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THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

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Abstract

Context Health Technology Assessment (HTA) plays an increasingly important role in the process of allocating finite healthcare resources, especially in the context of innovative, high-cost, specialized medicines. Recent reforms of the value assessment of pharmaceuticals in both France and Germany provide the basis for a comparative analysis of the changing market access landscape for cancer drugs in these two countries.

Objectives To examine the commonalities and differences in the recently reformed benefit assessment processes of the two countries; to understand the priorities of each HTA agency by focusing on the process and methodology of HTAs; and finally, to derive the effects thereof on final outcomes, patient access to and list prices of cancer drugs.

Methodology A descriptive analysis and an in-depth comparison of cancer medications appraised by both agencies was undertaken based on the publicly available databases of the Federal Joint Committee (*Gemeinsamer Bundesausschuss* – G-BA) in Germany and the National Authority for Health (*Haute Autorité de Santé* – HAS) in France between 2011 and 2014.

Results Similarities were observed in the process and evidence requirement of the HTAs undertaken by the G-BA and the HAS but the clinical benefit ratings awarded for the same drug-indication pair often differed; arguably, due to differing methods used to assess the relevance of clinical endpoints in the submitted evidence. Sub-group analyses were very common in the G-BA assessments, and clinical added benefit was often awarded for only a subset of patients. The HAS emphasized unmet medical need and availability of therapeutic alternatives in its reasoning for positive decisions. None of the agencies provided economic evaluations for the appraisals. There was no direct correlation between the added benefit ratings and the list prices.

Conclusion Increasing transparency of HTA processes and improving the quality of clinical evidence submitted are shared goals for both HTA bodies and manufacturers. Therefore detailed information on the determinants of certain levels of added clinical benefit and robust guidelines for manufacturers on submission requirements are necessary. Furthermore, economic evaluations of high-cost, innovative technologies are vital to make decisions about the reimbursement status and pricing of such medications.

What this study adds:

- Evidence on similarities in the process and some methodologies employed by the agencies but divergence in the reasons and criteria prioritized when granting added clinical benefit rating to new technologies
- In-depth perspective of the very recent developments in the changing HTA processes and requirements in France and Germany
- Detailed description of the endpoints used and other reasons considered by the evaluating bodies in all cancer drug assessments since 2011
- Evidence on the lack of enforcement of economic evaluation requirements in the HTA procedure of cancer drugs

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1. Background

Economic sustainability of the pharmaceutical market is a global concern amid rapid improvement in health technologies that enable patients to live longer with previously untreatable diseases. While the desirability of new and improved health technologies is uncontested, the scarcity of resources in healthcare necessitates rationing mechanisms and prioritising to allocate finite healthcare budgets. Health technology assessments (HTAs) aim to evaluate the added benefit of new technologies relative to their cost in order to derive their opportunity cost, that is the health gain forgone by not reimbursing other medications. Different evidence requirements, data interpretation techniques and country-specific regulation in HTAs allow disparate value assessment outcomes for the same medicines in the various pharmaceutical markets, giving rise to concerns about inequitable access to medicines across countries.

Oncological diseases present a growing concern for payers and public health budget holders due to increasing patient numbers and treatment costs. Rising incidence of cancer is accompanied by increasing survival rates due to improvement in the effectiveness of treatments; an estimated 32.5 million men and women were still alive in 2012, who were diagnosed up to five years before that date. The most common diagnoses have been breast (females only), bowel (including anus) and prostate cancer[1]. The improvement in survival rates for cancer patients (see Figure 1.) implies longer treatment time and higher treatment costs. From a health economic point of view, cancer types that can be controlled for years, such as chronic lymphocytic leukaemia, and those that are recurrent, allowing patients to live with cancer for years, can be treated as chronic illnesses[2]. Health technology assessments are therefore necessary tools for policy-makers to decide which new technologies provide greatest value for money, both on the individual and on the population level.

The notion of "value" provided by medicines varies in different country contexts but it provides a key insight into country-specific priorities regarding new medicinal products. The novelty of this paper lies in the evaluation of the German value assessments of cancer drugs

[1]Ferlay *et al*. 2012
[2]Cancer Research UK, 2013

since the recently passed Act on the Reform of Market for Medicinal Products (*Arzneimittelmarkt-Neuordnungsgesetz* - AMNOG), the introduction of a comparative clinical benefit assessment of products with new active ingredients. The act, which came into force on the 1st of January 2011, obliges new pharmaceutical products to undergo an early evaluation procedure by the Federal Joint Committee (*Gemeinsamer Bundesausschuss* – G-BA). Evidence on comparative effectiveness plays a key role in this reformed benefit assessment and therefore also in pricing and reimbursement (P&R) decisions. In France, medical benefit (*Service Médical Rendu* – SMR) and improvement in medical benefit (*Amélioration du Service Médical Rendu* – ASMR) granted by the National Authority for Health (*Haute Autorité de Santé* – HAS) had already been the key drivers of P&R decisions prior to 2011. The passing of two laws in the same year nevertheless altered the pharmaceutical market access conditions for companies in France to a great extent; including the requirement to submit comparative evidence for reimbursement. Given the recent reforms of the appraisal processes, a comparative study of the two HTA procedures in the context of cancer drugs has not been carried out in a depth similar to this paper.

The increasing public scrutiny surrounding cancer treatment costs coincides with a move towards improved and more transparent HTA procedures in both Germany and France; in particular, strengthening the comparative nature of evaluations to existing treatments. The resulting similarities and differences can therefore be showcased through the in-depth comparison of the cancer drug assessments that have taken place in both countries since the passing of the AMNOG. This paper aims to inform both policy-makers and pharmaceutical companies about the changing market access landscape for cancer drugs in the chosen countries through the comparison of the process and methods of the reformed benefit assessment procedures.

The objectives of this paper can therefore be summarized as follows:

- Conduct an in-depth comparison of the early benefit evaluation process in Germany to the medical benefit assessment in France through the analysis of common cancer drug appraisals carried out in the period between 2011-2014
- Examine the differences in the outcome of the appraisals of the same drug-indication pairs with regards to the evidence used (randomized controlled trial – RCT – results

submitted), sub-group analyses, the general indicators and disease-specific endpoints considered when reaching a final decision

- Assess whether differences in the process, methods and criteria used by the two HTA agencies could have given rise to different recommendation results for the same drug-indication pairs; particular attention should be paid to cases where the same evidence was used to determine added clinical benefit
- Compare list prices of oncology treatments with regards to their added clinical benefit rating to present the market access landscape in the two countries
- Draw conclusion about general convergence or divergence of HTA practices in France and Germany
- Synthesize the information collected to arrive at policy-recommendations to increase the transparency and efficiency of future HTAs

2. Methodology

The first part of this thesis provides a static review of the HTA processes of cancer drugs in France and Germany since the passing of the AMNOG, in the period between 2011-2014 (section 3.1). This section includes an overview of the appraisal process and methodology used by the two HTA agencies, including the decision-making process, the evidence requirement, the appropriate comparator therapy, the endpoints and criteria used by the two agencies, and the role economic evaluations play in the assessment process. The second part (section 3.2) aims to highlight the most significant differences and similarities in the methods and focus of HTAs, aided by a case study section (section 3.3.), including a comparison of publicly disclosed list prices of cancer medicines to their added clinical benefit rating.

2.1 Data and Sample Selection

The reasons and levers for granting cancer medicines a specific SMR and ASMR status in France, or a specific level and probability of additional clinical benefit status in Germany are presented through the comparative analysis of cancer appraisals since 2011.

The publicly available online drug review databases were used to obtain appraisal documents in original languages from the websites of the German G-BA and the French HAS. In Germany, a further comparison was undertaken between the recommendation of the advisory body of the G-BA, the Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* – IQWiG) and the final decision of the G-BA.

The website of the European Medicines Agency (EMA) provides a list of cancer drugs that were granted market authorization (MA) since 2011 through the central European procedure, however, manufacturers can apply directly to national authorities as well, therefore, the EMA website was not complete. Cancer drug assessments were collected separately from the HAS and the G-BA websites, which were obtained by selecting drug appraisals with cancer

indication after 2011 that did not have orphan-indication[3]. The search function on the G-BA website allowed all these criteria to be selected at the same time; this was unfortunately not the case for the HAS website, therefore in this case all the different cancer indications had to be screened separately.

A master database was created with all the drug-indication pairs that were appraised by either the G-BA or the HAS (or both, see Appendix 1.). This database contains the name of the active ingredient and the brand name of the drug and its general indication. SMR and ASMR ratings granted by the HAS were recorded, if there were more than one assessment then the most recent decision is indicated with the date of the decision. Outcomes produced by the German HTA body were recorded as "Favourable", "Favourable with restrictions" and "Non-favourable", including the specific level and probability of clinical added benefit in the most favourable sub-group.

From this master database, the 15 commonly appraised drugs (and 16 drug-indication pairs) were selected and detailed information on their value assessment was collected (see Appendix 2., 4. and 5.). Each medicine was assessed for the same indication, therefore comparisons of final added clinical benefit ratings could be made. Marketing authorization (MA) dates and final appraisal dates were recorded for these drugs and they were compared across the two agencies (See Figure 2). Only prescription drugs, including vaccines were considered.

Section 3.2 gives an overview of the outcomes for these common assessments first, describing the decision timeframe and the listings. Afterwards it aims to drill deeper in the analysis by looking at the reasons and levers of the two agencies for arriving at specific benefit ratings by providing information for all the 16 commonly appraised drug-indication pairs on:

- Comparative clinical evidence (or the lack thereof) used when assessing the medicine
- Subgroup analyses (including those not used in the marketing authorization process)
- Appropriate comparator (or the lack thereof) used in the clinical study

[3] Orphan drugs have specific appraisal procedures that are different to the ones associated with non-orphan drugs, therefore they are not considered in this paper.

- Primary and secondary endpoints used in the clinical study to assess clinical effectiveness, such as overall survival (OS), progression-free survival (PFS), time until progression and quality of life (QoL)
- Consideration of safety, such as adverse effects (AEs)
- Any country-specific information that was relevant to the assessment outcome

The rationale behind the decisions on the added clinical value will largely depend on the endpoints used in the clinical studies and their relative importance in the country-specific HTA procedure. The manufacturers of drugs that were assessed by both agencies provided the agencies with the same clinical evidence; therefore it is particularly relevant to study uniform and divergent decisions. It is also crucial to analyse whether differences in the priorities associated with the above mentioned criteria could lead to substantially disparate ratings on added clinical benefit for the same drug-indication pairs. This study aims to uncover how the divergence in the HTA processes, methods and criteria used in these two countries could lead to a more favourable decision in one country for the same drug, which could imply inequitable access to cancer drugs among German and French patients.

2.2 Case Studies and Pricing

The case study section (3.3) aims to complement the analysis by presenting the most pertinent cases to show the similarities and differences between the newly reformed HTA processes of Germany and France. This section draws on specific cases of appraisals where 1) the same evidence was used to arrive at the same added clinical benefit rating, or 2) the added clinical benefit rating was granted to certain sub-groups of patients in Germany or 3) the same evidence used resulted in different benefit rating decision for the same drug-indication pair. Given that the official evidence requirement for pricing and reimbursement has converged in the two countries, this section aims to highlight the key drivers behind different HTAs, particularly how the importance attached to different analysis endpoints and subgroup analyses can lead to different appraisal outcomes.

In order to bring a dynamic element into the analysis, publicly available list prices of medicines were also recorded for each drug and have been compared to their benefit ratings. The German list prices were readily available in the G-BA reports for the drug assessments,

with the detailed description of the prices after the deduction of the statutory discounts. Since the passing of the AMNOG law such discounts are publicly disclosed alongside with the amount of refund paid after medicines ("*Erstattungsbetrag*") according to the §130b SGB V[45]. In France, list prices were obtained from the website of the French National Agency for Medicines and Health Products Safety (*Agence Nationale de Sécurité du Médicament et des Produits de Santé* – ANSM), a public medicines regulator body under the supervision of the Ministry of Health[6]. These prices bear limited meaning because further discounts may be agreed upon and the final net prices are not publicly disclosed. In Germany the additional clinical benefit rating is the basis for rebate negotiations but these rebates are not publicly disclosed while list prices remain unchanged. These peculiarities make the German pricing system particularly challenging to evaluate in this context. Nevertheless, a comparison of the list prices (or prices after statutory discounts) to benefit ratings, and secondary research data on net prices, provide a useful insight into consequences of HTAs on drug prices and potential profit margins for pharmaceutical companies.

The methodology and structure of this paper can therefore be summarized as follows: an overview of the decision-making procedure and assessment of added clinical benefit for products with new active ingredients in France and Germany since 2011; an in-depth assessment of the HTAs in the two countries focusing on the reasons and criteria for arriving at certain decisions about the commonly appraised drug-indication pairs; three case studies of the most pertinent cases that truly highlight the similarities and differences between the procedures; finally, a comparison between the benefit rating of the medicines and their published list prices within the case study section. Discussion and policy recommendations will conclude.

[4] According to §130 SGB V 2011 (5th Book of the Social Code, Germany), sickness funds receive a statutory €2.05 discount after prescription drugs from pharmacies and according to § 130a SGB V sickness funds receive a statutory discount on prescription drugs of either 7% or 16% of the list price from manufacturers.
[5] According to § 130b SGB V 2011, the amount of refund will be negotiated directly between the National Association of Statutory Health Insurance Funds (*Die Gesetzliche Krankenversicherung – Spitzenverband* – GKV-SV) and the pharmaceutical company as a discount on the list price and will be publicly disclosed.
[6] The ANSM website had a more comprehensive list of prices for medicines than the Ministry of Health website.

3. Results

3.1 HTA: Decision-making Process and Methods in Germany and France

Since the passing of the AMNOG, every new medicine in Germany with a new active ingredient is subject to an early assessment of additional clinical benefit by the G-BA, based on IQWiG recommendation. If no additional benefit is proven compared to the appropriate comparative therapy (ACT), the price of the medication will be set according to the price in the reference group with comparable active ingredients[7]. If additional clinical benefit is proven, the GKV negotiates a rebate with the manufacturer that will lead to a higher reimbursement price than that of the comparator therapy. This central arrangement has ended pricing freedom and the price monopoly of pharmaceutical manufacturers in Germany (see Table 3.1. and Figure 3.)

In France, medicines post-MA undergo a scientific assessment by the Transparency Committee (*Commission de la Transparence* – CT), when a request has been submitted for the inclusion of the drug on the reimbursable drugs formulary. The CT makes a recommendation regarding the efficacy and appropriate use of the drug and determines its SMR and ASMR level. Reimbursement rate of the medicines is based on their SMR level and is decided by the National Healthcare Insurances (UNCAM), the French equivalent of the German GKV – SV (National Association of Statutory Health Insurance Funds). ASMR is a key indicator in drug price negotiations between the Economic Committee on Healthcare Products (CEPS) and the manufacturer[8]. Table 3.1. provides additional information on the HTA processes in France and Germany.

France also followed suit after Germany and 2011 saw the passing of two legislations, which obligate comparative evidence submission when a reimbursement request is made by a manufacturer and imposed de-reimbursement for medicines with insufficient SMR ratings[9]. Subsequently there has been a shift in the effect size that is required to achieve a given ASMR level.

[7] If no such reference group exists, it will be subject to reimbursement negotiations.
[8] Rémuzat et al. 2013
[9] The new drug safety law (Law no. 2011-2012 of 29 December 2011) and the Social Security Funding Law of 2012.

Table 3.1. Cancer drug review and decision-making processes since AMNOG

	Review				Decision-making		
	Agency	**Role**	**Relationship to government**	**Function**	**Reimbursement**	**Pricing**	**Pricing decision**
Germany	IQWiG	Advisory	Arms-length	Guidance on level of added clinical benefit	Negotiation based on dossier, IQWiG assessment and G-BA decision on added clinical benefit	Negotiation between GKV-SV and manufacturer	If additional benefit: rebate negotiated but higher reimb. than comparator. If no additional benefit: reference-priced group or negotiation - net price to sick funds cannot exceed cost of comparator therapy
France	HAS, Transparency Commission (CT)	Advisory	Integrated	SMR and ASMR guidance	Based on SMR Major:100%, Major/Important:65%, Moderate:30%, Weak:15%, Insufficient: 0%	Negotiation between CEPS and manufacturer	Pricing based on ASMR: ASMR I, II, III: price premium ASMR IV: context-specific ASMRV: no price premium

Table 3.2. Cancer drug review methods since AMNOG

	Methods						
	Drugs assessed	**Clinical evidence**	**Clinical assessment**	**Choice of comparator**	**Principle outcome measures**	**Costs**	**Economic Evaluation**
Germany	All new drugs	Comparative, phase III RCT required	Added clinical benefit based on patient-relevant endpoints	Defined by G-BA can be non-medication	Mortality, Morbidity, QoL, Adverse events	Direct costs recorded	Required but not enforced
France	All new drugs	Comparative, phase III RCT required	Actual clinical benefit (incl. public health impact) and improvement in actual clinical benefit	Currently available therapy	Mortality, Morbidity, QoL, Adverse events	No costs recorded in appraisal documents	Not required

3.1.1. Clinical Evidence

Both the HAS and the G-BA request pharmaceutical manufacturers to submit comparative clinical evidence (evidence from phase III randomized controlled trials) for value assessments, therefore non-inferiority of drugs has to be proven along with safety, quality and efficacy[10][11].

3.1.2. Appropriate Comparator Therapy

The definition of an appropriate comparator therapy (ACT) has received much scrutiny both from the public and the policy-making side, because defining the ACT has a substantial impact on the added clinical benefit level: if a drug is compared to a medicine that is known to be inferior, there will be greater added benefit than if it had been compared to the appropriate comparator. Pharmaceutical companies often get accused of evaluating their products to placebo or treatments known to be inferior to the tested drug, producing unreasonably positive results on additional clinical benefit[12].

In Germany, since the passing of the AMNOG, it is no longer the manufacturer, but the G-BA, who defines what the appropriate comparator therapy ("*zweckmäßige Vergleichstherapie*") should be. The new pricing law also broadened the options of comparators to non-medication therapies such as surgical interventions, physiotherapeutic treatments and best supportive or palliative care (BSC)[13][14]. Although the requirements for selecting the ACT have been defined, the wording of the reform received criticism for not precisely defining when and by whom the ACT should be set, only that the final decision is taken by the G-BA[15].

In France, the manufacturer sets the ACT and the chosen comparator has to be justified. The appropriate comparator medicine has a rather vague definition in the CT report; the level of improvement in medical benefit is evaluated to the currently available therapies ("*traitements*

[10] Dr. Forstmeier Health Care Consulting, [Patient-relevant Added Benefit]
[11] Rémuzat *et al.* 2013b
[12] Goldcare 2013, p.182
[13] Defined as treatment to control symtoms resulting from serious illness and imporving quality of life, in: Hui *et al.*, 2013
[14] G-BA Code of Procedure 2014, p.112
[15] BDI 2014

disponibles"), which can be the reference medicinal product ("*médicament de référence*") or the best mode of treatment ("*meilleures modalités de prise en charge*")[16].

3.1.3 Endpoints and Criteria

In both countries, the general parameters to evaluate the clinical benefit of medicines were safety, quality, efficacy and potential effectiveness, including adverse effects and quality of life indicators. The SMR in France also takes into account public health impact, which considers the burden of disease or its impact on the healthcare system[17].

According to the EMA guidelines of 2013, improvement in overall survival (OS) is the most persuasive clinical study endpoint; thereby reimbursement status and a price premium should only be granted to medications that can prove to increase length of survival for patients[18]. However, it has been recognised that specifically for oncology treatments, prolonged disease-free or progression-free survival (DFS/PFS)[19] should be considered as primary endpoint and OS should only be considered as a subordinate endpoint. Furthermore, disease-free or progression-free survival rates are also morbidity-related endpoints, which are particularly relevant for complex diseases such as cancer.

The IQWiG requests the endpoints in the study to be relevant to the indication of the product and to be "patient-relevant" ("*patientenrelevant*"); this means that the tested parameters should have direct effect on the health status of the patient, and it should be possible to observe and discern these parameters from the health status of the patient as well. Clinical added benefit derived from surrogate endpoints, such as tumour response rate, have to be validated by the manufacturer on case-by-case basis[20].

3.1.4 Economic Evaluations

The "fourth hurdle", or the pharmaco-economic evaluation of medicines is a formal requirement in the clinical benefit assessment procedures of new medications in both France and Germany[21] [22]. However, explicit cost-effectiveness or cost-utility analyses were not

[16] Presentation of the Transparency Commission 2014
[17] Rémuzat *et al.* 2013a
[18] EMA 2012
[19] Defined as the time between randomization and disease progression or death; disease progression is usually measured by a change in size of the tumour (Booth and Eisenhauer 2012, p.1030)
[20] Dr. Forstmeier Health Care Consulting, [Patient-relevant Added Benefit]
[21] Decree no. 2012-1116 of the 2nd of October 2012 in: HAS, Department of Economics and Public Health Assessment 2012
[22] §35a SGB V, Article 5a

conducted or reported in either country as part of the official benefit assessment reports studied in this paper.

3.1.5 Country-specific factors affecting decisions – recommendation restrictions

Both agencies grant reimbursement status to medicines with restrictions to the approval indication, sometimes to a subgroup of patients within the broader indication population and based on product positioning. Only the HAS restricted the use of all medicines studied in this paper to specialist prescription and to hospital use only. The HAS also explicitly states on the appraisal report that some medications require special monitoring during treatment in case severe adverse effects occur.

Table 3.3.

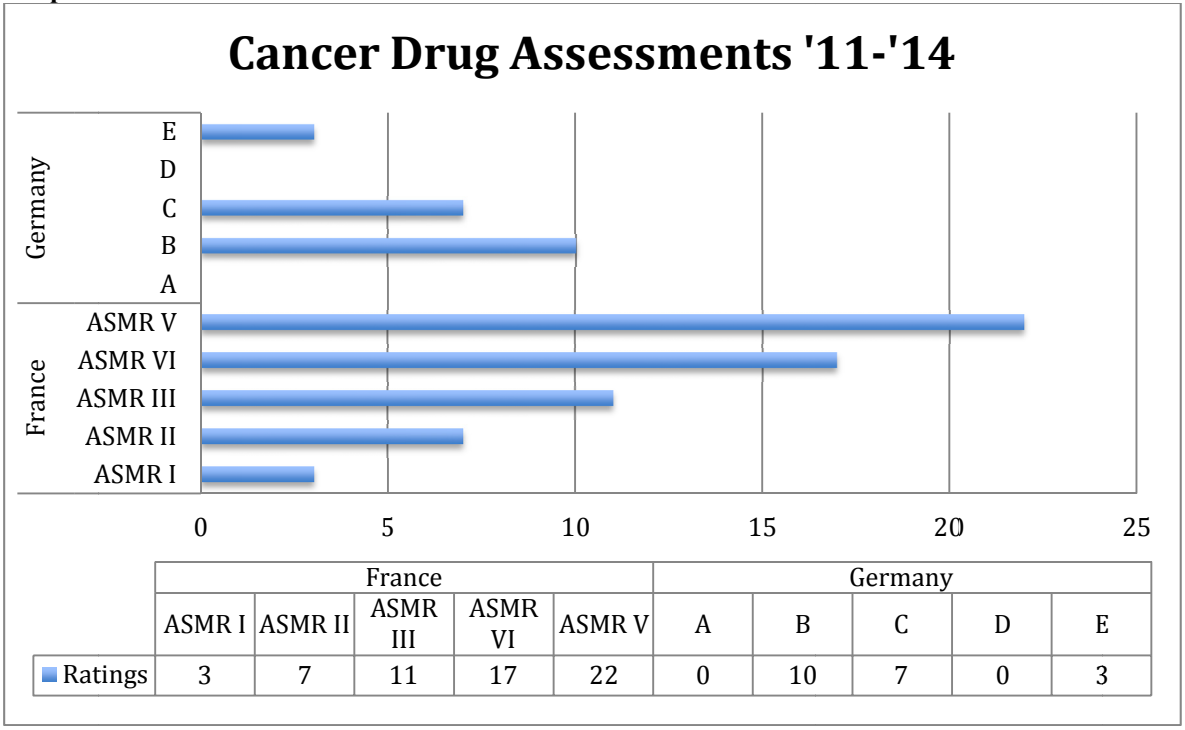
Recommendation restrictions	GBA	HAS
Restrictions based on approval indication	✓	✓
Restriction to specific subgroups of patients	✓	✓
Restrictions based on product positioning	✓	✓
Restrictions by type of prescriber (e.g. specialist only) apply		✓
Administration restricted (e.g. hospital use only)		✓
Special monitoring necessary while treatment is administered		✓

3.2 Comparison of the Outcomes and Methodologies for Common Appraisals

3.2.1. Overall Results

The master database (Appendix 1.), which includes all the drugs assessed by either or both agencies, contains 85 drug-indication pairs, 82 of them assessed by HAS[23] and 20 of them appraised by the G-BA. Graph 3.1 shows a graphic display of overall assessments and benefit ratings (see Table 3.4 for detailed description of the possible ratings). Eight of the drugs in Germany were granted added benefit as applied for and nine drugs proved added benefit in only a subset of the indication population. Out of the drugs appraised by the HAS, 21 received an ASMR rating I, II or III, most of them could prove no additional benefit (ASMR V).

Graph 3.1.



	France					Germany				
	ASMR I	ASMR II	ASMR III	ASMR VI	ASMR V	A	B	C	D	E
Ratings	3	7	11	17	22	0	10	7	0	3

Decision timeframe

An appraisal time-line was drawn to illustrate the differences in the timeframe for decisions on the clinical benefit of each medicine conducted by the French and German HTA agencies (see Figure 2.)[24]. The medicines on top of the timeline are arranged according to their decision date in France, and according to their decision date in Germany below the timeline.

[23] Some medicins were appraised but did not receive an ASMR rating.
[24] This timeline shows the first assessment of each medicine undertaken by the relevant agency, if there were several assessments.

It can be seen from the timeline that decisions in Germany in many cases lagged behind decisions made in France, although the clinical added benefit assessment is equally important in the pricing and reimbursement decisions in both countries. There are several plausible explanation for this phenomenon: whereas the CT is integrated in the HAS, IQWiG is an arms-length institution to the G-BA, therefore the recommendation of the IQWiG has to be formally appraised by the G-BA, which may be a less formal procedure in France. Furthermore, as it will be shown in the case study section, in many instances the IQWiG recommendation restricts the indication defined in the assessment dossier to a narrower subgroup ("indication slicing"[25]). Therefore the appraisal procedure can be viewed as a more thorough process in Germany than in France.

Listings

A very general overview of the appraisal results shows a tendency towards marginally more favourable results for the same drug-indication pair in Germany than in France, when comparing ASMR ratings to the added clinical benefit level in Germany. The next section will present a thorough analysis of the appraisal results for the 15 drugs that were assessed in both countries, aided by a case study section, to illustrate the similarities and the differences in the appraisal processes and methods within the French and the German clinical benefit assessment procedures of cancer drugs.

Although both countries conduct their added clinical benefit assessments using two rating systems, the SMR and ASMR are not directly comparable to the German system, where the quality of the evidence and the added clinical benefit level are evaluated (Table 3.4.)[26].

[25] Ecker + Ecker GmbH 2013

[26] Translation of labels is based on the official English language translation of report documents published on the websites of the respective HTA agencies.

Table 3.4.

G-BA		HAS	
Quality of Evidence	**Extent of Benefit**	**SMR**	**ASMR**
1. Proof ("*Beleg*")	A) Major ("*Erheblich*")	Major ("*Majeur*")	ASMR I (Major)
2. Indication ("*Hinweis*")	B) Considerable ("*Beträchtlich*")	Important ("*Important*")	ASMR II (Important)
3. Hint ("*Anhaltspunkt*")	C) Minor ("*Gering*")	Moderate ("*Modéré*")	ASMR III (Moderate)
4. Not proven ("*Nicht belegt*")	D) Not quantifiable additional benefit ("*Liegt vor, ist aber nicht quantifizierbar"*)	Weak ("*Faible*")	ASMR IV (Minor)
	E) No additional benefit shown ("*Kein Zusatznutzen belegt*")	Insufficient ("*Insuffisant*")	ASMR V (Non-existent)
	f) Benefit less than alternative ("*Nutzen geringer als der Nutzen der zweckmäßigen Vergleichstherapie*")		

The SMR defines the severity of the illness targeted by the medicine, including factors such as the public health benefit on top of safety, quality, efficacy and effectiveness, but it is not a comparative effectiveness assessment. The ASMR rating reflects the degree of clinical improvement of the new medicine relative to any existing treatments. In Germany, the quality of the comparative evidence submitted is classified in one of the four categories, based on the bias potential of the study that is evaluated on the level of the different endpoints used in the study. The extent of added benefit can range from "major" to "less than therapeutic alternative" on six different levels. Table 3.5. compares the criteria of each added clinical benefit rating in the two countries.

Table 3.5.[27]

	Germany Therapeutic Benefit	GBA/IQWiG Assessment Criteria	France ASMR	ASMR criteria
1	Major added therapeutic benefit (MAB)	- curing of illness - significant increase in length of survival - long-term freedom from serious symptoms - far-reaching avoidance of serious side-effects	ASMR I	- major therapeutic advance
2	Significant (considerable) improvement in efficacy or side effects (CB)	- easing of serious symptoms - moderate increase in length of survival - tangible alleviation of disease - relevant avoidance of serious side-effects - meaningful avoidance of other side-effects	ASMR II	- important improvement in terms of clinical efficacy and/or in terms of side effects
3	Slight (marginal) but not minor improvement in efficacy or side effects	- reduction of not serious side-effects - relevant avoidance of side-effects	ASMR III	- pharmaceutical equivalent exists - moderate improvement in terms of therapeutic efficacy and/or in terms of reduction of side-effects
4	Additional but unquantifiable added therapeutic benefit		ASMR IV	-minor improvement in terms of efficacy and/or utility - clinically: acceptability, convenience of use, observance - justified extension of range - potential advantage lying in pharmacokinetic properties or in the lower risk of drug interaction
5	No demonstrated added therapeutic benefit (NB)		ASMR V	- no improvement but still granted recommendation to be listed
6	Less therapeutic benefit than comparator			- negative opinion in terms of inclusion on the reimbursement list

In terms of comparing the ratings in the two countries, although both agencies employ a scale of five possible added benefit levels, they are not directly comparable. Therefore, the author of this paper suggests comparing the ASMR rating with the added clinical benefit rating in Germany. The proposed method here is to group together medicines receiving either "major" or "considerable" added clinical benefit in Germany to ASMR ratings I, II or III; pairing a "minor" or "unquantifiable" added benefit rating in Germany to an ASMR IV; and finally, equating "no additional benefit" to an ASMR V rating. This categorization, although fairly arbitrary, can accommodate uncertainties surrounding the differences between each level of added clinical benefit, which are not clearly specified in either country. However, there is a clear difference in medications that prove no additional clinical benefit to the comparator (3), some additional benefit (2) and that bring considerable added benefit (1, in Table 3.6.). This

[27] Pfizer Germany Online, [AMNOG for Patients – Package Instruction Leaflet for the Law] and La Revue Prescrire 2002

comparison method forms the basis of the case study section, when classifying decisions made by the G-BA and the HAS as “uniform” and “divergent” decisions.

Table 3.6.

	G-BA	HAS
(1) Substantial added benefit	“Major” (A) or “Considerable” (B)	ASMR I, II, or III
(2) Some minor added benefit	“Minor” (C) or “Unquantifiable” (D)	ASMR IV
(3) No added benefit	“No added benefit proven” (E)	ASMR V

3.2.2. Comparison of HTA Methods and Criteria for Common Appraisals

Table 3.7. HTA methods and criteria for common appraisals – subset (full dataset in Appendix 5.)

Drug	Brand Name	Agency	Best added benefit rating	Clinical evidence	Comparator	Endpoints of clinical study	Endpoints considered	Reason for decision
Axitinib	Inlyta	GBA	2C	Sub-group analysis; Open-label, parallel group	Sorafenib	Mortality, Morbidity, QoL, AEs, Progression	Mortality, Morbidity, QoL, AEs	Benefit rating granted to sub-population due to study design
		HAS	ASMR IV	Open-label, parallel group	Sorafenib	Mortality, Morbidity, QoL, AEs, Progression	All endpoints in study considered	No comparative data on treatment after sunitinib (compared to everolismus)
Crizotinib	Xalkori	GBA	3B	Sub-group analysis; open-label	Chemotherapy	Mortality, morbidity, QoL, AEs, Progression	Mortality, morbidity, QoL, AEs	GBA grants added benefit in one sub-group, against IQWIG recommendation
		HAS	ASMR III	Open-label	Chemotherapy	Mortality, morbidity, QoL, AEs, Progression	All endpoints in study considered	No therapeutic alternative available, also considered phase II trials
Eribulin Mesylate	Halaven	GBA	3C	Sub-group analysis; open-label	Treatment of Physician's Choice	Mortality, Morbidity, AEs, Progression	Mortality, AEs	No complex AEs data provided
		HAS	ASMR IV	Open-label	Treatment of Physician's Choice	Mortality, Morbidity, AEs, Progression	All endpoints in study considered	Small number of patients treated with capecitabine chemotherapy agent - standard practice in France
Ipilimumab	Yervoy	GBA	2B	Direct comparison	gp100	Mortality, QoL, AEs	Mortality, QoL, AEs	Significant immune-mediated adverse events
		HAS	ASMR IV	Direct comparison	gp100	Mortality, QoL, AEs	All endpoints in study considered	Absence of alternative, choice of comparator
Trastuzumab emtansine	Kadcyla	GBA	2B	Sub-group analysis; Direct comparison	Lapatinib + Capecitabin	Mortality, morbidity, QoL, AEs, Progression	Mortality, QoL, AEs	Comparator only ACT for one sub-population for which benefit rating 2B granted
		HAS	ASMR II	Direct comparison	Lapatinib + Capecitabin	Mortality, morbidity, QoL, AEs, Progression	All endpoints in study considered	Based on PFS, OS and acceptable tolerance profile
Vismodegib	Erivedge	GBA	3C	Sub-group analysis; indirect comparison	-	Mortality, morbidity, QoL, AEs, Progression	Mortality, morbidity, QoL, AEs	Deviation from G-BA defined ACT, ORR as primary outcome is not patient-relevant
		HAS	ASMR IV	Indirect comparison	-	Mortality, morbidity, QoL, AEs, Progression	All endpoints in study considered	Non-comparative study data but lack of therapeutic alternative

Table 3.7. presents the detailed analysis of the outcomes and the methods, endpoints and reasons behind clinical benefit ratings for the drugs commonly assessed by both agencies. "Best rating" entails the most favorable rating in any sub-group, according to the latest appraisal. Endpoints considered were categorised into mortality, morbidity, quality of life, adverse events and progression endpoints, where the last one includes all the endpoints related to disease progression and response to treatment (detailed description in Appendix. 3.). The "Reasons for decisions" coloumn recorded any case-specific justification for a certain benefit rating stated explicitly by the corresponding agency in the report document.

3.2.2.1 Clinical Evidence

Clinical evidence submitted for appraisal is assumed to be a double-blind, comparative RCT unless otherwise stated. Although both the HAS and the G-BA require comparative evidence to be submitted, only phase II studies were available in the assessment dossier of two drugs. It was only in the case of Tafinlar© (dabrafenib) that this lack of head-to-head trial data lead to unfavourable decision from both agencies; in the case of Erivedge© (vismodegib), both the HAS and the G-BA granted the medicine some added clinical benefit. Although the HAS considered phase II studies alongside head-to-head trials as well, such as in the case of Xalkori© (crizotinib), the pivotal study and the main driver of clinical benefit rating was always the comparative RCT.

3.2.2.2. Appropriate Comparator Therapy

Given the importance attached to the ACT in the assessment process, most submitted trials used the ACT in the control arm. Derivations from the ACT were rare; in case of Kadcyla© (trastuzumab emtansine), the comparator in the clinical study was only appropriate for one sub-group of the indication population and therefore the G-BA only granted quantifiable added clinical benefit to that subgroup[28]. Such analysis was not undertaken by the HAS, rather, an ASMR IV was decided for the whole indication group. In the case of Erivedge© (vismodegib), although there was deviation from the ACT, and against the recommendation of IQWiG, the G-BA and the HAS both appraised the medicine to have some added clinical benefit. The HAS usually did not comment on the appropriateness of the comparator therapy, except in the case of Yervoy© (ipilimumab), where concerns have been raised about the

[28] Patients after treatment with anthracycline, taxane or trastuzumab.

gp100, a vaccination without MA. In the case of Halaven© (eribulin mesylate), the HAS commented on the fact that only a small number of patients were treated with capecitabine chemotherapy agent, which is the standard practice in France.

3.2.2.3 Endpoints and Criteria

The clinical studies submitted for evaluation provided measures on mortality, morbidity, adverse events, quality of life and other measures related to the progression of the disease. Mortality was mostly expressed by comparing overall survival rates in Germany in the treatment arms; in France progression-free survival was also often considered a primary endpoint in the appraisal process. It is interesting to note that even though it is argued in section 3.1.3 that progression-free survival is an appropriate measure of mortality and morbidity for complex diseases such as cancer, IQWiG tended to disregard PFS as a non-patient-relevant endpoint. A detailed list of the different endpoints that have been assessed in the RCTs can be found in Appendix 3.

The IQWiG consistently examines the patient-relevance of all included endpoints in the analysis and disregards those endpoints for which this relevance cannot be proven. In the case of vismodegib, the company claims objective response rate to be a patient-relevant outcome but the IQWiG does not accept it as one. It is argued in the IQWiG report, that although the size of the externally visible tumour in this case is burdensome for the patients, the actual burden should manifest itself in a change of quality of life or the severity of symptoms associated with the tumour. The IGWiG and the G-BA therefore did not consider objective response rate (ORR) as a patient-relevant outcome. HAS considered all endpoints that were included in the RCT.

Subgroup analyses were regularly undertaken by the IQWiG, especially in those cases where the ACT or the endpoints were only relevant for a specific subset of patients. The IQWiG considered sub-group analyses undertaken in the RCT itself if they were related to the patient-relevant endpoints. In case of crizotinib, for example, the company provided sub-group analyses on sex and age to surrogate endpoints only. Therefore these analyses were not considered in the value assessments. In the case of Jevtana© (cabazitaxel), the IQWiG assessed the added clinical benefit in three different sub-populations; the G-BA recommendation contains two of them and awards an indication of minor added benefit to cabazitaxel only compared to best supportive treatment.

Although much less frequently, but the HAS also conducted sub-group analyses, and in the case of cabazitaxel, a re-assessment of the effectiveness in a specific sub-group[29] granted the medicine an ASMR rating of III instead of IV.

3.2.2.4 Economic Evaluations

Economic evaluations have not been undertaken or made publicly available even though both agencies request them. All G-BA reports contain estimates of medicine prices before and after statutory discounts. Yearly therapy cost of the new medicine versus the old medicine per patients is also provided. There were no economic evaluations in the publicly available database of the HAS for the drugs studied in this paper.

3.2.2.5 Country-specific factors affecting P&R decisions

Although the SMR has not been the focus of this study, given its importance in P&R decisions, it should be briefly discussed. Out of all the studied drugs, only regorafenib had a "weak" SMR rating, justified by the lack of public health benefit it may bring. However, eribulin could also not prove any public health benefit, but was granted "important" SMR level. The availability of therapeutic alternative and the unmet medical need within the therapeutic indication therefore seem to bear more relevance to the SMR rating, and subsequently for the ASMR rating as well, than the public health benefit the medicine may provide.

[29] Those patients for whom docetaxel therapy was halted due to disease progression.

3.3. Case Studies

In order to move the analysis from the theoretical to the empirical level, this paper continues with a case study section to present three cases of appraisals in detail from the commonly assessed medicines. The axis of comparison between the two countries will be the scientific evidence used and the final added clinical benefit rating the same drug received in both countries.

The section is organized as follows: first of all, cases where the same clinical added benefit rating was decided based on the method described in Table 3.6. will be presented. In the first case study of Zelboraf© (vemurafenib), the added benefit rating was the same in both countries based on the same clinical evidence.
The second case study will present a situation where the added clinical benefit rating was the same based on the same clinical evidence, however, the recommendation is restricted to specific sub-groups in Germany (eribulin mesylate).

The third case study presents a very critical part of this paper, showing that based on the same clinical evidence divergent decisions are possible - Zytiga© (abiraterone) was granted substantially different ratings in the two countries.

3.3.1. Uniform Decisions

3.3.1.1. Vemurafenib (Zelboraf ©) – 240mg, 56 tablets

Submission and recommendation timeframe

Vemurafenib was granted MA by the EMA on the 17th of February 2012 and was reviewed by the HAS and the G-BA in the same year; recommendation of the CT was published on the 3rd October 2012. The G-BA decision was first published on the 6th September 2012, with a limited mandate of one year. The manufacturer was required to submit further evidence by the end date of the mandate, which was received by the IQWiG on the 5th September 2013.

Both agencies considered vemurafenib for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Clinical evidence and comparator therapy

Both agencies based their decision on the BRIM-3 study, a randomized, open-label study, comparing vemurafenib with dacarbazine in patients with BRAF V600 mutation-positive unresectable stage IIIc or metastatic (stage IV) melanoma as a first-line treatment. Dacarbazine was determined to be the appropriate comparator therapy by the G-BA.

Clinical effectiveness and safety

In the case of vemurafenib, the BRIM-3 study provided a statistically significant increase in overall survival, which was the basis of granting added clinical benefit rating by both agencies. IQWiG also considered other endpoints in the study, such as pain (in terms of morbidity), quality of life and adverse effects. The HAS considered OS and progression-free survival as joint primary endpoints and considered further secondary endpoints such as tumour response rate (see Table 3.8). The IQWiG chose different patient-relevant outcomes than the manufacturer, because progression-free survival and tumour response as outcomes used in the dossier were not included in the added benefit assessment of vemurafenib by the manufacturer, according to the assessment report.

Table 3.8

	G-BA	HAS
Mortality (OS)	✓	✓
Progression-free survival		✓
Percentage best overall response		✓
Delay in response		✓
Duration of response		✓
Morbidity (pain, VAS Pain questionnaire)	✓	
QoL (FACT-M questionnaire)	✓	
Adverse events	✓	✓

Recommendation – criteria and concerns

Based on the increase in the overall survival rate but the substantial negative adverse effects, the G-BA granted an "indication" (*"Hinweis")* of "considerable" ("beträchtlichen") added clinical benefit to vemurafenib. The HAS determined the ASMR level of vemurafenib to be "moderate" based on the same reasoning and the targeted nature of the medicinal product.

These two ratings can be viewed as belonging to the same category using Table 3.6., that is considerable added benefit.

Table 3.9.

Criteria	G-BA	HAS
Restriction based on indication	✓	✓
Product positioning	✓	✓
Prescriber (e.g. specialist only)		✓
Administration (e.g. hospital use only)		✓
Special monitoring necessary		✓

Economic Evaluations and Pricing

Although both the German and the French HTA body officially require economic evaluations to accompany added benefit assessments, explicit cost-effectiveness or cost-benefit analyses were not conducted alongside the appraisal procedures or were not made publicly available for the studied medicines.

The price of Zelboraf© in Germany after statutory discounts was quoted to be €2516,55; and the yearly therapy cost per patient €131.220,12 (plus necessary biannual mutation test, €100 p.a.) compared to €4.180,30 for dacarbazine.

The HAS did not publish economic evaluation for vemurafenib; the price of Zelboraf© on the ASNM website is quoted as €2288,98, with a 100% reimbursement rate.

Table 3.10

Zelboraf©	**Rating**	**Official List Price**	**IMS Data[30]**
G-BA	2b	€2888.2	Net price = 42% of list price (€1213.04)
HAS	ASMR III	€2288,98 [31]	Assumed the same[32]
Price difference (German vs French price)		+20% (higher price in Germany)	- 53% (lower price in Germany)

[30] Dehnen *et al.* 2013
[31] ANSM Frane Online
[32] Based on empirical testing of numbers from the IMS publication.

As table 3.10. presents, the officially published price of Zelboraf© is about 20% higher in Germany than in France, which cannot be aligned with their similar added benefit levels. However, it should be noted that the prices quoted here do not reflect additional discounts and clawbacks negotiated on the wholesaler or pharmacy level, given that these are not officially disclosed. Furthermore, IMS Consulting Group (IMSCG) published data on the negotiated rebates in Germany, where they claimed the rebate negotiated on Zelboraf© to be 58% of the original list price. The percentage difference between the French and the Germany price is stated as 53%, with the medicine being cheaper in Germany[33][34]. Neither the list prices nor the net prices according to the IMS publication bear any relevance to the very similar added clinical benefit rating of Zelboraf© in the two countries.

3.3.1.2. Eribulin Mesylate (Halaven©) – 0.88mg/2ml

Submission and recommendation timeframe

Eribulin mesylate was given MA by the EMA on the 17th of March, 2011; was appraised by the HAS on the 20th of July, 2011 and on the 19th of April, 2012 by the G-BA.

Both agencies considered eribulin mesylate for the treatment of locally advanced or metastatic breast cancer, for patients who have had at least two chemotherapeutic regimens. Prior therapy is supposed to include an anthracycline and a taxane unless patients were not suitable for these treatments.

Clinical evidence and comparator therapy

Both agencies based their added clinical benefit rating on the open-label, randomized phase III study EMBRACE, comparing eribulin mesylate with an active treatment, left to the choice of the physician. The bias potential of the study was rated as low in the IQWiG report for eribulin, both on the overall and on the endpoint level.

Clinical effectiveness and safety

G-BA considered overall survival as primary endpoint for Halaven© and adverse events as secondary endpoints. The HAS also included progression-free survival, objective response rate and the duration of the response in the analysis. In the HAS report the final secondary

[33] IMSCG 2013, p. 15

[34] The IMS publication claims its sources to be the ANSM Online, which is the source of the French medicine prices in this study as well. The report also claims access to the Lauer Taxe Online, which is a German database for pharmacist and doctors providing information on pharmaceutical prices; unofficial publication of that data is, however, against the law. Therefore such data could not be included in this study.

endpoint is names as “tolerance”, which is later described by the occurrence of adverse events, therefore, it is here included under “adverse events”.

Table 3.11.

	G-BA	HAS
Mortality (OS)	✓	✓
Progression-free survival		✓
Objective response rate		✓
Duration of response		✓
Adverse events	✓	✓

Recommendation – criteria and concerns

IQWiG recommends that eribulin has no proven added benefit compared to the ACT, neither for patients for whom treatment with taxanes or anthracyclines is no longer an option, nor for whom they still are, due to insufficient data provided by the manufacturer. The lack of complex adverse data is disregarded in the final decision of the G-BA, which granted a hint of minor added benefit to both sub-groups of patients.

The CT report of HAS also does not mention the lack of data on complex adverse effects, and does not divide the eligible population into the subgroups IQWiG has. Eribulin mesylate is granted a minor added benefit rating (ASMR IV) for patients who have received either anthracycline or taxane therapy before, except if patients were not able to receive these treatments. It is important to point out that the IQWiG report states that the differentiation between the two subgroups must be made for the evaluation, and the enclosed clinical study also makes the division between them.

Table 3.12.

Criteria	G-BA	HAS
Restriction based on indication	✓	✓
Product positioning	✓	✓
Prescriber (e.g. specialist only)		✓
Administration (e.g. hospital use only)		✓
Special monitoring necessary		✓

Economic evaluation and pricing

The G-BA calculated the yearly therapy costs of eribulin to be €44.411,82; compared to the yearly therapy cost of €7.438,08 for the ACT, capecitabine, and €7.439,12 for vinorelbine.

The comparison of the official list prices showed a rather large price difference, with an over 20% higher price in Germany than in France. However, according to IMS data, the difference in net prices were a mere 8%, with prices lower in Germany, which is more in accordance with the similar added clinical benefit ratings.

Table 3.13.

Halaven©	Rating	Official List Price	IMS Data[35]
G-BA	3C	€435.41[36]	Net price = 73%[37] of list price (€317.85)
HAS	ASMR IV	€320[38]	Assumed the same
Price difference (German vs French price)		+26% (higher price in Germany)	- 8%[39] (lower price in Germany)

3.3.2. Divergent Decisions

3.3.2.1. Abiraterone (Zytiga©) – 250mg, 120 tablets

Submission and recommendation timeframe

Abiraterone was granted MA by the EMA on the 5th of September 2011, and was given an extension of indication on the 18th of December 2012, whereby it was approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC) before chemotherapy treatment. For this particular indication, abiraterone was appraised by IQWiG and was granted added benefit rating by the G-BA on the 4th of July 2013 and on the 12th of June 2013 by the HAS.

Clinical evidence and comparator therapy

Both agencies based their decision on the randomized, double-blind phase III study, COU-AA-302, that compared the efficacy and safety of abiraterone acetate to placebo, combined with both prednisone or prednisolone, in asymptomatic or mildly asymptomatic patients with mCRPC.

[35] Dehnen *et al.* 2013
[36] The officially quoted list price of eribulin in the G-BA report is €2612,46 for 6 vials, the price in the table corresponds to the price per vial.
[37] IMSCG 2013, p.13
[38] Vidal Online via http://www.vidal.fr/Medicament/halaven-106376-prescription_delivrance_prise_en_charge.htm. Viewed August 2014
[39] IMSCG 2013, p. 15

The IQWiG rated the study bias potential to be low on the overall level and also on the endpoint level for OS and severe pain; the analyses of AEs were rated as highly biased because of the "uncertainty of model assumptions"[40], which is later explained to be the lack of evaluable data on adverse events.

Clinical effectiveness and safety

The CT of the HAS considered all clinical effectiveness endpoints that were included in the benefit assessment dossier submitted by the pharmaceutical company. The complete IQWiG recommendation examines the patient-relevance of all endpoints included in the study and considers only those that are deemed relevant, in section 2.7.2.4.3.4 of the IQWiG report (Nr. 160) of Zytiga©.

It is relevant to point out that although the IQWiG final report states that quality of life measures were considered, the Institute did not consider the FACT-P and BPI-SF questionnaires to be either valid or patient-relevant measures of quality of life, but used the time until the need for opiate treatment to measure pain level[41].

Table 3.14.

	G-BA	HAS
Mortality (OS)	✓	✓
Radiological progression-free survival	✓	✓
Time until need for treatment with opiates	✓	✓
Time until the start of cytotoxic chemotherapy		✓
Time until deterioration in ECOG performance[42]		✓
Time until PSA progression[43]		✓

[40] IQWiG Report, Commission No. A13-06, p. 2

[41] It is argued that the BPI-SF questionnair has a not verifyable methodology and that the FACT-P questionnair has an „anchor-based" system to measure quality of life, which is based on clinical tests or physician's opinion, which cannot be validated as patient-relevant outcome measures.

[42] Defined as the time between randomisation and the date when ECOG PS (The Eastern Cooperative Oncology Group Performance Status) deteriorated by at least 1point/grade subject to post-hoc analysis; HAS (2013) "Transparency commission opinion – ZYTIGA (Extension of Indication)", p.6

[43] Defined as the time between randomisation and PSA (Prostate Specific Antigen) progression according to PCWG2 (Prostate Cancer Working Group) criteria; ibid. p. 7.

	G-BA	HAS
PSA response rate[44]		✓
Objective response rate		✓
Duration of response		✓
Time until an increase in need for analgesics		✓
Quality of life (FACT-P and BPI-SF questionnaires)		✓
Adverse events	✓	✓

Recommendation – criteria and concerns

The G-BA's final decision regarding Zytiga© for this indication states that there is a hint of considerable added clinical benefit versus ACT (watchful waiting while maintaining conventional ADT [androgen deprivation therapy]).

The HAS granted a minor level of added clinical benefit to abiraterone acetate. It is relevant to note that this is a fairly large difference to the considerable added benefit declared by the G-BA for Zytiga©. The HAS does not specify any particular reason for the minor level of added benefit granted.

These two ratings are viewed as divergent decisions under the proposed comparison method of the two rating systems based on Table 3.6.

Table 3.15.

Criteria	G-BA	HAS
Restriction based on indication	✓	✓
Product positioning	✓	✓
Prescriber (e.g. specialist only)		✓
Administration (e.g. hospital use only)		✓

[44] Defined as the proportion of patients showing a reduction in PSA by at least 50% compared with baseline according to PCWG2 criteria; ibid.

Economic evaluation and pricing

The G-BA final report provides information on the yearly therapy cost of Zytiga© per patient, which is €52.023,69; this sum is additional to the conventional androgen deprivation therapy provided for the treatment of patients with mCRPC. The HAS document only states the CT's recommendation of 100% reimbursement for Zytiga©.

According to the IMS publication used for pricing data, abiraterone acetate had a 28% price reduction through official and negotiated rebates in Germany, which was then used in IMS report comparing French and German prices of Zytiga©[45]. The IMS report comparing French and German prices of medicines does not include information on negotiated rebates on French drug prices and empirical calculations of this paper confirms that the price differences are equivalent to those between the price found on the ANSM France Online and the German price after the official and negotiated rebates quoted by the IMS report.

Table 5.16.

Zytiga©	**Rating**	**Official List Price**	**IMS Data[46]**
G-BA	3B	€4743,86	Net price = 72%[47] of list price (€3415,58)
HAS	ASMR IV	€3612,58	Assumed the same
Price difference (German vs French price)		+31% (higher price in Germany)	- 4%[48] (lower price in Germany)

[45] IMSCG 2013
[46] Dehnen *et al.* 2013
[47] IMSCG 2013, p.15
[48] ibid.

4. Discussion

4.1 Process

France assessed a much larger sample of drugs than Germany, there were only three drugs that were assessed by the G-BA and not by the HAS, but there were 62 drugs that were appraised by the HAS but not by the G-BA.

The rigour of the process in France and Germany is slightly different based on the sub-group analyses done and data interpretation presented in the appraisal documents. The HAS rarely conducts sub-group analyses other than what is already determined in the indication, even if the submitted clinical evidence would allow for such analysis to be made (see eribulin mesylate case study, section. 3.3.1.2.). The IQWiG conducts a very thorough analysis, which also includes detailed reasoning to why some study endpoints have and have not been considered (see abiraterone case study, section 3.3.2.1.). The G-BA also collects evidence on therapy costs, which is not the case in the HAS report documents. It can therefore be argued that the rigour of the process and the information collection on costs play an important role in the slightly longer evaluation process in Germany compared to France.

4.2 Methods

4.2.1. Clinical evidence

One of the most important finding of this paper is the relatively weak evidence used to assess comparative clinical benefit of cancer treatments in France and Germany. For all the studied medicines, both agencies had the same clinical evidence submitted to them for evaluation, usually one phase III study. Although comparative effectiveness cannot be evaluated without comparative evidence, in the case of vismodegib, certain circumstances lead to a favourable decision in both countries despite of the lack of appropriate clinical evidence to test added clinical benefit.

Missing evidence altered benefit ratings substantially in both countries. In the case of Halaven© (eribulin mesylate), for example, the IQWiG recommended the G-BA not to grant added clinical benefit status. It is argued in the report that even though there was a statistically significant difference in overall survival in one of the sub-groups treated with

eribulin mesylate, the lacking data on complex adverse events prevented the exclusion of possible greater harm.

4.2.2. Sub-group analysis

The German HTA body often considered the added clinical benefit of medicines in more sub-groups than the HAS did, and added benefit was proven in many cases just for a specific subset of the target population identified by the manufacturer. The HAS granted added clinical benefit on overall level and never on a sub-group level; one exception was Jevtana© (cabazitaxel), where the re-assessment of the medicine in a specific sub-population of eligible patients (put forward by the manufacturer) increased the benefit rating from ASMR IV to ASMR III.

It is expected that sub-group analyses will form an increasing important part of assessments in both countries as medicines are developed for ever more specialized indications, which increases research and development costs. This will in turn lead to HTA bodies targeting even narrower sub-groups of patients, for whom actual improvement in effectiveness can be proven in order to control costs but not to hinder access to medicines.

4.2.3 Endpoints and recommendation

Both HTA agencies were consistent in their methods of considering endpoints in studies, Germany focused on patient-relevant outcomes whereas the HAS tended to consider all primary and secondary endpoints that were included in the assessment dossier submitted by the manufacturer. Although there was usually a detailed explanation of why certain endpoints were used by the IQWiG, the exact correlation between clinical effectiveness data and added benefit level was not explicitly stated in the appraisal reports.

Overall the added clinical benefit levels granted to medicines were only marginally different in the two countries. Safety, clinical efficacy and non-inferiority evidently play the most important roles in determining added clinical benefit; France puts more emphasis on the need for the medication or the availability of therapeutic alternatives whereas Germany focuses on the quality of clinical evidence provided.

4.2.4 Economic evaluation and pricing

There were no economic evaluations published by the HTA bodies, although in Germany the clinical benefit rating is stated alongside with the therapy costs for the evaluated treatment

and the ACT as well. It could be possible to develop a method that would combine the two figures into a ratio showing the incremental costs relative to the added benefit, similarly to the method employed by the English HTA body, the National Institute for Health and Care Excellence.

Based on secondary research data on pricing, it can be concluded that there is currently no correlation between the level of added clinical benefit provided by drugs and their list prices, or net prices based on publicly available data. Ideally in the future, there should be a move towards greater correlation between added clinical benefit rating and price premiums awarded to new medications over existing treatments.

4.3. Limitations

This study has several limitations. It is possible that the construction of the master database lacks drugs that were appraised by the HAS only, given that there was not a way to select for cancer indication as a whole, rather all the different types of cancer indications had to be screened separately. Given that the analysis was based on publicly available information, the criteria and reasons agencies base their decisions on may lack some confidential information that would have uncovered some subtleties in the decision processes. Finally, full reports of assessments were only available in original languages, which may have resulted in translational errors.

5. Conclusion and Policy Recommendations

Recent reforms point to convergence in the French and German HTA methods in terms of strengthening the comparative nature of added clinical benefit assessment of new cancer drugs. Decisions have subsequently been only marginally different both in terms of the timing of the decisions and in terms of the added clinical benefit rating they received. An overall inequity of access to medicines therefore cannot be observed. Disparities in decisions, even if marginal, highlight differing priorities of HTA bodies regarding the criteria used to award benefit levels and the consideration of different endpoints from the clinical study. In pursuit of more efficient HTAs in the future, it will be increasingly important for HTA bodies to establish a system in which the level of added clinical benefit corresponds to the net price of the medication to ensure patient access to the most effective medicines across all markets.

The transparency and legitimacy of HTA processes is in the common interest of manufacturers, HTA bodies and policy-makers. The implementation of certain measures would help to overcome the weaknesses of current HTAs highlighted in this paper.

- In order to improve the quality of the evidence submitted to HTA bodies and thereby improve efficiency and reduce rejections, HTA agencies need to set explicit and detailed guidelines on the clinical evidence that is required from manufacturers for HTAs
- To increase transparency in terms of methodology, HTA bodies should also provide detailed information on their process indicators, how they define differences between achieved levels of clinical added benefit, what are the determinants of such ratings and what manufactures can do to achieve the highest possible rating
- To reduce disparities, cancer drug assessments should be standardized across all HTA bodies
- In order to increase the uptake of new technologies and to maximize access and health benefit, HTAs should take place as soon as possible alongside with economic evaluations including budget impact analysis
- There should be a correlation between clinical benefit ratings and price premiums awarded to medicines; a methodology should also be developed to ensure a transparent way of setting prices of new cancer drugs

- HTA bodies should also consider improving their image in the media; assessment agencies are often pictured as the entities that prevent patient access to life-saving medicines. Greater collaboration with policy-makers and manufacturers could ensure that the common goal of making the most effective medications available for people is shared between the stakeholders and is effectively communicated to the public.

Figures

Figure 1.

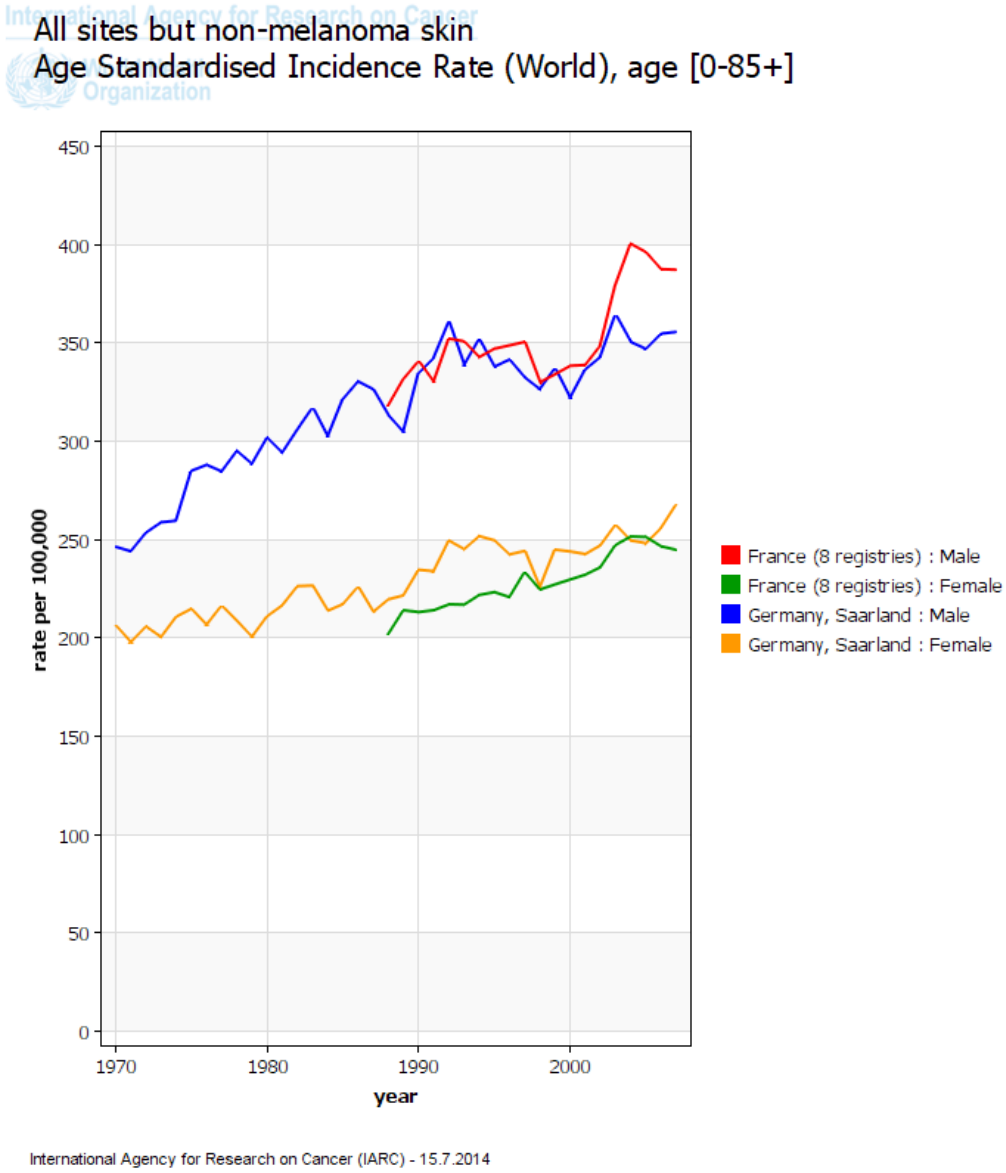
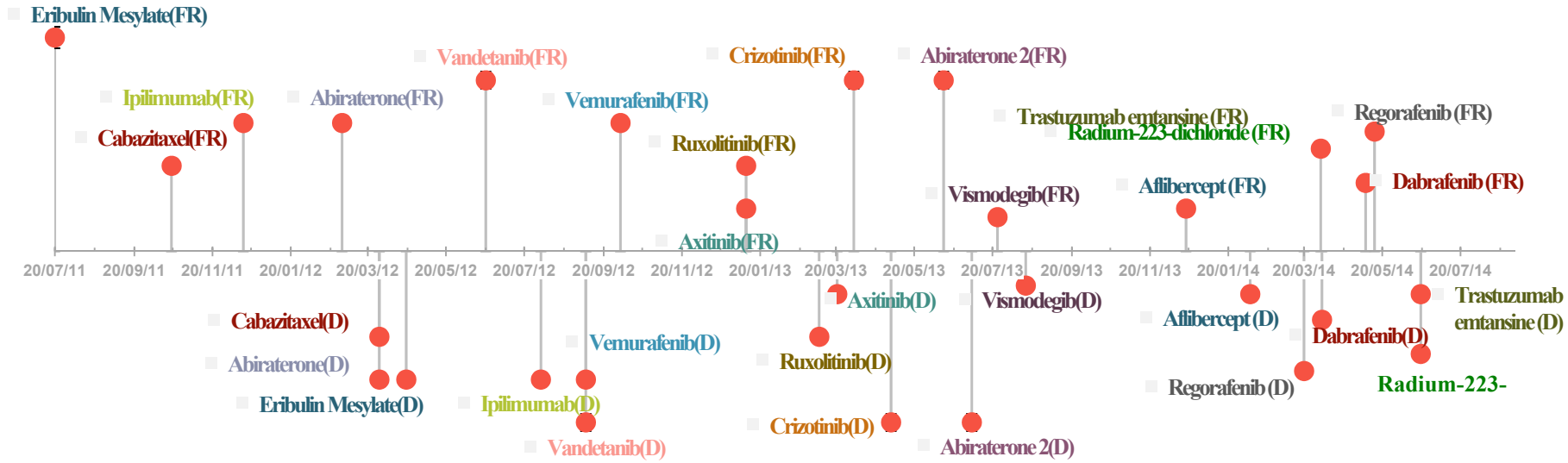


Figure 2.


Eribulin Mesylate(FR)
Ipilimumab(FR)
Cabazitaxel(FR)
Abiraterone(FR)
Vandetanib(FR)
Vemurafenib(FR)
Ruxolitinib(FR)
Axitinib(FR)
Crizotinib(FR)
Abiraterone 2(FR)
Vismodegib(FR)
Trastuzumab emtansine (FR)
Radium-223-dichloride (FR)
Aflibercept (FR)
Regorafenib (FR)
Dabrafenib (FR)
20/07/11
20/09/11
20/11/11
20/01/12
20/03/12
20/05/12
20/07/12
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20/11/12
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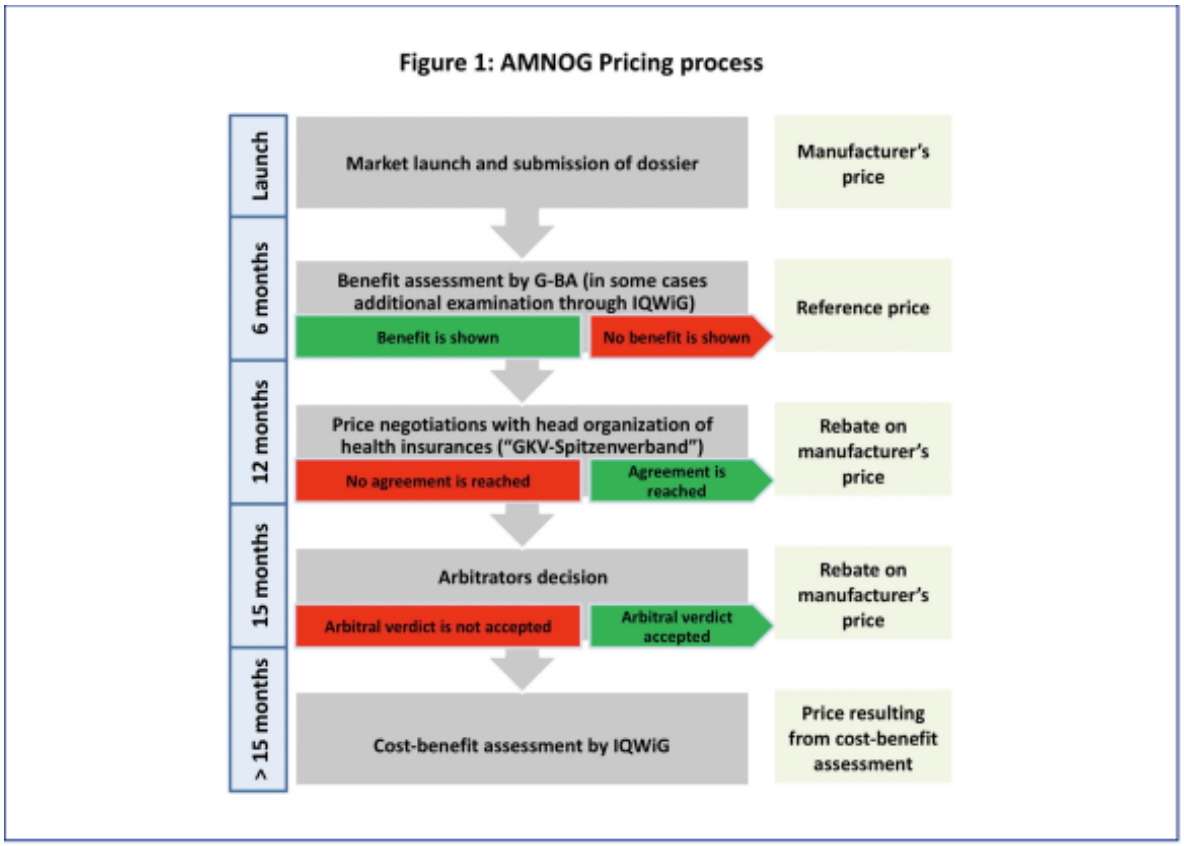
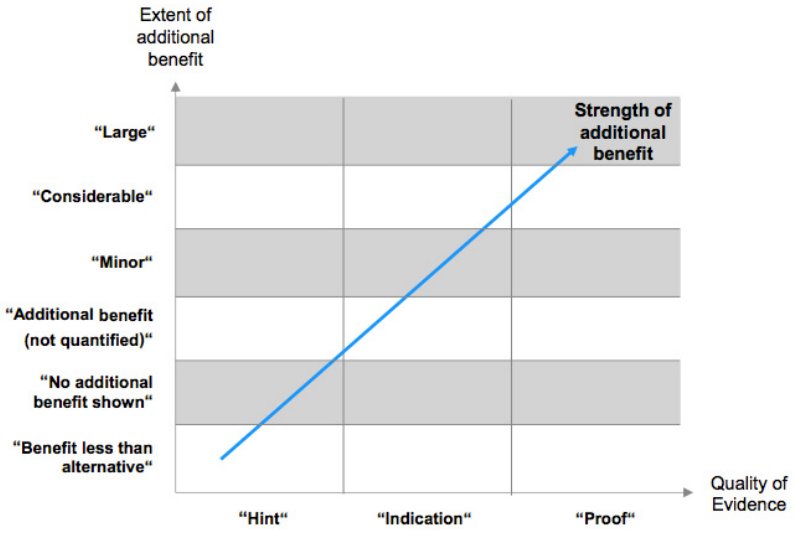
20/05/13
20/07/13
20/09/13
20/11/13
20/01/14
20/03/14
20/05/14
20/07/14
Cabazitaxel(D)
Abiraterone(D)
Eribulin Mesylate(D)
Ipilimumab(D)
Vandetanib(D)
Vemurafenib(D)
Ruxolitinib(D)
Crizotinib(D)
Axitinib(D)
Abiraterone 2(D)
Vismodegib(D)
Aflibercept (D)
Regorafenib (D)
Dabrafenib(D)
Trastuzumab emtansine (D)
Radium-223-

Figure 3.



Source: Schoonveld *et al.* 2011

Figure 4.



Large – erheblich; Considerable – beträchtlich; Minor – gering; Additional benefit (not quantified) - liegt vor, ist aber nicht quantifizierbar; No additional benefit shown – kein Zusatznutzen belegt; Benefit less than alternative – Nutzen geringer als der Nutzen der zweckmäßigen Vergleichstherapie; Hint – Anhaltspunkt; Indication – Hinweis; Proof – Beleg

Ecker + Ecker Reimbursement Germany

Source: Ecker + Ecker GmbH 2013

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Appendix

Appendix 1. Master database

	Drug	Brand Name	ATC Code	Drug Indication	France (HAS)			Germany (G-BA)		
					SMR	ASMR	HAS date	Overall Decision*	Best outcome	month/year
A	**Abiraterone**	Zytiga	L02BX03	mCRPC	Important	AMR III	29-Feb-2012	2	2B	29-Mar-2012
	Abiraterone 2	Zytiga	L02BX03	mCRPC before chemotherapy	Important	ASMR IV	12-Jun-2013	1	3B	4-Jul-2013
	Afatinib	Giotrif	L01XE13	Metastatic NSCLC	-			2	2B	8-May-2014
	Aflibercept	Zaltrap	L01XX44	Colorectal cancer	Important	ASMR V	24-Jun-2013	1	2C	15-Aug-2013
	Axitinib	Inlyta	L01XE17	Renal cell carcinoma	Important	ASMR IV	9-Jan-2013	2	2C	21-Mar-2013
B	**Bendamustine**	Levact	L01AA09	Chronic lymphoid leukaemia	Important	AMSR III	6-Oct-2010	0		
	Bendamustine 2	Levact	L01AA09	Multiple Myeloma	Important	ASMR V		0		
	Bevacizumab 1	Avastin	L01XC07	Metastatic breast cancer	Important	ASMR V	25-May-2011	0		
	Bevacizumab 2	Avastin	L01XC07	Metastatic carcinoma of the colon or rectum	Important	ASMR IV	4-Mar-2009	0		
	Bevacizumab 3	Avastin	L01XC07	Renal cell cancer	Important	ASMR IV	3-Sep-2008	0		
	Bevacizumab 4	Avastin	L01XC07	NSCLC	Important	ASMR V	14-May-2008	0		
	Bevacizumab 5	Avastin	L01XC07	Metastatic breast cancer	Important	ASMR III	5-Dec-2007	0		
	Bexarotene	Targretin	L01XX25	NHL	Important	ASMR V	28-Mar-2012	0		
C	**Cabazitaxel**	Jevtana	L01CD04	Prostate cancer	Important	ASMR III	17-Nov-2012	1	2C	29-Mar-2012
	Chlorambucil	Chloraminophene	L01AA02	Chronic Myeloid Leukaemia	Important	-	7-Nov-2012	0		
	Cladribine	Leustatine	L01BB04	Leukaemia	Important	ASMR II	25-Jun-2014	0		
	Crizotinib	Xalkori	L01XE16	NSCLC	Important	ASMR III	3-Apr-2013	2	3B	2-May-2013
	Cyproterone	Androcur	G03HA01	Prostate cancer (palliative)	Important	-	19-Dec-2012	0		

	Drug	Brand Name	ATC Code	Drug Indication	France (HAS)☞			Germany (G-BA)		
	Cytarabine	Cytarabine Accord	L01BC01	Acute Myeloid Leukaemia (AML)	Important	ASMR V	6-Nov-2013	0		
	Cytarabine	Aracytine	L01BC01	AML, CML	Important	-	19-Jan-2011	0		
D	**Dabrafenib**	Tafinlar	L01XE	Unresectable or metastatic melanoma with BRAF V600E mutation	Important	ASMR V	7-May-2014	3	-	3-Apr-2014
	Daunorubicine	Cerubidine	L01DB02	Leukaemia	Important	ASMR V	2-Apr-2014	0		
	Denosumab 1	Xgeva	M05BX04	Skeletal event prevention by breast or prostate cancer	Important	ASMRI V	11-Apr-2012	0		
	Denosumab 2	Prolia	M05BX04	Bone loss in patients with prostate cancer	Insufficient	-	14-Dec-2011	0		
	Diethylstilbestrol	Distilbene	G03CB02	Prostate cancer	Weak	-	21-Sep-2011	0		
E	**Enzalutamide**	Xtandi	L01XX	mCRPC	Important	ASMR III	20-Nov-2013	1	2B	20-Feb-2014
	Eribulin Mesylate	Halaven	L01XX41	Metastatic breast cancer	Important	ASMR IV	20-Jul-2011	1	3C	19-Apr-2012
	Erlotinib 1 ∀	Tarceva	L01XE03	Metastatic NSCLC	Important	ASMR IV	6-Jun-2012	0		
	Erlotinib 2 ∀	Tarceva	L01XE03	Metastatic pancreatic cancer	Insufficient	-	19-Mar-2008	0		
	Erlotinib 3 ∀	Tarceva	L01XE03	Metastatic NSCLC after chemotherapy	Important	ASMR IV (only as 3rd line)	15-Mar-2006	0		
	Everolimus 1 ∃	Afinitor	L01XE10	Breast cancer	Important	ASMR V	3-Apr-2013	0		
	Everolimus 2 ∃	Afinitor	L01XE10	pNET	Important	ASMR IV	28-Mar-2012	0		
	Everolimus 3 ∃	Afinitor	L01XE10	Renal cell carcinoma	Important	ASMR IV	13-Jan-2010	0		

	Drug	Brand Name	ATC Code	Drug Indication	France (HAS)☞			Germany (G-BA)		
F	**Fentanyl**	Breakyl	N02AB03	Paroxysmal cancer-related pain (palliative)	Important	ASMR V	6-Sep-2012	0		
	Fotemustine	Muphoran	L01AD05	Brain tumour	Important	ASMR V	9-Jul-2014	0		
H	**Histrelin acetate**	Vantas	H01CA03	Prostate cancer (palliative)	Moderate	ASMR V	29-Feb-2012	0		
I	**Imatinib 1**∃	Glivec	L01XE01	ALL (with chemotherapy for children)	Important	ASMR I	28-May-2014	0		
	Imatinib 2∃	Glivec	L01XE01	Gastrointestinal stromal tumour	Important	ASMR III	9-Sep-2009	0		
	Imatinib 3∃	Glivec	L01XE01	Dermatofibrosarcoma protuberans	Important	ASMR IV	23-Jan-2008	0		
	Imatinib 4∃	Glivec	L01XE02	Hypereosinophilic syndrome	Important	ASMR III	7-Nov-2007	0		
	Imatinib 5∃	Glivec	L01XE04	ALL (monotherapy)	Important	ASMR II	14-Feb-2007	0		
	Imatinib 6∃	Gilvec	L01XE06	ALL (with chemotherapy)	Important	ASMR I	14-Feb-2007	0		
	Ipilimumab	Yervoy	L01XC11	Melanoma	Important	ASMR IV	14-Dec-2011	1	2B	2-Aug-2012
L	**Leuprorelin**	Eligard	L02AE02	Prostate cancer	Important	-	24-Jul-2013	0		
M	**Medroxyprogesterone acetate**	Depo-Prodasone	L02AB02	Endometrial cancer	Insufficient	-	18-Sep-2013	0		
	Medroxyprogesterone acetate 2	Farlutal	L02AB02	Endometrial cancer	Insufficient	-	16-Feb-2011	0		
	Melphalan	Alkeran	L01AA03	Multiple Myeloma, Ovarian Cancer	Important	-	21-Sep-2011	0		
	Methyl aminolevulinate	Metvixia	L02BG04	Bowen's disease	Important	ASMR IV	5-Mar-2014	0		
N	**Nilutamide**	Anandron	L02BB02	Prostate cancer	Important	-	15-May-2013	0		
O	**Octreotide**	Sandostatine	H01CB02	Gastro-entero-pancreatic endocrine tumour	Important	-	6-Nov-2013	0		
	Oxycodone	Targinact	N02AA55	Severe cancer-related pain (palliative)	Insufficient	-	7-Dec-2011	0		
P	**Paclitaxel**∀	Paclitaxel AHCL	L01CD01	Ovarian cancer	Important	ASMR V	9-Jul-2014	0		

	Drug	Brand Name	ATC Code	Drug Indication	France (HAS)☞			Germany (G-BA)		
	Panitumumab 1	Vectibix	L01XC08	Metastatic colorectal cancer	Important	ASMR V	17-Oct-2012	0		
	Panitumumab 2	Vectibix	L01XC08	Metastatic colorectal cancer (KRAS)	Important	ASMR V	30-Apr-2008	0		
	Pazopanib 1 ∀	Votrient	L01XE11	Soft-tissue sarcoma	Important	ASMR IV	9-Jan-2013	0		
	Pazopanib 2 ∀	Votrient	L01XE11	Renal cell carcinoma	Weak	ASMR V (1st line treatment)	26-Jun-2013	0		
	Pentostatine	Nipent	L01XX08	Leukaemia	Important	ASMR II	25-Jun-2014	0		
	Pertuzumab	Perjeta	L01XC13	Breast neoplasms	-			2	3B	1-Oct-2013
	Pixantrone dimaleate	Pixuvri	L01DB11	NHL	-			3	-	16-May-2013
	Procarbazine	Natulan	L01XB01	HL and NHL (ganglionic and intestinal), brain tumours	Important	-	20-Jun-2012	0		
	Profimer sodium	Photofrin	L01XD01	Lung cancer	Weak	ASMR V	9-Jul-2014	0		
	Propranolol ∀	Hemangiol	D11AX	Hemangioma	Important	ASMR III	25-Jun-2014	0		
R	**Radium-223-dichloride**	Xofigo	V10XX	CRPC	Important	ASMR IV	2-Apr-2014	2	2B	19-Jun-2014
	Raltitrexed	Tomudex	L01BA03	Metastatic colorectal cancer	Important	ASMR V	9-Jul-2014	0		
	Regorafenib monohydrate	Stivarga	L01XE21	Metastatic colorectal cancer	Weak	ASMR V	14-May-2014	1	3C	20-Mar-2014
	Rituximab 1 ∀	Mabthera	L01XC02	Follicular lymphoma	Important	ASMR II	18-Jul-2012	0		
	Rituximab 2 ∀	Mabthera	L01XC02	CLL	Important	ASMR III	18-Jul-2012	0		
	Rituximab 3 ∀	Mabthera	L01XC02	CLL (not previously treated)	Important	ASMR III	25-May-2011	0		
S	**Sunitinib 1** ∃	Sutent	L01XE04	pNET	Moderate	ASMR V	21-Sep-2011	0		

	Drug	Brand Name	ATC Code	Drug Indication	France (HAS)☞			Germany (G-BA)		
	Sunitinib 2[∃]	Sutent	L01XE04	Metastatic renal cell carcinoma	Important	ASMR II	23-May-2007	0		
	Sunitinib 3[∃]	Sutent	L01XE04	Metastatic renal cell carcinoma (second-line)	Important	ASMR III	20-Sep-2006	0		
	Sunitinib 4[∃]	Sutent	L01XE04	Gastrointestinal stromal tumour	Important	ASMR II	20-Sep-2006	0		
T	**Tamoxifen**	Nolvadex	L02BA01	Breast cancer	Important	-	7-Sep-2011	0		
	Tegafur/gimeracil/oteracil[∀]	Teysuno	L01BC53	Advanced gastric cancer	Insufficient	N/A	3-Oct-2012	3	-	20-Dec-2012
	Tegafur+ uracil	UFT	L01BC53	Metastatic colorectal cancer	Important	-	11-Apr-2012	0		
	Temozolomide[∀]	Temozolomide Mylan	L01AX03	Glioblastoma multiforme	Important	ASMR V	20-Nov-2013	0		
	Trastuzumab 1[∀]	Herceptin	L01XC03	HER2+ early breast cancer	Important	-	9-Jan-2013	0		Expected mid June 2014
	Trastuzumab 2[∀]	Herceptin	L01XC03	Metastatic gastric cancer	Important	ASMR IV	16-Feb-2011	0		
	Trastuzumab 3[∀]	Herceptin	L01XC03	Breast cancer overexpress HER2	Important	ASMR V	19-Mar-2008	0		
	Trastuzumab 4[∀]	Herceptin	L01XC03	Breast cancer overexpress HER2 (second-line)	Important	ASMR I	4-Oct-2006	0		
	Trastuzumab emtansine	Kadcyla	L01XC	HER2+ breast cancer	Important	ASMR II	19-Mar-2014	2	2B	19-Jun-2014
V	**Vandetanib**[∀]	Caprelsa	L01XE12	Medullary thyroid cancer	Important	ASMR IV	20-Jun-2012	2	3C	5-Sep-2013
	Vemurafenib	Zelboraf	L01XE15	Melanoma	Important	ASMR III	3-Oct-2012	1	2B	6-Mar-2014
	Vinorelbine	Navelbine	L01CA04	Breast cancer and NSCLC	Important	-	6-Jun-2012	0		
	Vismodegib[∀]	Erivedge	L01XX43	Basal cell carcinoma	Important	ASMR IV	18-Dec-2013	2	3C	6-Feb-2014

[∀]Medicinal products that are intended for rare diseases in Europe with European MA without orphan designation in Europe.
[∃]Medicinal products that have been removed or withdrawn from the European Community Register (ECR) of orphan medicinal products.

* If the medicine is only found to bring added clinical benefit for a specific subgroup of patients, or the medicine has not been compared to the ACT defined by the G-BA, but certain circumstances lead to a favourable decision anyway, the decision by the GBA is recorded as “Favourable with restrictions”. If the medicine was approved for the same indication and for the same target population as applied for, and was compared to the ACT, the decision was recorded as “Favourable”. When added clinical benefit was not proven, the decision was “Not favourable”.

Key to overall G-BA decision: (0) Not appraised, (1) Favourable, (2) Favourable with restrictions, (3)Not favourable

☞*Key from section 3.2.1:*

G-BA		**HAS**	
Quality of Evidence	**Extent of Benefit**	**SMR**	**ASMR**
1. Proof ("*Beleg*")	A) Major ("*Erheblich*")	Major ("*Majeur*")	ASMR I (Major)
2. Indication ("*Hinweis*")	B) Considerable ("*Beträchtlich*")	Important ("*Important*")	ASMR II (Important)
3. Hint (“*Anhaltspunkt*")	C) Minor ("*Gering*")	Moderate ("*Modéré"*)	ASMR III (Moderate)
4. Not proven (“*Nicht belegt*”)	D) Not quantifiable additional benefit ("*Liegt vor, ist aber nicht quantifizierbar”*)	Weak ("*Faible*")	ASMR IV (Minor)
	E) No additional benefit shown ("*Kein Zusatznutzen belegt*")	Insufficient ("*Insuffisant*")	ASMR V (Non-existent)
	f) Benefit less than alternative ("*Nutzen geringer als der Nutzen der zweckmäßigen Vergleichstherapie*")		

Appendix 2. Common appraisals - detailed comparison

	Drug	Brand Name	GBA						HAS		
			G-BA (overall)	Further subgroup	IQWIG Rec.	Added benefit	GBA date	Clinical Study	HAS Rating	Date	Clinical Study
A	**Abiraterone**	Zytiga	2	BSC	2B	2B	29-Mar-2012	COU-AA-301	ASMR III	29-Feb-2012	COU-AA-301
				Docetaxel	4						
		Zytiga	1		3B	3B	4-Jul-2013	COU-AA-302	ASMR IV	12-Jun-2013	COU-AA-302
	Aflibercept	Zaltrap	1		2C	2C	15-Aug-2013	VELOUR	ASMR V	24-Jul-2013	VELOUR
	Axitinib	Inlyta	2	Post cytokine-treatment	3B	2C	21-Mar-2013	AXIS (A4061032)	ASMR IV	9-Jan-2013	AXIS study (A4061032)
				Post sunitinib treatment	4	4			ASMR V	8-Jan-2014	
C	**Cabazitaxel**	Jevtana	2	BSC over 65	2B	2C	29-Mar-2012	TROPIC STUDY (EFC6193)	ASMRIII	17-Nov-2012 (first assessment: 19-Oct-2011)	TROPIC STUDY (EFC6193)
				BSC under 65	3D						
				Docetaxel		4					
	Crizotinib	Xalkori	2	Chemotherapy is indicated	4	3B	2-May-2013	PROFILE 1007	ASMR III	3-Apr-2013	PROFILE 1007 (Phase III), Study 1001(Phase I), 1005 (Phase II)
				Chemotherapy not indicated	4	4					
D	**Dabrafenib**	Tafinlar	3			4	3-Apr-2014	BREAK-3	ASMR V	7-May-2014	BREAK-2, BREAK 3
E	**Enzalutamide**	Xtandi	1	Visceral metastasis	3B	2B	20-Feb-2014	AFFIRM	ASMR III	20-Nov-2013	AFFIRM
				No visceral metastasis	3A						

	Drug	Brand Name	GBA						HAS		
			G-BA (overall)	Further subgroup	IQWIG Rec.	Added benefit	GBA date	Clinical Study	HAS Rating	Date	Clinical Study
	Eribulin Mesylate	Halaven	1	Taxanes or anthracyclines no longer an option	4	3C	19-Apr-2012	EMBRACE	AMSR IV	20-Jul-2011	EMBRACE and Study 201, 211 (phase II)
				Taxanes or anthracyclines still possible	4	3C					
I	**Ipilimumab**	Yervoy	1		2B	2B	2-Aug-2012	MDX010-20	ASMR IV	14-Dec-2011	MDX010-20
			3	No prior therapy, compared to Dacarbazine	4	4	5-Jun-2014	Only indirect comparison submitted	ASMR IV	06-Nov-2013 (re-assessment)	
R	**Radium-223-dichloride**		2	Docetaxel is still possible		4	19-Jun-2014		ASMR IV	2-Apr-2014	
				Docetaxel is not possible		2B		ALSYMPCA (BC1-06) – data only for this sub-group			ALSYMPCA (BC1-06) – data only for this sub-group
	Regorafenib	Stivarga	1		3C	3C	20-Mar-2014	CORRECT	ASMR V	14-May-2014	CORRECT
T	**Trastuzumab emtansine**	Kadcyla	2	Inoperable breast cancer	4	4	19-Jun-2014				
				Post anthracycline, taxane or trastuzumab treatment	2B	2B		EMILIA – data only for this sub-group	ASMR II	19-March-2014	EMILIA – data only for this sub-group, THERESA
				After treatment not with anthracycline	4						
V	**Vandetanib**	Caprelsa	2		4	3C	5-Sep-2013	ZETA/58 Study	ASMR IV	20-Jun-2012	ZETA/58 Study
					4	4	6-Sep-2012				
	Vemurafenib	Zelboraf	1		2B	2B	6-Mar-2014 (first: 06-Sep-2102)	Study NO25026 (BRIM-3)	ASMR III	3-Oct-2012	Study NO25026 (BRIM-3)

	Drug	Brand Name	GBA						HAS		
			G-BA (overall)	Further subgroup	IQWIG Rec.	Added benefit	GBA date	Clinical Study	HAS Rating	Date	Clinical Study
	Vismodegib	Erivedge	2	Local advanced basal-cell-carcinoma, neither operation nor radiotherapy is suitable (smBCC)	4	3C	6-Feb-2014	ERIVANCE	ASMR IV	18-Dec-2013	ERIVANCE (Phase II), STEVIE (Phase II)
				Symptomatic metastatic basal-cell carcinoma (lsBCC)	4	4					

Appendix 3. Endpoints defined

	Endpoint	Definition (HAS Reports)
Mortality / Morbidity	rPFS (Radiological progression-free survival)	Time between randomisation and radiological progression or death.
	VAS (Visual Analogue Scale) Pain	
	Time to first skeletal-related event	Radiotherapy or bone surgery, a pathological fracture, spinal cord compression, a change in antineoplastic treatment, in line with the protocol, to treat bone pain.
	Time until need for treatment with opiates	Time between randomisation and the use of an opiate for the treatment of cancer pain.
	FKSI-DRS	FACT Kidney Symptom Index - Disease-Related Symptoms
	PPI-Scores	Palliative Prognostic Index (for pain)
	EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
Progression/ Response	Time until the start of cytotoxic chemotherapy	Time between randomisation and administration of cytotoxic chemotherapy for the treatment of prostate cancer (sometimes used as QoL indicator)
	Time until deterioration in ECOG performance	Time between randomisation and the date when ECOG PS (The Eastern Cooperative Oncology Group Performance Status) deteriorated by at least 1point/grade subject to post-hoc analysis.
	Time until PSA (Prostate Specific Antigen) progression	Time between randomisation and PSA (Prostate Specific Antigen) progression according to PCWG2 (Prostate Cancer Working Group) criteria.
	PSA response rate	Proportion of patients showing a reduction in PSA by at least 50% compared with baseline according to PCWG2 criteria.
	Objective response rate	Proportion of patients showing an objective response (i.e. a complete response [CR] or a partial response [PR]) identified with CT-CAT scan or MRI.
	Duration of response	Time between the first response and the appearance of progression identified with CT-CAT scan or MRI.
	Time until an increase in need for analgesics	Time between randomisation and the date of an increase of ≥30% in score for analgesics used over a 4 week period.
Quality of Life	FACT-P	Functional Assessment of Cancer Therapy – Prostate
	BPI-SF	Brief Pain Inventory (Short Form)
	FKSI-15	FACT Kidney Symptom Index
	EQ-5D	EuroQoL: quality of health-related life

Appendix 4: Common appraisals - information

	Drug	Brand Name	MA holder	Form	Additional Monitoring	MA date by EMA	ATC code
A	**Abiraterone**	Zytiga	Janssen-Cilag International N.V.	250mg, 120tablets	Yes	5-Sep-2011	L02BX03
		Zytiga	Janssen-Cilag International N.V.	250mg, 120tablets	Yes		L02BX03
	Aflibercept	Zaltrap	Sanofi-Aventis Groupe	25mg/ml, 4 or 8ml vial, 1or 3 vials	Yes	1-Feb-2013	L01XX44
	Axitinib	Inlyta	Pfizer Ltd.	5mg 56 tablets	Yes	3-Sep-2012	L01XE17
D	**Dabrafenib**	Tafinlar	Glaxosmithkline PLC	50/75mg, 120 tablets	Yes	26-Aug-2013	L01XE
C	**Cabazitaxel**	Jevtana	Sanofi-Aventis Groupe S.A.	60mg/1.5ml, 1 vial of 1.5ml	Yes	17-Mar-2011	L01CD
	Crizotinib	Xalkori	Pfizer Ltd.	200/250mg, 60 tablets	Yes and Conditional approval[Ψ]	23-Oct-2012	L01XE16
E	**Eribulin Mesylate**	Halaven	Eisai Europe Ltd.	0.88mg/2ml, 1/6 vials of 5ml with 2ml solvent	Yes	17-Mar-2011	L01XX41
	Enzalutamide	Xtandi	Astellas Pharma Europe B.V.	40mg, 120tablets	Yes	21-Jun-2013	
I	**Ipilimumab**	Yervoy	Bristol-Myers Squibb Pharma EEIG	5mg/ml, 10ml/40ml vial	Yes	13-Jul-2011	L01XC11
R	**Radium-223-dichloride**	Xofigo	Bayer Pharma AG	1000 kBq/ml, 6ml vial	Yes	1-Nov-2013	V10XX03
	Regorafenib	Stivarga	Bayer Pharma AG	40mg, 84 tablets	Yes	26-Aug-2013	L01XE21
T	**Trastuzumab emtansine**	Kadcyla	Roche Registration Ltd	100/160mg, 1 vial of 15/20ml	No	15-Nov-2013	L01XC14
V	**Vandetanib**	Caprelsa	AstraZeneca AB	300mg, 30tablets	Yes and Conditional Approval	17-Feb-2012	L01XE18
	Vemurafenib	Zelboraf	Roche Registration Ltd.	240mg, 56 tablets	Yes	17-Feb-2012	L01XE15
	Vismodegib	Erivedge	Roche Registration Ltd	150mg, 28 tablets	Yes and Conditional Approval	12-Jul-2013	L01XX43

[Ψ]Conditional approval: approval based on non-comprehensible data, that nevertheless proves that the benefits of the medicine outweigh its risks; the medicine must address "unmet medical need" and the company is required to fulfill certain obligations and the approval is re-evaluated on yearly basis (EMA website).

Appendix 5. HTA methods and criteria for common appraisals – full sample

Drug	Brand Name	Agency	Best added benefit rating[49]	Clinical evidence use[50]	Comparator	Endpoints of clinical study[51]	Endpoints considered	Reason for decision
Abiraterone	Zytiga	GBA	2B	Sub-group analysis; Direct comp.	Placebo + prednisolone + BSC	Mortality, Morbidity, QoL, AEs, Progression	Mortality, Morbidity, AEs	AEs data cannot prove less harm, QoL not evaluable
		HAS	ASMR III	Direct comp.	Placebo + prednisolone +BSC	Mortality, Morbidity, QoL, AEs, Progression	All endpoints in study considered	Efficacy and tolerance
	Zytiga	GBA	3B	Direct comp.	Placebo + prednisone	Mortality, Morbidity, QoL, AE, Progression	Mortality, Morbidity	Bias potential of AEs data, QoL not evaluable
		HAS	ASMR IV	Direct comp.	Placebo+ prednisone	Mortality, Morbidity, QoL, AE	All endpoints in study considered	Efficacy
Aflibercept	Zaltrap	GBA	2C	Direct comp.	Placebo+FOLFIRI[52]	Mortality, AEs, Progression	Mortality, AEs	Possible greater harm due to serious AEs
		HAS	ASMR V	Direct comp.	Placebo+FOLFIRI	Mortality, AEs, Progression	All endpoints in study considered	High frequency of treatment discontinuation due to AEs
Axitinib	Inlyta	GBA	2C	Sub-group analysis; Open-label, parallel group	Sorafenib	Mortality, Morbidity, QoL, AEs, Progression	Mortality, Morbidity, QoL, AEs	Benefit rating granted to sub-population due to study design
		HAS	ASMR IV	Open-label, parallel group	Sorafenib	Mortality, Morbidity, QoL, AEs, Progression	All endpoints in study considered	No comparative data on treatment after sunitinib (compared to everolismus)
Cabazitaxel	Jevtana	GBA	2C	Sub-group analysis; Open-label	Mitoxantrone	Mortality, Morbidity, QoL, AEs, Progression	Mortality, Morbidity, AEs	Benefit rating granted to sub-population due to study design
		HAS	ASMR III	Sub-group analysis; Open-label	Mitoxantrone	Mortality, Morbidity, QoL, AEs, Progression	All endpoints in study considered	ASMR III instead of ASMR IV based on sub-group analysis

[49] The most favorable rating in any sub-group, according to the latest appraisal.
[50] Assumed to be a double-blind, comparative RCT unless otherwise stated.
[51] List of possible endpoints included in studies with definitions can be found in Appendix 3.
[52] Irinotecan with fluorouracil (5FU) and folinic acid (FOLFIRI)

Drug	Brand Name	Agency	Best added benefit rating[49]	Clinical evidence use[50]	Comparator	Endpoints of clinical study[51]	Endpoints considered	Reason for decision
Crizotinib	Xalkori	GBA	3B	Sub-group analysis; open-label	Chemotherapy	Mortality, morbidity, QoL, AEs, Progression	Mortality, morbidity, QoL, AEs	GBA grants added benefit in one sub-group, against IQWIG recommendation
		HAS	ASMR III	Open-label	Chemotherapy	Mortality, morbidity, QoL, AEs, Progression	All endpoints in study considered	No therapeutic alternative available, also considered phase II trials
Dabrafenib	Tafinlar	GBA	4	Indirect comparison	Dacarbazine	Mortality, Morbidity, QoL, AEs, Progression	Mortality, Morbidity, QoL, AEs	Methodological shortcomings of study
		HAS	ASMR V	Indirect comparison	Dacarbazine	Mortality, Morbidity, QoL, AEs, Progression	All endpoints in study considered	No direct comparison between dabrafenib and vemurafenib
Enzalutamide	Xtandi	GBA	2B	Sub-group analysis; Direct comparison	Placebo	Mortality, Morbidity, QoL, AEs, Progression	Mortality, Morbidity, AEs	-
		HAS	ASMR III	Direct comparison	Placebo	Mortality, Morbidity, QoL, AEs, Progression	All endpoints in study considered	No active comparator data
Eribulin Mesylate	Halaven	GBA	3C	Sub-group analysis; open-label	Treatment of Physician's Choice	Mortality, Morbidity, AEs, Progression	Mortality, AEs	No complex AEs data provided
		HAS	ASMR IV	Open-label	Treatment of Physician's Choice	Mortality, Morbidity, AEs, Progression	All endpoints in study considered	Small number of patients treated with capecitabine chemotherapy agent - standard practice in France
Ipilimumab	Yervoy	GBA	2B	Direct comparison	gp100	Mortality, QoL, AEs	Mortality, QoL, AEs	Significant immune-mediated adverse events
		HAS	ASMR IV	Direct comparison	gp100	Mortality, QoL, AEs	All endpoints in study considered	Absence of alternative, choice of comparator
Radium-223-dichloride	Xofigo	GBA	2B	Direct comparison	Placebo	Mortality, morbidity, QoL, AEs, Progression	Mortality, morbidity, AEs	Study only provides valid data for BSC population
		HAS	ASMR IV	Direct comparison	Placebo	Mortality, morbidity, QoL, AEs, Progression	All endpoints in study considered	No active comparator data, uncertain extrapolation
Regorafenib	Stivarga	GBA	3C	Direct comparison	Placebo	Mortality, morbidity, QoL, AEs, Progression	Mortality, morbidity, AEs	Only patients with ECOG PS 0 or 1 in the study population
		HAS	ASMR V	Direct comparison	Placebo	Mortality, morbidity, QoL, AEs, Progression	All endpoints in study considered	Toxicity concerns
Trastuzumab emtansine	Kadcyla	GBA	2B	Sub-group analysis; Direct comparison	Lapatinib + Capecitabin	Mortality, morbidity, QoL, AEs, Progression	Mortality, QoL, AEs	Comparator only ACT for one sub-population for which benefit rating 2B granted
		HAS	ASMR II	Direct comparison	Lapatinib + Capecitabin	Mortality, morbidity, QoL, AEs, Progression	All endpoints in study considered	Based on PFS, OS and acceptable tolerance profile

Drug	Brand Name	Agency	Best added benefit rating[49]	Clinical evidence use[50]	Comparator	Endpoints of clinical study[51]	Endpoints considered	Reason for decision
Vandetanib	Caprelsa	GBA	3C	Direct comparison	Placebo	Mortality, morbidity, QoL, AEs, Progression	Mortality, Morbidity	High risk of study bias, no evaluable data for most AEs
		HAS	ASMR IV	Direct comparison	Placebo	Mortality, morbidity, QoL, AEs, Progression	All endpoints in study considered	Limited effectiveness given unrepresentative sample of study population
Vemurafenib	Zelboraf	GBA	2B	Direct comparison	Dacarbazine	Mortality, morbidity, QoL, AEs, Progression	Mortality, morbidity, QoL, AEs	Potential greater harm
		HAS	ASMR III	Direct comparison	Dacarbazine	Mortality, morbidity, QoL, AEs, Progression	All endpoints in study considered	Safety concerns, negative impact on QoL cannot be excluded
Vismodegib	Erivedge	GBA	3C	Sub-group analysis; indirect comparison	-	Mortality, morbidity, QoL, AEs, Progression	Mortality, morbidity, QoL, AEs	Deviation from G-BA defined ACT, ORR as primary outcome is not patient-relevant
		HAS	ASMR IV	Indirect comparison	-	Mortality, morbidity, QoL, AEs, Progression	All endpoints in study considered	Non-comparative study data but lack of therapeutic alternative

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