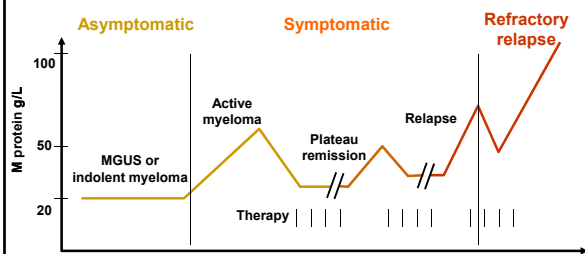


TREATMENT OF RELAPSED MULTIPLE MYELOMA

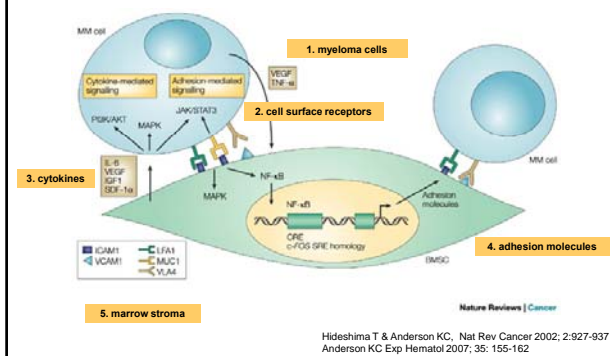
How to design and interpret clinical trials in relapsed MM: definition of the population and of the objectives

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Multiple myeloma disease course



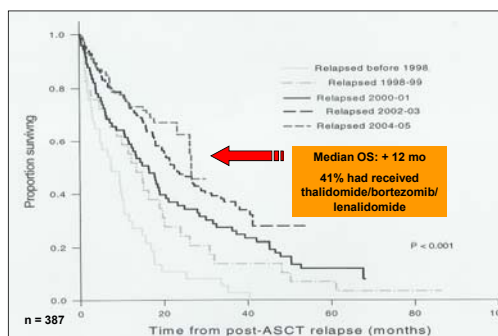
Relapsed/refractory myeloma factors contributing to drug resistance



Treatment of relapsed MM criteria for therapeutic decision making

- disease-related factors:**
 - prognostic factors ?
 - biochemical/clinical relapse ?
 - extramedullary plasmacytoma(s)? bone lesions ?
- patient-related factors:**
 - age ?
 - comorbidities ?
 - renal function ?
 - expectations ?
 - mobility ?
- previous treatment(s):**
 - which drugs ?
 - duration of the response (early vs late relapse) ?
 - treatment-related toxicity ?

Treatment of relapsed MM impact of the 'new' drugs



New drugs in relapsed/refractory MM response rates

Regimen	Trial	ORR, %	CR or nCR, %	≥ VGPR, %	DOR, mo.	PFS or TTP med, mo.	OS med, mo.
Len + Dex	MM-009 ¹	61	24	NE	16	11	35 ⁵
Len + Dex	MM-010 ²	60	25	NE	17	11	
Bortezomib	APEX ³	43	16	NE	8	6	30
Thal + dex	13 studies	46%	4%	NA	8-12	NE	NE

1. Weber DM, et al. N Engl J Med. 2007;357:2133-42.
2. Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32.
3. Richardson PG, et al. Blood. 2007;110:3557-60.
4. Von Lilienfeld et al. Eur J Haematol 2008;81:247
5. Weber DM, et al. Blood. 2007;110:[abstract 412].
DOR = duration of response; NE = not evaluable; Vdoo = bortezomib + pegylated liposomal doxorubicin.

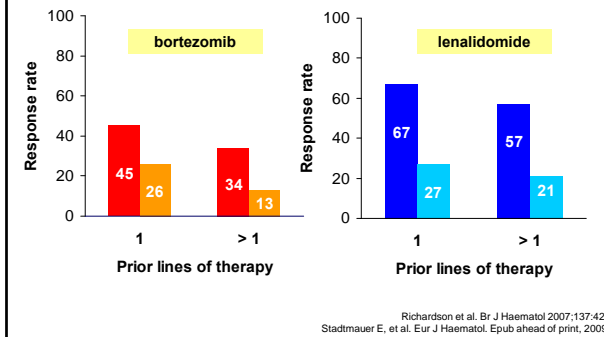
New drugs in relapsed/refractory MM impact of quality of response (bortezomib)

	CR	VGPR	PR	MR	NR
Patients, n (%)	27 (9)	31 (10)	77 (24)	21 (7)	159 (50)
Median cycles	8	10	10	8	4
TTP, months	9.7	10.8	8.5	4.9	2.8
Treatment-free interval, months (last bortezomib to next Tx)	24.1	6.9	6.4	3.8	2.3
Time to next therapy, months (first bortezomib to next Tx)	27.1	13.6	14.0	8.7	6.2
OS, months	NR	NR	NR	24.9	18.7

NR: not reached

Niesvizky et al. Br J Haematol 2008; 143:46

New drugs in relapsed/refractory MM impact of treatment line



New drugs in relapsed/refractory MM impact of previous treatment (lenalidomide)

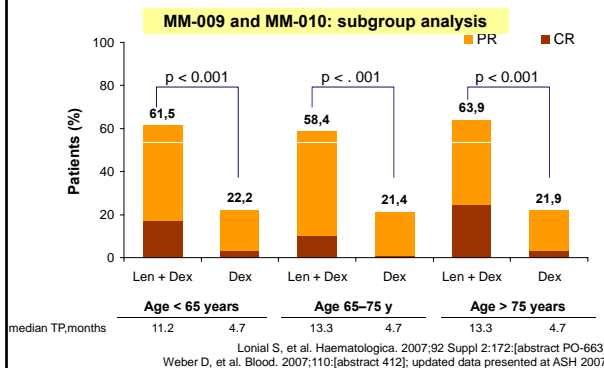
thalidomide naive vs thalidomide exposed

- median time from diagnosis: 2.8 yrs vs 4.0 yrs (p < 0.05)
- median lines of prior therapy: 2 vs 3 (p < 0.05)

	n	Overall response rate, %	Median TTP, months
Thalidomide naive	226	65	13.9
Prior thalidomide	127	54	8.4
Thal sensitive	54	65	9.3
Relapsed on Thal	31	42	7.8
Refractory to Thal	20	50	7.2

Wang, M. et al. Blood 2008;112:4445-51.

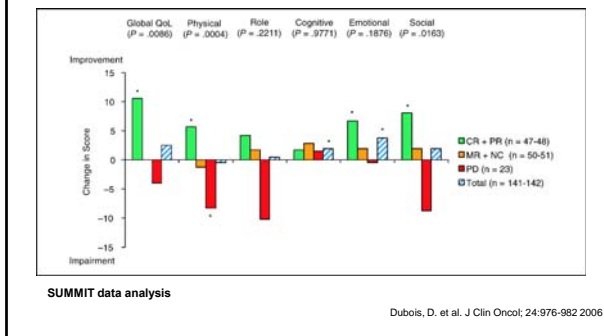
New drugs in relapsed/refractory MM impact of age (lenalidomide)



Side effect management most common side effects of the new drugs

	thalidomide	lenalidomide	bortezomib
Hematological			
myelosuppression	rare	anemia, neutropenia, thrombocytopenia	thrombocytopenia
Non-Hematological			
gastro-intestinal	constipation	constipation, diarrhoea	constipation, diarrhoea
polyneuropathy	++	-/+	++
thrombogenicity	in combination	in combination	-
fatigue	+	+	+
teratogenicity	++	+	-
skin reactions	+	+	+

New drugs in relapsed/refractory MM impact of quality of life (bortezomib)



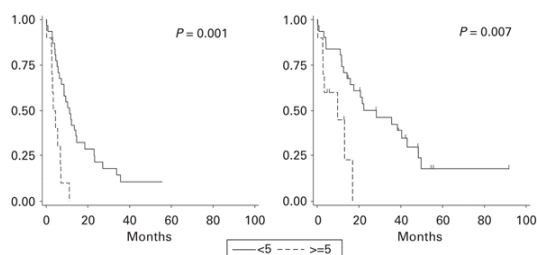
Improving responses in relapsed/refractory MM the strength of combination

- Treatment regimens are based on **additive** and/or **synergistic** effects
- Frequently used combinations:
 - Combinations with **dexamethasone**:
 - synergy with the new agents
 - common practice for the majority of myeloma physicians
 - Combinations with **chemotherapy**:
 - additive effect/synergy with the new agents
 - most experience with melphalan, cyclophosphamide and doxorubicin
 - side effects: hematological toxicity can be important
 - Combinations between **IMiDs and bortezomib**:
 - promising data from phase I and II studies
- Combinations enhance activity but can also increase toxicity

New drugs in relapsed/refractory MM is retreatment with new agents feasible ? (bortezomib)

Design	N	Initial bortezomib treatment Response rates	Bortezomib retreatment Response Rates	Reference
Retrospective	22	ORR: 68% CR: 14% PR: 54%	ORR: 50% CR: 9% PR: 41%	Wolf ASH 2006; Abstract 3532
Retrospective	82	ORR: 59% VGPR: 27% PR: 32%	ORR: 21% VGPR: 6% PR: 15%	Conner Clin Lymphoma Myeloma 2008;8:140-5
Retrospective	49	ORR: 100% (per protocol)	ORR: 63% nCR: 4% PR: 49%	Hrusovsky EHA 2008 (Abstract 645)
Prospective	28	ORR: 100% (per protocol) CR: 43% PR: 57%	ORR: 39% ≥75% M-protein reduction: 13% 50-74% M-protein reduction: 26%	Sood Ann Oncol 2006; 17(Suppl 9): Abstract 679P

high-dose therapy in relapsed MM has it a role ?



second autograft for salvage treatment if:

- > 12 mo TTP after first autograft
- not postponed until refractory relapse

Olin et al. Bone Marrow Transplant 2009;43:417

Conclusions

- the outcome of patients with relapsed/refractory myeloma has improved due to the introduction of new agents (thalidomide, bortezomib, lenalidomide):
 - high-quality responses can be achieved
 - sequential use of new drugs is effective
 - combination with existing drugs is additive/synergistic
 - retreatment is feasible (bortezomib)
- highly effective regimens should not be postponed until later relapses/refractory disease
- preservation of quality of life if :
 - you remember “one size does not fit all MM patients”
 - rapid and appropriate side effect management