Trends and Factors Affecting the Initiation of Denosumab and Zoledronic Acid among Patients with Metastatic Lung, Breast, and Prostate Cancer in the United States

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Background: Patients with Metastatic lung, breast, and prostate cancer (MLBPC) experience skeletal related events (SREs), which significantly decrease survival. Denosumab (DS) and Zoledronic acid (ZA) are recommended for these patients to prevent such SREs. However, there is a lack of evidence in the patterns and predictors of real-world initiation of DS versus ZA in older MLBPC patients in the United States.
Objective: To examine the trends and factors associated with DS or ZA initiation among older MLBPC patients in the US.

Methods

Data Source: SEER-Medicare linked database

Inclusion

- Patients with primary cancers of lung, breast, or prostate during 2012-2017 were identified using International Classification of Diseases for Oncology (ICD-O-3 site: C50.0-50.9 for breast, C61.9 for prostate, and C33.9, C34.0-34.3, C34.8, C34.9 for lung cancer) codes.
- Those with stage IV disease according to the American Joint Committee on Cancer (AJCC) staging Manual
- Patients who had at least one Medicare Part B claim based on Healthcare Common Procedure Coding System (HCPCS) J codes for BMAs of interest: DS (J0897) or ZA (J3487) within 12 months after their first observed MLBPC diagnosis (between January 2012-December 2018).

Exclusion

- <66 years old at cancer diagnosis;
- cancer diagnosis date missing;
- cancer diagnosis was from autopsy/death;
- enrollment in Health Maintenance Organizations (HMOs),
- non-continuous Medicare Parts A and B coverage during the washout period

Statistical Analysis

- **Cochran-Armitage Trend Test**

Denominator for each index year= number of patients with first observed MLBPC diagnosis within that calendar year (ni)
Numerator for each index year= among those in the denominator, the number of patients who initiated either DS/ZA within 12 months of their first observed MLBPC diagnosis (n1i)
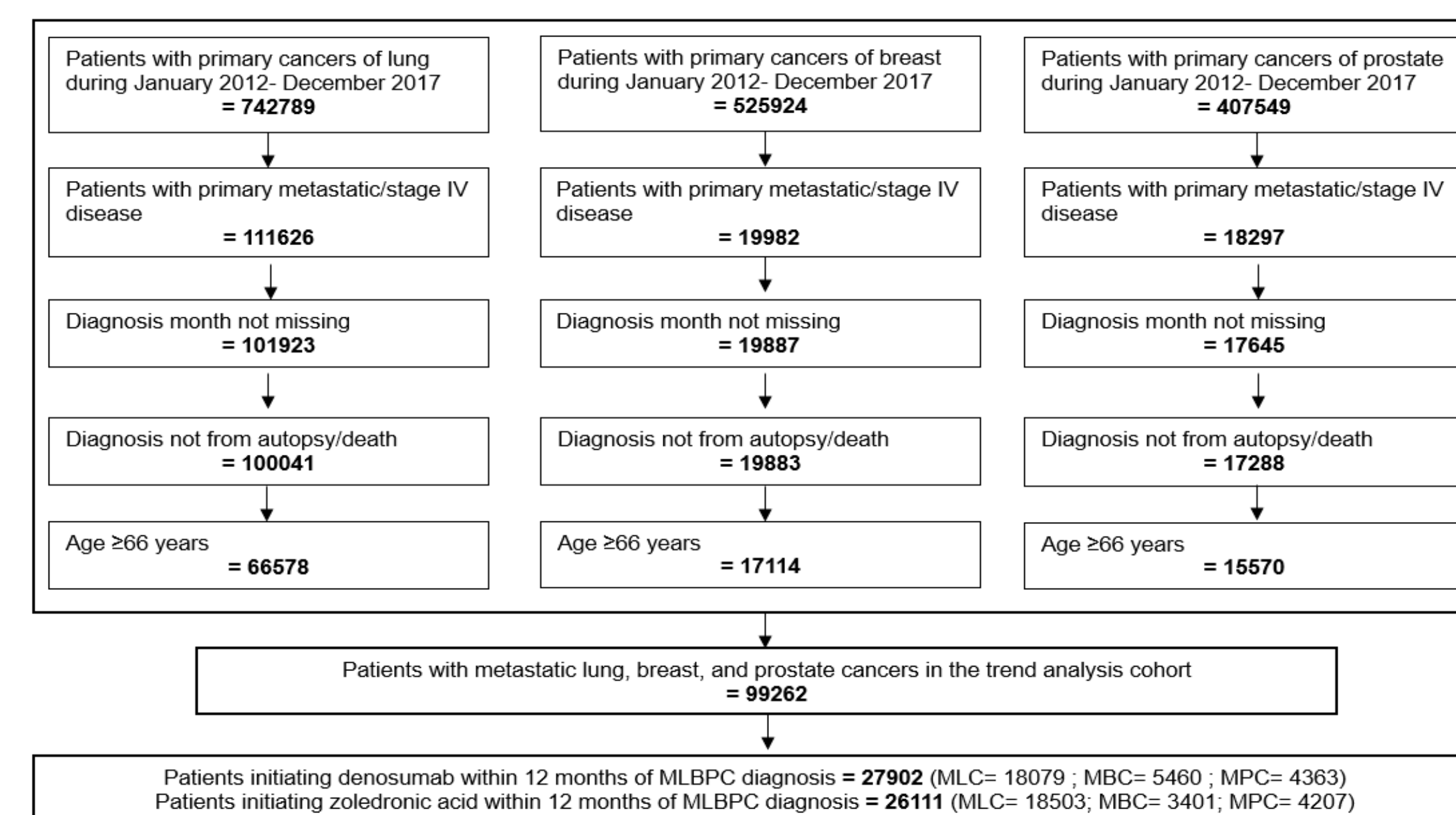
	Index Year					
	2012	2013	2014	2015	2016	2017
Denominator (MLBPC, n_i)	n_1	n_2	n_3	n_4	n_5	n_6
Numerator (DS/ZA yes, n_{ii})	n_{11}	n_{21}	n_{31}	n_{41}	n_{51}	n_{61}
Binomial proportion (p_i)	(n_{11}/n_1)	$(n_{21}/n2)$	(n_{31}/n_3)	(n_{41}/n_4)	(n_{51}/n_5)	(n_{61}/n_6)

- **Bivariate analyses** (Two sample T-tests, Chi-squared tests, Fisher's exact tests)
- **Multiple logistic regression models** were fitted to explore predictors affecting the initiation of DS versus ZA (event=1 when DS is initiated and event=0 when ZA is initiated) across different patient cohorts

Variables of Interest

Category	Variables
Demographic and socio-economic characteristics	Age
	Sex
	Race/ethnicity
	Marital status
	Residence in metropolitan/urban/rural area
	SEER region (Northeast, Midwest, South, and West)
	Medicare low-income subsidy
Comorbidities	Charlson comorbidity index
	History of osteoporosis
	Hypercalcemia
	Impaired renal function
Healthcare utilization	Physician office visits
	Emergency department (ED) visits
	Hospitalizations
Disease characteristics	Primary Site
	Histology
	Derived AJCC Stage Group, 6th edition
Treatment characteristics	Receipt of DS and/ZA; Receipt of other IV chemotherapy
	Receipt of aromatase inhibitor
	Receipt of androgen deprivation therapy
	Receipt of radiation

Flow Diagram of Patient Inclusion & Exclusion

Patients with primary cancers of lung during January 2012- December 2017 = 742789
Patients with primary cancers of breast during January 2012- December 2017 = 525924
Patients with primary cancers of prostate during January 2012- December 2017 = 407549

Patients with primary metastatic/stage IV disease = 111626
Patients with primary metastatic/stage IV disease = 19982
Patients with primary metastatic/stage IV disease = 18297

Diagnosis month not missing = 101923
Diagnosis month not missing = 19887
Diagnosis month not missing = 17645

Diagnosis not from autopsy/death = 100041
Diagnosis not from autopsy/death = 19883
Diagnosis not from autopsy/death = 17288

Age ≥66 years = 66578
Age ≥66 years = 17114
Age ≥66 years = 15570

Patients with metastatic lung, breast, and prostate cancers in the trend analysis cohort = 99262

Patients initiating denosumab within 12 months of MLBPC diagnosis = 27902 (MLC= 18079 ; MBC= 5460 ; MPC= 4363)
Patients initiating zoledronic acid within 12 months of MLBPC diagnosis = 26111 (MLC= 18503; MBC= 3401; MPC= 4207)

Trend Analysis

MLC

	Index Year						P-Value*
	2012	2013	2014	2015	2016	2017	
DS (Yes %)	22.90	23.75	25.87	27.46	32.80	32.53	<0.0001
ZA (Yes %)	28.07	29.81	28.76	28.15	28.58	28.06	0.007

MBC

	Index Year						P-Value
	2012	2013	2014	2015	2016	2017	
DS (Yes %)	29.08	26.42	31.91	34.14	36.10	36.42	<0.0001
ZA (Yes %)	31.33	25.07	21.28	20.74	17.62	17.39	<0.0001

MPC

	Index Year						P-Value
	2012	2013	2014	2015	2016	2017	
DS (Yes %)	24.89	25.55	27.46	27.90	30.95	31.75	<0.0001
ZA (Yes %)	27.22	28.30	28.13	27.36	27.45	25.36	0.06

MLBPC

	Index Year						P-Value
	2012	2013	2014	2015	2016	2017	
DS (Yes %)	24.29	24.51	27.15	28.69	33.09	33.06	<0.0001
ZA (Yes %)	29.31	28.73	27.38	26.73	26.51	24.88	<0.0001

Figures 1-3 : Trend Analysis of Initiation of Denosumab or Zoledronic Acid within 12 months of MLBPC Diagnosis

Figures 4-6: Trend Analysis of Initiation of Denosumab or Zoledronic Acid within 6 months of MLBPC Diagnosis

Factors Affecting Initiation

Figure 7-9: Factors affecting initiation of Denosumab vs Zoledronic acid in MLC, MBC, and MPC cohorts
[Independent variable in the logistic regression is DS=1; LIS= Low-income subsidy; PO= Physician office; CCI= Charlson comorbidity index]
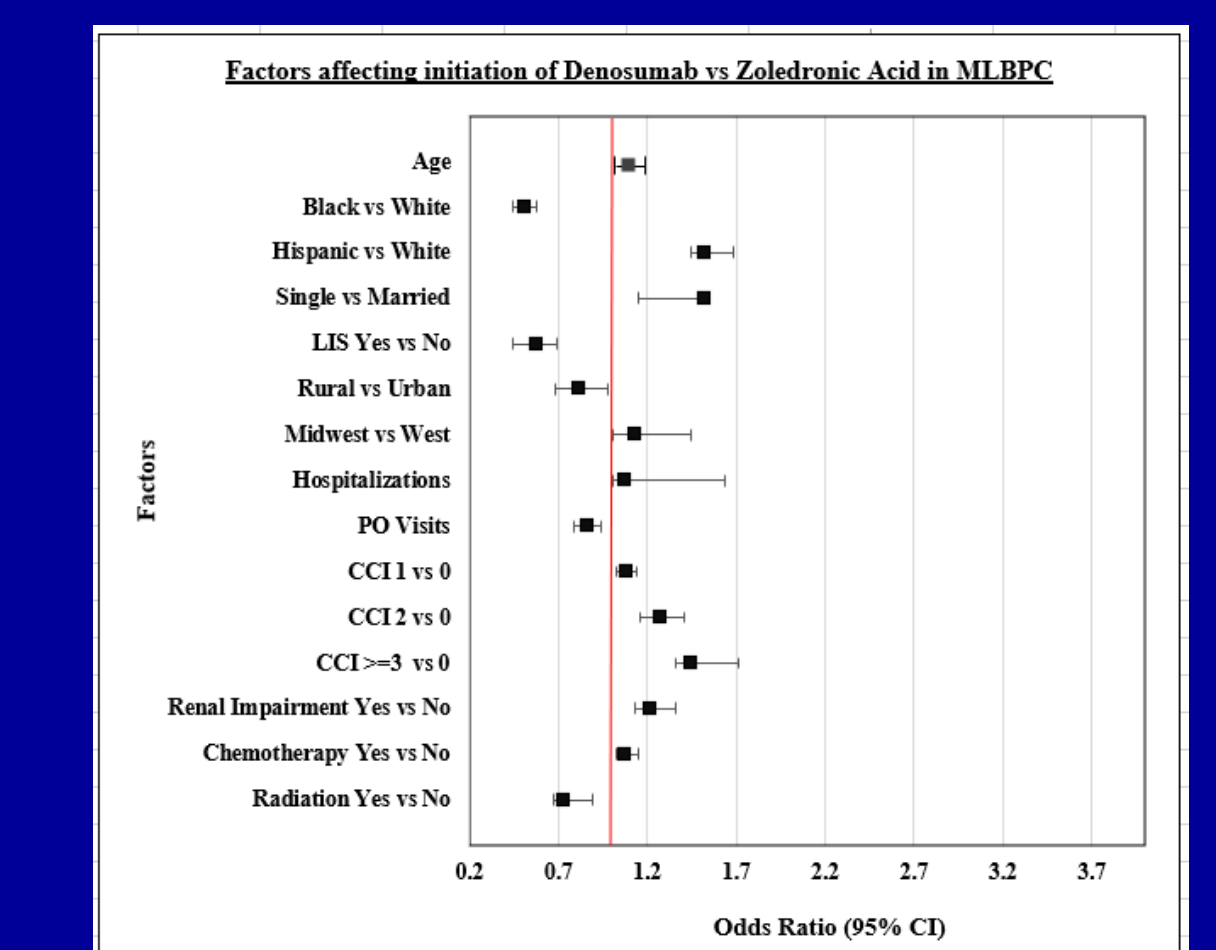
Factors Affecting Initiation

Figure 10: Factors affecting initiation of Denosumab vs Zoledronic acid in MLBPC
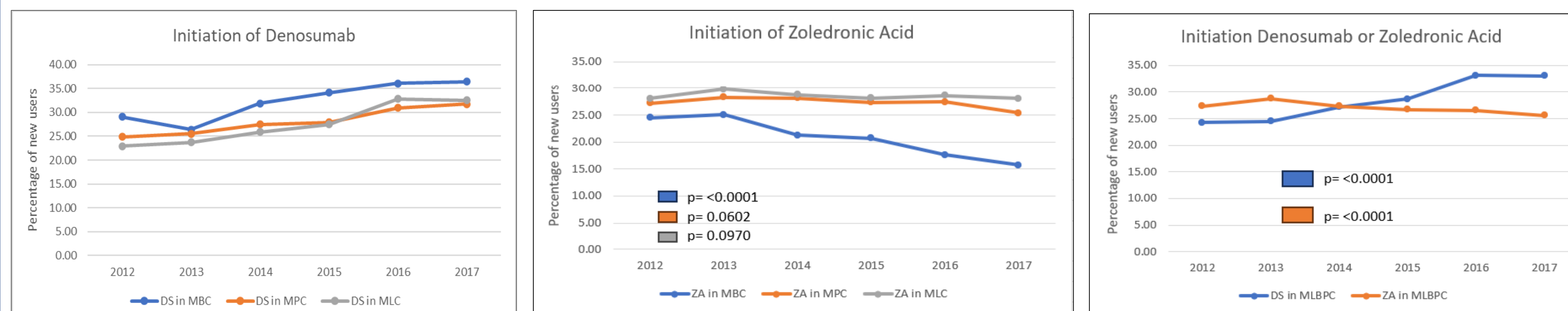
Summary of Results

- Overall, we found significantly increasing trends in DS initiation within the 6 & 12 months of diagnosis during the study period.
- Even at this rate, it is possible that approximately half of the MLBPC patients did not receive optimal treatment to prevent SREs.
- The patients in rural areas are significantly less likely to receive DS compared to ZA.
- Patients eligible for low-income subsidy were less likely to initiate DS than ZA
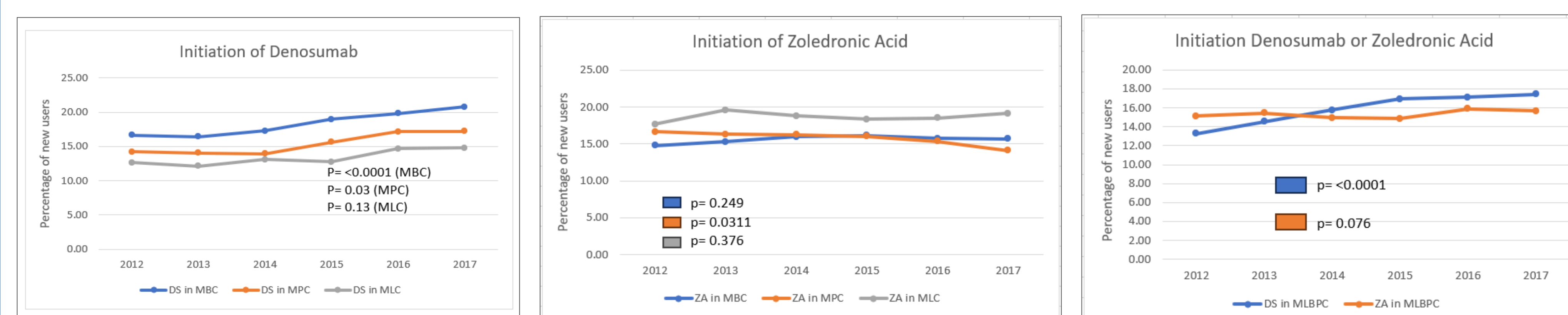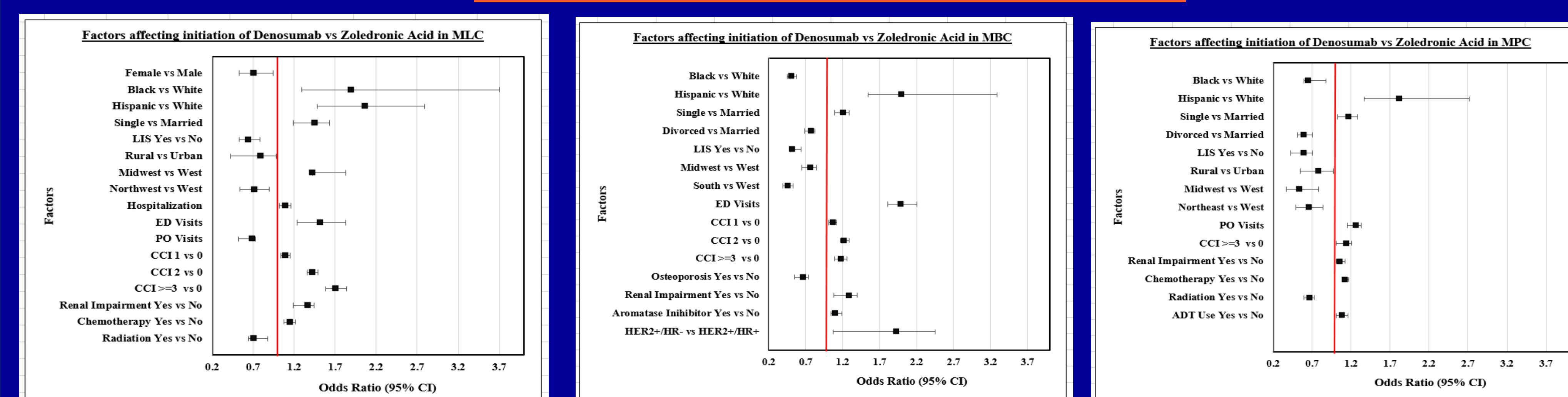
Conclusions

- This study revealed important differences in the trends in DS and ZA initiation among the older MLBPC patients.
- Findings serve as a basis to build evidence regarding comparative benefits and assist clinicians and policymakers in decision-making in treatment uptake.
- Further research is warranted with focus on patients having bone metastasis and assess information on important biomarkers and clinical characteristics related to the use of DS & ZA.

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