Demographic Differences Between Unselected Patients and Participants of Multiple Myeloma Clinical Trials in the US: A Threat to External Validity

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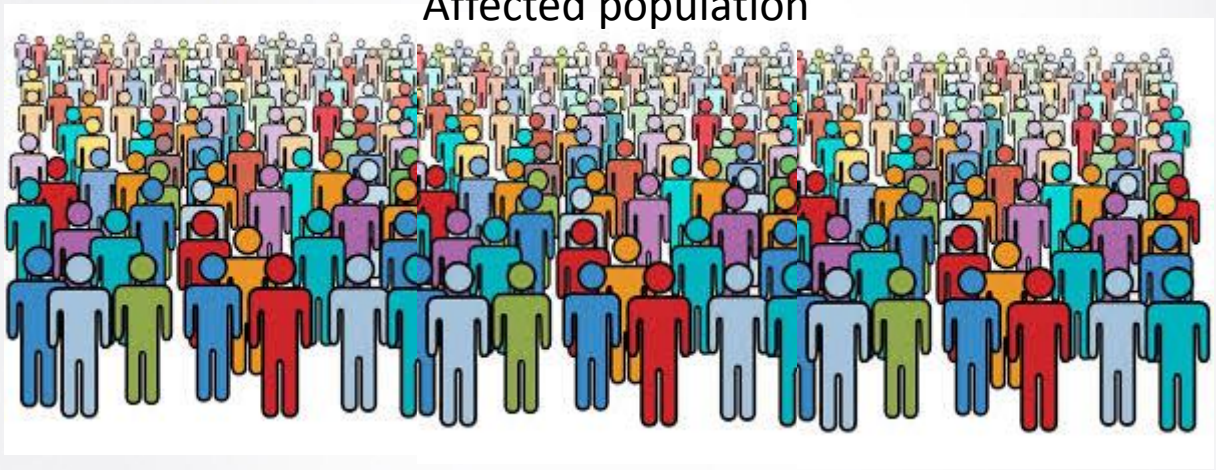
Background

- Multiple myeloma affects predominantly older individuals.
- Treatment tolerance and prognosis affected by age.
- Incidence of MM in blacks is nearly twice the incidence in white Americans.
- Disease biology and possible interaction with therapy are different between blacks and whites.
- Improvements in outcomes seen primarily among young individuals and more pronounced in whites.

Pulte et al. Leuk Lymphoma 55:1083, 2014
Baker et al. Blood 121:3147, 2013

Clinical trial results are primary source of information to guide patient management

Affected population



Clinical Trial Subjects

External validity = Findings are applicable to affected population

Internal validity = Study conducted without bias

Rothwell . Lancet 365:82, 2005

Objective

To compare composition of MM trials in US with MM population at large

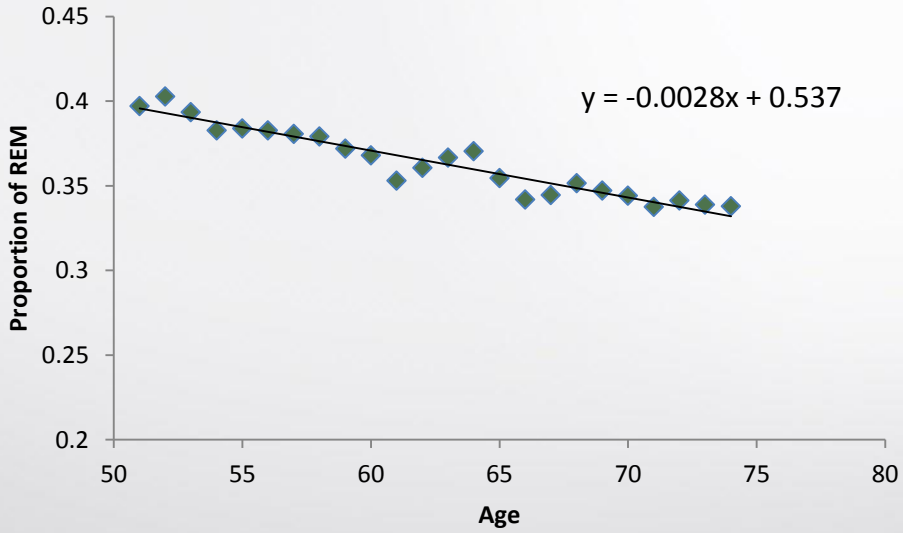
- Age
- Disease stage
- Gender
- Race/ethnicity

Methods

- PubMed search of MM trials performed in US
  - Keyword “myeloma” and “clinical trial” followed by manual screening
  - Trials published 2007-2014
  - MM-directed intervention
  - Trials performed entirely in US
- Reference population from SEER-18.

- Information extracted from each trial
  - Median age
  - Gender composition
  - Proportion of racial/ethnic minorities (Hispanic and/or non-white)
  - Study phase (I/II vs. III)
  - Sponsor (investigator vs. NCI vs. Industry)
  - Population (untreated vs. R/R vs. other)
  - International Staging System (ISS) for trials of untreated patients

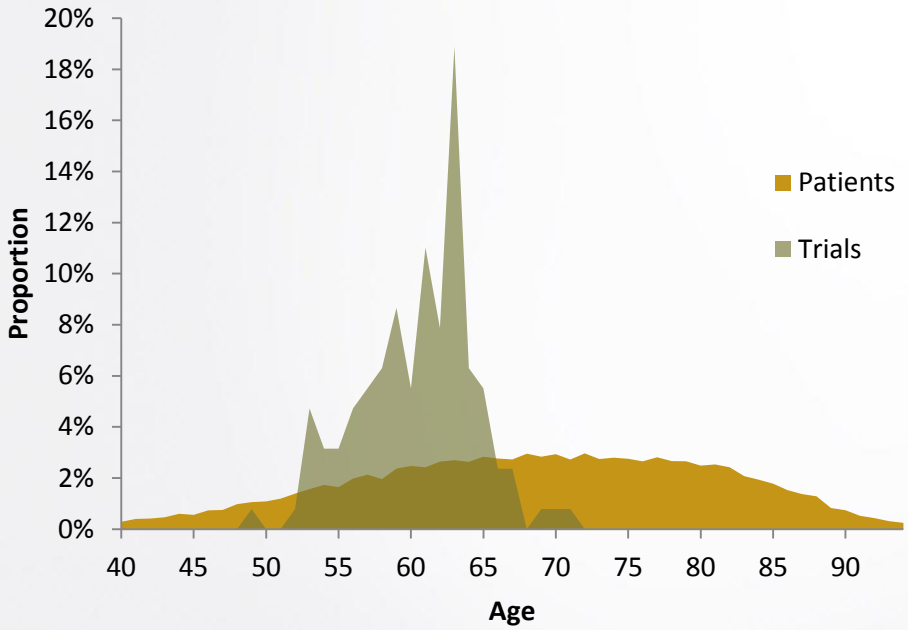
- Information extracted from SEER-18
  - Age composition of unselected population
  - Expected gender composition
  - Expected proportion of minorities according to median age



Results

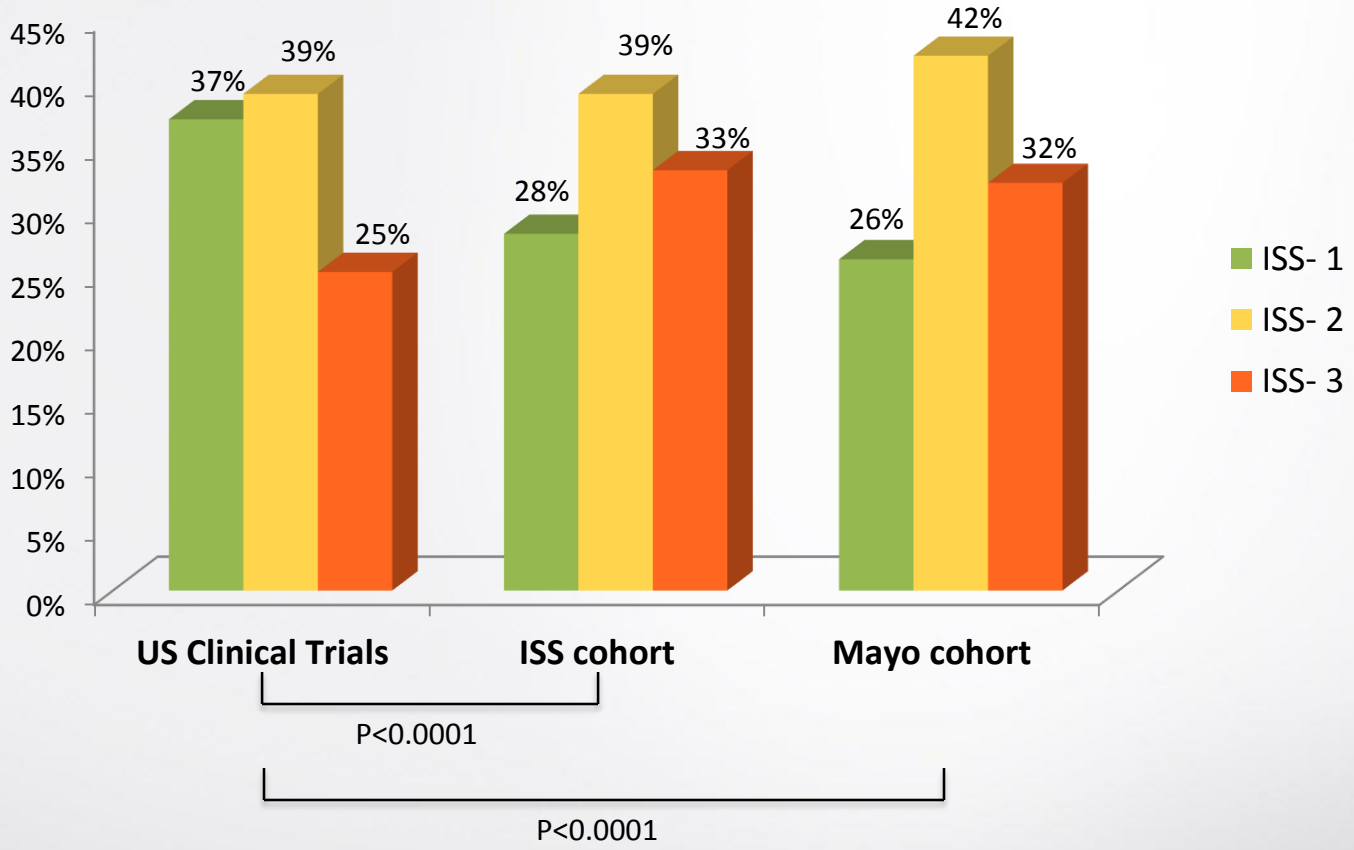
- 128 clinical trials (8,869 subjects)
  - •26% untreated, 54% R/R, 20 % other
  - •94% Phases I/II, 6% phase III
  - •54% Investigator, 13% NCI, 33% Industry-sponsored
- Age of subjects was reported in 127 (99.2%) trials.
- Gender composition reported in 120 (93.8%) trials.
- Racial-ethnic composition reported in only 51 (39.8%) trials (4,853 subjects).

- Median of median age of subjects 61 years vs. 69 years in unselected patients.



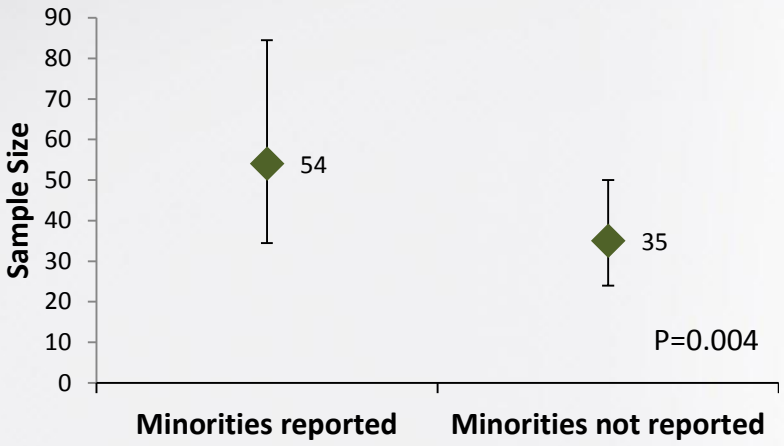
- 58.4% subjects were men vs. expected 56.9% (O:E ratio 1.03, 95% C.I. 0.99-1.05)

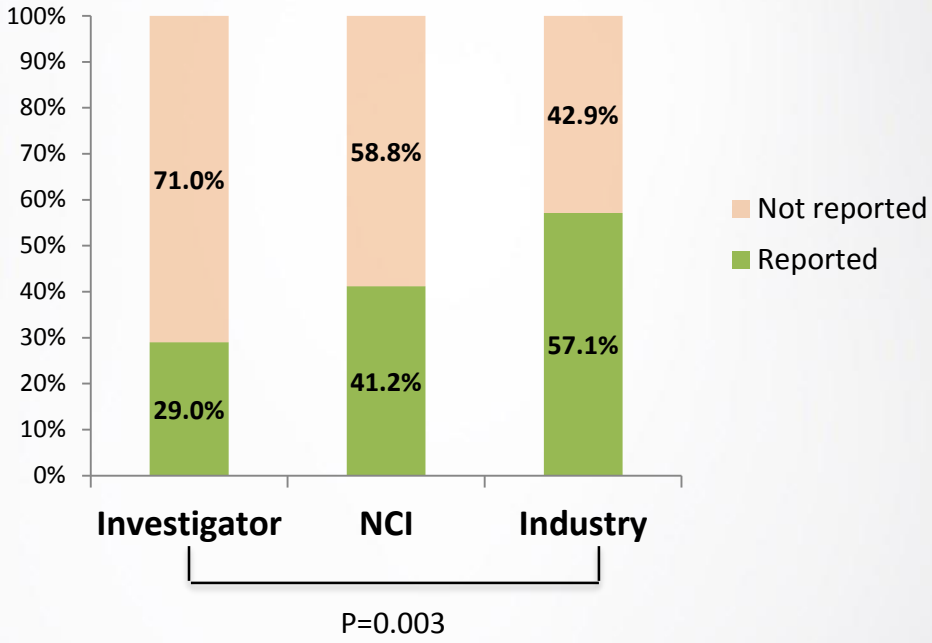
- Stage distribution – preferential accrual of lower risk patients



Greipp et al. J Clin Oncol 23:3412, 2005
Kumar et al. Leukemia 28:1122, 2014

- Minority participation – reported in 39.8% of trials only

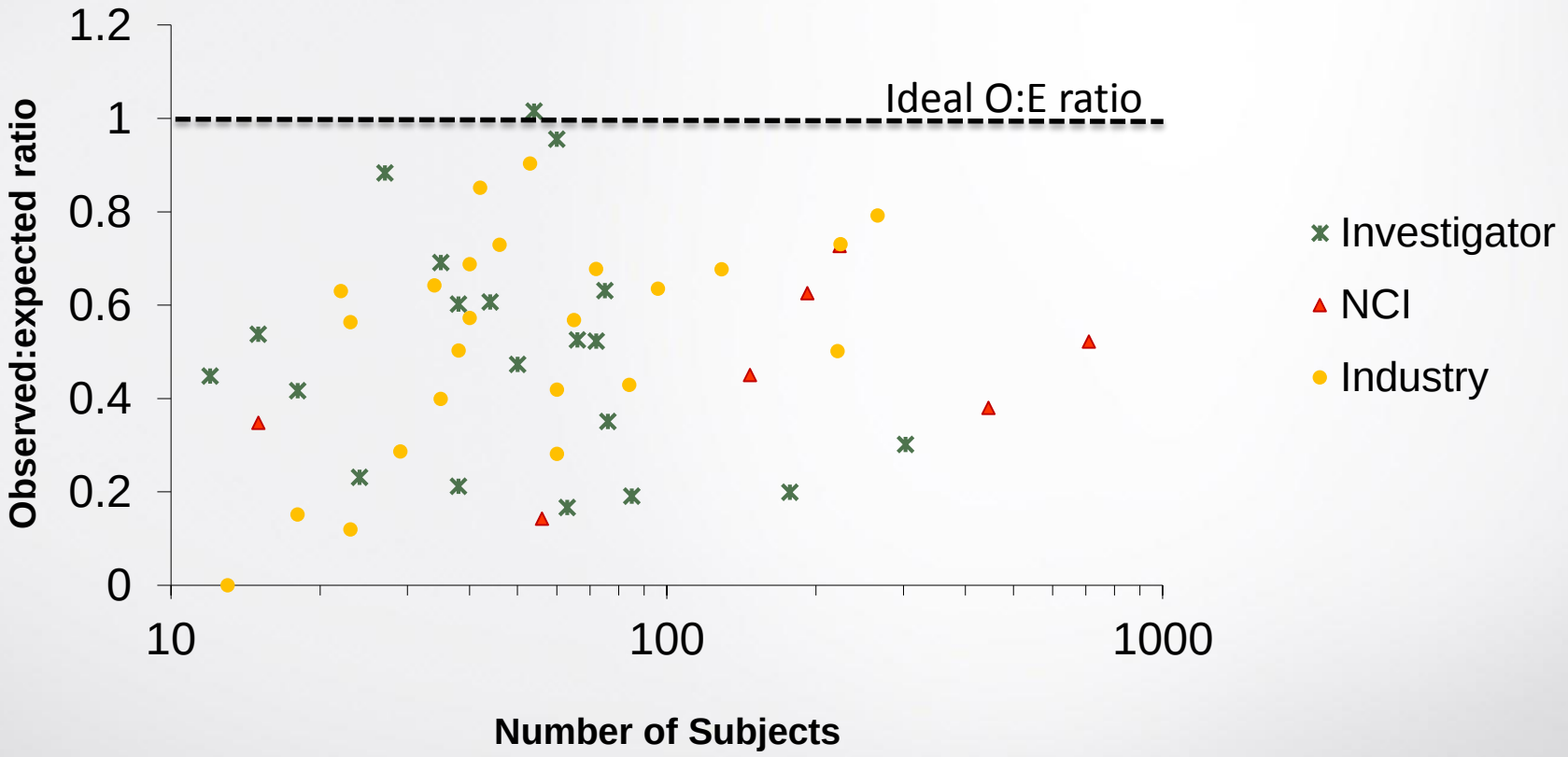




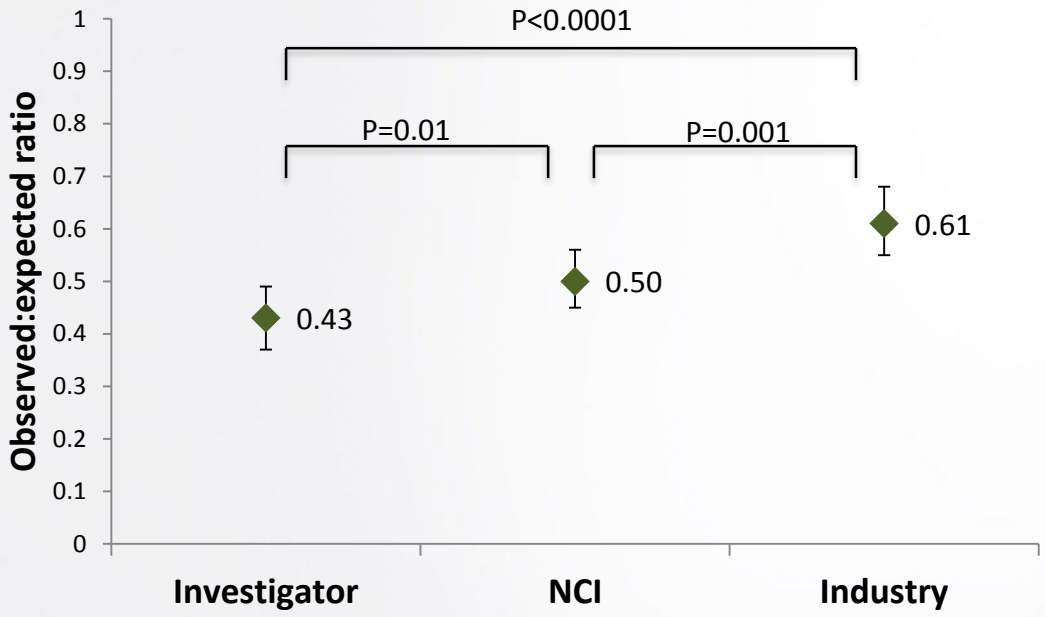
Trials reporting were larger than trials not reporting minority accrual

Accrual of minorities more often reported in industry-sponsored than investigator-sponsored trials

- Minority participation – per sponsor



- Minority participation- per sponsor



	Investigator	NCI	Industry
N trials	20	7	24
N subjects	1332	1788	1733
Observed N Minorities	212 (15.9%)	334 (18.7%)	382 (22.0%)
Expected N Minorities	496 (37.2%)	663 (37.1%)	624 (36.0%)

Conclusions

- Accrual of minorities is not reported for the majority of MM trials in US
  - Industry > NCI > Investigator-sponsored trials
- Accrual of subjects to US MM is highly biased towards preferential accrual of:
  - Younger patients
  - Patients with lower-risk MM
  - Non-Hispanic whites
- Minority accrual Industry > NCI > Investigator-sponsored trials
- No evidence of gender bias

Conclusions – Possible interventions

- Consistent reporting of minority accrual
  - Ethnicity/race as variable for stratification and/or subset analysis
- Engagement of clinical trial navigators
- Development of age-specific, comorbidity-specific clinical trials
  - Age ≥ 70
  - Renal dysfunction
- Use of less restrictive eligibility criteria