PCN58

Healthcare Cost Comparison Analysis of Nivolumab + Ipilimumab Regimen (NIVO+IPI), Nivolumab Monotherapy (NIVO) and Ipilimumab Monotherapy (IPI) Utilizing Clinical Trial Data: A European Perspective

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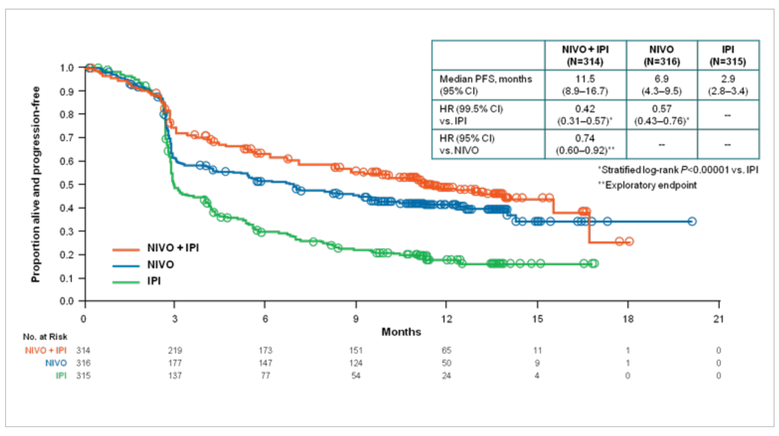
INTRODUCTION

- Melanoma, an aggressive form of skin cancer, is less common than other cutaneous malignancies such as basal cell and squamous cell carcinoma but accounts for a majority of skin cancer-related deaths.[1,2]
- Survival rates vary significantly by the extent of the disease, with early stage melanoma being frequently curable by surgery alone and metastatic disease having a historic 5-year survival rate of only 17.9%, underscoring the lack of effective treatments in patients with advanced disease.[3]
- In the UK, an estimated 14,509 new cases of malignant melanoma were reported in 2013, the most recent year for which incidence data are available, representing 4% of all cancer cases reported during the year.[4] Approximately half of all cases were diagnosed in adults 65 years of age and above.[4]
- In 2012, the most recent year for which mortality data are available, there were 2,148 deaths in the UK due to malignant melanoma, accounting for 1% of all cancer-related deaths.[5]
- Treatment of melanoma experienced a significant advance with the discovery of immune modulators including the immune checkpoint inhibitor ipilimumab (IPI) and more recently the anti PD-1 antibodies pembrolizumab and nivolumab, which have shown increased overall survival in recent trials.[6–8]
- The anti-PD1 human monoclonal antibody nivolumab (NIVO) was recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of advanced (unresectable or metastatic) melanoma in the UK in January 2016,[9] mainly on the basis of evidence of its clinical effectiveness from 3 Phase 3 randomized controlled trials, the CheckMate 037, 066, and 067 trials.[8,10,11] The NIVO + IPI combination regimen ("NIVO+IPI regimen") is currently being assessed by NICE for the same indication.
- The recommended dose and schedule for NIVO mono is 3 mg/kg as an intravenous (i.v.) infusion administered over 60 minutes every two weeks.[12] However, when used in combination with ipilimumab, the recommended dose and schedule for nivolumab is 1 mg/kg administered as an i.v. infusion, followed by ipilimumab on the same day, every 3 weeks for four doses. The recommended subsequent dose of nivolumab, as a single agent, is the same as that for NIVO mono.[12]
- Results of the CheckMate 067 trial showed that the NIVO + IPI regimen and NIVO monotherapy ("NIVO mono") significantly improved PFS compared with IPI monotherapy ("IPI mono") (median PFS was 11.5, 6.9, and 2.9 months, respectively)[11] **(Figure 1)**; however, not much is known regarding the healthcare costs incurred over time by patients initiated on these new therapies.

FIGURE 1. PROGRESSION-FREE SURVIVAL CURVES FROM THE CHECKMATE-067 TRIAL



OBJECTIVE

- To compare the total melanoma-specific healthcare costs in patients treated with the NIVO + IPI regimen, NIVO mono, and IPI mono in the European subset of advanced melanoma patients initiating first-line (1L) treatment in the CheckMate 067 trial from the UK-NHS perspective.

METHODS

DETERMINATION OF RESOURCES UTILIZED

- Individual patient level data for European Union patients enrolled in the CheckMate 067 trial[11] was used to source the resource utilization associated with the use of the NIVO + IPI regimen (N = 177), NIVO mono (N = 170), and IPI mono (N = 167).
- Event level data available for each patient was first converted into longitudinal form (across time) and then consolidated on a monthly basis to derive the month-by-month use of resources for each patient.
- All melanoma-specific healthcare resources occurring during the first year of treatment including before and after disease progression (defined by RECIST, v.1.1) during this period were aggregated.
- The analysis was carried out by separately analyzing the resource utilization for the following cost categories:
  - Drug costs: Index medications, other melanoma drugs, concomitant medications
  - Non drug costs:
    - Hospitalizations
    - Surgery
    - Outpatient/office visits
    - Emergency room visits
    - Procedures, and
    - Laboratory costs
- Specific unit costs were applied to the most utilized drug and non-drug resources from CheckMate 067, listed in **Table 1** and **Table 2** respectively, and an average cost applied to the rest of the resources.

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

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

[a]Unless otherwise specified, unit costs were derived from the UK National Health Service (NHS) Drug Tariff List (November 2015) and the British National Formulary (BNF) 67

[b]Derived from the National Institute for Health and Care Excellence (NICE) Technology Appraisal guidance 321

[c]Derived from the Monthly Index of Medical Specialities (MIMS)

[d]Derived from the UK Medicines Information (UKMi)

METHODS (CONT.)

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, pancreatic tests , endocrine tests, Quantitative WBC
Procedures	Biopsy, blood culture, colonoscopy, CT scan, ECG/EKG, MRI, PET, radiotherapy, stool culture, urine culture, X-ray, ultrasound, gastroscopy, pulmonary angiogram, chest angiogram
Hospitalizations	Diarrhea, fever, colitis, hepatotoxicity, infection, pneumonitis, hypophysitis
Surgery	Skin, brain, lymph, small intestine, leg, biopsy, abdomen, intestine, bone
Miscellaneous resources	Hospital outpatient, physician office visit, ER admission, hemogram, telephone contact, home health care, specialist consultations

- For the index treatment drugs - ipilimumab and nivolumab - each record of drug usage in the CheckMate 067 trial 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 month-by-month resource use was obtained.
- Each non-drug resource was tagged and aggregated into two cost heads: outpatient and inpatient, based on whether the date of use corresponded to a hospital stay.

ESTIMATION OF UNIT COSTS

- Unit costs for the analysis were ascribed from a UK NHS perspective.
- The unit costs and pack size for NIVO and IPI considered at their list price were :
  - NIVO - 40 mg vial: £439; 100 mg vial: £1,097
  - IPI - 50 mg vial: £3,750; 200 mg vial: £15,000
- The unit costs for all the other drugs were determined as explained in the footnotes to **Table 1**.
- Unit cost related to non-drug resources were based upon the corresponding healthcare resource group (HRG) codes and other currencies description in the National Schedule Reference Cost 2013-14.
- The costs were adjusted to 2015 prices using the medical component of the Consumer Price Index.

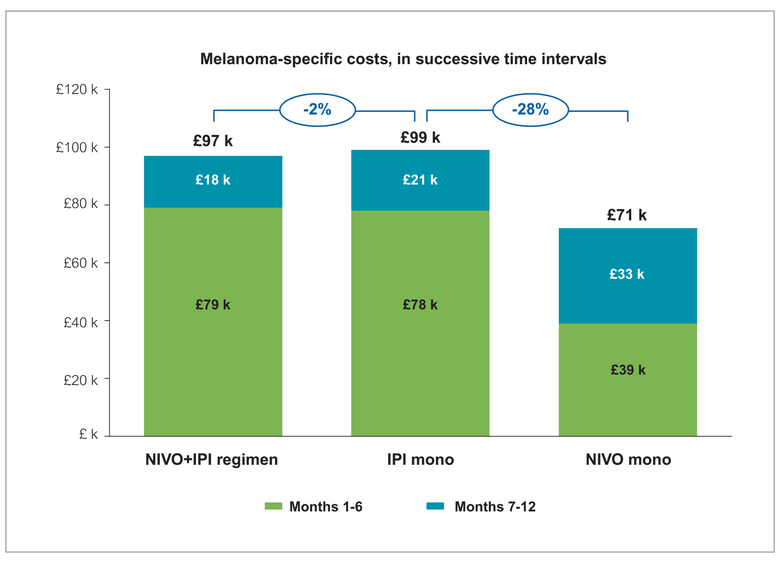
ESTIMATION OF MONTH-BY-MONTH CENSORING-ADJUSTED COSTS

- 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 associated with patients initiated with the respective treatments of interest.

RESULTS

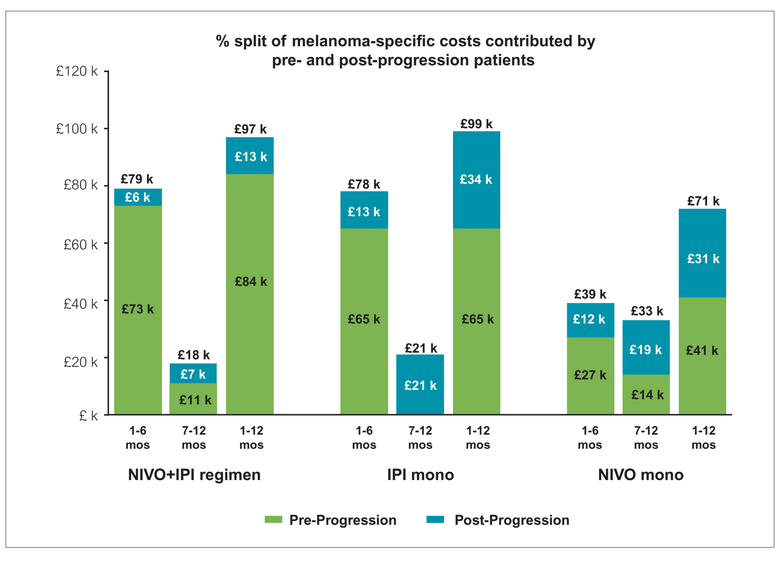
- The melanoma-specific healthcare costs incurred by advanced melanoma patients treated with the NIVO + IPI regimen (£97 k) as the frontline treatment within the first 12 months of initiation of treatment were actually marginally lower than those incurred by patients initiated with IPI mono (£99 k) **(Figure 2)**. Corresponding costs for the NIVO mono-initiated patient cohort (£71 k) were 28% lower than for the IPI mono cohort.

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



- The pre-progression costs incurred by the NIVO + IPI cohort were higher by only 29% than by the IPI mono cohort, despite being treated with a combination. The costs were 107% higher than with the NIVO mono cohort **(Figure 3)**.

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



RESULTS (CONT.)

- The post-progression costs incurred by the NIVO + IPI regimen cohort were 63% lower vs the IPI mono cohort and 59% lower vs the NIVO mono cohort due to a reduction in the use of subsequent therapies, reflecting the longer time to progression associated with the combination, and a sustained duration of response **(Figure 3).**
- Drug costs account for more than 90% of the total costs for each of the cohorts **(Figure 4)**. Of these drug costs, concomitant drug costs are insignificant **(Figure 5).**

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

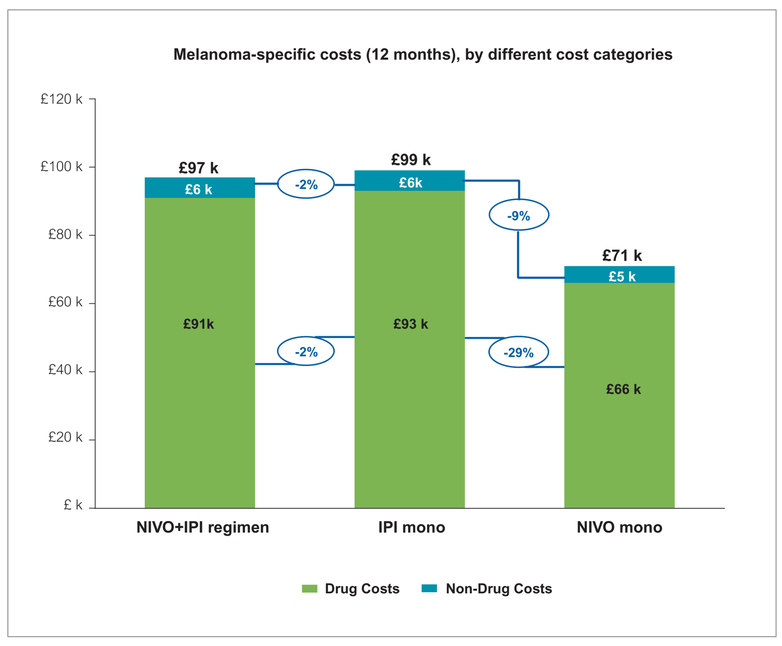
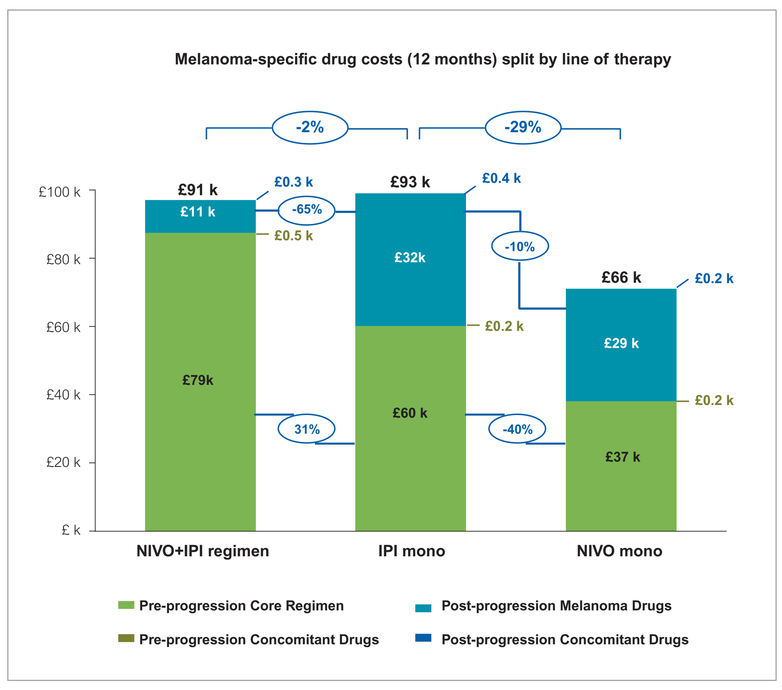


FIGURE 5. DISTRIBUTION OF MELANOMA-SPECIFIC DRUG COSTS ANALYZED BY TYPE AND PROGRESSION STAGE FOR DIFFERENT REGIMEN COHORTS IN THE CHECKMATE 067 TRIAL



CONCLUSIONS

- **These results suggest that 1L advanced melanoma patients treated with NIVO + IPI regimen may actually benefit from lower melanoma-specific healthcare costs as compared to IPI monotherapy. This adds to the significant clinical benefit offered by the combination.**
- **The higher costs seen for the NIVO + IPI regimen cohort in the pre-progression period are compensated for in the post-progression period, due to a reduction in the use of subsequent therapies reflective of its superior and more durable efficacy.**
- **To understand the impact of the interventions on healthcare costs over the longer term, the analysis should be replicated when more mature data becomes available.**

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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. Javier Sabater and Srividya Kotapati are employees of Bristol-Myers Squibb.

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