Systematic Review of Cost Effectiveness Assessment Reports of Immune Checkpoint Inhibitors in Early and Advanced/Metastatic Stages of Cancer in France

EE511

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Background

Context

- In France, all new treatments that have received marketing authorization are assessed by the Haute Autorité de Santé (HAS), the national Health Technology Assesment if the company seek for their reimbursement. The assessment is carried out by two commissions:
  - The Commission de la Transparence (CT), which assesses the value of the clinical benefit and the clinical added value of the therapies in relation to the current therapeutic strategy.
  - The Commission d'évaluation économique et de santé publique (CEESP), which assesses the methodology of health economics dossiers for therapies claiming major to moderate clinical added value and whose expected expenditure is significant. The CEESP then publishes a cost-effectiveness assessment report (CEAR). When validated, these CEAR provide decision-making tools for price negotiations between the Comité économique des produits de Santé (CEPS) and the health technology developer (HTD).

- Immune checkpoint inhibitors (ICI) have rapidly become the standard of care in many advanced cancers and have significantly changed the way cancer is managed. Compared to cytotoxic chemotherapies, the previous standard of care, immunotherapies stimulate the immune system to eliminate the tumor allowing better survival benefits [1]. ICI demonstrated their efficacy in extending survival and improving patients' quality of life in many advanced cancer.

- ICI were initially available for advanced/metastatic stages (AMS) of cancer. nivolumab in non-small cell lung cancer was the first ICI CEAR to be validated by the CEESP on December 8, 2015. However, there is a growing trend of making them accessible at earlier stages of cancer (ESOC), since nivolumab was assessed in adjuvant setting on 16th April 2019 for melanoma.

Objective

- The objective of this study was to better understand ICI cost-effectiveness and key structural choices to evaluate them in France based on disease stage (AMS and ESOC).

Methods

Identification and selections of CEAR

- PICO and PRISMA methods were used to identify and report the CEAR of ICI published by the HAS.
- AMS was defined as advanced/metastatic cancer.
- ESOC was defined as local/locally advanced stages.

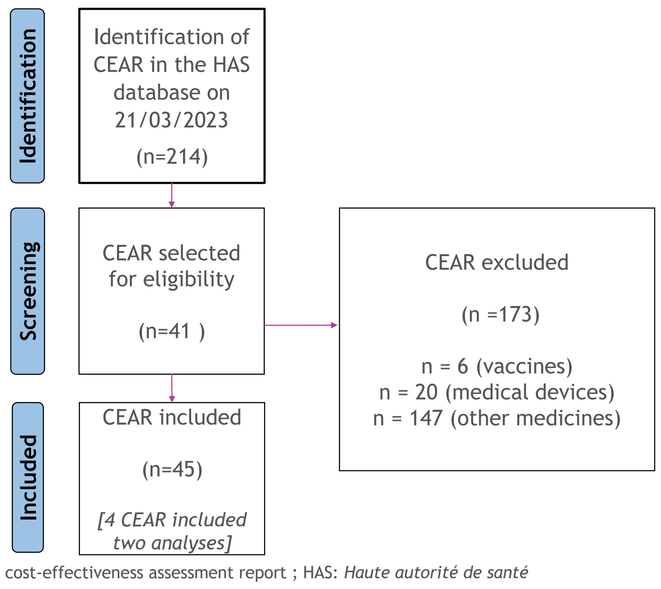
Data extraction

- The following outcomes were extracted depending on AMS and ESOC :
  - Investigational therapy
  - Location of primory tumor
  - Year of CEAR publication
  - Modeling time horizon
  - Type of model
  - Use in monotherapy or in combination
  - Validation of CEAR
  - Number of methodological reservations
  - Average incremental quality-adjusted life years (QALY)
  - Average incremental costs
  - Incremental cost-effectiveness ratio (ICER).

Results

Identification of CEAR

- Overall, 214 CEAR were available on the HAS database and 41 were related to ICI. 4 CEAR included two analyses so 45 CEAR are presented in this study. (Figure 1)



CEAR: cost-effectiveness assessment report ; HAS: *Haute autorité de santé*

Figure 1: Prisma flow diagram illustrating the selection of CEAR

Concerned disease stage among included CEAR

- Of the 45 CEAR selected, 36 (80%) treatments were for AMS and 9 (20%) for ESOC.

Investigational therapy

- The proportions of drugs used in the two disease stages did not vary from one stage to another. However, for now, no published CEAR for Tecentriq® in ESOC was identified.

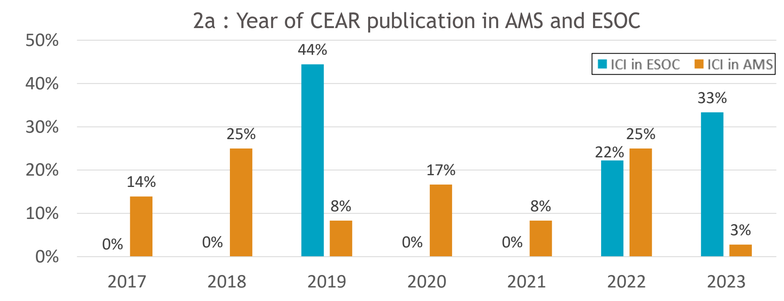
Year of CEAR publication

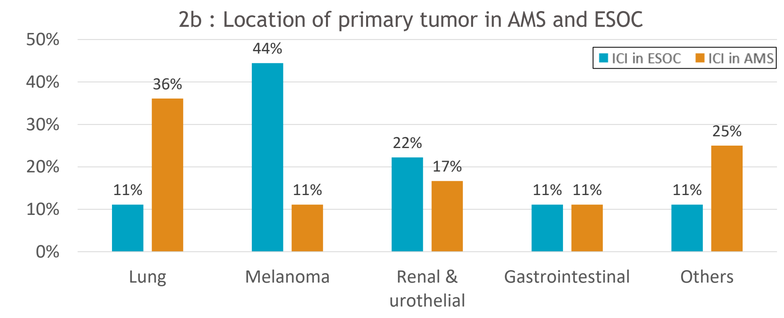
- The breakdown by year shows an increase in ICI assessments in recent years. For the ESOC group, all evaluations took place between 2019 and 2023.

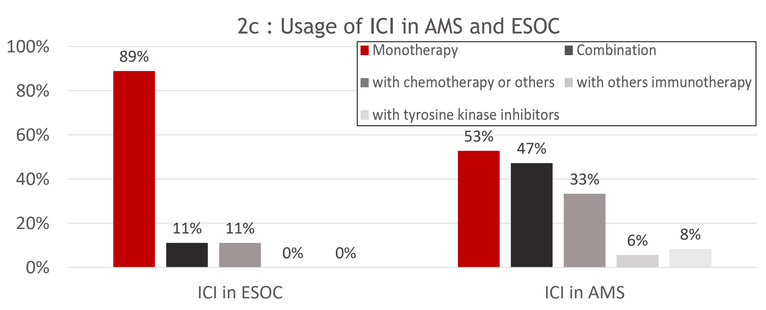
Table 1: Main results CEAR of ICI in advanced/metastatic and early stage of cancer

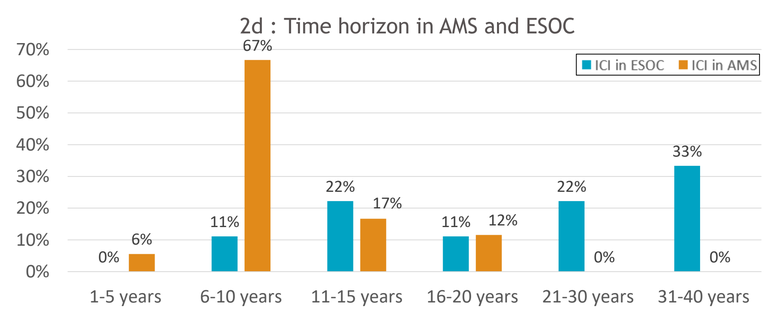
	AMS (n=36)	ESOC (n=9)	Total (n=45)
General characterisics, n (%)			
ICI			
Pembrolizumab	17 (47%)	5 (56%)	22 (49%)
Nivolumab	10 (28%)	3 (33%)	13 (29%)
Atezolizumab	6 (17%)	0 (0%)	6 (13%)
Others	3 (8%)	1 (11%)	4 (9%)
Year of CEAR publication			
2015-2018	14 (39%)	0 (0%)	14 (31%)
2019-2023	22 (61%)	9 (100%)	31 (69%)
Location of primary tumor			
Lung	13 (36%)	1 (11%)	14 (31%)
Melanoma	4 (11%)	4 (45%)	8 (18%)
Renal & urothelial	6 (17%)	2 (22%)	8 (18%)
Others	13 (36%)	2 (22%)	18 (40%)
ICI use in monotherapy or in combination			
Monotherapy	19 (54%)	8 (89%)	27 (60%)
In combination	17 (46%)	1 (11%)	18 (40%)
with others immunotherapy	2 (6%)	0 (0%)	2 (4%)
with tyrosine kinase inhibitors	3 (8%)	0 (0%)	3 (7%)
with chemotherapy or others	12 (33%)	1 (11%)	13 (29%)
Methodology			
Time Horizon			
Time horizon, median	10 years	30 years	10 years
Model type			
Markov like	2 (6%)	8 (89%)	10 (22%)
Area under the curve	34 (94%)	1 (11%)	35 (78%)
CEESP assesment of CEAR			
Validation of CEAR			
Validated	27 (75%)	5 (56%)	32 (71%)
Invalidated	9 (25%)	4 (44%)	13 (29%)
Methodological reservations			
Major reservation, mean	0.3	0.4	0.3
Important reservation, mean	2.3	2.3	2.3
Minor reservation, mean	5.1	4.7	5.0
Cost effectiveness outcomes			
Mean incremental cost, euro	71,580	42,322	65,310
Mean incremental QALY, QALY	0.61	1.18	0.73
ICER, €/QALY gained	117,344	35,866	89,466

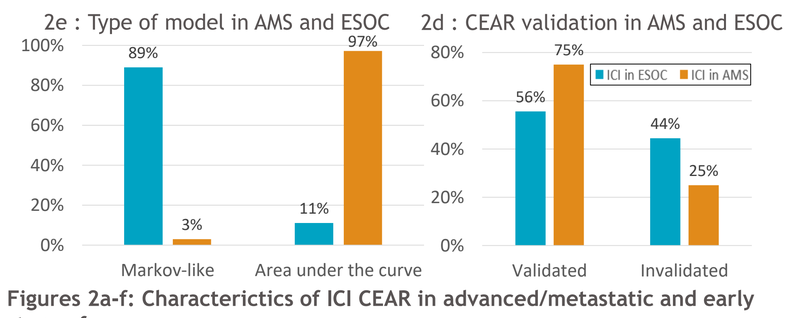
AMS: advanced/metastatic stage; CEAR: cost-effectiveness assessment report; CEESP: *Commission d'évaluation économique et de santé publique;* ESOC: early stage of cancer; ICER: Incremental cost-effectiveness ratio; ICI: Immune checkpoint inhibitors; QALY: quality adjusted life years.











Figures 2a-f: Characterictics of ICI CEAR in advanced/metastatic and early stage of cancer

Monotherapy / Combination therapy

- ICI in AMS are used both in monotherapy and in combination. However, in ESOC, ICI are mainly used as monotherapy. Only one CEAR reports use of ICI in combination for ESOC, it was related to pembrolizumab plus chemotherapy in breast cancer as neoadjuvant treatment, then continued after surgery as monotherapy for adjuvant treatment.

Methodology

Time horizon

- Median time horizon used within CEAR relative to ICI in AMS was 10 years and increased up to 30 years for ICI in ESOC.
- Time horizon ranged from 5 to 20 years for ICI in AMS and from 10 to 40 years in ESOC.

Model type used

- Markov-like model allowing flexibility was preferred for ICI in ESOC.

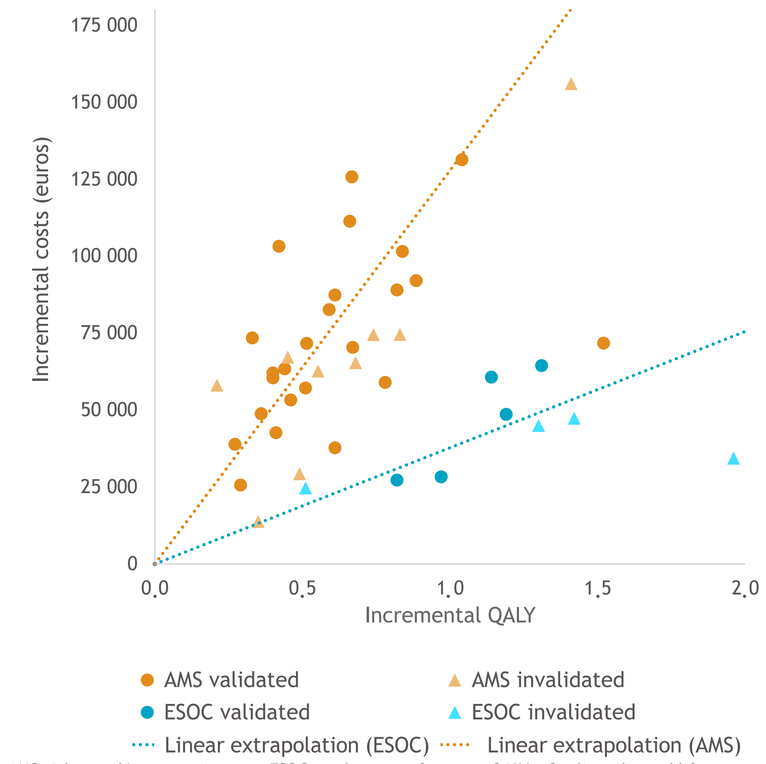
CEESP assesment of CEAR

Validation of CEAR

- CEAR of ICI in AMS were more often validated by CEESP (i.e CEESP did not rise any major reservation and/or did not deem there was too much uncertainty around cost effectiveness analysis) than CEAR relative to ICI in ESOC, with respectively 75% and 56% validation rate.

Mean number of methodological reservations

- There was no difference of average number of reservations raised by CEESP between CEAR of ICI in AMS or in ESOC.



AMS: Advanced/metastatic stage; ESOC: early stage of cancer; QALYs: Quality adjusted life years

Figure 5: Cost effectiveness plan for immune checkpoint inhibitors according to stage of cancer

Cost effectiveness outcomes

- On average, incremental costs for ICI in AMS are around 72 K € for AMS and 42 K € in ESOC.
- Mean incremental QALY generated from ICI in AMS is 0.61 whereas it is 1.18 in ESOC.
- Mean resulting ICER is 117 K €/QALY for ICI in AMS and 36 K €/QALY in ESOC.

Conclusions

- Markov-like models were more used at ESOC than AMS, to overcome the lack of mature data by allowing integration of external data to model overall survival.

- Use of ICI in ESOC showed meaningful reduction of additional costs compared to its use in AMS. Lower costs in ESOC might be explained by ICI limited treatment duration (1-year stopping rule), potential avoidance or delay of more expensive subsequent treatments and more frequent monotherapy use in ESOC.

- ICI in ESOC demonstrated a nearly two-fold higher gain in QALY compared to in AMS. This benefit might be attributed to longer time horizon capturing more health outcomes and to potential for cure in this setting.

- Although structural choices in efficiency analyses of ICI may differ depending on stage of disease, it appears that due to increased incremental QALY and lower incremental costs of ICI at ESOC compared to AMS, this results in a lower favorable ICER for ICI at ESOC.

References

1. Marshall HT & Djamgoz MBA. Front Oncol. 2020 8: 315

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