis</i>) Ixazomib (<i>Ninlaro</i>)	2003 2012 2015
Immunomodulators (IMiDs)	Cereblon	Thalidomide (<i>Thalidomid/generic</i>) Lenalidomide (<i>Revlimid</i>) Pomalidomide (<i>Pomalyst/Imnovid</i>)	1998 2006 2013
Histone Deacetylase Blocker	Histone Deacetylase	Panobinostat (<i>Farydak</i>)	2015
Monoclonal Antibodies	CD38	Daratumumab (<i>Darzalex</i>) Isatuximab (<i>Sarclisa</i>)	2015 2020
	CS1/SAMF7	Elotuzumab (<i>Empliciti</i>)	2015
Nuclear Export Inhibitors	Exportin-1	Selinexor (<i>Xpovio</i>)	2019
Antibody Drug Conjugate	BCMA	Belantamab mafodotin-blmf (<i>Blenrep</i>)	2020

* Date is referring to wide spread in MM

Multiple Myeloma Treatment Pathways

First-Line Treatment



Multiple Myeloma Treatment Pathways

Simplified algorithm for relapsed-refractory disease

First relapse

Relapse after lenalidomide-based combination

Preferred: Pomalidomide + bortezomib + dex
Alternatives: Carfilzomib/bortezomib + dex
Daratumumab combinations

Relapse after bortezomib-based combination

Two or three drug combinations containing:
Daratumumab, lenalidomide, pomalidomide,
carfilzomib, dexamethasone

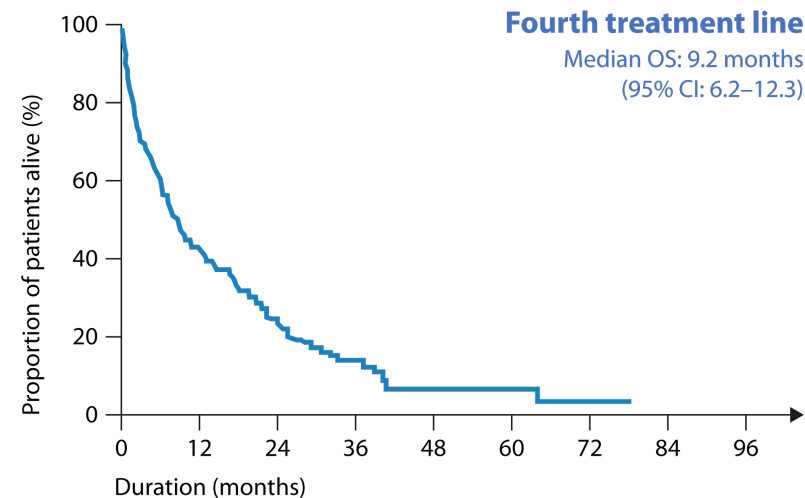
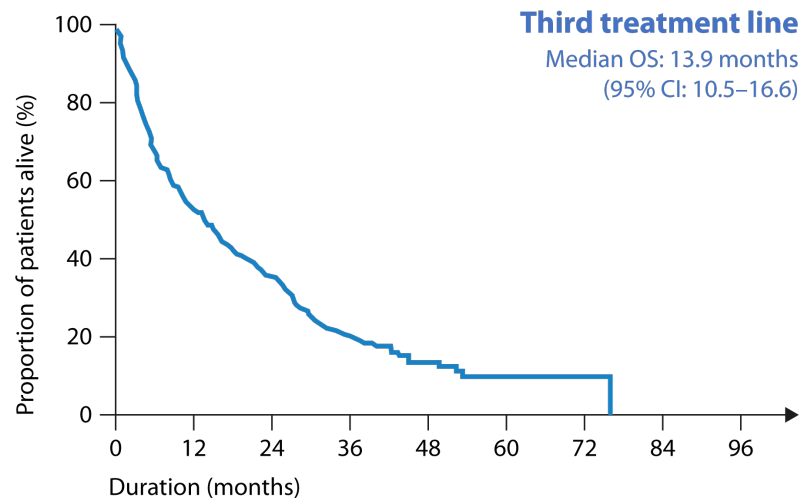
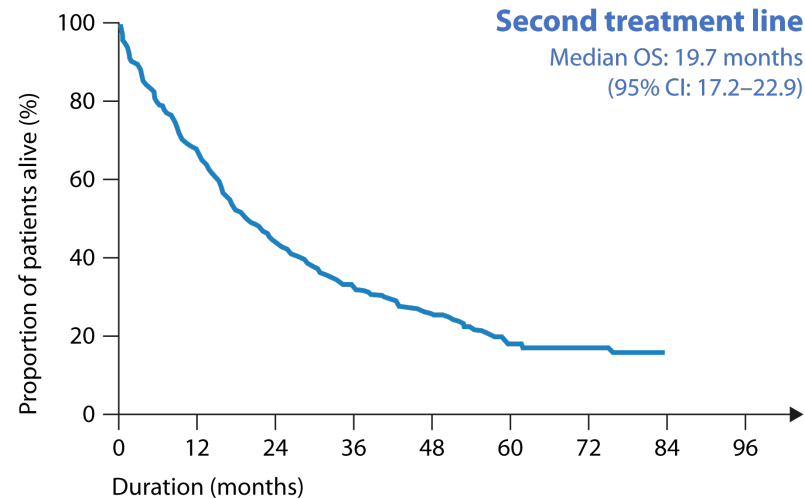
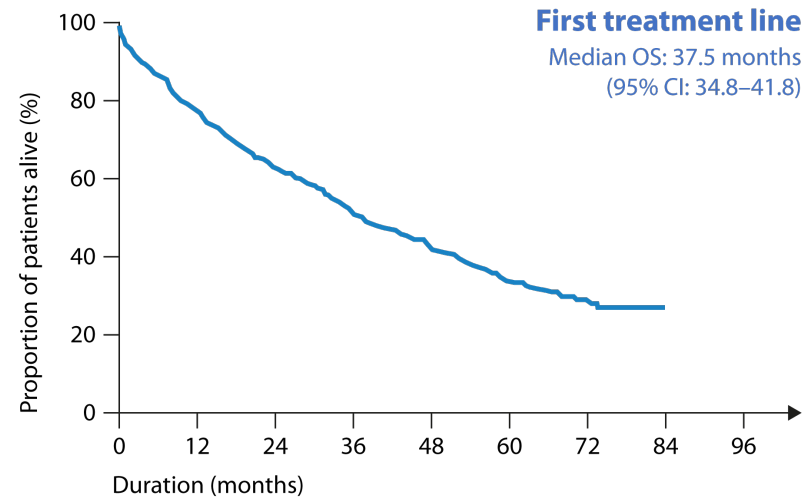
Further relapse

Approved agents (selection):

Frequently used:	Daratumumab, pomalidomide, carfilzomib, cyclophosphamide
Less frequently used:	Elotuzumab, ixazomib, panobinostat, bortezomib, bendamustin
Newly approved:	Selinexor, belantamab mafodotin
Likely approved in 2021:	Melflufen, BCMA CAR-T (liso-cel)

Overall Survival by Treatment Line

2008-2013, Dutch MM Registry



Key Prognostic Factors (selection)

Patient-related

- Age
- Comorbidity/Fragility

Disease-related

- Tumour genetics
- ISS stage
- Response to previous therapy

Treatment-specific

- Residual toxicity

Summary: Multiple Myeloma

Epidemiology

- Nearly 80.000 new patients per year in US and Europe
- Absolute incidence and prevalence increasing due to demography and prolonged survival

Treatment

- New drugs in last 15 years have significantly improved survival
- Therapeutic strategy based on combination of different drug classes and switching between non-cross resistant drug classes upon relapse
- Long treatment duration (until progression / maintenance therapy)

Significant unmet medical need

- Overall survival in relapsed-refractory patients is poor
- Toxicity of some new treatments is increased
- New agents from non-cross-resistant drug classes are needed