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Treatment patterns for patients with initial diagnosis of smoldering multiple myeloma in the United States: a SEER-Medicare analysis

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Running Heads: Treatment patterns for smoldering multiple myeloma

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Authors' Contributions:

S-Y.W. and S-H.C. initiated and conceptualized the study; R.W, S-H.C., and S-Y.W. performed methods; R.W, S.H.H., N.N., M.W. S., S-H.C., and S-Y.W. performed investigation; R.W. and S.H.H. wrote the original draft, S-H.C. and S-Y.W. acquired funding; S.H.H., N.N., M.W. S., S-H.C., and S-Y.W. performance supervision and project administration; S-Y.W. and S-H.C. were co-senior authors; and all authors reviewed and edited the manuscript.

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Dr. Rong Wang reported receiving grants from Flatiron Health. Dr. Neparidze reported receiving research funding to Yale Cancer Center from Glaxo-Smith-Kline, Johnson&Johnson; consulted and holds equity interest with Cellsbin, Inc. outside the submitted work. The remaining authors declare no conflict of interest.

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Data Availability Statement:

The datasets used to conduct this study are available upon approval of a research protocol from the National Cancer Institute. Instructions for obtaining these data are available at https://healthcaredelivery.cancer.gov/seermedicare/obtain/

Smoldering multiple myeloma (SMM) is an asymptomatic premalignant condition. Patients with SMM had a high risk of progression to multiple myeloma (MM) at an annual rate of 10% in the first 5 years after diagnosis.[1] While watchful waiting is the current standard of care for SMM, emerging evidence suggests that early treatment may delay progression and offer survival advantages especially for high-risk patients.[2-5] Little is known about the treatment patterns for SMM in clinical practice. To our knowledge, this is the first study using the pathology-confirmed diagnosis data from the Surveillance, Epidemiology and End Results (SEER17) and the Medicare claims to understand the treatment pattern and trend for patients initially classified as SMM in the United States.

We used the SEER17 recently released MM site-specific information to identify patients diagnosed with SMM; the MM site-specific information, based on pathology reports and clinician statements in the medical records, categorized MM into symptomatic MM (SxMM), SMM, and other/unknown.[6,7] Patients included in the analysis were limited to those have continuous Parts A & B and no managed care coverage from 12 months before diagnosis to end of follow-up (one year after diagnosis or death, whichever first) and continuous Part D from diagnosis to end of follow-up. We collected the treatment data within 12 months after SMM diagnosis from the Medicare claims for inpatient, outpatient, provider, and prescription coverage with relevant International Classification of Diseases and Healthcare Common Procedure Coding System codes for injectable drugs and generic names for prescription drugs. Because patients initially diagnosed with SMM in the SEER17 might have progressed and required SxMM-related treatments, we classified the initial regimens as all agents received within the first 30 days of treatment. New treatments after the 30-day window were also identified, which could be viewed

as treatments for SxMM. The treatments included the receipt of any of monoclonal antibodies/immunotherapy (e.g., daratumumab), immunomodulatory agents (IMiDs, including lenalidomide/pomalidomide/thalidomide), proteasome inhibitors (PIs, including bortezomib/carfilzomib/ixazomib), and chemotherapy/others.[8] We prioritized daratumumab-based regimens, which might include IMiDs and/or PIs and then categorized the rest into IMiD plus PI-based, IMiD-based, PI-based, and chemotherapy. We also assessed steroid (dexamethasone or prednisone) usage during the first 30 days of treatment.

We calculated the percentages of patients initially diagnosed with SMM receiving treatments each year and used the Cochrane-Armitage test for the trend from 2012 through 2021. As diagnostic criteria for SMM/MM in the USA were changed in 2014,[9] which shifted high-risk SMM to SxMM and increased diagnostic imaging for patients with monoclonal gammopathy of undetermined significance (MGUS).[10] Thus, we conducted a sensitivity analysis of the trend between 2015 and 2021. We used a multivariable logistic regression model to examine the factors associated with the treatment receipt. The Yale Human Investigation Committee determined no ethical review needed as no human subjects were involved in this study.

During the period between 2012 and 2021, 803 patients were initially diagnosed with SMM, 61 in 2012 to 107 in 2021 (**Figure 1**); 53.1% were male; 75.6% were non-Hispanic White, 12.3% non-Hispanic Black, and 5.6% Hispanic; and 81.6% resided in metropolitan areas. The median age at diagnosis was 74 (interquartile range [IQR] 70-79) years. 216 of the 803 patients (26.9%) received treatments within one year following diagnosis; the percentage ranged from 36.2% in 2014 to 21.3% in 2016 (**Figure 1**). The decreasing trend over time was marginally statistically

significant (p-value for trend = .07) while the sensitivity analysis of the trend between 2015 and 2021 showed no significant variation over time. Patients initially diagnosed with SMM in 2015-2017 were less likely to receive treatments, compared to those in 2012-2014 (multivariable-adjusted odds ratio: 0.64; p-value= 0.04). Patient demographics were not significantly associated with treatments received (data not shown; complete results to be provided upon request).

The analysis of the Medicare claims data showed the most common initial regimen was IMiD-based regimen (34.7%), followed by PI-based (24.1%), IMiD-PI-based (20.8%), chemotherapy (14.1%), and daratumumab-based (6.0%; **Figure 2**). Lenalidomide (n=125; 57.9%) was the most commonly used IMiD; Bortezomib (n=103; 47.7%) was the most commonly used PI. Daratumumab was the only monoclonal antibodies or immunotherapy received by patients in this cohort, with majority of them diagnosed in 2021. Approximately 72% (n=155) received dexamethasone or prednisone, highest in patients receiving IMiD-PI-based regimens, followed by IMiD-based therapy. The percentage of patients receiving IMiD-based regimens decreased overtime (p-value for trend <0.01); the percentage of patients receiving PI and/or daratumumab remained stable (p-value=.87). The distribution of regimens after the initial treatment was not shown (complete results to be provided upon request).

During our study period, IMiD was the recommended treatment for high-risk SMM. Our results showed that only 75 patients (9.3% of the total population) received IMiD-based regimens in the initial treatment, which was compatible with SMM-directed therapy; more than 85.4% of the IMiD-based regimens was monotherapy. In contrast, all PI-based and IMiDs-PI-based regimens

in our cohort contained chemotherapy, and all daratumumab-based regimens included PI, IMiD, and/or chemotherapy; these treatments were likely for progression from SMM to SxMM. The results showed that within one year of the initial SMM diagnosis, 16.7% of patients had at least one claim for SxMM treatments, including PI or daratumumab after initial treatment of IMiD or chemotherapy, 59 patients receiving triplet and less than 11 patients receiving quadruplet. The rate was higher than the annual 10% SMM progression rate previously reported in the literature,[1] which might indicate a significant percentage of overtreatment in the smoldering phase; another potential reason of the higher-than-expected rate of progression to SxMM was that patients in our cohort were older (median, 74) than those in the Kyle et al. study (median, 64). Because SMM is asymptomatic and often detected incidentally during the workup of other conditions, the SMM diagnosis in these senior patients may be at the timing close to MM progression. Additionally, patients might receive guideline-discordant therapy. Further studies integrating clinical information are warranted to better characterize the treatment patterns for SMM.

We found that the percentage of patients initially diagnosed with SMM receiving treatments decreased from 34% in 2012 to 21.5% in 2021; this decrease was marginally statistically different. One plausible explanation of the decreasing trend might be due to the change in the diagnostic criteria of SMM/SxMM in 2014, which added SLiM criteria to define SxMM, including clonal bone marrow plasma cells (BMPC) ≥60%, serum free light chain (FLC) ratio ≥100, and >1 focal lesion on magnetic resonance imaging.[9] As such criteria were changed, patients who could have been diagnosed as high-risk SMM were diagnosed as SxMM after 2014 and were excluded in our sample of SMM. Given that treatments were only considered among patients with high-risk SMM, the percentage of SMM patients who received treatments

decreased after 2014. Extant research suggested that observation/active surveillance for patients with SMM and the treatment was best given in randomized controlled trials,[13] which would also partially explain no increase in the percentage of patients who received treatments.

The results showed that the percentage of patients initially diagnosed with SMM who received treatments increased from 2013 to 2014 and from 2016 to 2017. The increases were likely due to the QuiRedex trial which demonstrated the benefits of lenalidomide plus dexamethasone for SMM patients.[4] This trial was published in 2013, and then a long-term follow-up study was published in 2016.[11] More than 20 percent of patients received IMiD monotherapy in 2012-2013 before the QuiRedex trial was published. Indication creep might be a plausible explanation for the use of IMiD monotherapy before the trial was published.[14]

We acknowledge the limitations of our study. First, while the MM site-specific indicator to distinguished SMM from SxMM was derived from pathology reports and clinician statements in medical records, the validity of this indicator has not been confirmed. Future studies are needed to examine the validity of this indicator. Second, we identified patients who were initially diagnosed with SMM and the treatments in the Medicare claims within one year after diagnosis; we did not have clinical data regarding disease progression within one year after SMM diagnosis. Thus, we were unable to distinguish whether the treatments were for SMM itself or for SxMM progressed from SMM. Nevertheless, our study was the first population study to report the treatment patterns within one year after initial SMM diagnosis. Third, because we identified therapy based on the Medicare claims, detailed trial information was unavailable, preventing us from determining whether these trials were specific for myeloma. Notably, among

the 35 (4.4%) patients participating in a clinical trial during the first year after diagnosis, 24 patients did not receive any documented myeloma therapy, suggesting that their trial participation might involve non-myeloma-related interventions. Fourth, our population was limited to patients aged older than 66. Finally, data regarding individual's prognostic factors, such as M-protein, BMPC percentage and FLC ratio, were unavailable.

To conclude, we found that approximately one-fourth of Medicare beneficiaries who were initially diagnosed with SMM in the US received treatments within one year after diagnosis. There was a decreasing trend in receiving treatments during 2012-2021, indicating that the physicians followed the standard of care for SMM as observation/active surveillance. As recent clinical trials have demonstrated promising outcomes for early treatments for high-risk SMM, the percentage of patients receiving treatment may increase. Our results provide benchmark information which will facilitate further evaluation of the adoption of novel treatments for patients initially diagnosed with SMM.

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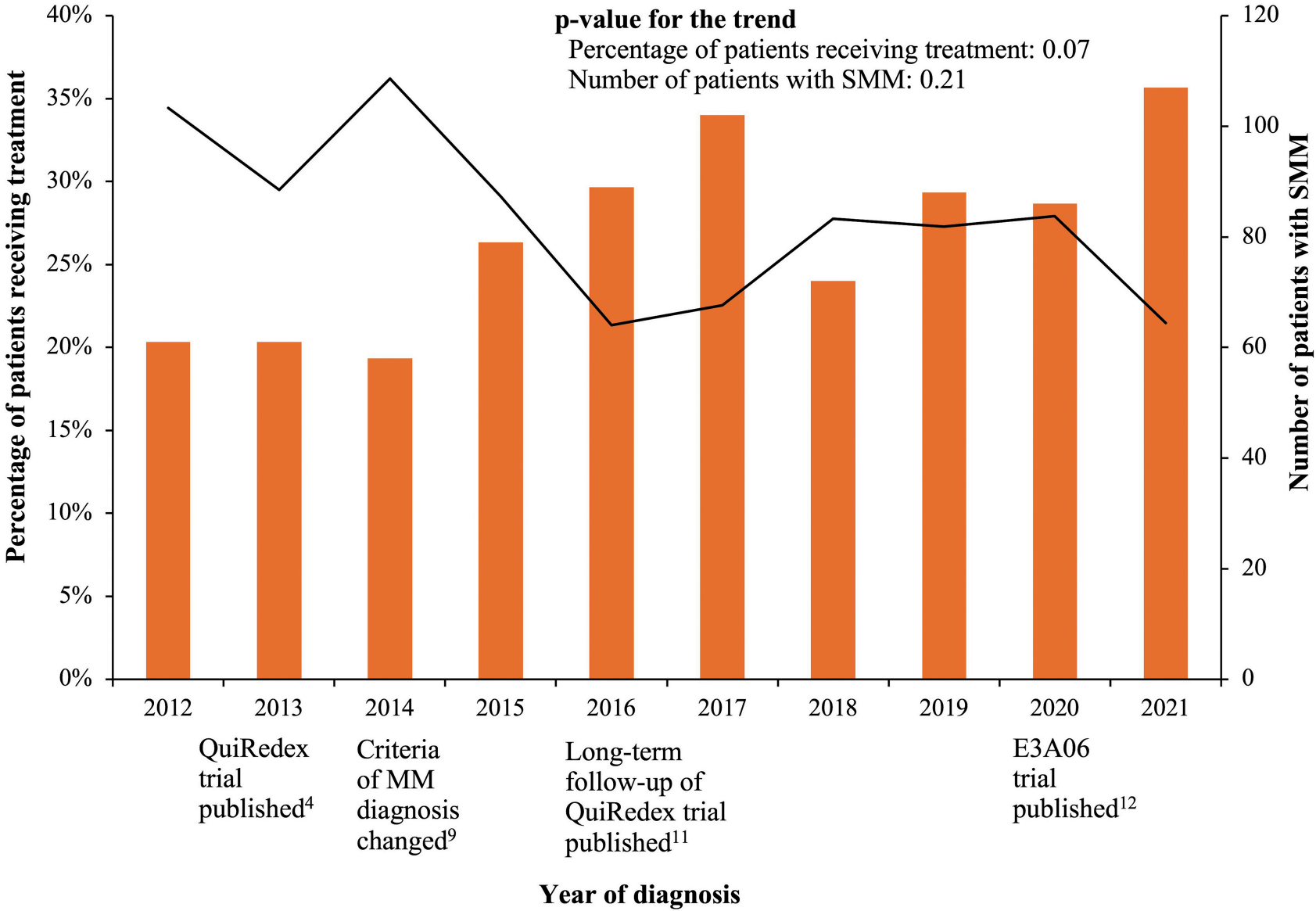
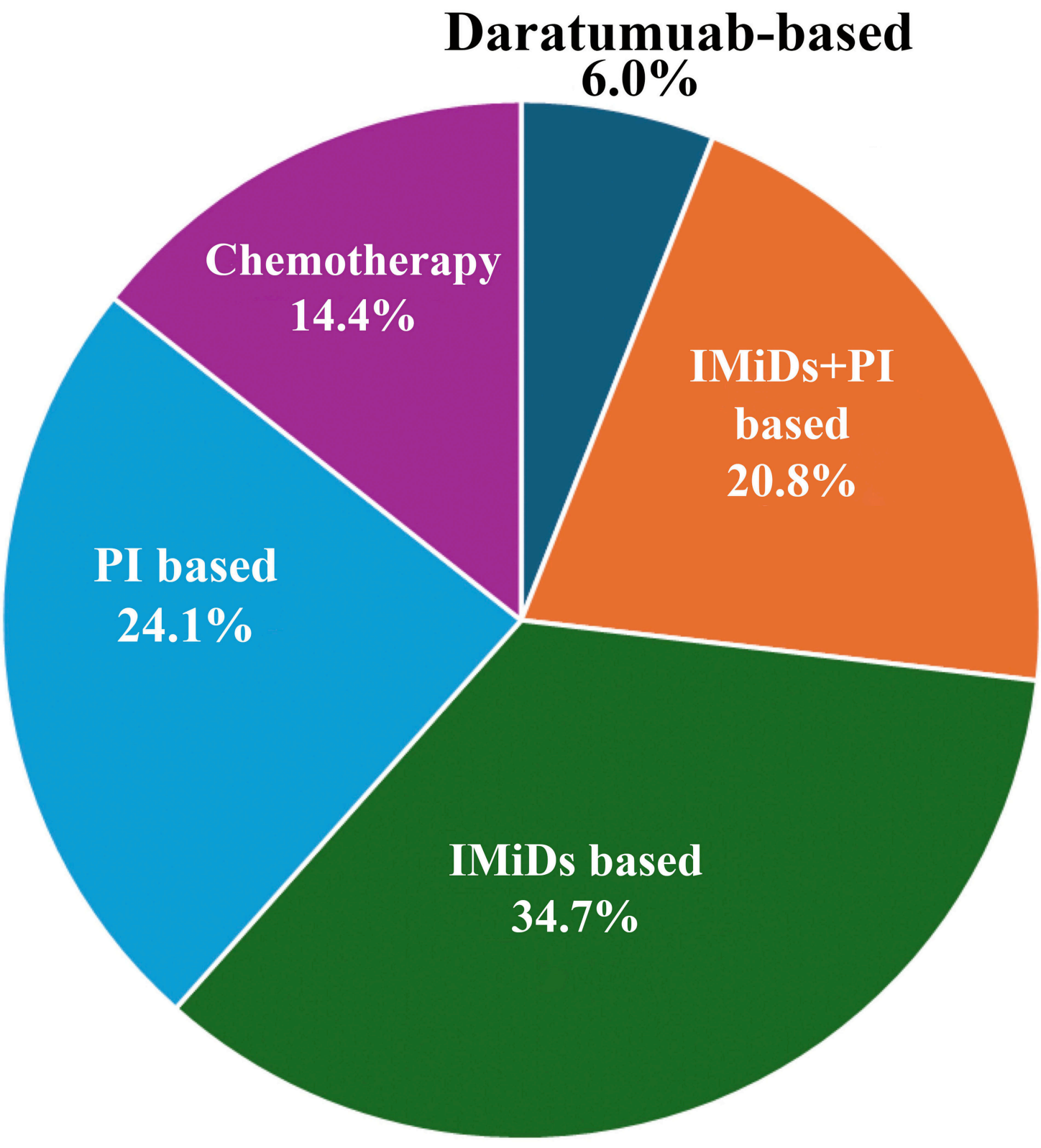
Figure 1. Percentage of patients with initial diagnosis of SMM who received treatments within the first year of diagnosis by year of diagnosis

Figure 2. Type and percentage of regimens used in the first 30 days of SMM treatments


p-value for the trend
Percentage of patients receiving treatment: 0.07
Number of patients with SMM: 0.21
Percentage of patients receiving treatment
Number of patients with SMM
40%
35%
30%
25%
20%
15%
10%
5%
0%
120
100
80
60
40
20
0
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
QuiRedex trial published[4]
Criteria of MM diagnosis changed[9]
Long-term follow-up of QuiRedex trial published[11]
E3A06 trial published[12]
Year of diagnosis


Daratumuab-based
6.0%
IMiDs+PI
based
20.8%
IMiDs based
34.7%
PI based
24.1%
Chemotherapy
14.4%