

# Nivolumab-adjuvant therapy for resected stage III-IV melanoma: a cost-effectiveness analysis for Spain

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## Background

- Melanoma is a type of cancer that begins in the melanocytes<sup>1</sup>
- The incidence of melanoma has risen in the last few decades<sup>1</sup>. In 2019, approximately 6,205 cases are predicted to be diagnosed in Spain<sup>2</sup>
- Surgical resection is the standard treatment for localized melanoma<sup>3,4</sup>; however, the 5-year risk of melanoma relapse was estimated at 68% for stage IIIB and 89% for stage IIIC<sup>5</sup>
- According to the main guidelines, to reduce the risk of relapse, stage III-IV patients are candidates for adjuvant treatment after complete surgical excision<sup>3,4</sup>
- Nivolumab, a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), has been recently approved as monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection<sup>6</sup>

## Objective

- This study aimed to assess the incremental cost-utility ratio (ICUR) of nivolumab for the adjuvant treatment of adults with melanoma stage III-IV who have undergone complete resection compared to observation, ipilimumab and high-dose interferon (HDI) in Spain

## Methods

- A partitioned survival model comprising recurrence-free, post-recurrence and death was used to estimate in 28-day cycles, the lifetime accumulated cost and benefits in terms of quality-adjusted life years (QALYs)
- Recurrence-free survival (RFS) curves for nivolumab and ipilimumab derived from CheckMate 238<sup>7</sup>. RFS for observation was estimated from an indirect treatment comparison of CheckMate 238<sup>7</sup> and CA184-029<sup>8</sup>
- A network meta-analysis (NMA) including 24 randomized control trials was used to estimate RFS and overall survival (OS) for HDI
- OS for nivolumab was derived from a correlation equation given the RFS data. For observation and ipilimumab, OS data were taken from CA184-029<sup>8</sup>
- QALYs were estimated using utility values derived from EQ-5D data obtained in CheckMate-238<sup>7</sup>. Utility decrements<sup>9</sup> associated to immune related disorders, diarrhea and other adverse event were applied
- Subsequent treatments according to recurrence type and adjuvant treatment received were considered, apart from ipilimumab (due to insufficient information, representing a conservative scenario for nivolumab given the lower total cost associated to ipilimumab arm).
- The analysis was performed from the Spanish National Health System perspective
- The total costs (€, 2019) included drug acquisition cost (ex-factory prices<sup>10</sup> with mandatory deduction applied<sup>11</sup>) and intravenous administration of adjuvant and subsequent treatments, health-state disease-management and end-of-life costs (Table 1)
- Healthcare resource consumption and treatment pattern for subsequent therapies were defined by oncologists
- Unitary costs derived from local cost databases<sup>10,12</sup>
- A 3% annual discount rate was applied for cost and outcomes<sup>13</sup>
- Probabilistic sensitivity analyses (PSA) were performed

Table 1. Costs (€, 2019)

Drugs	Dosage	Cost per treatment cycle*	Subsequent treatment cost (one-off cost)	
			Local/regional recurrence	Distant recurrence
Nivolumab	3 mg/kg IV every 2 weeks for a maximum of 12 months	€2,768.06	€19,185.66	€130,299.37
Ipilimumab	10 mg/kg IV every 3 weeks for 4 doses, then every 12 weeks up to 1 year	€5,503.75	€0.00	€0.00
HDI	Induction: 20 MIU/m <sup>2</sup> /day IV, 5 days/week for 4 weeks Maintenance: 10 MIU/m <sup>2</sup> /day SC, 3 days/week for 48 weeks	Induction: €1,318.90 Maintenance: €659.40	€63,029.00	€114,286.91
Health states	Year 1	Year 2	Year 3-5	Year 5+
Recurrence-free	€1,163.31	€1,163.31	€762.84	€199.49
Unresectable local/regional recurrence	€3,089.09	€3,089.09	€3,089.09	€3,089.09
Resectable local/regional recurrence	€1,163.31	€1,163.31	€762.84	€199.49
Distant recurrence	€3,089.09	€3,089.09	€3,089.09	€3,089.09
End-of-life	€3,284.53	-	-	-

\*Ex-factory prices<sup>10</sup> with mandatory deduction applied<sup>11</sup>  
HDI, High-dose interferon; IV, Intravenous; MIU, Million international unit; SC, Subcutaneous

## Results

- Nivolumab provided higher QALYs than observation (3.68 additional QALYs), ipilimumab (2.10 additional QALYs), and HDI (3.17 additional QALYs) (Table 2)
- The lifetime total costs per patient accounted €143,051 with nivolumab, versus €98,663 with observation, €246,943 with ipilimumab and €134,621 with HDI (Table 2)
- Nivolumab resulted a dominant option compared to ipilimumab (Table 2)
- The ICUR was €12,052/QALY gained with nivolumab versus observation, and €2,653/QALY versus HDI (Table 2)
- In the PSA, 97% (vs observation) and 100% (vs ipilimumab and HDI) of the 1,000 simulations performed were below a €20,000/QALY gained willingness-to-pay-threshold<sup>14</sup> (Figure 1, Figure 2 and Figure 3)

Table 2. Base case results

	Nivolumab	Observation	Ipilimumab	HDI
Life years gained (LYG)	13.64	9.38	11.24	9.95
QALYs	11.38	7.70	9.28	8.21
<b>Total costs</b>	<b>€143,050.90</b>	<b>€98,662.60</b>	<b>€246,942.83</b>	<b>€134,621.48</b>
Acquisition costs	€54,338.54	€0.00	€226,346.27	€6,316.03
Administration costs	€8,404.81	€0.00	€1,760.80	€33,848.27
Monitoring costs	€15,915.61	€15,416.30	€16,605.98	€14,740.65
Subsequent treatment costs	€62,398.97	€80,831.98	€0.00	€77,358.83
End-of-life costs	€1,992.97	€2,414.32	€2,229.78	€2,357.70
<b>ICUR (€/QALY) nivolumab vs.</b>	<b>-</b>	<b>€12,051.81/QALY</b>	<b>Dominant</b>	<b>€2,652.91/QALY</b>

HDI, High-dose interferon; ICUR, Incremental cost-utility ratio; QALY, Quality-adjusted life year

Figure 1. Probabilistic sensitivity analyses results – Nivolumab vs observation

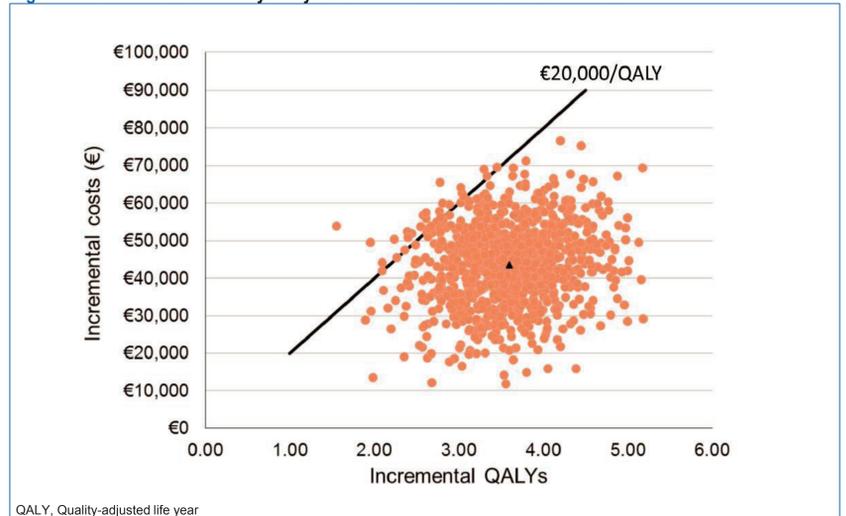


Figure 2. Probabilistic sensitivity analyses results – Nivolumab vs ipilimumab

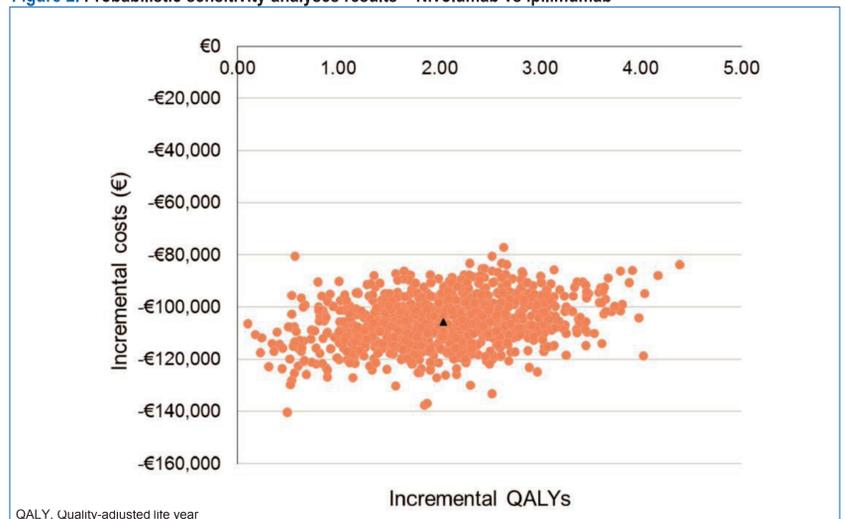
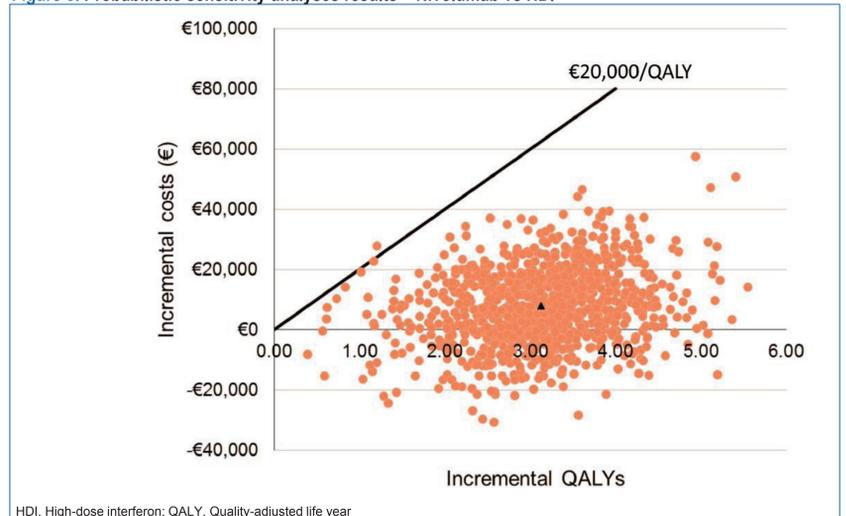


Figure 3. Probabilistic sensitivity analyses results – Nivolumab vs HDI



## Conclusions

- Nivolumab is a cost-effective option versus observation and HDI and a dominant option compared to ipilimumab for the adjuvant treatment of resected stage III-IV melanoma in Spain

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