Methodological concerns in the medico-economic modeling of adjuvant management

EE629,2022-11, ISPOR Europe 2022, Vienna, Austria



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Background

In the adjuvant stage, disease evolution is uncertain. Patients may progress through different metastasic localization with different disease evolution or eventually be cured. Furthermore, observation of death events at this stage of the disease is limited, resulting in immature survival data, especially with the innovative treatment. Therefore, modeling at the adjuvant stage raises many challenges, such as choosing the model structure to reflect the disease evolution or modeling the effectiveness of immature data observed in clinical trials and extrapolating them over a large time horizon.

These challenges are more difficult to capture given the limited number of health economic (HE) appraisals in the adjuvant stage and absence of clear modelling recommendations. In France, 92% of HE appraisals in oncology therapeutic area concern the advanced stage and no analysis has been conducted to capitalize on the modeling experience in the adjuvant stage.

The objective of this study was to review the HE appraisals published by the CEESP (Commission d'Evaluation Economique et de Santé PubFrance to provide a summary of the methodological concerns (MCs) regarding modelling approach reported in adjuvant indication.

Methods

All appraisals published by the CEESP until June 2022 were reviewed. The HE appraisals available in adjuvant treatment were selected according to the inclusion and exclusion criteria presented in Table 1, according to the PICOS criteria.

Table 1: Inclusion and exclusion criteria for HE appraisals published by the CEESP

Criteria	Inclusion criteria	Exclusion criteria
Population	No population specified	-
Intervention	Adiumant trootmant	Locally advanced / metastatic /
	Adjuvant treatment	unresectable treatment
Comparator	No comparator specified	-
Results	No results specified	_
Study design	Cost-effectiveness	Budget impact analysis

The comparative analysis of HE appraisals was conducted through a reading grid which allowed us to target MCs in the adjuvant modeling, including type of model to be preferred in the context of immature data and considering disease natural history; assumptions about modeling recurrence-free survival and patient progression between health states; sources and methods for modeling unobserved events in the trial.

Results

Identification of HE appraisals

Since June 2022, 63 HE appraisals were published by the CEESP, including 5 appraisals in the adjuvant stage. Three of them concerned treatments for melanoma, one for breast cancer and one for gastroesophageal cancer (Table 2).

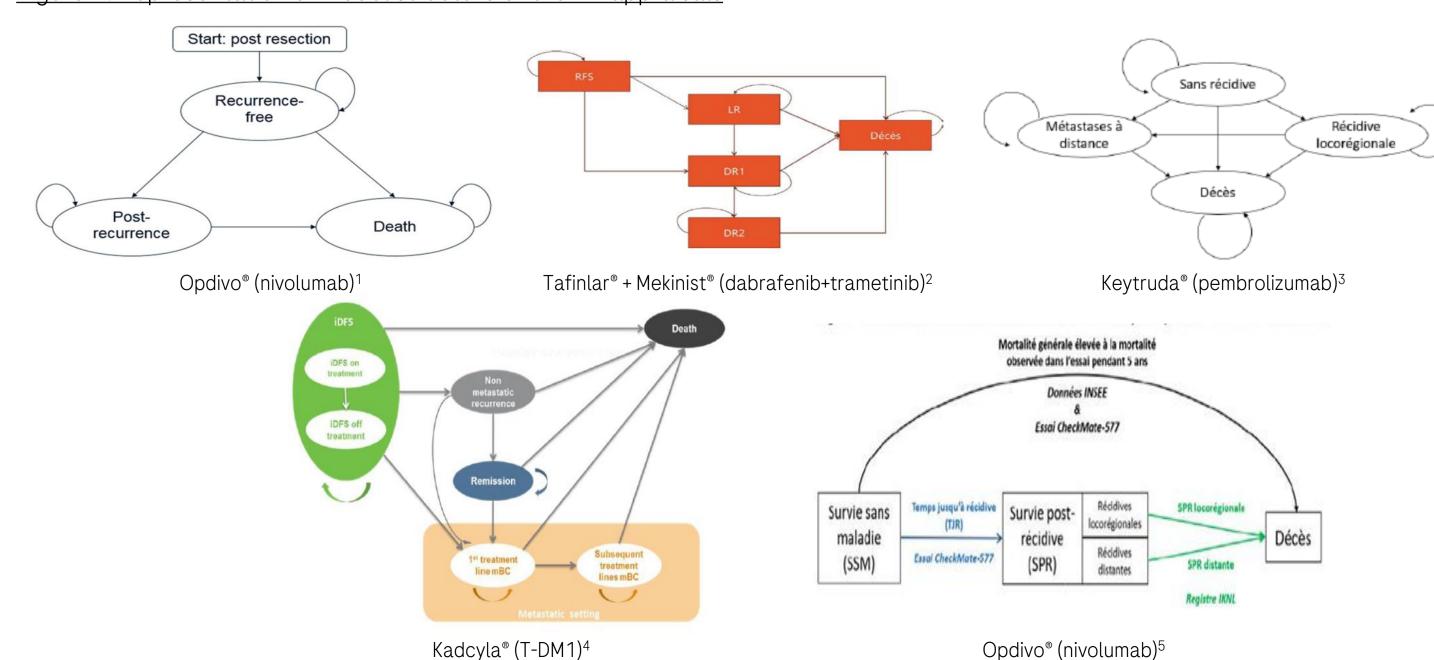
Table 2: Presentation of HE appraisals published by the CEESP in adjuvant management

Specilaty	Indications	
As monotherapy in the adjuvant treatment of adult patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection		16/04/2019
Tafinlar® + Mekinist® (dabrafenib+trametini b) ²	First-line adjuvant management of adult patients with BRAF V600 mutation-positive stage III melanoma after complete resection	14/05/2019
Keytruda® (pembrolizumab)³		
Kadcyla® (T-DM1) ⁴	Adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease in the breast and/or lymph nodes after neoadjuvant taxane and anti-HER2 therapy	12/05/2020
Opdivo® (nivolumab) ⁵	As a single agent in the adjuvant treatment of adult patients with esophageal or esogastric junction cancer who have residual disease after neoadjuvant chemoradiotherapy	08/06/2022

Model structure

The schemas of the models are presented in figure 1.

Figure 1: Representation of model structure of the HE appraisals



Results

Methological reservations analysis

Among the 5 HE appraisals identified, 2 appraisals had at least one major reservation and all appraisals have at least one important reservation (Table 3). In total, 33% of the major and 50% of the important reservations correspond to methodological concerns previously identified in the reading grid and matching the modelling MCs at the adjuvant stage.

Table 3: Major and important reservations raised by the CEESP by appraisal

Reservations level	Opdivo® (nivolumab)¹	Tafinlar®- Mekinist® (dabrafenib- trametinib)²	Keytruda® (pembrolizumab)³	Kadcyla® (T-DM1)4	Opdivo® (nivolumab) ⁵
Major reservations	2	0	1	0	0
Important reservations	6	4	4	5	1

Among the methodological concerns related to modelling in the adjuvant stage, the major and important reservations could be classified into 3 categories (Table 4).

Table 4: Major and important reservations related to specific methodological concerns in the adjuvant stage by category

Reservations level	Model structure	Modeling "Recurrence-free survival" health state	Modeling of post- recurrence health states
Major reservations	1	O	0
Important reservations	O	4	6

Model structure

Four of the 5 models assessed used semi-markovian approach which include type of relapse. Although these models seem more appropriate for modeling post recurrence-free evolution, minor reservation was made for 1 model on the choice of number of heath state - to high - regarding disease history and data availabilities. The last model assed used AUC approach, which lead to major reservation related to the non-compatibility of this type of model with consideration of immature data, modeling of patient outcome to distinguish recurrence, and inappropriate modeling of recurrence.

Modeling "Recurrence-free survival" (RFS) health state

In 2 appraisals, it was assumed that in absence of recurrence in adjuvant stage after a given time, patients were cured. One important reservation was stated by the CEESP regarding this assumption, given the lack of data to document the proportion of cured patients in the model.

Distribution of patients across alternative health states upon exit from the "Recurrence-free survival" health state was subject to important reservations in 3 appraisals.

Generally, the modeling of RFS state raises two concerns: estimating the time spent in RFS and the distribution of patients upon exit from this state. As an example, in an HE appraisals it was chosen to use the Kaplan Meier curve to estimate the time spent in RFS associated with external data to model the distribution of patients upon exit from this state. In this appraisals, the two concerns in this health state are modeled separately. In a different HE appraisals, the time spent in RFS and the distribution of patients upon exit from this state were modeled via competitive risk modeling, using only one approach to consider these two concerns. This choice is the only one that did not raise any reservations.

Modeling of post-recurrence health states

Among the 5 appraisals, 3 used external data to model survival post-recurrence, including 2 with real-world data.

Modeling post-recurrence states was the subject of 6 important reservations. Four reservations concerns the uncertainty generated by modelling these states, in particular the modelling methods and data sources used, which require strong assumptions of transposability or modelling. One reservation concerns the lack of explanation of the method and one other concerns the choice of post-recurrence treatments.

Conclusion

The analysis of all the reservations expressed by the CEESP shows that the use of the reading grid makes it possible to capture all the reservations specific to modelling at the adjuvant stage. Reservations not specific to adjuvant management represent 2/3 of major reservations and 50% of important reservations. Despite a lower proportion of reservations specific to adjuvant modeling, the analysis allows identification of MCs and orientation of modeling choices at the adjuvant stage.

The major methodological issue in adjuvant management is the consideration of temporality in the modeling, which intervenes at several levels:

- Choice of the model structure in coherence with the available data and the natural history of the disease;
- Definition of time-dependent transitions between states;
- Integration of the cured assumption in adequation with the natural history of the disease and the treatment effect;
- Modeling of the entire care pathway, involving the consideration of treatment sequences.

In conclusion, the analysis of the 5 HE appraisals allowed us to identify the challenges to be anticipated in adjuvant management. In particular, concerns related to data immaturity and modeling of post-relapse states with the issue of integrating treatment sequences. In this context, use of real-world data could be a potential solution.

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