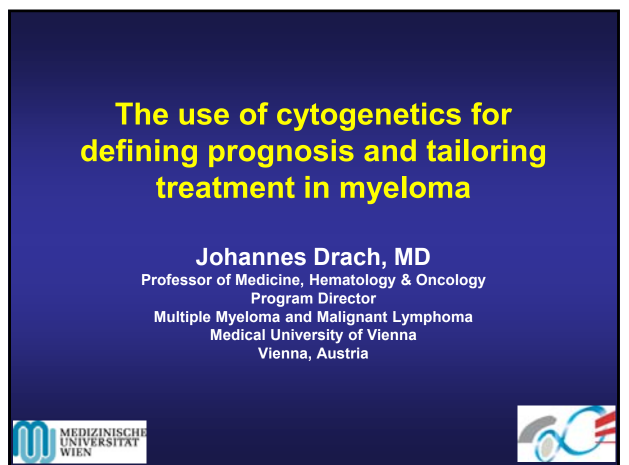
The use of cytogenetics for defining prognosis and tailoring treatment in myeloma
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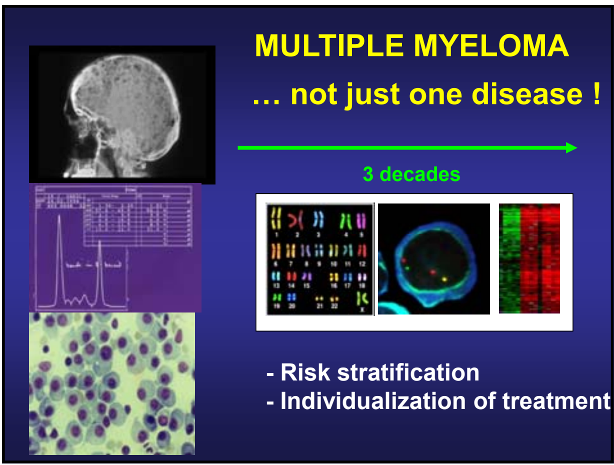
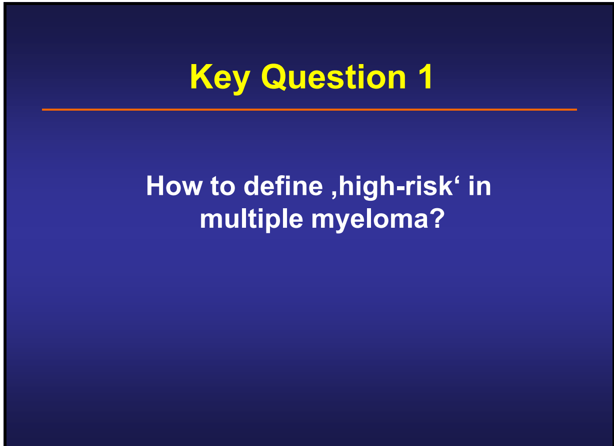
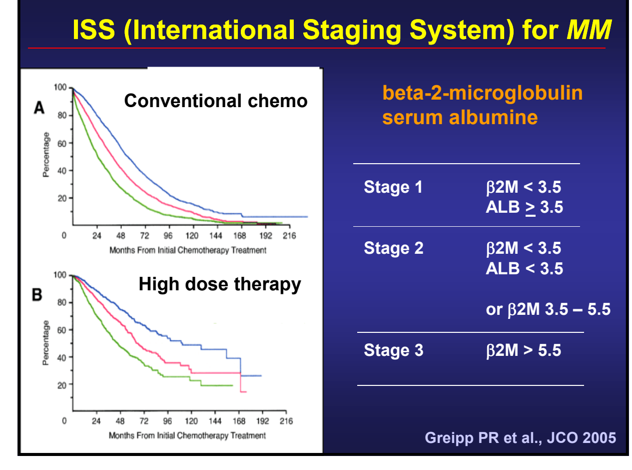
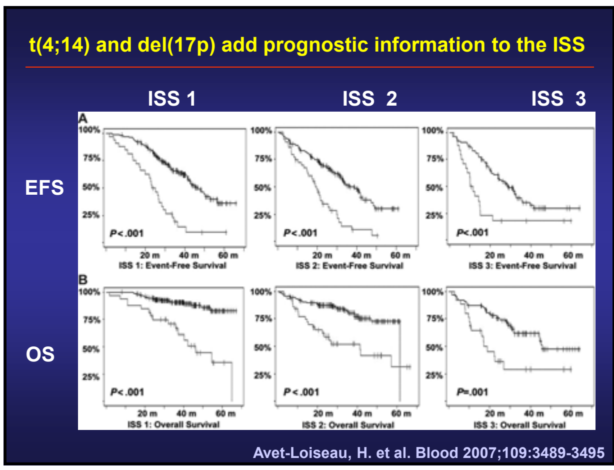
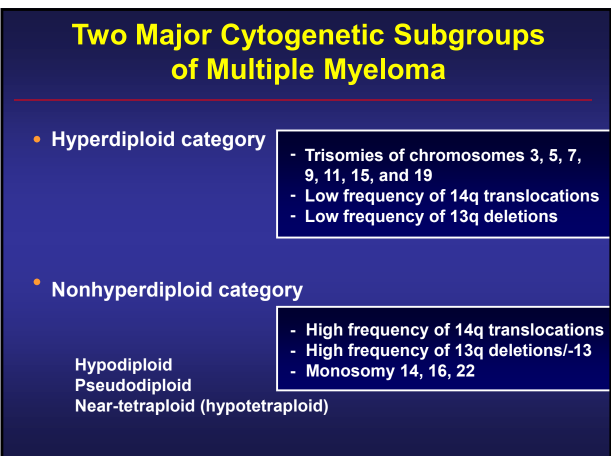
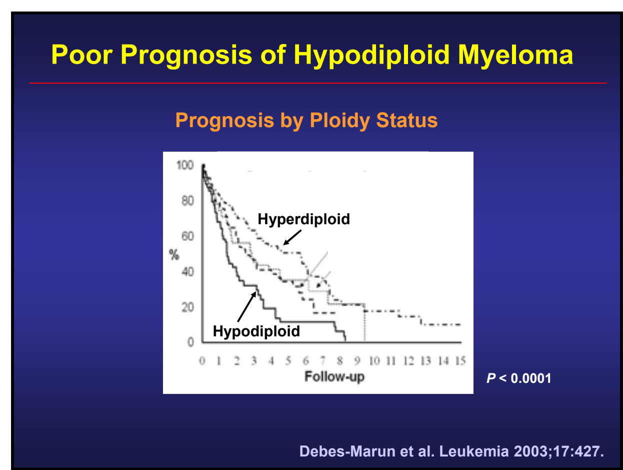

MULTIPLE MYELOMA
… not just one disease !
3 decades
- Risk stratification
- Individualization of treatment

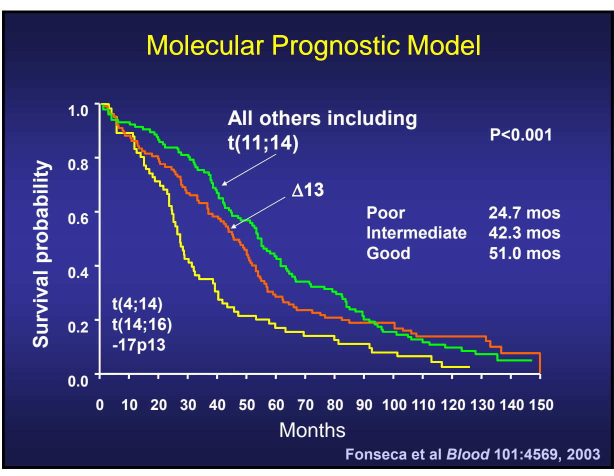

Key Question 1
How to define ‚high-risk' in multiple myeloma?

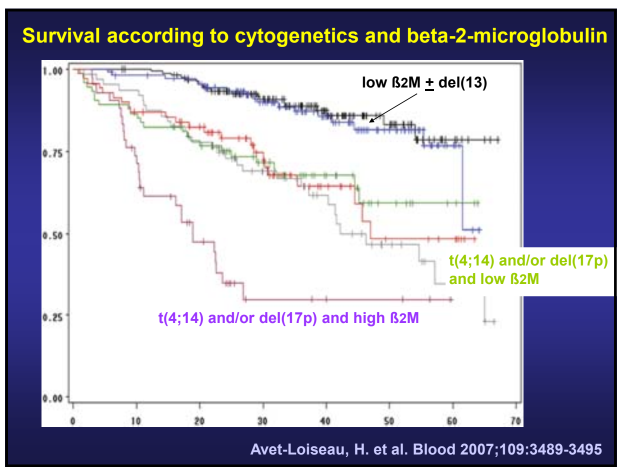

ISS (International Staging System) for MM
Conventional chemo
High dose therapy
Months From Initial Chemotherapy Treatment
beta-2-microglobulin
serum albumine
Stage 1 β2M < 3.5 ALB ≥ 3.5
Stage 2 β2M < 3.5 ALB < 3.5
or β2M 3.5 – 5.5
Stage 3 β2M > 5.5
Greipp PR et al., JCO 2005

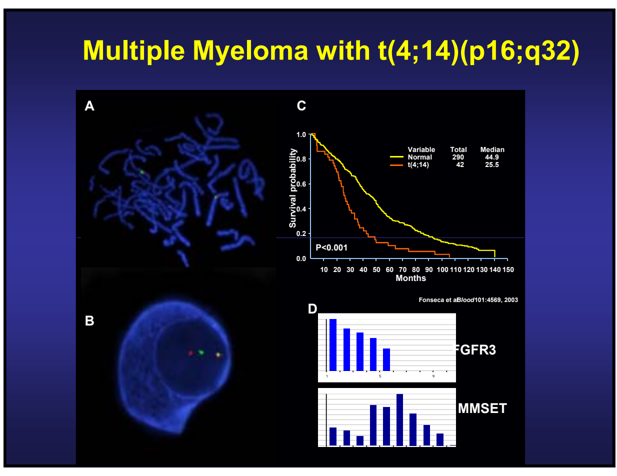

t(4;14) and del(17p) add prognostic information to the ISS
ISS 1
ISS 2
ISS 3
EFS
OS
ISS 1: Event-Free Survival
ISS 2: Event-Free Survival
ISS 3: Event-Free Survival
ISS 1: Overall Survival
ISS 2: Overall Survival
ISS 3: Overall Survival
Avet-Loiseau, H. et al. Blood 2007;109:3489-3495

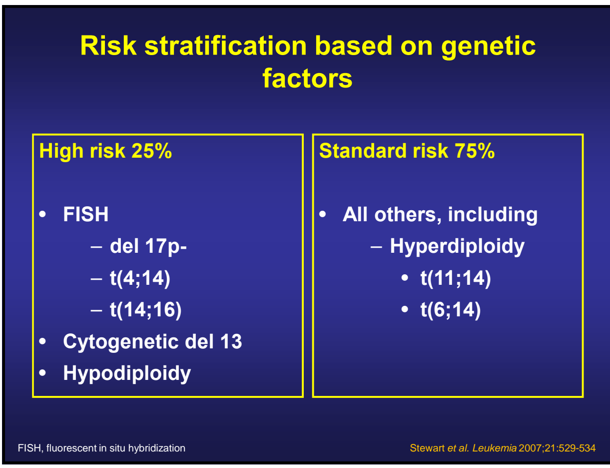

Two Major Cytogenetic Subgroups of Multiple Myeloma
Hyperdiploid category
- Trisomies of chromosomes 3, 5, 7, 9, 11, 15, and 19
- Low frequency of 14q translocations
- Low frequency of 13q deletions
Nonhyperdiploid category
- High frequency of 14q translocations
- High frequency of 13q deletions/-13
- Monosomy 14, 16, 22
Hypodiploid
Pseudodiploid
Near-tetraploid (hypotetraploid)

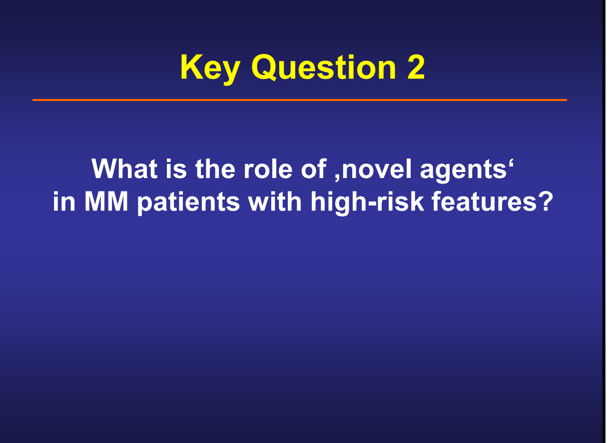

Poor Prognosis of Hypodiploid Myeloma
Prognosis by Ploidy Status
Hyperdiploid
Hypodiploid
%
Follow-up
P < 0.0001
Debes-Marun et al. Leukemia 2003;17:427.

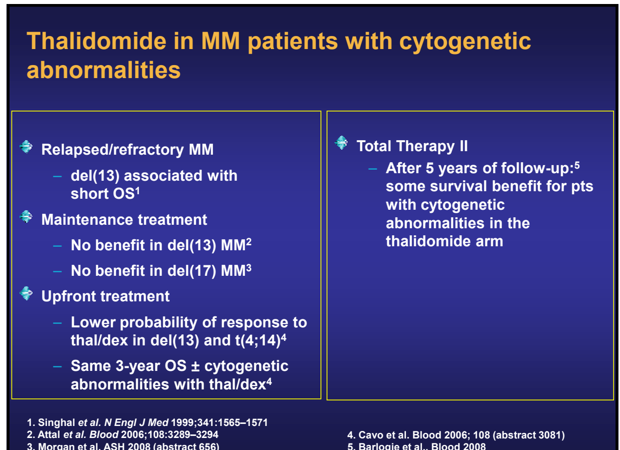

Molecular Prognostic Model
Survival probability
All others including
t(11;14)
P<0.001
Δ13
Poor 24.7 mos
Intermediate 42.3 mos
Good 51.0 mos
t(4;14)
t(14;16)
-17p13
Months
Fonseca et al Blood 101:4569, 2003

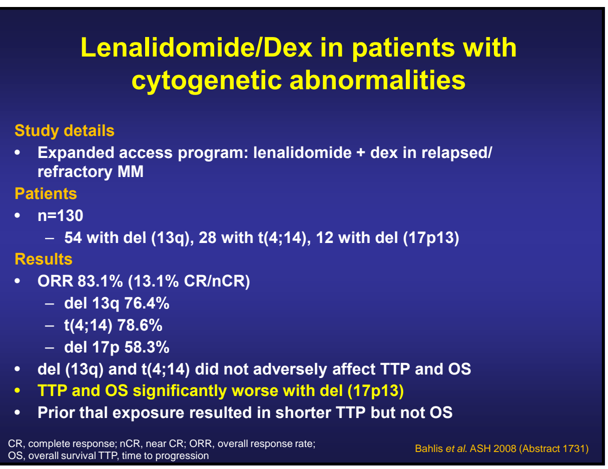

Survival according to cytogenetics and beta-2-microglobulin
low ß2M + del(13)
t(4;14) and/or del(17p)
and low ß2M
t(4;14) and/or del(17p) and high ß2M
Avet-Loiseau, H. et al. Blood 2007;109:3489-3495

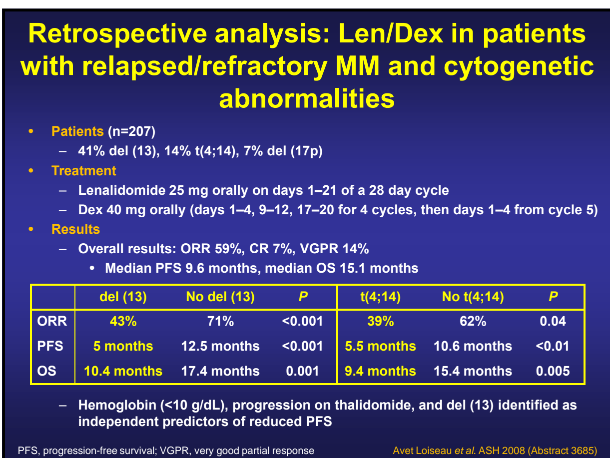

Multiple Myeloma with t(4;14)(p16;q32)
A
B
C
D
P<0.001
Months
FGFR3
MMSET

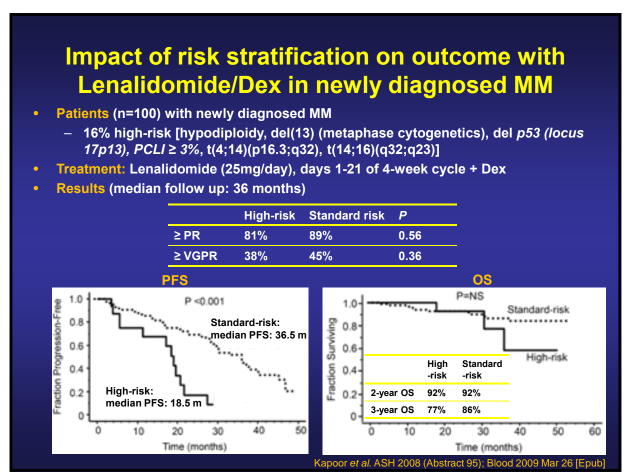

Risk stratification based on genetic factors
High risk 25%
• FISH
– del 17p-
– t(4;14)
– t(14;16)
• Cytogenetic del 13
• Hypodiploidy
Standard risk 75%
• All others, including
– Hyperdiploidy
• t(11;14)
• t(6;14)
FISH, fluorescent in situ hybridization
Stewart et al. Leukemia 2007;21:529-534

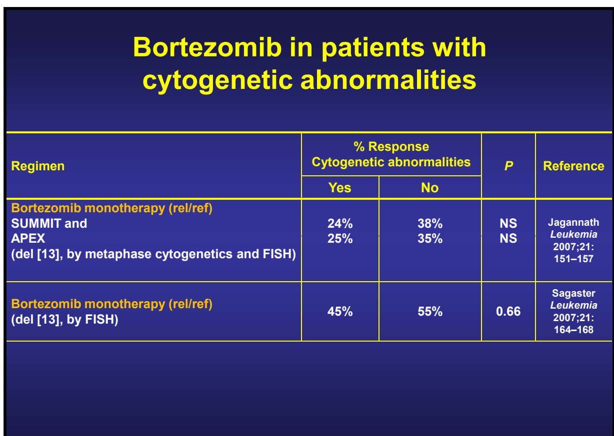

Key Question 2
What is the role of ‚novel agents‘
in MM patients with high-risk features?

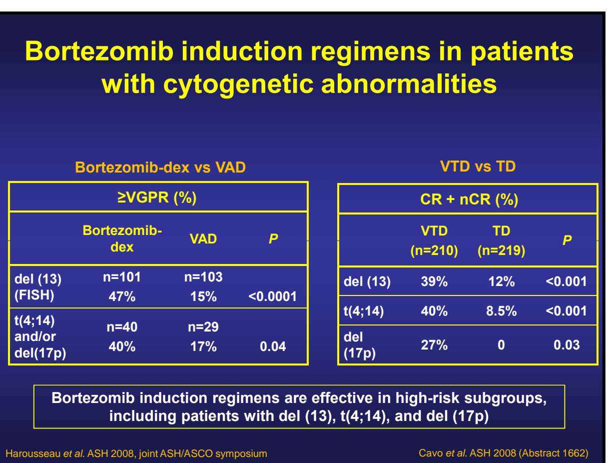

Thalidomide in MM patients with cytogenetic abnormalities
Relapsed/refractory MM
del(13) associated with short OS[1]
Maintenance treatment
No benefit in del(13) MM[2]
No benefit in del(17) MM[3]
Upfront treatment
Lower probability of response to thal/dex in del(13) and t(4;14)[4]
Same 3-year OS ± cytogenetic abnormalities with thal/dex[4]
Total Therapy II
After 5 years of follow-up:[5] some survival benefit for pts with cytogenetic abnormalities in the thalidomide arm
1. Singhal et al. N Engl J Med 1999;341:1565–1571
2. Attal et al. Blood 2006;108:3289–3294
3. Morgan et al. ASH 2008 (abstract 656)
4. Cavo et al. Blood 2006; 108 (abstract 3081)
5. Barlogie et al., Blood 2008

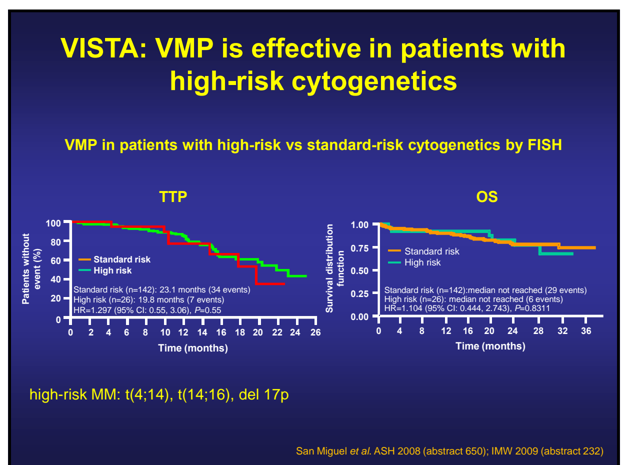

Lenalidomide/Dex in patients with cytogenetic abnormalities
Study details
Expanded access program: lenalidomide + dex in relapsed/refractory MM
Patients
n=130
54 with del (13q), 28 with t(4;14), 12 with del (17p13)
Results
ORR 83.1% (13.1% CR/nCR)
del 13q 76.4%
t(4;14) 78.6%
del 17p 58.3%
del (13q) and t(4;14) did not adversely affect TTP and OS
TTP and OS significantly worse with del (17p13)
Prior thal exposure resulted in shorter TTP but not OS
CR, complete response; nCR, near CR; ORR, overall response rate; OS, overall survival TTP, time to progression
Bahlis et al. ASH 2008 (Abstract 1731)

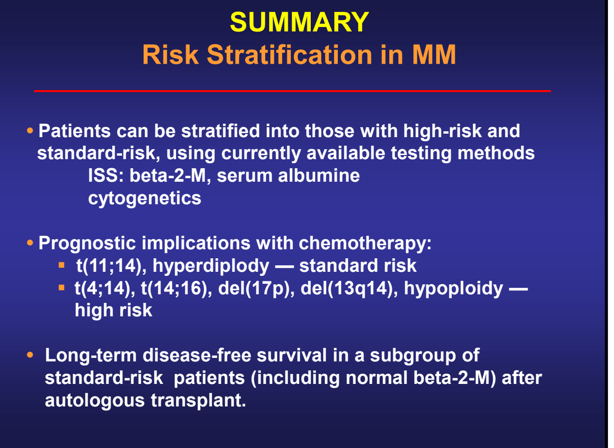

Retrospective analysis: Len/Dex in patients with relapsed/refractory MM and cytogenetic abnormalities
Patients (n=207)
41% del (13), 14% t(4;14), 7% del (17p)
Treatment
Lenalidomide 25 mg orally on days 1–21 of a 28 day cycle
Dex 40 mg orally (days 1–4, 9–12, 17–20 for 4 cycles, then days 1–4 from cycle 5)
Results
Overall results: ORR 59%, CR 7%, VGPR 14%
Median PFS 9.6 months, median OS 15.1 months
	del (13)	No del (13)	P	t(4;14)	No t(4;14)	P
ORR	43%	71%	<0.001	39%	62%	0.04
PFS	5 months	12.5 months	<0.001	5.5 months	10.6 months	<0.01
OS	10.4 months	17.4 months	0.001	9.4 months	15.4 months	0.005
Hemoglobin (<10 g/dL), progression on thalidomide, and del (13) identified as independent predictors of reduced PFS
PFS, progression-free survival; VGPR, very good partial response
Avet Loiseau et al. ASH 2008 (Abstract 3685)


Impact of risk stratification on outcome with Lenalidomide/Dex in newly diagnosed MM
Patients (n=100) with newly diagnosed MM
16% high-risk [hypodiploidy, del(13) (metaphase cytogenetics), del p53 (locus 17p13), PCLI ≥ 3%, t(4;14)(p16.3;q32), t(14;16)(q32;q23)]
Treatment: Lenalidomide (25mg/day), days 1-21 of 4-week cycle + Dex
Results (median follow up: 36 months)
	High-risk	Standard risk	P
≥ PR	81%	89%	0.56
≥ VGPR	38%	45%	0.36
PFS
P <0.001
Standard-risk: median PFS: 36.5 m
High-risk: median PFS: 18.5 m
Fraction Progression-Free
Time (months)
OS
P=NS
Standard-risk
High-risk
Fraction Surviving
	High-risk	Standard-risk
2-year OS	92%	92%
3-year OS	77%	86%
Time (months)
Kapoor et al. ASH 2008 (Abstract 95); Blood 2009 Mar 26 [Epub]


Bortezomib in patients with cytogenetic abnormalities
Regimen	% Response Cytogenetic abnormalities: Yes	No	P	Reference
Bortezomib monotherapy (rel/ref) SUMMIT and APEX (del [13], by metaphase cytogenetics and FISH)	24% 25%	38% 35%	NS NS	Jagannath Leukemia 2007;21: 151–157
Bortezomib monotherapy (rel/ref) (del [13], by FISH)	45%	55%	0.66	Sagaster Leukemia 2007;21: 164–168


Bortezomib induction regimens in patients with cytogenetic abnormalities
Bortezomib-dex vs VAD
≥VGPR (%)	Bortezomib-dex	VAD	P
del (13) (FISH)	n=101 47%	n=103 15%	<0.0001
t(4;14) and/or del(17p)	n=40 40%	n=29 17%	0.04
VTD vs TD
CR + nCR (%)	VTD (n=210)	TD (n=219)	P
del (13)	39%	12%	<0.001
t(4;14)	40%	8.5%	<0.001
del (17p)	27%	0	0.03
Bortezomib induction regimens are effective in high-risk subgroups, including patients with del (13), t(4;14), and del (17p)
Harousseau et al. ASH 2008, joint ASH/ASCO symposium
Cavo et al. ASH 2008 (Abstract 1662)





CONCLUSION

- While all patients likely benefit from combinations including the novel agents bortezomib and lenalidomide, those with high-risk disease may benefit most, and should be especially targeted for these therapies
- Prognostic factors need to be re-evaluated in the era of novel agents