NIVOLUMAB FLAT DOSE, CLINICAL-ETHICAL AND ECONOMIC IMPLICATIONS

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Background
In Italy, on 2nd of May 2018, was approved the use of nivolumab (Opdivo) in monotherapy in the 240 mg dose every two weeks to replace the weight based dosage (3 mg/kg) for all approved indications (melanoma, non-small cell lung cancer -NSCLC-, renal cell carcinoma -RCC- ) and a dose of 480 mg every four weeks (melanoma and RCC). The dosage change was based on pharmacokinetic data that showing good safety up to a dose of 10 mg/kg. The previous dosage was defined OFF-LABEL.

Purpose
The purpose of this estimation is to evaluate any change in the drug-related adverse (ADR) events and any additional costs after the transition to the FLAT-DOSE.

Materials & methods
We collected data from the National Pharmacovigilance Network (NPN) from the 2nd of May to 15th October in the years 2016, 2017 and 2018. The number of reported ADRs and the percentage of severe ADR has been compared (deaths were not considered). For the estimation of costs we considered all patients who received nivolumab treatment from 2016. For the naive patients after the 2nd of May, the dose was calculated with the old scheme of 3 mg/kg. For patients who have already discontinued therapy the dose difference was calculated with the flat-dose. The price ex-factory per mg was € 13,44.

Results
The reported ADRs in NPN were respectively: 174 (35,1% serious), 192 (34,4% serious) and 175 (58,3% serious). For the estimation of costs, was measured an average increase of 35,3 mg for a single administration, corresponding to an increase of € 474,43.

Conclusion
Since the flat-dose was calculated on a hypothetical patient weighing of 80kg, it was easy to view a rapid increase in direct costs related to the drug (11 out of 15 of the patients considered had lower weight). Despite the bias related to the applied methodology, it is possible to think that the costs associated with nivolumab will increase. Furthermore, it is not clear why the 3 mg/kg dosage is to be considered off-label. Furthermore, it is interesting to note that the number of serious ADRs has increased. However, pharmacovigilance monitoring is required to evaluate changes in the safety profile.

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