A microsimulation model to assess the economic impact of immunotherapy in non-small cell lung cancer

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ABSTRACT

Introduction: Immunotherapy has become the standard of care in advanced non-small cell lung cancer (NSCLC). We aimed to quantify the economic impact, in France, of anti-PD-1 therapy for NSCLC.

Methods: We used patient-level data from the national ESCAP-2011-CPHG cohort study to estimate time to treatment failure and mean cost per patient for the four label indications approved by the European Medicines Agency (EMA) for NSCLC in May 2018. To compute the budget impact, we used a microsimulation model to estimate the target populations of anti-PD-1 therapy over a 3-year period, which were combined with the annual cost of treatment.

Results: Overall, 11,839 patients with NSCLC were estimated to be eligible for anti-PD-1 therapy 3 years after the introduction of anti-PD-1 therapies. The mean annual cost per patient in the control group ranged from €2,671 (95% CI €2,149–3,194) to €6,412 (95% CI €5,920–6,903) across the four indications. The mean annual cost of treatment for the four EMA-approved indications of anti-PD-1 therapy was estimated to be €48.7 million in the control group and at €421.8 million in the immunotherapy group. The overall budget impact in 2019 is expected to amount to €373.1 million. In the sensitivity analysis, flat doses and treatment effect had the greatest influence on the budget impact.

Conclusion: Anti-PD-1 agents for NSCLC treatment are associated with a substantial economic burden.

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Introduction

Lung cancer is the second most common and deadliest cancer in France, with 50,000 new cases (French national hospital discharge database) and >30,000 deaths per year. The 1-year overall survival rate remains poor, with an estimate of ∼40% [1, 2].

Recent improvements in therapeutics have involved immunotherapy, namely anti-PD-1 agents, immune checkpoint blockade targeting PD-1. In May 2018, nivolumab and pembrolizumab were the first two anti-PD-1 drugs to be approved by the European Medicines Agency (EMA) for the treatment of advanced non-small cell lung cancer (NSCLC). These treatments radically changed the pathway of care for patients suffering from NSCLC, extending overall survival, whether as first [3] or second [4–6] line therapy. Since 2016, anti-PD-1 agents have become the new standard of care for patients with advanced NSCLC that have progressed during or after platinum-based chemotherapy.

However, these new agents are extremely expensive [7–10], and nationwide data on budget impact are scarce. We identified only one study that showed 105 NSCLC patients per year would be eligible for anti-PD-1 treatment in Norway, with an annual budget impact amounting to €5 million [11]. However, only 2500 new NSCLC cases are diagnosed each year in Norway and this study was limited to pembrolizumab as second-line therapy for NSCLC.

Our objectives were to estimate the target population of immunotherapy in France (number of patients eligible for anti-PD-1 treatment), and to assess the budget impact at the national level for the four indications of nivolumab and pembrolizumab in advanced NSCLC, which was approved by the EMA at the time of analysis (May 2018).

Materials and methods

Data sources

We used three data sources. First, the real-world observational KBP-2010-CPHG study, which included all consecutive patients diagnosed with a primary lung cancer during 2010, in 104 general hospitals, located all over the French territory [1, 2]. This is currently the largest cohort of lung cancer patients in France. The ESCAP-2011-CPHG cohort study [12], an ancillary study of the KBP-2010-CPHG study, aimed to collect treatment details, such as regimen and treatment duration, for a subgroup of patients (N=3943 lung cancer patients among whom 2315 had advanced NSCLC) during a 2-year period (2011 and 2012). The study was conducted before the introduction of immunotherapy. The second source of data was the French national hospital discharge database from 2016, which contains all hospital stays in all acute care hospitals in France with International Classification of Diseases (ICD)-10 diagnosis codes for each stay. Finally, a third source of data was used to estimate the treatment effect for each indication (hazard ratio for progression-free survival) and was extracted from the pivotal randomised controlled trials (RCTs) for each indication [3–6].

Target populations of anti-PD-1 agents in NSCLC

Target populations were estimated for nivolumab and pembrolizumab, in treatment for advanced NSCLC, with the four following label indications. Indication 1: pembrolizumab in the first-line setting for metastatic patients with expression of PD-L1 in ≥50% of the tumour cells, not previously treated and EGFR/ALK-negative. Indication 2: pembrolizumab in the second-line setting for grade IIb or IV patients who have progressed after platinum-based chemotherapy and with PD-L1 expression on ≥1% of tumour cells. EGFR/ALK-positive patients should have received a tyrosine kinase inhibitor prior to receiving pembrolizumab. Indication 3: nivolumab in the second-line setting for grade IIb or IV nonsquamous NSCLC patients whose disease progressed during or after platinum-based chemotherapy, with an Eastern Cooperative Oncology Group performance status of 0 or 1. Indication 4: nivolumab in the second-line setting for grade IIb or IV squamous cell NSCLC patients whose disease progressed during or after platinum-based chemotherapy.

In France, the approval for funding in these indications was obtained between December 2016 for nivolumab in squamous cell NSCLC (indication 4) and December 2017 for pembrolizumab in the first-line setting (indication 1).

The target population, NSCLC patients eligible for immunotherapy, for each indication was estimated at the national level for 2016 using the French national hospital discharge database, ESCAP-2011-CPHG cohort study, and Keynote-024 and Keynote-010 trials (figure 1 and table 1). From the French national hospital discharge database, we selected all patients hospitalized for primary lung cancer (ICD-10 diagnosis code C34) in 2016, without prior hospitalisation for lung cancer in the two previous years. The population eligible for anti-PD-1 treatment was selected using a treatment decision algorithm based on drug labelling and routine use. We assumed that immunotherapy was introduced, for each indication, as
soon as possible in the course of treatment of advanced NSCLC patients eligible for immunotherapy treatment. A patient who received anti-PD-1 treatment was not eligible for a subsequent line of immunotherapy. All criteria used by our algorithm were defined by the treatment indications of each drug as described in figure 1. We assumed an overall rate of 5% of contraindications (immune diseases etc.) to immunotherapy treatment [13].

To estimate target populations of immunotherapy over a 3-year time period, we performed a microsimulation analysis using patient-level data from the ESCAP-2011-CPHG cohort study. Time to treatment failure (TTF) was used as a proxy for treatment duration as performed by GOLDSTEIN et al. [14] due to the short life expectancy of these patients. TTF was estimated for the four indications of immunotherapy for advanced NSCLC patients who did not receive immunotherapy. TTF was defined as the time from the chemotherapy start date until treatment discontinuation or last follow-up, using the Kaplan–Meier method. The event was discontinuation of chemotherapy for any reason including progression or death. For each indication, a hypothetical cohort of patients not treated by immunotherapy (control group) was randomly drawn from the ESCAP-2011-CPHG study data with a sample size equal to the target population in France (figure 2). For each indication, TTF was estimated in the control group using an exponential survival function. TTF in the immunotherapy group was estimated by combining TTFs in the control group and the hazard ratios (HRs) for progression-free survival reported in the pivotal RCTs [3–6]. We assumed that the HR for TTF was equal to the HR for progression-free survival. Annual target populations over a 3-year period were then estimated from the simulated data.

FIGURE 1 Target populations for the four European Medicines Agency-approved indications of anti-PD-1 therapy for non-small cell lung cancer (NSCLC) in France in 2016. TPS: tumour promotion score; ECOG: Eastern Cooperative Oncology Group. Data source: #: French national hospital administrative database, 2016; ¶: ESCAP-2011-CPHG study; #: French Health Authority; §: Keynote-024 and Keynote-010 trials.
Cost of treatments

Costs (drug costs and administration costs) were assessed from the French national health insurance perspective. We estimated the mean cost per patient and per year for each indication in both groups. In the control group, the cost of treatment was estimated by using treatment details in the ESCAP-2011-CPHG cohort study until treatment failure, selecting four populations corresponding to the four indications of immunotherapy. In the control group, most drugs administered at the hospital, mostly third-generation platinum-based regimens, were covered by the diagnosis-related group (DRG) price. Administrative costs are included in the DRG price, which covers medical charges, drugs and procedures but also overheads, which account for ~25% of the DRG cost (innovative expensive drugs excluded) for DRG 28Z07Z. In our data, the only drugs paid in addition to DRGs were bevacizumab (€2.21 per mg, 7.5 mg·kg\(^{-1}\) every 3 weeks) and pemetrexed (€1.20 per mg, 500 mg·m\(^{-2}\) every 3 weeks). The prices of oral drugs were extracted from the French national health insurance database. In France, systemic intravenous therapies, as well as immunotherapies, are administered in day hospitals (outpatient). In the immunotherapy group, for each anti-PD-1 agent, we used the mean TTF to estimate the mean number of injections (nivolumab at 3 mg·kg\(^{-1}\) every 2 weeks and pembrolizumab 200 mg every 3 weeks for indication 1, and 2 mg·kg\(^{-1}\) every 3 weeks for indication 2). Unit prices were €10.58 per mg and €26.84 per mg for nivolumab and pembrolizumab respectively [15].

Budget impact

Budget impact analysis was conducted following the framework proposed by the International Society for Pharmacoeconomics and Outcomes Research 2012 Budget Impact Analysis Good Practice II Task Force [16]. Budget impact was estimated from the French national health insurance perspective. For each indication, the annual target population was combined with the cost of treatment per year to compute the budget impact (cost difference between immunotherapy group and control group), per year, and over a 3-year period to comply with the guidelines from the French National Authority for Health. A one-way

### Table 1: Patient characteristics for the populations selected from the ESCAP-2011-CPHG study that fit the European Medicines Agency-approved indications of anti-PD-1 therapy for non-small cell lung cancer

| Indication | Indication 1 | Indication 2 | Indication 3 | Indication 4 |
|------------|-------------|-------------|-------------|-------------|
| Patients n | 631         | 407         | 203         | 105         |
| Men        | 502 (79.56%)| 307 (75.43%)| 149 (73.4%) | 93 (88.57%) |
| Age years mean (95% CI) | 63.0 (62.2–63.9) | 61.0 (60.0–61.9) | 59.7 (58.3–61.1) | 63.7 (61.9–65.6) |
| Performance status |              |              |              |              |
| 0          | 177 (28.05%)| 162 (39.8%)  | 83 (40.89%) | 37 (35.24%) |
| 1          | 454 (71.95%)| 245 (60.2%)  | 120 (59.11%)| 68 (64.76%) |
| Histology  |              |              |              |              |
| Squamous   | 157 (24.88%)| 105 (25.8%)  |              | 105 (100%)  |
| Adenocarcinoma | 348 (55.15%)| 236 (57.99%)| 146 (71.92%)|              |
| Large cell | 98 (15.53%) | 56 (13.76%)  | 48 (23.65%) |              |
| Bronchioloalveolar | 6 (0.95%) | 1 (0.25%) | 1 (0.49%) |              |
| Others     | 15 (2.38%)  | 7 (1.72%)    | 6 (2.96%)   |              |
| Composite  | 7 (1.11%)   | 2 (0.49%)    | 2 (0.99%)   |              |
| First-line therapy |              |              |              |              |
| Platinum-based combination | 524 (83.04%) | 337 (82.8%) | 166 (81.77%)| 100 (95.24%) |
| Other combination | 62 (9.83%)  | 45 (11.06%)  | 34 (16.75%) | 1 (0.95%)   |
| Monotherapy | 43 (6.81%)  | 8 (1.97%)    | 3 (1.48%)   | 3 (2.86%)   |
| Targeted therapy | 2 (0.32%)   | 17 (4.18%)   |              | 1 (0.95%)   |
| Second-line therapy |              |              |              |              |
| Monotherapy | 190 (30.11%)| 327 (80.34%)| 170 (83.74%)| 87 (82.86%) |
| Platinum-based combination | 31 (4.91%)  | 70 (17.2%)   | 25 (12.32%) | 18 (17.14%) |
| Other combination | 8 (1.27%)   | 10 (2.46%)   | 8 (3.94%)   |              |
| No treatment | 402 (63.71%)|              |              |              |
| OS months median (IQR) | 6.4 (5.9–7.2) | 5.9 (5.2–6.8) | 4.3 [3.9–5.2] | 5.8 [3.9–7.4] |
| TTF months median (IQR) | 3.3 (3.05–3.5) | 2.7 [2.4–3.0] | 2.5 [2.2–3.0] | 2.4 [2.3–3.0] |

Data are presented as n (%), unless otherwise stated. Indication 1: pembrolizumab first-line therapy; indication 2: pembrolizumab second-line therapy; indication 3: nivolumab for nonsquamous non-small cell lung cancer (NSCLC); indication 4: nivolumab for squamous NSCLC. OS: overall survival; IQR: interquartile range; TTF: time to treatment failure.
sensitivity analysis was performed to identify the variables with the largest effect on the budget impact of immunotherapy. The following parameters were varied: the price of anti-PD-1 agents (flat doses and a variation of ±10% in drug price), the cost of the immunotherapy line of ±10% (to reflect a variation in treatment duration more than a price effect), the treatment effect (HRs were varied in between the lower and upper confidence intervals limits issued from the pivotal clinical trials), the cost of treatment in the control group (no additional payment for pemetrexed) and the number of incident cases of lung cancer in France (±5%).

All statistical analyses were performed using SAS (SAS Institute, Cary, NC, USA; version 9.4).

**Results**

**Target populations**

Patient characteristics selected from the ESCAP-2011-CPHG cohort study for each of the four EMA-approved indications of anti-PD-1 therapy, for advanced NSCLC, are shown in table 1. The median overall survival ranged between 4.3 months (interquartile range (IQR) 3.9–5.2 months) for indication 3 (advanced squamous NSCLC in second line) and 6.4 months (IQR 5.9–7.2 months) for indication 1 (advanced NSCLC in first line). Most of the patients had received platinum-based combination as first-line therapy. The decision algorithm applied to the number of incident lung cancer cases in France (±5%).

All statistical analyses were performed using SAS (SAS Institute, Cary, NC, USA; version 9.4).

![FIGURE 2 Time to treatment failure (TTF): a) indication 1, pembrolizumab first-line therapy; b) indication 2, pembrolizumab second-line therapy; c) indication 3, nivolumab for nonsquamous non-small cell lung cancer (NSCLC); d) indication 4, nivolumab for squamous NSCLC. The numbers within the graphs for the control and treatment groups are the number of patients at risk.](https://doi.org/10.1183/23120541.00174-2019)
Overall, 9939 NSCLC patients were estimated to be eligible to receive anti-PD-1 treatment according to the four indications approved by EMA in May 2018. TTF for the simulated cohorts of patients, both in the control group and in the immunotherapy group, are shown in figure 2. The mean treatment duration across the four indications varied from 3.13 months (95% CI 2.94–3.32 months) to 4.17 months (95% CI 4.04–4.31 months) in the control group and from 3.75 months (95% CI 3.63–3.87 months) to 6.61 months (95% CI 6.42–6.77 months) in the immunotherapy group (table 2).

Combining target populations in 2016 with the estimated mean duration of treatment under immunotherapy (table 2), we estimated the target population at 3 years to be 3772 for indication 1, 3876 for indication 2, 3146 for indication 3 and 1045 for indication 4. Overall, 11 839 patients with NSCLC were estimated to be under treatment with anti-PD-1 therapy 3 years after routine use of these drugs (table 2).

Cost of treatments and budget impact
In the ESCAP-2011-CPHG cohort study, >80% of the patients received platinum-based chemotherapy combined with a third-generation chemotherapy agent (supplementary tables 1–4). The mean annual cost per patient in the control group was estimated to be €6412 (95% CI €5920–6903) for indication 1, €3914 (95% CI €3463–4364) for indication 2, €4409 (95% CI €3669–5150) for indication 3 and €2671 (95% CI €2149–3194) for indication 4 (table 2). Detailed data for each subgroup of patients can be found in the supplementary data. Overall, the mean annual cost of treatment for the four EMA-approved indications of anti-PD-1 therapy in NSCLC was estimated to be €48.7 million in the control group and €421.8 million in the immunotherapy group. The budget impact in 2019, 3 years after the introduction of anti-PD-1 therapies in routine use is expected to amount to €373.1 million (table 2 and figure 3). Sensitivity analysis showed that flat doses and treatment effect had the greatest influence on the budget impact (figure 4).

Discussion
This is the first study to estimate the budget impact of immune therapies for the four EMA-approved indications reimbursed in France in NSCLC at the time of our analysis. The overall budget impact of anti-PD-1 therapies 3 years after their introduction into routine use would amount to €373.1 million per year for a target population of 11 839 patients. However, immunotherapy therapies have been shown to improve overall survival and quality of life of patients. Therefore, indirect costs might be reduced through a lower burden on informal caregivers and return to work for some patients.

### TABLE 2 Treatment duration, cost per patient and budget impact for the four European Medicines Agency-approved indications of anti-PD-1 therapy for non-small cell lung cancer

| Treatment duration in ESCAP-2011-CPHG study months mean (95% CI) | Treatment duration in simulations months mean (95% CI) | Targeted population in 2019# | Annual cost per patient from ESCAP-2011-CPHG study € mean (95% CI) | Annual¶ cost for target population in 2019 € millions | Annual budget impact in 2019 € millions |
|---|---|---|---|---|---|
| **Control group** | | | | | |
| Indication 1 | 4.07 (3.82–4.32) | 4.17 (4.04–4.31) | 3015 | 6412 (5920–6903) | 19.3 |
| Indication 2 | 3.45 (3.17–3.73) | 3.39 (3.29–3.49) | 3357 | 3914 (3463–4264) | 13.1 |
| Indication 3 | 3.44 (3.01–3.88) | 3.49 (3.38–3.60) | 3103 | 4409 (3669–5150) | 13.7 |
| Indication 4 | 3.27 (2.77–3.77) | 3.13 (2.94–3.32) | 954 | 2671 (2149–3194) | 2.5 |
| All 4 indications | | | 10429 | | 48.7 |
| **Immunotherapy group** | | | | | |
| Indication 1 | 6.61 (6.4–6.77) | 3772 | 54 993 (53 672–56 314) | 207.4 | 188.1 |
| Indication 2 | 5.44 (5.30–5.58) | 3876 | 32 642 (31 805–33 479) | 126.5 | 113.4 |
| Indication 3 | 3.75 (3.63–3.87) | 3146 | 19 796 (19 165–20 427) | 62.3 | 48.6 |
| Indication 4 | 4.63 (4.38–4.88) | 1045 | 24 471 (23 167–25 776) | 25.6 | 23.0 |
| All 4 indications | | | 11 839 | | 421.8 |

Indication 1: pembrolizumab first-line therapy; indication 2: pembrolizumab second-line therapy; indication 3: nivolumab for nonsquamous non-small cell lung cancer (NSCLC); indication 4: nivolumab for squamous NSCLC. #: number of patients eligible for immunotherapy; ¶: treatment durations are truncated at 12 months to estimate the annual cost budget impact.

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Our results are consistent with the study by Norum et al. [11], who estimated the annual budget impact in Norway to be €5 million for 105 NSCLC patients treated with pembrolizumab as a second-line therapy. Our results are also consistent with the IFCT-1502 CLINIVO study [17] that collected data for 902 patients treated with nivolumab in France in 2015 before EMA approval (temporary authorisation for use), which are real-life data. In the CLINIVO study, the median treatment duration was 2.4 months, the median overall survival was 9.9 months (95% CI 9.1 – 11.3 months) and the median progression-free survival was 2.0 months (95% CI 1.9 – 2.2 months). This highlights the importance of real-world data to complement RCT data, which provide an unbiased estimation of treatment effect but are likely to provide better outcomes due to patient selection. The low cost per patient per year for each treatment line based on real-world data is driven by a shorter duration of treatment lines in real-life data compared to RCTs. Indeed, most of the clinical research studies are developed in academic hospitals, which do not represent the average health system in France, with specifically selected patients.

Our work has several strengths. First, we performed a comprehensive analysis of the budget impact of the four EMA-approved indications for anti-PD-1 therapy in NSCLC, a high-volume disease. Second, we used

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**FIGURE 3** Annual budget impact of anti-PD-1 therapies for non-small cell lung cancer (NSCLC) for the years 2016 and 2019. Indication 1: pembrolizumab first-line therapy; indication 2: pembrolizumab second-line therapy; indication 3: nivolumab for nonsquamous NSCLC; indication 4: nivolumab for squamous NSCLC.

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**FIGURE 4** Tornado diagram showing one-way sensitivity analysis for variables with the largest impact on the budget impact of anti-PD-1 therapies for advanced non-small cell lung cancer over a 3-year period. CI: confidence interval; HR: hazard ratio.
patient-level data from a national observational study, which is representative of lung cancer patients treated in local hospitals, the main hospital care providers in France for NSCLC [18]. These datasets are recognised as reference real-world data in France. These data were used in all regulatory dossiers for the reimbursement of immunotherapies in lung indications as well as cost-effectiveness appraisal. These real-world data show survival estimates lower than in RCTs for the control group, with a median overall survival ranging from 4.3 months (95% CI 3.9–5.2 months) in second-line therapy for nonsquamous NSCLC to 6.4 months (95% CI 5.9–7.2 months) in first-line therapy versus 9.4 months (95% CI 8.1–10.7 months) to ~8.5 months in second-line RCTs [4–6] and not reached in first line [3]. However, our data are consistent with other worldwide, real-world data [19–22]. Third, we used microsimulation, an innovative method, to combine real-world data from the ESCAP-2011-CPHG cohort study [12] with unbiased estimates of treatment effects from RCTs. This was a multidisciplinary work with close collaborations between clinicians, statisticians and health economists allowing the selection of relevant groups of patients from the ESCAP-2011-CPHG cohort study as primary data to simulate a target population for anti-PD-1 therapies (but did not actually receive immunotherapy) in each indication at the national level. To our knowledge, this study is the first of its kind, and provides a methodological framework for evaluating target populations and budget impact at the national level.

However, our study also has some limitations. It is a modelling exercise involving several hypotheses and performed at a given point in time. Recent changes in indications are likely to modify the budget impact estimated in our study. First, the association of the cisplatin-based regimen with pembrolizumab has been approved by the US Food and Drug Administration (FDA) for all grade IV NSCLC patients as first-line therapy as of June 2018. Other indications were also recently approved by the FDA, such as nivolumab plus ipilimumab in patients with high tumour mutational burden and atezolizumab for second-line therapy. However, these indications are not yet approved for reimbursement in France and in other European countries. Second, changes in the price of anti-PD-1 agents are also expected with the availability of flat doses (price increase) and future price negotiation (price cut) with the increase in volumes. We attempted to address the two latter issues in the sensitivity analysis.

In conclusion, we provided the budget impact, in France, of immune therapies for NSCLC, the cancer site with the highest volume of patients among all the indications of immunotherapy. Anti-PD-1 agents for treatment of advanced NSCLC are associated with a substantial economic burden.
References

1. Debievre D, Locher C, Neidhardt A-C, et al. Évolution en 10 ans du cancer bronchique non à petites cellules en fonction du sexe. Résultats de l’étude KKP-2010-CPHG du Collège des pneumologues des hôpitaux généraux. [Ten-year evolution in non-small-cell lung cancer according to sex. Results of the KKP-2010-CPHG study by the College of General Hospital Respiratory Physicians.] Rev Mal Respir 2014; 31: 805–816.

2. Debievre D, Oster J-P, Riou R, et al. The new face of non-small-cell lung cancer in men: results of two French prospective epidemiological studies conducted 10 years apart. Lung Cancer Amst Neth 2016; 91: 1–6.

3. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016; 375: 1823–1833.

4. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015; 373: 123–135.

5. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015; 373: 1627–1639.

6. Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016; 387: 1540–1550.

7. National Institute for Health and Care Excellence. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer. www.nice.org.uk/guidance/ta483. Date last accessed: November 10, 2018.

8. National Institute for Health and Care Excellence. Pembrolizumab for treating PD-L1-negative non-small-cell lung cancer. www.nice.org.uk/guidance/ta484. Date last accessed: November 10, 2018.

9. National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. www.nice.org.uk/guidance/ta531. Date last accessed: November 10, 2018.

10. National Institute for Health and Care Excellence. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. www.nice.org.uk/guidance/ta428. Date last accessed: November 10, 2018.

11. Norum J, Antonsen MA, Tollåli T, et al. Pembrolizumab as second-line therapy in non-small cell lung cancer in northern Norway: budget impact and expected gain—a model-based analysis. ESMO Open 2017; 2: e000222.

12. Pinquié F, Goupil F, Oster J-P, et al. Stratégies thérapeutiques chez les patients opérés pour un carcinome bronchique non à petites cellules. Résultats de l’étude ESCAP-2011-CPHG réalisée par le Collège des pneumologues des hôpitaux généraux (CPHG). [Therapeutic strategies in patients undergoing surgery for non-small cell lung cancer. Results of the ESCAP-2011-CPHG study, promoted by the French College of General Hospital Respiratory Physicians (CPHG).] Rev Mal Respir 2017; 34: 976–990.

13. Remon J, Hendriks L, Aspeslagh S, et al. Is there room for immune checkpoint inhibitors in patients who have NSCLC with autoimmune diseases? J Thorac Oncol 2019; 14: 1701–1703.

14. Goldstein DA, Gordon N, Davidescu M, et al. A phamacoeconomic analysis of personalized dosing vs fixed dosing of pembrolizumab in firstline PD-L1-positive non-small cell lung cancer. J Natl Cancer Inst 2017; 109: djx063.

15. ATIH. Unités communes de dispensation prises en charge en sus. www.atih.sante.fr/unites-communes-de-dispensation-prises-en-charge-en-sus. Date last accessed: November 10, 2018.

16. Sullivan SD, Maukopf JA, Augustowski F, et al. Budget impact analysis—principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value Health 2014; 17: 5–14.

17. Girard N, Audigier Valette C, Cadranel J, et al. 1302PDIFCT-1502 CLINIVO: real-life experience with nivolumab in 600 patients (pts) with advanced non-small cell lung cancer (NSCLC): efficacy and safety of nivolumab and post-nivolumab treatment in the French Expanded Access Program (EAP). Ann Oncol 2017; 28: Suppl. 5.

18. Chouaid C, Debievre D, Durand-Zaleski I, et al. Survival inequalities in patients with lung cancer in France: a nationwide cohort study (the TERRITOIRE Study). PLoS One 2017; 12: e0182798.

19. Nadler E, Espirito JL, Pavlack M, et al. Treatment patterns and clinical outcomes among metastatic non-small-cell lung cancer patients treated in the community practice setting. Clin Lung Cancer 2018; 19: 360–370.

20. Lunacek OE, Ravelo A, Coutinho AD, et al. First-line treatment with bevacizumab and platinum doublet combination in nonsquamous non-small cell lung cancer: a retrospective cohort study in US oncology community practices. Drugs Real World Outcomes 2016; 3: 333–343.

21. Arunachalam A, Li H, Bittioni MA, et al. Real-world treatment patterns, overall survival, and occurrence and costs of adverse events associated with second-line therapies for medicare patients with advanced non-small-cell lung cancer. Clin Lung Cancer 2018; 19: e783–e799.

22. Davis KL, Goyal RK, Able SL, et al. Real-world treatment patterns and costs in a US Medicare population with metastatic squamous non-small cell lung cancer. Lung Cancer Amst Neth 2015; 87: 176–185.