PCN60

Healthcare Cost Comparison Analysis of Nivolumab + Ipilimumab Regimen (NIVO+IPI) and Nivolumab (NIVO) Monotherapy Versus Established Advanced Melanoma Therapies Utilizing Clinical Trial and Real World Data

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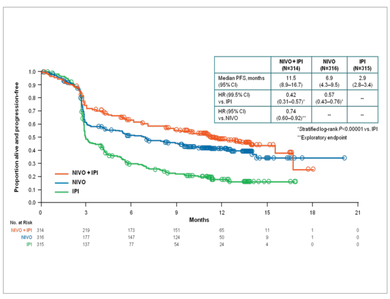
INTRODUCTION

- The American Cancer Society estimates that 76,380 new cases of melanoma and 10,130 deaths resulting from this malignancy will be reported in 2016.[1]
- While early stage melanoma is frequently curable by surgery alone, metastatic disease is associated with a 5-year survival rate of only 17.9%, highlighting the need for more effective treatment options.[2]
- Several innovative treatment options have been approved over the past few years that have improved response and/or survival in advanced melanoma patients. These include the CTLA-4 inhibitors (ipilimumab), targeted therapies such as the selective BRAF and MEK inhibitors vemurafenib, dabrafenib, trametinib, cobimetinib, mekanist and their combinations focused on patients with melanoma harboring the BRAF V600 mutation, and anti-PD1 inhibitors (nivolumab, and pembrolizumab).[3-6]
- Nivolumab was approved in the United States for the treatment of unresectable or metastatic (advanced) melanoma as a monotherapy in December 2014,[7] and as combination therapy with ipilimumab in September 2015.[8]
- In the randomized controlled Phase 3 CheckMate 067 trial, nivolumab in combination with ipilimumab ("NIVO + IPI regimen") and nivolumab alone ("NIVO") have been shown to have superior efficacy when compared to IPI alone ("IPI") (median progression-free survival [PFS] was 11.5, 6.9, and 2.9 months, respectively **(Figure 1);** the rates of investigator-assessed objective response for the 3 regimens were 57.6%, 43.7%, and 19.0% respectively.[9]
- Although the NIVO + IPI regimen and NIVO have been shown to significantly improve objective response rates (ORR), PFS, and overall survival (OS) compared with IPI,[9] little is known about the healthcare costs incurred over time by patients initiating these newer therapies.

FIGURE 1. PROGRESSION-FREE SURVIVAL (INTENT-TO-TREAT POPULATION)



OBJECTIVE

- To compare the total melanoma-specific healthcare costs, from a US perspective, in patients treated with the NIVO+IPI regimen and NIVO with those treated with the established advanced melanoma therapies (EAMTs).

METHODS

ESTIMATION OF COSTS INCURRED BY PATIENTS INITIATING TREATMENT WITH THE EAMTs

- The EAMTs were identified using healthcare claims data from the Truven Health MarketScan® Commercial and Medicare Supplemental Databases (MarketScan).
- Identification of EAMTs was based on the percentage of patients treated with various regimens in the first line of treatment (LOT1), regardless of the treatments in subsequent lines. The five most frequently used regimens (ipilimumab, vemurafenib, temozolomide, interleukin, and interferon) were included in the cost comparison analysis as the EAMTs.
- The key criteria for patients to be included in the analysis were:
  - Stage III/IV advanced melanoma patients
  - 6 months continuous enrolment prior to index diagnosis
  - Diagnosed between April 1, 2011, and June 30, 2013.
- The patient-level cost data were aggregated across all patients separately for various cost categories (drug, inpatient, outpatient, and emergency room), and adjusted for censoring to provide the month-by-month costs (in 2015 US dollars) incurred by patients initiating treatment with the five EAMTs.

ESTIMATION OF COSTS INCURRED BY PATIENTS INITIATING TREATMENT WITH NIVO + IPI REGIMEN AND NIVO

- Healthcare resource utilization data was collected for all randomized subjects in the CheckMate 067 trial.[9] Unit costs from MarketScan were applied to resources from CheckMate 067 to derive healthcare costs for the NIVO + IPI regimen and NIVO. Further, resource utilization for IPI from the trial was also considered to be used to benchmark the resource utilization in a clinical trial setting with that seen in the real world (MarketScan).
- While all the patients enrolled in the CheckMate 067 trial were included in the base case analysis, a sensitivity analysis that limited the study population to only the US patients was additionally carried out.

Determination of resources utilized

- Individual patient level data from the CheckMate 067 trial was used to source the month-by-month use of resources for each patient.
- The analysis was carried out by separately analyzing all melanoma-specific resources (including before and after progression) for the following cost categories:
  - Drug costs: Index medications, other melanoma drugs, and concomitant medications **(Table 1)**
  - Non drug costs: Hospitalizations, surgeries, outpatient/office visits, emergency room visits, procedures, and laboratory costs **(Table 2)**
- For the index treatments, IPI and NIVO, each record of drug usage in CheckMate 067 was analyzed to estimate the actual amount of drug used by multiplying the recorded dose level and patient weight. Based on this quantity, the number of vials required in each instance was estimated. Vial sharing was not assumed. To account for vial wastages, all the available vial sizes were considered.
- For the other melanoma and concomitant medications, duration of drug use as available in the CheckMate 067 trial was used. Based on the dosing schedule from the label and published literature, month-by-month resource use was obtained.
- Each non-drug resource was tagged and aggregated into two cost categories: outpatient and inpatient, based on whether the date of use corresponded to a hospital stay.

Estimation of unit costs

- The unit costs for the various drugs (listed in Table 1), and resources (listed in Table 2) were obtained, where available, from an analysis of MarketScan to enable comparison of costs of NIVO + IPI regimen and NIVO cohorts with the costs of the EAMT cohorts.

METHODS (CONT.)

TABLE 1. MELANOMA DRUGS AND CONCOMITANT MEDICATIONS FOR WHICH UNIT COSTS WERE DERIVED

CATEGORY	LIST OF DRUGS
Index medications	Nivolumab and ipilimumab
Post-progression melanoma medications	Dabrafenib, vemurafenib, dacarbazine, ipilimumab, pembrolizumab, trametinib, cisplatin, paclitaxel, interleukin-2, interferon alfa 2b, carboplatin, temozolomide, imatinib, gemcitabine, vinblastine, vincristine, melphalan
Concomitant medications	Prednisone, prednisolone, methylprednisolone, acetaminophen, dexamethasone, hydrocortisone, pantoprazole, levothyroxine, loperamide, sodium chloride

TABLE 2. FREQUENTLY USED RESOURCES FOR WHICH UNIT COSTS WERE DERIVED

CATEGORY	LIST OF RESOURCES
Lab tests	WBC differential count, electrolytes, liver function tests, erythrocyte/platelet attributes, kidney function tests, glucose tests
Procedures	Biopsy, blood culture, colonoscopy, CT scan, ECG/EKG, MRI, PET, radiotherapy, stool culture, urine culture, X-ray
Hospitalizations	Diarrhea, fever, colitis, hepatotoxicity, infection, pneumonitis, vomiting, dehydration
Miscellaneous resources	Hospital outpatient, physician office visit, emergency room visit, rehabilitation center, telephone contact, home health care, consultation, several types of surgeries

- The unit costs for drugs that were not available in MarketScan (nivolumab, pembrolizumab, melphalan, and acetaminophen), were based on the listed wholesale acquisition cost (WAC) as available in RED BOOK.
- The drugs that had insignificant usage or where the drugs were under investigation in trials and not commercially available yet, are not listed in Table 1; for such drugs, the average unit cost of the concomitant drugs listed in Table 1 was applied.
- The resources that had insignificant usage are not listed in Table 2; for such resources, the average unit cost of the respective category of resources listed in Table 2 was applied.
- A sensitivity analysis was separately carried out in which the unit costs for all the drugs were taken from the listed WAC from RED BOOK.
- The costs were adjusted to 2015 prices using the medical component of the Consumer Price Index.

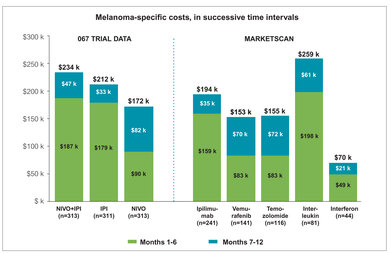
Estimation of month-by-month censoring-adjusted costs

- The month-by-month costs were calculated separately for each resource type by multiplying the respective unit costs and month-by-month duration/number of resources used. The costs were then grouped into drug, inpatient, outpatient, and ER cost categories.
- The costs in each category were then aggregated across all patients and adjusted for censoring, to provide the month-by-month costs incurred by patients initiating the respective regimens of interest.

RESULTS

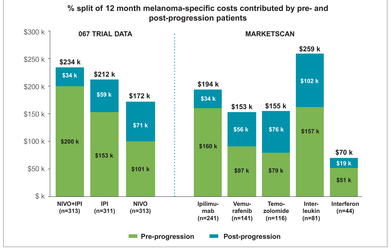
- Ipilimumab (33%, n=241), vemurafenib (19%, n=141), temozolomide (16%, n=116), interleukin (11%, n=81) and interferon (6%, n=44) were the most widely prescribed therapies according to MarketScan. The average melanoma-specific healthcare costs per patient over the first 12 months of treatment for patients initiating these regimens were $194k, $153k, $155k, $259k and $70k respectively **(Figure 2)**.
- The total melanoma-specific healthcare costs incurred per patient in CheckMate 067 over the first 12 months of treatment were $234k by patients initiating NIVO + IPI regimen (n=313), $212k by those initiating IPI (n=311) and $172k by those initiating NIVO (n=313) **(Figure 2)**.

FIGURE 2. AGGREGATE MONTH-BY-MONTH COSTS DURING THE FIRST 6- AND 12-MONTH PERIODS



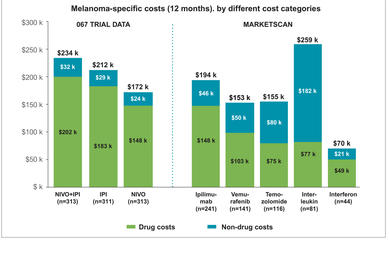
- Compared with the NIVO + IPI regimen cohort, the pre-progression costs were 49% lower for the NIVO cohort and 24% lower for the the IPI cohort. Conversely, the post-progression costs were 111% higher for NIVO cohort and 76% higher for IPI cohort when compared with costs incurred by the NIVO+IPI regimen cohort. **(Figure 3)**.

FIGURE 3. DISTRIBUTION OF MELANOMA-SPECIFIC COSTS BY TREATMENT PHASE FOR THE DIFFERENT REGIMEN COHORTS INTO PRE- AND POST-PROGRESSION COSTS



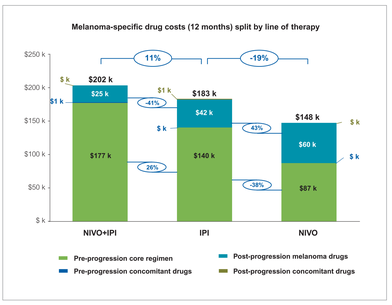
- Melanoma drug costs accounted for a majority of total costs for each of the treatments, with non-drug costs representing only a small proportion of total melanoma costs except for interleukin **(Figure 4)**. Costs of concomitant drugs also represented only a small proportion of total melanoma costs both before and after disease progression **(Figure 5)**.

FIGURE 4. AGGREGATE MONTH-BY-MONTH MELANOMA-SPECIFIC COSTS (12 MONTHS), BY COST HEAD



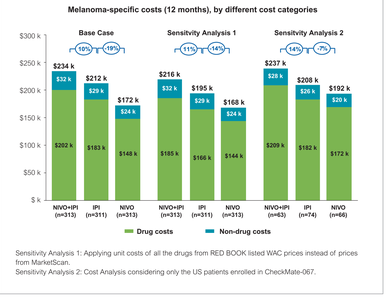
RESULTS (CONT.)

FIGURE 5. DISTRIBUTION OF MELANOMA-SPECIFIC DRUG COSTS ANALYZED BY TYPE AND PROGRESSION STAGE FOR DIFFERENT REGIMEN COHORTS IN THE CHECKMATE 067 TRIAL



- Sensitivity analyses:
  - Using RED BOOK listed WAC prices: This resulted in a decrease in total melanoma costs to $216k, $195k, and $168k for NIVO+IPI, IPI and NIVO cohorts respectively **(Figure 6).** Costs associated with NIVO+IPI regimen patient cohort were 11% higher than IPI cohort; while costs with NIVO cohort were 14% lower than those initiating treatment with IPI.
  - Only US patients: This resulted in an increase in total melanoma costs for NIVO cohort. Total melanoma costs were $237k, $208, and $192 for NIVO+IPI, IPI and NIVO cohorts respectively **(Figure 6).** Total costs associated with NIVO+IPI regimen cohort were 14% higher than IPI cohort; while total costs with NIVO cohort were 7% lower compared to IPI cohort.

FIGURE 6. COMPARISON OF SPLIT OF MELANOMA-SPECIFIC COSTS BY DIFFERENT COST CATEGORIES - BASE CASE VS. SENSITIVITY ANALYSIS



Sensitivity Analysis 1: Applying unit costs of all the drugs from RED BOOK listed WAC prices instead of prices from MarketScan.
Sensitivity Analysis 2: Cost Analysis considering only the US patients enrolled in CheckMate-067.

STUDY LIMITATIONS

- Resource utilization data were sourced from MarketScan for the EAMTs while the data for the NIVO regimens were sourced from a clinical trial. However, for the IPI regimen, where data were sourced from both of these sources, the 12-month costs incurred by patients initiating this regimen were found to be comparable suggesting similarities in resource use in the real world and in the CheckMate 067 clinical trial.
- Some of the treatments used in patients in the real world setting following progression with the index regimen may not be in conformity with prescribed treatment guidelines.
- MarketScan suffers from the same limitations typically seen with any data gathered from the real world, such as coding inaccuracies.
- The study results for the EAMTs are reflective of the period from April 1, 2011 to June 30, 2013, a time since which practice patterns may have changed.

CONCLUSIONS

- These results suggest that advanced melanoma patients may realize significant clinical benefit with first-line NIVO+IPI regimen and NIVO monotherapy, with only modest cost increases over the EAMTs.
- The higher costs seen for the NIVO + IPI regimen in the pre-progression period are compensated for in the post-progression period **(Figure 3)**, driven by a reduction in the need for subsequent melanoma treatment costs after first line, and reflective of NIVO + IPI regimen's superior efficacy in terms of PFS, ORR and duration of response compared to NIVO or IPI alone.[9]
- Costs derived for the cohort initiating with IPI from the CheckMate 067 trial and from MarketScan are quite comparable.
- Non-drug costs had a small impact on total healthcare costs except for interleukin.

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DISCLOSURES

- Ravi Potluri, Hitesh Bhandari, and Sandip Ranjan are employees of SmartAnalyst Inc. or its subsidiaries. SmartAnalyst Inc. was contracted by Bristol-Myers Squibb to perform this analysis. Tony Okoro, Javier Sabater, and Srividya Kotapati are employees of Bristol-Myers Squibb.

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