

# Declining multiple myeloma mortality rates in the United States following the introduction of novel therapies

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## Disclosures

- Employment or leadership position: none
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- Testimony: none
- Other remuneration: none

## Background

- **1969** – Alexanian<sup>1</sup> reported the first chemotherapy regimen to improve survival in patients with multiple myeloma ( **6 month OS improvement** )
- **1980-90s**- introduction of autologous stem cell transplantation was 2nd major milestone in improved survival<sup>2,3</sup> ( **1 - 1.5 years gained in OS** )
- **2000** - arrival of novel agents (thalidomide, bortezomib and lenalidomide) ushered in further improvements in OS<sup>4</sup> ( **50% improvement in OS (44.8 vs 29.9 months; P < .001)** )

1. Alexanian et al. JAMA 1969;208:1680-85.
2. McElwain TJ,et al. Lancet. 1983;2:822-824
3. Attal,M. N Engl J Med. 1996;335:91-97
4. Kumar et al. Blood. 2008;111: 2516-2520.

## Background

- **1969** - Alexanian reported the first chemotherapy regimen to improve survival in patients with multiple myeloma
- **1980s**- the introduction of autologous stem cell transplantation was 2nd major milestone in improved survival
- **2000** - arrival of novel agents (thalidomide, bortezomib and lenalidomide) ushered in further improvements in OS

**PATIENTS  
< 65**

## Major milestones in therapeutic options for myeloma

	Milestone	Notes
1962	Melphalan-Prednisone	Introduction melphalan in 1960s was associated with improved survival
1996	Autologous SCT	Several randomized trials demonstrated survival advantage for SCT compared to conventional chemotherapy
1999	Thalidomide	Improved response and PFS compared to dexamethasone. When added to MP, it improves OS compared to MP alone
2003	Bortezomib	improved survival compared to high-dose dexamethasone in relapsed MM
2003	Tandem auto-transplant	Tandem SCT improved OS compared with single transplantation (in pts failing to achieve a VGPR to first SCT)
2005	Lenalidomide	Lenalidomide and dexamethasone improve OS compared with dexamethasone in relapsed myeloma

## Background

- Data on improvements in survival for MM based on results of randomized studies
- OS benefit for patients  $\leq 65$  convincing<sup>1-4</sup>
- OS benefit for elderly patients is uncertain
- Average age of newly diagnosed patients with myeloma is 70

1. Brenner et al . Blood. 2008;111:2521-2526
2. Turesson et al J Clin Oncol . 2009 28:830-834
3. Kastiris 2009 Leukemia 23, 1152–1157.
4. Kumar et al. Blood. 2008:111: 2516-2520

## Background

- Use caution when comparing randomized trial results
- Spectrum of patients may not represent general population
- Older patients and those with poor performance status often excluded
- Patients treated in referral centers and those included in clinical trials often represent a selected patient population
- Many trials comprise only a minority of all patients in the recruitment area limiting the generalizability

## Background

- Success reported in clinical research trials may not translate to impact on the MM general population
- There are a handful of results that indicate the introduction of novel agents is increasing the OS of MM patients treated outside the context of clinical trials
- We studied a national database of unselected patients to analyze the impact of the novel agents on mortality and survival rates for MM patients of all ages

Mention other presentations that looked at survival at this meeting

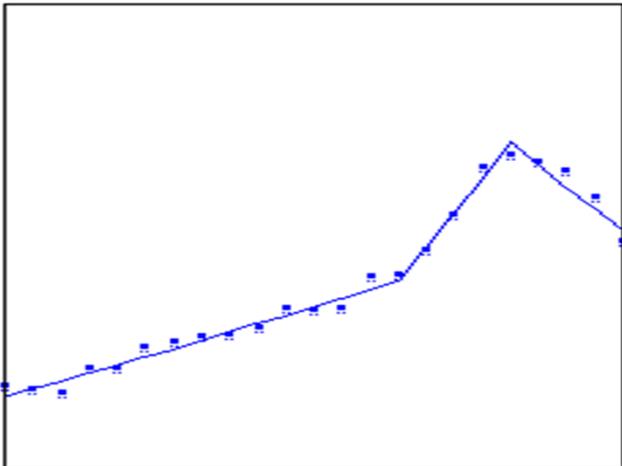
## Methods

- Death records from the US National Center for Health Statistics (CDC) were used to characterize time trends in MM mortality rates in the United States during the period 1969-2007
- Represents all mortality data for all 50 states
- Temporal trends in MM mortality rates were characterized with joinpoint regression techniques

## Methods

- Search criteria: 1) deaths due to myeloma; 2) Deaths occurring during calendar years 1969-2008 (inclusive); 3) deaths occurring among residents of the US
- Based on death certificate data
- Mortality and survival analysis was performed separately for two age cohorts (< 65 years of age and  $\geq 65$ ) based on the age limit used for application of HDT-SCT

## Joinpoint Regression Program

- Statistical software (e.g., SAS) is used to fit the model
  - Cancer incidence rates are calculated using the SEER\* software for vital statistics
  - Joinpoint regression analysis is used to identify and estimate the number and location of "knots" or "knots" in the data series
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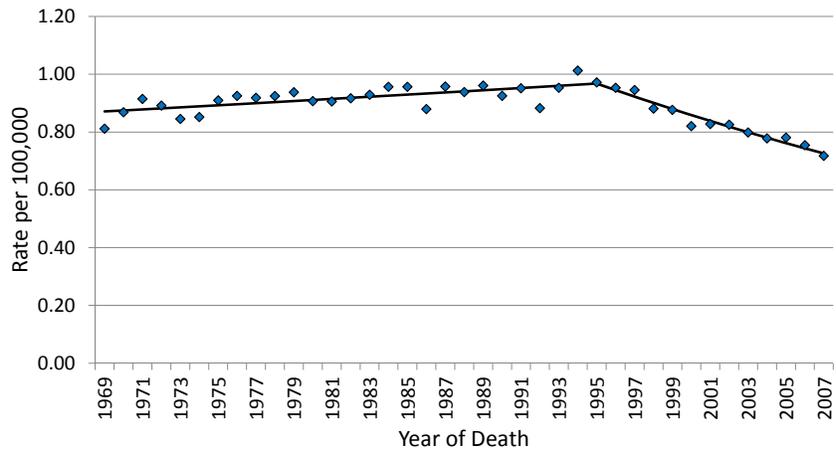
## RESULTS 1969-2007

NUMBER OF MYELOMA DEATHS STUDIED	
AGE < 65	64,161
AGE ≥ 65	198,175
TOTAL	262,336

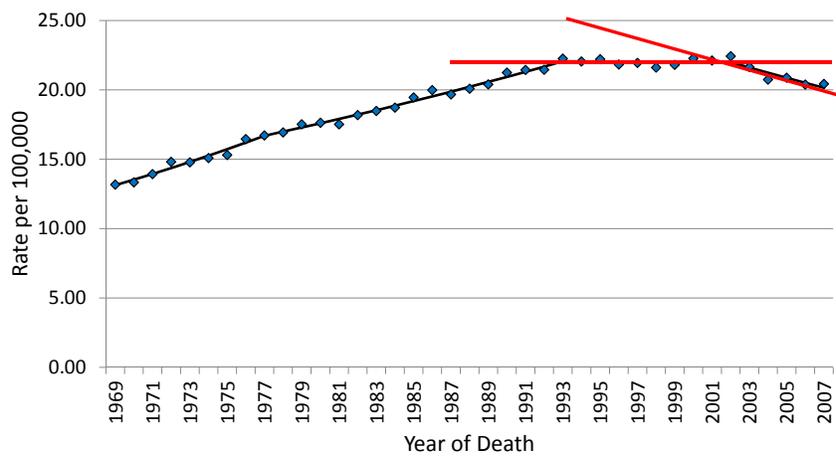
### Results

- In the US population under 65 years of age, MM mortality increased from 1969-1995 (Annual Percent Change (APC) = +0.5% ;  $p < 0.01$ ) and decreased rapidly thereafter (APC= -2.35 %;  $p < 0.01$ )
- Among those 65 years of age and older, increasing MM mortality rates from 1969-93 were followed by a plateau during the period 1993-2002
- Rates among the elderly declined after 2002 (APC = -1.77%;  $p < 0.01$ )

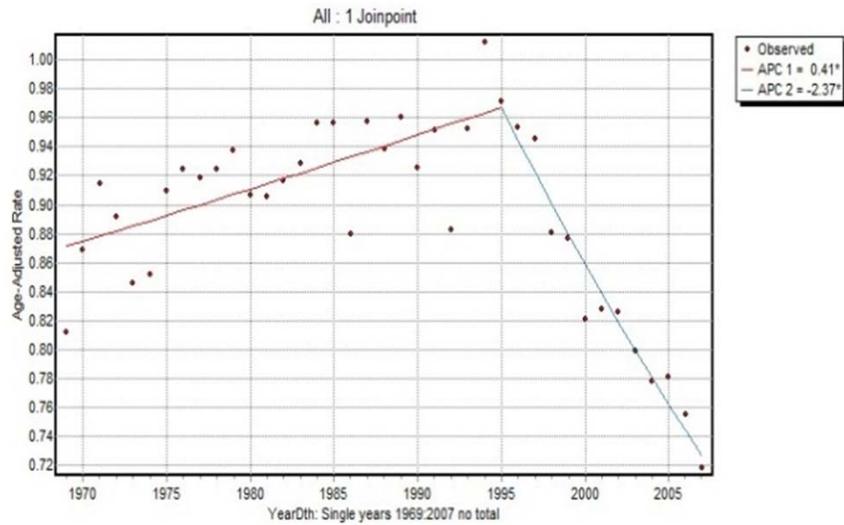
**Myeloma Mortality: <65 Years of Age**  
 Age-specific mortality rates per 100,000  
 1969-2007



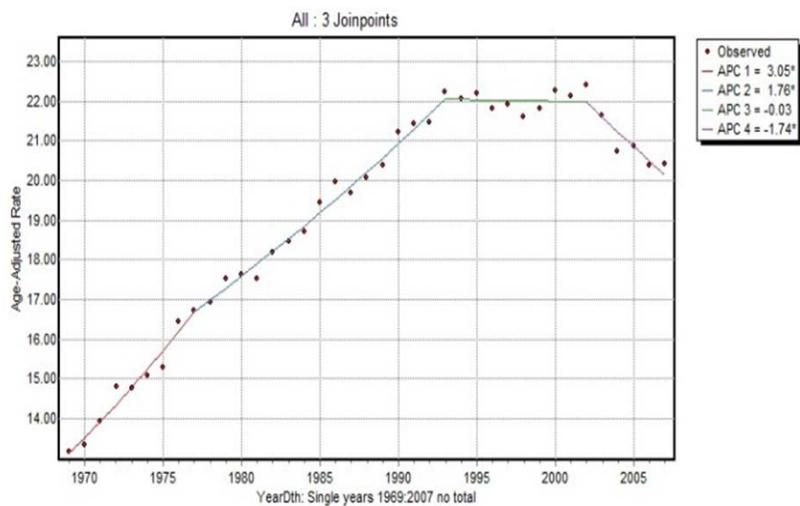
**Myeloma Mortality: ≥ 65 years of age**  
 Age-specific mortality rates per 100,000  
 1969-2007

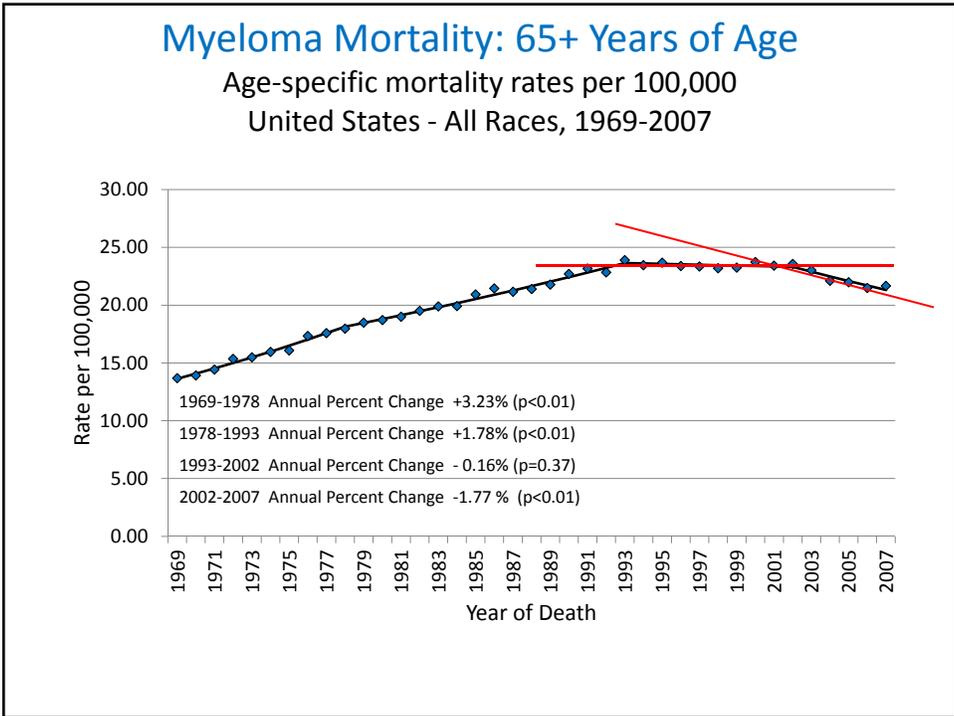
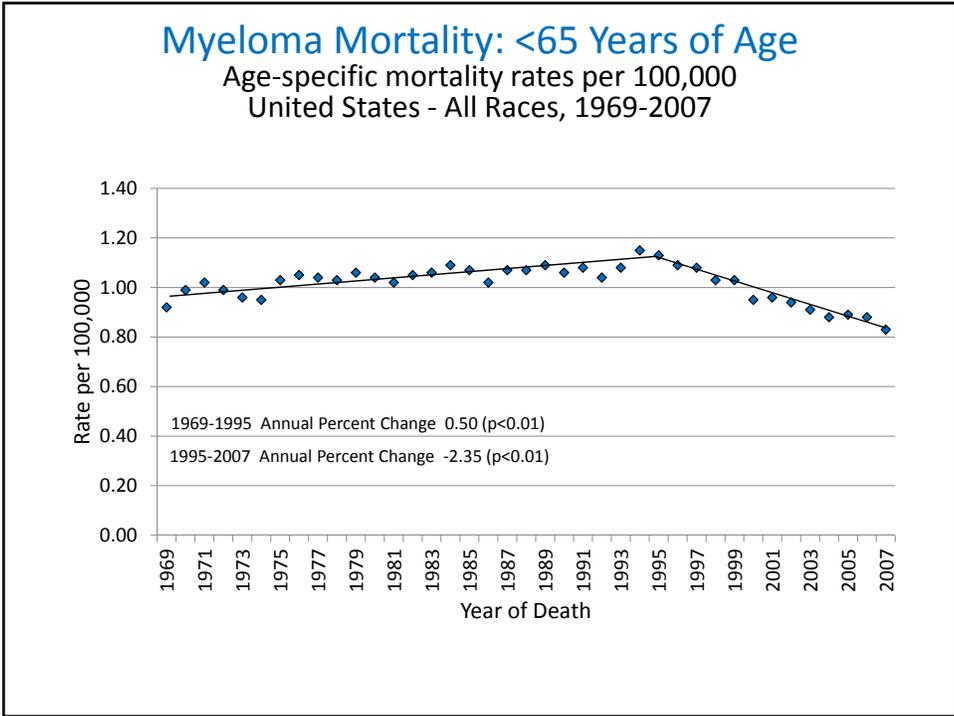


## Joinpoint Analysis <65 years of age



## Joinpoint Analysis ≥ 65 years of age





- Queried SEER for survival rates of MM patients 1980-2007
- SEER collects and publishes cancer incidence and survival data from population-based cancer registries covering  $\approx 28\%$  of US population
- Data included in SEER database are from population-based cancer registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound, and San Francisco-Oakland that together cover a population of  $> 30$  million people

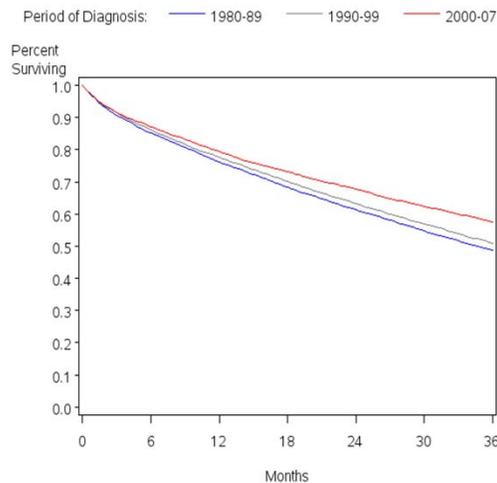
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### Myeloma Survival: All Ages SEER Program, 1980-2007

**SUBJECTS:**  
Newly diagnosed (incident) cases of Myeloma diagnosed in 9 core areas of the SEER Program during the time period 1980-2007

**NUMBER OF SUBJECTS:**  
Diagnosed 1980-89: 7901  
(48.82 % alive after 3 years)  
Diagnosed 1990-99: 9353  
(50.56 % alive after 3 years)  
Diagnosed 2000-2007: 8300  
(57.64% alive after 3 years)

**Total subjects = 25,554**  
**P-Value: <0.0001**



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## Myeloma Survival: < 66 Years of Age at Diagnosis SEER Program, 1980-2007

**SUBJECTS:**

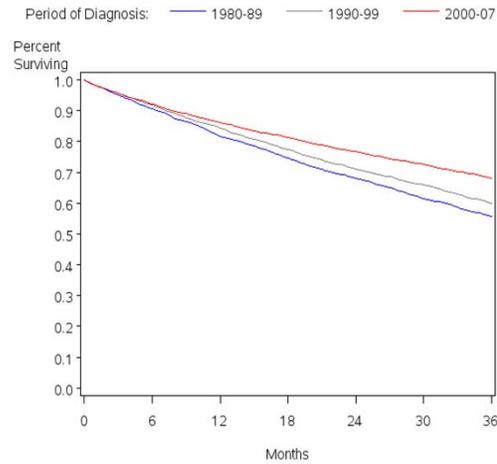
Newly diagnosed (incident) cases of Myeloma diagnosed in 9 core areas of the SEER Program during the time period 1980-2007

**NUMBER OF SUBJECTS:**

Diagnosed 1980-89: 3124  
(55.66% alive after 3 years)  
Diagnosed 1990-99: 3550  
(59.97% alive after 3 years)  
Diagnosed 2000-2007: 3623  
(68.15% alive after 3 years)

**P-Value: <0.0001**

**Total = 10,297 patients**



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## Myeloma Survival: 66+ Years of Age at Diagnosis SEER Program, 1980-2007

**SUBJECTS:**

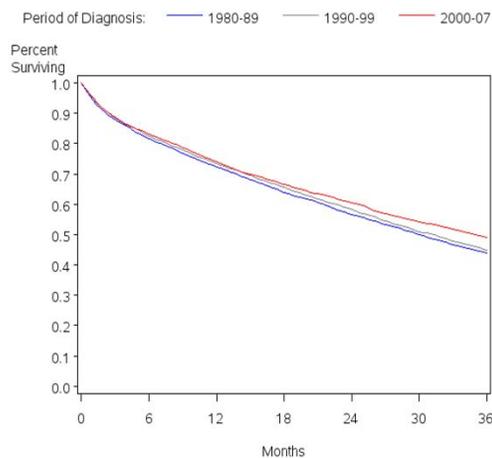
Newly diagnosed (incident) cases of Myeloma diagnosed in 9 core areas of the SEER Program during the time period 1980-2007

**NUMBER OF SUBJECTS:**

Diagnosed 1980-89: 4777  
(44.01% alive after 3 years)  
Diagnosed 1990-99: 5803  
(44.89 % alive after 3 years)  
Diagnosed 2000-2007: 4677  
(49.03 % alive after 3 years)

**P-Value: 0.005**

**Total # patients = 15,257**



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## Strengths /Weaknesses

- Analysis of long time period
- Large sample size (s)
- Unselected patients
- Death certificate data
- Variables such as supportive care could have contributed to improved survival
- Changes in survival can be influenced by changes in diagnostic practice and access to health care, causing earlier detection of the disease
- Lack of treatment information

## Conclusion(s)

- Results confirm earlier reports showing improvement in the outcome of younger myeloma patients
- Declining MM mortality rates in young patients were observed during a time period after bone marrow transplantation became the preferred therapy for patients in this age group
- Similarly, declining MM mortality rates for elderly patients were observed shortly after thalidomide was licensed by the FDA for treatment of this disease in 2001
- **Conclusion: the novel agents are contributing to improved survival for myeloma patients of all ages**

