COST-EFFECTIVENESS ANALYSIS OF DABRAFENIB+TRAMETINIB VERSUS WATCHFUL WAITING IN THE ADJUVANT TREATMENT OF PATIENTS WITH RESECTED BRAF V600 POSITIVE STAGE III MELANOMA : A FRENCH PERSPECTIVE

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BACKGROUND

- **Melanoma** is the 6th and 7th most frequent cancer in women and men respectively in France. In terms of incidence, it accounts for about 4% of all cancers with **15,404 new cases diagnosed in 2017** [1], which has increased steadily and strongly over the past decades [2].
- **BRAF mutation** is expressed in 37.2% [3] of melanomas, and more than 90% [4] of cases are codon 600 mutations. This **mutation is** a factor of **poor prognosis**, with higher relapse rate and lower survival [5].
- In **2016**, **French recommendations** [6,7] highlighted the interest of an adjuvant treatment but mentioned the lack of consensus on the treatment to be used. Interferon alfa-2b was the only approved option in the EU despite its toxicity profile. Patients were mainly recommended to be included in clinical trials where **watchful waiting** (WW) was considered an acceptable comparator arm.
- The combination of dabrafenib + trametinib (D+T) demonstrated its efficacy in the adjuvant treatment of melanoma after complete surgical resection in the **COMBI-AD trial**: a randomized, double-blind, placebo-controlled phase III trial. This trial included 852 patients who received the adjuvant treatment for 12 months.

OBJECTIVE

To evaluate the cost-effectiveness of D+T compared to WW in the adjuvant treatment of patients with BRAFV600+ stage III melanoma after complete resection, from a French collective perspective.

MATERIALS & METHODS

Methods were based on French HEOR guidelines (HAS) and international good research practices for modelling [8,9].

Model structure

- A **non-homogeneous semi-Markov cohort model** was used with states defined on recurrence and death (Figure 1). This model structure is consistent with previously published economic evaluations in melanoma adjuvant therapy and adjuvant strategies in general.
- This approach should be preferred to "area under the curve" models (more frequently used in oncology) when extrapolation of the patient's pathway [10] :
  - requires considering more than 3 states
  - may be based on marginal survival curves
  - aims to take into account several treatment lines
- The model includes **5 health states**:
  - Relapse-free (RFS)
  - Locoregional recurrence (LR)
  - Distant recurrence 1st line (DR1)
  - Distant recurrence 2nd line (DR2)
  - Death
- Its key model assumptions are summarized in Table 1.

Figure 1. Model framework

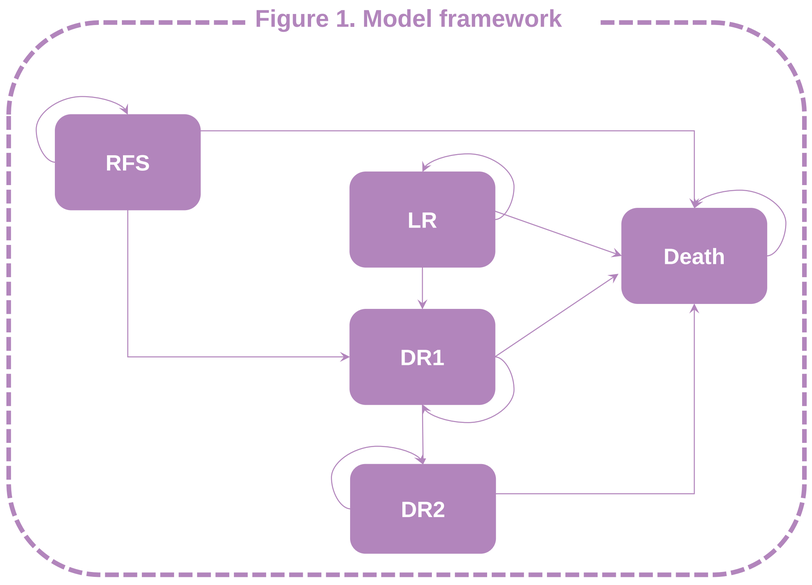

Table 1. Key model assumptions

	Basecase assumption	Rationale
Time horizon	Lifetime	Allow to capture all meaningful differences between interventions Median age in COMBI-AD: 50.4 yo
Outcomes	Quality-adjusted life years (QALYs) and life years saved (LYs)	QALYs were the primary preference-based outcome evaluated
Discount rate	4.0% (first 30 years) and 2.0% thereafter	As per HAS HEOR guidelines [8]
Cycle length	Cycle of 2 months	Trade-off between speed of calculation and accuracy of estimates.

MATERIALS & METHODS (Cont'd)

Costs measures

Measures of French costs calculated for each comparator included the following: drug acquisition, administration, transport, recurrence management, adverse events management, follow-up and end-of-life.

Survival extrapolation

- Marginal survival functions defined from the patient's entry into a health state were adjusted from the COMBI-AD trial data and controlled by published data.
- Transition probabilities were estimated from 4 clinical data sets: RFS ("Relapse-Free Survival"), TT2L ("Time To Second Line"), 2LOS ("Second-line Overall Survival") survival curves and general population mortality data.
- Parametric distributions were tested for each curve.
- A proportion of cured patients was considered and tested in a cure model.
- The best fitting approach (Log-Logistic (U) Cure model) was selected based on visual inspection, statistical fit and discussion with clinicians.

Utility values and QALYs

- The economic endpoints in the model were quality-adjusted life years (QALYs) and life years saved (LYs).
- In the COMBI-AD trial, EQ-5D data were collected at inclusion and during the trial follow-up (Table 2). A health state was associated with each completed quality of life questionnaire in the trial in order to derive utility scores and populate the cost-effectiveness model.

Table 2. Utility score by health state

Health state	Utility score (SE)	
	UK tariffs	French tariffs
RFS - On treatment	0.854 (0.006)	**0.865 (0.006)**
RFS - Post-treatment	0.869 (0.005)	**0.877 (0.005)**
After locoregional recurrence	0.836 (0.013)	**0.846 (0.014)**
After distant recurrence	0.792 (0.017)	**0.807 (0.017)**

RESULTS

- In the COMBI-AD trial and after extrapolation, D+T showed significant advantage in reducing the risk of recurrence vs. WW :
  - This strategy delays the onset of locoregional recurrence and metastatic onset by approximately 1 year;
  - This strategy also prevents a distant recurrence in about 13% of patients over lifetime.
- The comparison of D+T vs. WW led to a situation of generalized dominance of the combination in the basecase analysis, with +1.68 QALY and an economic benefit of €20,140 (Table 3).
- Deterministic and probabilistic sensitivity analyses generally showed consistency with base case findings (Table 4 and Figure 2).
- Results were mainly sensitive to variations in extrapolation of the RFS and therapeutic patterns defined for each arm in the metastatic setting.

Table 3. Base case results

Treatment	Costs	QALY	ICER
Dabrafenib+ Trametinib	209 939 €	11,91	Reference
Watchfull waiting	230 079 €	10,24	**Dominated**

Figure 2. PSA simulations scatterplot

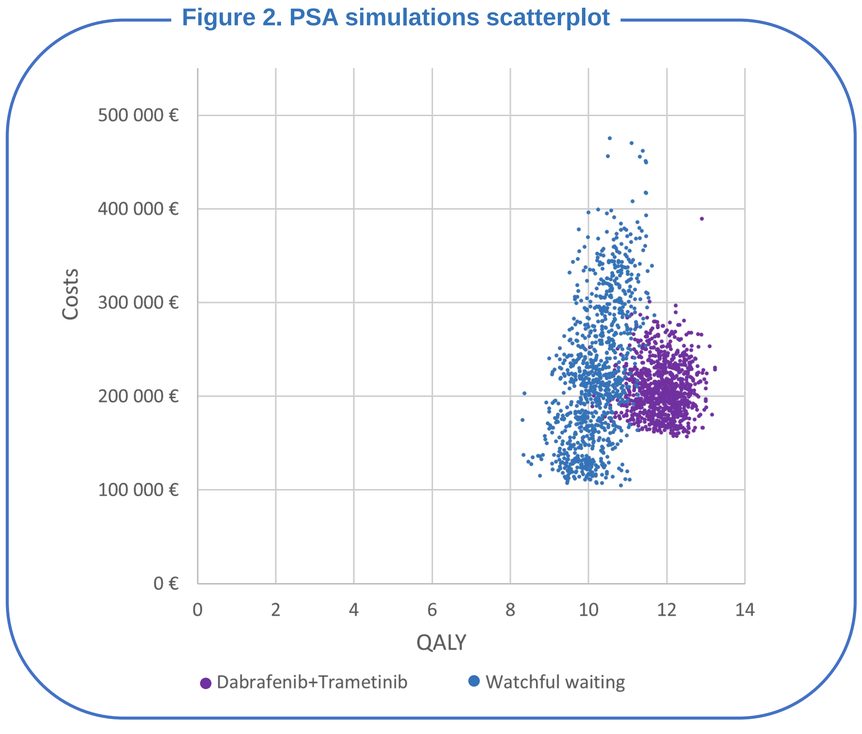

Table 4. DSA and scenario analysis

Scenario		Differential : D+T vs WW	
Parameter	**Bound**	**Δ QALY (% vs basecase)**	**Δ Costs (% vs basecase)**
Base Case analysis		**+ 1.67**	**-20 140 €**
Discount rate	0%	+ 3.17 *(+90%)*	- 90 200 € *(+348%)*
	6%	+ 1.29 *(-22.8%)*	- 1 170 € *(-94.2%)*
Time horizon	5 years	+ 0.38 *(-77.2%)*	+ 39 000 € *(-294%)*
	20 years	+ 1.21 *(-27.5%)*	+ 3 000 € *(-115%)*
Age* *(50.4 ± 14.2)*	Low.	+ 1.7 *(+1.8%)*	- 21 103 € *(+4.8%)*
	Up.	+ 1.65 *(-1.2%)*	- 19 334 € *(-4%)*
RFS utility	Low.	+ 1.75 *(+4.8%)*	- 21 972 € *(+9.1%)*
	Up.	+ 1.60 *(-4.2%)*	- 18 291 € *(-9.2%)*
LR utility	Low.	+ 1.58 *(-5.4%)*	- 16 218 € *(-19.5%)*
	Up.	+ 1.78 *(+6.6%)*	- 24 099 € *(0%)*
DR utility	Low.	+ 1.68 *(+0.6%)*	- 20 140 € *(0%)*
	Up.	+ 1.68 *(+0.6%)*	- 20 140 € *(0%)*
DR2 disutility	Low.	+ 1.68 *(+0.6%)*	- 20 140 € *(0%)*
	Up.	+ 1.68 *(0.6%)*	- 20 140 € *(0%)*
RFS extrapolation – Weibull (U) Cure		+1.86 *(+11.4%)*	-21 000 € *(+4.3%)*
RFS extrapolation – Gompertz (U) Cure		+ 2.11 *(+26.3%)*	- 31 000 € *(+54%)*
RFS extrapolation – Lognormal (U)		+ 1.13 *(-32.3%)*	- 39 000 € *(+93.6%)*
Therapeutic patterns – KOLs opinions		+ 1.37 *(-18%)*	+ 21 425 € *(-206%)*
Therapeutic patterns – Sassolas et al.		+ 1.62 *(-3%)*	+ 45 546 € *(+326%)*
Administration cost	Low.	+ 1.62 *(-3%)*	- 15 788 € *(-21.6%)*
	Up.	+ 1.73 *(-3.6%)*	- 23 941 € *(+19%)*
End of life cost	Low.	+ 1.68 *(+0.6%)*	- 20 140 € *(0%)*
	Up.	+ 1.68 *(+0.6%)*	- 20 140 € *(0%)*
LR cost	Low.	+ 1.64 *(-1.8%)*	- 21 884 € *(+8.7%)*
	Up.	+ 1.72 *(+3%)*	- 18 396 € *(-8.7%)*
Cost of follow-up	Low.	+ 1.76 *(+5.4%)*	- 16 764 € *(-16.8%)*
	Up.	+ 1.6 *(-4.2%)*	- 23 497 € *(+16.7%)*
AEs costs – D+T	Low.	+ 1.68 *(+0.6%)*	- 24 556 € *(+22%)*
	Up.	+ 1.68 *(+0.6%)*	- 15 843 € *(-21.3%)*
AEs costs – WW	Low.	+ 1.68 *(+0.6%)*	- 20 140 € *(0%)*
	Up.	+ 1.68 *(+0.6%)*	- 20 140 € *(0%)*

** Age (mean ± SD) of patients from COMBI-AD clinical trial*
AEs : Adverse Events

CONCLUSIONS

- Dabrafenib + trametinib represents a clinically significant advancement for adjuvant treatment of completely resected BRAF V600 mutation positive high-risk stage III melanoma.
- This cost-effectiveness analysis demonstrated that dabrafenib + trametinib dominates the watchful waiting strategy with gains in QALYs and lower costs.
- New melanoma adjuvant treatments including immune checkpoint inhibitors have shown great results vs. watchful waiting by delaying recurrences and increasing the proportion of cured patients. Latest guidelines published in November 2018 by the Société Française de Dermatologie recommend the use of either nivolumab, pembrolizumab or dabrafenib+trametinib for the treatment of patients with resected BRAF V600 positive stage III melanoma [11]. The relative positioning of these new strategies still needs to be defined.

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