



ISSN: 0976-3031

Available Online at <http://www.recentscientific.com>

CODEN: IJRSFP (USA)

*International Journal of Recent Scientific Research*  
Vol. 8, Issue, 8, pp. 18924-18932, August, 2017

**International Journal of  
Recent Scientific  
Research**

DOI: 10.24327/IJRSR

## Research Article

### MULTIPLE COMPARISON PROCEDURE FOR CURE RATE MODELS

**Elangovan R\* and Jayakumar B**

Department of Statistics Annamalai University Annamalai Nagar-608 002  
Tamilnadu, India

DOI: <http://dx.doi.org/10.24327/ijrsr.2017.0808.0594>

#### ARTICLE INFO

##### Article History:

Received 17<sup>th</sup> May, 2017  
Received in revised form 21<sup>th</sup>  
June, 2017  
Accepted 28<sup>th</sup> July, 2017  
Published online 28<sup>th</sup> August, 2017

##### Key Words:

Adaptive Design Accrued Data,  
Multiple Comparison Procedures and  
Cure Rate Models.

#### ABSTRACT

An adaptive design allows adaptations of trial and statistical procedures after its initiation without undermining the validity and integrity of the trial. In recent years, the use of adaptive designs in clinical research and development based on accrued data has become very popular due to its flexibility and efficiency. Multiple comparison procedures after using adaptive design methods in clinical trials have received much attention in recent literature. Certain types of cancers, like breast cancer, leukemia, a substantial proportion of patients may now be cured by treatment, i.e., cured proportion. The patients who are cured are called immunes or long-term survivors, while the remaining patients who develop a recurrence of the diseases are termed susceptible. The population of interest is thus divided into two groups viz., cured and noncured. Cure rate models provides satisfactory models in such cases. In this paper, it is proposed to discuss the adaptive design methods and its multiple comparison procedures concerning the development of Velcade intended for multiple myeloma using cure rate models. Numerical example is provided.

**Copyright © Elangovan R and Jayakumar B, 2017**, this is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

#### INTRODUCTION

The concept of adaptive design can be traced back to 1970s when the adaptive randomization and a class of designs for sequential clinical trials were introduced. As a result, most adaptive design methods in clinical research are referred to as adaptive randomization, group sequential designs with the flexibility for stopping a trial early due to safety, futility and/or efficacy, and sample size re-estimation at interim for achieving the desired statistical power.

The use of adaptive design methods for modifying the trial and/or statistical procedure of on-going clinical trials based on accrued data has been practiced for years in clinical research. Adaptive design methods in clinical research are very attractive to clinical scientists due to the following reasons. First, it reflects medical practice in real world. Second, it is ethical with respect to both efficacy and safety (toxicity) of the test treatment under investigation. Third, it is not only flexible, but also efficient in the early and late phase of clinical development. However, it is a concern whether the p-value or confidence interval regarding the treatment effect obtained after the modification is reliable or correct. For a detailed study, refer to [Chow et.al \(2005\)](#), [Jennison and Turnbull \(2000\)](#), [Hung et.al \(2005\)](#).

In recent years, the potential uses of adaptive design methods in clinical trials have attracted much attention. An adoptive design allows adaptations of trial and statistical procedures after its initiation without undermining the validity and integrity of the trial. In recent years, the use of adaptive designs in clinical research and development based on accrued data has become very popular due to its flexibility and efficiency. Multiple comparison procedures after using adaptive design methods in clinical trials have received much attention in recent literature. Cure rate models, used for modeling time-to-event data, consist of a surviving fraction and have become increasingly popular in the analysis of data from clinical trials. Recently, the developments of new drugs and treatment regimens have resulted in patients living longer with certain types of cancer and heart disease. Cure rate models have applications in a wide array of areas such as biomedical studies, criminology, finance, demography, manufacturing, and industrial reliability. At an individual level, diagnosis of cancer is regarded as a human tragedy. At the level of society, cancer is one of the major chronic diseases, causing a notable amount of health administrative costs. Prognosis and possible cure from cancer are thus important measures of lifetimes which can be assessed by analyzing the survival of cancer patients. Different statistical approaches are used for analyzing the cancer survival data. The results of survival analysis for cancer

\*Corresponding author: **Elangovan R**

Department of Statistics Annamalai University Annamalai Nagar-608 002 Tamilnadu, India

patients have been widely presented and reported for different human sub populations of the globe Woolson (1981), Kardaun (1983), Beadle *et al.*, (1984), Sedmak *et al.*, (1989). However, very few survival results at national level are available for the populations of Pakistan refer to Khan *et al.*, (2004). McGarty (1974) has mentioned that for adopting any suitable. Statistical technique for analyzing survival data for certain types of cancers, like breast cancer, leukemia, a substantial proportion of patients may now be cured by treatment, i.e., cured proportion. The patients who are cured are called immunes or long-term survivors, while the remaining patients who develop a recurrence of the diseases are termed susceptible. The population of interest is thus divided into two groups viz., cured and noncured. Cure rate models provides satisfactory models in such cases. In this paper, it is proposed to discuss the adaptive design methods in clinical trials using multiple comparison procedures concerning the development of Velcade intended for multiple myeloma. Numerical example is provided.

### Adaptive Design

In clinical trials, it is not uncommon to modify trial and/or statistical procedures during the conduct of clinical trials based on the review of interim data. The purpose is not only to efficiently identify clinical benefits of the test treatment under investigation, but also to increase the probability of success of clinical development. Trial procedures are referred to as the eligibility criteria, study dose, treatment duration, study endpoints, laboratory testing procedures, diagnostic procedures, criteria for evaluability, and assessment of clinical responses. Statistical procedures include randomization, study design, study objectives/hypotheses, sample size, data monitoring and interim analysis, statistical analysis plan, and/or methods for data analysis. Thus, an adaptive design is defined as a design that allows adaptations to trial and/or statistical procedures of the trial after its initiation without undermining the validity and integrity of the trial. An adaptive design as a clinical trial design that uses accumulating data to decide on how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial. In many cases, an adaptive design is also known as a flexible design

### Type of adaptive designs

Based on (primarily prospective) adaptations employed, commonly considered adaptive design methods in clinical trials include, but are not limited to: (i) an adaptive randomization design, (ii) a group sequential design, (iii) a sample size re-estimation design, (iv) a drop-the-loser design, (v) an adaptive dose finding (e.g., dose escalation) design, (vi) a biomarker-adaptive design, (vii) an adaptive treatment-switching design, (viii) a hypothesis-adaptive design, (ix) an adaptive seamless phase II/III trial design, and (x) a multiple adaptive design.

### Multiple adaptive design

A multiple-adaptive design is any combinations of the above adaptive designs. Commonly considered multiple-adaptation designs include (i) the combination of adaptive group sequential design, drop-the-losers design, and adaptive seamless trial design and (ii) adaptive dose-escalation design with adaptive randomization. In practice, since statistical inference for a multiple-adaptation design is often difficult, it is

suggested that a clinical trial simulation be conducted to evaluate the performance of the resultant multiple adaptive design at the planning stage.

### Development of Velcade intended for Multiple Myeloma

Multiple myeloma is a cancer of the blood. Some people with multiple myeloma have many symptoms, while others have few, if any. Common signs and symptoms of multiple myeloma may include: bone pain and broken bones, nausea and vomiting, fatigue, frequent infections, nervous system problems, anemia, and hypercalcemia. These symptoms may be referred to as CRAB:

C=elevated Calcium, R=Renal (kidney) problems, A=Anemia, B=Bone lesions.

Multiple myeloma affects the part of your bone called bone marrow. Your blood is produced in your bone marrow, which is made up of many different types of cells, including red blood cells, white blood cells, platelets, and plasma cells. A plasma cell is a type of white blood cell that normally produces antibodies to fight infections. If you have multiple myeloma, you have abnormal plasma cells, also called myeloma cells. These myeloma cells push out normal cells. They form tumors in bones and, sometimes, in various soft tissues of the body. Myeloma cells can collect over time and build up in the bone marrow. When they do, they prevent bone marrow from making enough blood cells for the body to fight infection and other diseases. Although multiple myeloma is not curable, there are many treatment options available. See the Appendix.

### Cox's Regression Model

Cox's regression model (1972, 1975) based on the method of 'Partial likelihood' plays a very important role in analyzing the data in a more realistic way on survival or fertility on any other kind involving population characteristics using Stochastic models. Suppose we are interested in the survival of patients suffering from hypertension. The hazard rate at any point of time need not necessarily depend on time only but also on a host of explanatory variables or covariates, some of which may not be expressed in quantitative form. For example, other conditions affecting the hazard rate of an individual may be factors such as age, blood pressure, occupation, general health condition and the presence of other related complications etc. Cox's regression model not only takes into account of all the explanatory variables but also is based on estimation techniques which estimate the parameters concerning the individual covariates independent of the parameters concerning the hazard rate on time t.

To put the idea in concrete form let us take the simplest form of the Cox's model.

$$\lambda_j(t) = \lambda_0(t) \exp \left[ \begin{matrix} \beta' z_j(t) \\ \sim \sim \end{matrix} \right]$$

where

$\lambda_j(t)$   $\equiv$  hazard rate of the  $j^{\text{th}}$  individual at any time t.

$\lambda_0(t)$   $\equiv$  hazard function with respect to time only ignoring the other covariates i.e., keeping  $z_{ij} = 0 \forall i = 1, 2, \dots, p; j = 1, 2, \dots, n$ .

$Z_j'$   $= (z_{j1}, z_{j2}, \dots, z_{jp})$  is the p-component covariate vector for the  $j^{\text{th}}$  individual,  $j=1, 2, \dots, n$ .

Corresponding to every individual  $j=1, 2, \dots, n$ . the random variable  $T_j$  is the time of death, which in a randomly censored

sample is observed upto a period  $c_j$  for the  $j^{\text{th}}$  individual ( $j=1,2,\dots,n$ ). Taking logarithm on both sides of Cox's model we have.

$$\log \lambda_j(t) = \log \lambda_0(t) - [\beta_1 z_1(t) + \beta_2 z_2(t) + \dots + \beta_p z_p(t)]$$

The equation could have been treated as a single equation log-linear model for the estimation of  $\beta_i$ 's ( $i=1,2,\dots,p$ ) as well as  $\lambda_0(t)$ . However, the innovativeness of Cox's approach is that Cox proposed the estimates of the regression parameters  $\beta_1, \beta_2, \dots, \beta_p$  independent of  $\lambda_0(t)$ . Let  $R(t) = \{j: T_j \geq t, c_j\}$  to be the risk set i.e the set of individual exposed to the risk under observations (the  $j^{\text{th}}$  individual reserved observed between  $(0, c_j)$ ). Given that we have a set of  $n$  persons in the sample and that a person dies in the set the probability that the  $j^{\text{th}}$  person dies (assuming that the deaths occur independently) is given by

$$\frac{\lambda_c(t) \exp[\beta' z_j(t)]}{\sum_{j \in R(t)} \lambda_c(t) \exp[\beta' z_j(t)]} = \frac{\exp[\beta' z_j(t)]}{\sum_{j \in R(t)} \exp[\beta' z_j(t)]} = P_L$$

the summation being extended over all the persons in the risk set  $R$ , Cox defined,

$$L(\beta) = \prod_{T_j \leq c_j} \frac{\exp[\beta' z_j(t)]}{\sum_{j \in R(t)} \exp[\beta' z_j(t)]}$$

$j=1,2,\dots,n$  (the product being extended over all  $j \forall T_j \leq c_j, j=1,2,\dots,n$ ). The partial likelihood estimating the parameters by the method of maximum likelihood conjectured that the method would give estimates of  $\beta_1, \beta_2, \dots, \beta_p$  which would have otherwise the asymptotic properties of the maximum likelihood estimators.

**Cox's Partial likelihood**

The instantaneous propensity of leaving a job (or a profession) at time  $t$  is defined as the conditional probability of leaving a job (or profession) during an infinitesimal interval  $(t, t + dt)$  given that the person was in job till the time  $t$ , denoting the hazard rate by  $h(t)$ , we have

$$h(t)dt = \frac{f(t)dt}{R(t)}$$

where  $R(t)$  is the Survival function or the probability of continuing the job at least upto a period  $t$  and  $f(t) dt$  is the probability of leaving the job between  $(t, t + dt)$ . It can be shown that  $R(t) = \exp \left[ - \int_0^t h(T) d(T) \right]$  and

$$f(t) = \frac{d}{dt} (1 - F(t)) = \frac{d}{dt} R(t).$$

The Cox hazard model as indicated by (vide Gill (1984)),

$$h(t) = h_0(t) \exp (\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \dots + \beta_k X_k)$$

where  $h_0(t)$  represents the hazard rate or the rate of propensity of leaving at time  $t$  purely on the consideration of time or CLS in the profession.  $h_0(t)$  is called the base line hazard rate. The probability that the  $i^{\text{th}}$  person will leave the job at time  $t$  in  $(0, T)$  is given by

$$\frac{h_0(t) e^{\beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i}}}{h_0(t) \sum_{i=1}^n e^{\beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i}}}, \quad (i=1,2,\dots,n) \quad \dots(1)$$

where  $X_{1i}, X_{2i}, X_{3i}$  are the scores of the covariates 1, 2 and 3 respectively of the  $i^{\text{th}}$  person. Note that the ratio in equ. (1) is

independent of  $t$ , the length of service. If we take the product of all such terms for all the professionals with serial number 1, 2, ...,  $k$ , we get a simplified form of Cox's partial likelihood given by

$$P_L = \prod_{i=1}^k \frac{e^{\beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i}}}{\sum_{i=1}^k e^{\beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i}}} \quad \dots (2)$$

Maximizing  $P_L$  (or  $\log P_L$ ) with respect to  $\beta_1, \beta_2$  and  $\beta_3$  respectively, we get three estimating equations for estimating  $\beta_1, \beta_2$  and  $\beta_3$  (assuming  $e^{\beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i}} \cong 1 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i}$ ) approximately both in the numerator and denominator of equ. (2) as follows:

$$\sum_{i=1}^k X_{1i} - k \frac{\sum_{i=1}^k X_{1i} (1 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i})}{\sum_{i=1}^k (1 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i})} = 0 \quad \dots (3)$$

$$\sum_{i=1}^k X_{2i} - k \frac{\sum_{i=1}^k X_{2i} (1 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i})}{\sum_{i=1}^k (1 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i})} = 0 \quad \dots (4)$$

$$\sum_{i=1}^k X_{3i} - k \frac{\sum_{i=1}^k X_{3i} (1 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i})}{\sum_{i=1}^k (1 + \beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i})} = 0 \quad \dots (5)$$

Having estimated the parameters  $\beta_1, \beta_2$  and  $\beta_3$  relating to the covariates, the parameters affecting the leaving from profession for personal reason or covariates, we estimate the parameter of the CLS corresponding to the base line hazard function.

**Bayesian Variable selection for Cox's Regression model**

A proportional hazards model is denoted by a hazard function of the form

$$h(t, x) = h_b(t) \exp(x' \beta)$$

where  $h_b(t)$  denotes the baseline hazard function at time  $t$ ,  $x$  denotes the covariate vector for an arbitrary individual in the population, and  $\beta$  denotes a vector of regression coefficients.

**Prior and Posterior Distribution for  $h_b$**

Let  $G(\alpha, \lambda)$  denote the gamma distribution with shape parameter  $\alpha > 0$  and scale parameter  $\lambda > 0$ , where the density is given by

$$f(x|\alpha, \lambda) = \begin{cases} \frac{\lambda^\alpha x^{\alpha-1} e^{-\lambda x}}{\Gamma(\alpha)} & x > 0 \\ 0 & \text{otherwise} \end{cases}$$

Consider a discrete gamma process prior for the baseline hazard rate. To denote the discrete gamma process, we first construct a finite partition of the time axis. Let  $0 \leq s_0 < s_1 < \dots < s_m$  denote this finite partition, with  $s_m > t_j$ , for all  $j = 1, \dots, n$ .

$$\text{Let } \xi_i = h_b(s_i) - h_b(s_{i-1})$$

denote the increment in the baseline hazard in the interval  $(s_{i-1}, s_i)$ ;  $i = 1, \dots, M$ . The  $\xi_i$ 's are random variables since the baseline hazard is assumed random. The  $\xi_i$ 's are independent a priori, and have gamma distributions, which are induced by the underlying gamma process. Thus, the  $\xi_i$ 's have independent gamma distributions with shape parameters  $\alpha(s_i) - \alpha(s_{i-1})$  and scale parameter  $\lambda$ . The variance of the gamma process is controlled by choosing  $\lambda$  large or small to reflect vague prior beliefs at various time intervals. Letting  $\tau = (\xi_1, \dots, \xi_m)$ ; the prior density of  $\tau$  is given by

$$P_r = \psi(\tau) = \prod_{i=1}^m f(\xi_i)$$

where  $f(\xi_i)$  is a  $G\{\alpha(s_i)-\alpha(s_{i-1}), \lambda\}$  density. The prior parameters of the  $\xi_i$ 's may be chosen to depend on  $m$ . Choices of prior parameters for  $\tau$  can be made in several ways. One may take vague choices of prior parameters for the  $\xi_i$ 's such as  $\alpha(s) = s_i - s_{i-1}$  for  $s_{i-1} \leq s \leq s_i$ , and take  $\lambda$  large. This choice may be suitable if there is little prior information available on the baseline hazard rate.

We assume a priori independence between the baseline hazard rate and the regression coefficients, and thus the joint prior density of  $(\beta^{(m)}, \tau)$  under model  $m$  is given by

$$\psi(\beta^{(m)}, \tau | m) = \psi(\beta^{(m)} | m) \psi(\tau)$$

We consider a fully parametric multivariate normal prior for  $\beta^{(m)}$ , since the normal prior has proved to be a flexible and useful class of priors for many regression problems, refer to Geisser (1993). Thus let  $N_p(\mu, T)$  denotes the  $p$  dimensional multivariate normal distribution with mean  $\mu$  and precision matrix  $Q$ . Thus, under model  $m$ , we take

$$\beta^{(m)} \sim N_{k_m}(\mu^{(m)}, c_0 Q_m)$$

where  $c_0$  is a scalar quantifying the degree of prior belief one wishes to attach to  $\mu^{(m)}$ . Under model  $m$ , we have the prior information  $W_0 = (n_0, y_0, X_{0,m}, \delta_0)$  and  $c_0$ , where  $X_{0,m}$  is an  $n_0 \times k_m$  design matrix,  $y_0$  is an  $n_0 \times 1$  vector of prior predictions, and  $\delta_0$  is the corresponding  $n_0 \times 1$  vector of censoring indicators. We take the prior mean of  $\beta^{(m)}$  to be the solution to Cox's partial likelihood equations for  $\beta^{(m)}$  using  $W_0$  as data. Suppose there are  $r$  failures and  $n_0 - r$  right censored values in  $y_0$ . Cox's partial likelihood for  $\beta^{(m)}$  based on  $W_0$  is given by

$$L^*(\beta^{(m)}) = \prod_{i=1}^r \frac{\exp\{x_{0i}^{(m)'} \beta^{(m)}\}}{\sum_{t \in R(y_{0i})} \exp\{x_{0i}^{(m)'} \beta^{(m)}\}} \quad \dots (6)$$

where  $x_{0i}^{(m)'$  is the  $i^{th}$  row of  $X_{0,m}$ ,  $(y_{01}, \dots, y_{0r})$  are the ordered failures and  $R(y_{0i})$  is the set of labels attached to the individuals at risk just prior to  $y_{0i}$ . Now we take  $\mu^{(m)}$  to be the solution to

$$\frac{\partial \log\{L^*(\beta^{(m)})\}}{\partial \beta_j^{(m)}} = 0$$

$j = 1, \dots, k_m$ . The matrix  $Q_m$  is taken to be the Fisher information matrix of  $\beta^{(m)}$  based on the partial likelihood in (5). Thus

$$Q_m = \left[ \frac{-\partial^2}{\partial \beta_i^{(m)} \partial \beta_j^{(m)}} \log\{L^*(\beta^{(m)})\} \right] \Bigg|_{\beta^{(m)} = \mu^{(m)}}$$

Given the prior prediction  $y_0$ , the prior probability of model  $m$  for the current study based on an update of  $y_0$  via Bayes theorem is given by

$$p(m) = p(m|D_0) = \frac{p(W_0|m)p_0(m)}{\sum_{m \in M} p(W_0|m)p_0(m)} \quad \dots (7)$$

where

$$p(W_0|m) = \iint L(\tau, \beta^{(m)}; W_0) \psi_0(\beta^{(m)}|m) \psi_0(\tau) d\beta^{(m)} d\tau$$

and  $L(\tau, \beta^{(m)}, W_0)$  is the likelihood function of the parameters based on  $D_0$ . The posterior probability of model  $m$  (for the current study) is given by

$$p(m|W) = \frac{p(W|m)p(m)}{\sum_{m \in M} p(W|m)p(m)}$$

where  $p(W|m)$  denotes the marginal distribution of the data given model  $m$ , and  $p(m)$  denotes the prior probability of model  $m$  given by (7). The marginal density  $p(W|m)$  corresponds precisely to the normalizing constant of the joint posterior density of  $(\tau, \beta^{(m)})$ . That is,

$$p(W|m) = \iint L(\tau, \beta^{(m)}; W) \psi(\beta^{(m)}|m) \psi(\tau) d\beta^{(m)} d\tau$$

Finally, we let  $p(\beta, \tau | W)$  denote the posterior distribution of the full model, that is,

$$p(\beta, \tau | W) \propto L(\beta, \tau | W) \psi(\beta | K) \psi(\tau)$$

where  $\beta = (\beta_1, \beta_2, \dots, \beta_k)'$ ;  $m = 1, 2, \dots, k$ ;  $k$  is the dimension of the model and is denoted by full model.

### Real data example: Cox's proportional hazard model

Assume the Completed Length of Service (CLS) distribution follows Gamma, the probability density function is

$$f_x(t) = \frac{(\lambda t)^{n-1}}{\Gamma(n)} \lambda e^{-\lambda t}, \lambda > 0, n > 0, t > 0$$

The reliability function is

$$R_x(t) = \frac{1}{\Gamma(n)} \int_{\lambda t}^{\infty} u^{n-1} e^{-u} du, \lambda > 0, n > 0, t \geq 0 \quad \dots (8)$$

which can be recognized as incomplete Gamma function.

$$h_x(t) = \frac{(\lambda t)^{n-1} \lambda e^{-\lambda t}}{\int_{\lambda t}^{\infty} u^{n-1} e^{-u} du},$$

In this case it can be observed that  $h_x(t)$  is an increasing function of  $t$ , when  $n > 1$ . The calculations of  $h_x(t)$  is rather complex as it involves incomplete gamma integrals. However, the expression for  $h_x(t)$  is obtained using computer. First, the least square estimate of the  $\lambda$  and  $n$  are obtained for the stimulated observations.

**Table 1** Variable Recorded-Multiple Myeloma Patients

Notation	Variable Name
$t$	Survival time from diagnosis to nearest month +1
$t'$	Maximum observed survival time from diagnosis +1
A/D	0 – Alive, 1 – Dead
$X_0$	Constant = 1.0
$X_1$	log BUN at diagnosis
$X_2$	Hemoglobin at diagnosis
$X_3$	Platelets at diagnosis 0 – abnormal, 1 – normal
$X_4$	Infection at diagnosis 0 – none, 1 – present
$X_5$	Age at diagnosis (complete years)
$X_6$	Sex 1 – Male, 2 – Female
$X_7$	log WBC at diagnosis
$X_8$	Fractures at diagnosis 0 – none, 1 – present
$X_9$	log %BM (log % of plasma bone marrow)
$X_{10}$	% Lymphocytes in peripheral blood at diagnosis
$X_{11}$	% Myeloma cells in peripheral blood at diagnosis
$X_{12}$	Proteinuria at diagnosis
$X_{13}$	Bence Jone protein in urine at diagnosis 1 – present, 2 – none
$X_{14}$	Total serum protein at diagnosis
$X_{15}$	Serum globins (gm%) at diagnosis
$X_{16}$	Serum calcium (mgm%) at diagnosis

**Table 2 Data Set-Multiple Myeloma\***

Case No.	t	t'	A/D	X <sub>0</sub>	X <sub>1</sub>	X <sub>2</sub>	X <sub>3</sub>	X <sub>4</sub>	X <sub>5</sub>	X <sub>6</sub>	X <sub>7</sub>	X <sub>8</sub>	X <sub>9</sub>	X <sub>10</sub>	X <sub>11</sub>	X <sub>12</sub>	X <sub>13</sub>	X <sub>14</sub>	X <sub>15</sub>	X <sub>16</sub>
1	1.25	40	1	1.0	2.2175	9.4	1.0	0.0	67.0	1.0	3.6628	1.0	1.9542	0.0	0.0	12.0	2.0	11.0	7.0	10.0
2	1.25	51	1	1.0	1.9395	12	1.0	1.0	38.0	1.0	3.9868	1.0	1.9542	0.0	0.0	20.0	1.0	6.0	3.0	18.0
3	2.00	21	1	1.0	1.5185	9.8	0.0	1.0	81.0	1.0	3.8751	1.0	2.0000	0.0	0.0	2.0	1.0	11.0	8.0	15.0
4	2.00	54	1	1.0	1.7482	11.3	0.0	0.0	75.0	1.0	3.8062	1.0	1.2552	13.0	52.0	0.0	2.0	9.0	6.0	12.0
5	2.00	41	1	1.0	1.3010	5.1	1.0	0.0	57.0	1.0	3.7243	1.0	2.0000	0.0	0.0	3.0	1.0	10.0	6.0	9.0
6	3.00	29	1	1.0	1.5441	6.7	1.0	1.0	46.0	2.0	4.4757	0.0	1.9345	3.0	5.0	12.0	2.0	9.0	3.0	10.0
7	5.00	19	1	1.0	2.2355	10.1	1.0	0.0	50.0	2.0	4.9542	1.0	1.6628	8.0	27.0	4.0	1.0	6.0	4.0	9.0
8	5.00	29	1	1.0	1.6812	6.5	1.0	0.0	74.0	1.0	3.7324	0.0	1.7324	1.0	25.0	5.0	2.0	10.0	7.0	9.0
9	6.00	90	1	1.0	1.3617	9	1.0	1.0	77.0	1.0	3.5441	0.0	1.4624	7.0	51.0	1.0	2.0	7.0	5.0	8.0
10	6.00	85	1	1.0	2.1139	10.2	0.0	0.0	70.0	2.0	3.5441	1.0	1.3617	6.0	68.0	1.0	2.0	9.0	7.0	8.0
11	6.00	14	1	1.0	1.1139	9.7	1.0	0.0	60.0	1.0	3.5185	1.0	1.3979	11.0	30.0	0.0	2.0	11.0	7.0	10.0
12	6.00	25	1	1.0	1.4150	10.4	1.0	0.0	67.0	2.0	3.9294	1.0	1.6902	10.0	33.0	0.0	2.0	10.0	6.0	8.0
13	7.00	93	1	1.0	1.9777	9.5	1.0	0.0	48.0	1.0	3.3617	1.0	1.4682	9.0	41.0	5.0	2.0	9.0	3.0	10.0
14	7.00	61	1	1.0	1.0414	5.1	0.0	0.0	61.0	2.0	3.7324	1.0	2.0000	0.0	0.0	1.0	2.0	8.0	4.0	10.0
15	7.00	92	1	1.0	1.1761	11.4	1.0	0.0	53.0	2.0	3.7243	1.0	1.5185	13.0	42.0	1.0	1.0	9.0	6.0	13.0
16	9.00	89	1	1.0	1.7243	8.2	1.0	0.0	55.0	1.0	3.7993	1.0	1.7407	4.0	31.0	0.0	2.0	9.0	6.0	12.0
17	11.00	68	1	1.0	1.1139	14	1.0	0.0	61.0	1.0	3.8808	1.0	1.2788	8.0	49.0	0.0	2.0	8.0	5.0	10.0
18	11.00	15	1	1.0	1.2304	12	1.0	0.0	43.0	1.0	3.7709	1.0	1.1761	7.0	48.0	1.0	1.0	12.0	8.0	9.0
19	11.00	35	1	1.0	1.3010	13.2	1.0	0.0	65.0	1.0	3.7993	1.0	1.8195	4.0	21.0	1.0	2.0	8.0	4.0	10.0
20	11.00	78	1	1.0	1.5682	7.5	1.0	0.0	70.0	1.0	3.8865	0.0	1.6721	5.0	35.0	0.0	2.0	7.0	5.0	12.0
21	11.00	41	1	1.0	1.0792	9.6	1.0	0.0	51.0	2.0	3.5051	1.0	1.9031	5.0	10.0	0.0	2.0	7.0	3.0	9.0
22	13.00	93	1	1.0	0.7782	5.5	0.0	1.0	60.0	2.0	3.5798	1.0	1.3979	12.0	55.0	2.0	2.0	10.0	8.0	10.0
23	14.00	28	1	1.0	1.3979	14.6	1.0	1.0	66.0	1.0	3.7243	1.0	1.2553	7.0	51.0	2.0	1.0	9.0	4.0	10.0
24	15.00	39	1	1.0	1.6021	10.6	1.0	0.0	70.0	1.0	3.6902	1.0	1.4314	16.0	46.0	0.0	2.0	9.0	5.0	11.0
25	16.00	62	1	1.0	1.3424	9	1.0	0.0	48.0	1.0	3.9345	1.0	2.0000	0.0	0.0	0.0	2.0	8.0	4.0	10.0
26	16.00	93	1	1.0	1.3222	8.8	1.0	0.0	62.0	2.0	3.6990	1.0	0.6990	5.0	41.0	17.0	2.0	8.0	4.0	10.0
27	17.00	79	1	1.0	1.2304	10	1.0	0.0	53.0	1.0	3.8808	1.0	1.4472	9.0	50.0	4.0	2.0	10.0	7.0	9.0
28	17.00	60	1	1.0	1.5911	11.2	1.0	1.0	68.0	1.0	3.4314	0.0	1.6128	1.0	46.0	1.0	2.0	9.0	6.0	10.0
29	18.00	49	1	1.0	1.4472	7.5	1.0	0.0	65.0	2.0	3.5682	0.0	0.9031	17.0	46.0	7.0	2.0	6.0	4.0	8.0
30	19.00	44	1	1.0	1.0792	14.4	1.0	0.0	51.0	1.0	3.9191	1.0	2.0000	0.0	0.0	6.0	2.0	13.0	7.0	15.0
31	19.00	52	1	1.0	1.2553	7.5	0.0	0.0	60.0	2.0	3.7924	1.0	1.9294	2.0	10.0	5.0	1.0	6.0	3.0	9.0
32	24.00	39	1	1.0	1.3010	14.6	1.0	0.0	56.0	2.0	3.0899	1.0	0.4771	12.0	52.0	0.0	2.0	4.0	3.0	9.0
33	25.00	56	1	1.0	1.0000	12.4	1.0	0.0	67.0	1.0	3.8195	1.0	1.6435	3.0	23.0	0.0	2.0	7.0	3.0	10.0
34	26.00	34	1	1.0	1.2304	11.2	1.0	0.0	49.0	2.0	3.6021	1.0	2.0000	0.0	0.0	27.0	1.0	6.0	3.0	11.0
35	32.00	48	1	1.0	1.3222	10.6	1.0	0.0	46.0	1.0	3.6990	1.0	1.6335	6.0	32.0	1.0	2.0	12.0	8.0	9.0
36	35.00	66	1	1.0	1.1139	7	0.0	0.0	48.0	1.0	3.6502	1.0	1.1761	16.0	42.0	4.0	1.0	12.0	9.0	10.0
37	37.00	237	1	1.0	1.6021	11	1.0	0.0	63.0	1.0	3.9542	0.0	1.2041	10.0	53.0	7.0	1.0	7.0	4.0	9.0
38	41.00	58	1	1.0	1.0000	10.2	1.0	0.0	69.0	1.0	3.4771	1.0	1.4771	5.0	30.0	6.0	1.0	10.0	6.0	10.0
39	41.00	73	1	1.0	1.1461	5	1.0	0.0	70.0	2.0	3.5185	1.0	1.3424	18.0	53.0	0.0	2.0	7.0	4.0	9.0
40	51.00	61	1	1.0	1.5682	7.7	0.0	0.0	74.0	1.0	3.4150	1.0	1.0414	10.0	50.0	4.0	1.0	12.0	8.0	13.0
41	52.00	57	1	1.0	1.0000	10.1	1.0	0.0	60.0	2.0	3.8573	1.0	1.6532	1.0	27.0	4.0	1.0	10.0	7.0	10.0
42	54.00	94	1	1.0	1.2553	9	1.0	0.0	49.0	1.0	3.7243	1.0	1.6990	8.0	37.0	2.0	1.0	8.0	3.0	10.0
43	58.00	74	1	1.0	1.2041	12.1	1.0	0.0	42.0	2.0	3.6990	1.0	1.5798	9.0	35.0	22.0	1.0	7.0	4.0	10.0
44	66.00	74	1	1.0	1.4472	6.6	1.0	0.0	59.0	1.0	3.7853	1.0	1.8195	4.0	22.0	0.0	2.0	5.0	3.0	9.0
45	67.00	97	1	1.0	1.3222	12.8	1.0	0.0	52.0	1.0	3.6435	1.0	1.0414	24.0	54.0	1.0	1.0	11.0	7.0	10.0
46	88.00	90	1	1.0	1.7161	10.6	1.0	0.0	47.0	2.0	3.5560	0.0	1.7559	22.0	17.0	21.0	1.0	6.0	3.0	9.0
47	89.00	121	1	1.0	1.3222	14	1.0	1.0	63.0	1.0	3.6532	1.0	1.6232	7.0	38.0	1.0	1.0	9.0	7.0	9.0
48	92.00	11	1	1.0	1.4314	11	1.0	0.0	58.0	2.0	4.0755	1.0	1.4150	12.0	36.0	4.0	1.0	9.0	6.0	11.0
49	4.00	4	0	1.0	1.9542	10	1.0	0.0	59.0	1.0	4.0453	0.0	0.7782	21.0	51.0	12.0	1.0	7.0	3.0	10.0
50	4.00	4	0	1.0	1.9243	10	1.0	1.0	49.0	2.0	3.9590	0.0	1.6232	21.0	24.0	0.0	2.0	17.0	12.0	13.0
51	7.00	7	0	1.0	1.1139	12.4	1.0	0.0	48.0	2.0	3.7993	1.0	1.8573	1.0	11.0	0.0	2.0	6.0	3.0	10.0
52	7.00	7	0	1.0	1.5315	10.2	1.0	1.0	81.0	1.0	3.5911	0.0	1.8808	1.0	16.0	0.0	2.0	12.0	10.0	11.0
53	8.00	8	0	1.0	1.0792	9.9	1.0	0.0	57.0	2.0	3.8325	1.0	1.6532	1.0	40.0	0.0	2.0	8.0	4.0	8.0
54	12.00	12	0	1.0	1.1461	11.8	1.0	0.0	46.0	2.0	3.6435	0.0	1.1461	7.0	47.0	0.0	2.0	7.0	3.0	7.0
55	11.00	11	0	1.0	1.6128	14	1.0	0.0	60.0	1.0	3.7324	1.0	1.8451	0.0	0.0	3.0	1.0	6.0	2.0	9.0
56	12.00	12	0	1.0	1.3979	8.8	1.0	0.0	66.0	2.0	3.8388	1.0	1.3617	8.0	50.0	0.0	2.0	9.0	5.0	9.0
57	13.00	13	0	1.0	1.6628	4.9	0.0	0.0	71.0	2.0	3.6435	0.0	1.7924	2.0	21.0	0.0	2.0	10.0	11.0	9.0
58	16.00	16	0	1.0	1.1461	13	1.0	0.0	55.0	1.0	3.8573	0.0	0.9031	13.0	53.0	0.0	2.0	9.0	5.0	9.0
59	19.00	19	0	1.0	1.3222	13	1.0	0.0	59.0	2.0	3.7709	1.0	2.0000	0.0	0.0	1.0	2.0	8.0	4.0	10.0
60	19.00	19	0	1.0	1.3222	10.8	1.0	0.0	69.0	2.0	3.8808	1.0	1.5185	0.0	0.0	0.0	2.0	10.0	7.0	10.0
61	28.00	28	0	1.0	1.2304	7.3	1.0	1.0	82.0	2.0	3.7482	1.0	1.6721	7.0	40.0	0.0	2.0	7.0	4.0	9.0
62	41.00	41	0	1.0	1.7559	12.8	1.0	0.0	72.0	1.0	3.7243	1.0	1.4472	2.0	56.0	1.0	1.0	7.0	3.0	9.0
63	53.00	53	0	1.0	1.1139	12	1.0	0.0	66.0	1.0	3.6128	1.0	2.0000	0.0	0.0	1.0	2.0	6.0	3.0	11.0
64	57.00	57	0	1.0	1.2553	12.5	1.0	0.0	66.0	1.0	3.9685	0.0	1.9542	0.0	0.0	0.0	2.0	8.0	4.0	11.0
65	77.00	77	0	1.0	1.0792	14	1.0	0.0	60.0	1.0	3.6812	0.0	0.9542	4.0	50.0	0.0	2.0	6.0	3.0	12.0

\*source [Krall et. al. \(1975\)](#) and [Kailash \(1992\)](#)



hazard model using real data example, refer to Elangovan (1998) and Elangovan *et.al.*(2006).

### Multiple Myeloma Study

A real data example has been taken from Krall *et.al.* (1975) and Kailash (1992). The former study of Krall *et.al.* Analyze data from study on multiple myeloma in which  $n_0=65$  patients with alkylating agent. Of those patients, 48 died during the study and 17 survived. The response variable measured for these data at diagnosis. These are blood urea nitrogen, hemoglobin, platelet count age, white blood cell count, bone fractures, percentage of the plasma cells in bone marrow, proteinuria, and serum calcium. These are typical covariates measured in multiple myeloma studies. Another multiple myeloma study using similar alkylating agents was studied by Kailash (1992), had  $n = 479$  patients with the same set of covariates being measured.

Based on the Myeloma study by Krall *et. al.* (1975) and Kailash (1992) given in table 1 and table 2, taking  $k=8$  covariates  $x_1, x_2, x_3, x_4, x_5, x_6, x_7$  and  $x_8$ . Standardization can be done to avoid computational difficulties using the method suggested by Gills and Wild (1992). For the prior distribution of  $\beta^{(m)}$  the prior mean was chosen to be the solution to Cox partial likelihood using the data given in table 2 and the prior precision matrix was computed using the equ. Given in (6) with data  $W_0$ . Using the simulation by Gibbs sample, refer to Rubinstein (1981), with the following data values as an input  $c_0 = n_0 / n = 65/339 = 0.19$  and  $(r_1, r_2) = (0.10, 0.15)$ . For each value of  $c_0$  in model with largest prior probability and the model with largest posterior probability has been obtained and is given in table 3. For the ranges of  $c_0$  given in Table 2, the  $(x_1, x_2, x_3, x_4, x_7, x_8)$  model consistently obtains the largest posterior probability. Also, we note that when we use a uniform prior on the model space, the  $(x_1, x_2, x_3, x_4, x_7, x_8)$  model obtains the largest posterior model probability with value 0.403.

The real data example shown in previous section using proportional hazard model based on three covariates only. If more number of covariates are used in such a case computation will be so difficult and it is observed that most of the covariate combinations, the propensities to leave increase with time. It is not so in the case of computing prior and posterior probability using multiple myeloma study. The prior and posterior probability can be calculated only moderate variable selecting problem involving 15 - 20 covariates. For more than 20 covariates and for large regression problem, the method suggested by George and McCulloch (1993) can be adopted for the proportional hazard model. As is well known that in the case of Cox's proportional hazard model and Bayesian variable selection model based on the real data example, it is observed that both the model are perhaps equally suitable. Based on the Myeloma data example the simulation results showed that the posterior models probabilities were not sensitive to the increasing hazard rate assumption and this is not to be true in general. Once the figures or information's are made available, the application of the models would be really helpful for future decision. Hence it shows that Bayesian variable selection for Cox's regression model performs effectively. Finally the proposal methodology (in both proportional hazard and Bayesian variable selection) can be used as a tool for screening

suitable subsets of models which could be consider for future analysis. The adaptive design methods in clinical trials using multiple comparison procedures concerning the development of Velcade intended for multiple myeloma based on Bayesian perspective and Cox's approach is best suited to data set and gives better estimates and more consistent results for the Velcade intended for multiple myeloma. The methodology used for the real data example using multiple myeloma is found to be best fit for the cure rate models discussed in the recent literature.

### References

1. Bauer P, Kieser M. (1999). Combining different phases in development of medical treatments within a single trial. *Stat Med.*, 18, pp 1833-48.
2. Chow SC, Chang M, Pong A. (2005). Statistical consideration of adaptive methods in clinical development. *J Biopharm Stat.*, 15, pp 575-91.
3. Elangovan, R. and Lokeshmaran, A. (2013). The LASSO method for variable selection in the Cox model using lung cancer and liver data. *Int. Jour. of Operations Research and Optimization*, 3(2), 321-331.
4. Elangovan, R. and Lokeshmaran, A. (2013). Variable selection for the accelerated failure time model as an alternative to the Cox proportional hazards model. *Int. Jour. of Operations Research and Optimization*, 3(2), 271-281.
5. Elangovan, R. and Lokeshmaran, A. (2014). Bayesian variable selection for Cox's regression model. *Asia Pacific Journal of Research*, 1(XIII), 11-23.
6. Geisser, S. (1993). Predictive Inference. New York: Chapman and Hall.
7. Gilks, W. R., and Wild, P. (1992). Adaptive rejection sampling for Gibbs sampling. *Appl. Statist.*, 41, 337-48.
8. Hung HM, Cui L, Wang SJ, Lawrence J. (2005). Adaptive statistical analysis following sample size modification based on interim review of effect size. *J Biopharm Stat.*, 15, pp 693-706.
9. Jennison C, Turnbull BW (2005). Meta-analysis and adaptive group sequential design in the clinical development process. *J Biopharm Stat.*, 15, pp 537-58.
10. Kalish, L. A. (1992). Phase III multiple myeloma: evaluation of combination chemotherapy in previously untreated patients. Technical Report # 726E, Department of Biostatistics, Dana-Farber Cancer Institute, Boston, MA.
11. Krall, J.M., Uthoff, V.A. and Harley, J.B. (1975). A Step-Up Procedure for Selecting Variables Associated with Survival, *Biometrics*, 31(1), 49-57.
12. Rubinstein, R. Y. (1981). Simulation and the Monte Carlo Method. John Wiley and Sons, New York.
13. Sampson AR, Sill MW (2005). Drop-the-loser design: Normal case. *Biom J.*, 47, pp 257-81.
14. Wang M, Wu YC, Tsai GF (2008). A regulatory view of adaptive trial design. *J Formos Med Assoc*, 107, pp 3-8.
15. Woodcock J, Woosley R. (2008). The FDA critical path initiative and its influence on new drug development. *Annu Rev Med*, 59, pp 1-12.
16. Woolson, R. F., (1981). Rank test and a one-sample log rank test for comparing observed survival data to a standard population. *Biometrics*, 37: 687-696.

17. Khan, T. H., S. Iqbal, M. Abram and A. S. Warriach, (2004). The relationship of age, sex and marital status with the prevalence of cancer in the patients visiting Nishtar Hospital, Multan, Pakistan.

## APPENDIX

### *Supporting Medical Necessity for Velcade Indications:*

**Velcade (bortezomib) is indicated for the treatment of patients with multiple myeloma and patients with mantle cell lymphoma.**

**Contraindications:** Velcade is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. Velcade is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of Velcade.

**Warnings and Precautions:** Velcade is for subcutaneous or IV administration only. Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

1. Peripheral neuropathy, including severe cases, may occur. Patients should be monitored for symptoms and managed with dose modification or discontinuation. Patients with preexisting symptoms may experience worsening peripheral neuropathy (including  $\geq$ Grade 3). Starting with Velcade subcutaneously may be considered for patients who either have preexisting or are at high risk for peripheral neuropathy.
2. Hypotension: Caution should be used when treating patients receiving antihypertensives, those with a history of syncope, and those who are dehydrated.
3. Cardiac toxicity, including acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction, has occurred. Isolated cases of QT-interval prolongation have been reported. Patients with risk factors for, or existing, heart disease should be closely monitored.
4. Pulmonary toxicity: Acute respiratory distress syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology have occurred (sometimes fatal). Pulmonary hypertension, in the absence of left heart failure or significant pulmonary disease, has been reported. In the event of new or worsening cardiopulmonary symptoms, consider interrupting VELCADE until a prompt and comprehensive diagnostic evaluation is conducted.
5. Posterior reversible encephalopathy syndrome has occurred. Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected.
6. Gastrointestinal toxicity, including nausea, diarrhea, constipation, and vomiting, has occurred and may require use of antiemetic and antidiarrheal medications or fluid replacement. Interrupt Velcade for severe symptoms.
7. Thrombocytopenia/Neutropenia: Manage with dose and/or schedule modifications. Complete blood counts should be monitored frequently during treatment. There have been reports of gastrointestinal and intracerebral hemorrhage. Support with transfusions and supportive care, according to published guidelines.

8. Tumor lysis syndrome: Closely monitor patients with high tumor burden and take appropriate precautions.
9. Hepatic toxicity: Monitor hepatic enzymes during treatment. Upon occurrence, interrupt therapy with VELCADE to assess reversibility.
10. Embryo-fetal risk: Women should avoid breast-feeding or becoming pregnant while on VELCADE.
11. Patients with diabetes may require close monitoring and adjustment of the antidiabetic medications.

**Drug Interactions:** Closely monitor patients receiving VELCADE in combination with strong CYP3A4 inhibitors. Avoid concomitant use of strong CYP3A4 inducers.

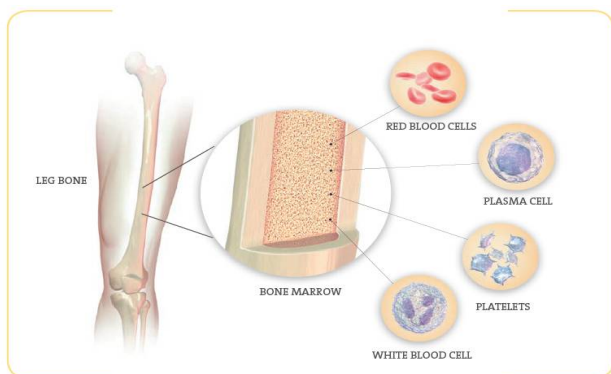
### **Adverse Reactions**

1. Previously untreated multiple myeloma (MM): In the phase 3 study of VELCADE administered intravenously with melphalan and prednisone (MP) vs MP alone, the most commonly reported adverse reactions (ARs) were thrombocytopenia (48% vs 42%), neutropenia (47% vs 42%), peripheral neuropathy (46% vs 1%), nausea (39% vs 21%), diarrhea (35% vs 6%), neuralgia (34% vs <1%), anemia (32% vs 46%), and leukopenia (32% vs 28%).
2. Relapsed MM subcutaneous vs IV: In the phase 3 study of VELCADE administered subcutaneously vs intravenously in relapsed MM, safety data were similar between the two treatment groups. The most commonly reported ARs in the subcutaneous vs IV treatment groups were peripheral neuropathy (37% vs 50%) and thrombocytopenia (30% vs 34%). The incidence of serious ARs was similar in the subcutaneous treatment group (20%) and the IV treatment group (19%). The most commonly reported serious ARs were pneumonia and pyrexia (each 2%) in the subcutaneous treatment group and pneumonia, diarrhea, and peripheral sensory neuropathy (each 3%) in the IV treatment group.
3. Previously untreated mantle cell lymphoma (MCL): In a phase 3 study of VELCADE administered intravenously with rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) vs vincristine, rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHOP), the most commonly reported ARs were neutropenia (87% vs 71%), thrombocytopenia (72% vs 17%), leukopenia (48% vs 36%), anemia (44% vs 29%), lymphopenia (28% vs 12%), peripheral neuropathy (30% vs 27%), diarrhea (25% vs 5%), nausea (23% vs 12%), and pyrexia (20% vs 10%).
4. Relapsed MM and MCL: In the integrated analysis of 1163 patients in phase 2 and 3 studies of VELCADE administered intravenously, the most commonly reported ARs were nausea (49%), diarrhea NOS (46%), fatigue (41%), peripheral neuropathy NEC (38%), and thrombocytopenia (32%). A total of 26% of patients experienced serious ARs. The most commonly reported serious ARs included diarrhea, vomiting, and pyrexia (each 3%); nausea, dehydration, and thrombocytopenia (each 2%); and pneumonia, dyspnea, peripheral neuropathies NEC, and herpes zoster (each 1%).

### **Multiple Myeloma. Getting the facts**

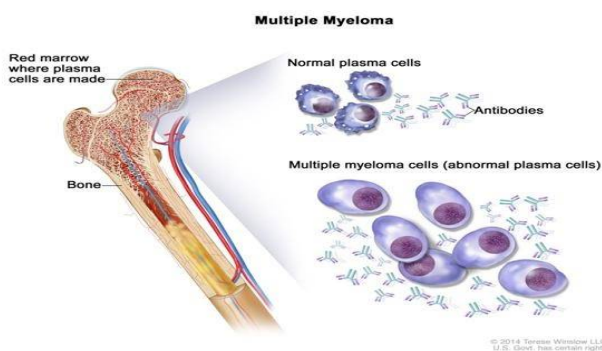
Multiple myeloma is a cancer of the blood. Some people with multiple myeloma have many symptoms, while others have

few, if any. Common signs and symptoms of multiple myeloma may include: bone pain and broken bones, nausea and vomiting, fatigue, frequent infections, nervous system problems, anemia, and hypercalcemia. These symptoms may be referred to as CRAB. C=Elevated Calcium; R=Renal (kidney) problems; A=Anemia; B=Bone lesions;



### Multiple myeloma

A cancer arising from plasma cells



Multiple myeloma affects the part of your bone called bone marrow. Your blood is produced in your bone marrow, which is made up of many different types of cells, including red blood cells, white blood cells, platelets, and plasma cells. A plasma cell is a type of white blood cell that normally produces antibodies to fight infections. If you have multiple myeloma, you have abnormal plasma cells, also called myeloma cells. These myeloma cells push out normal cells. They form tumors in bones and, sometimes, in various soft tissues of the body. Myeloma cells can collect over time and build up in the bone marrow. When they do, they prevent bone marrow from making enough blood cells for the body to fight infection and other diseases.

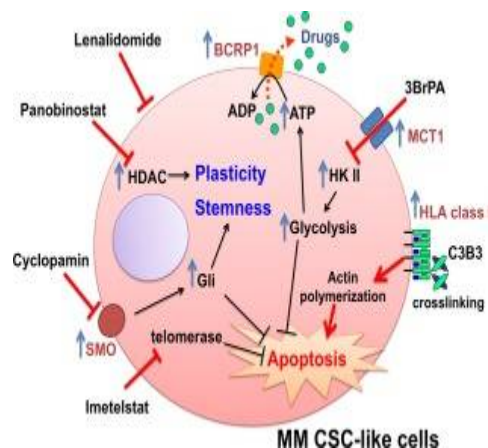
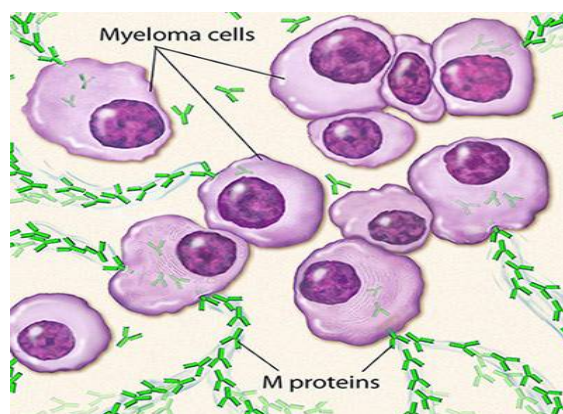


Figure targeting multiple myeloma cancer stem cell (MM CSC)-like cells. Targeting MM CSC-like cells or side population cells is clinically relevant to improve therapeutic efficacy. Different approaches have been preclinically investigated to target molecular, metabolic and epigenetic signatures, and the self-renewal signaling pathways characteristic of MM CSC-like cells. Abbreviations: ATP, adenosine triphosphate; ADP, adenosine diphosphate; C3B3: anti-HLA class I Fv diobody; 3BrPA, 3-bromopyruvate; BCRP1: breast cancer resistance protein 1; HDAC, histone deacetylase; HKII, hexokinase II; MCT1, monocarboxylate transporter1; SMO: smoothened.



Dr. R. Elangovan, is working as Professor, Department of Statistics, Annamalai University, Annamalai nagar, Tamilnadu. He is having more than 27 years of P.G. teaching experience. He obtained his B.Sc., M.Sc., Degrees in Statistics from Annamalai University in 1982-1984, and M.Phil., Ph.D., degree from the same institution in 1988 and 2000. He obtained the B.Ed., and M.Ed., degrees also in Education from Annamalai University in 1987 and 1994.

He obtained the M.B.A. (H.R.M.) from the same institution during 2013. He has an excellent academic record of guiding 43 students for M.Phil. Degrees also and he has published 86 research papers in leading National and International journals, currently guiding 6 students for the Ph.D. programme in statistics. Twelve Students are already awarded Ph.D. degrees under his guidance. He has attended nearly 55 International



and 25 National level seminars and presenting papers. He is the editor of various reputed journals in India. He has written 3 books and written 5 lessons and reports for the Directorate of Distance Education of Annamalai University. He visited France, Hang Hong, Paris and USA(three times) and delivered invited talk and also chaired the technical session in the conference. Prof. Elangovan visited United Arab Emirates, which includes Dubai, Abu Dhabi, Sharjah, Al Ain, Ajman, Ras al-Khaimah and Ummal- Quwain. He worked as a Statistician in Aravind Eye Hospital, Madurai from (1987-1988), as Assistant Technical Officer in Christian Medical College, Vellore (1988-1989) before joining Annamalai University (1990) as Lecturer. He has gained the reputation of being an excellent teacher.



B. Jayakumar, currently pursuing Ph.D., Degree as a full time Research Scholar in the Department of Statistics, Annamalai University. He obtained his M.Sc., Integrated Degrees in Statistics from Annamalai University in 2004-2009 and M.Phil., degree from the same institution in 2012. He has attended nearly 3 International and 7 National seminars and presenting papers. He worked as Assistant Professor in the Thiruvalluvar Arts and Science College, Kurinjipadi during the period 2012-2014. He has gained the knowledge of being a good researcher

**How to cite this article:**

Elangovan R and Jayakumar B.2017, Multiple Comparison Procedure for Cure Rate Models. *Int J Recent Sci Res.* 8(8), pp. 18924-18932. DOI: <http://dx.doi.org/10.24327/ijrsr.2017.0808.0594>

\*\*\*\*\*