Public health impact of immunotherapies in advanced cancers in France: a national retrospective estimate until end of 2020

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Introduction

Context

- Cancer is a major public health challenge in many countries. In 2020, the incidence of cancer is estimated to 19.3 million and almost 10.0 million cancer deaths occurred worldwide.[1] In France, each year around 382,000 patients are newly diagnosed with cancer.[2]
- Immune-checkpoint inhibitors (ICIs) have rapidly established as the standard of care in many advanced cancers and strongly modified cancer management.[3,4] Compared to cytotoxic chemotherapies, the previous standard of care, immunotherapies stimulate the immune system to eliminate the tumor allowing better survival benefits.[5] ICIs demonstrated their efficacy in extending survival and improving patients' quality of life in many advanced cancer.[6, 7, 8, 9, 10]
- All new treatments require a health technology assessment (HTA) to inform decisions on reimbursement or pricing. In France, all new treatments that have received marketing authorization are evaluated by the Haute Autorité de Santé (HAS), the National HTA. The assessment is composed of two commissions:
  - The Transparency Commission which evaluates the benefit value and added benefit value of therapies compared to the current therapeutic strategy. The opinions published also present the target population of the treatment
  - The Economic Evaluation and Public Health Commission (called CEESP) which evaluates the methodology of cost-effectiveness (CE) dossiers for therapies claiming a major to moderate added benefit value and with significant expected expenditures. The CE analyses require economic models to quantify the incremental impact of the new intervention on costs and on health outcomes compared to the current standard of care over a lifetime or a specified period

Study rationale

- Clinical trials enable to evaluate the clinical benefit in a small group of patients and survival benefits, in HTA submission, are estimated at indication level
- However, little information is available on survival benefits at the population level of each indication or overall ICIs benefits

Objective

The main objective of this study was to retrospectively estimate the public health impact of immunotherapies compared to their comparators from their introduction in 2014 the until end of 2020 in France. This involves the estimation of LY and QALY gained at a population level. Secondly, we explored the impact of early access in the gains.

Methods

Identification and selection of indications

- Firstly, the HAS website was searched for all published assessments immunotherapies indicated for the treatment of metastatic cancer, assessed by the economic evaluation committee (CEESP) of HAS from inception (2013) until 31st December 2021 (cut-off).[11] Only CE assessment reports including extrapolated curves and without methodological reservation on modelling were retained
- Secondly, Transparency Opinion of the HAS and Official Journal publication were searched to identify if the treatments in the selected indications obtained reimbursement and the date of availability. Only treatments with early access or reimbursement before the end of 2020 were retained. Treatments delisted during the period of follow-up were excluded from the analysis

Data extraction

- In CE assessment reports, the following information was extracted: non-proprietary name of the ICI, extrapolated progression free survival (PFS) and overall survival (OS) curves, extrapolated OS rate at specific landmark, utility for PFS and OS, and comparators on the cost-effectiveness frontier *(Step 1)*
- In Transparency Opinion, benefit value and clinical added value were retrieved to estimate if the treatment was eligible to reimbursement. Then, in the Official Journal, the date of reimbursement ore early access if applicable was extracted to calculate the period of availability in France
- Publications of real-world cohorts, studies or reports based on the French Hospital Medical Information database (*Programme de Médicalisation des Systèmes d'Information* – PMSI) or official documents reporting all patients treated per year were used to estimate the population initiating an immunotherapy. When no information was reported for an incident patient, we applied the prevalent patients if the mean duration of treatment in the clinical trials was inferior to 6 months. If only a global number of patients for multiple indications in a tumor type was available, we applied the target population algorithm from transparency opinion to estimate the target population in each indication

Data analysis

Extrapolated survival curves obtained from French CE assessments were digitized and then plotted in R Studio software ©. *(Step 2)* The accuracy of digitization was validated by comparing it with claimed PFS and OS in CE assessment reports. The number of treated patients estimated per year was divided based on the number of months of availability and the date of the availability for the months. Using this number of patient, we created incident cohorts *(Step 3)*

First objective analyses

- **Probability of deaths avoided**

The survival rate per month was assessed for each immunotherapy evaluated and selected comparators. The difference in survival probability between the immunotherapy and its comparator was calculated per month. The difference was multiplied by the number of incident patients included each month.

- **LY analysis**

The restricted mean survival time per month was assessed for each immunotherapy evaluated and selected comparators. The difference in restricted mean survival time for OS between the treatments was calculated per month. The difference was multiplied by the number of patients included each month.

- **QALY analysis**

The difference in restricted mean survival time between treatment for PFS and OS was calculated per months. Those differences were multiplied by the utility of the specific state. Then they were adjusted based on the discount rate recommended by the HAS (2.5%). These results were then multiplied by the number of patients included each month.

Second objective analyses

For treatment with early access, we simulated the results based of the official date of reimbursement to estimate the share of the early access in the gains.

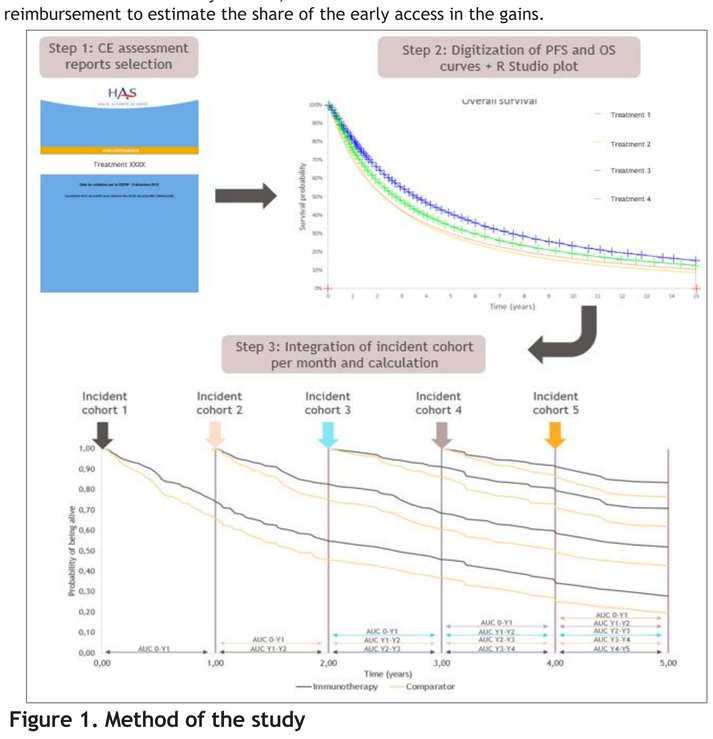
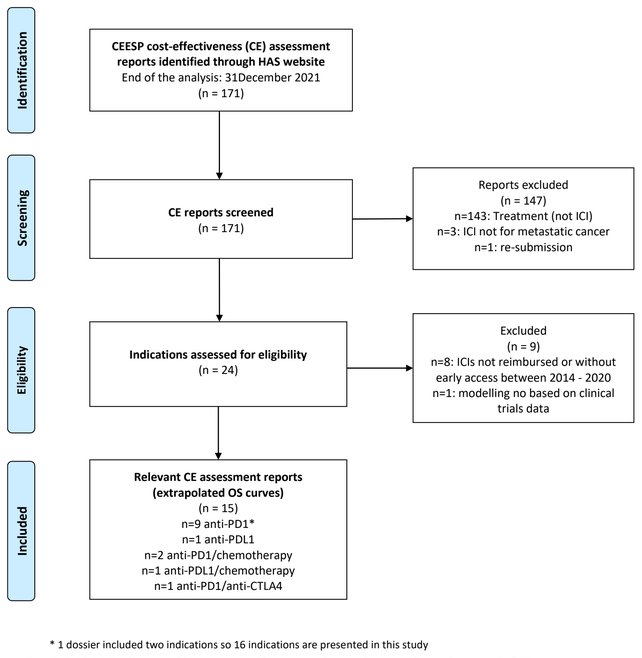


Figure 1. Method of the study

Results - Dossiers identification

- Overall, 171 CE assessment reports were available on the HAS but only 24 were related to immunotherapies in advanced or metastatic cancer. Nine dossier were excluded since they were no reimbursed during in the period nor available in early access or was delisted during the period.
- Fifteen CE assessment reports met the inclusion criteria representing 16 treatment indications. (**Figure 2**)



* 1 dossier included two indications so 16 indications are presented in this study

Figure 2. PRISMA flow diagram illustrating the selection of CE assessment reports

- Of the selected dossiers, 2 were indicated for metastatic melanoma (MEL), 8 for non-small cell lung cancer (NSCLC), 3 for renal cell carcinoma (RCC), 2 squamous cell cancer of head and neck (SCCHN) and 1 for small cell lung cancer (SCLC).
- Early access program concerned 5 out of the 16 indications selected. (**Table 1**)

Table 1. Characteristics of selected case studies

Cancer	Indication	Immunotherapy	Comparator	Early access date	Official reimbursment date	Utility scores used in the CE assessment report	
						PFS	OS
mMelanoma	1st line	Nivolumab	Fotemustine	January 2015	January 2017 (27.12.2018)	0.823	0.729
	1st line	Pembrolizumab	Fotemustine	Mid September 2014	Mid January 2017 (10.01.2017)	0.810	0.680
NSCLC	2nd line squamous a/m	Nivolumab	Docetaxel	May 2015	January 2017 (27.12.2016)	0.723	0.530
	2nd line non squamous a/m	Nivolumab	Docetaxel	June 2015	March 2017 (04.03.2017)	0.743	0.659
	2nd line m	Pembrolizumab	Docetaxel	N.A	Mid-May 2017 (11.05.2017)	0.737	0.628
	2nd line m	Atezolizumab	Docetaxel	N.A	Mid-february 2019 (20.02.2019)	0.7043	0.550
	1st line squamous m (PD-L1 ≥50%)	Pembrolizumab	Platinum based chemotherapy	N.A	December 2017 (06.12.2017)	0.760	0.641
	1st line non squamous m (PD-L1 ≥50%)	Pembrolizumab	Bevacizumab + paclitaxel	N.A	December 2017 (06.12.2017)	0.760	0.641
	1st line non squamous m	Pembrolizumab (+chemotherapy)	Platinum + gemcitabine/vinorelbine	N.A	Mid November 2019 (22.11.2019)	0.720	0.644
	1st line squamous m	Pembrolizumab (+chemotherapy)	Platinum + paclitaxel	N.A	June 2020 (05.06.2020)	0.741	0.618
mRCC	2nd line	Nivolumab	Sorafenib	N.A	January 2017 (27.12.2016)	0.824	0.744
	1st line	Nivolumab (+ ipilimumab)	Pazopanib	N.A	March 2020 (03.03.2020)	0.749	0.687
	1st line	Pembrolizumab (+ axitinib)	Pazopanib	N.A	June 2020 (05.06.2020)	0.7846	0.7529
aSCCHN	2nd line	Nivolumab	Standard treatments	N.A	June 2018 (05.06.2018)	0.743	0.628
	1st line	Pembrolizumab	Platinum + 5-FU + cetuximab	N.A	November 2020 (30.10.2020)	0.764	0.676
mSCLC	1st line	Atezolizumab (+chemotherapy)	Platinum + etoposide	May 2019	N.A	0.7291	0.7118

a: advanced; m: metastatic; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; SCCHN: squamous cell cancer of head and neck; SCLC: small cell lung cancer

Results - Deaths avoided

- Overall, 111,818 patients were treated with an immunotherapy between 2014 and 2020. NSCLC was the most common cancer treated with immunotherapy (68% of patients).
- By the end of 2020, 12,788 deaths were avoided thanks to immunotherapy compared to previous standard of care. (**Figure 3**)
- NSCLC immunotherapy treatment accounted for 71% of deaths avoided, MEL for 14%, RCC and SCCHN for 6% and SCLC for 3%.

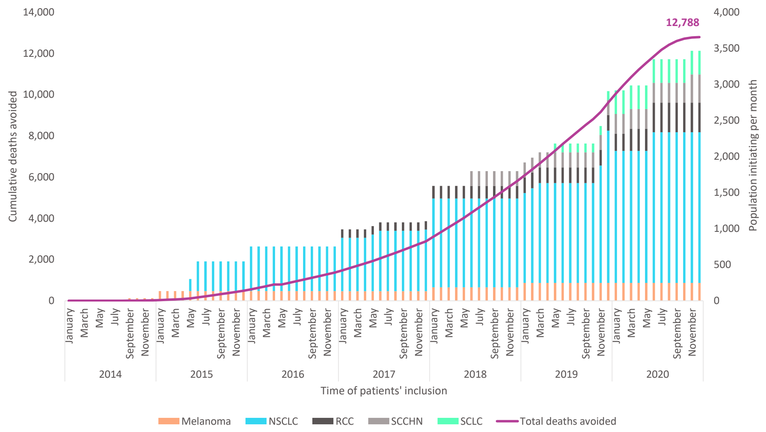


Figure 3 - Cumulative death avoided with immunotherapies and patients treated per indication

Results - Life years

- By the end of 2020, 23,784 LYs were gained thanks to immunotherapy compared to previous standard of care. (**Figure 4**)
- NSCLC accounted for 72% of total LYs gain rate, MEL for 19%, RCC for 5% and SCCHN for 4% and SCLC for 1%. (**Figure 5**)
- Nivolumab was associated with the most gains with 71% of LYs. Pembrolizumab accounted for 27% of LYs gained and atezolizumab for 1%. (**Figure 6**)

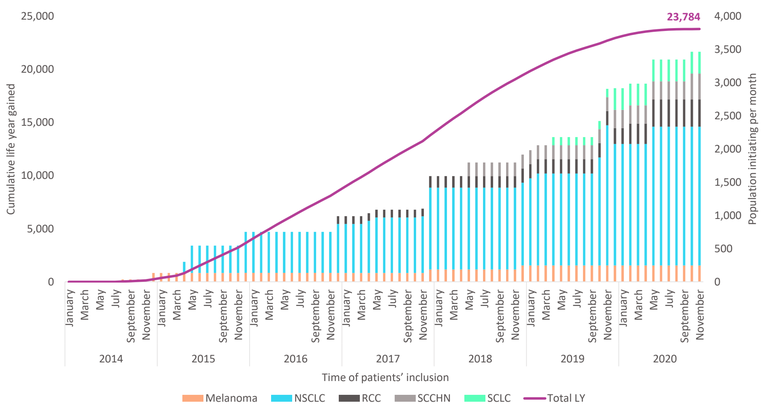


Figure 4 - Cumulative life years gained with immunotherapies and patients treated per indication

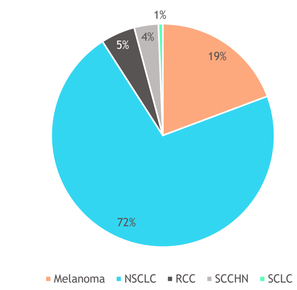


Figure 5 - Share of each tumor type in the LYs gained

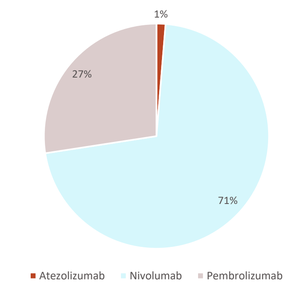


Figure 6 - Share of each treatment in the LYs gained

Results - QALYs

- By the end of 2020, 18,369 QALYs were gained thanks to immunotherapy compared to previous standard of care. (**Figure 7**)

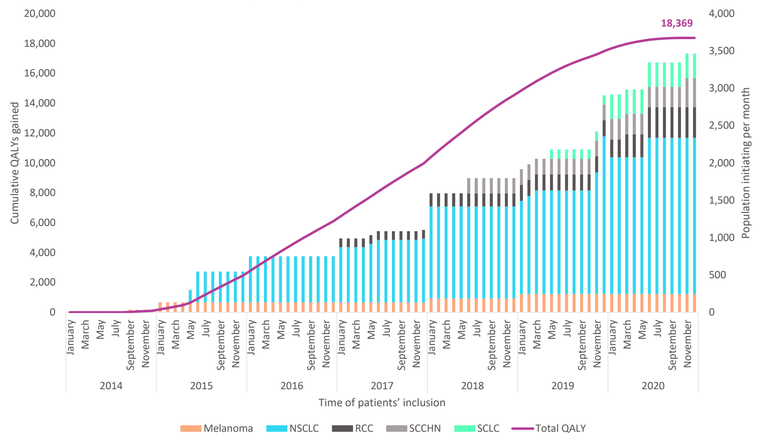


Figure 7 - Cumulative QALYs gained with immunotherapies and patients treated per indication

- NSCLC accounted for 69% of total QALYs gain rate, MEL for 21%, RCC for 6% and SCCHN for 3% and SCLC for 1%. (**Figure 8**)
- Nivolumab was associated with the most gains with 69% of QALYs. Pembrolizumab participated for 30% of QALYs gained and atezolizumab for 1%. (**Figure 9**)

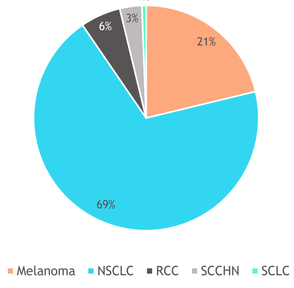


Figure 8 - Share of each tumor type in the QALYs gained

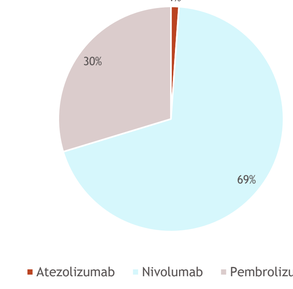


Figure 9 - Share of each treatment in the QALYs gained

Results - Early access share

- By the end of 2020, approximately 18,733 patients initiated an immunotherapy thanks to the early access. For NSCLC, 11,293 patients received an immunotherapy in early access, 3363 for melanoma and 4919 for SCLC.
- Patients who initiated an immunotherapy in early access program represent 36% of overall LYs gained (**Figure 10**) and 35% of overall QALYs gained (**Figure 11**).

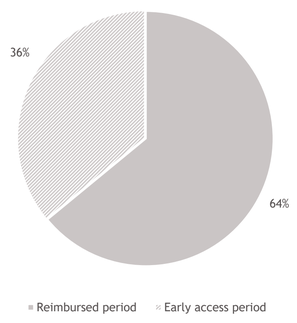


Figure 10 - Share of early access patients in the LYs gained

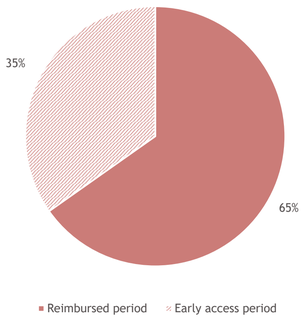


Figure 11 - Share of early access patients in the QALYs gained

Conclusions

- This is the first study evaluating retrospectively the LY and QALY gained owing to immunotherapies at a national population level from 2014 to 2020
- This study underlines significant gains in LYs (n=23,784) and QALYs (n=18,369) with immunotherapies since their introduction and considerable deaths prevented (n=12,788)
  - Non-small cell lung cancer was the tumor type with the most indications and represented more than 70% of the gains due to their larger population treated and the historic market availability
  - Nivolumab, was the largest contributor to gains thanks to its early availability on French market
- Early access, when possible, was a real opportunity for French patient benefit; as patients initiating in early access represent 36% of LYG and 35% of QALYs
- This study presents the minimum gains since the analysis stops in 2020 and does not count gains of new immunotherapies or indications after this date

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Disclosure

- FEC, AFG, and VG are employed by Bristol Myers Squibb.
- IB has no conflicting interests

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