Myeloma Steering Committee In-Person Meeting
March 2, 2011
Conclusions and Recommendations

The NCI Myeloma Steering Committee held a face to face strategy meeting in Rockville, MD on March 2, 2011. The goal of the meeting was to develop a working definition for high risk myeloma and share ideas for clinical trials, translational studies, and accrual issues for myeloma patients. The meeting included NCI and extramural participants, with expertise in myeloma patient management, clinical trials, biostatistics, translational science, and patient advocacy.

1. **Definition of High Risk Myeloma:** *(*Incomplete agreement; accept as working definition)*
   - Patients with 14(16), 14(20), del (17p)*
   - Poor risk genomics as defined by GEP or SNP array*
   - LDH $\geq$ 2x normal
   - Plasma cell leukemia

2. **Potential trial for high risk patients:**
   - RVD based platform
   - +/- 4th agent
   - 2 arms (experimental and control); 2 "place-holder" experimental arms ready when first arm closes
   - Consider selection design
   - Concern about accrual given size of patient population
   - SWOG will take the lead on this trial

3. **Potential trial for non-high risk patients**
   - Controversial: include all patients?
   - What clinical question should be asked?
   - Include quality of life and cost effectiveness questions
   - ECOG will take the lead on this trial

4. **Investigate the role of transplant**
   - In high risk patients
   - In low risk patients
   - Support ongoing BMTCTN trial

5. **Investigate salvage therapies**

6. **Evaluate response after 4 cycles of therapy**

7. **Investigate the roles of**
   - Consolidation
   - Maintenance

8. **Address accrual barriers**
   - Community oncologists' and patients' perspectives
   - Need for NCI-designated sites to administer treatment
   - Access to investigational agents
   - Complex consent process

- Financial burden on participating sites
- IRB review process

9. Design trials to investigate myeloma biology

- Standardize sample collection
- Include genomic studies
- Design across studies and banks where possible

Myeloma Steering Committee In-Person Meeting
March 2, 2011
Meeting Summary

Attendees

MYSC Leadership:
Morie Gertz
Richard Little
Nikhil Munshi

MYSC Members:
Kenneth Anderson
Bart Barlogie
Boris Freidlin
Sergio Giralt
Antje Hoering
Susanna Jacobus
Michael Katz
Ola Landgren
James Omel
Vincent Rajkumar
Donna Reece
Howard Streicher
Dan Sullivan
Matthias Weiss

MYSC Alternates:
Asher Chanan-Khan
Jatin Shah

Invited Participants:
Hervé Avet-Loiseau
John Crowley
Craig Hofmeister
Shaji Kumar
Pieter Sonneveld
Hajime Uno

FDA Staff:
Mark Rothmann

NCI Staff:
LeeAnn Jensen
John Jessup
Peter Ujhazy
Roy Wu

EMMES Staff:
Heather Johnson

The Myeloma Steering Committee held an in-person meeting on March 2nd, 2011 in Rockville, MD to discuss Multiple Myeloma (MM) and set goals to define high-risk (HR) disease, treatment interventions, discuss barriers to accrual for MM trials, and obtain a general consensus from all participants on how to approach the next clinical trials and how to move forward.

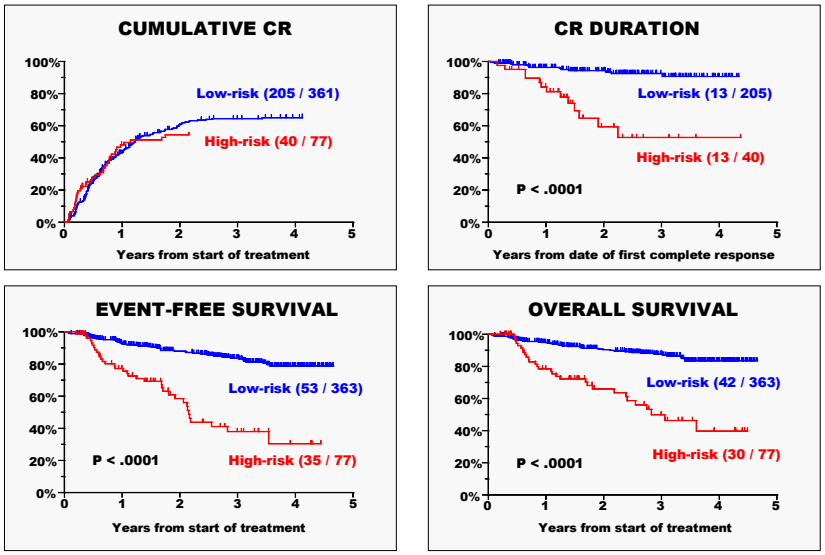
Defining High-Risk Multiple Myeloma

Defining Parameters of High-Risk Myeloma: The University of Arkansas Experience
Bart Barlogie

Dr. Barlogie presented data supporting the ability of gene expression profiling (GEP) to define a subset of ~15% of patients with HRMM faring poorly with their progressive Total Therapy regimens. Total Therapy 3 (TT3) consists of combination chemotherapy for induction and consolidation prior to and after Melphalan based tandem transplants. During the first year of maintenance, patients receive VTD (Velcade, Thalidomide, Dexamethasone) and thereafter only THAL plus DEX. In contrast to the results in high risk MM, progress in low-risk MM has been good, especially with the introduction in TT3 of Velcade (bortezomib.)

According to multivariate modeling, GEP-defined high-risk status ranked first in determining short OS, EFS and CR duration.

TREATMENT OUTCOMES BY GEP-DEFINED RISK
all TT3 patients



PROGNOSTIC POWER OF GEP-DEFINED RISK VALIDATED

The utility of GEP was supported by the R^2 statistics, which portray the variability in clinical outcomes.

R2 CAPTURING OUTCOME VARIABILITY REACHES 50% IN TT3 PROGNOSTIC MODELS

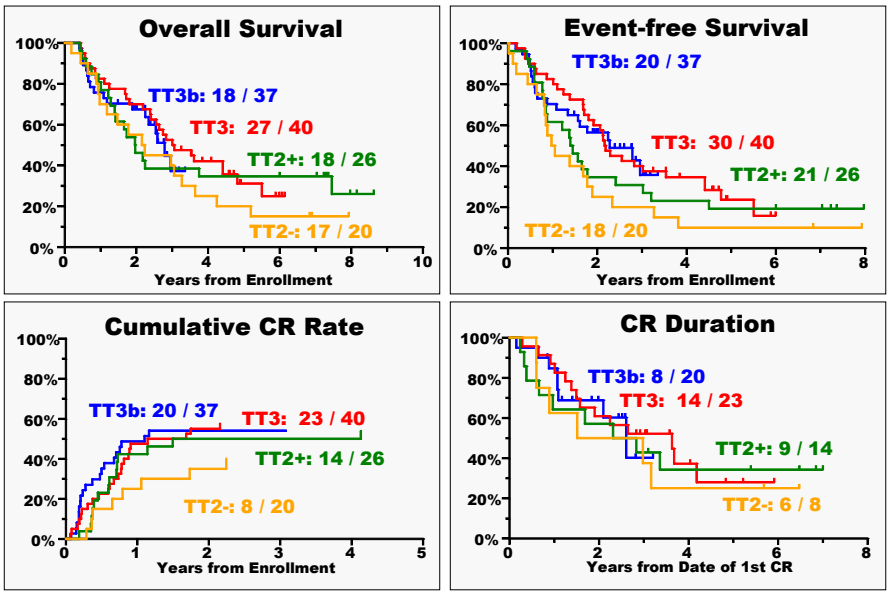
ENDPOINT	Variable	%	HR	P	R^2 %
Overall Survival (N=432)	*Cytogenetic abnormalities*	*38*	*2.39*	*<.001*	*28*
	GEP high-risk	**17**	**2.47**	**<.001**	**34**
	B2M > 5.5 mg/L	25	1.87	0.010	38
Event-free Survival	**GEP high-risk**	**17**	**2.40**	**<0.001**	**22**
	Cytogenetic abnormalities	*38*	*1.69*	*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

In examining GEP high-risk-associated features, both standard and GEP-derived factors were apparent.

Factor	GEP-70 Defined Risk Groups		P-value
	GEP-70 Low Risk (N = 705)	GEP-70 High Risk (N = 151)	
Median Age (Yrs)	**58.5 (24.8-76.3)**	**58.3 (35.1-75.0)**	
Age >= 65 yr	171/705 (24%)	39/151 (26%)	0.684
Female	274/705 (39%)	67/151 (44%)	0.210
IgA Isotype	164/701 (23%)	39/145 (27%)	0.369
IgG Isotype	390/701 (56%)	73/145 (50%)	0.244
Albumin < 3.5 g/dL	**156/700 (22%)**	**74/151 (49%)**	**<.001**
B2M >= 3.5 mg/L	**300/702 (43%)**	**105/151 (70%)**	**<.001**
B2M > 5.5 mg/L	**132/702 (19%)**	**69/151 (46%)**	**<.001**
Creatinine >= 2 mg/dL	**48/696 (7%)**	**25/150 (17%)**	**<.001**
CRP >= 8 mg/L	**226/701 (32%)**	**62/150 (41%)**	**0.033**
Hb < 10 g/dL	**190/704 (27%)**	**74/151 (49%)**	**<.001**
LDH >= 190 U/L	**182/704 (26%)**	**73/151 (48%)**	**<.001**
Platelet Count < 150 x 10^9/L	**79/704 (11%)**	**51/151 (34%)**	**<.001**
Cytogenetic abnormalities	**197/701 (28%)**	**108/150 (72%)**	**<.001**
GEP-80 high-risk	**21/705 (3%)**	**61/151 (40%)**	**<.001**
TP53 deletion	**87/705 (12%)**	**32/151 (21%)**	**0.004**
GEP Proliferation Index >= 10	**26/705 (4%)**	**79/151 (52%)**	**<.001**
GEP Centrosome Index >= 3	**117/705 (17%)**	**100/151 (66%)**	**<.001**

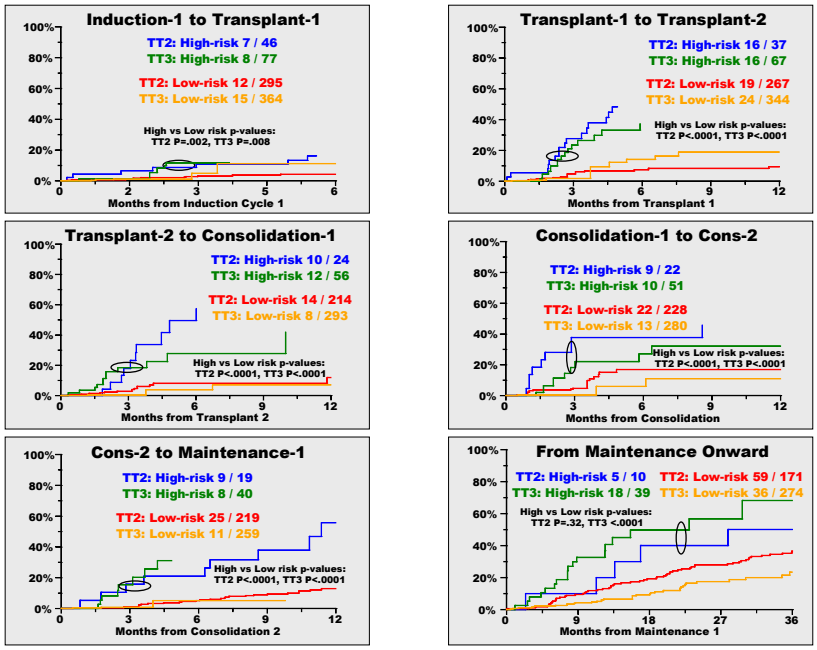
The lack of progress in HRMM is readily apparent when comparing TT2 control arm, TT2 thalidomide arm and 2 successive TT3 trials with VTD maintenance in TT3A and TT3B, in which Revlimid (lenalidomide) replaced thalidomide.

TOTAL THERAPIES 2, 3 FOR UNTREATED MM
GEP HIGH-RISK – DATA AS OF JUNE 10, 2010



Analyzing the “weak links” in TT protocols, it was apparent that in HRMM any interruption of therapy was detrimental. This led to the current approach in TT5 of reduced dose intensity therapy with more frequent treatment, thus affording greater dose density overall.

TREATMENT FAILURE BY PROTOCOL PHASE AND GEP RISK



To determine whether more favorable subsets could be identified within HRMM, Cox regression analysis was performed. PFS and OS were decreased in the presence of GEP-defined p53 deletion and in case of GEP-80-defined risk, a model developed on the basis of 48hr post-bortezomib test-dose administration.

	Variable	n/N (%)	TT3 Overall Survival		TT3 Progression-Free Survival	
			HR (95% CI)	P-value, R-squared *	HR (95% CI)	P-value, R-squared *
Univariate	TT3B	37/77 (48%)	1.24 (0.69, 2.24)	P-val: 0.467, R2 = 1.3%	1.01 (0.57, 1.79)	P-val: 0.964, R2 = 0.0%
	Age >= 65 yr	21/77 (27%)	1.67 (0.90, 3.09)	P-val: 0.104, R2 = 4.4%	1.42 (0.77, 2.60)	P-val: 0.261, R2 = 2.0%
	Female	37/77 (48%)	1.14 (0.65, 1.98)	P-val: 0.652, R2 = 0.4%	1.01 (0.59, 1.75)	P-val: 0.968, R2 = 0.0%
	IgA Isotype	19/75 (25%)	1.72 (0.92, 3.23)	P-val: 0.090, R2 = 5.2%	1.80 (0.98, 3.33)	P-val: 0.059, R2 = 6.1%
	IgG Isotype	35/75 (47%)	0.85 (0.48, 1.51)	P-val: 0.583, R2 = 0.6%	0.79 (0.45, 1.39)	P-val: 0.419, R2 = 1.2%
	Albumin < 3.5 g/dL	41/77 (53%)	1.88 (1.06, 3.32)	P-val: 0.030, R2 = 9.6%	1.67 (0.96, 2.91)	P-val: 0.070, R2 = 6.9%
	B2M >= 3.5 mg/L	57/77 (74%)	1.34 (0.70, 2.58)	P-val: 0.376, R2 = 1.7%	1.41 (0.73, 2.72)	P-val: 0.304, R2 = 2.7%
	B2M > 5.5 mg/L	41/77 (53%)	1.24 (0.71, 2.17)	P-val: 0.453, R2 = 1.2%	1.38 (0.79, 2.39)	P-val: 0.257, R2 = 2.6%
	Creatinine >= 2 mg/dL	13/77 (17%)	0.92 (0.43, 1.97)	P-val: 0.837, R2 = 0.1%	1.00 (0.49, 2.06)	P-val: 0.993, R2 = 0.0%
	CRP >= 8 mg/L	35/77 (45%)	1.04 (0.60, 1.83)	P-val: 0.878, R2 = 0.0%	1.12 (0.65, 1.94)	P-val: 0.682, R2 = 0.3%
	LDH >= 190 U/L	37/77 (48%)	1.54 (0.88, 2.69)	P-val: 0.133, R2 = 4.3%	1.68 (0.97, 2.92)	P-val: 0.065, R2 = 6.4%
	Platelet Count < 150 x 10^9/L	24/77 (31%)	1.03 (0.56, 1.89)	P-val: 0.921, R2 = 0.1%	1.13 (0.62, 2.05)	P-val: 0.687, R2 = 0.5%
	Cytogenetic abnormalities	57/76 (75%)	1.31 (0.68, 2.52)	P-val: 0.419, R2 = 1.1%	1.23 (0.66, 2.32)	P-val: 0.515, R2 = 0.7%
	GEP 80-gene high-risk	30/77 (39%)	2.34 (1.32, 4.13)	P-val: 0.003, R2 = 16.4%	2.21 (1.27, 3.85)	P-val: 0.005, R2 = 15.0%
	TP53 deletion	11/77 (14%)	2.54 (1.26, 5.12)	P-val: 0.009, R2 = 11.6%	2.78 (1.37, 5.63)	P-val: 0.005, R2 = 11.6%
	GEP Proliferation Index >= 10	42/77 (55%)	1.63 (0.91, 2.90)	P-val: 0.099, R2 = 5.6%	1.72 (0.98, 3.02)	P-val: 0.061, R2 = 6.9%
	GEP Centrosome Index >= 3	59/77 (77%)	1.20 (0.62, 2.35)	P-val: 0.584, R2 = 0.4%	1.03 (0.55, 1.93)	P-val: 0.930, R2 = -0.0%
OS Multivariate	TT3b	36/75 (48%)	0.91 (0.48, 1.74)	P-val: 0.784, R2 = 1.3 %		
	GEP 80-gene high-risk	**29/75 (39%)**	**2.49 (1.36, 4.58)**	**P-val: 0.003, R2 = 17.7 %**		
	TP53 deletion	**11/75 (15%)**	**2.55 (1.22, 5.31)**	**P-val: 0.013, R2 = 23.9 %**		
	Albumin < 3.5 g/dL	**40/75 (53%)**	**2.18 (1.17, 4.05)**	**P-val: 0.014, R2 = 28.6 %**		
	IgA Isotype	**19/75 (25%)**	**1.89 (0.99, 3.58)**	**P-val: 0.052, R2 = 34.6 %**		
PFS Multivariate	TT3b	36/75 (48%)			0.75 (0.40, 1.42)	P-val: 0.38, R2 = 1.3 %
	TP53 deletion	**11/75 (15%)**			**2.27 (1.06, 4.83)**	**P-val: 0.034, R2 = 13.1 %**
	GEP 80-gene high-risk	**29/75 (39%)**			**2.12 (1.15, 3.89)**	**P-val: 0.015, R2 = 24.6 %**
	Albumin < 3.5 g/dL	**40/75 (53%)**			**2.44 (1.30, 4.55)**	**P-val: 0.005, R2 = 29.3 %**
	IgA Isotype	**19/75 (25%)**			**2.70 (1.33, 5.49)**	**P-val: 0.006, R2 = 35.3 %**
	LDH >= 190 U/L	**36/75 (48%)**			**1.95 (1.01, 3.79)**	**P-val: 0.048, R2 = 40 %**

Updated data on the high-risk features that identify patients with a 30% or lower 2-year PFS will be provided to the MYSC by Arkansas/CRAB/SWOG. Arkansas/CRAB/SWOG was also asked to determine how many GEP70-indentified high-risk patients are also identified by FISH, cytogenetics and/or ISS-3 stage. The relative contributions of all standard and GEP plus FISH-derived variables should be determined.

Attempt to Define Parameters of High-Risk Myeloma
Hajime Uno

Drs. Uno and Jacobus from the ECOG statistical center performed an analysis with the UAMS data to characterize prognostic abilities of the following known prognostic factors: age, ISS, LDH, Cytogenetic Abnormality, FISH, Proliferative Index, and GEP70, where FISH information was derived from GEP data using TC class. Random cross-validation estimates for the concordance rates (C-statistics) were calculated to quantify prognostic abilities of various prediction models constructed with these parameters for overall survival. A summary of their findings through this empirical modeling approach is as follows:

1. These "relatively new parameters" (GEP70, Proliferative Index, Cytogentic Abnormality and FISH) improve prediction of prognosis over the conventional clinical parameters (Age, ISS, LDH).

2. The clinical parameters (Age, ISS, LDH) further improve the prediction of prognosis even when one of the "relatively new parameters" is in the prognostic model. This suggested that the empirical derivation of a prognostic model by combining those parameters would provide an even better model.

3. Incremental value of GEP70 on top of Age, ISS, LDH and FISH in predicting prognosis was small, while the dataset used for their analysis was not independent of the one used for the derivation of the GEP70 score.

4. The incremental value of these markers should be assessed in other cohorts to validate results in different treatment settings.

5. In this empirically-established prognostic model, the results were highly time-dependent. A short-term prediction model and long-term prediction model might be different. The ECOG analysis implies that longer-term risk prediction is comparable among models. By contrast, proliferation index was a strong second to GEP in predicting 3-year overall survival.

Ultra High-Risk Multiple Myeloma
Hervé Avet-Loiseau

There is a need for a single definition for high risk multiple myeloma (HRMM). An arbitrary definition being used is patients whose survival is less than 24 months. Characteristics of HRMM include:

- Three DNA abnormalities: patients with del(12p13.31) alone or amp(5q31.3) and del(12p13.31) and high $S\beta_2M$ had a very poor outcome (5-year overall survival, 20%). 4;14 alone is not a good prognostic factor while del(17p) is a good candidate for identifying those patients with a median OS of less than 2 years
- Poor risk genomics as defined by GEP or SNP array
- ISS stage 3

It is important to note that fragile patients are not usually eligible for clinical trials; therefore, information about their disease is excluded from all analyses. Their information would be useful and alteration of eligibility criteria to include them should be considered.
Panel Discussion: Defining High-Risk Multiple Myeloma

- The discussion addresses patients in the up-front setting.

- Prognostic factors of the extremely ill patients that expire prior to registering for trials (or who are ineligible) need to be captured.
- Dr. Barlogie recommended identifying HRMM patients by a steep drop in the EFS curve.
- Dr. Uno recommended that after HR patients are defined clinically, their GEP should be analyzed to develop a model. It is important to identify patients who were misclassified and determine the cause.
- HRMM needs to be defined biologically so that therapies can be developed against molecular targets. Biologically defined high risk factors must be related to tumor and distinguished from host characteristics that confer poor prognosis.
- In a European trial where GEP was an ancillary study, quality samples were obtained from 58% of patients. In a national US study requiring GEP analysis, the ability to obtain useable samples from at least 90% of patients must be demonstrated.
- While it was agreed that GEP 70 is an important assay, alternate methods such as FISH are needed for patients at centers that do not have ready access to GEP. Also, these methods could serve as a back-up for patients with poor GEP samples.
- Predictive markers that reflect the biology of the disease and that can be therapeutically targeted are needed. Candidates for predictive markers should be built into the trials. There might be one trial that includes both HR and LR patients. LR patients might benefit from HR treatment and predictive models could be used to gain more data.

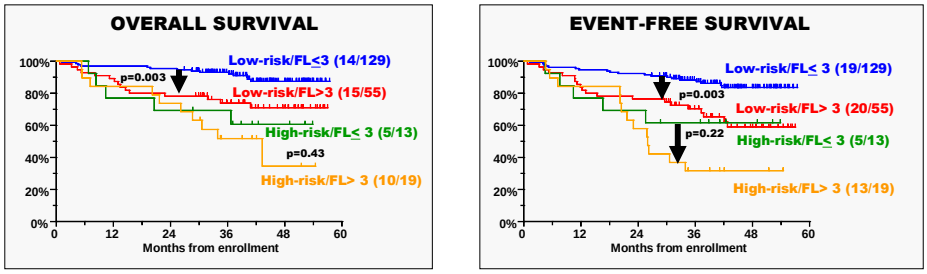
Future Trials

Characteristics for the Ideal Clinical Trial for High-Risk Disease: SWOG Consensus
Bart Barlogie

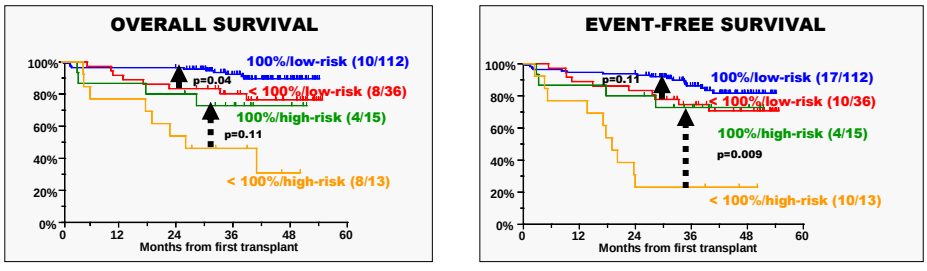
Important components of a trial design for HRMM include the following:

1. building on Arkansas TT5 data employing dose-dense and less dose-intense therapy;
2. new drug combination phase 2 trial with VRD backbone after VTD-PACE induction and PBSC collection:
    a. consider phasing in with early novel agents
    b. adding HDAC inhibitors, anti-IL6R, PSMD4-amplification-targeting drugs
3. emphasizing PET and MRI as part of high-risk trial and use imaging-defined CR as additional endpoint, having demonstrated the importance of FDG suppression early after induction in high-risk MM

TT3 SURVIVAL BY GEP RISK & FDG-FL AT BASELINE



TT3 SURVIVAL BY 100% FDG SUPPRESSION PRE-Tx



4. built-in therapy design for rescue of high-risk MM
    a. could be cytotherapy with expanded NK cell product, etc.

5. ancillary research

Translational Components

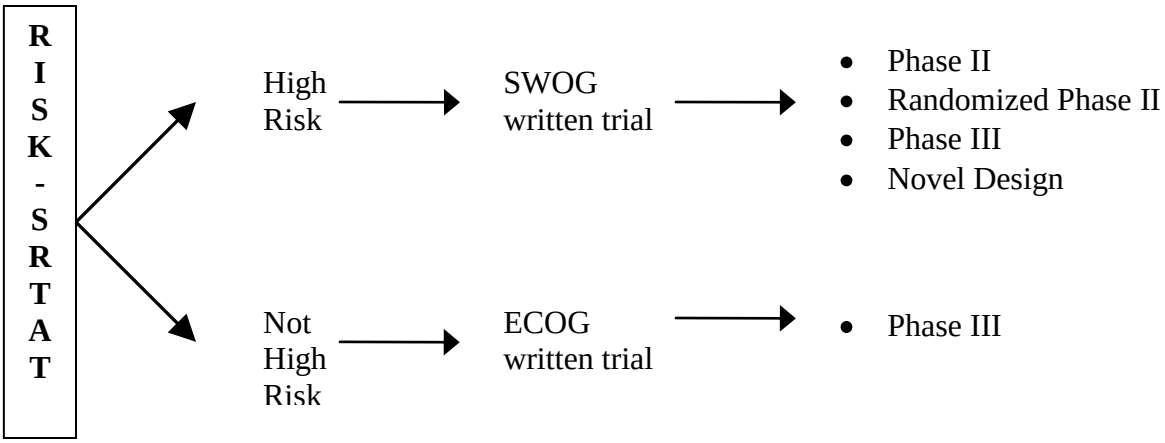
1. PET-CT (and MRI?) at baseline and monthly x3, then Q3 months in first year and Q6 months for years 2 and 3
2. Genomics at baseline and relapse
3. I-FISH: 1Q21, Del(p53), FGFR3/MMSET, MAF/MAFB, CNND1 translocations
4. Metaphase cytogenetics
5. Serial S-IL6R levels: Serum cryopreservation for proteinomics

The Next Newly Diagnosed MM Trials

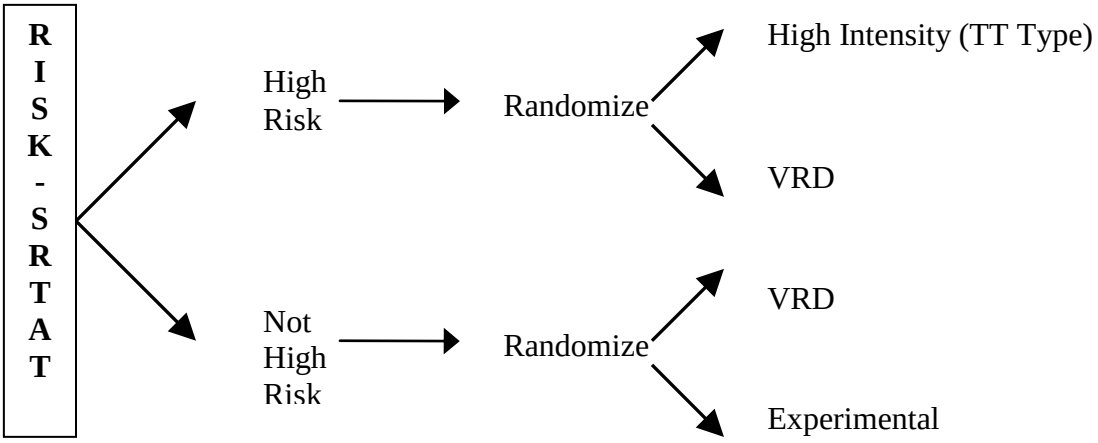
S. Vincent Rajkumar, Shaji Kumar

Two approaches were presented for the next large MM clinical trial(s):

Option 1 – Risk-stratification to determine optimal trial; 1 prior therapy cycle allowed



Option 2 – One mega trial; 1 prior therapy cycle allowed



Panel Discussion: Interventions for High-Risk Multiple Myeloma

- It was agreed that HRMM will be defined as patients with one (or more) of the following:
    - del(17p)*
    - 14;16*
    - 14;20*
    - High LDH (Dr. Barlogie will provide data to justify the cut off)
    - Plasma cell leukemia (standard definition)
    - GEP 70 high-risk signature

    * all identified by FISH
- There are regulatory issues related to the use of GEP 70 for treatment decisions. Use of GEP 70 as an "integrated" assay would mean that the test was performed on all patients but not used for treatment assignment or eligibility. The information gathered could be used for future clinical trials.
- A consensus was not reached regarding use of an adaptive design in this patient population.
- The maximum accrual for HRMM patients is ~50 patients/year.

Barriers to Accrual and Correlative Studies

Barriers to MM Clinical Trial Accrual
Matthias Weiss

Multiple barriers to accrual, either community or academic center based, were identified. After the issues were presented, the significance of each barrier was identified and possible strategic developments to overcome these obstacles were discussed.

Potential Barriers

- Acuity of disease presentation often requires immediate intervention, leaving little time to consider a clinical trial (academic)
- Complexity of disease and management options overwhelms patients (community)
- MM clinical trial treatment options may not represent perceived current "best care" or standard of care (academic & community)
- The issues presented by complex clinical trials
    - Busy provider discouraged by trial design, testing table(s), treatment regimen, form, etc. (community)
    - Experienced CRC/CRN staff required (community)
    - Biomarker submission too extensive; CT potentially requiring duplication of tests (academic & community)
    - Follow-up testing too extensive (academic)
- Insurance companies denial of clinical trial participation or coverage of specific tests (community)
- Phase II trials require local IRB approval delaying opening of clinical trial, increasing cost (academic & community)
- Small phase II trials offer lower potential for accrual, increasing cost (academic & community)
- Differing patient population and stage of disease presented to academic and community centers
- General barriers from patient perspective
    - Effective standard of care available
    - Experimental nature of clinical trial
    - Randomization concerns
    - Frequent tests and procedures
    - Delay of treatment initiation
    - Need to make a decision without complete comprehension
    - Insurance coverage concerns

Validate perceived accrual barriers
- Create a survey item list
- Rate each item 0 – 5 (Likert scale)
    - 0 – not important, not impeding accrual
    - 5 – very important, significantly impeding accrual
- Distribute item list via survey monkey to MYSC members with room for additional comments
- Then, distribute updated item list to academic centers, CCOP, MBCCOP, NCCCP members via ECOG, SWOG, CALGB, NCCTG
- Analyze data (50-100 responses expected)

Develop strategies to overcome validated barriers
- Integrate the feedback into clinical trial designs
- Insurance pre-approval (CMS)
- Standard of care determination of required tests and availability of appropriate funding if not standard of care
- CIRB availability for larger phase II trials

Patient Perspectives on Barriers to Accrual
Michael Katz, James Omel

Patient enrollment onto a clinical trial occurs only after several conditions and decisions have been met and made. Many patients are lost after each step:
- Patient meets eligibility criteria
- Doctor is aware of trial and either has access or is willing to refer
- Doctor decided to present trial as an option to patient
- Patient decides to enroll in trial

If the trial has been presented to the patient as an option, there are many general reasons why patient may or may not decide to participate.

<u>Possible Reasons Patients Consent</u>
- Access to new drugs not available outside of trials
- Limited standard treatment options
- Reduced costs for care/drugs provided in trial
- Desire to help other patients/advance the science
- Access to better care and attentiveness than standard treatments
- Trust in physician's recommendation

<u>Possible Reasons Patients Refuse</u>
- Concern about using "experimental" treatments (effectiveness, side-effects, risk), feeling that trial should be "last resort"
- Availability of good, standard options
- Randomization, not being able to choose their treatment
- Not wanting the treatment(s) in the trial
- Concern about time, inconvenience and discomfort of additional tests
- Time and costs of travel to treatment center
- Concern about delays in starting treatment if enrolling in trial
- Insurance coverage issues
- Overwhelmed by diagnosis, complex protocols, consent documents

There are implications for the trial design chosen by cooperative groups, making some trials more ideal than others.

Easier to Accrue to Trials

- Providing access to new agents, Phase I/II for relapsed/refractory
- Oral drugs provided by pharma, not covered or poorly covered by insurance
- Non-randomized Phase II maintenance trials
- Personalization of treatment using new technology to tailor treatment choice

Harder to Accrue to Trials

- Up-front trials for standard risk patients
- Trials using new combinations or doses of drugs already approved
- Randomization of big decisions (e.g., transplant vs. no transplant)
- Trials with burdensome requirements for office visits and additional time-consuming or painful test

In the spring of 2000, the Coalition of National Cancer Cooperative Groups, Inc conducted a Harris survey of nearly 6000 cancer patients:

- 85% of respondents said they were unaware that participation in a clinical trial was a treatment option; however, the majority of these individuals said that would have been receptive to the idea of a clinical trial if they knew it was an option.
- 97% of respondents who participated in clinical trials reported they were treated with dignity and respect and received excellent or good quality care.
- The major reasons cited by patients for participating in a clinical trial include:
    - The belief that trials provide access to the best quality of care (76%)
    - Participation would benefit future cancer patients (72%)
    - Participants receive newer/better treatment (63%)
    - Participants get more care and attention (40%)
- 76% of trial participants said they would recommend clinical trial participation to someone with cancer.
- Most of adult cancer patients who participate in clinical trials say that a physician had a great deal of influence on their decision to participate.

Panel Discussion

- Successful trials need to be examined to determine what needs and can be changed. For example, ECOG had a successful trial where both treatment arms received the new agent; patients need and want access to new drugs. Also, if a trial is randomized, both treatment arms need to be attractive and credible.
- Protocols also need to be more user friendly, as the simpler the trial is, the better the participation may be. In Canada, they have been asked to reduce the consent form by half of the size of the US's.
- Regulatory and eligibility requirements need to be re-examined. Most patients who are screened for a trial after receiving initial treatment are ineligible.
- In Europe (specifically the Netherlands and France), the problems are different as there are no private hematologists. Also, patients are not able to select their own treatment as that is the physician's responsibility. For example, France has a bone marrow transplant trial that opened 2 months ago (at the time of the meeting) and has already accrued 12 patients. Also, patients only receive their transplant at academic centers; all other treatments are administered at the community center.
- There is an institutional financial disincentive for private practice physicians to enroll patients on trials as their salaries are dependent on the number of patients seen and treated. At the academic center, salaries are independent of patient volume.

- With the consolidation of the cooperative groups in the future, it needs to be thought about how the remaining groups can be more readily compensated to ensure that trials reach completion. The current reimbursement figure is not enough to cover costs.

Final Discussion and Next Steps

- Different approaches to a clinical trial were discussed, with an early focus placed on practical ways for patients to enter trials to increase accrual. Assignment to a trial could be a multi-step process:
    - Step 1: patient diagnosed with MM
        - At diagnosis, sample collection is taken for eligibility, etc; patient could also be enrolled in sample collection trial, E3A05
    - Step 2: standard of care treatment is administered (RVD, 2x)
        - Sample analysis is performed concurrently with treatment
        - All future trials need to allow 2 cycles of RVD in the eligibility criteria
    - Step 3: based on sample analysis, patient is categorized into disease subtype and enrolled into appropriate treatment trial or no treatment
- As the trials will be conducted by SWOG and ECOG, they will submit the concept for the trial to NCI. However, since steering committee approval is required for NCI-funded studies, early collaboration with the MYSC is recommended to make the process as efficient as possible.
- SWOG is most interested in a trial for HRMM. Suggestions were made for this trial to focus on a "VRD plus new drug" regimen with rapid achievement of CR as its primary endpoint.
- ECOG is interested in a trial for patients with standard risk disease. The 3 main options discussed were: VRD versus Carfilzomib RD; VRD versus an oral proteasome inhibitor plus RD; and VRD versus VRD plus new drug.

NCI Myeloma Steering Committee Meeting
Wednesday, March 2, 2011
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