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# Correspondence on 'Outcomes of stage IV melanoma in the era of immunotherapy: a National Cancer Database (NCDB) analysis from 2014 to 2016' by Sussman et al

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We read with interest in the recent edition of JITC the publication by Sussman *et al* on outcomes of stage IV melanoma in the era of immunotherapy from analysis of National Cancer Database (NCDB).[1] We are reassured to see recent publications including the study by Sussman *et al* and similarly by Lamba *et al* in August further confirm the real-world overall survival benefit of immunotherapy in patients with stage IV melanoma from NCDB cases diagnosed through 2016.[1 2] We previously showed similar survival benefit with immunotherapy in patients with stage IV melanoma using NCDB Participant User Profile (PUF) for cases diagnosed between 2013 and 2015 following the first single-agent checkpoint approvals in 2011 for ipilimumab and 2014 for both nivolumab and pembrolizumab.[3]

Disparities with regard to immunotherapy receipt and survival among patients with stage IV melanoma have been observed based on age, comorbidities, education level, geographical location, insurance status treatment center characteristics, insurance status, and socioeconomic status.[2 3] The present work by Sussman *et al* confirms these findings, however, patients within their study with Medicaid and Medicare as their primary payor were grouped together as 'government insurance'. Review of the NCDB PUF file of their year cohorts find that 13% of patients categorized as 'government insurance' within each immunotherapy era to have Medicaid as primary payor (2004–2010: 690/5434, 2011–2014: 658/4902, 2015–2016: 400/3179).

The sociodemographic make-up between Medicaid and Medicare patients and their access to care and payor benefits are quite different. For instance, Medicare targets individuals who are older than 65, individuals with disabilities, and individuals with end-stage renal disease. This is quite different from Medicaid which includes low-income individuals and families and may include subsets of patients who qualify for Medicare but are not mutually exclusive. Given the differences in administration of these plans and the sociodemographic make-up, it is not surprising that they have disparate cancer outcomes. For instance, Adamson *et al* demonstrated an association of delays in surgery for melanoma patients with Medicaid when compared with Medicare patients.[4]

Since the Affordable Care Act's full effects came in 2014, more patients have gained access to both private insurance and state-administered Medicaid plans. The newly accessed plans vary widely and are not nearly as uniform as Medicare plans and vary by age and geography. Both the eligibility differences for these two plans and the contrasting outcomes in patient care for these two populations further confound the evidence demonstrated by Sussman *et al*. Hence in our opinion findings based on 'government insurances' cannot accurately recognize the impact of immunotherapy utilization or impact of insurance status/primary payor on receipt of immunotherapy when multiple distinct types of government insurances are treated as a single population. In fact, we found melanoma diagnosis within a Medicaid expansion state compared with those diagnosed in a state without Medicaid expansion to be associated with increased likelihood of receiving immunotherapy.[3]

Furthermore, we note that the effect of targeted therapies for melanoma were not considered within the current analysis. Actionable BRAF alterations occur in up to 50% of cutaneous melanomas, and targeted therapies improve survival in melanoma when BRAF single-agent or BRAF and MEK inhibitor combinations are given. Single-agent BRAF inhibitor approvals began with vemurafenib in 2011 and the combination of dabrafenib and trametinib was approved in 2014. Within the NCDB PUF, not only are marginally effective cytotoxic chemotherapies categorized as 'systemic chemotherapy', but highly effective targeted therapies such as BRAF and MEK inhibitors are also placed within this category without more granular data of the specific agent used. However, those receiving systemic chemotherapy (28%, n=6855/23,850) were not excluded within their analysis or counted as a separate treatment arm. This obfuscates the true effect of immunotherapy in the real-world setting.

Analyzing the current release of the NCDB PUF (2019) for cases diagnosed between 2015 and 2016, we find that among 5117 stage IV melanoma cases with first-line systemic treatment data available; 2054 (40.10%) received no systemic therapy, 2109 (41.2%) received immunotherapy, 772 (15.1%) received chemotherapy alone, and 182 (3.6%) were noted to receive both chemotherapy and immunotherapy. The Kaplan-Meier estimates for overall survival for these groups are 5.3 months for neither chemotherapy or immunotherapy, 31.4 months for immunotherapy alone, 11.9 months for chemotherapy alone, and 15.6 months for immunotherapy and chemotherapy. This result shows that once those receiving non-immunotherapy active systemic chemotherapies (which includes targeted therapies such as BRAF/MEK inhibitors) alone or in combination with immunotherapy are separated into a different treatment cohorts within the analysis, the outcomes are further disparate between those receiving immunotherapy and those receiving other combinations. This median survival, as well as the median survival reported by the authors, of 25 months is well within the error of the median survival reported within the results of KEYNOTE-006 for single-agent pembrolizumab of 32.7 months (95% CI 24.5 to 41.6).[5]

This supports the drastic effect of checkpoint inhibitors in advanced melanoma that can be reflected both in clinical trials and a real-world database. We are very encouraged to find the survival benefits of immunotherapy in the real-world setting nearing the outcomes of clinical trials and look forward to future findings from real-world data in melanoma.

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## REFERENCES

1 Sussman TA, Knackstedt R, Wei W, *et al*. Outcomes of stage IV melanoma in the era of immunotherapy: a national cancer database (NCDB) analysis from 2014 to 2016. *J Immunother Cancer* 2022;10:e004994.
2 Lamba N, Ott PA, Iorgulescu JB. Use of first-line immune checkpoint inhibitors and association with overall survival among patients with metastatic melanoma in the anti-PD-1 era. *JAMA Netw Open* 2022;5:e2225459.
3 Moyers JT, Patel A, Shih W, *et al*. Association of sociodemographic factors with immunotherapy receipt for metastatic melanoma in the US. *JAMA Netw Open* 2020;3:e2015656.
4 Adamson AS, Zhou L, Baggett CD, *et al*. Association of delays in surgery for melanoma with insurance type. *JAMA Dermatol* 2017;153:1106–13.
5 Robert C, Ribas A, Schachter J, *et al*. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol* 2019;20:1239–51.