PCN362: Do anticancer drugs entering the French market provide significant evidence of their clinical efficacy?

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Introduction

In 2017 an article from Davis et al. published in the British Medical Journal criticized an almost nonexistent regulation regarding the market entry of anticancer drugs assessed by the European Medicine Agency (EMA), claiming that oncology molecules did not provide sufficient evidence of their clinical benefit specifically in terms of prolongation of Overall Survival (OS) or improvement of quality of life (QoL). However, after the EMA authorization, drugs must be evaluated at a national level to be granted a price and a reimbursement. In France, drugs are going through Health Technology Assessment by the Haute Autorité de Santé (HAS) to obtain an SMR/ASMR. The objective of this study was to evaluate if recent anticancer drugs which could enter the French market provided evidence of clinical benefit.

Study structure

In order to assess whether the oncology molecules which obtained a Market Authorization (MA) by the EMA over the past 4.5 years have met the promises of efficacy and clinical benefit they claimed, an analysis of the conditions for access to reimbursement and pricing of these drugs was conducted. The purpose of this study is to identify the level of evidence provided by anticancer drugs that could enter the French market thereby obtaining a sufficient SMR.

Methodology: In order to compare the two periods the methodology used is similar to that developed in the BMJ article entitled*: Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13*, which denounced an insufficient level of evidence of anticancer drugs that had obtained a MA over the period 2009-2013. The molecules in our study have obtained a MA and are then evaluated by the French agency: HAS. An analysis on certain anticancer drugs evaluated by the Transparency Commission between 01/01/2014 and 31/05/2018 and published on the HAS website was carried out. This sample allows us to understand the HAS method for evaluating the level of evidence provided through its SMR/ASMR rating.

Simplifications:

- Choice of cancer: the study focused on TC opinions of drugs used to treat hematological cancer (all) and four of the most common solid tumors (breast, colorectal, NSCLC and prostate cancer)
- Exclusion of certain drugs: our interest was focused on new active principles that are evaluated for the first time, on extension of indications but also on re-evaluations only when new data had been submitted, as a consequence 181 TC advices were excluded (me too, generics, biosimilars…)
- Collected data: it was divided into 3 areas being general information, data from the TC evaluation and clinical data. A simplification of the clinical part was carried out, only the most robust studies related to the MA were detailed.

These structuring choices lead to the selection of 77 opinions from 54 different molecules in 91 indications.

Structuring choices

- Selection of therapeutic areas:

Hematology + the 4 most frequent solid tumors (breast, colorectal, non small cell lung, prostate)

- Period of the study: 2014 – 2018
- Exclusion of existing active principles

Study design

258 TC advices

77 selected TC advices in 91 indications

52  39 solid tumors

10  5  20  4 

Limitations:

- Choice of cancer: choosing certain cancer does not allow us to be exhaustive. Specifically, excluding melanoma which management has been revolutionized by the arrival of immunotherapy is a source of bias.
- Inadequate representation of small samples: some therapeutic areas have seen little innovation in recent years and the samples are too small to make conclusions (e.g prostatic cancer)
- Counting by indication: the count was done by indication since the Transparency Commission assigns SMR/ASMR per indication. Some clinical studies may be counted several times if they include populations from two different indications.

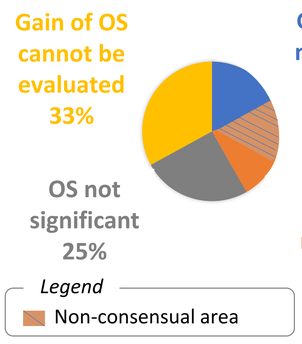
Results

The HAS specific requirements for the design of clinical studies which anticancer drugs trials often don't meet

HAS HAUTE AUTORITÉ DE SANTÉ

		Conclusion Difficulties in oncology
Design of the pivotal trials	RCT, double blind trials	30 % of single arm trials, 77% open label trials
Comparator	Active comparator, SoC	27% placebo, 22% add on
Primary endpoint	OS (with benefit between median OS)	Very long to demonstrate a gain in OS
Secondary endpoints	QoL	Demonstration of an improved QoL = very unusual

An OS gain is not considered by the TC when the median is not reached



- **20%** have demonstrated a gain on the median OS
- **22% median OS not reached of which 10% have demonstrated a gain of OS but the median is not reached yet**
- In 33% of cases a gain of OS cannot be evaluated (OS not in the protocol/exploratory endpoint, single arm trial) and in 25% of cases the results for OS are not significant.

The demonstrated gain on OS represents 30% of indications if we include the trials for which the median OS is not reached yet.

70% of pivotal studies are now RCT with an active comparator in 40% of cases. The typical pivotal study is a Phase 3 study evaluating PFS as primary endpoint and OS and QoL as secondary endpoints. However, this improvement in the methodology of the clinical trials submitted does not result in better ASMR granted. Thus the proportion of SMRi and ASMR 5 increases for new anticancer drugs (e.j in 2017 the TC granted 11% of SMRi ; 12% ASMR ≤3 ; 35% ASMR 4 and 42% of ASMR 5). The pharmaceutical industries' claims are often disappointed, resulting in a significant number of hearings reaching 50% of the indications evaluated in 2017. The main problem remains the 24% of indications with no phase 3 of which 85% have single arm pivotal trials which are condemned to an unsuccessful evaluation by the HAS.

According to the HAS recommendation, the gold standard to be granted an ASMR ≤3 is to demonstrated an OS gain with benefit between median OS. However, it can be possible to obtain an ASMR ≤3 without having reached the median OS and fortunately since it represents 80% of the indications (Table 1).
Obtaining an ASMR ≤3 is possible under several conditions: the OS HR suggests a good median of OS even if it has not yet been reached, the results of PFS are very encouraging (>8 months), OS is not the most relevant criterion in the study (e. g. transfusion independence for Revlimid®, reduction in spleen volume for Jakavi®). The medical need also seems to play an important role in the requirement of the level of evidence (see Iclusig® in CML T315I).
There would seem to be thresholds of relevance of OS gains justifying ASMR levels (Table 2), so an OS of more than 5 months is an asset to qualify for an ASMR ≤3 and an OS gain of 2 months would help obtaining an ASMR<5.

Table 1. 11 indications were granted an ASMR 3 without reaching the median OS

Trade name	IMNOVID Hemato	REVLIMID Hemato	VELCADE Hemato	GAZYVARO Hemato	ICLUSIG Hemato	IMBRUVICA Hemato	ZYDELIG Hemato	JAKAVI Hemato	IMBRUVICA Hemato	KEYTRUDA NSCLC	ZYTIGA Prostate
Year of TC advice	2014	2014	2014	2015	2015	2015	2015	2016 **RE**	2017 **RE**	2017	2018
Explanation (PFS gain in month)	PFS GAIN 1,9	No CRC	PFS GAIN 27,6	PFS GAIN 11,5	No CRC	HR (OS) = 0,434	HR (OS) = 0,28	No CRC	HR (OS) = 0,76 PFS GAIN 8,4	HR (OS) = 0,6 PFS GAIN 4,3	HR (OS) = 0,621 PFS GAIN 18,2
	Transfusion independance				Unmet medical need in LMC m T315I			Reduction of Vspleen			

Legend
RE Re-evaluation (new data)
CRC Clinically Relevant Comparator

Table 2. Demonstration of median OS gain and expectations of ASMR levels

Trade name	BESPONSA	STIVARGA	CYRAMZA	LONSURF	KEYTRUDA	XOFIGO	OPDIVO	BLINCYTO	TECENTRIQ	ZYTIGA	TYVERB	KADCYLA	KYPROLIS	REVLIMID
Year of TC advice	2018	2014	2016	2016	2017	2014	**2016**	2017	2018	2015	**2014**	**2014**	2018	2017
ASMR	5/NQ	5	5	5/NQ	4	4	**3**	4	4/NQ	4	**5**	**2**	3	3
OS Gain (in month)	1	1,4	1,6	1,8	1,9	2,8	**3,2**	3,7	4,2	4,4	**4,5**	**5,8**	7,9	10

Legend
ASMR 5
ASMR 4
ASMR 1-3
NQ = Non Quantifiable due to insufficient SMR
Exceptions
Hypothetical thresholds

Quality of life:

It is often not possible to demonstrate a benefit in terms of QoL for patients in open label trials due to the difference of toxicity profiles between molecules. When the trials are double-blind, it is necessary that the data collected by the patients be sufficient to be able to conclude. And even when there is sufficient data collected, the difference observed must be clinically relevant. It is therefore not surprising to observe that only 3% of the indications showed a relevant improvement of the QoL in their trials.
Even molecules that have successfully demonstrated a benefit in terms of QoL for patients are not valued by the TC due to the lack of comparative data with other treatments. It is therefore very difficult to assess the impact of quality of life outcomes on evaluation, it seems to be relatively low.

Conclusion

Our study would conclude according to the BMJ methodology that **31% of indications have demonstrated a gain on OS and QoL** which seems restrictive to us. If we include the PFS, then, 58 indications out of 91 evaluated which represents **64% of indications showed an improvement in OS and/or PFS and/or QoL**.
The majority of the 33 remaining indications obtained an ASMR 5 on the basis of non-comparative data, often from phase 2 trials with median OS and PFS not achieved.
The HAS chooses to maintain a clear posture, it does not wish to take any risks and decide on a good ASMR before having been able to analyze robust phase 3 data on which to base its judgments, there are very few exceptions. This position does not seem to be likely to change (no conditional VTR planned).
Unfortunately, it can take 10 years to demonstrate a benefit between median OS for a molecule (example of Revlimid with the FIRST study). By the time the proof is provided, the molecule may be obsolete and already overtaken by new therapeutic innovations.
France is indeed a land of expertise, and French healthcare professionals are often leaders in their field, but is it still a land of innovation?

Davis, C. et al. (2017). Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. BMJ, p.j4530. ; The 77 TC opinions come from the HAS website https://www.has-sante.fr ; Haute Autorité de Santé – Etat des lieux sur le niveau de preuve et la gradation des recommandations de bonne pratique - Available at : https://www.has-sante.fr/portail/upload/docs/application/pdf/2013-06/etat_des_lieux_niveau_preuve_gradation.pdf [Accessed 23 May 2018] ; Grande, M. (ESMO 2017 Madrid). How to assess a cancer therapy? Feedback from the French Technology Assessment body (HAS) on the ESMO-MCBS.