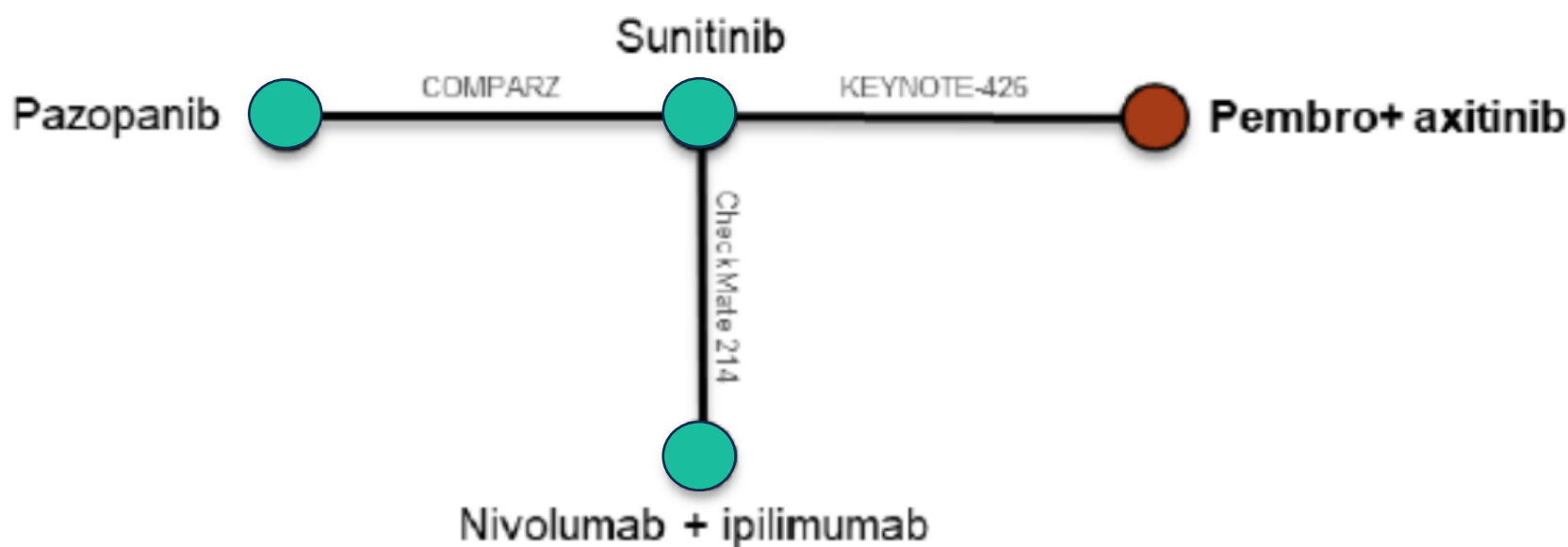


CONTEXT

When applying for reimbursement for a therapeutic innovation, many efficiency dossiers involve clinical trials evaluating the efficacy of the innovative treatment *versus* placebo, and not *versus* a comparator treatment. According to the French National Authority for Health (HAS) guidelines, **indirect comparisons are necessary** to account for all relevant comparators in the cost-effectiveness assessment.

In the absence of direct comparisons between alternative healthcare interventions within cost-utility studies, the HAS recommends performing **network meta-analysis – NMA** (cf. Figure 1). These analyses gather all the available evidence and estimate the relative effectiveness of the treatments investigated.

FIGURE 1 : Example of structure of a network meta-analysis [1]



The network structure **reinforces the evidence** when direct comparisons are available and **allows for inference** if not. However, NMA are not always feasible whenever a common comparator between the selected alternatives is lacking. Several indirect pairwise comparisons, such as matching-adjusted indirect comparisons (MAIC) and propensity score, can then be performed.

RESULTS

All efficiency opinions were investigated, most of them evaluating monotherapies in oncology (cf. Figure 2.a). Among the 76 dossiers analyzed from 2020 to 2022, 26 used indirect comparison methods to evaluate the different therapeutic alternatives. **According to our review, the validity of pairwise comparison methods in the assessment of new treatments efficiency was not accepted by the HAS yet.** Comments on the heterogeneity of the studies questioning the robustness of the comparisons were made by the HAS when the selected approach was not an NMA (12/26, 46%).

FIGURE 2a
Distribution mono and bi-therapies

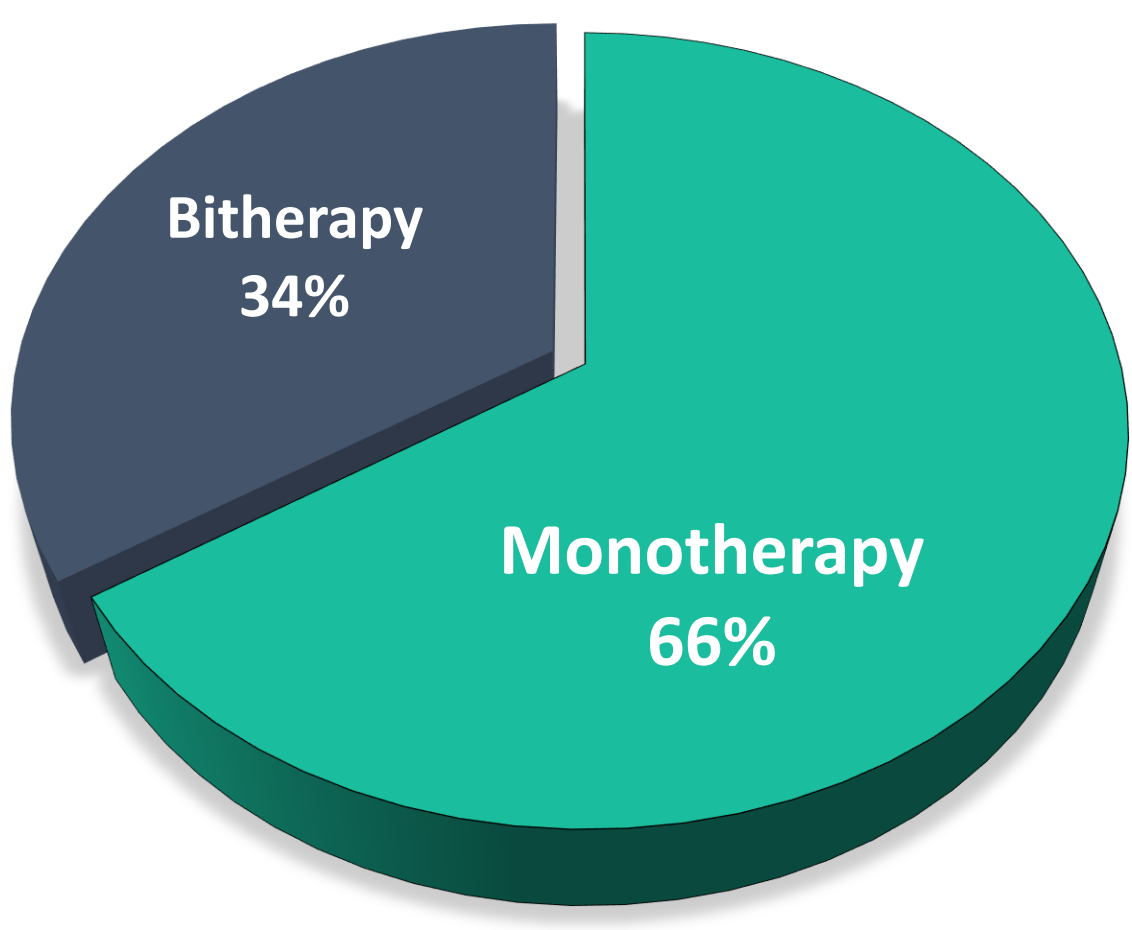
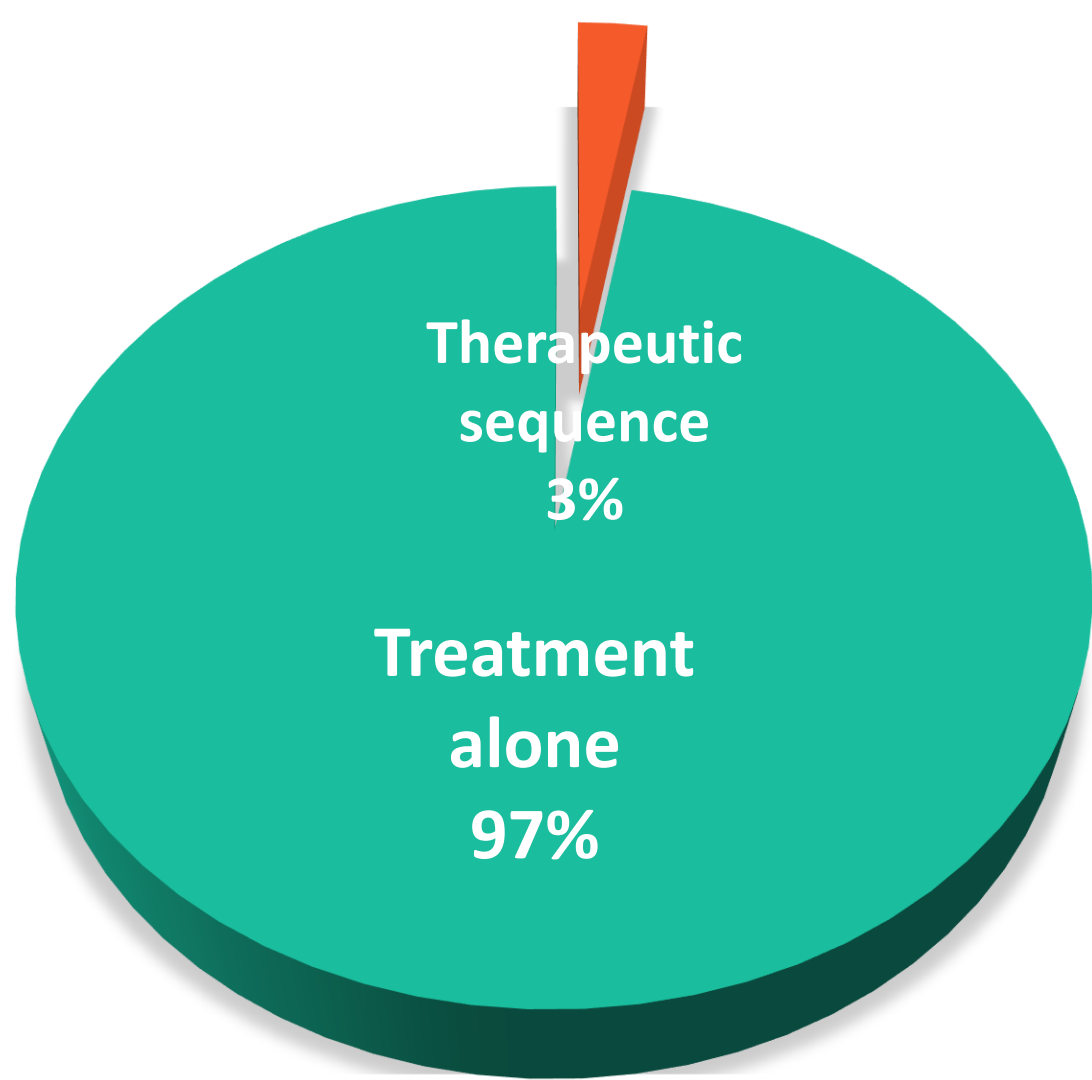


FIGURE 2b
Therapeutic sequences ratio



DISCUSSION

- The trade-off between completeness of comparators and methodological robustness is a major issue in efficiency dossiers, especially as market access authorizations tend to be sought using less robust trials (phase II trials only). [2] **Effectiveness data derived from indirect comparisons is increasingly accepted by the HAS when the methodology is robust.** [3] It would be essential to apply these estimation methods when only pairwise comparisons are available, to avoid invalidation of the dossier on the grounds of a major methodological reservation.

CONCLUSION

The use of unadjusted pairwise comparisons to obtain a multi-option efficiency frontier was not validated so far by the HAS. In these cases, the HAS recommends that **only one comparison should be retained to respect methodological validity, despite lack of comparators comprehensiveness** in the base case analysis.

MAIC Modification of the weights of individual patient data (IPD) from one study based on the baseline summary statistics of another study.
Propensity scores Assessment of the impact of a treatment or exposure while considering the covariates that forecast the likelihood of receiving that treatment or exposure.

OBJECTIVES

The aim of the study was to evaluate whether alternative methods for indirect comparisons were accepted by the HAS.
The responses from the HAS were also investigated when these methods were not deemed sufficiently robust.

METHODS

A retrospective analysis of the HAS efficiency opinions published from January 1st, 2020, until December 31, 2022, was carried out. Dossiers using clinical data from indirect comparisons were identified, as well as the method of comparison and their approval.

However, the HAS mainly warned on the difficulty to estimate the efficiency of the evaluated treatment, as constructing an efficiency frontier is impossible without the accurate outcomes. In evaluations based on pairwise comparisons (such as comparisons of treatment sequences – cf. Figure 3), two ICERs are estimated making it difficult to draw any conclusion.

The HAS suggested checking whether one of the analyses could be considered more relevant and able to support the main analysis.

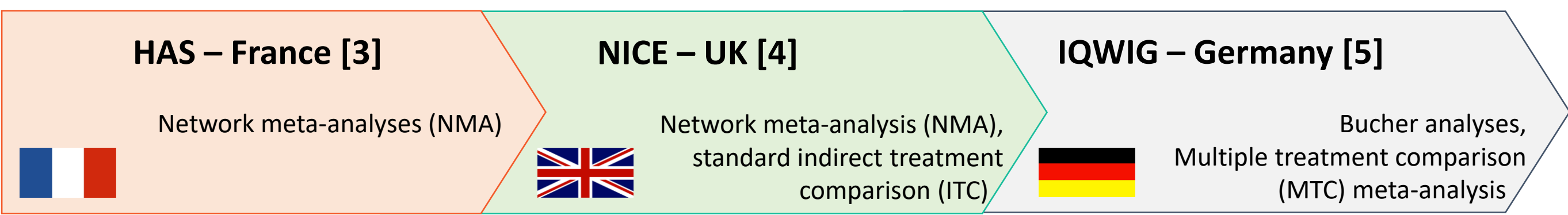
TABLE 1. Use of indirect comparison methods and associated reservations

Number of studies (N (%))	Type of indirect comparison	Reservation	Justification
14 (18,4%)	NMA	Minor (7,1%)	--
		Important (28,6%)	Unjustified constant HR
		Major (42,9%)	Unjustified constant HR, heterogeneity of studies, poorly documented meta-analysis
4 (5,3%)	MAIC	Minor (25%)	--
		Important (50%)	Matching variables
6 (7,9%)	Propensity score	Minor (16,7%)	--
		Important (66,7%)	Matching variables
		Major (16,7%)	Matching variables
5 (6,6%)	Others (Cox model adjusted for covariates, transition probabilities estimated from the literature)	Important (40%)	Impossibility of constructing an efficiency frontier
		Major (40%)	Comparability
31*			

*Each dossier may include several indirect comparison methods.
MAIC Matching adjusted indirect comparison ; NMA Network meta-analysis

- Compared with its European neighbors, **France is still rather reluctant to accept indirect comparisons other than network meta-analyses** (cf. Figure 4).

FIGURE 4 : HTAs and their recommended methodology



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