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**Commentary**

# Trends, Changes, and Disruptions: The Fragile Economics of Cancer Treatments

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It has been less than a decade, 2014 to be precise, that the FDA approved the PD-1 inhibitors pembrolizumab[1] and nivolumab[2] for the treatment of advanced melanoma, joining the CTLA-4 inhibitor ipilimumab[3] approved in 2011. With the concurrent introduction of inhibitors targeting the *BRAF* V600 mutation paired with MEK inhibitors, clinicians now have an array of (pricy) treatment options—giving payers some latitude in (responsibly) deciding which options to cover, for whom, and under what conditions.

Many factors enter into the clinical and economic equations that determine patient access to cancer treatment. Foremost are the efficacy and safety of agents and therapeutic regimens—as documented initially in clinical trials and, in time, adjusted for real-world effectiveness and safety.[4] Evidence-based guidelines may prioritize some treatments over others. Variations in regimens and administrations may yield better clinical benefits, greater convenience, and improved quality of life. The challenge is to find a defensible balance between clinical benefit and economic accountability.

In this issue of *The Oncologist*, Qian et al[5] report on a 5-year (2016-2020) claims database analysis of treatment related and total healthcare costs in patients with metastatic melanoma treated with either nivolumab, pembrolizumab, ipilimumab-plus-nivolumab, or *BRAF/MEK* inhibitor regimens. In ascending order, per-patient treatment costs (in parentheses, total healthcare costs) varied from $17.2K/month ($25.4K/month) for nivolumab and $21.2K/month ($30.5K/month) for pembrolizumab monotherapy, $22.3K/month ($32.5K/month) for *BRAF/MEK* inhibitor regimens, and $59.2K/month ($74.5K/month) for ipilimumab-plus-nivolumab.

Informative as the cost findings may be, the importance of the Qian et al study lies in the annual market share distribution of these systemic therapies (as shown in Figure 1 of their article[5]). These data show some stable patterns (trends) but also some remarkable variations over time (changes) in ways that may very well be attributable to external factors (disruptions).

At 8%-9%, the proportion of patients treated with molecularly targeted *BRAF/MEK* inhibitors was consistent over time, and at 18%-20% so was the proportion of patients treated with ipilimumab and nivolumab combination therapy—stable trends without notable changes over time.

In contrast, in 2016 and 2017 slightly over 70% of patients were treated with pembrolizumab or nivolumab. Both agents were approved by the FDA for advanced melanoma on, respectively, 4 September[1] and 22 December 2014[2]—109 days apart. Would those 109 days have given pembrolizumab a market advantage over nivolumab of 22% in 2016 and 20% in 2017? Though speculation, the advantage is more likely due to the scientific and clinical attention paid to pembrolizumab as the first approved PD-1 inhibitor, complemented by well-prepared market access and payer strategies, and, no doubt, hyped-up marketing to stakeholders.

If true, this early advantage for pembrolizumab had little long-term effect. In 2018, it lost 23% of its market share while nivolumab gained 27%, the latter assisted slightly by a few percentage points' decline in patients treated with the ipilimumab-plus-nivolumab regimen. This change in PD-1 inhibitor market share may be attributed to disruptive events that may have started in 2015 (or perhaps earlier). Qian et al cite (the positive disruptive) impact of the CheckMate-067 trial of nivolumab monotherapy, the results of which were presented at the 2015 ASCO meetings and e-published concurrently in the *New England Journal of Medicine*[6] (another positive disruptor). The FDA approved nivolumab[2] a few months later (a third positive disruptor). Add to this yet another disruptor in April 2018: the FDA approval of Q4W nivolumab dosing,[2] up from Q2W—perhaps of somewhat lesser disruptive intensity because of the relative time lag from regulatory approval to prescriber and payer adoption.

Interestingly, the shift in market share in 2018 was of remarkably short duration: the proportion of patients treated with nivolumab monotherapy declined in the subsequent 2 years into the low 40% range, while pembrolizumab monotherapy regained market share to about 30%. Though perhaps not as disruptive as those in 2015, here too Qian et al identify several events. Reports in 2017[7] and 2019[8] on the KEYNOTE-006 head-to-head trial of pembrolizumab versus nivolumab monotherapy demonstrated the superiority in survival benefit, up to 5 years, of pembrolizumab monotherapies.

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Though doubtful to have had a major impact on the 2020 data, the FDA approval in April 2020 of Q3W to Q6W pembrolizumab dosing[1] may have benefitted from early prescriber and payer adoption.

Did the COVID-19 pandemic have a disruptive effect in 2020? Qian et al speculate so cautiously; however, any effect would have been noticeable at the earliest in the second quarter of 2020 as the US went into lockdown. More likely, the COVID-19 effect was similar across treatment regimens—and across cancer treatments generally. The real effect of the pandemic may have been delays and disruptions in diagnosis and treatment across cancer types, affecting many patients with cancer.[9]

It is tempting to see a market share correction in pembrolizumab's rise and nivolumab's decline in market share in 2019 and 2020. Three data points (2018, 2019, and 2020) are insufficient to permit generalizations and infer a market correction. All one can say is that, year-on-year in 2019 and again in 2020, the market share of nivolumab declined while that of pembrolizumab increased. Further, the time-series is too short, the volatility too evident, and the data too sensitive to potential disruptors. A year may be too low in granularity to describe patterns of change; perhaps the 2018 switch-over may not have been as brusque as Figure 1 (in the Qian et al article[5]) suggests. Conceivably, there may have been an upward sloping trend—sharp, slow, or undulating—in weekly or monthly market share or a conical pattern of an increase, peak, and an onsetting decline. Greater time granularity might have enabled us to see the pembrolizumab-nivolumab switch-over emerge and materialize—an area for future research.

Even within these constraints, the Qian et al data beg the question as to what we might see in 2021 and beyond. Patents and other protections may expire and scientific advances translate into new treatments. Biosimilar versions of pembrolizumab and nivolumab are on the horizon[10]; but, in the shorter term, so may new checkpoint inhibitors, including foreign in-licensed drugs. It is not unlikely to see, in the coming years, a commoditization of cancer treatments that will exert significant downward pricing pressure.[11]

Qian et al's analysis of market share shifts provides valuable information. Its broader contribution, however, may be as a case of the fragility of the economics of cancer treatments and the need to contextualize economic cancer data, especially when evaluating longitudinal data.

What would make economic evaluations of cancer treatments more robust, revealing, and clinically supportive? As noted, data should be sufficiently granular to detect and describe patterns over time. In this, it is important to recognize that a calendar unit of time (such as year) imposes an external time structure, when the time-dependent phenomenon of interest may follow its own calendar. Contextual information should be collected and aligned, in a timeline, with the economic data. This should include positive seminal events that may impact the delivery of care, the associated costs, and the observed outcomes: approvals; payer and provider formulary adoptions; pricing, incentives, and actual price; inclusion in evidence-based guidelines; major conventions and other public events; and high-uptake dissemination, from the scientific to the applied, the complex to simple, print as well as digital. Equally important for understanding and contextualizing the economics of cancer care are negative seminal events: safety concerns; contradicting trial efficacy or real-world effectiveness data; removals from formularies; competition; suspension of coverage; to name the major.

From a statistical and econometric perspective, and as the Qian et al data imply, linear models may prove insufficient to capture temporal variability; non-linear models may need to be applied. Interaction effects of seminal events on clinical or economic outcomes should be integrated into the models. Lag times between approval, clinical adoption, and payer coverage should be considered. Where multiple lines of cancer treatments are common, economic evaluations should consider the patient trajectories, in treatment and in duration, by incorporating all treatment lines. In all, models should comprehensively capture dynamic within-patient and between-patient variation as opposed to the static assumption of all patients being equal.

Too often still, economic evaluations of cancer treatments apply "classical" methods of pharmacoeconomic analysis, mainly cost-effectiveness and cost-utility analyses with fixed (if not arbitrary and intransigent) willingness-to-pay thresholds. Almost invariably, these analyses conclude that a given treatment is too expensive and that the price should be lowered significantly—ignoring the cost of developing novel treatments and bringing them to the point of care. Studies like Qian et al's attempt to describe and understand the issue of affordability and patient access to innovation in cancer treatment within the intensely dynamic, ever accelerating, and highly competitive space of cancer treatments and metastatic melanoma specifically. Such studies provide an important checkpoint (pun intended) as to market uptake of treatments, associated costs, and changes therein as other treatment options come online.

In the end, economic analysis is to inform policy, not set policy. Despite the confines of their data, Qian et al brought attention to a striking market share shift, hypothesized possible factors and drivers, and helped identify the next steps, methods, and analytics to optimize affordability and patient access.

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## Conflict of Interest

Ivo Abraham declares no competing interests specific to this article. He is the Quantitative Methods Editor of *JAMA Dermatology* and the Deputy Editor-in-Chief of the *Journal of Medical Economics*. He holds equity in Matrix45, LLC, which provides scientific and consulting services to biopharmaceutical, diagnostics, and medical device companies on a non-exclusivity basis; government and international agencies; and academic or health care institutions. By company policy, owners and employees are prohibited from holding equity in client and sponsor organizations (except through mutual funds or other independently administered collective investment instruments), contracting independently with client and sponsor organizations, or receiving compensation independently from such organizations. Any compensation related to the provision of services to government and international agencies, academic institutions, and health care institutions by equity owners is collected by Matrix45.

## References


1. Keytruda®. https://www.drugs.com/history/keytruda.html. Date accessed 7 November 2022.
2. Opdivo®. https://www.drugs.com/history/opdivo.html. Date accessed 7 November 2022.
3. Yervoy®. https://www.drugs.com/history/yervoy.html. Date accessed 7 November 2022.
4. U.S. Food and Drug Administration. *Real-world data: assessing electronic health records and medical claims data to support regulatory decision-making for drug and biological products*. Draft Guidance for Industry; 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory. Date accessed 7 November 2022.
5. Qian MF, Betancourt NJ, Pineda A, et al. Health care utilization and costs in systemic therapies for metastatic melanoma from 2016-2020. *Oncologist*. 2023;28(3):268-275. https://academic.oup.com/oncolo/advance-article/doi/10.1093/oncolo/oyac219/6776043?login=false.
6. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34. https://doi.org/10.1056/NEJMoa1504030.
7. Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet*. 2017;390(9):1853-1862. https://doi.org/10.1016/S0140-6736(17)31601-X.
8. 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(9):1239-1251. https://doi.org/10.1016/S1470-2045(19)30388-2.
9. Riera R, Bagattini AM, Pacheco RL, et al. Delays and disruptions in cancer health care due to COVID-19 pandemic: systematic review. *JCO Global Oncol*. 2021;7:311-323. https://doi.org/10.1200/GO.20.00639.
10. Jeremias S. *Dr. Nabil Saba shares his hope for future opdivo, keytruda biosimilars*. https://www.centerforbiosimilars.com/view/dr-nabil-saba-shares-his-hope-for-future-opdivo-keytruda-biosimilars. Date accessed 7 November 2022.
11. Abraham, I. *Biosimilars and the commoditization of treatments*. https://www.centerforbiosimilars.com/view/dr-ivo-abraham-column-biosimilars-and-the-commoditization-of-treatments. Date accessed 7 November 2022.