THE ARKANSAS APPROACH TO THE TREATMENT OF MULTIPLE MYLEOMA: CURE OF LOW-RISK DISEASE WITH TOTAL THERAPY 3

ATHENS CONFERENCE ON PLASMA CELL DYSCRASIA
September 10-11, 2009

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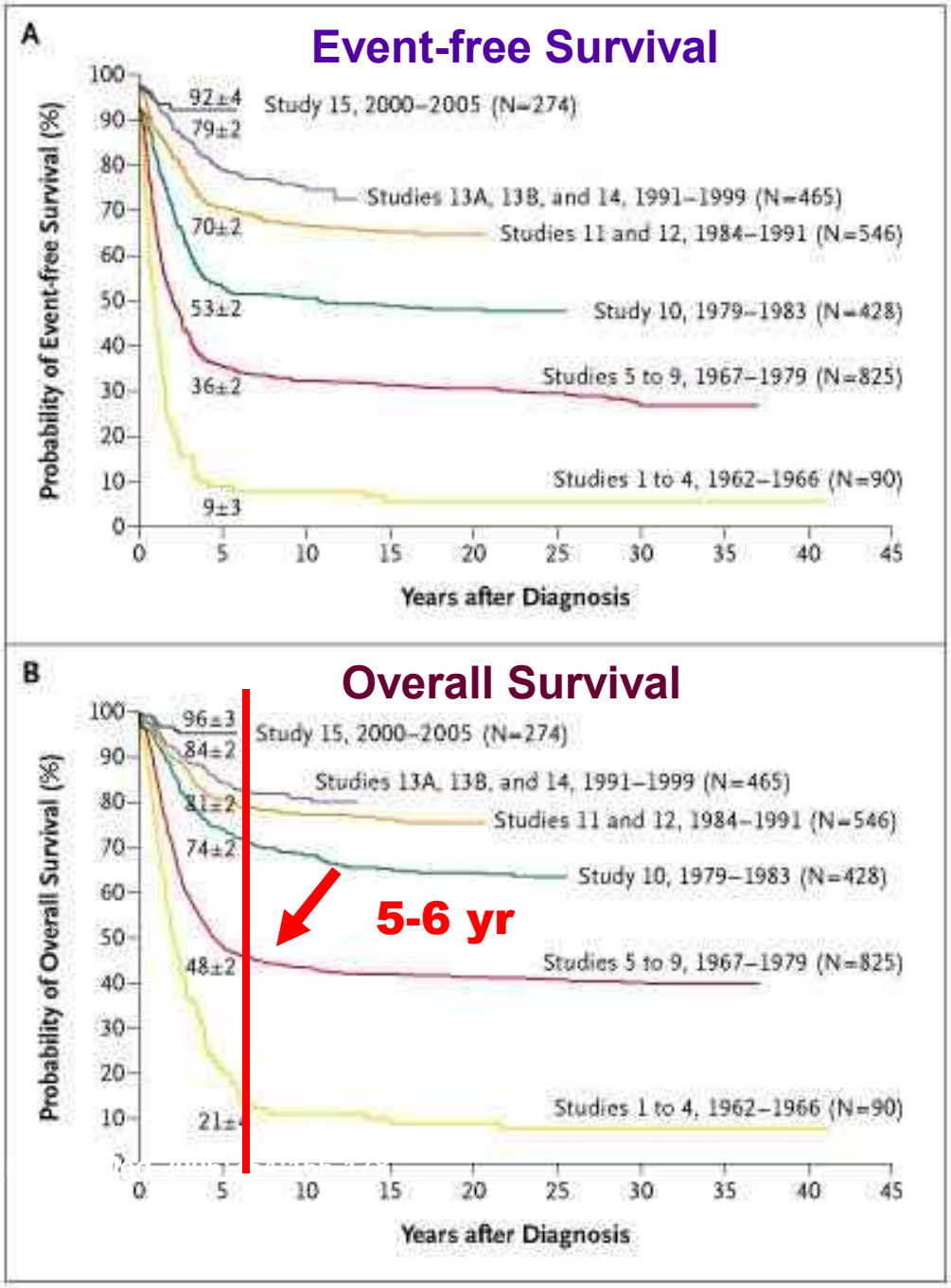
Myeloma Institute for Research and Therapy
University of Arkansas for medical Sciences
Little Rock AR, USA

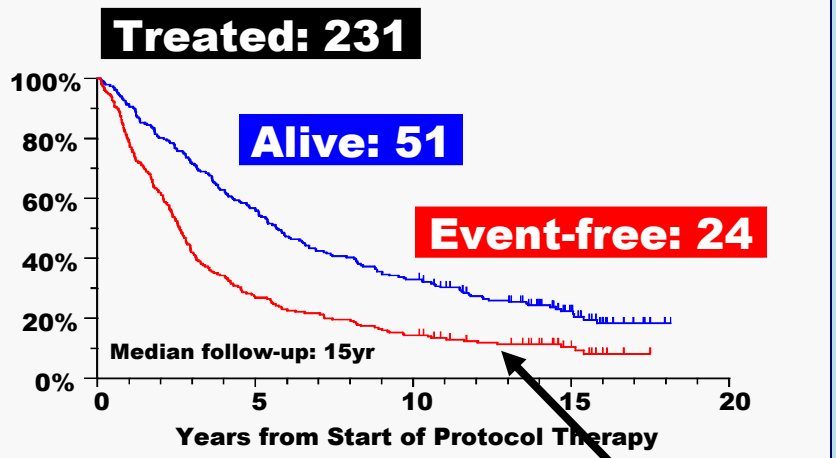
2628 CHILDREN WITH NEWLY DIAGNOSED ALL

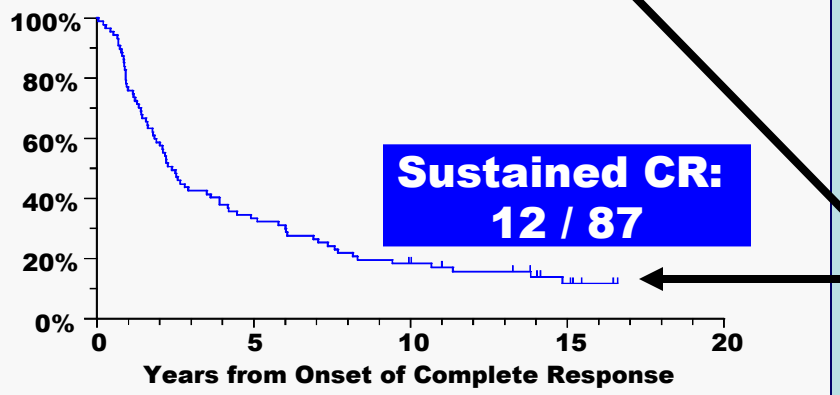
Learn from our pediatric colleagues! Superior outcomes in young ALL when treated on pediatric versus adult trials



Pui C-H and Evans E:
Treatment of acute lymphoblastic leukemia.
N Engl J Med 2006;354;166-178

TOTAL THERAPY 1 – UPDATED 2/09

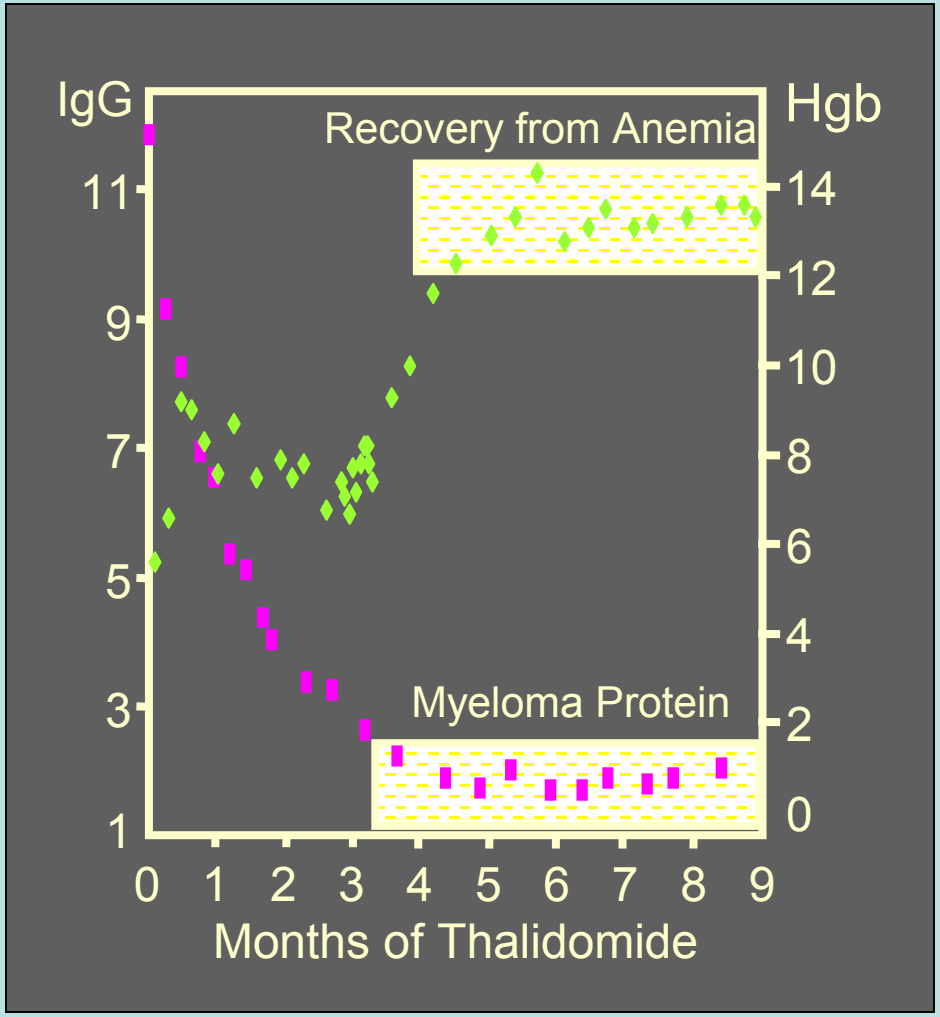




- PURSUIT OF DOSE INTENSITY UP-FRONT TO RAISE CR RATE AND THEREBY EXTEND SURVIVAL
- "TANDEM" TRANSPLANT IS NO MORE THAN 2 CYCLES OF MTD MEL200
- LOW TRM DESPITE AGE UP TO 75YR
- ADVERSE ROLE OF CA

- ***CURE PRINCIPLE ESTABLISHED***

THAL Response Occurs Rapidly



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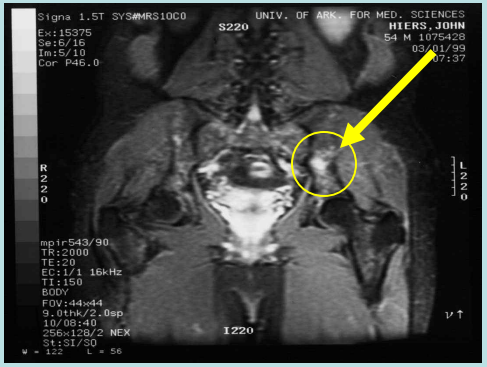

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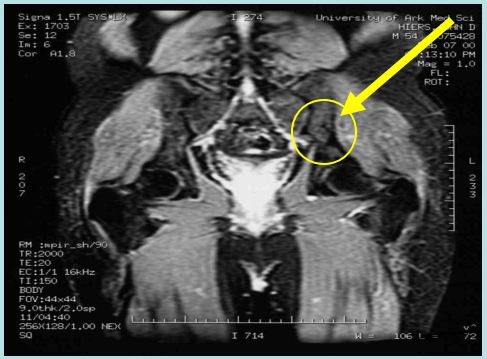
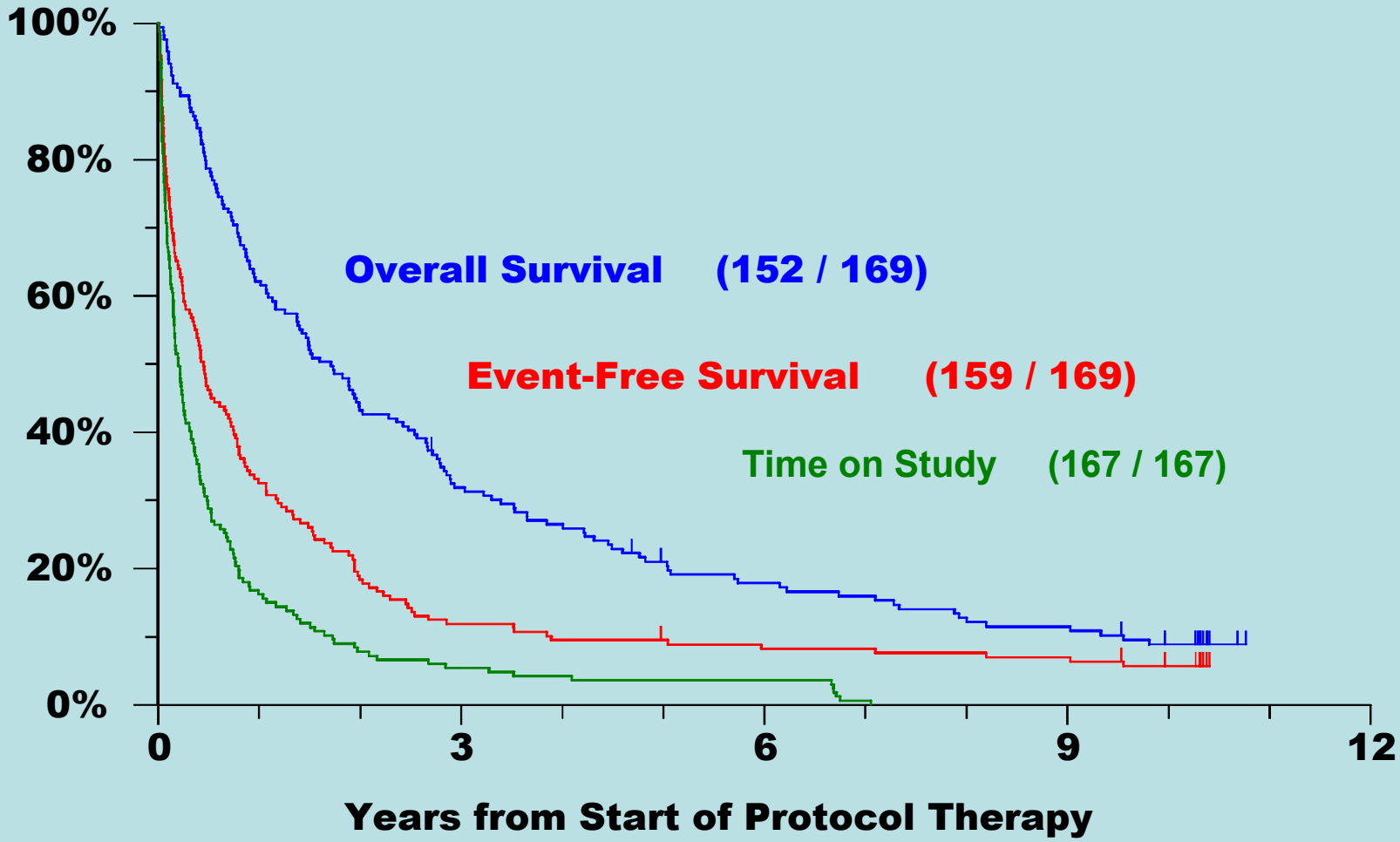


NEJM 1999

THE POWER OF ANECDOTES

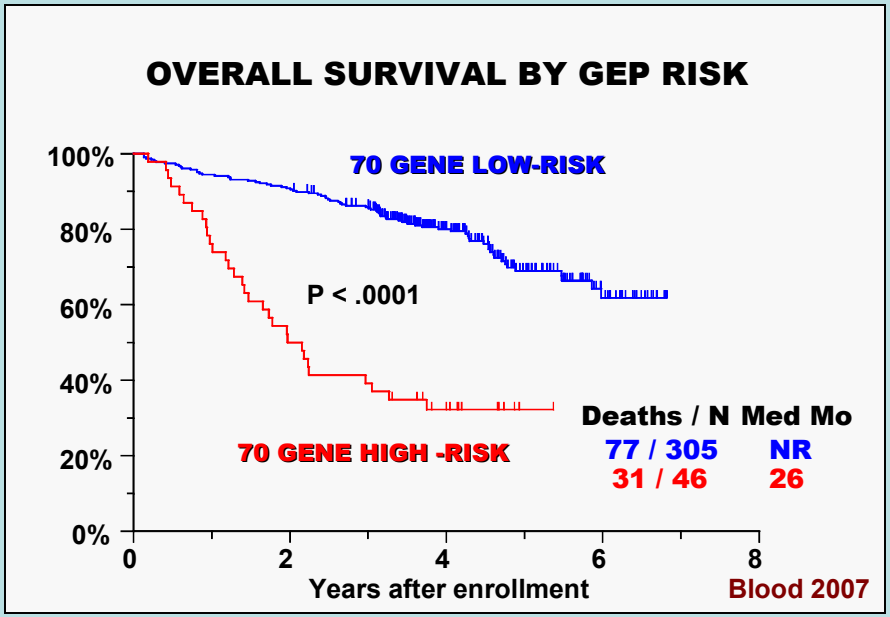
First Thalidomide Trial: UARK 90-003

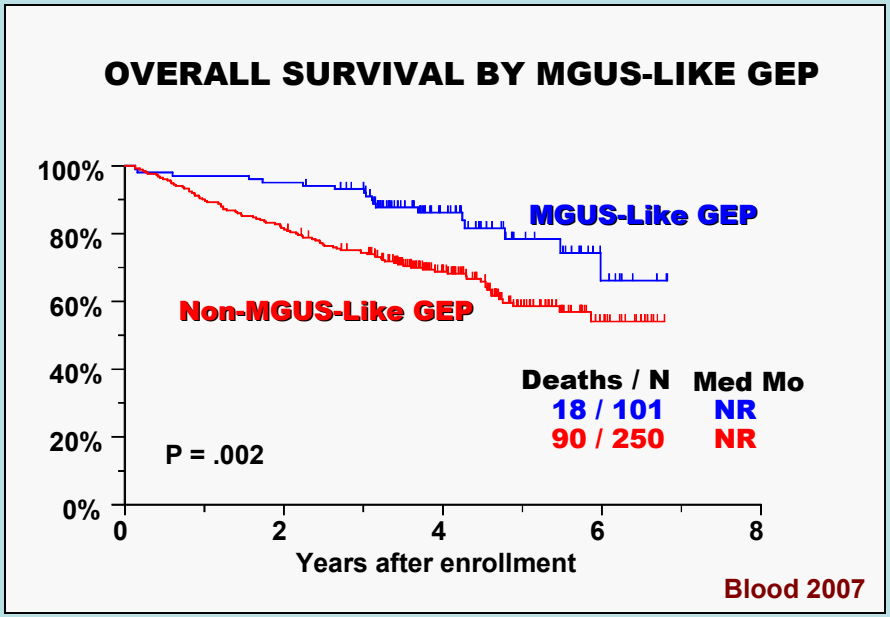
Median follow-up, 10yr; data as of 02/19/09

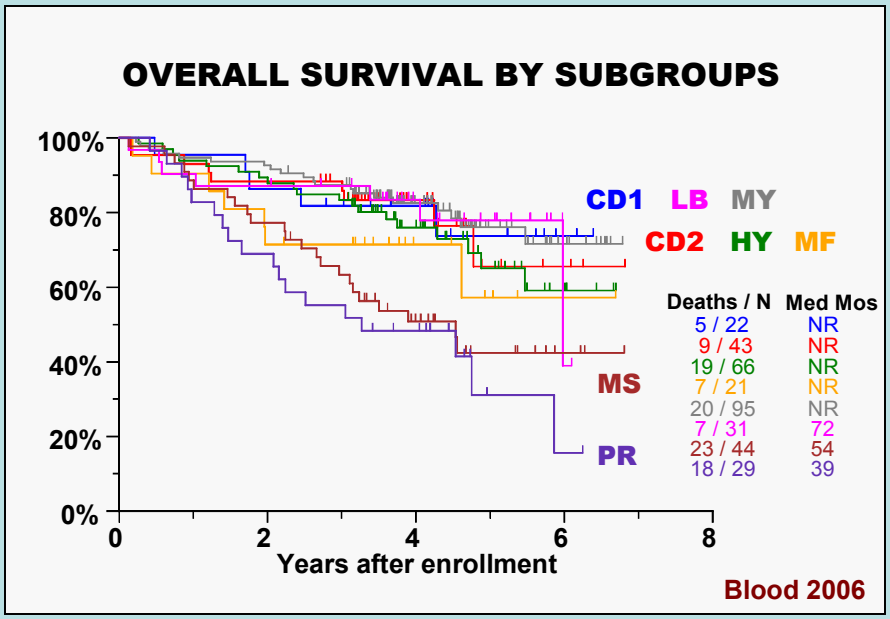


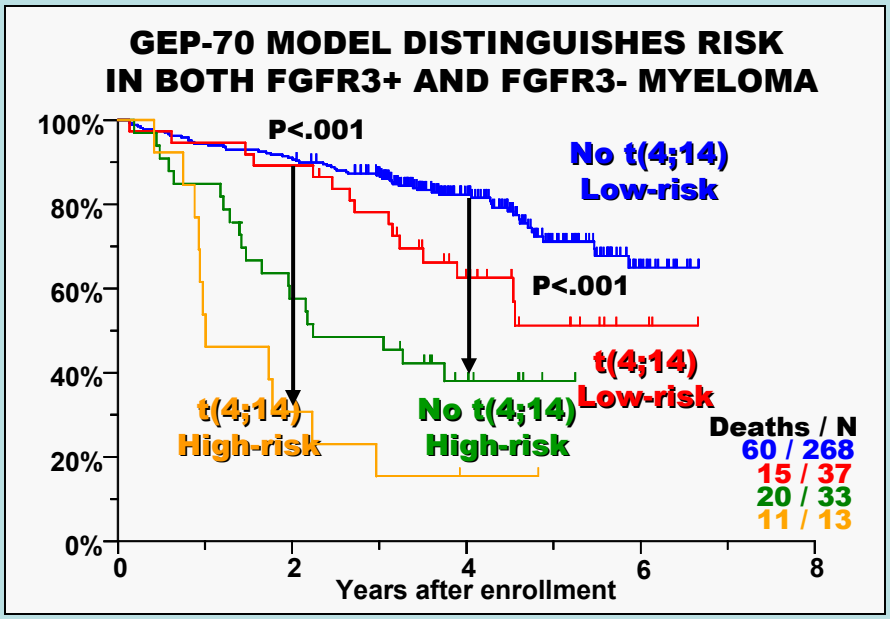
Blood 2001

TT2: 3 GEP MODELS WITH CLINICAL IMPACT





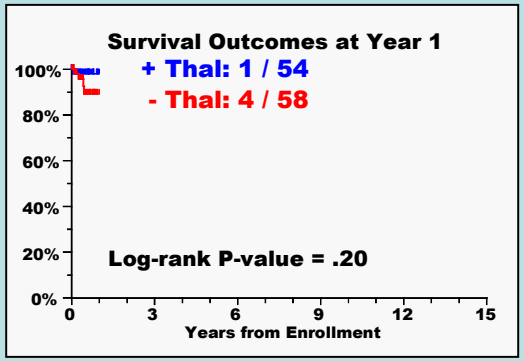


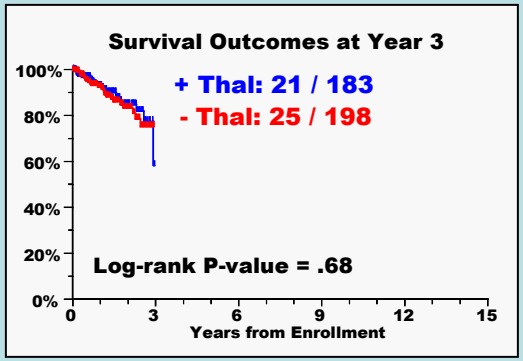


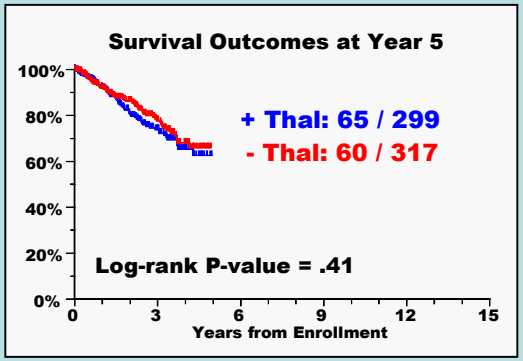
PREMATURE REPORTING OF MYELOMA TRIALS

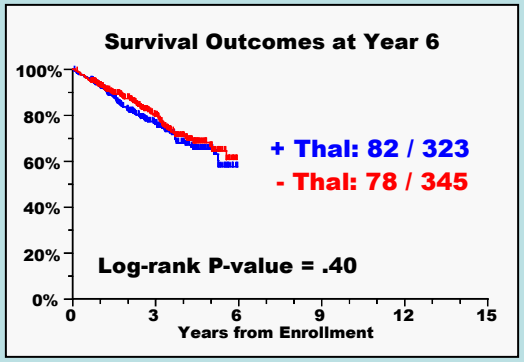
Lessons from Total Therapy 2 +/- Thalidomide

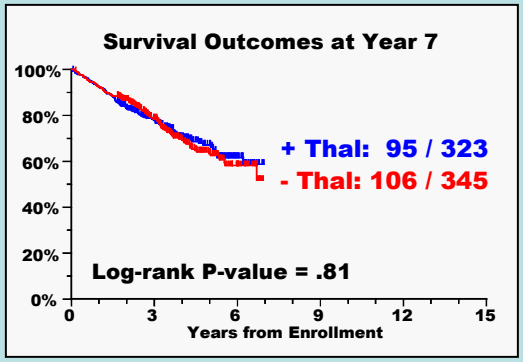
RE-ITERATING SURVIVAL ANALYSES

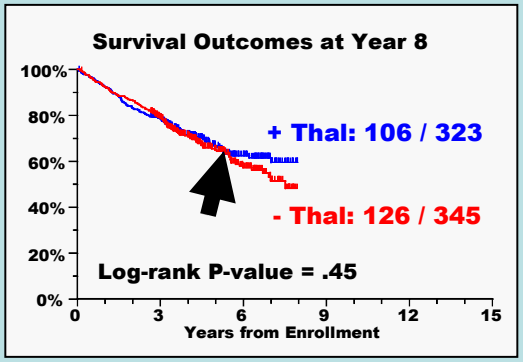


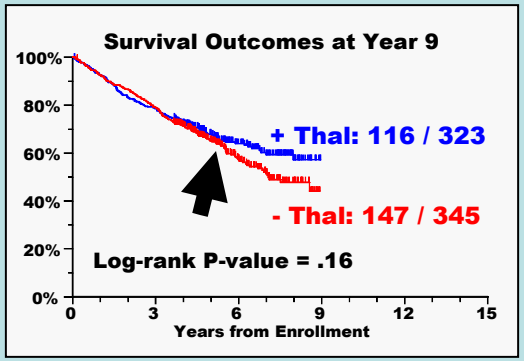


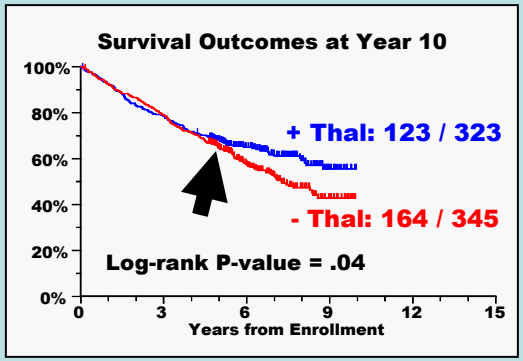






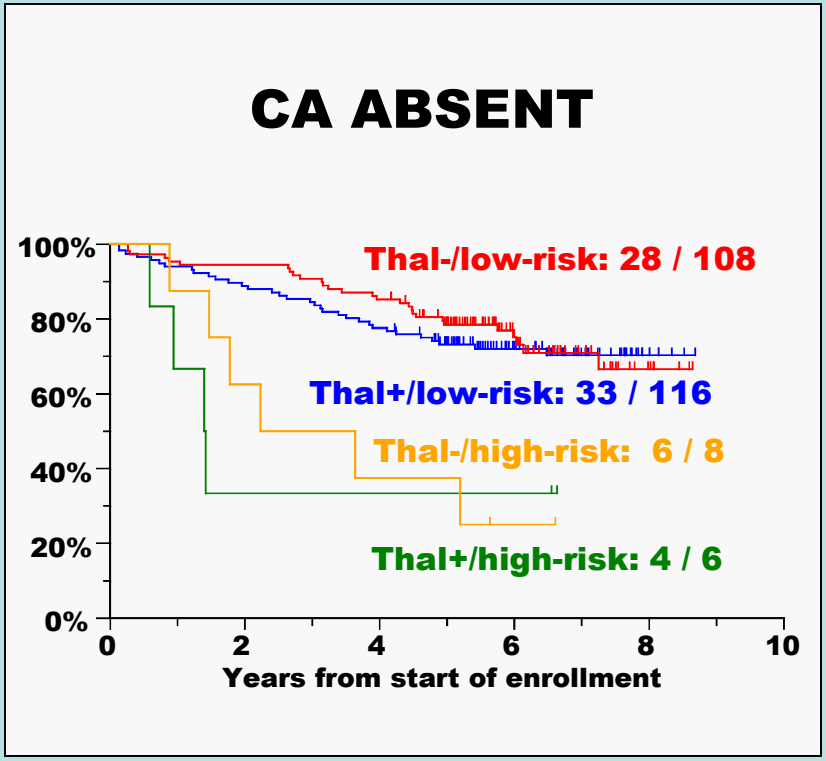


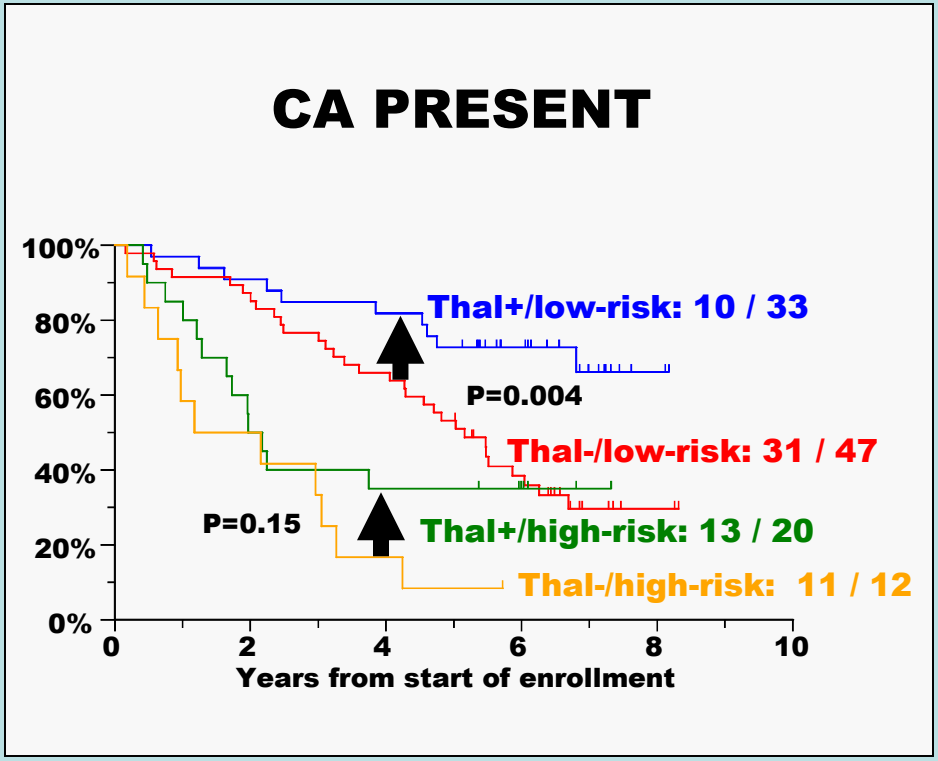




NOTE THE LATE DIVERGENCE OF SURVIVAL CURVES AFTER 5 YEARS

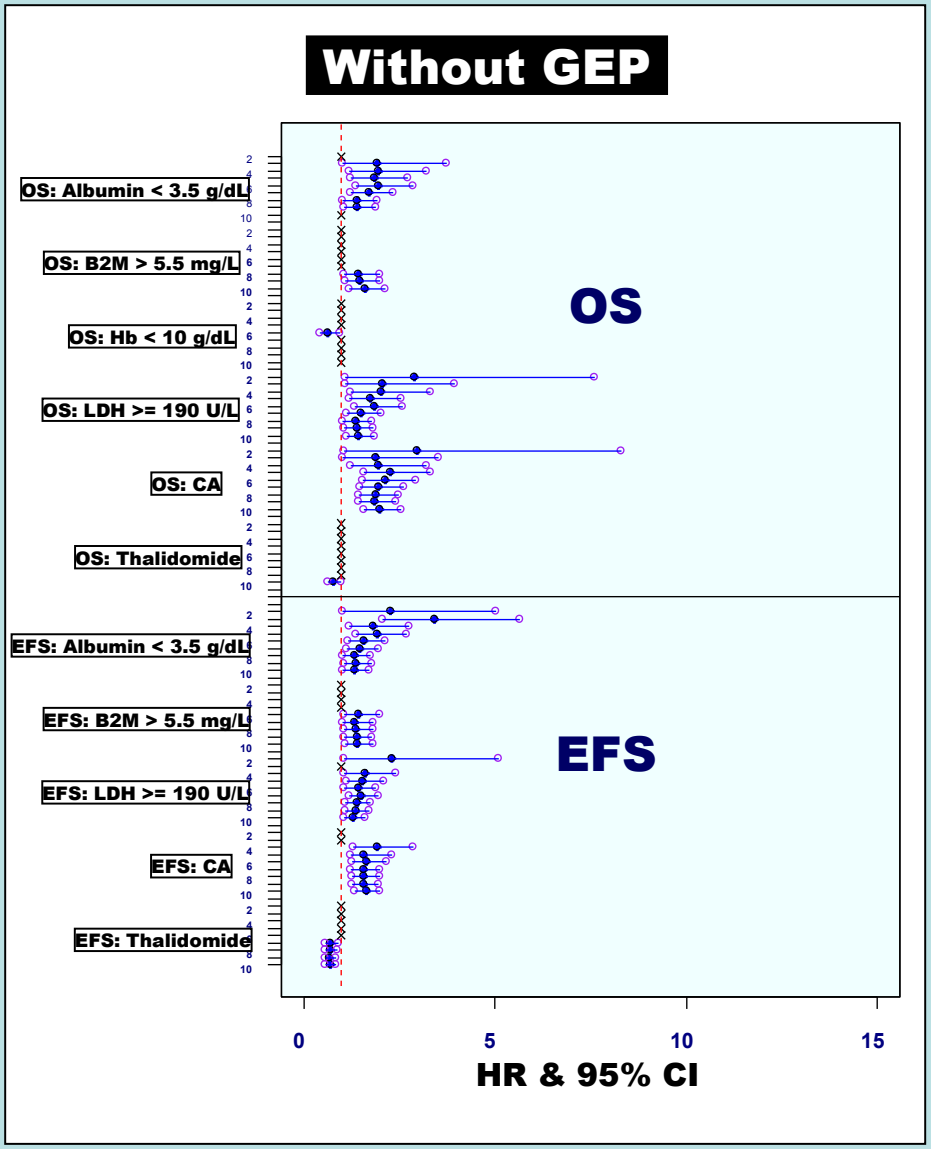
TT2: THAL SURVIVAL BENEFIT LIMITED TO CA-TYPE MYELOMA WITH LOW-RISK FEATURES

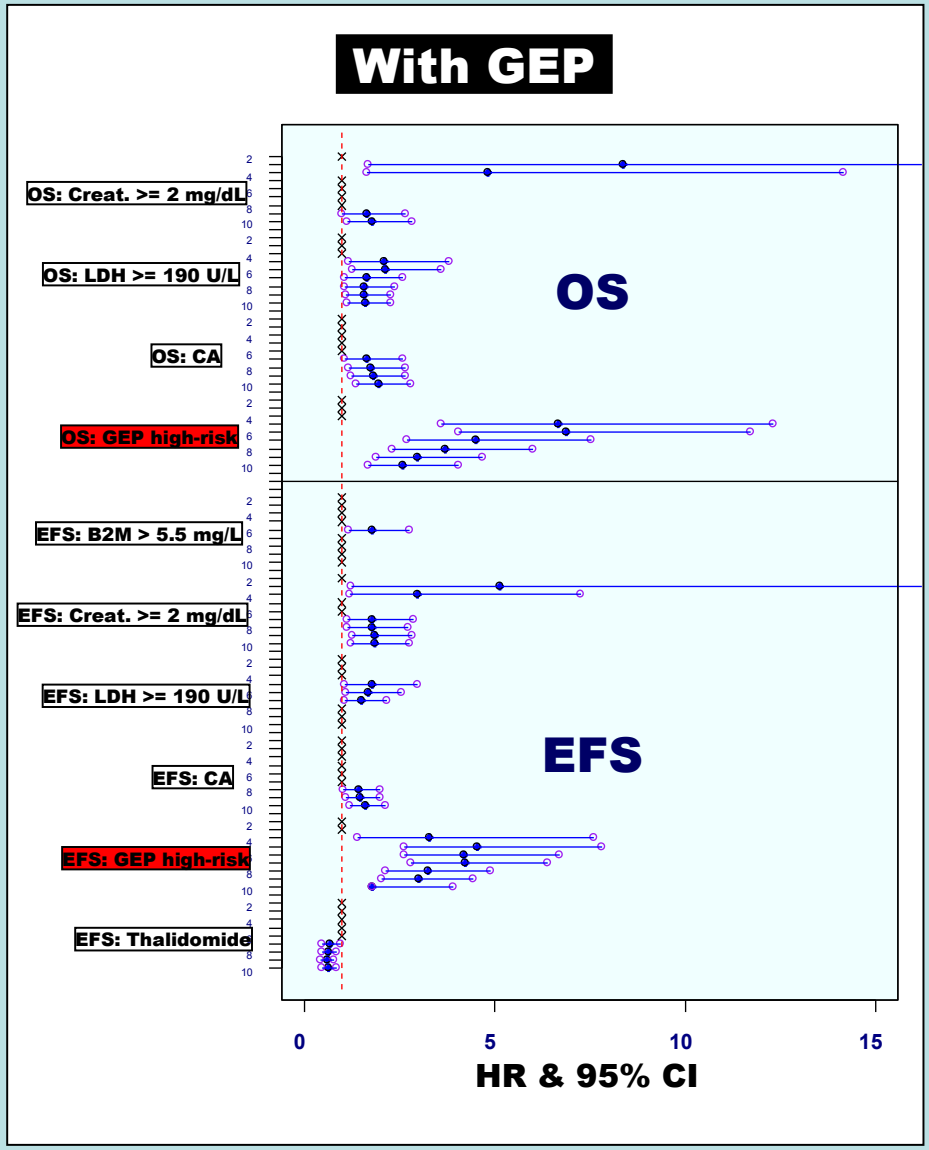




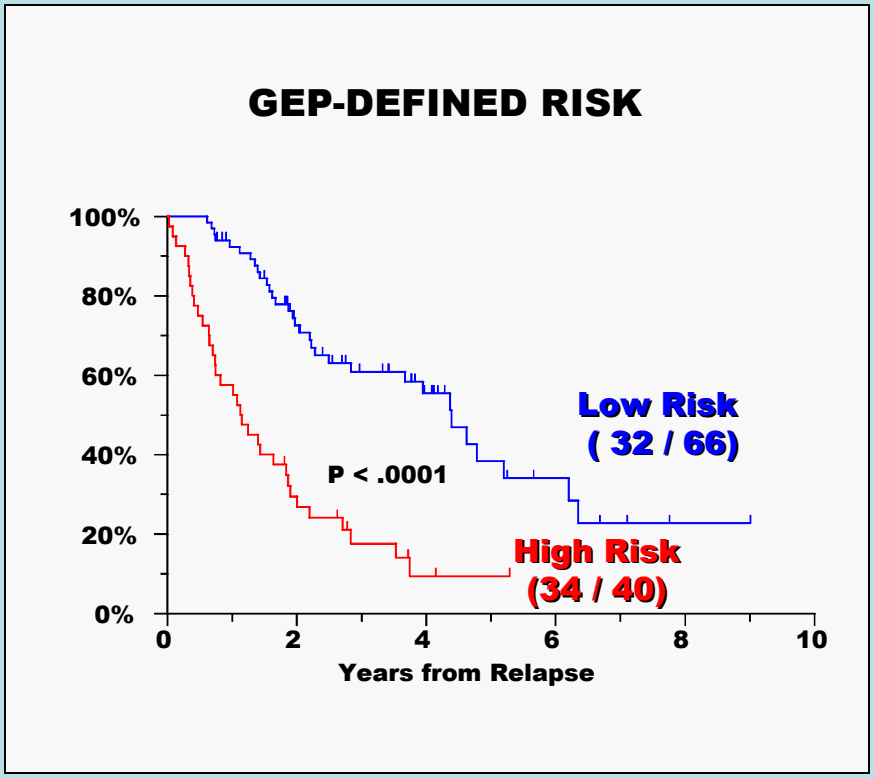
Blood 2008

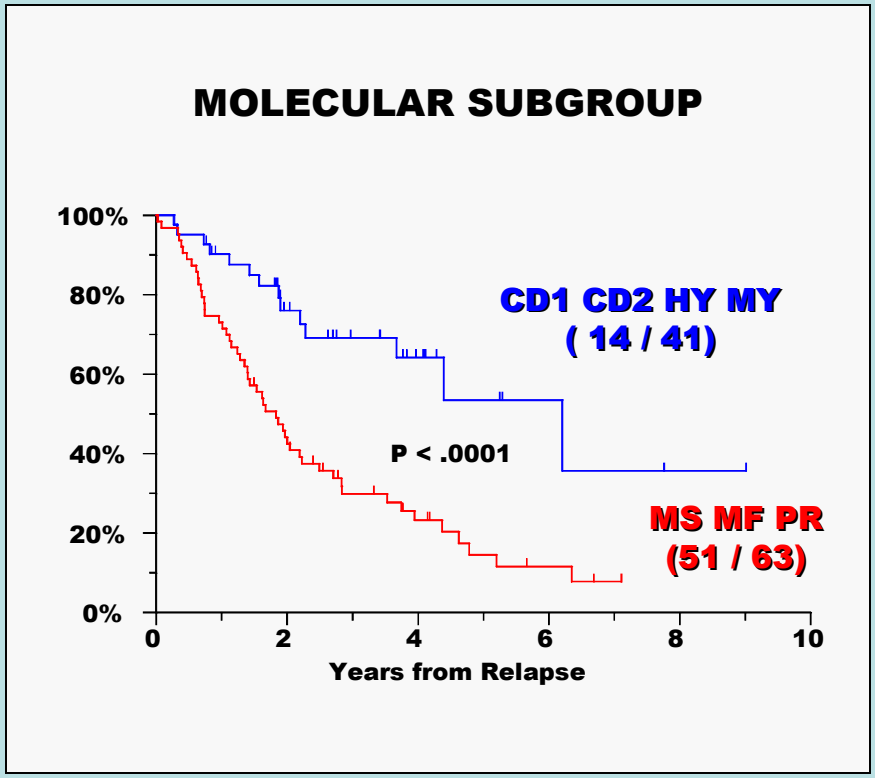
TT2: MV OF VARIABLES AFFECTING OS & EFS: REITERATIVE ANALYSES YEAR 2 TO 10





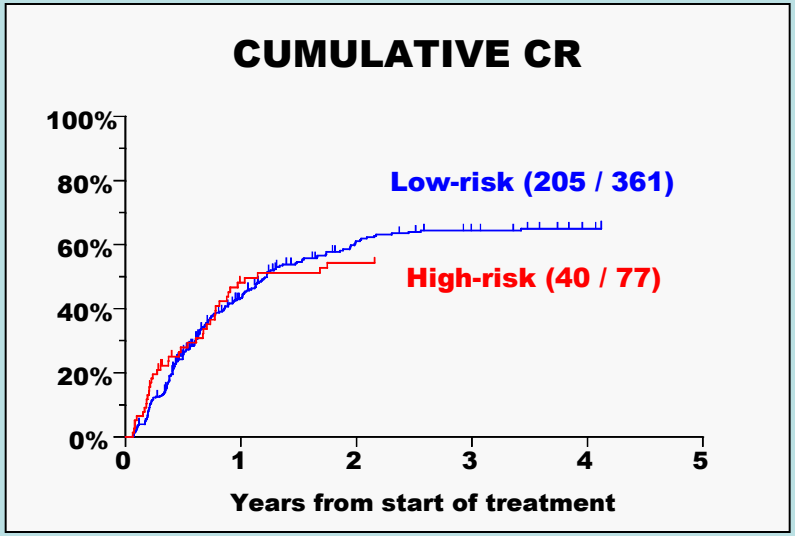
TT2: POST-RELAPSE SURVIVAL IMPACTED BY GEP AT RELAPSE

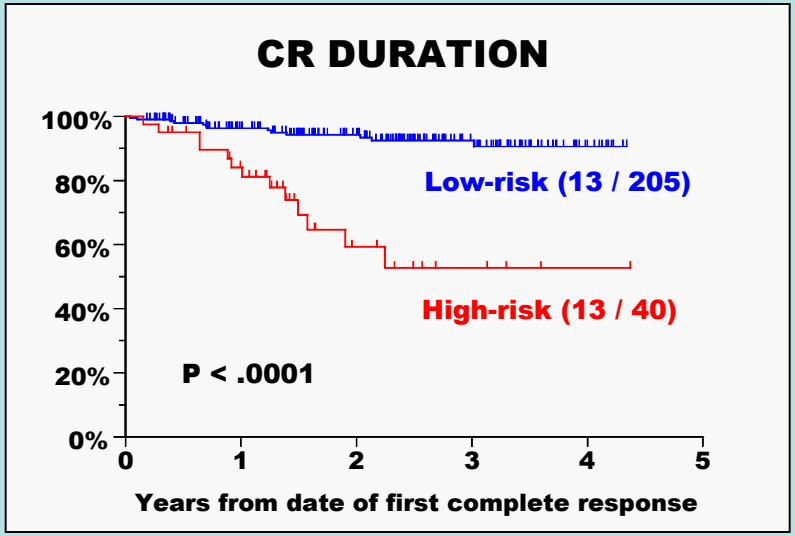


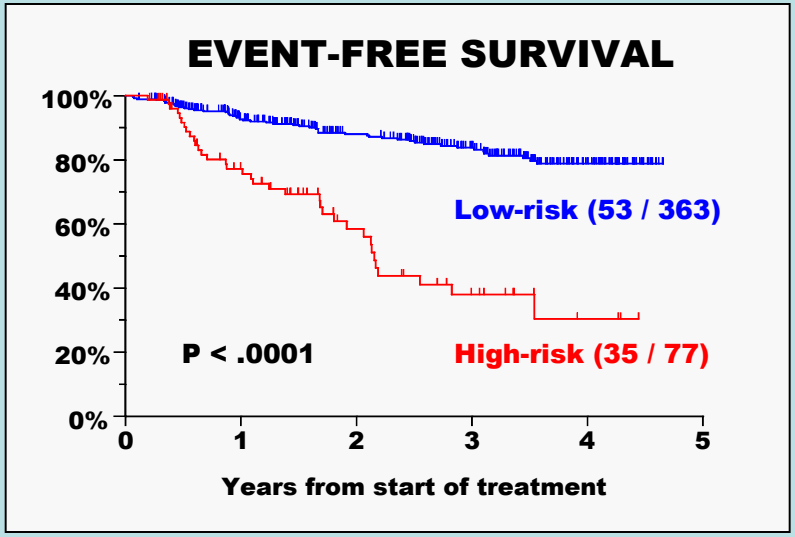


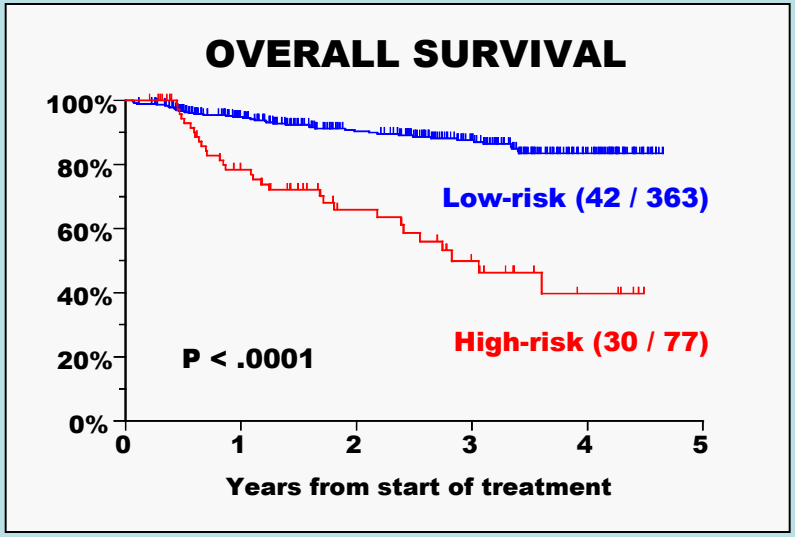
TREATMENT OUTCOMES BY GEP-DEFINED RISK

all TT3 patients





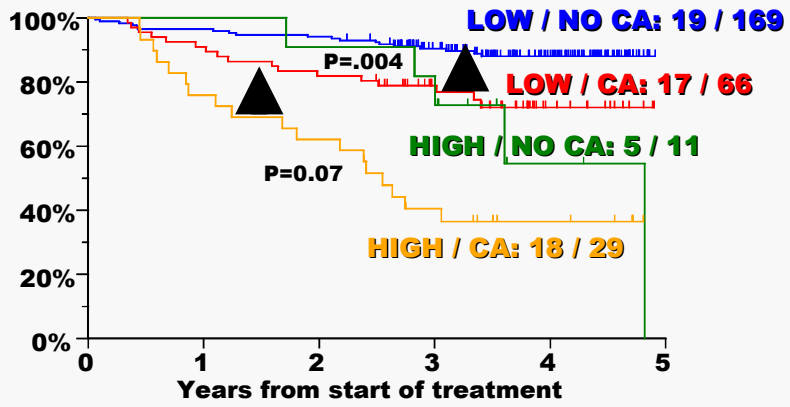




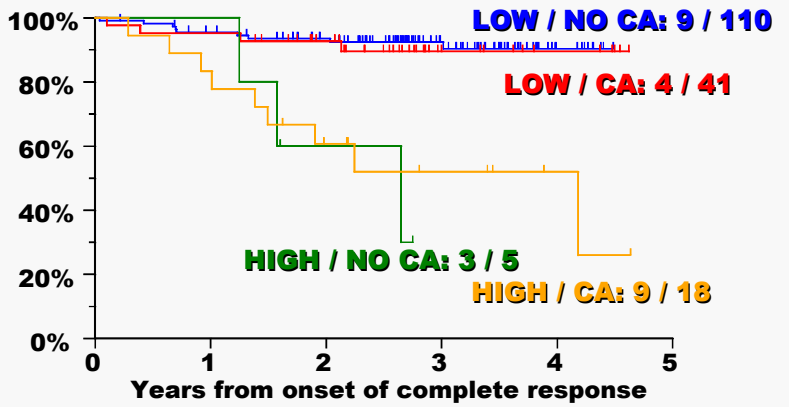
PROGNOSTIC POWER OF GEP-DEFINED RISK VALIDATED

TT3 OUTCOMES IN CONTEXT OF GEP RISK, CA & MOLECULAR SUBGROUPS

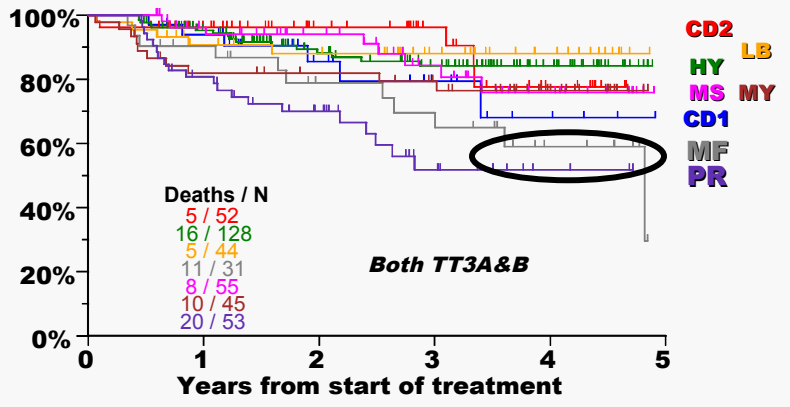
OVERALL SURVIVAL BY RISK & CA



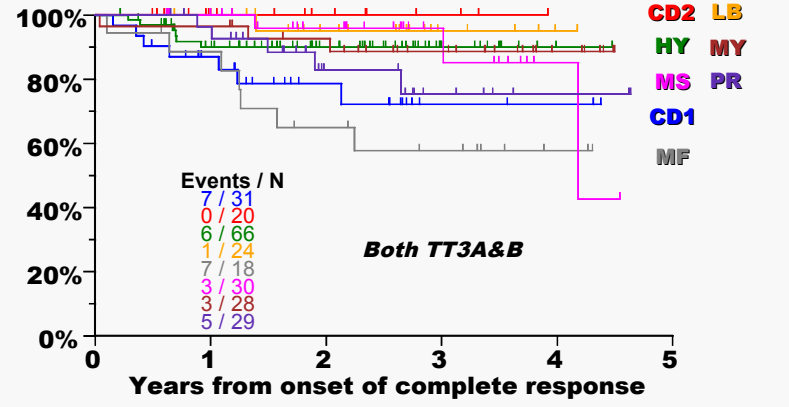
CR DURATION BY RISK & CA



OVERALL SURVIVAL BY MOL. GROUP



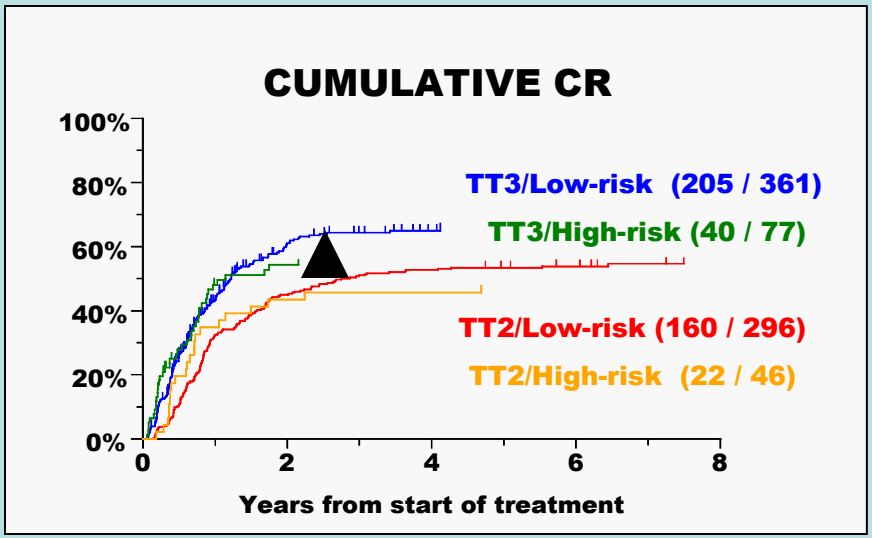
CR DURATION BY MOL. GROUP

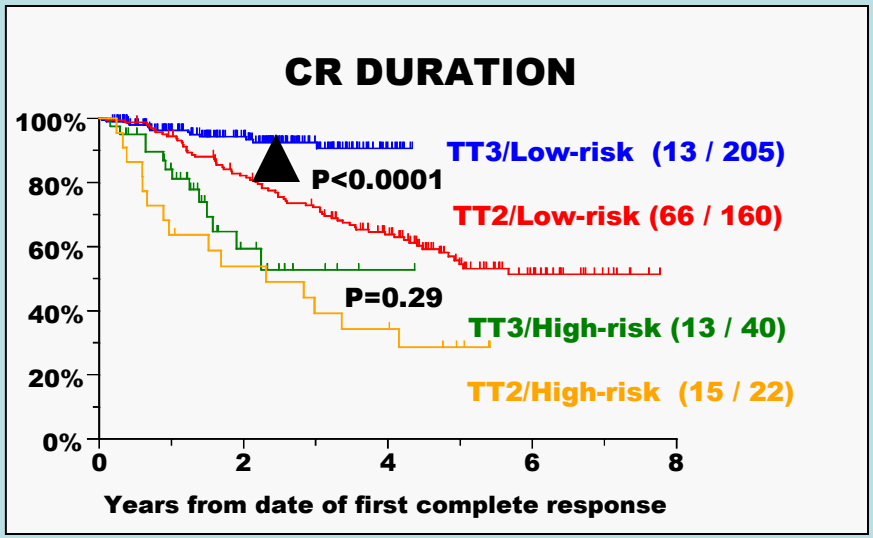


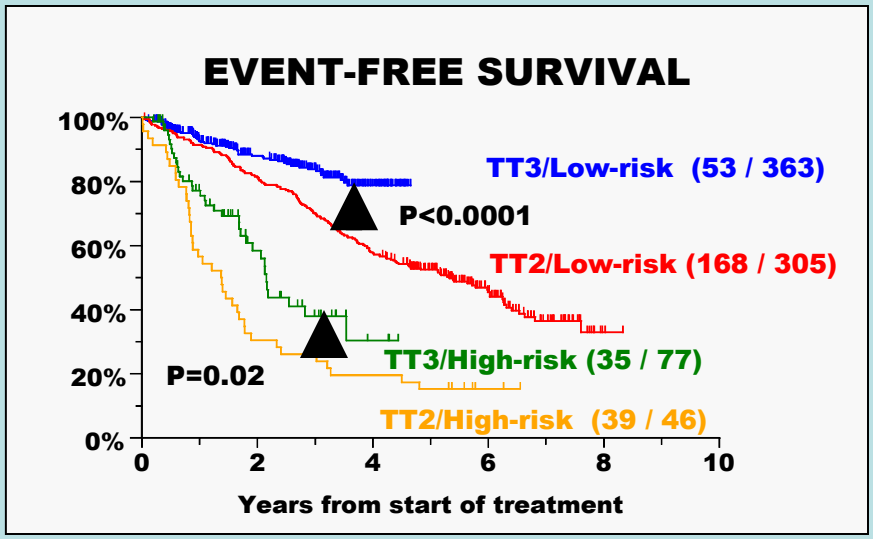
R2 CAPTURING OUTCOME VARIABILITY REACHES 50% IN TT3 PROGNOSTIC MODELS

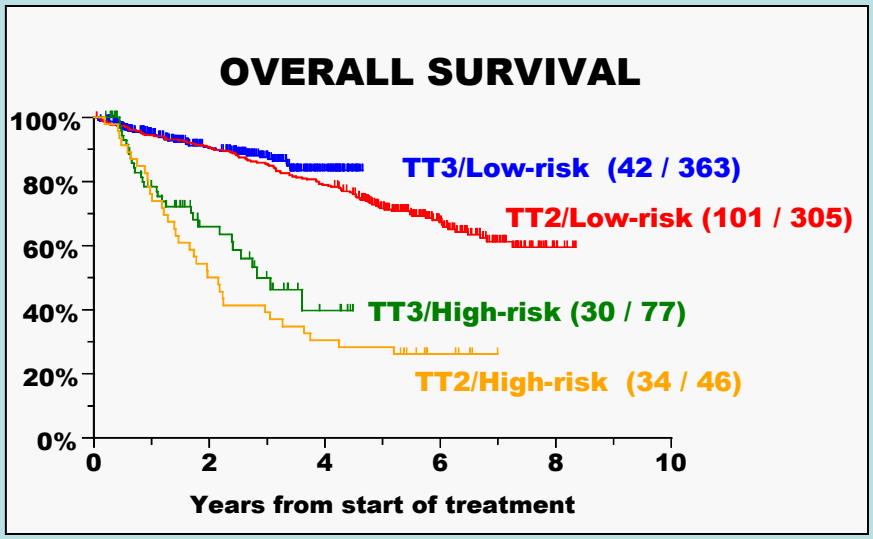
ENDPOINT	Variable	%	HR	P	R^2 %
Overall Survival (N=432)	***Cytogenetic abnormalities***	***38***	***2.39***	***<.001***	***28***
	GEP high-risk	**17**	**2.47**	**<.001**	**34**
	B2M > 5.5 mg/L	25	1.87	0.010	38
Event-free Survival	**GEP high-risk**	**17**	**2.40**	**<0.001**	**22**
	Cytogenetic abnormalities	***38***	***1.69***	***0.020***	***30***
	LDH >= 190 U/L	26	1.72	0.012	35
	B2M > 5.5 mg/L	25	1.72	0.015	38
	Albumin < 3.5 g/dL	32	1.72	0.011	40
CR Duration (N=231)	**GEP high-risk**	**16**	**8.20**	**<.001**	**40**
	IgA Isotype	28	3.63	0.002	45
	GEP CD1 subgroup	**12**	**4.24**	**0.003**	**50**
	Creatinine >= 2.0 mg/dL	5	4.75	0.004	52

TREATMENT OUTCOMES BY GEP RISK
both TT3A & TT3B *versus* TT2



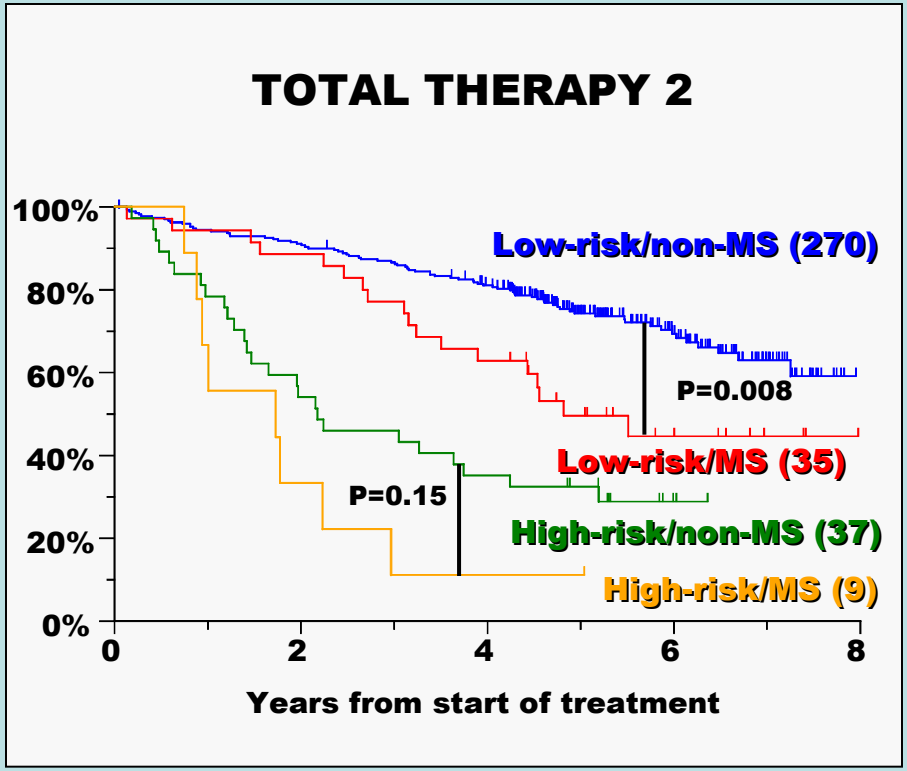


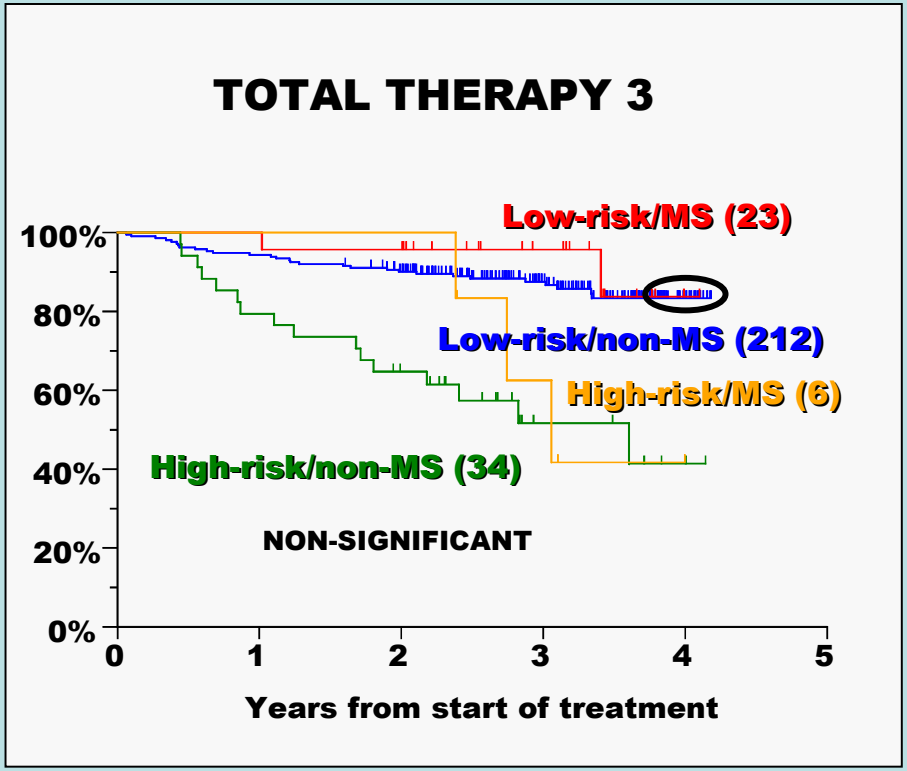




STRIKING BENEFIT OF TT3 v TT2 IN LOW-RISK MYELOMA

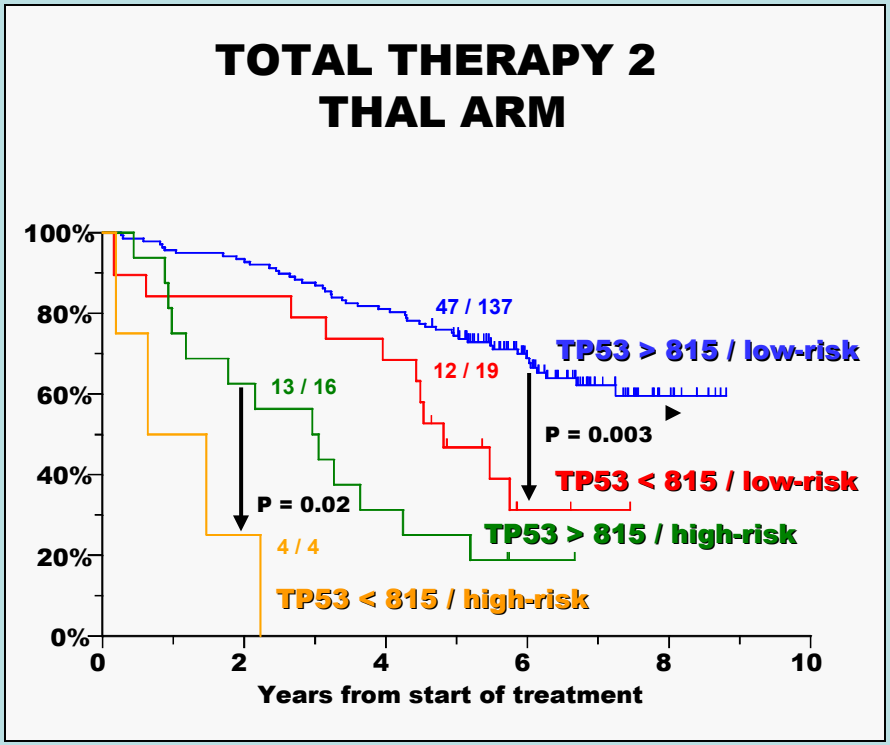
TT3 / TT2: SURVIVAL IN T(4;14)-TYPE MYELOMA ACCORDING TO GEP-DEFINED RISK

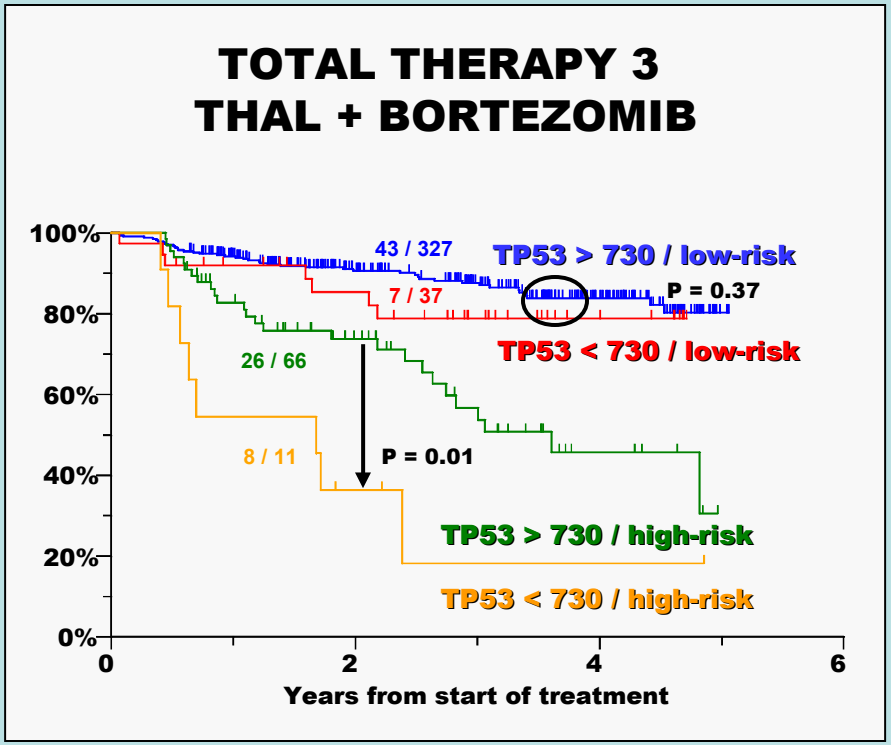




TRANSLOCATION (4;14) NO LONGER ADVERSE FEATURE IN TT3

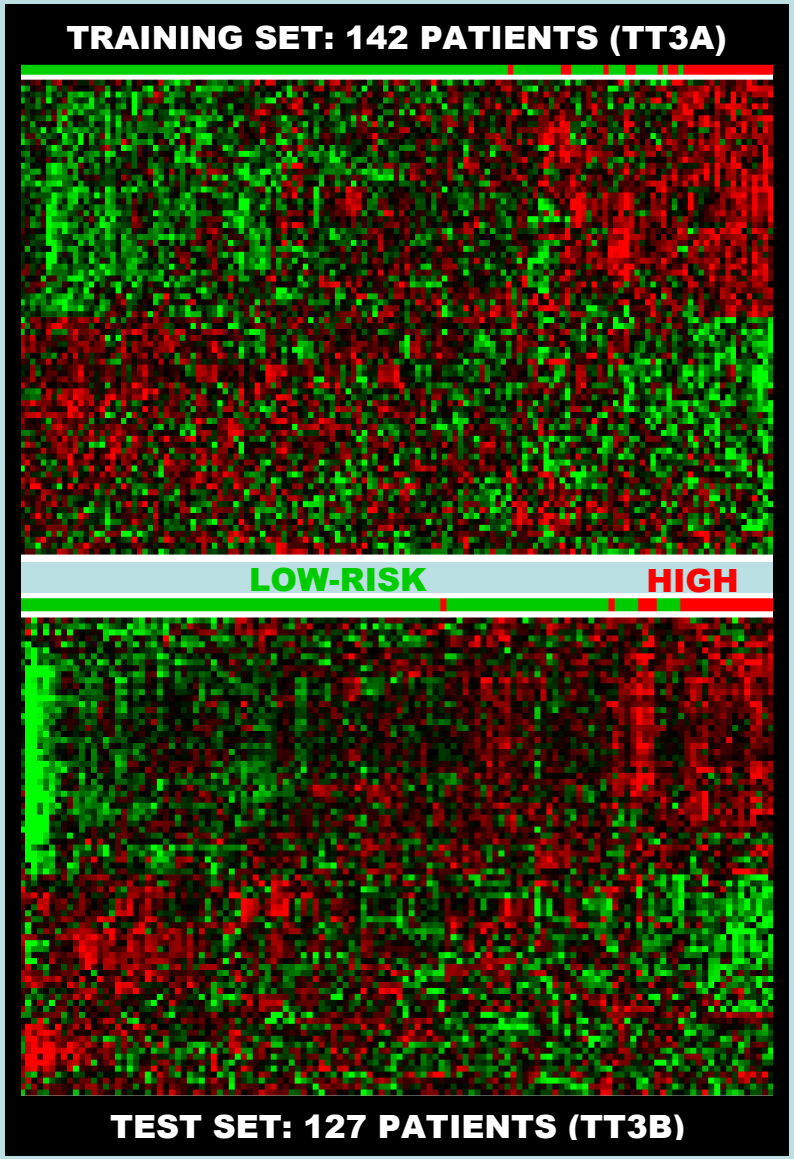
TT3 / TT2 SURVIVAL ACCORDING TO GEP-DEFINED TP53 STATUS AND RISK

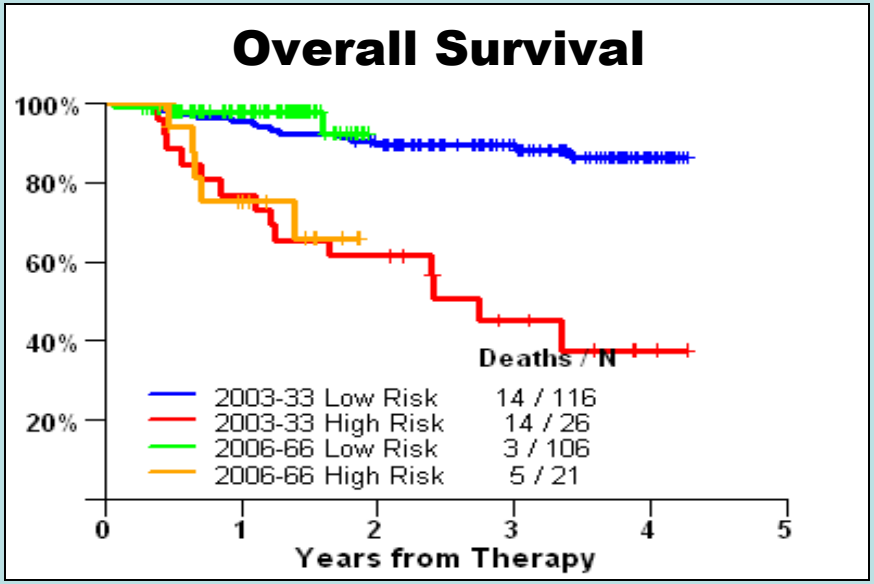


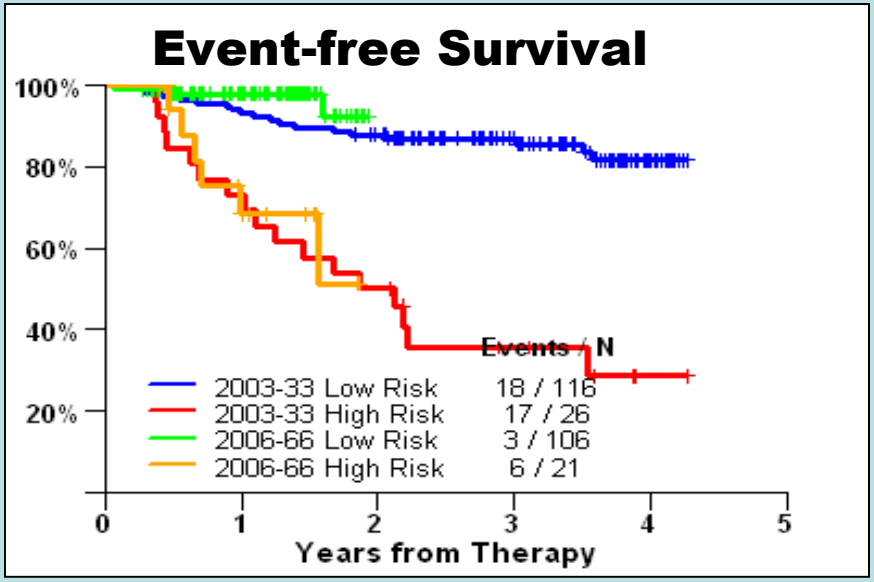


BORTEZOMIB IN TT3 OVERCOMES ADVERSE IMPLICATIONS OF DEL-TP53 IN LOW-RISK DISEASE

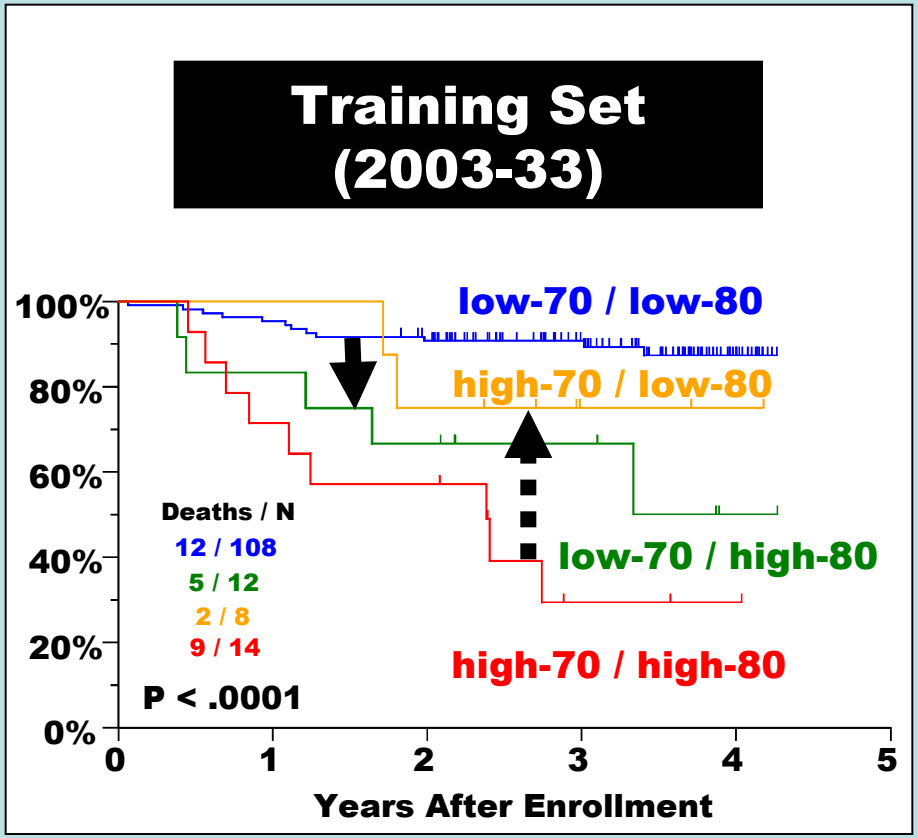
TT3 SURVIVAL OUTCOMES ACCORDING TO POST-BORTEZOMIB PC-GENE MODEL

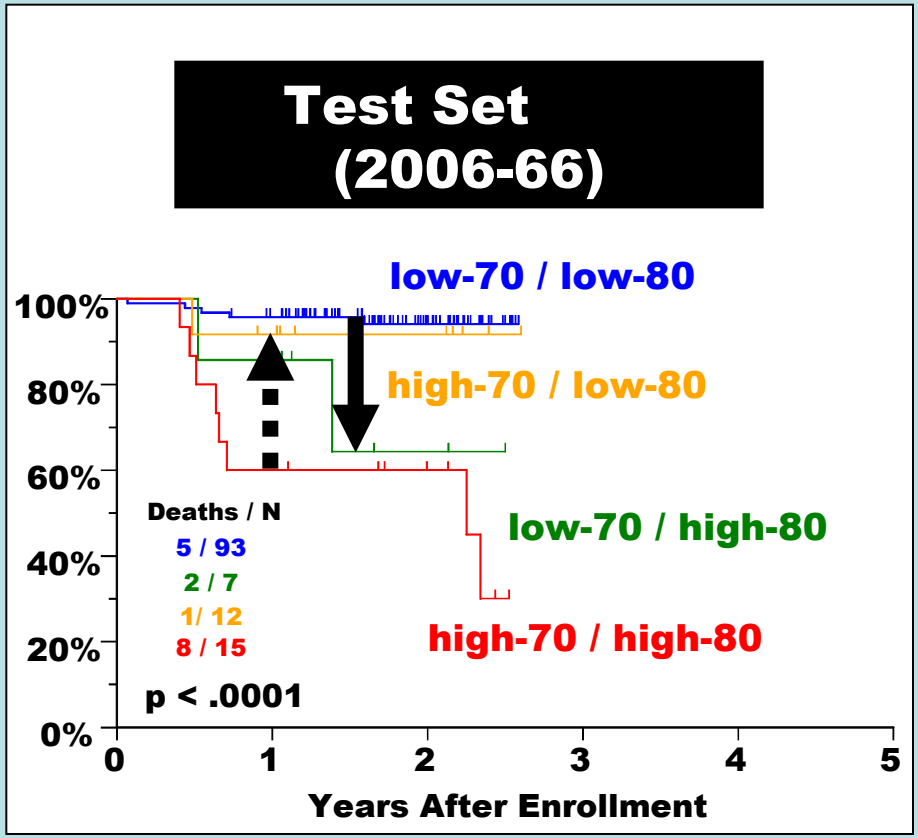






POST-BORTEZOMIB-DERIVED 80-GENE MODEL FURTHER REFINES 70-GENE BASELINE MODEL



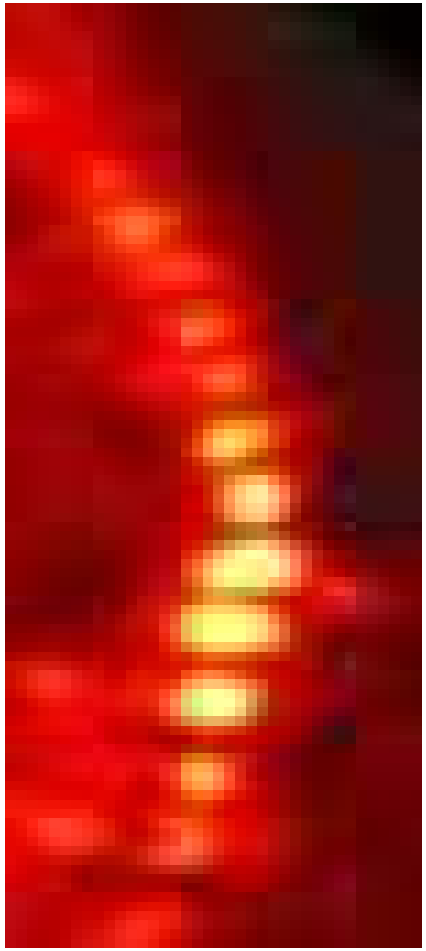


80-GENE MODEL DRIVEN BY PROTEASOME GENES

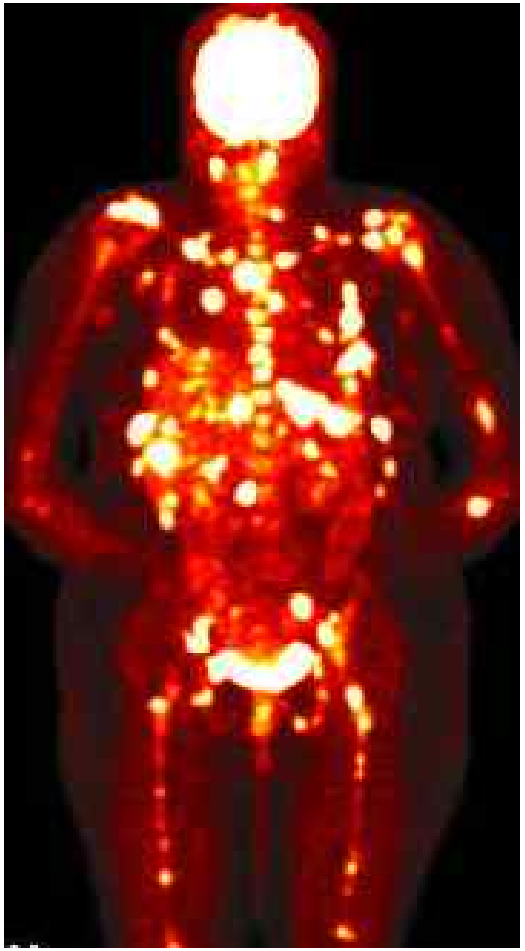
MRI & FDG-PET REVEAL ENORMOUS DISEASE BURDEN/ACTIVITY OFTEN WITH NORMAL X-RAYS

FOCAL LESIONS TYPICALLY PERSIST IN CLINICAL CR, RESOLVE WITH LONG LAG TIME AND ARE SITES OF MYELOMA RELAPSE

Sagittal STIR MRI

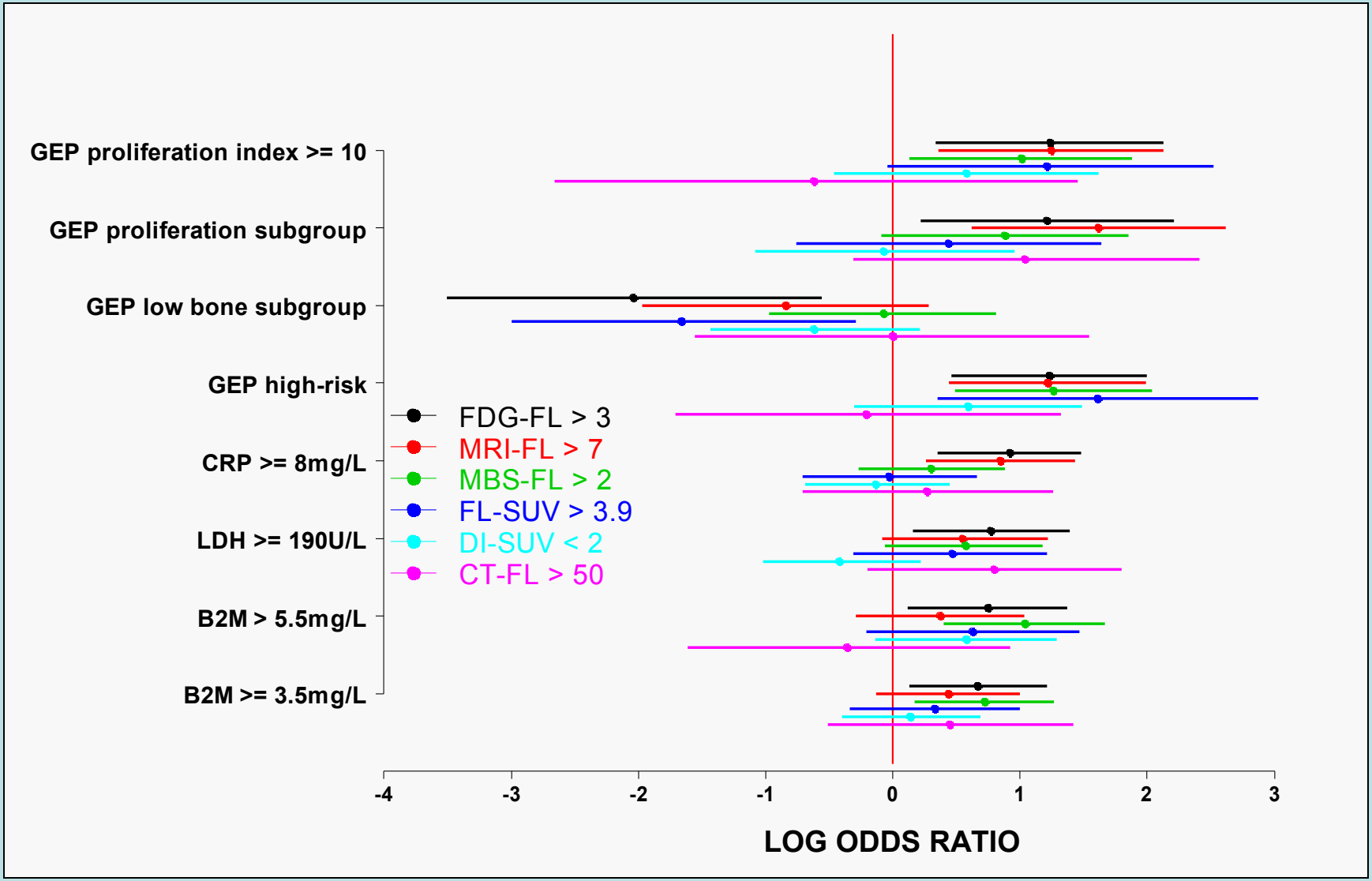


Sagittal FDG PET



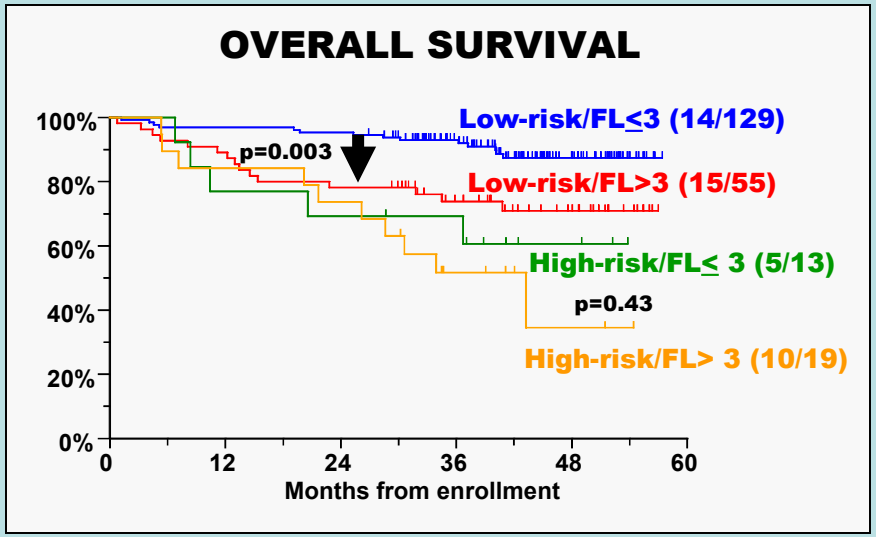
AP FDG PET

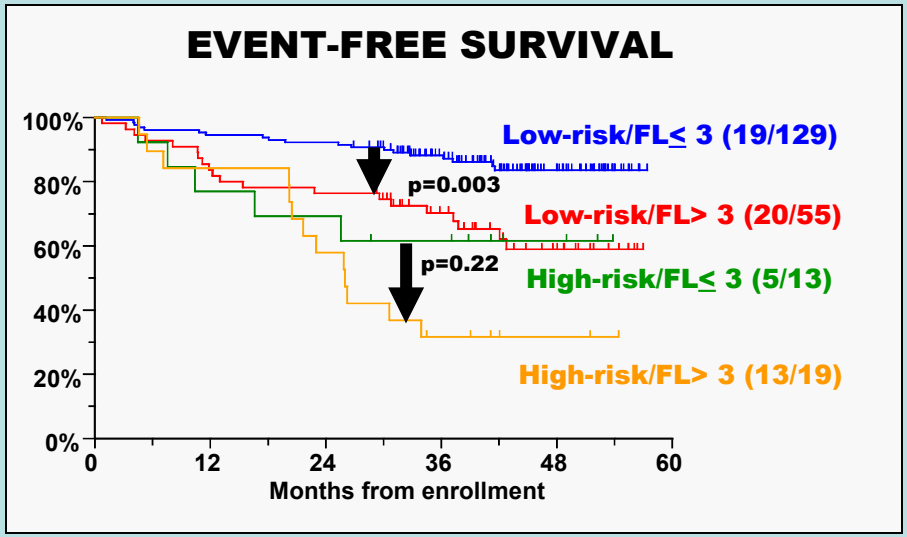
METASTATIC BONE SURVEY, MRI & PET-CT DEFINED FOCAL LESIONS (FL) IN MYELOMA



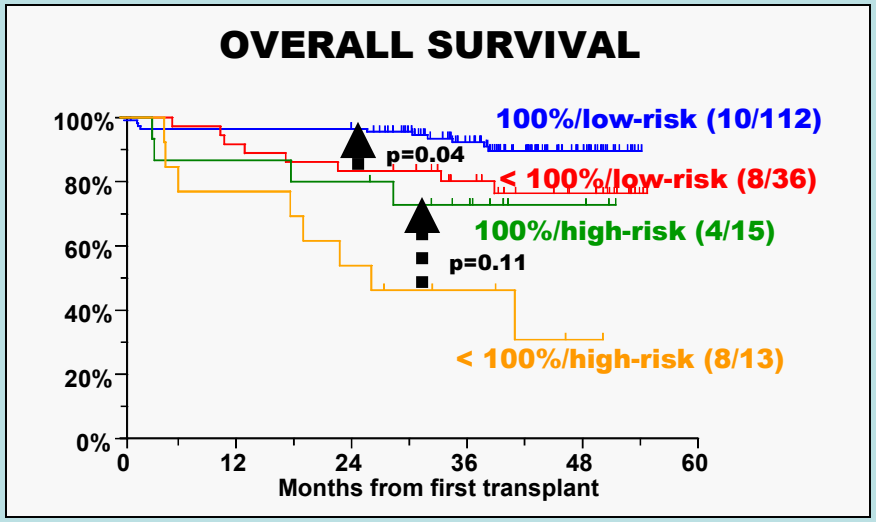
FL LINKED TO STANDARD PROGNOSTIC FACTORS & GEP VARIABLES

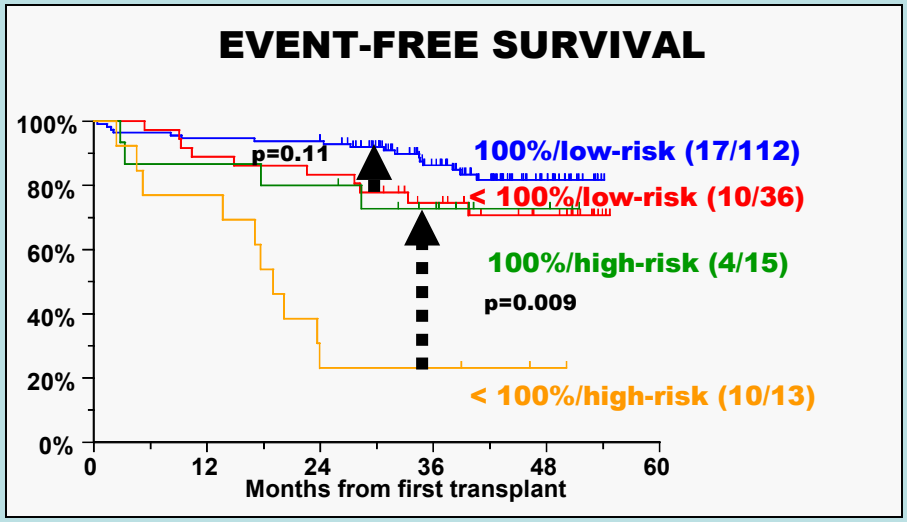
TT3 SURVIVAL BY GEP RISK & FDG-FL AT BASELINE





TT3 SURVIVAL BY 100% FDG SUPPRESSION PRE-Tx

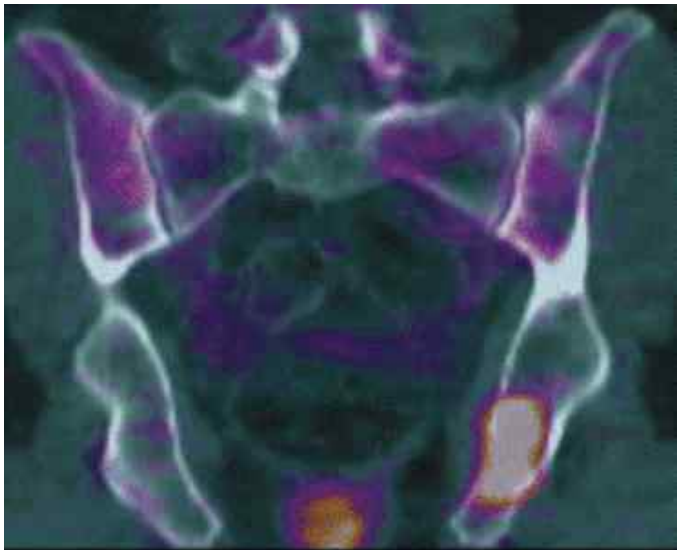




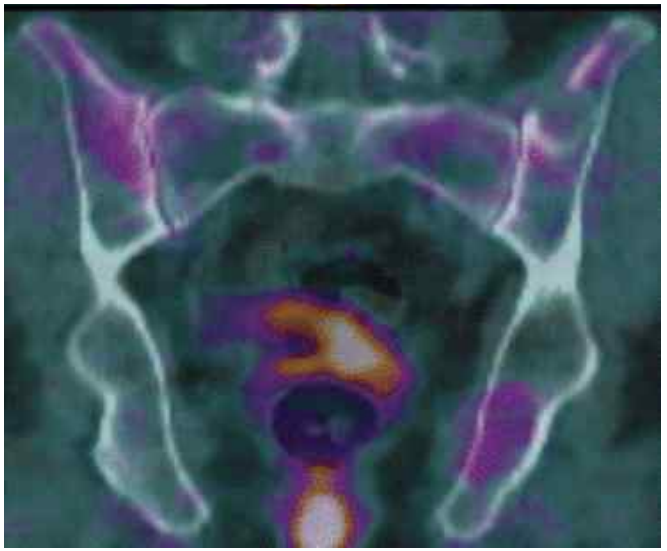
MV ANALYSIS OF BASELINE VARIABLES & 100% FDG SUPPRESSION ON TT3 SURVIVAL

Multivariate Analysis		Overall Survival from 1st transplant			Event-free Survival from 1st transplant		
without gene array data (n = 196)	%	HR	P	R^2	HR	P	R^2
100% FDG-FL reduction	**71**	**0.33**	**0.001**	**37%**	**0.47**	**0.013**	**48%**
FDG-FL > 3	**35**	NS	NS	NS	**2.01**	**0.028**	**37%**
LDH >= 190 U/L	**23**	**2.27**	**0.024**	**43%**	**2.61**	**0.002**	**25%**
B2M > 5.5 mg/L	**19**	**2.45**	**0.015**	**49%**	**2.00**	**0.033**	**43%**
with gene array data (n = 175)	%	HR	P	R^2	HR	P	R^2
100% FDG-FL reduction	**72**	**0.41**	**0.017**	**37%**	**0.51**	**0.038**	**56%**
GEP high-risk	**16**	**2.64**	**0.015**	**52%**	**2.12**	**0.032**	**48%**
Cytogenetic abnormalities	**35**	**2.59**	**0.018**	**58%**	NS	NS	NS
CRP >= 8 mg/L	**33**	**2.43**	**0.018**	**57%**	NS	NS	NS

Clinical CR did not enter the model!



A highly F18-FDG-avid focal myeloma lesion (top image) resolved on follow-up PET-CT examination after 2 cycles of induction therapy (bottom image). When systematically examined as part of Total Therapy 3, such PET-CR status achieved prior to first transplantation was a prognostic indicator of reduced risk of relapse by 49% and of death by 59%, independent of risk as defined by gene array analysis.



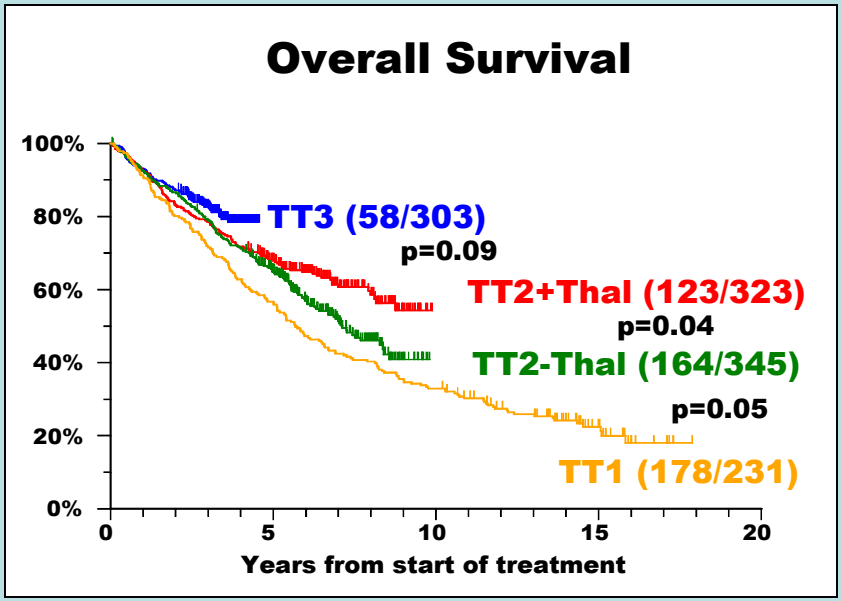
F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma

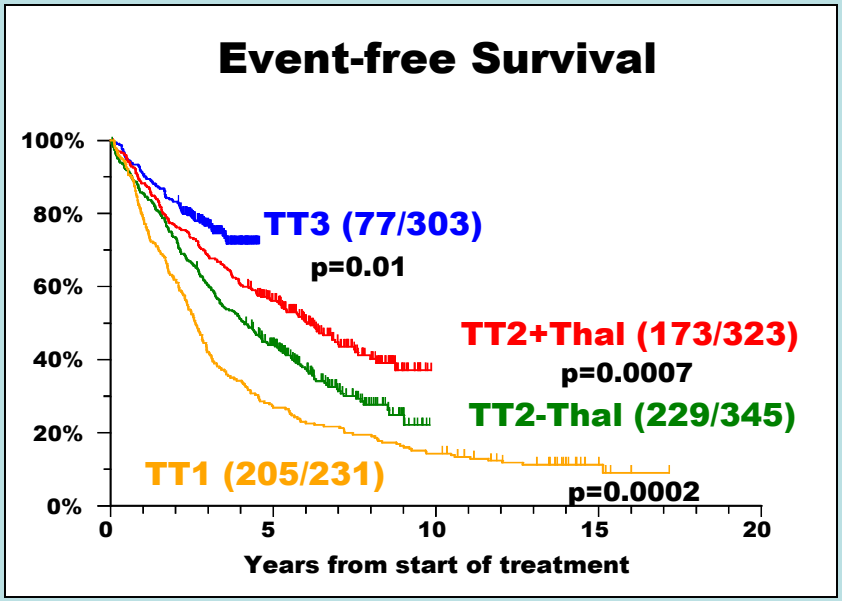
Twyla B. Bartel, Jeff Haessler, Tracy L. Y. Brown, John D. Shaughnessy, Jr, Frits van Rhee3, Elias Anaissie, Terri Alpe, Edgardo Angtuaco, Ronald Walker, Joshua Epstein, John Crowley, and Bart Barlogie

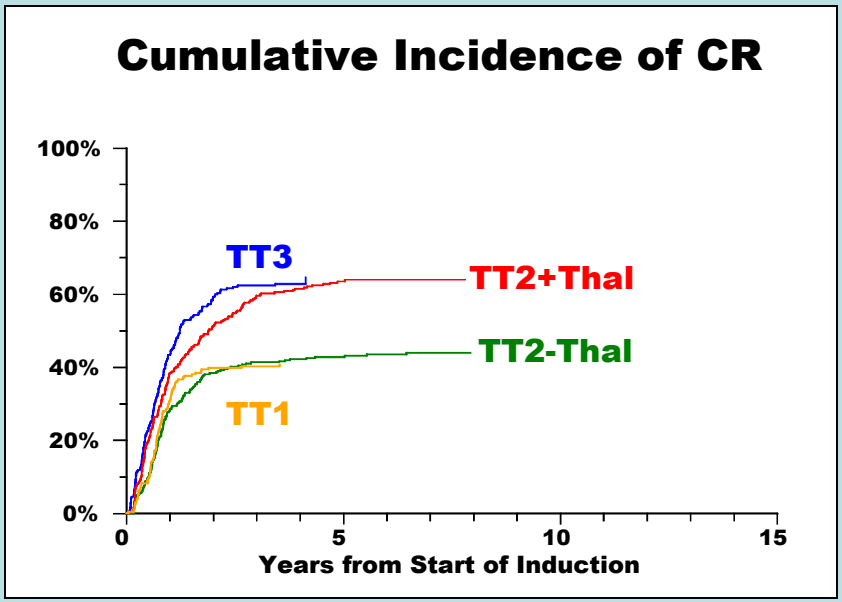
Blood 2009 114:2068-2076

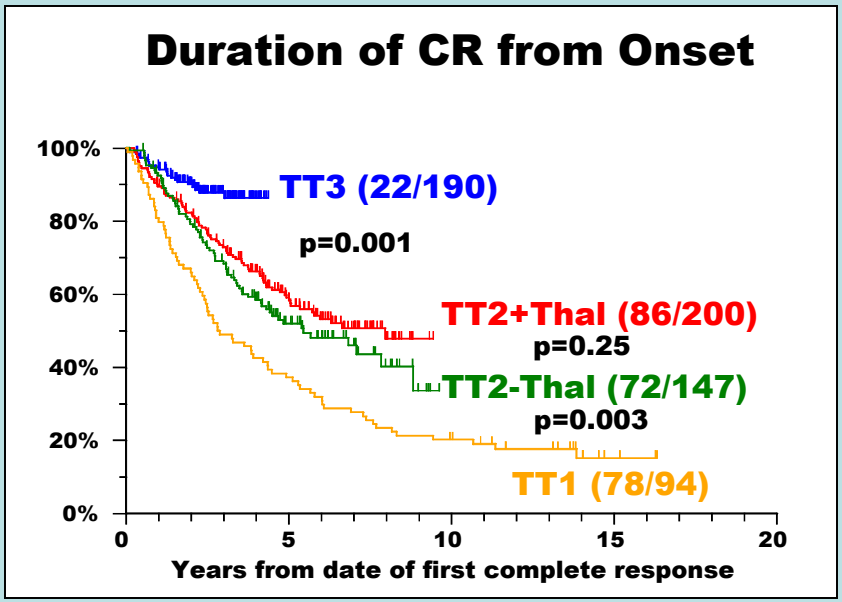
http://bloodjournal.hematologylibrary.org/cgi/content/full/114/10/2068

ADVANCING OUTCOMES WITH TOTAL THERAPY

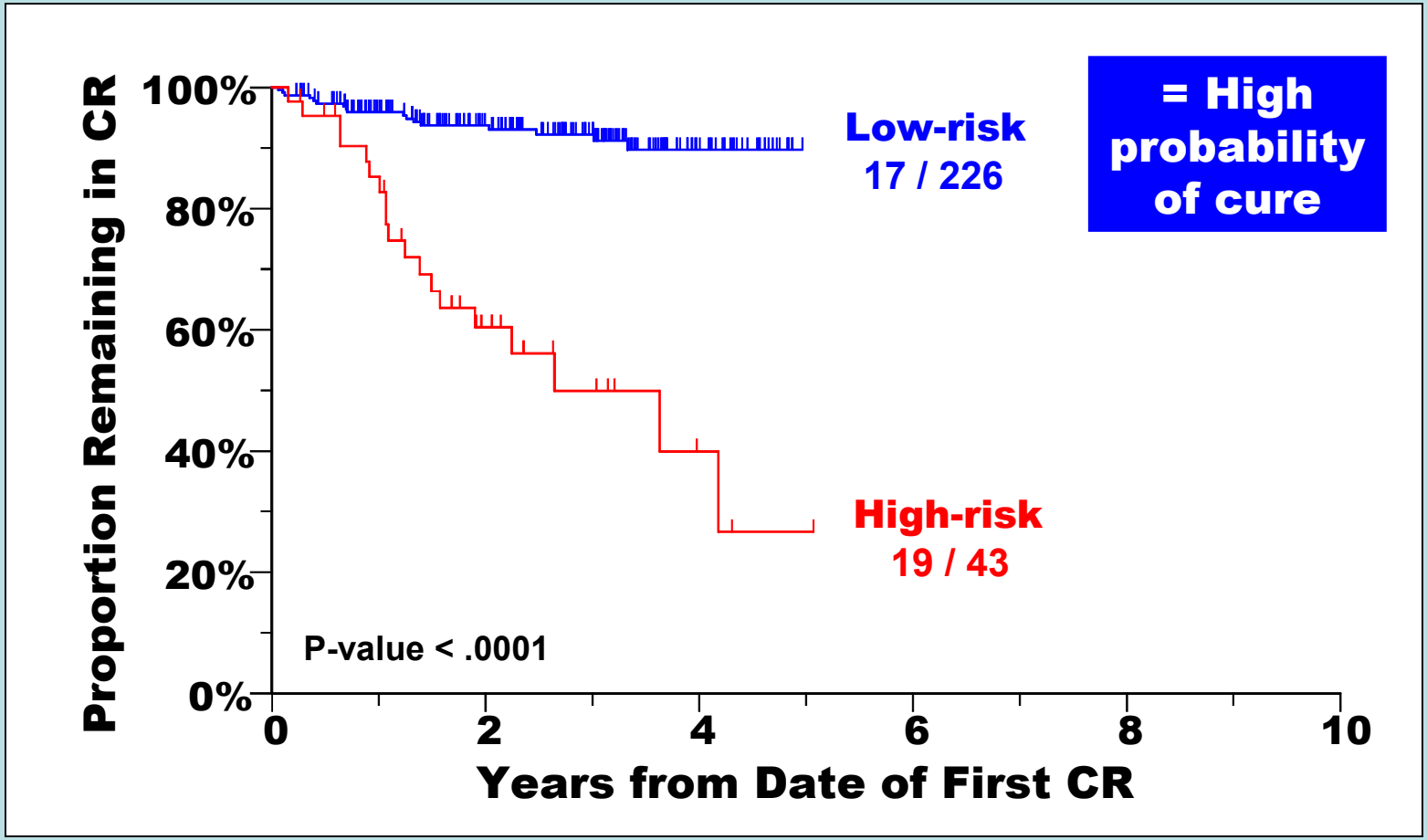






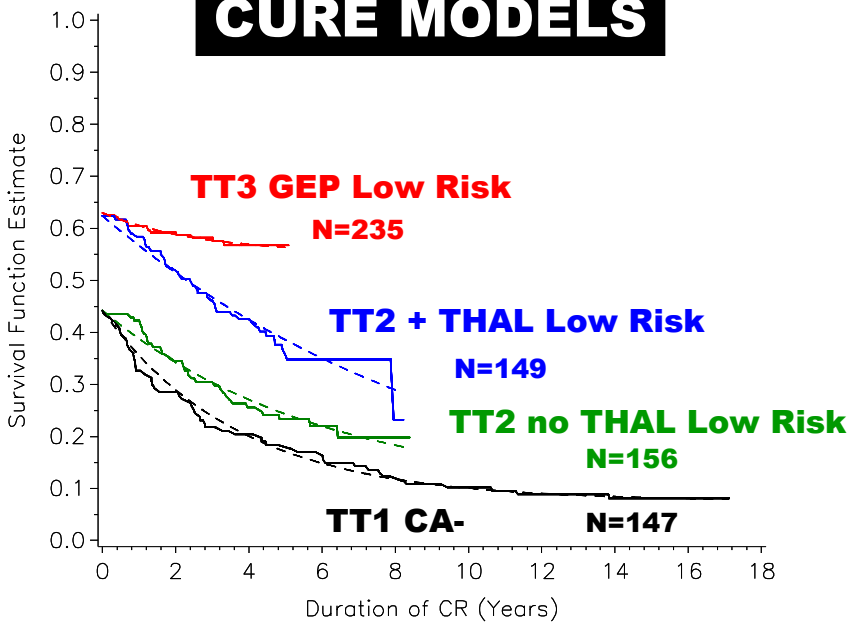


CR DURATION WITH TOTAL THERAPY 3 (2003-33 & 2006-66) ACCORDING TO GENE EXPRESSION PROFILING -DEFINED RISK



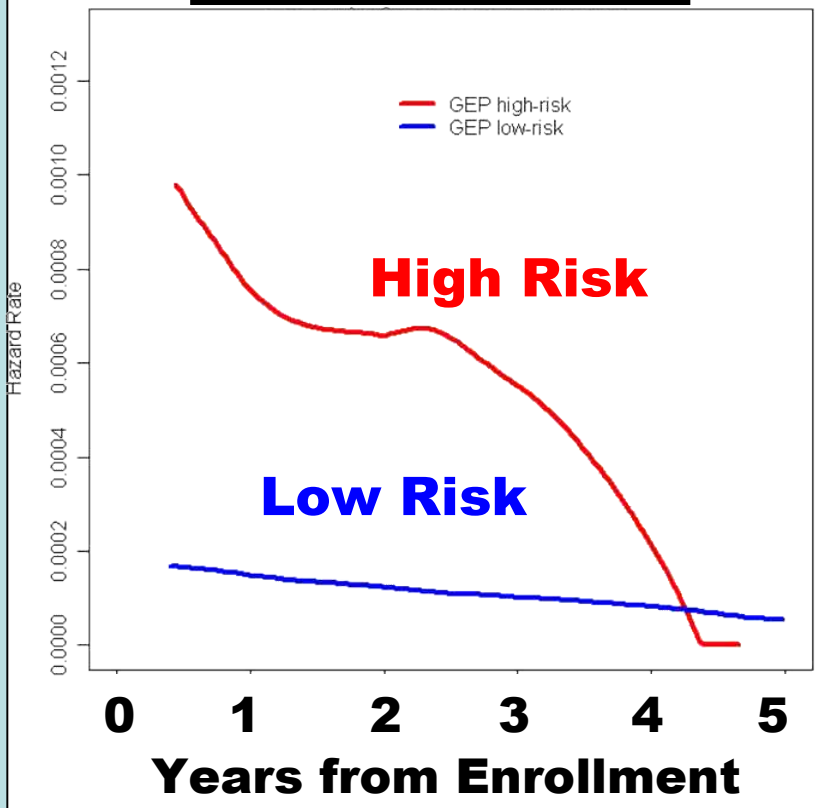
MODELING CURE FROM CR DURATION PLOT IN LOW-RISK MYELOMA TREATED WITH TT1/2/3

CURE MODELS

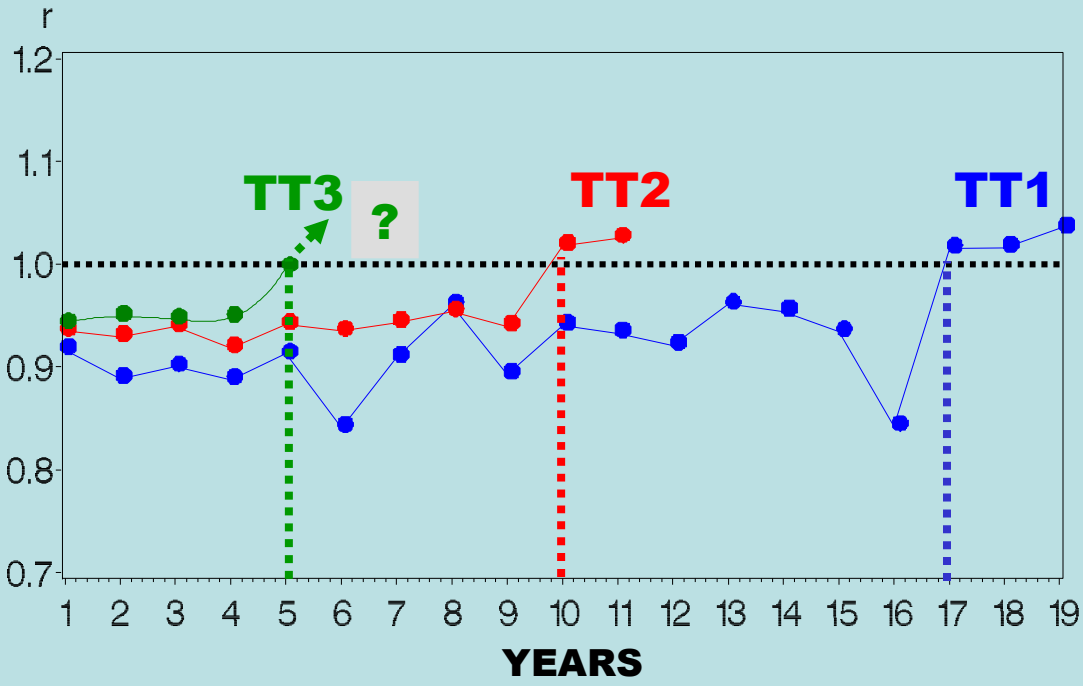


Protocol	CR %	Cure Fraction for CR	p-value	% Cure
TT3: Low Risk	63.0%	0.876	<0.001	55
TT2+thal: Low Risk	62.4%	0.009	NS	5
TT2-thal: Low Risk	44.2%	0.425	NS	19
TT1: no CA	44.2%	0.172	<0.001	8

HAZARD RATE OVER TIME



RELATIVE SURVIVAL RATIOS FOR TT PROTOCOLS



NOTE THE PROGRESSIVELY FASTER RECOVERY OF RELATIVE SURVIVAL RATIOS WITH TRANSITION FROM TT1 TO TT2 TO TT3

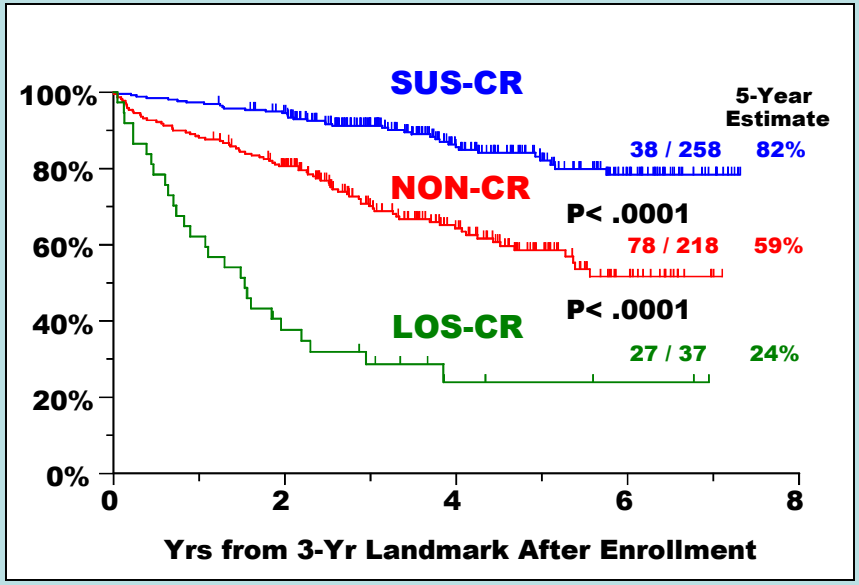
The relative survival ratio is the observed survival in the patient group divided by the expected survival of a comparable group from the general population.
A ratio of 1 indicates that the observed survival is equal to the expected survival.
Annual (interval specific) ratios are shown.

IMPACT OF TIME-DEPENDENT ONSET AND DURATION OF CR ON SURVIVAL

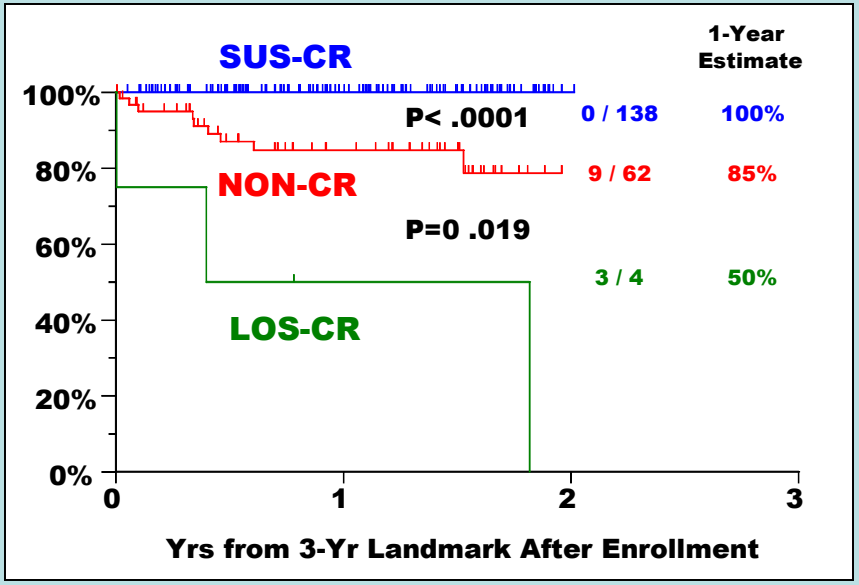
Multivariate Analysis		TT2 & TT3 Combined		
		%	HR	P-value
No GEP	CA	31%	1.93	<.001
	B2M > 5.5 mg/L	19%	1.63	<.001
	CRP ≥ 8 mg/L	NS	NS	NS
	LDH ≥ 190 U/L	30%	1.45	0.002
	Los-CR		10.09	<.001
	Non-CR		4.31	<.001
With GEP	LDH ≥ 190 U/L	31%	1.66	<.001
	CA	33%	2.05	<.001
	GEP high-risk	14%	2.07	<.001
	GEP HY/LB	39%	0.53	<.001
	GEP MGUS-like	26%	0.63	0.034
	Los-CR		10.12	<.001
	Non-CR		5.41	<.001

IMPACT OF CR STATUS (SUS/NON/LOS) ON OVERALL SURVIVAL IN TT2 & TT3

Total Therapy 2



Total Therapy 3



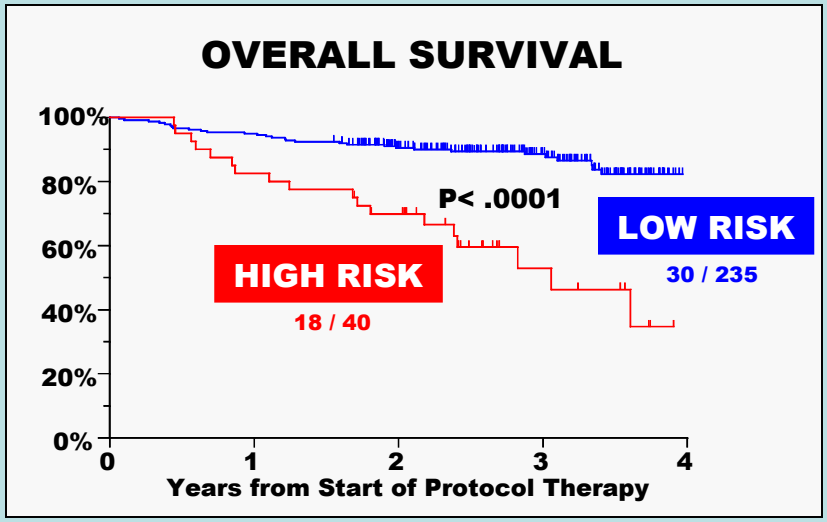
MV ANALYSIS OF BASELINE & TIME-DEPENDENT CR AND 2ND TRANSPLANT IN ALL TT PROTOCOLS

Multivariate Analysis		OS		EFS	
Variable (N = 935)	%	HR	P	HR	P
Albumin < 3.5 g/dL	21%	1.29	0.042	1.31	0.014
B2M > 5.5 mg/L	19%	1.70	<.001	1.49	<.001
LDH ≥ 190 U/L	30%	1.64	<.001	1.52	<.001
Cytogenetic abnormalities	31%	1.81	<.001	1.44	<.001
Completed Transplant 2		**0.69**	**0.002**	**0.73**	**0.002**
Achieved CR		**0.47**	**<.001**	**0.36**	**<.001**

TOWARD TOTAL THERAPIES 4 AND 5:

LOW-RISK MYELOMA: ***DIFFICULT TO IMPROVE UPON TT3 RESULTS***

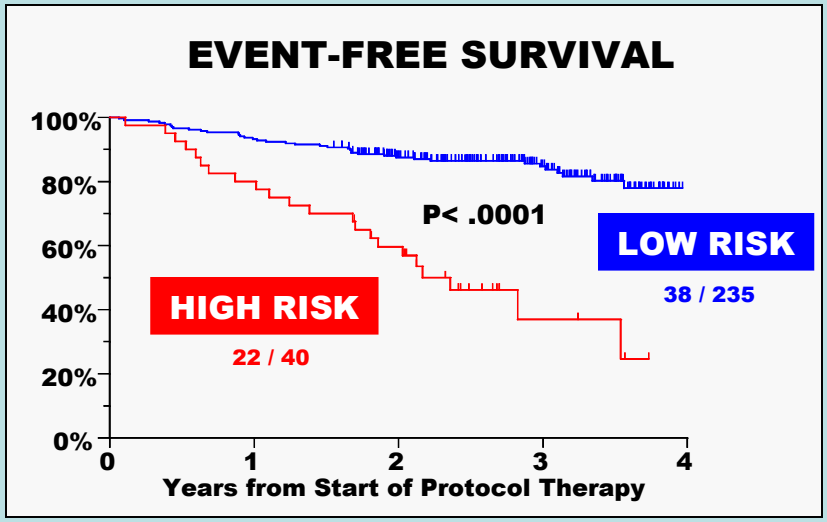
HIGH-RISK MYELOMA: ***HIGH RATE BUT SHORT DURATION OF CR***

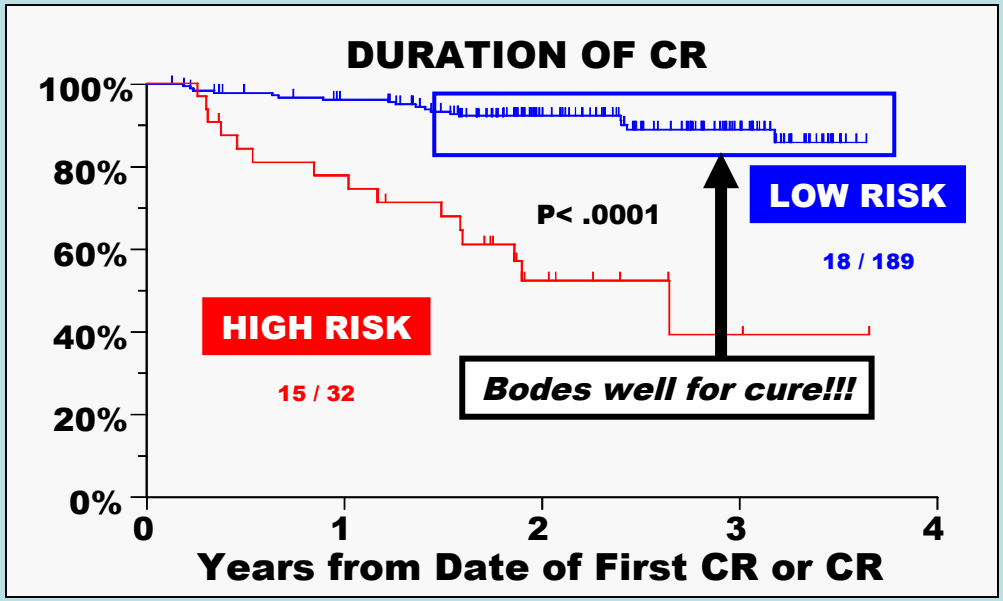


NEW PROTOCOLS:

Low risk: TT4 (*reduce toxicities*)
Randomize TT3 v TT3-lite

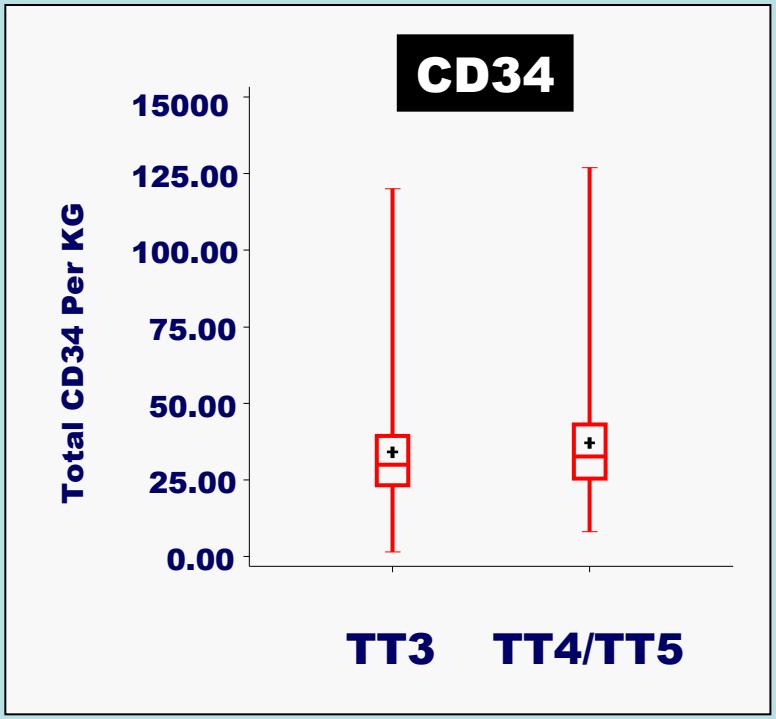
High risk: TT5 (*sustain CR*)
MEL80-VTD- PACE
R-VD / M-VD maintenance

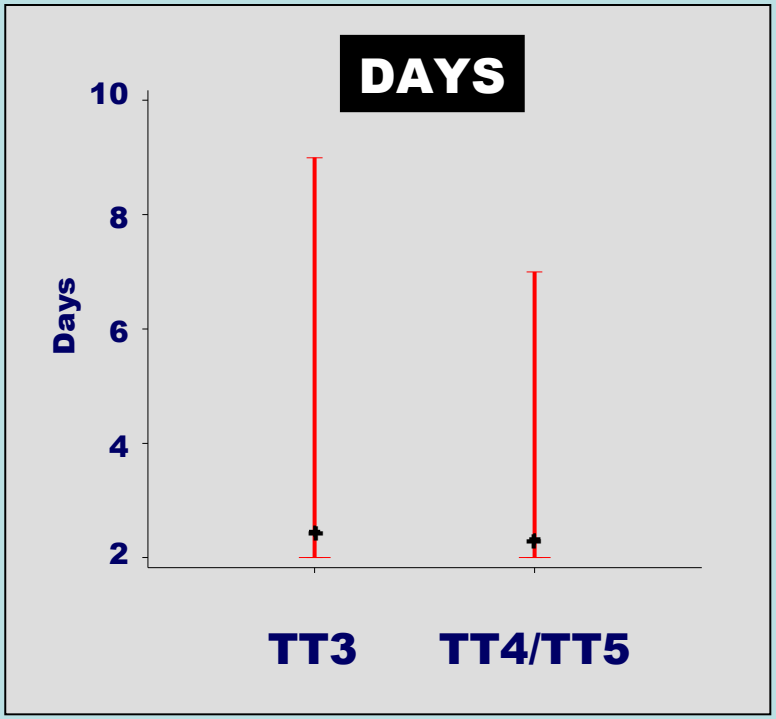




HPC COLLECTION: CD34 TOTAL & DAYS FOR TT3 AND TT4/5

Adding melphalan 10/m2 test-dose to VTD-PACE in TT4 & TT5 does not compromise CD34 yield or days of collection in comparison with TT3 data



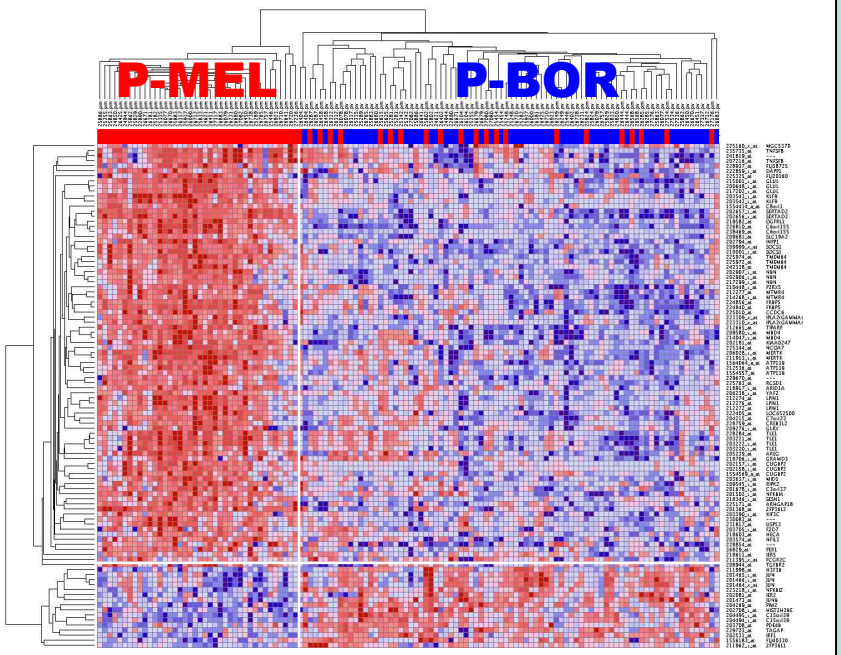


	X 10^6CD34 / kg			
	Min	Median	Mean	Max
TT3	1.45	30.03	33.99	120.11
TT4/5	8.10	32.73	37.07	126.86

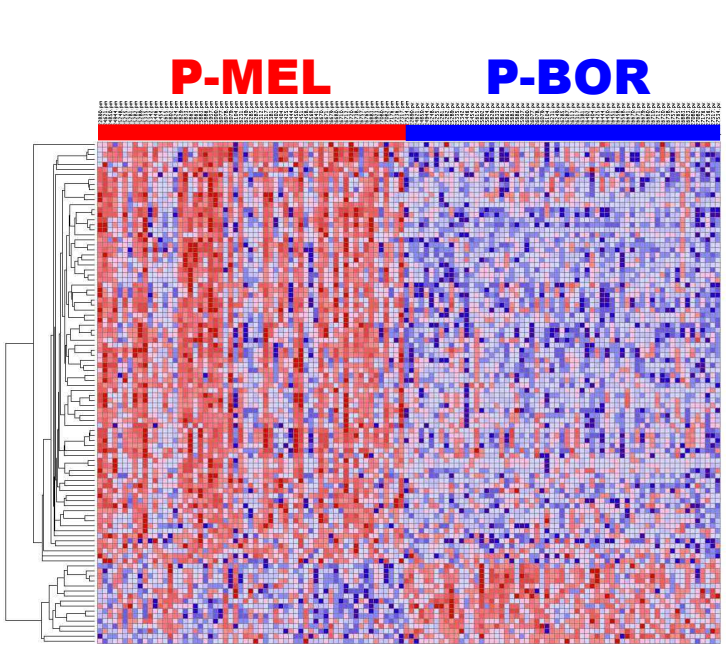
	Days of collection			
	Min	Median	Mean	Max
TT3	2.00	2.00	2.46	9.00
TT4/5	2.00	2.00	2.33	7.00

CLUSTER ANALYIS OF TOP 100 DIFFERENTIALLY EXPRESSED GENES POST MEL-10 IN TT4 & TT5

UNSUPERVISED



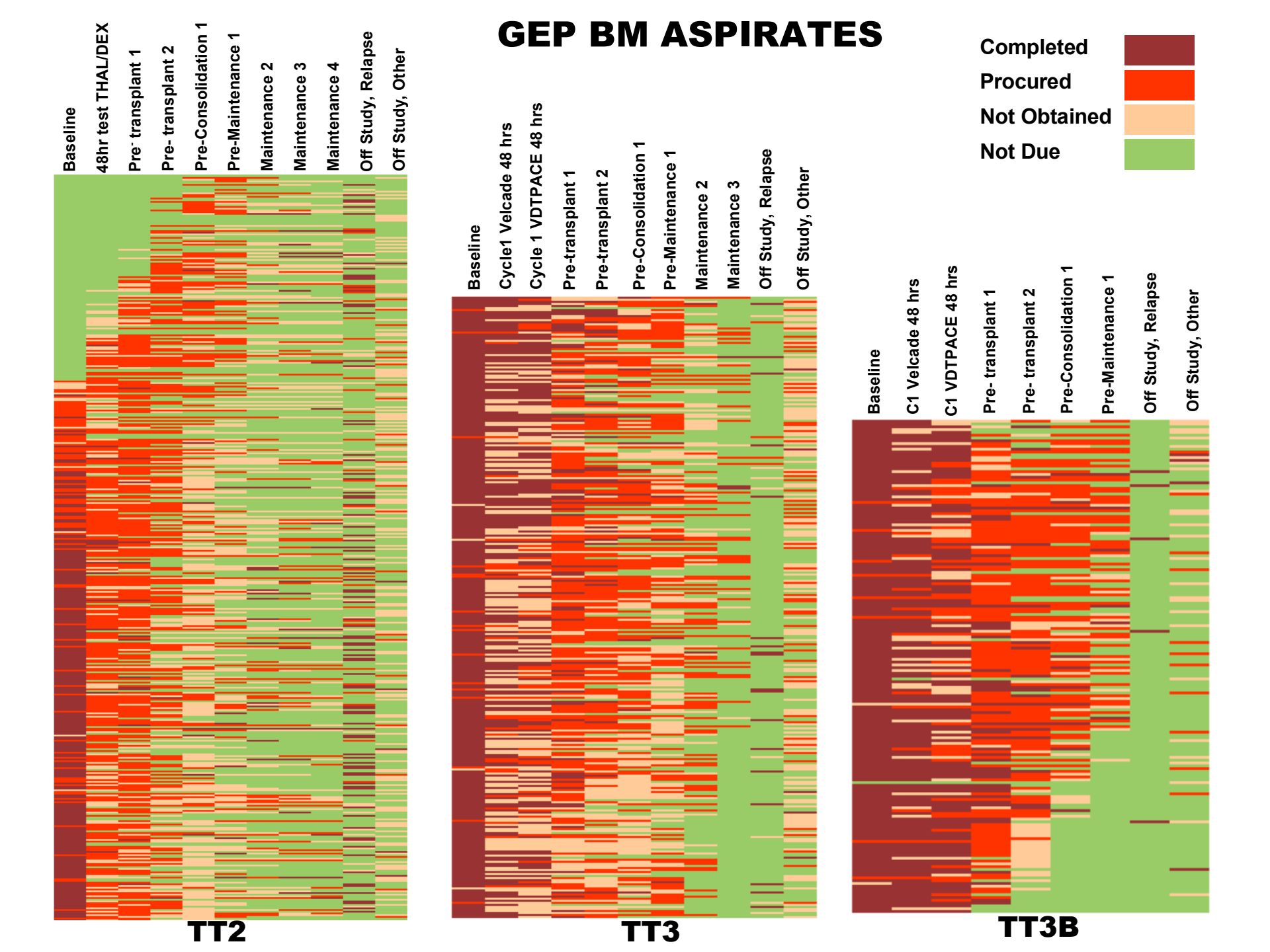
SUPERVISED



IRF4 SIGNIFICANTLY DOWN-REGULATED

TOTAL THERAPIES – WHAT WE HAVE LEARNED

- Steady progress by introducing new treatment principles and novel agents up-front
- Introduced and validated metaphase karyotyping and gene expression profiling as powerful prognostic variables
- 90% sustained CR at 5 yr in low-risk MM with TT3 bodes well for high cure rate of > 65% at 10yr
- Provided rationale for GEP risk-driven treatment assignment in TT4 and TT5 – first real step toward personalized medicine
- Clarified biological and prognostic implications of X-ray, MRI & PET-CT
- Provided basis for targeting focal lesions (anti-DKK1) as their persistence (dormant myeloma stem cells?) may be source of relapse


GEP BM ASPIRATES
Completed
Procured
Not Obtained
Not Due
Baseline
48hr test THAL/DEX
Pre transplant 1
Pre- transplant 2
Pre-Consolidation 1
Pre-Maintenance 1
Maintenance 2
Maintenance 3
Maintenance 4
Off Study, Relapse
Off Study, Other
TT2
Baseline
Cycle1 Velcade 48 hrs
Cycle 1 VDTPACE 48 hrs
Pre-transplant 1
Pre-transplant 2
Pre-Consolidation 1
Pre-Maintenance 1
Maintenance 2
Maintenance 3
Off Study, Relapse
Off Study, Other
TT3
Baseline
C1 Velcade 48 hrs
C1 VDTPACE 48 hrs
Pre- transplant 1
Pre- transplant 2
Pre-Consolidation 1
Pre-Maintenance 1
Off Study, Relapse
Off Study, Other
TT3B

CURING MYELOMA

- ***How to get there?***
  - **Make an objective of therapy**
  - **Learn from anecdotes**
  - **Stay the course**
    - Also under duress in light of new agents
  - **Embrace principles of cancer biology and therapy: no cure to cure in 1970's**
  - **Be prepared for success**

THANK YOU!

- PATIENTS
- REFERRING MD'S
- MIRT STAFF
- NCI AND STAFF
- PRIVATE DONORS

CURING MYELOMA - MILESTONES

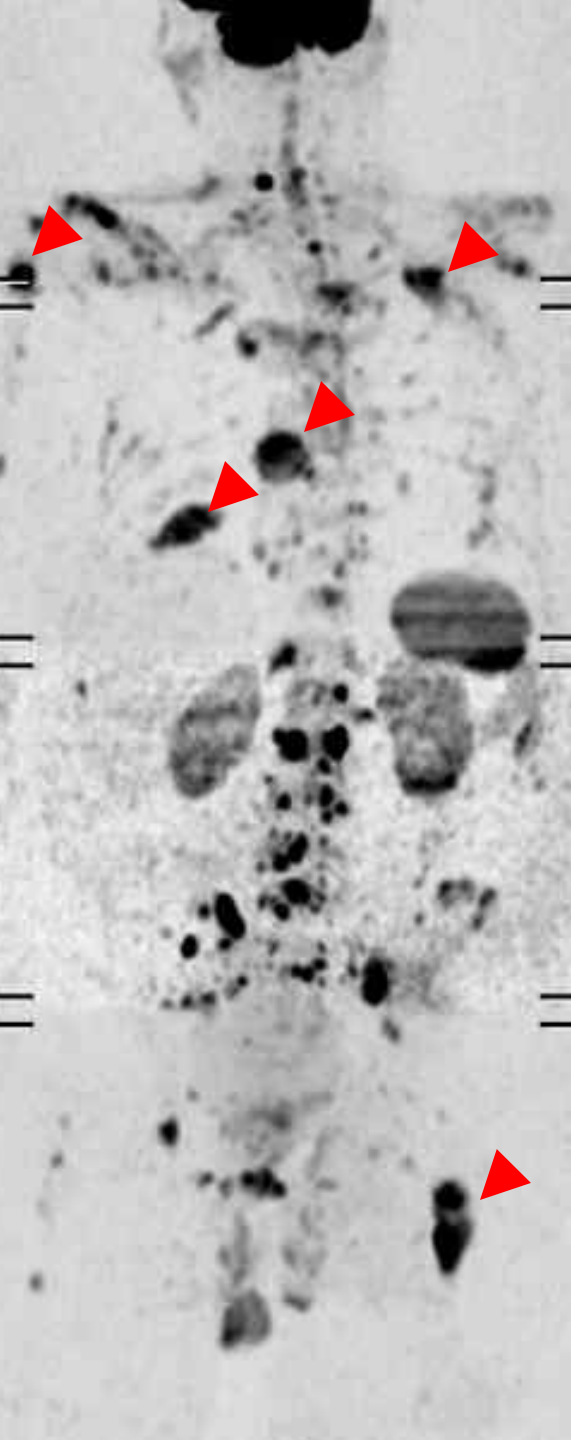
- **Total Therapy concept**
- **Adding agents active in refractory disease**
  - Thal (TT2), bortezomib (TT3)
  - Consolidation (TT2, TT3)
  - Allogeneic transplants – rapid relapse in high-risk myeloma after tandem auto/mini-allo-tx (TT2)
- **Identifying progress in context of prognostic factors**
  - LDH, CA, GEP

CURING MYELOMA

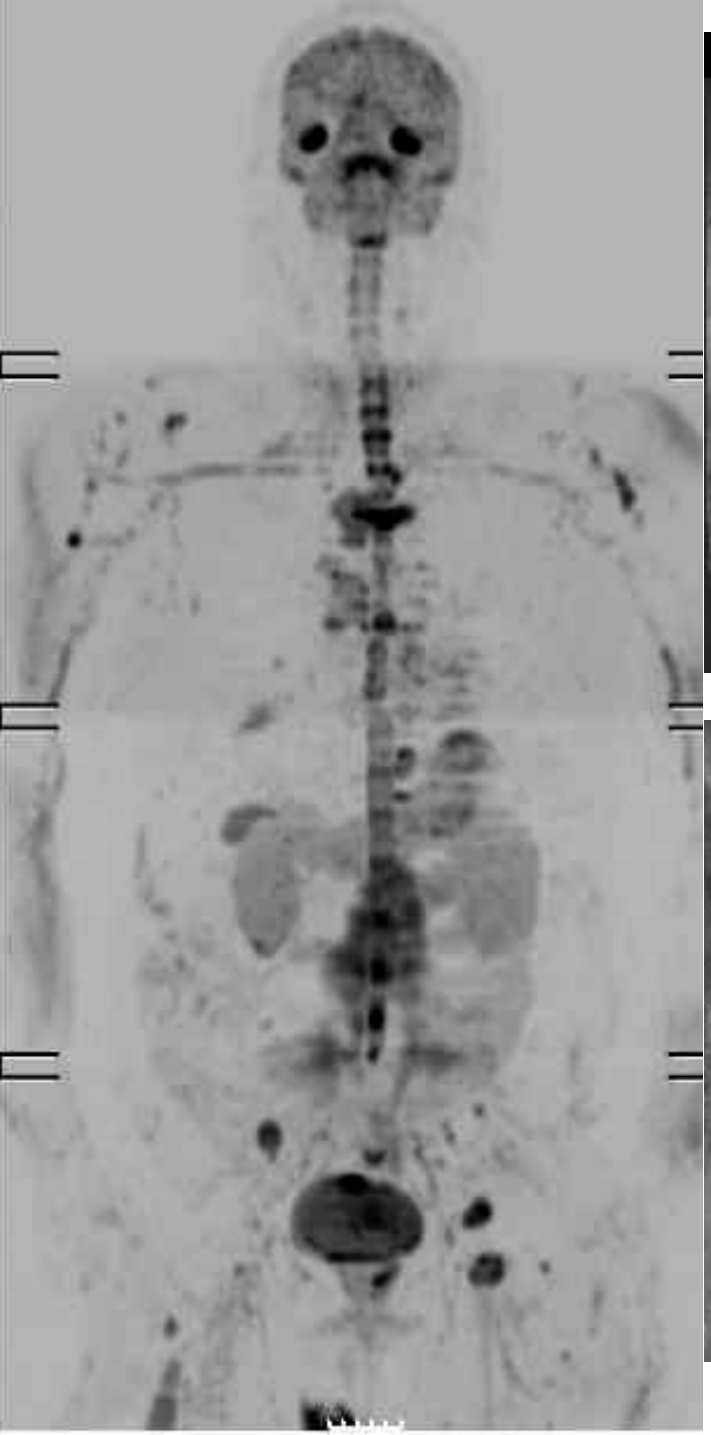
- ***Long-term follow-up is essential***
- ***Study patients with distinctly different conditions***
  - No relapse for >10, 15yr
    - GEP, MRI, PET-CT, immunology
  - 10-15yr survival with multiple relapses
  - Completely refractory long-term
  - Highly aggressive
    - Eventually v de novo

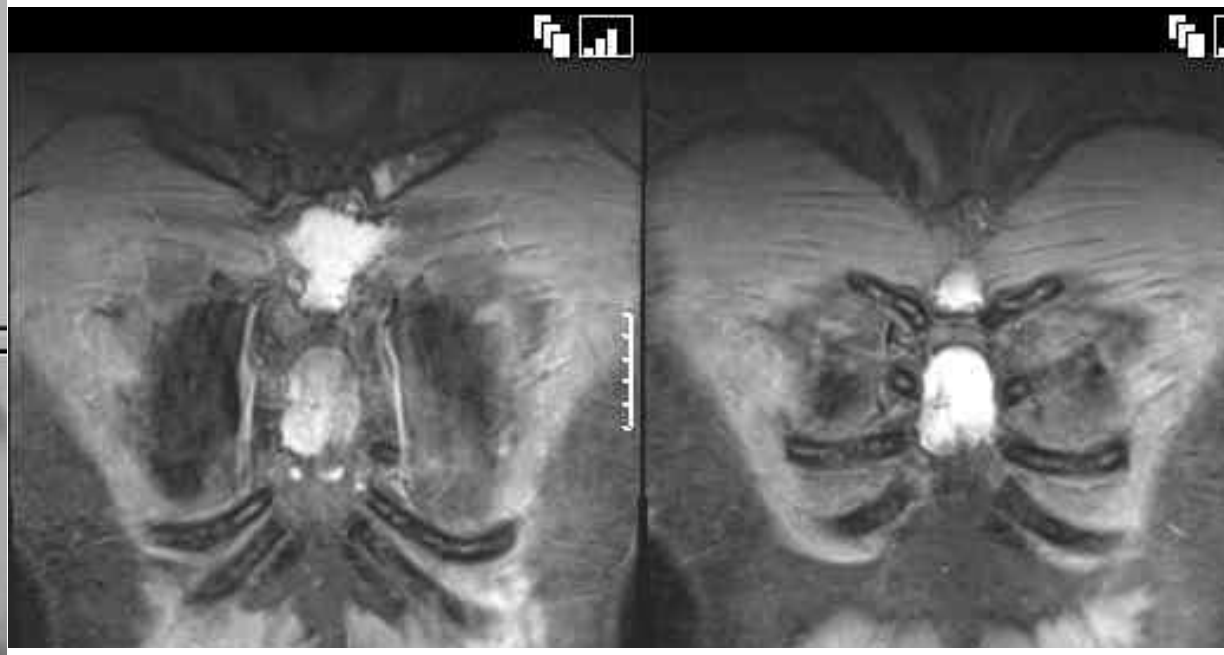
GUIDE TO MYELOMA THERAPY DESIGNS IN 2010 AND BEYOND

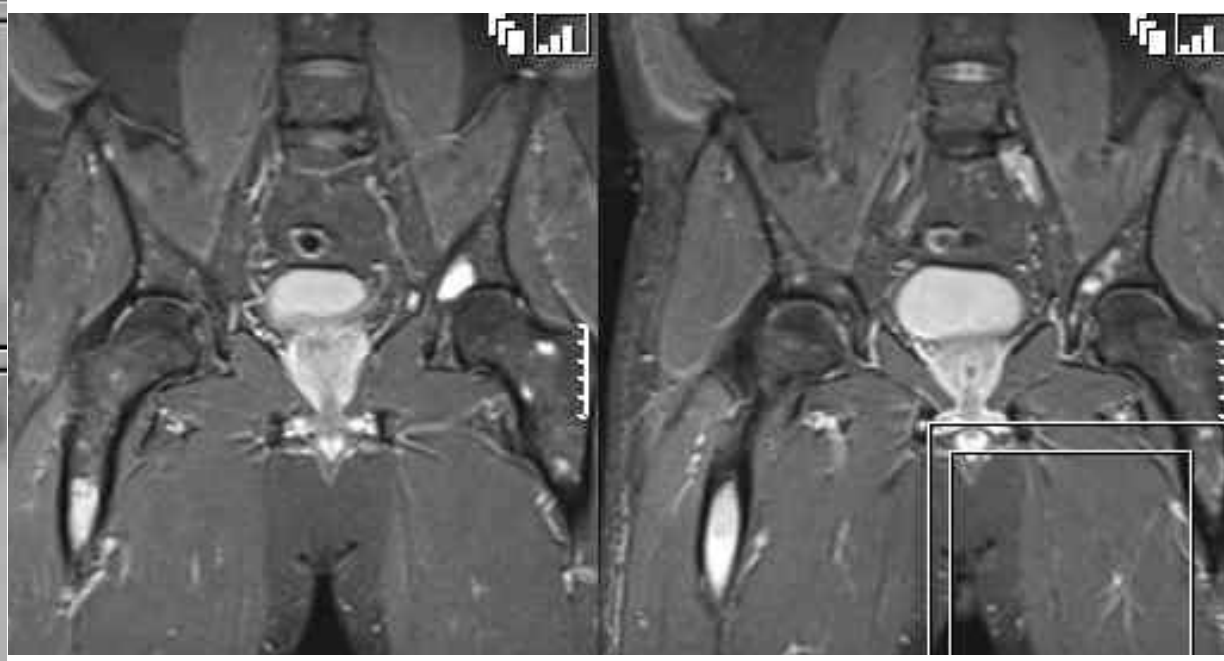
- Preserve accomplishments with 10-yr PFS expectation of >60%
- Build on best outcome results combining high-dose melphalan and novel agents
- Adopt myeloma-risk and host-risk oriented strategies



DWIBBS MRI IN MYELOMA

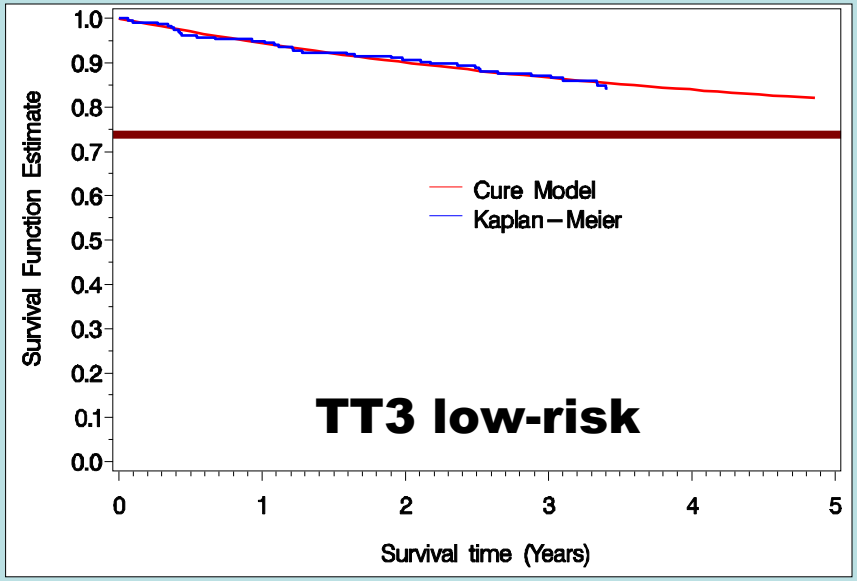


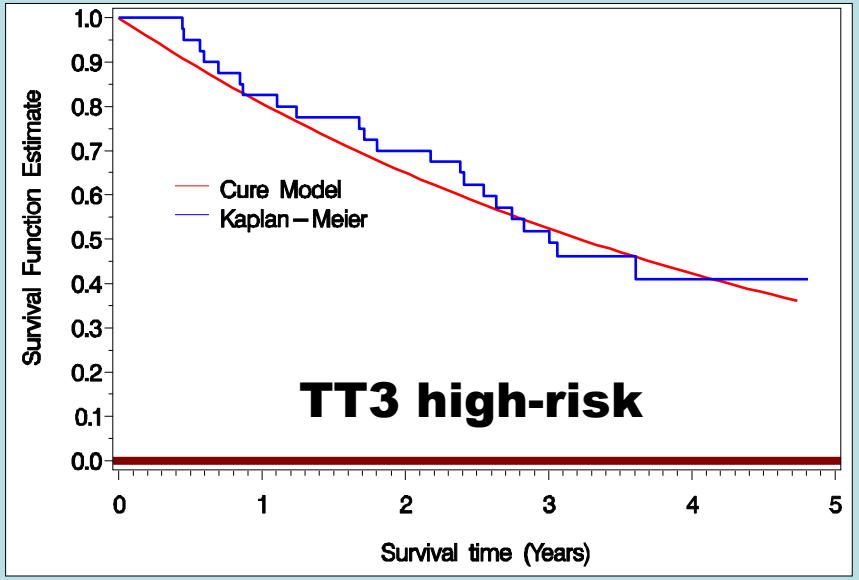




MODELING FOR CURE IN MULTIPLE MYELOMA

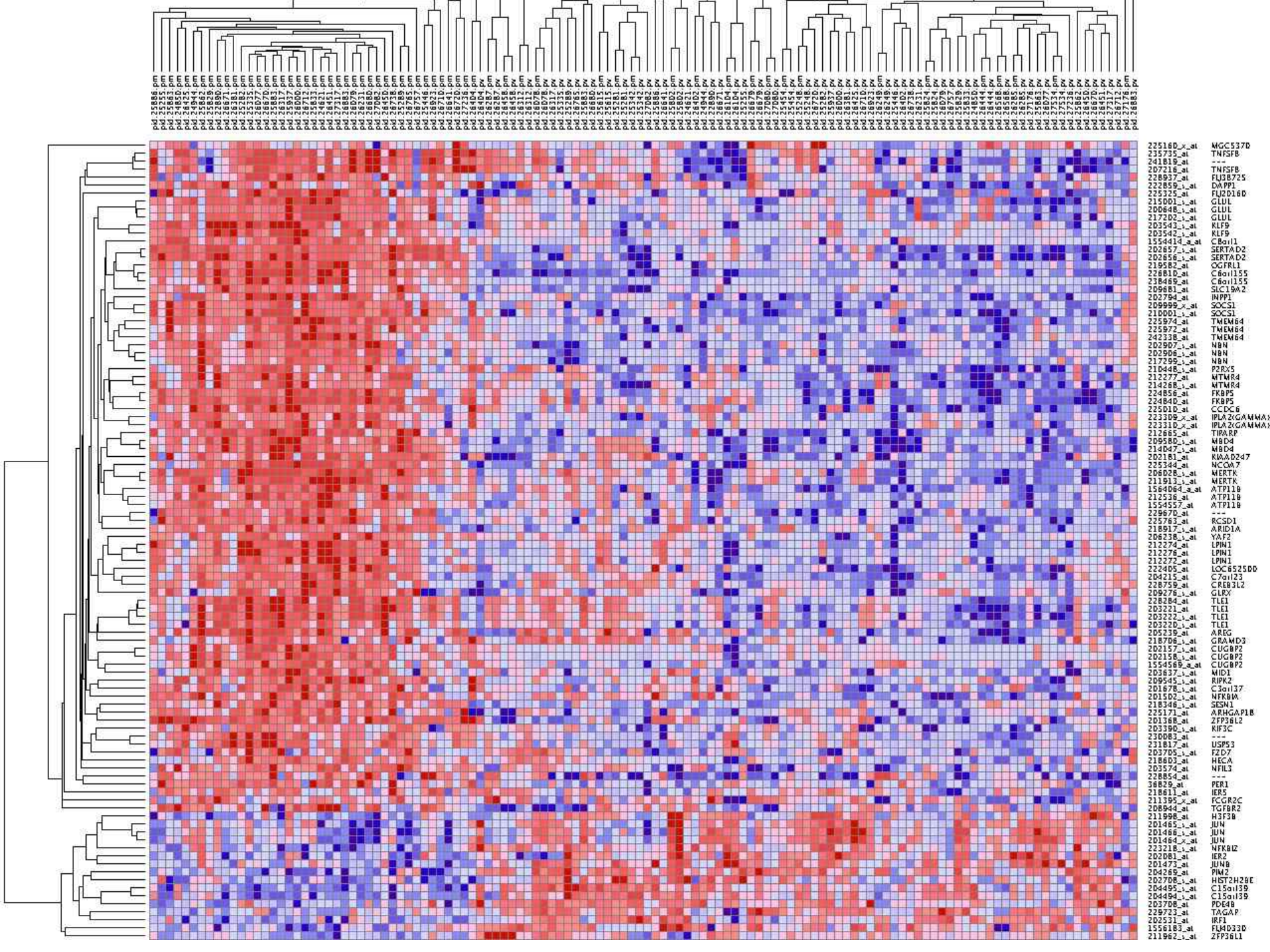
A Reality with TT3 in Low-Risk Disease?

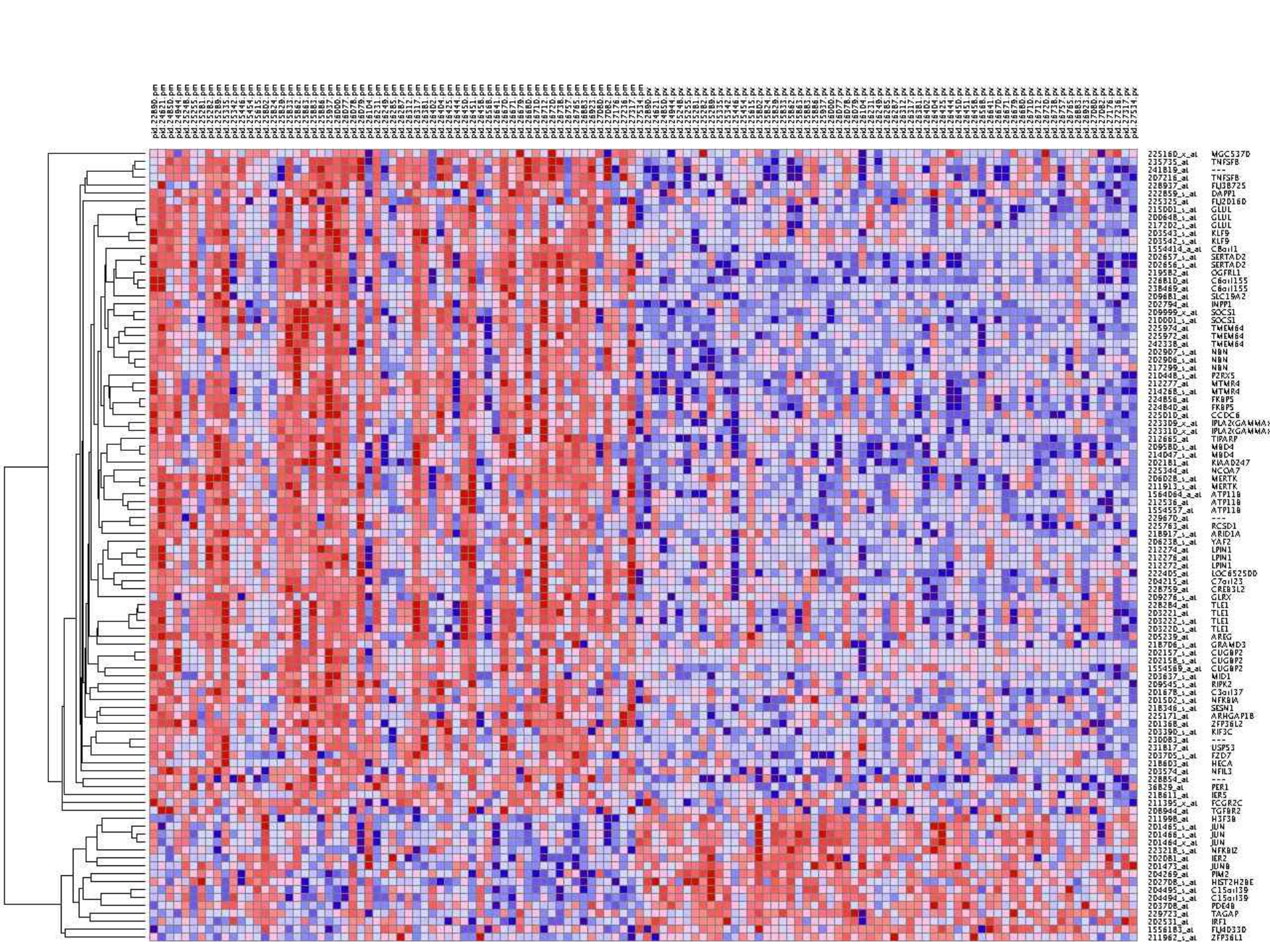




TT3	N	Cure Fraction	P Value
Low-risk	235	0.739	0.0640

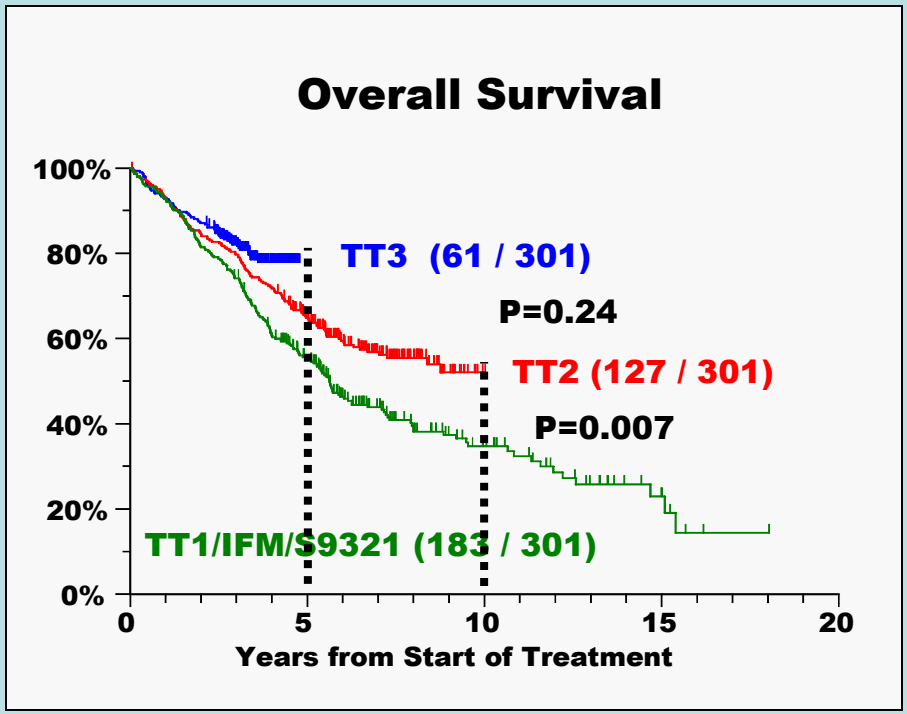
TT3	N	Cure Fraction	P Value
High-risk	40	0.00	0.9955

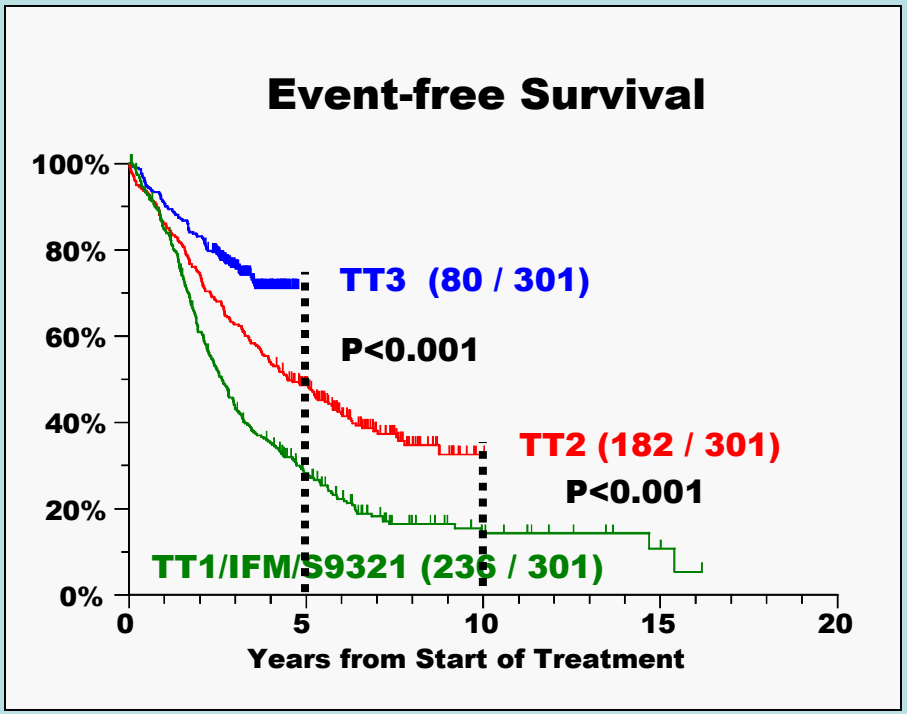




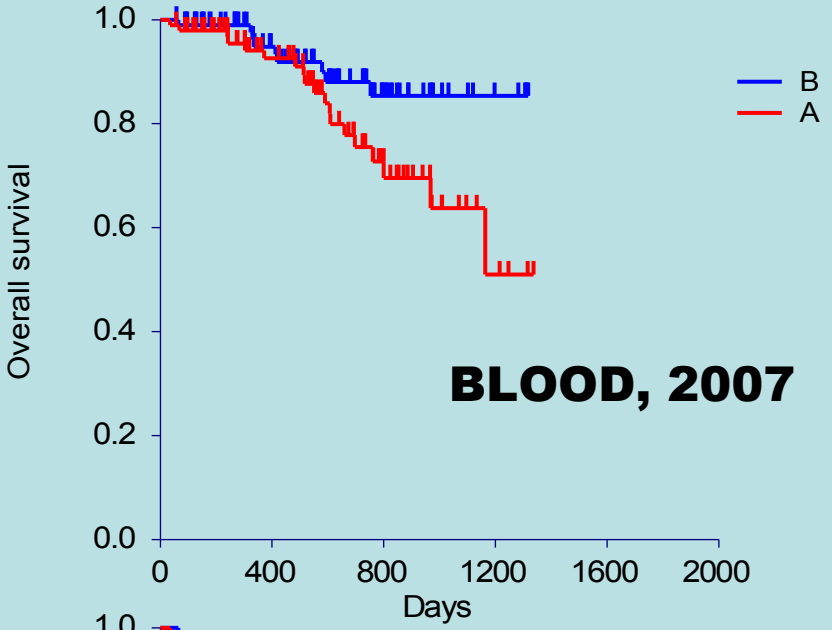
LONG-TERM FOLLOW-UP OF IFM, S9321 & TT

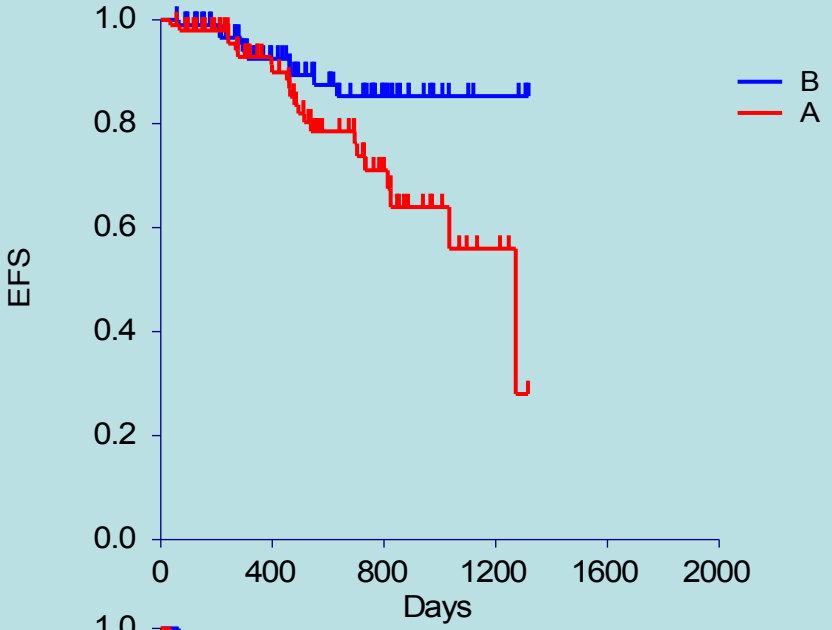
Pair-mate Analyses (Albumin, B2M, LDH, Hemoglobin)

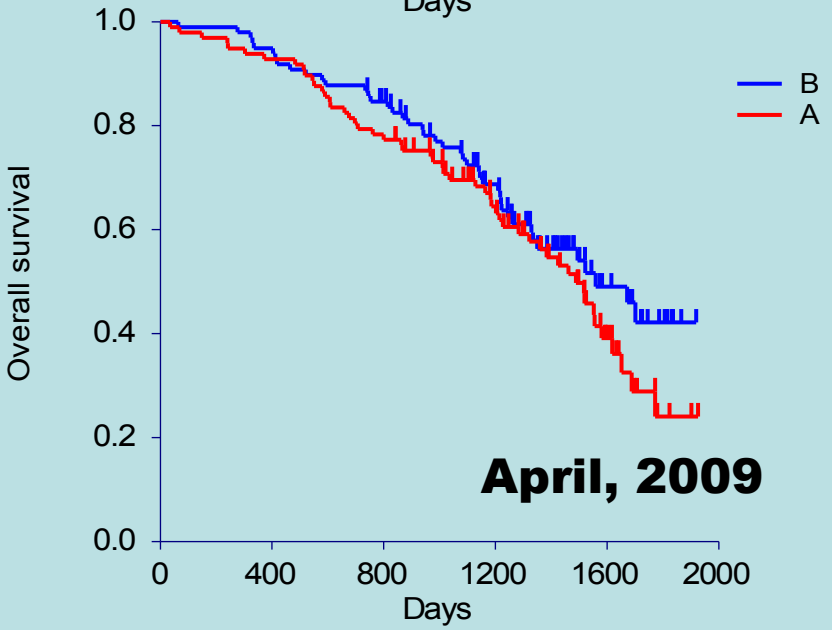


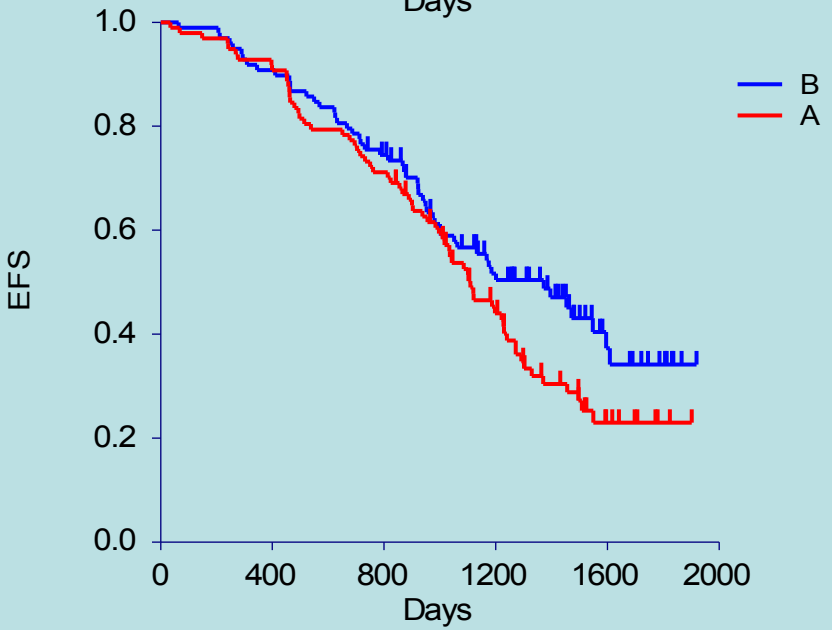


NOTE THE PROGRESSIVELY SUPERIOR OUTCOMES OBSERVED WITH TT3 > TT2 > TT1 AND OTHER TRIALS



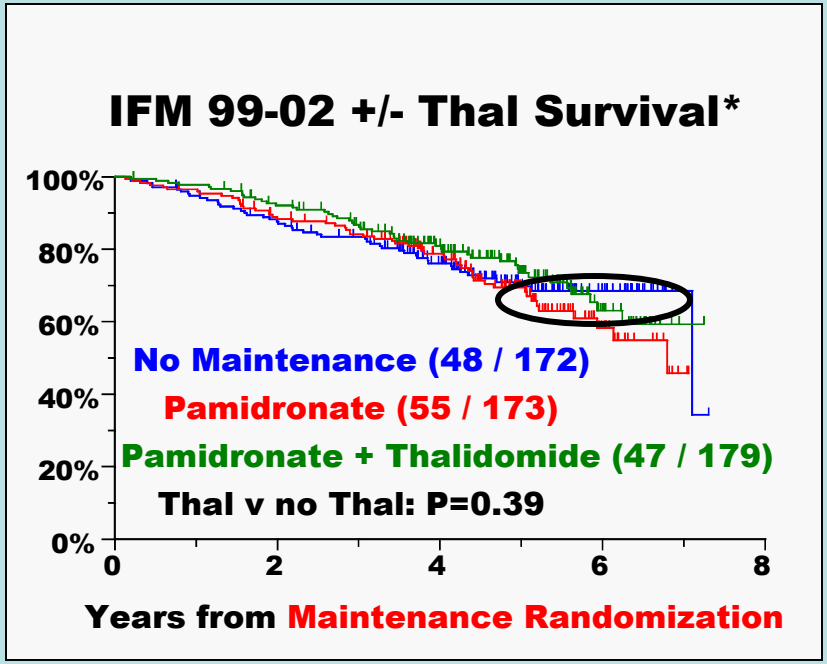


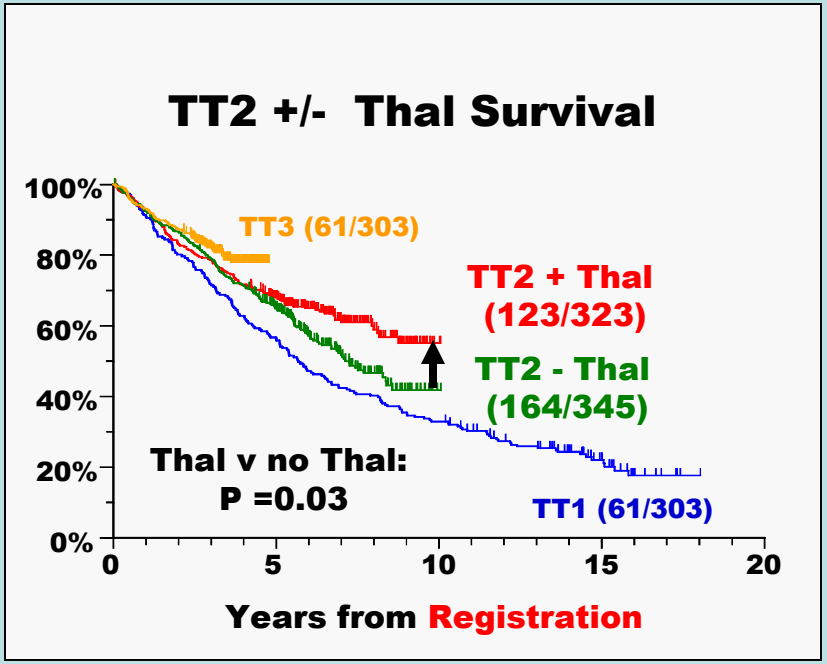




TUNISIAN TANDEM V SINGLE TRANSPLANT TRIAL

SURVIVAL BENEFIT FROM THALIDOMIDE IN TANDEM TRANSPLANT SETTING





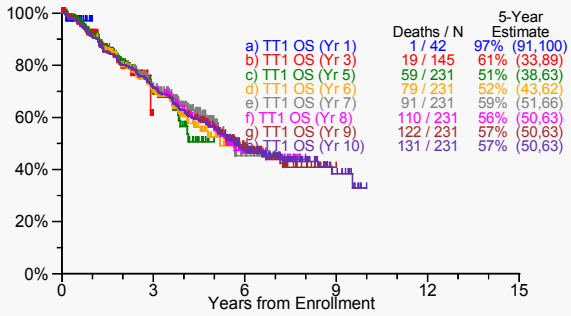
NO BENEFIT APPARENT WHEN EMPLOYED AS MAINTENANCE

BENEFIT APPARENT WHEN EMPLOYED FOR INDUCTION

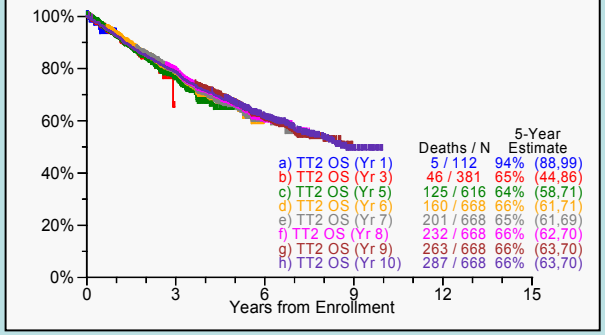
* Subset with available FISH data (88%)

RE-ITERATIVE SURVIVAL ANALYSES IN TT, S9321 & IFM TRIALS

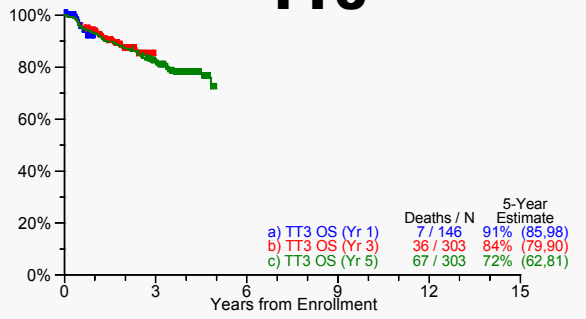
TT1



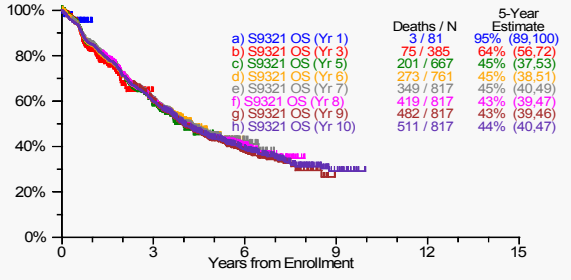
TT2



TT3

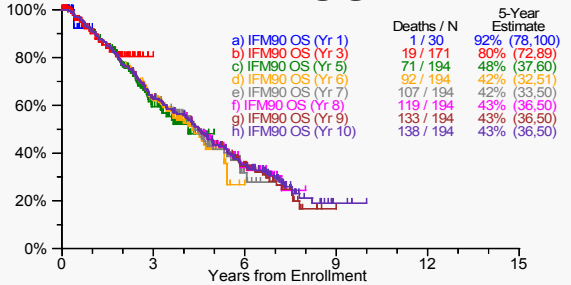


S9321

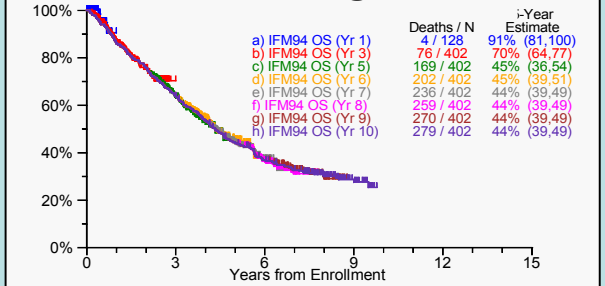


NO CHANGE IS OBSERVED AS DATA MATURE

IMF90



IMF94



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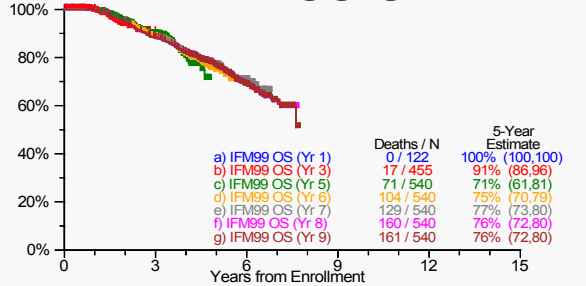


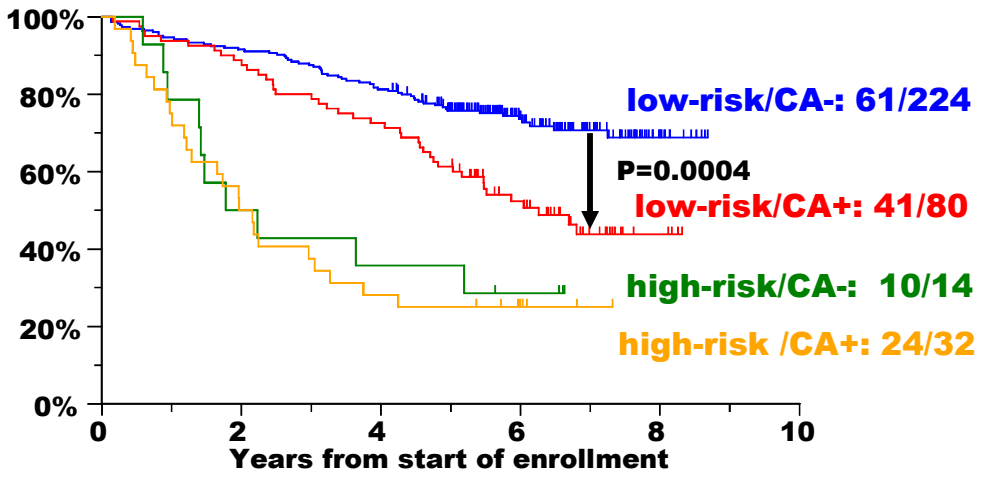
TOTAL THERAPY 2: IMPACT OF RESPONSE ON SURVIVAL

Mutlivariate Analyses			Overall Survival		Event-free Survival	
Group	Variable	%	HR	P	HR	P
All patients (N=632)						
	Cytogenetic abnormalities	30	1.75	<.001	1.36	0.005
	Randomized to thalidomide	49	NS	NS2	0.81	0.043
	Complete response		0.51	<.001	0.40	<.001
	Second transplant		0.67	0.004	0.75	0.009
No CA (N=444)						
	Complete response		0.44	<.001	0.33	<.001
	Second transplant		0.64	0.014	0.75	0.049
CA (N=188)						
	Randomized to thalidomide	47	0.51	<.001	0.66	0.022
	Complete response		NS2	NS2	0.50	<.001
	Second transplant		0.59	0.008	NS	NS2

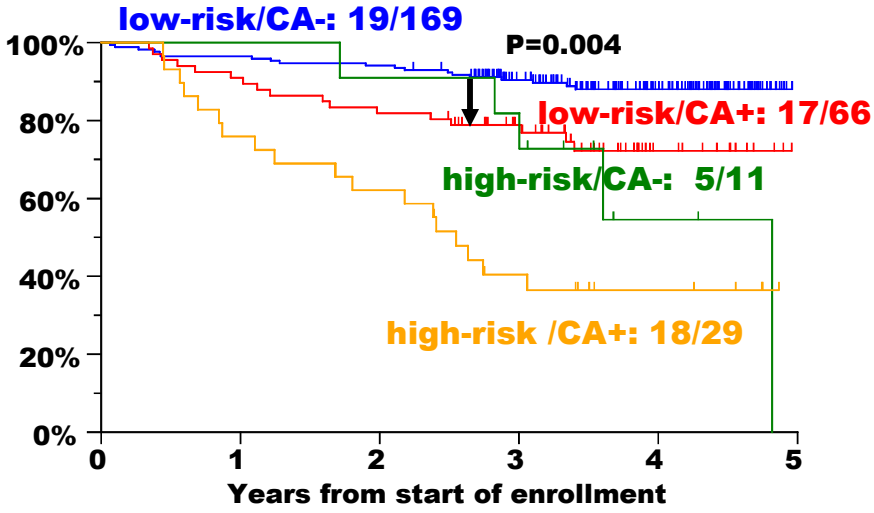
SURVIVAL IN CONTEXT OF GEP RISK AND CA

CA CONFERS SHORTER SURVIVAL IN LOW RISK MYELOMA

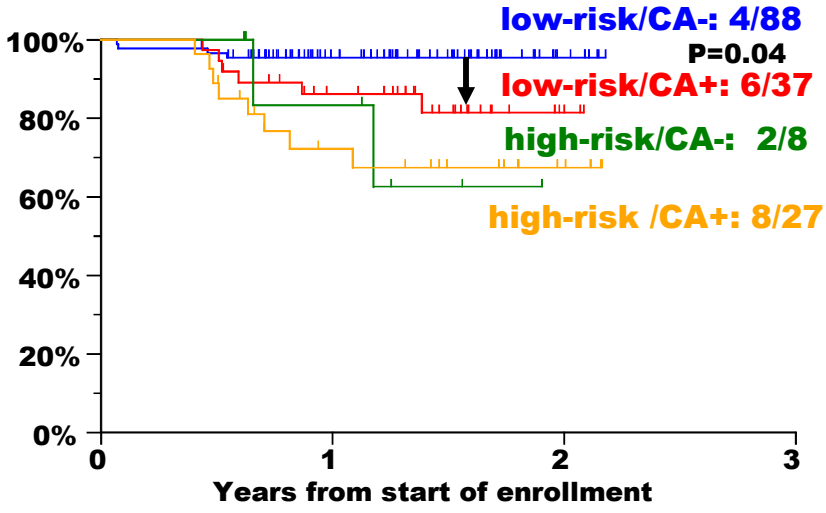
TOTAL THERAPY 2



TOTAL THERAPY 3A



TOTAL THERAPY 3B

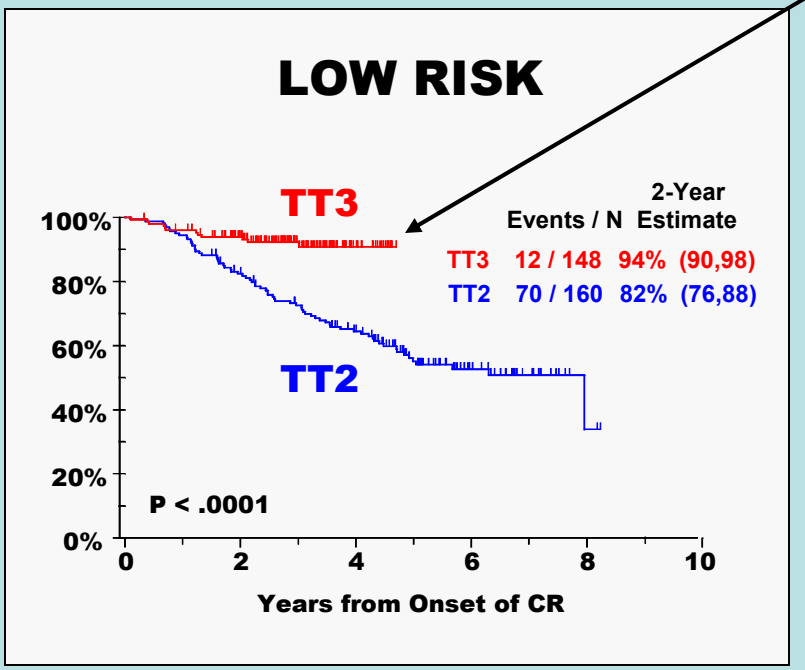


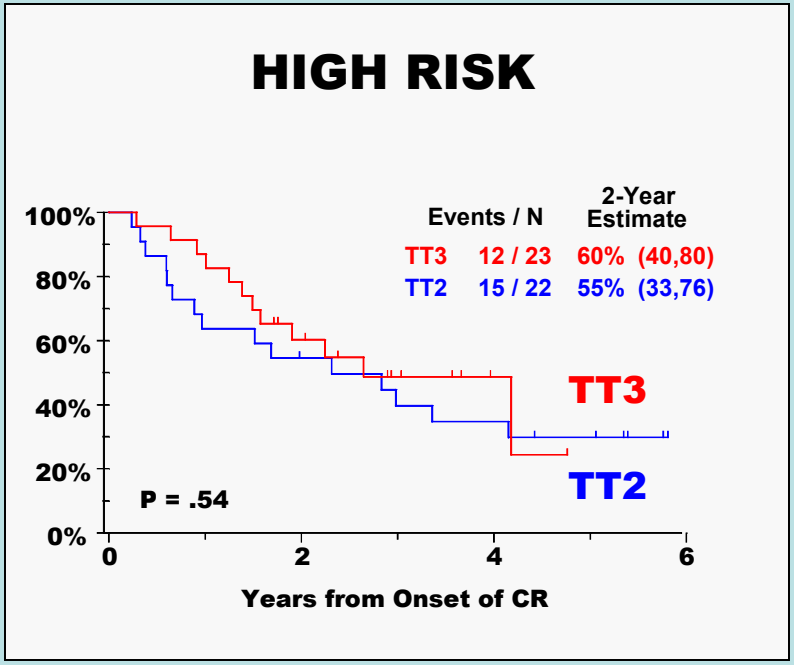
LOGISTIC REGRESSION ANALYSIS OF VARIABLES LINKED TO FDG-FL > 3

Multivariate Analysis N = 215	FDG-FL > 3	FDG – FL =< 3	OR	P
CRP >= 8 mg/L	48%	27%	1.98	0.045
GEP: LOW BONE DISEASE	7%	38%	0.14	0.012
MRI-FL > 7	64%	23%	4.09	<.001
MBS-FL > 2	53%	26%	2.32	0.018

COMPARISON OF CR DURATION IN TT3 *V* TT2 BY GEP-DEFINED RISK

HIGH CURE POTENTIAL





ENORMOUS IMPROVEMENT IN DURABILITY OF CR IN LOW-RISK MYELOMA IN TT3 V TT2

Updated 03/18/09

IMPACT OF TIME-DEPENDENT ONSET AND DURATION OF CR ON SURVIVAL

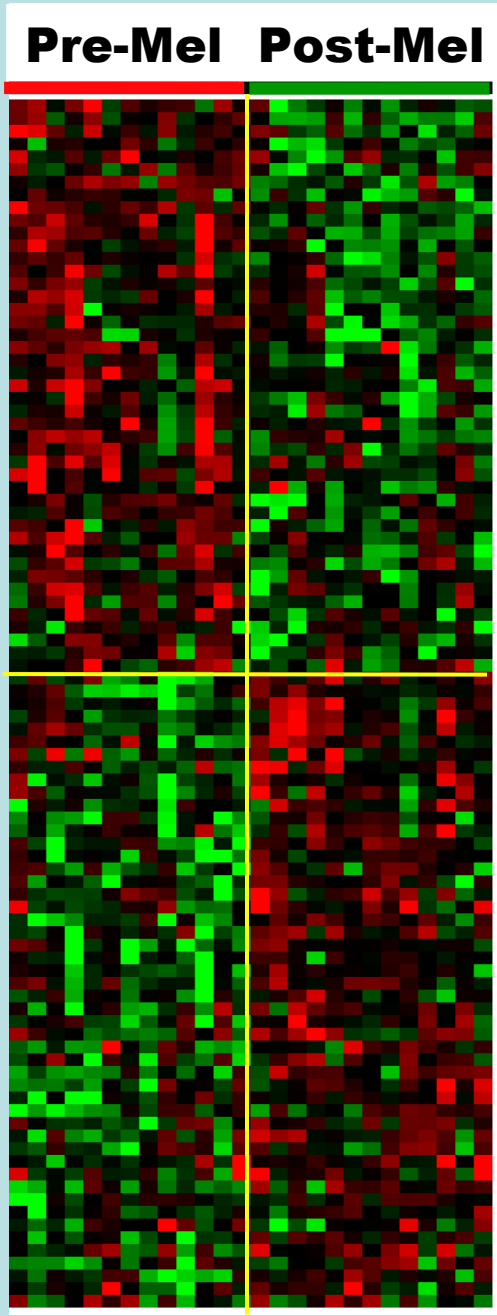
		Total Therapy 1 (n=214)			Total Therapy 2 (n=634, 334 w/ GEP)			Total Therapy 3 (n=301, 274 w/ GEP)		
		%	HR	P	%	HR	P	%	HR	P
No GEP	Age ≥ 65 yr	9	2.01	0.005	NS	NS	NS	NS	NS	NS
	CA	**35**	**1.74**	**<.001**	**30**	**1.77**	**<.001**	**33**	**2.77**	**<.001**
	B2M > 5.5 mg/L	NS	NS	NS	18	1.54	0.003	22	2.01	0.007
	CRP ≥ 8 mg/L	33	1.47	0.021	NS	NS	NS	NS	NS	NS
	LDH ≥ 190 U/L	NS	NS	NS	31	1.35	0.025	27	1.88	0.015
	Non-CR		**3.77**	**<.001**		**4.03**	**<.001**		**5.35**	**<.001**
	Los-CR		**7.71**	**<.001**		**8.89**	**<.001**		**23.01**	**<.001**
With GEP	**CA**	**NA**	**NA**	**NA**	**32**	**1.80**	**0.001**	**35**	**2.83**	**<.001**
	LDH ≥ 190 U/L	NA	NA	NA	34	1.71	0.003	27	1.82	0.031
	GEP High-risk	**NA**	**NA**	**NA**	**13**	**2.88**	**<.001**	**15**	**2.27**	**0.006**
	Non-CR	**NA**	**NA**	**NA**		**5.12**	**<.001**		**5.05**	**<.001**

REASONS FOR RETAINING TANDEM HIGH-DOSE MELPHALAN TRANSPLANTS FOR CURE OF MM

- Only modality which, together with novel agents, has generated cure platform, now projected at ~65% at 10yr, in the context of data going out to 20yr
- Difficulty of projecting >10-yr clinical outcomes from early surrogates currently being tested:
  - Flow cytometry-defined CR
  - GEP of bone marrow biopsy to define cure signature in comparison to normal donors
  - MRI/PET-defined CR

- Cave:
  - Reliance on secretory products
    - Non-secretory relapse increasingly more common
  - MM stem cells:
    - Likely non-secretory
    - "hiding" in focal lesions persisting long after s-CR onset
  - Are all CR's equal?
    - Issue of unmaintained remission after
      - Novel agents
      - Novel/cytotoxic combinations
      - Novel agents + mel transplants
- Focus on high-risk disease:
  - Likely a source of treatment failure also in low-risk MM
    - Transformation
    - Expansion of subclone

MM-GEP CHANGES 48HR AFTER *MEL 10MG/M2* TEST-DOSE APPLICATION



DOWNREGULATED GENES:

-IRF4

- *WWOX*
- *IRAK2*
- *UBE2B*
- *CDC20*
- *IL1RN*
- *PMS2*
- *YBX1*

UPREGULATED GENES:

- *PRDM10*
- *FAS*
- *BLVRA*
- *DDR1*

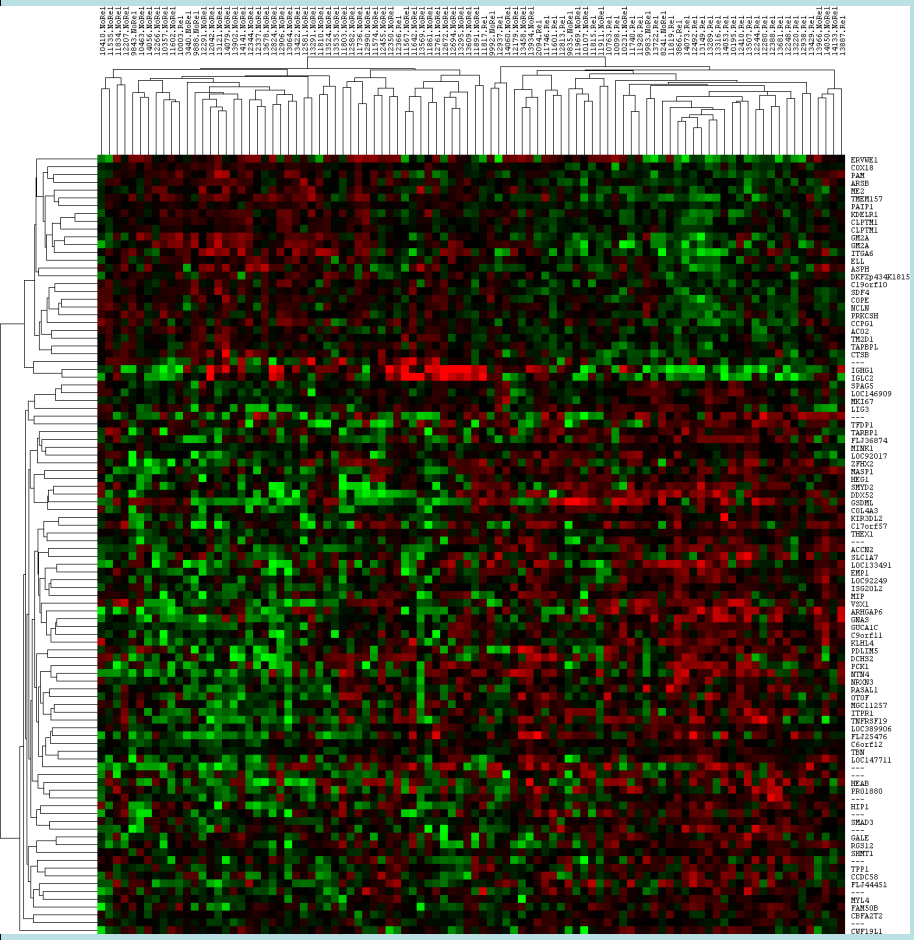
GEP ANALYSIS AT MIRT IN 2009

- Identify genes linked to progression of MGUS or AMM to symptomatic MM (S0120)
  - ECOG/SWOG Intergroup trial of Lenalidomide v Placebo for high-risk AMM
- Follow up on TT2 and TT3
  - In remission to define "cure signature" – may be sub-type dependent
  - At relapse to investigate clonal evolution in comparison with baseline features

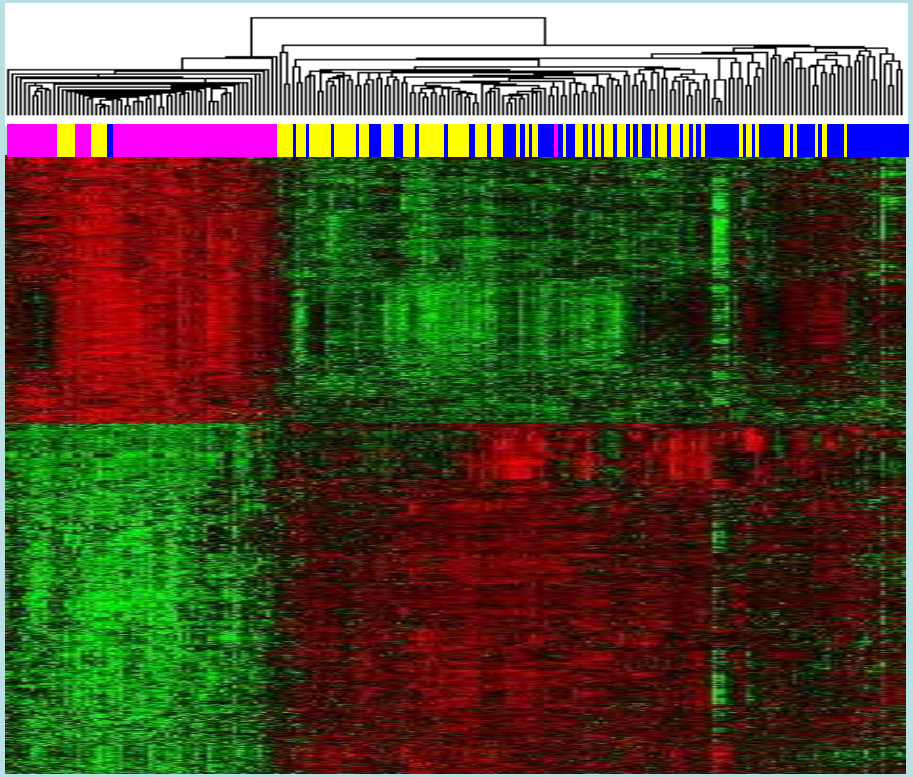
- Risk-adapted TT4 / TT5 (both PC and marrow biospies)
  - Baseline, 48hr post-bortezomib and post-melphalan
  - Serially in remission until relapse
- Comparison of diffusely infiltrative disease v focal lesion growth to identify distinguishing myeloma and stroma features – tumor dormancy / stem cell site?

GENE EXPRESSION PROFILING TO CAPTURE CURE AND HMCL SIGNATURES

NO CURE | **CURE**



PRIMARY MM & HMCL



HMCL
MM @ Dx
MM @ Relapse

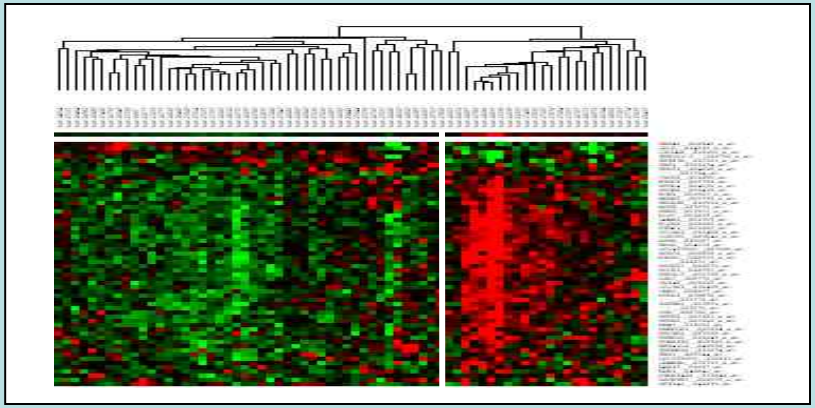
MM mostly separate from HMCL, baseline MM farthest to right, relapse MM next to HMCL, few among HMCL.

ADVERSE IMPLICATIONS OF POST-BORTEZOMIB HIGH-RISK SCORE OBSERVED IN TT3A VALIDATED IN TT3B

TRAINING SET		Overall Survival		Event-Free Survival	
Variable	%	HR	P	HR	P
LDH > 190U/L	26	3.60	0.004	2.83	0.004
Hb < 10g/dL	28	2.32	0.034	2.06	0.048
Post-BOR high-risk	18	3.17	0.006	4.40	<.001

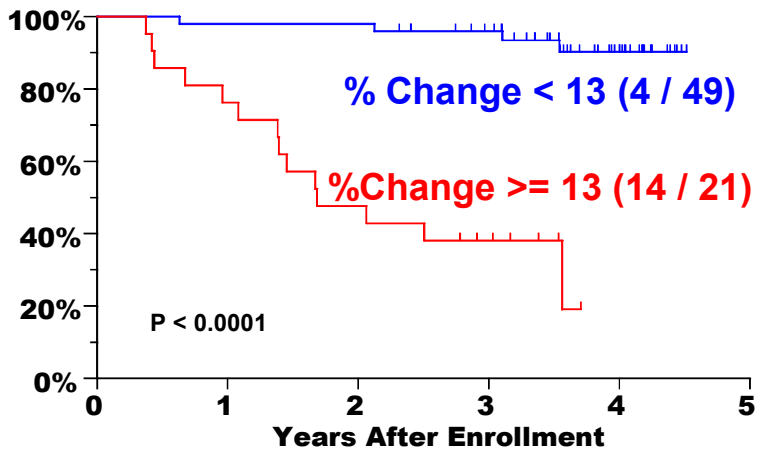
TEST SET		Overall Survival		Event-Free Survival	
Variable	%	HR	P	HR	P
Post-BOR high-risk	16	13.00	0.002	15.57	<.001

POST-BORTEZOMIB PC-GENE ALTERATIONS DOMINATE OUTCOMES SO THAT BASELINE 70-GENE MODEL IS NO LONGER SIGNIFICANT

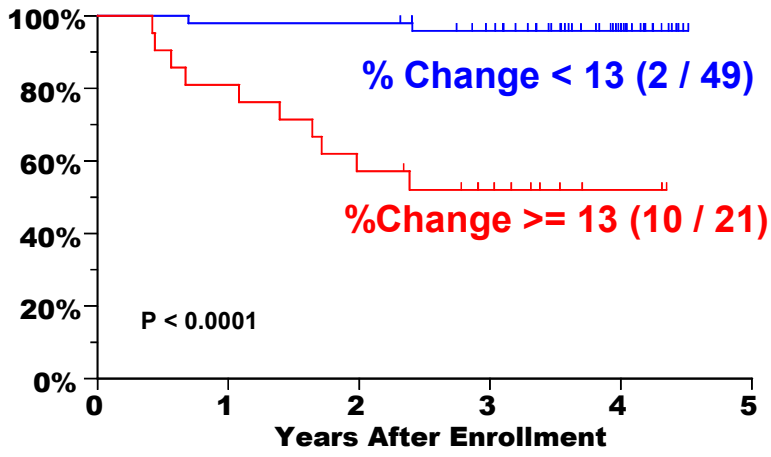


POOR TT3 OUTCOMES:
MAG-1 UPREGULATED
48HR POST-BORTEZOMIB
(HR-OS=13; HR-EFS=17)

EVENT-FREE SURVIVAL



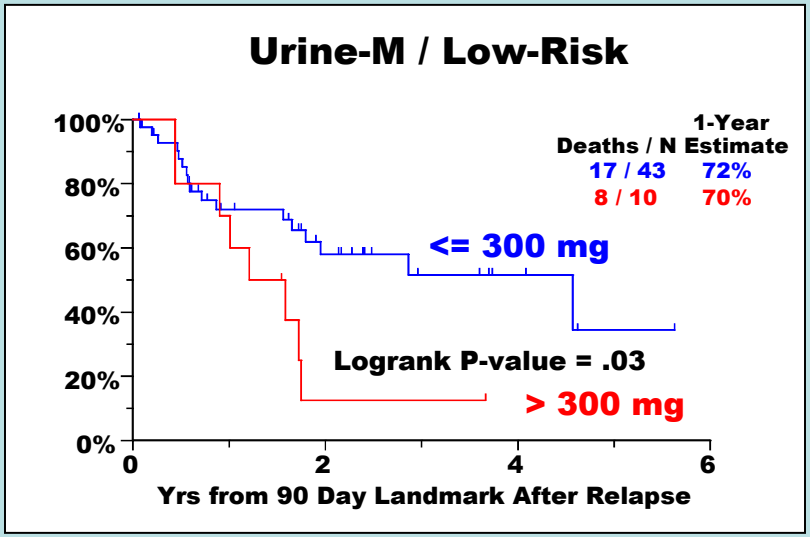
OVERALL SURVIVAL

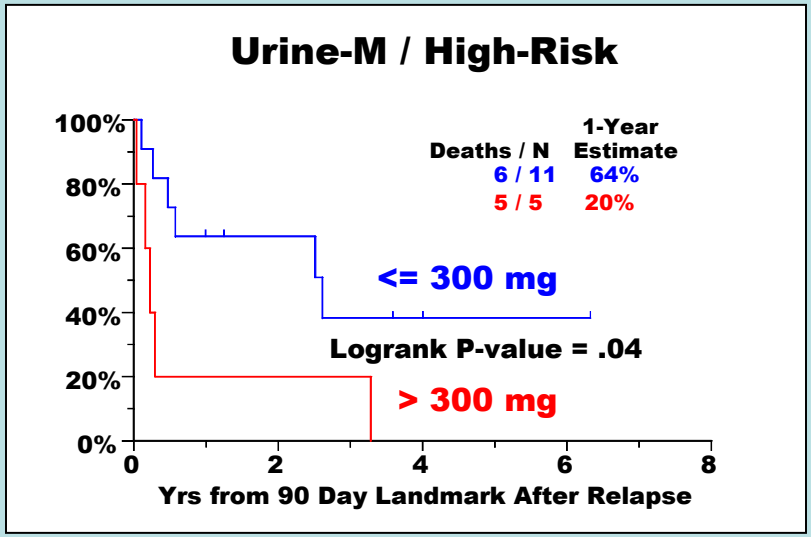


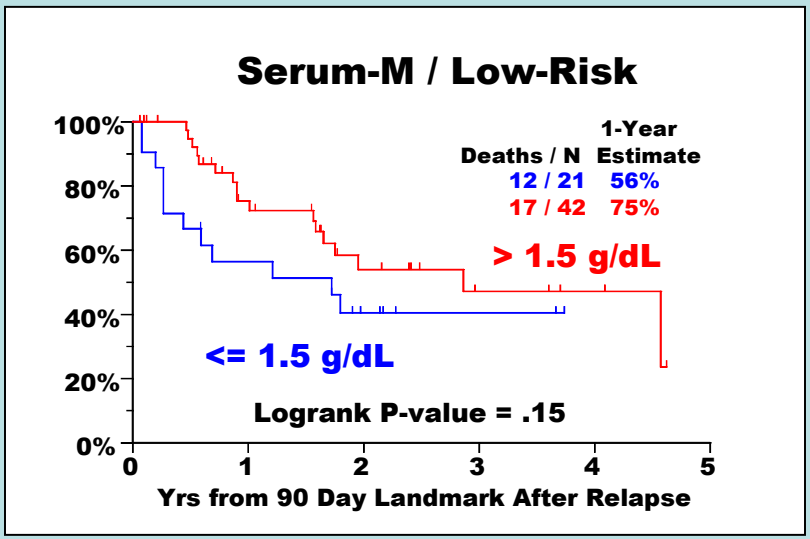
POST-BORTEZOMIB GEP DATA SEEM TO OUTPERFORM BASELINE INFO

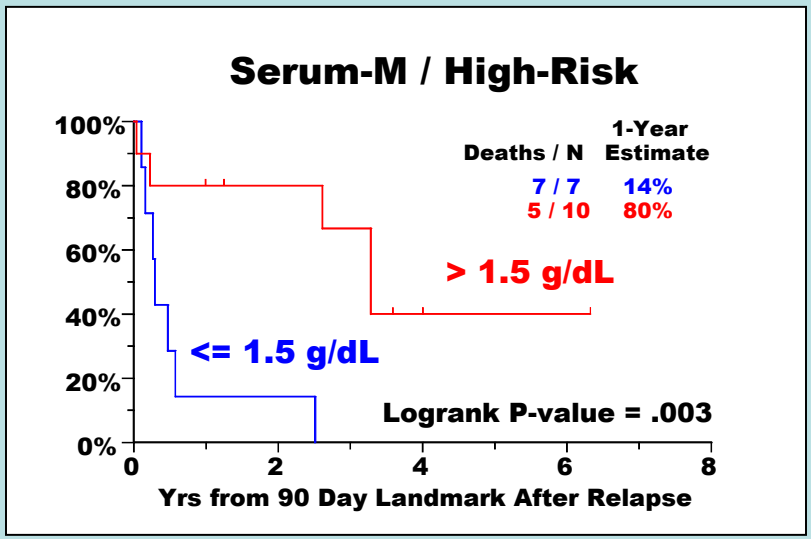
MV Analysis BL + PB	GEP Group	% Patients	OS HR	P value	EFS HR	P value
2 variables significant	BX-PB high	30	10.80	.003	13.33	<.001
	PC-PB high	21	5.37	.009	3.87	.010

POST-RELAPSE SURVIVAL IN TT1/2/3 BY SERUM- & URINE-M WITHIN 3 MONTHS



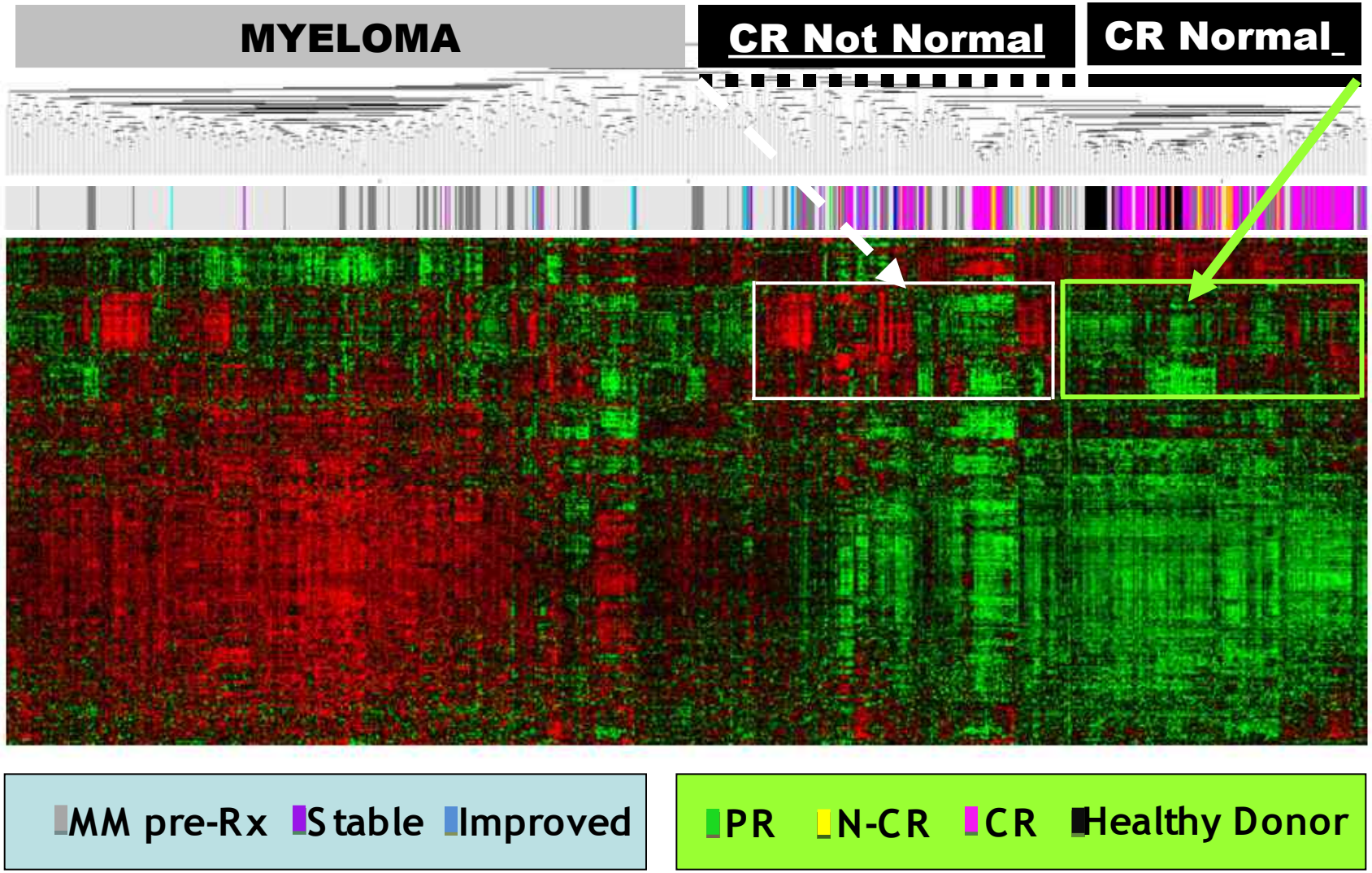






~ 50% OF CR BM BIOPSY APPEARS NORMAL-LIKE

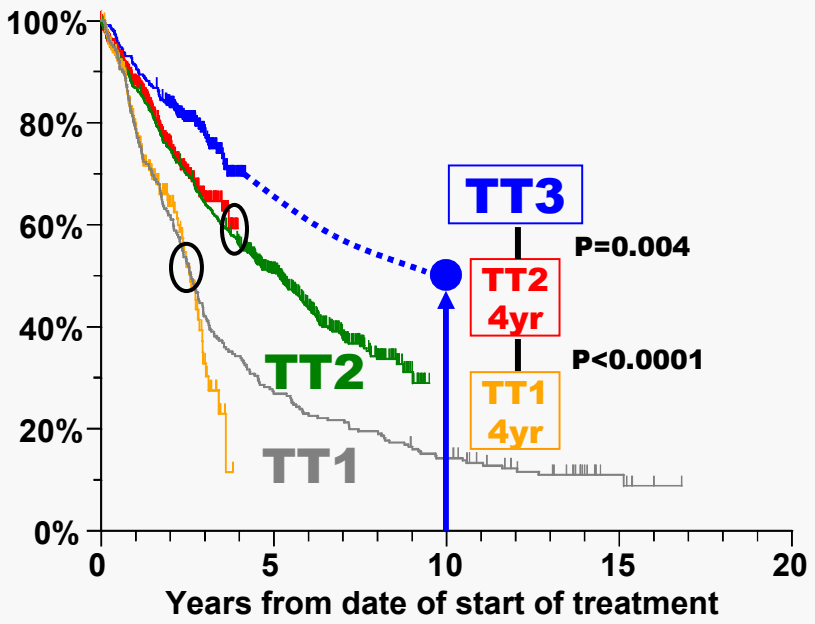
EMPLOYING GENES DISTINGUISHING MGUS & NORMAL



OUTCOME PROJECTIONS IN CONTEXT OF 4-YR TT3 & MATURE DATA WITH TT1 AND TT2:

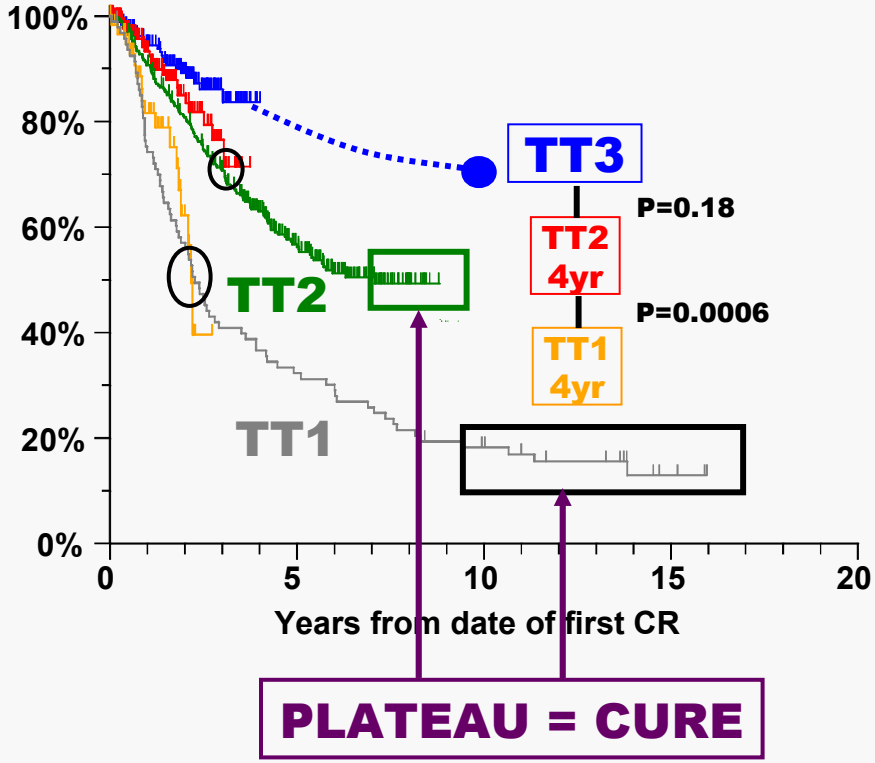
LET'S QUIT SAYING: "MYELOMA IS INCURABLE"

>50% 10-yr EFS w/ TT3

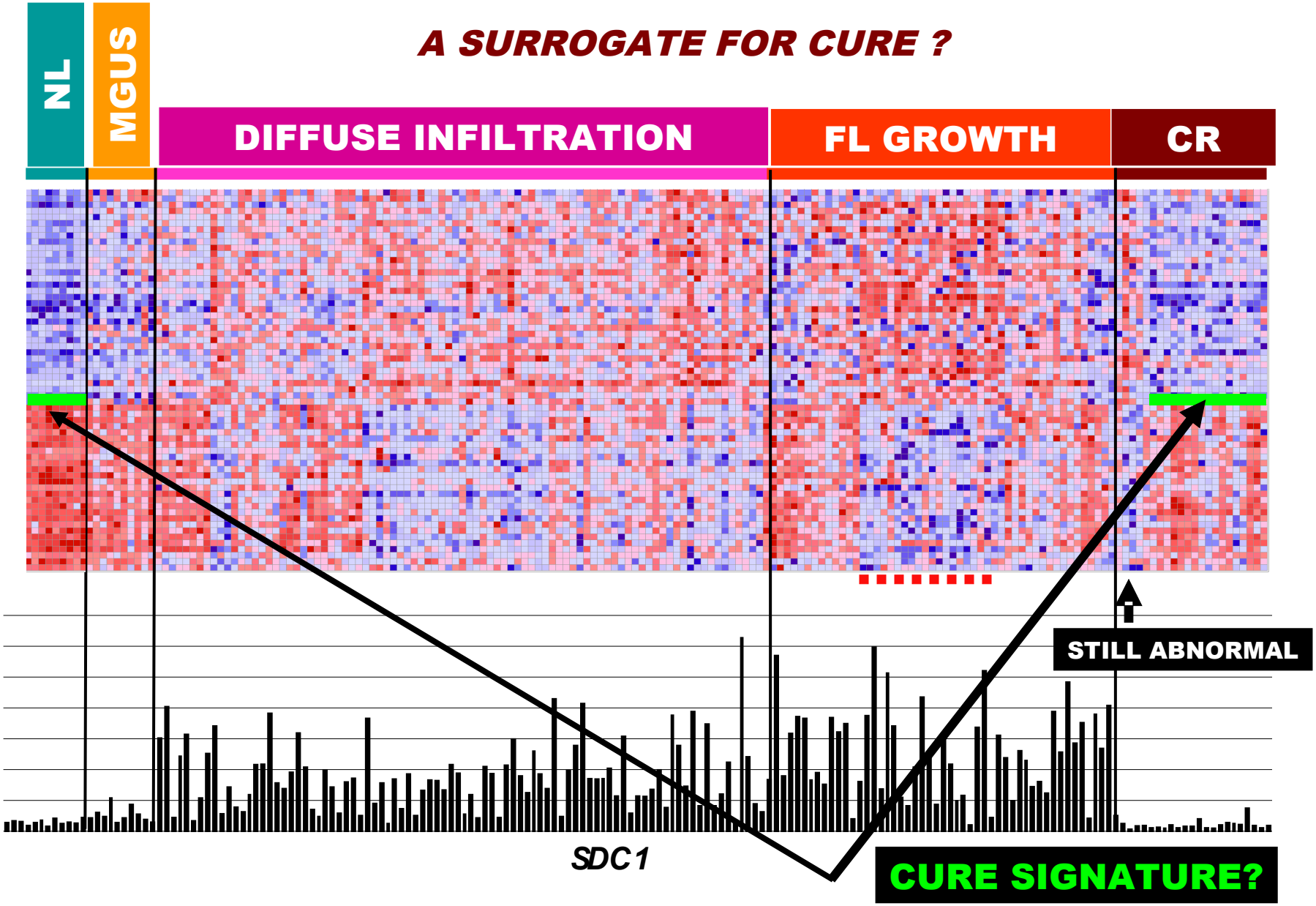


Initial 4-yr and current outcomes in TT1 and TT2 are super-imposable; hence, TT3 projections are realistic

>60% 10-yr CCR w/ TT3

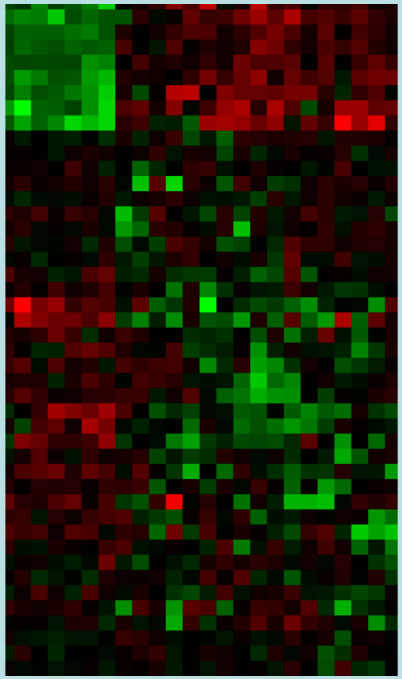


STROMA-ASSOCIATED GENES NORMALIZE OR BECOME MGUS-LIKE IN SOME CASES OF CR

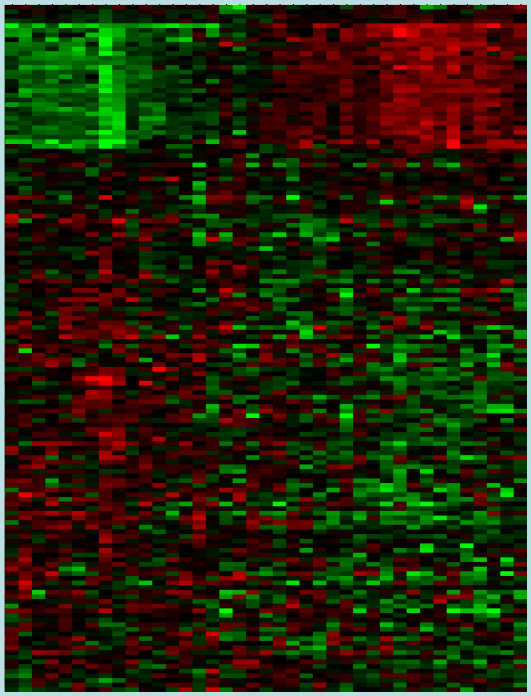


PURSUING A MM-PC CURE SIGNATURE IN TT3

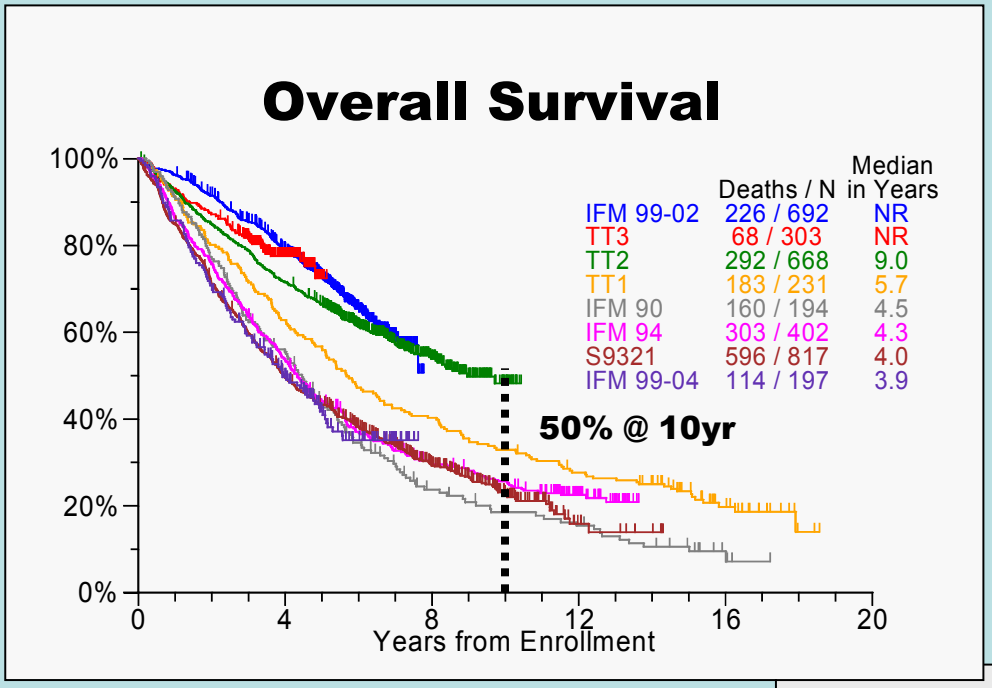
45 genes differentiate <1.5yr from >2.5yr CR duration in high-risk MM



148 genes differentiate <1yr from >4yr CR duration in low-risk MM



LONG-TERM FOLLOW-UP OF IFM S9321 TT PROTOCOLS



TT3: all risk, age <75

TT2: all risk, age <75

IFM99-02: low risk, age <65

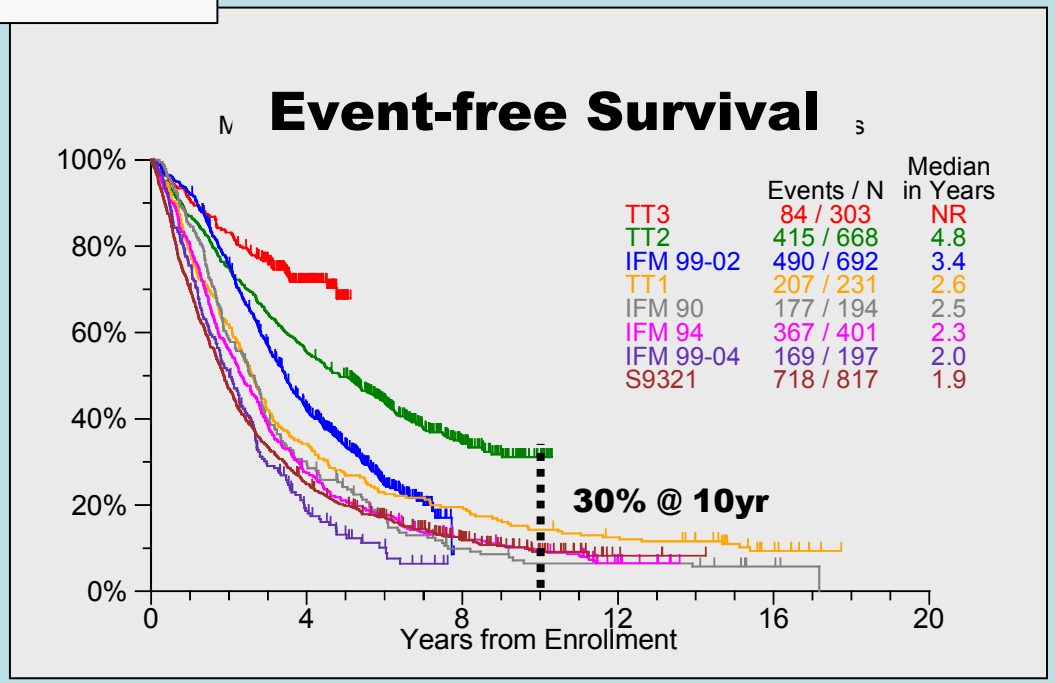
TT1: all risk, age <75

IFM90: all risk, age <65

IFM94: all risk, age <65

IFM99-04: high risk, age <65

S9321: all risk, age <70

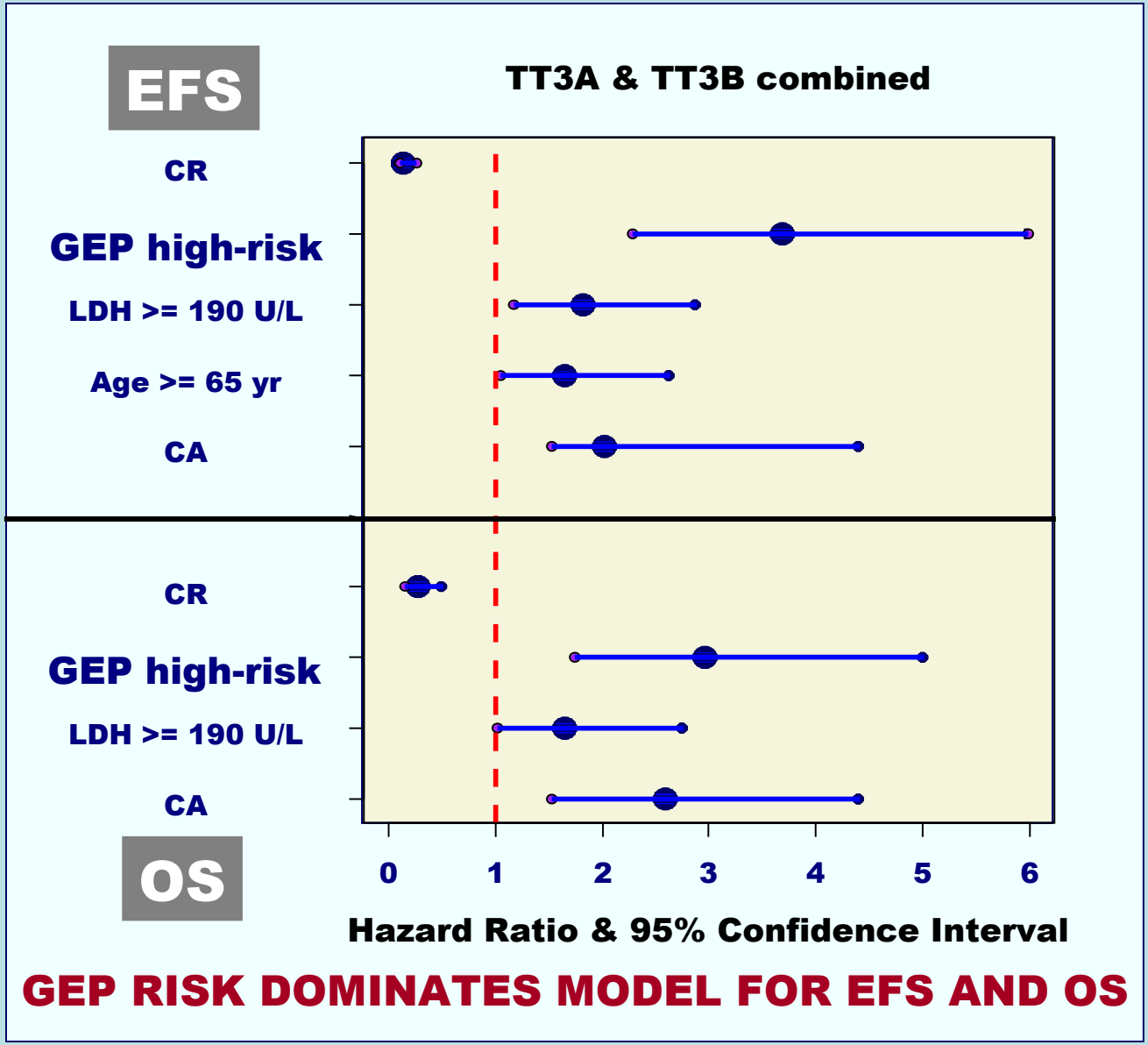


TOTAL THERAPY 2

- Extended survival in no THAL arm v TT1 by consolidation therapy
- THAL increased CR but not its duration
- THAL OS benefit revealed beyond 5yr
- THAL uniquely benefits CA with low-risk GEP
- CR crucial for high-risk MM
- Drawn attention to MDS-CA

- GEP
  - Molecular subgroups
  - MGUS-like myeloma
  - Risk prediction
  - 48hr post-THAL/DEX pharmacogenomics
- MRI-defined focal lesions
  - Linked to CRP
  - Precede osteolysis
  - Poor prognosis
  - Resolve slowly
  - Sites of MM dormancy
  - Cause of late relapse

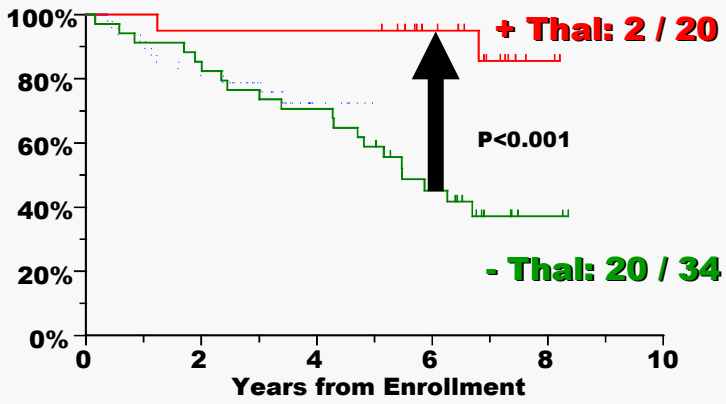
TT3: MULTIVARIATE ANALYSIS OF FEATURES ASSOCIATED WITH SURVIVAL



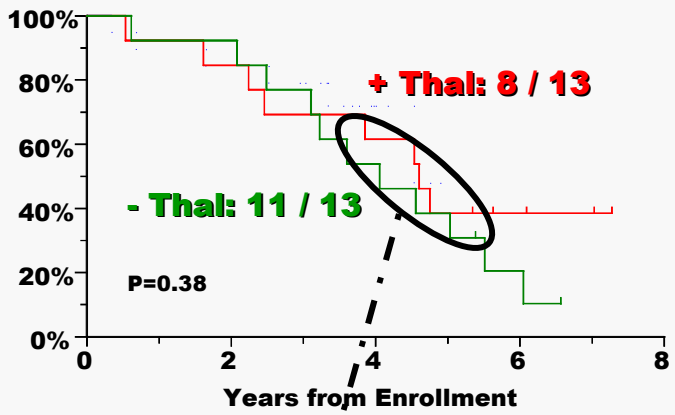
GEP RISK DOMINATES MODEL FOR EFS AND OS

TT2: THAL BENEFIT IN CASE OF CA1 OR CA13, NOT WITH BOTH CA1 PLUS CA13 - HIGH IL6R?

CA1 *or* CA13



CA1 + CA13

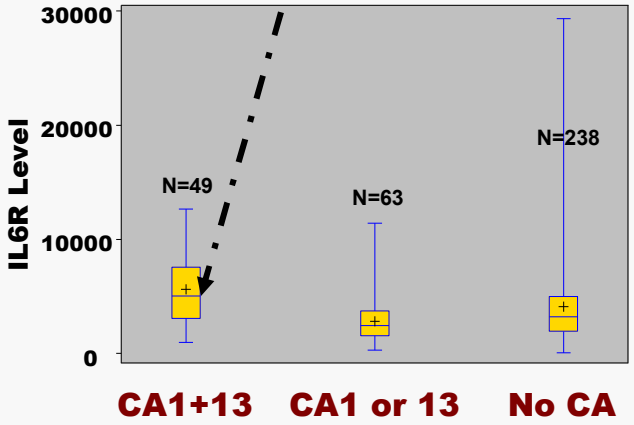


Survival inferior with high IL6R

304 low-risk patients	%	HR	P
CA present	26	3.17	<.001
CA with thal (interaction)	11	0.27	0.003
B2M > 5.5 mg/L	18	2.57	<.001
TP53 deletion	10	3.13	<.001
IL6R Expression ≥ 2900*	52	1.89	0.002

** Displaces CA1 and CA13*

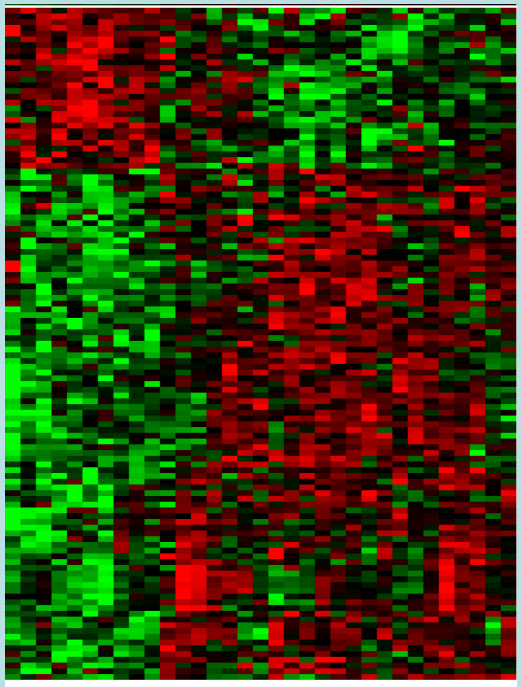
IL6R higher in presence of CA1+13

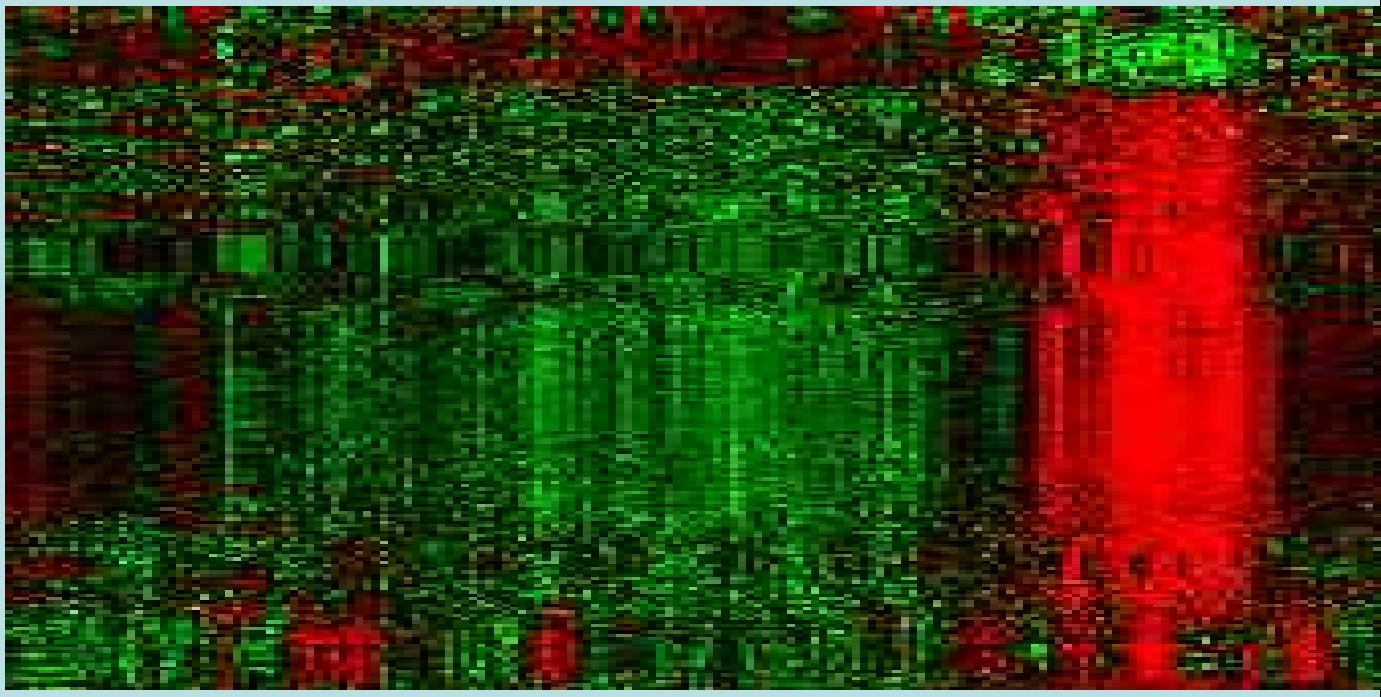


FOCAL LESIONS AND RANDOM BONE MARROW SAMPLES HAVE DIFFERENT GEP IN PC AND ME

PLASMA CELLS

BONE MARROW MICRO-ENVIRONMENT (ME)





FOCAL | **RANDOM** | **RANDOM** | **FOCAL**

DKK1

MAG1

THE RIGHT CLINICAL SETTING FOR TESTING THE POWER OF GENOMICS

- **Large sample size, uniform treatment, long follow-up in an era of vastly improved survival**
- **Thorough initial work-up, detailed serial analyses to judge value of genomics v conventional parameters**
- **The clinical challenge**
  - **50% expected to survive 10 years**
  - **15% succumb to myeloma in 2 years**
- **Statistical tools**
  - **Hazard ratio (HR) seldom exceeds 2.0 with standard factors**
  - **R-squared (R^2) value capturing variability in clinical outcomes accounted for by individual variables and, cumulatively, by those contributing to prognosis independently, seldom exceeds 20% with standard parameters**