HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

9 July 2014

MUPHORAN, powder and concentrate for parenteral use (infusion)

1 brown glass vial of 208 mg - 1 glass ampoule of 4 mL (CIP: 34009 331 870 2 6)

Applicant: SERVIER

INN	fotemustine
ATC code (year)	L02BG04 (nitrosourea)
Reason for the review	**Reassessment of the IAB following joint referral from the Ministry of Health, the Social Security Directorate and the Directorate-General for Health Services on 10 October 2013, in accordance with article R 163-19 of the Social Security Code.**
Lists concerned	**Hospital use (Public Health Code L.5123-2)**
Indications concerned	**“Disseminated malignant melanoma (including brain metastases).** **Primary malignant brain tumours.”**

Actual Benefit	**Substantial in melanoma, only in cases of brain metastases.** **Substantial in primary brain tumours, only as 2nd-line therapy.**
Improvement in Actual Benefit	**<u>Metastatic melanoma indication:</u>** **Taking into account:** - **the available data, based primarily on a comparative study versus dacarbazine that showed a modest increase in the overall response rate with no demonstrated improvement in clinical criteria such as progression-free survival or overall survival** **and** - **developments in the therapeutic strategy, with chemotherapy playing an increasingly limited role in favour of targeted therapies and immunotherapy,** **the Committee considers that MUPHORAN does not provide any improvement in actual benefit (level V, non-existent) in the management of metastatic melanoma.** **<u>Primary brain tumours indication:</u>** **As the data available are limited to non-comparative studies and there are no comparisons with the available treatments in this indication, the Committee considers that MUPHORAN does not provide any improvement in actual benefit (level V, non-existent) in the management of primary brain tumours.**
Therapeutic use	**In metastatic melanoma, MUPHORAN should only be used when there are brain metastases, as second-line or first-line therapy.** **In the treatment of primary brain tumours, MUPHORAN is a 2nd-line therapy.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	05/09/1994 (national procedure)
Prescribing and dispensing conditions / special status	List I Medicine for hospital prescription only, restricted to oncology, haematology and medical oncology specialists and departments. Medicinal product requiring special monitoring during treatment.

ATC Classification	2014 L: Antineoplastic and immunomodulating agents L01: Antineoplastic agents L01A: Alkylating agents L01AD: Nitrosoureas L01AD05: fotemustine

02 BACKGROUND

As part of the Hospitalisation Council's work updating the list of medicinal products that are chargeable in addition to hospital services, and pursuant to article R 163-19 of the Social Security Code, the Ministry of Health, the Social Security Directorate and the Directorate-General for Health Services have applied to HAS for a ruling on the IAB of proprietary medicinal products, including MUPHORAN powder and concentrate for parenteral use (infusion), the subject of this opinion. Due to the length of inclusion, starting at a time when the IAB was not part of the assessment as it is today, this criterion had not been assessed by the Committee.

The proprietary medicinal product MUPHORAN powder and concentrate for parenteral use (infusion) was included on the list of medicines approved for use by hospitals and various public services by the Decree of 21 July 1989, published in the Official Gazette on 6 August 1989, and was included on the list of medicines refundable by National Health Insurance in 1990. This proprietary medicinal product was included on the list of medicines that are chargeable in addition to hospital services in 2010 (Official Gazette of 10 May 2010).

03 THERAPEUTIC INDICATIONS

"- Disseminated malignant melanoma (including brain metastases).

- Primary malignant brain tumours."

04 DOSAGE

"Prepare the solution immediately before use.
Dissolve the contents of the MUPHORAN vial using the 4 mL ampoule of sterile alcohol solution.
Calculate the dose to inject, then dilute the solution in 5% isotonic glucose solution for intravenous infusion.
The prepared solution must be used away from a source of light and administered by intravenous infusion over one hour.

- ***As monochemotherapy, treatment consists of:***
  - o induction therapy: 3 consecutive administrations one week apart, followed by a treatment break of 4 to 5 weeks;
  - o maintenance therapy: one administration every 3 weeks.

The usual dose is 100 mg/m^2.
- ***As combination chemotherapy, the 3***rd administration of the induction therapy is omitted. The dose remains 100 mg/m^2.

Combination with dacarbazine
Rare cases of pulmonary toxicity (acute respiratory distress syndrome in adults) have been observed when fotemustine is administered simultaneously with high doses of dacarbazine, i.e. on the same day.
Simultaneous administration should be avoided (see section 4.5 of the SPC).
Administration should follow the recommended regimen below:
Induction therapy:
- Fotemustine 100 mg/m²/day on days 1 and 8
- Dacarbazine 250 mg/m²/day on days 15, 16, 17 and 18

A treatment break of five weeks, then:
Maintenance therapy: every 3 weeks
- Fotemustine 100 mg/m²/day on day 1
- Dacarbazine 250 mg/m²/day on days 2, 3, 4 and 5."

05 THERAPEUTIC NEED

Melanoma is a skin cancer with high metastatic potential, associated with the malignant transformation of melanocytes, skin pigment cells.
The cancer stage at the time of diagnosis is the factor that determines survival (NCCN, 2014):
- 82-85% of patients present with localised melanoma, which has an excellent prognosis, with a 5-year survival rate of more than 90% in patients whose tumour does not exceed 1 mm thickness, and 50% to 90% in patients whose tumour is more than 1 mm thick;
- 10-13% of patients present with locoregional melanoma, which approximately halves the survival rates above;
- 2-5% of patients present with melanoma with distant metastases. In this case, the risk of brain metastases is about 30% when the metastatic disease is diagnosed and can rise to 60% within 2 years in patients who are still alive.[1] The long-term survival rate in patients who have melanoma with distant metastases is less than 10%[2] (NCCN, 2014).

From diagnosis, current treatment involves selecting patients based on whether or not they have a BRAF mutation (this mutation is found in 40% to 60% of cases); in cases of mutation, the choice of treatment involves targeted therapy with BRAF inhibitors.

[1] Shapiro DG, Samlowski WE. Management of melanoma brain metastases in the era of targeted therapy. J Skin Cancer 2011;2011:845863. PE0100017.
[2] http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf

Malignant brain tumours in adults are a rare form of cancer, accounting for 1.4% of the incidence of all malignant solid tumours in men or women in 2012.[3]
Gliomas are the most common primary brain tumours in adults and make up 80% of malignant primary brain tumours in adults.[4]
Their prognosis varies greatly and is mainly affected by tumour grade, histology, size and location. In the 2007 WHO classification, gliomas are classed by tumour grade (grade I to IV) and by histological type (astrocytomas, oligodendrogliomas, oligoastrocytomas), which are prognostic factors for mortality.[5]
Grade I and II tumours (15% to 25% of glial tumours) have low proliferative potential. Surgical resection alone may lead to a cure in grade I tumours, whereas some grade II tumours tend to recur at a higher cancer stage.
Grade III and IV tumours are high-grade lesions with intense mitotic activity and may rapidly progress towards a fatal outcome (grade IV).
Anaplastic gliomas are grade III tumours (10% of gliomas) and include astrocytomas, oligodendrogliomas and oligoastrocytomas.
Glioblastomas (GBMs) are grade IV astrocytomas (70% of gliomas).[6] Glioblastomas account for 70% of primary malignant brain tumours. These are very aggressive tumours which are more common in older adults (50-70 years) and particularly in men. Despite the current therapies and diagnostic efforts, the average survival of patients with a GBM is 12 months.[7] Almost all patients will experience recurrence, with a median life expectancy from recurrence of about 30 weeks (95% CI: 27-33).[8]

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

In the treatment of metastatic melanoma, the relevant comparator is dacarbazine (DETICENE), which has had marketing authorisation since 12 December 1997 (company: Sanofi-Aventis). This proprietary medicinal product was included on the list of medicines approved for hospital use before the application of Law no. 99-554 of 2 July 1999 on the inclusion of medicines on the lists specified in articles L. 162-17 of the Social Security Code and L. 618 of the Public Health Code. As such, the TC did not rule on the IAB of this medicine.

YERVOY (ipilimumab) has marketing authorisation for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.
Patients included in the study that supported YERVOY's marketing authorisation (MDX010-20) had all **failed to respond to fotemustine** (p. 39/71, EPAR for YERVOY, 25 July 2011). Consequently, YERVOY cannot be considered a comparator to fotemustine (MUPHORAN).

It should be noted that ipilimumab was recently granted an extension of indication as first-line therapy for metastatic melanoma. The Transparency Committee has not assessed this new indication.

[3] http://www.invs.sante.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Cancers/Surveillance-epidemiologique-des-cancers/Estimations-de-l-incidence-et-de-la-mortalite/Estimation-de-l-incidence-et-de-la-mortalite-par-cancer-en-France-entre-1980-et-2012-Tumeurs-solides
[4] CBTRUS Statistical Report; Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004-2008. Central Brain Tumors Registry of the United States. 2012.
[5] Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97-109.
[6] Taillandier L, Bauchet L, Neuro-Oncologists Association of the French Language. ANOCEF referential for gliomas in adults. 21-12-2012.
[7] ISREC. Available at: http://www.isrec.ch/agora/thematiques_detail_eid_3_lid_633.html.
[8] Lamborn KR, Yung WK, Chang SM, Wen PY, Cloughesy TF, DeAngelis LM, et al. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. Neuro Oncol 2008;10:162-70.

In the treatment of primary brain tumours, the comparators are given in the table below.

Proprietary medicinal product/ company	Indication	Date of TC opinion	AB	IAB	Reimbursed
TEMODAL (Temozolomide) *Schering Plough*	• Adult patients with newly diagnosed GBM multiforme (an aggressive type of brain tumour) concomitantly with radiotherapy and subsequently as monotherapy. • Children from the age of 3 years, adolescents and adult patients with malignant glioma, such as GBM multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy (as monotherapy).	31/05/06	Substantial	Moderate IAB (level III) in the management of patients with newly diagnosed GBM multiforme, when prescribed concomitantly with radiotherapy (RT) and subsequently as monotherapy. The therapeutic strategy including TEMODAL has increased median survival by about 2 months (14.6 months vs 12.1 months) and has increased the 2-year survival rate (26.5% in the RT + TMZ arm vs 10.4% in the RT arm) with an acceptable safety profile.	Yes
BICNU (Carmustine) *Emcure Pharma*	• Primary or secondary brain tumours.	The TC has not ruled on the AB or IAB of these proprietary medicinal products.			Yes
BELUSTINE (Lomustine) *Prostrakan*	• Primary and secondary brain tumours.	The TC has not ruled on the AB or IAB of these proprietary medicinal products.			Yes
NATULAN (Procarbazine) *Sigma-Tau*	• Brain tumours.	20/06/12	Substantial	The TC has not ruled on the IAB of this proprietary medicinal product.	Yes

GBM: glioblastoma; RT: radiotherapy; TMZ: temozolomide

06.2 Other health technologies

None.

◗ Conclusion

For metastatic melanoma without brain metastases, the clinically relevant comparator is dacarbazine (DETICENE).

For primary malignant brain tumours, the relevant comparators are alkylating agents used alone or in combination (temozolomide - TEMODAL, carmustine - BICNU, lomustine - BELUSTINE, and procarbazine - NATULAN).

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

MUPHORAN is reimbursed in 9 European Union countries apart from France.

Country	Reimbursed	
	Yes (start date) / No / Assessment in progress or duly documented change	Scope (indications) and special condition(s)
Austria	Yes (02/1995)	Disseminated malignant melanoma (including brain metastases)
Belgium	Yes (11/2005)	Disseminated malignant melanoma without brain metastases
Spain	Yes (11/1999)	Disseminated malignant melanoma (including brain metastases)
Italy	Yes (05/2011)	
Czech Republic	Yes (01/2000)	
Greece	Yes (04/1998)	
Hungary	Yes (10/1996)	
Portugal	Yes (01/1991)	
Slovakia	Yes (03/2000)	

08 SUMMARY OF PREVIOUS ASSESSMENTS

Indications	- Disseminated malignant melanoma (including brain metastases) - Primary malignant brain tumours
Date of opinion (reason for the review)	01/02/2006 Renewal of inclusion (date of decree: 31/12/2005)
Actual Benefit (wording)	**Usual nature of severity** Disseminated melanoma is a malignant tumour that develops from melanocytes, occurring in the skin in 90% of cases. It has a very high metastatic potential. Its incidence was about 7,000 cases in 2000 and is constantly increasing. It is more common in women (60% of cases). Its 5-year survival rate is about 80% when all stages are considered together and about 18% in stage IV (using the Union for International Cancer Control classification), i.e. the metastatic stage. It led to the deaths of about 1,300 people in 2000. - Primary brain tumours The average incidence of brain tumours of any type is 15.5/100,000 in adults in France. This incidence increases to 33.4/100,000 in people aged 70-79 years. The most common histological types are glial tumours and meningiomas. Among glial tumours, glioblastoma (grade IV glioma in the 2000 WHO classification) is the most common. The average survival of patients with glioblastoma is 10 to 12 months. **Efficacy and therapeutic use** Fotemustine is intended as palliative therapy. - Disseminated melanoma There is no curative treatment for melanoma at this stage. The standard palliative treatment is still chemotherapy with dacarbazine (level of evidence B). Combination chemotherapies have not been shown to be superior to dacarbazine alone (level of evidence B). Dacarbazine, temozolomide and fotemustine used as monotherapy lead to a response in 18% to 24% of cases. According to INCa experts, fotemustine plays a major role in the treatment of disseminated malignant melanoma. - Primary brain tumours The therapeutic strategy for gliomas consists of the following stages:

	- optimal surgical resection - first-line external radiotherapy (level of evidence A) - possible chemotherapy If the chemotherapy option is chosen, nitrosoureas should be used as first-line treatment, particularly carmustine (level of evidence A). Lomustine and fotemustine may also be used (level of evidence C). Lomustine may be used in combination with procarbazine and vincristine (level of evidence B). As second-line therapy, temozolomide (variable level of evidence depending on histology), platinum salts as monotherapy or combination chemotherapy (level of evidence C), or procarbazine (expert opinion) may be used. Carmustine may also be used as a local implant in cases of recurrence. For other types of brain tumour, surgery is recommended as first-line treatment, then radiotherapy in some cases. If chemotherapy is also envisaged, there are no guidelines that mention using fotemustine. According to INCa experts, fotemustine does play a major role in the treatment of these tumours. The main side effects of fotemustine are: - thrombocytopenia and leukopenia - nausea and vomiting - moderate and transient elevation of transaminases, alkaline phosphatase and bilirubin The efficacy/adverse effects ratio for MUPHORAN is modest. **Conclusion on actual benefit** The actual benefit of MUPHORAN is substantial in disseminated malignant melanomas and in primary brain tumours.
Improvement in Actual Benefit	*The Transparency Committee did not rule on IAB.*
Target population	*The Transparency Committee did not rule on target population.*

09 ANALYSIS OF AVAILABLE DATA

09.1 Efficacy

A) METASTATIC MELANOMA INDICATION

For the reassessment of MUPHORAN, the company submitted a dossier containing:

- 5 non-comparative phase II studies
- one comparative phase III study versus dacarbazine

These studies pre-date the last TC opinion which was issued for renewal of inclusion.

No new efficacy and safety studies conducted as part of the product's current marketing authorisation were submitted.
The dossier cites data on combining fotemustine with monoclonal antibodies (ipilimumab or bevacizumab) from two non-comparative studies. As this is an off-label use, these data will not be taken into account.

I) Reminder of efficacy results from 4 non-comparative studies

Table 1 - Description of methodology in non-comparative phase II studies of fotemustine as monotherapy

Study	Type of study	n included **evaluable**	Population studied/inclusion criteria	Treatment regimens	Anti-tumour efficacy endpoints
Jacquillat et al, 1990 NP01400	-multicentre, France	169/**153**	Progressive metastatic melanoma (histologically confirmed), notably including patients with brain metastases	Fotemustine -induction 100 mg/m²/week for 3 weeks -break 4 to 5 weeks -maintenance 100 mg/m² every 3 weeks in responsive and stable patients	Response to treatment according to WHO criteria (CR, PR, SD, PD)
Calabresi et al, 1991 NP01424	-multinational	32/**30**			
Boote et al, 1989 NP01478	-single-centre, UK	27/**24**			
Kleeberg et al, 1995	-multicentre, Europe	144/**98**			
Schallreuter et al, 1991	-single-centre, Germany	19/**19**	Stage IV metastatic melanoma		

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; WHO: World Health Organisation

Table 2: Main efficacy results from phase II studies of fotemustine as monotherapy

Study	**N_{eval}.**	**Main baseline characteristics of patients**	**Objective response (CR+PR) N response/N eval 95% CI**		**Objective response Median duration in weeks (min-max)**
			Total	**Brain metastases**	
Jacquillat et al, 1990[9]	153	-Median age: 54 years -Median Karnofsky: 90% -Previous chemotherapy (n, %) .none: 62 (40.5%) .1 / 2+ lines: 61 (39.9%) / 30 (19.6%) -Previous surgery (n, %): 143 (93.5%) -Dominant site* (n, %) .brain:** 36 (23.5%) .visceral:** 73 (47.7%) .non-visceral (skin, subcutaneous tissue, bone or lymph node):** 44 (28.8%)	37/153 (24.2%) 95% CI: 17.4-31%	9/36 (25%)	22 (7-80)
Calabresi et al, 1991[10]	30	-Median age: 49 years -Median Karnofsky: 80% -Previous chemotherapy (n, %) .none: 13 (43.3%) .1 / 2+ lines: 1 (3.3%) / 16 (53.3%) -Previous surgery (n, %): 27 (90%) -Dominant site* (n, %) .brain:** 7 (23%) .visceral:** 15 (50%) .non-visceral:** 8 (27%)	6/30 (20%) 95% CI: 10-37%	1/7 (14.3%)	20 (12-60)
Boote et al, 1989[11]	24	-Median age: 52 years -Karnofsky: ≥ 60% (min-max: 60-100%)	4/24 (16.7%)	2/12 (16.7%)	23 (16-35+)

[9] Jacquillat C, Khayat D, Banzet P, Weil M, Fumoleau P, Avril MF, et al. Final report of the French multicenter Phase II study of the nitrosourea fotemustine in 153 evaluable patients with disseminated malignant melanoma including patients with cerebral metastases. Cancer 1990;66:1873-8.

[10] Calabresi F, Aapro M, Becquart D, Dirix L, Wils J, Ardizzoni A, et al. Multicenter phase II trial of the single agent fotemustine in patients with advanced malignant melanoma. Ann Oncol 1991;2:377-8.

		-Previous chemotherapy (n, %) .none: 8 (33.3%) . 1 / 2+ lines: 13 (54.2%) / 3 (12.5%) -Previous surgery (n, %): 23 (95.8%) -Dominant site* (n, %) .brain:** 12 (50%) .visceral:** 6 (25%) .non-visceral:** 6 (25%)			
Kleeberg et al, 1995[12]	98	-Median age: 53 years -Previous chemotherapy (n, %) .none: 79 (80.6%) . 1 or more lines: 19 (19.4%) -Dominant site* (n, %) .brain:** 12 (50%) .visceral:** 6 (25%) .non-visceral:** 6 (25%)	12/98 (12.2%)	4/35 (11%)	26 (17-70)
Schallreuter et al, 1991[13]	19	-Mean age: 54 years -Karnofsky: ≥ 90% -Brain metastases** (n, %): 5 (26.3%)	9/19 (47.4%)	3/5 (60%)	18 (13-52+)

N_{eval}. = number of evaluable patients; CI = confidence interval; CR: complete response, PR: partial response; * cancer lesions were grouped by metastatic site and ranked in 3 categories based on the dominant site; ** isolated or associated with other lesions

The non-comparative phase II studies suggest that with fotemustine treatment, the overall response rate is 12.2% to 24.2%, based on the two studies that included a relevant number of patients (Jacquillat et al, n=153 and Kleeberg et al, n=98); the other three studies included 19 to 30 patients depending on the study.

II) Reminder of efficacy data analysed at the last TC assessment (opinion of 01/02/2006)

A randomised trial compared the efficacy of fotemustine versus dacarbazine in 229 adult patients with disseminated malignant melanoma.[14]
The patients had not received chemotherapy previously.
The treatment regimen was as follows:
- Induction therapy:
  - IV fotemustine 100 mg/m^2 one day a week for 3 weeks, then 5 weeks without treatment before starting maintenance therapy
  - IV dacarbazine 250 mg/m^2 5 days a week every 4 weeks for 8 weeks.
- Maintenance therapy in stable patients until the disease progressed or significant toxicity occurred
  - IV fotemustine 100 mg/m^2 one day a week for 3 weeks
  - IV dacarbazine 250 mg/m² 5 days a week once a month.

[11] Unpublished study with results presented at a European oncology conference in 1989 (5th European Conference on Clinical Oncology).
[12] Kleeberg UR, Gawlik C, Brocker EB, Boewer C, Chatelain RP, Queisser W, et al. Interferon alpha2b and fotemustine in patients with disseminated melanoma. A multicenter phase II trial of the AIO Phase I/II Study Group of the German Cancer Society. Onkologie 1995;18:456-61
[13] Schallreuter KU, Wenzel E, Brassow FW, Berger J, Breitbart EW, Teichmann W. Positive phase II Study in the treatment of advanced malignant melanoma with fotemustine. Cancer Chemother Pharmacol 1991;29:85-7
[14] Avril MF et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol 2004; 22: 1118-25.

Table 3: Description of methodology in the phase III study of fotemustine as monotherapy

Avril study: Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma (Avril, 2004)	
Main objective of the trial	To compare the overall response rate (objective response) with fotemustine or dacarbazine in the treatment of disseminated malignant melanoma with or without brain metastases.
Methodology	Multicentre (18 centres, 7 countries), phase III, comparative, parallel-group (fotemustine versus dacarbazine), randomised, open-label study. Randomisation was stratified by country, by the presence or absence of brain metastases and by the diagnostic approach used for brain metastases (MRI or CAT).
Number of patients	Planned in the protocol: 204 patients (102 per treatment group) Included: 229 (fotemustine: 112 patients; dacarbazine: 117 patients)
Main inclusion criteria	-Disseminated, non-ocular malignant melanoma (histologically conformed) with or without asymptomatic or pauci-metastatic brain metastases -MRC-NPS performance score ≤ 2; WHO-ECOG performance status ≤ 1 -Tumour with at least one two-dimensional measurable target -Age: 18-75 years -Life expectancy ≥ 3 months -No previous chemotherapy (adjuvant immunotherapy tolerated if stopped at least 1 month before the date of randomisation)
Treatment groups	Fotemustine -induction: 100 mg/m²/week for 3 weeks -break: 4 to 5 weeks -maintenance: 100 mg/m² every 3 weeks in responsive and stable patients Dacarbazine: 250 mg/m² -induction: 2 courses at 3-week intervals (D1 to D5 and D29 to D33). Each course consists of one injection/day for 5 consecutive days -maintenance: 1 injection/day for 5 consecutive days every 3 weeks Treatment duration: Patients should receive 6 courses of fotemustine or dacarbazine. Responsive or stable patients could continue treatment after agreement between the investigator and the study sponsor
Primary efficacy endpoint	Objective response (i.e. CR + PR) evaluated at the end of the induction phase (primary analytical approach) and best objective response evaluated both for the induction phase and the maintenance phase (secondary analytical approach).
Secondary endpoints included	-duration of objective response by metastatic site -duration of progression-free survival -overall survival -change in number of metastatic sites -time to occurrence of brain metastases in patients with no brain metastases on inclusion -objective response in patients with inoperable brain metastases on inclusion -quality of life using the QLQ-C30 questionnaire, particularly change in overall score (value at end of induction phase – baseline value) -safety: AEs, vital signs, performance status (NPS, ECOG), blood chemistry
Calculation of the number of subjects required	A minimum of 102 patients/group was necessary to demonstrate the superiority of fotemustine as 1st-line therapy vs dacarbazine, with an estimated intergroup difference of 17% in the intention-to-treat population, an α risk of 5% and a power of 80%. The expected response rates were 30% (fotemustine group) and 13% (dacarbazine group). The overall objective response rate observed was lower and it was clinically impossible to achieve the expected difference of 17%. Odds ratios (OR) and their 95% CIs were proposed for evaluating the clinical benefit and its precision. The above-mentioned differences were equivalent to an expected odds ratio of 2.87, i.e. between 2 and 3 in favour of fotemustine. With an OR of 2.87 and an objective response rate of 6.3% (dacarbazine group), the power of the study (α risk of 5%, two-tailed) in the full analysis set (n=221) was 64%.
Statistical analysis	The efficacy analyses were performed on the full analysis set (FAS), the per-protocol set (PPS) for the primary efficacy endpoint and some secondary endpoints (progression-free survival and overall survival), and were confirmed in the population of randomised patients (intention-to-treat approach) for objective response and overall survival. Intergroup comparisons were carried out using the log-rank test for survival data, the chi² test or Fisher's exact test for qualitative variables, and the Student's t-test for quantitative variables. For quality of life (QoL), analyses were performed on the QoL FAS using a Mann-Whitney-Wilcoxon test.

Table 4: Main results from the phase III study

Treatment group	**Fotemustine (F)**	**Dacarbazine (D)**
Patient status (n, %)		
-included (randomised)	**112**	**117**
-not treated (non-medical reason)	**0**	**5 (4.3%)**
-completed the induction phase (F: Day 50, D: Day 57)	**108 (96.4%)**	**90 (76.9%)**
-started the maintenance phase*	**47 (42%)**	**29 (24.8%)**
-Reason for withdrawal from study		
-AE	**13 (11.6%)**	**9 (7.7%)**
-Lack of efficacy	**87 (77.7%)**	**95 (81.2%)**
-Remission, marked improvement	**3 (2.7%)**	**0**
-Non-medical reason	**4 (3.6%)**	**4 (3.4%)**
-Major deviation	**4 (3.6%)**	**2 (1.7%)**
Baseline characteristics (randomised patients)		
-Mean age (mean ± SD)	**55.4 ± 13.8**	**54.8 ± 13.1**
-ECOG status ≤ 1 (n, %)	**98.2%**	**97.4%**
-Previous treatment (n, %)	**100%**	**100%**
-surgery	***98.2%***	***98.3%***
-immunotherapy	***28.6%***	***19.7%***
-radiotherapy	***3.6%***	***6.0%***
-Dominant metastatic site		
- brain	**22 (19.6%)**	**21 (18.4%)**
- pulmonary / other visceral site	**61 (54.5%)/93 (83%)**	**73 (64%)/99 (86.8%)**
- skin or superficial lymph nodes	**51 (45.5%)**	**60 (52.6%)**

Efficacy results	**ITT (n=229)**	
	F (n=112)	**D (n=117)**
Objective response at the end of the induction phase (primary endpoint)**		
-n, % of patients	**15 (13.4%)**	**7 (6.0%)**
-p value	**0.057**	
Overall response (complete or partial) after maintenance treatment		
-n, % of patients	**17 (15.2%)**	**8 (6.8%)**
-p value	**0.043**	

No difference was observed between fotemustine and dacarbazine in terms of the response rate after induction therapy (13.4% versus 6% in the dacarbazine group, p=0.057).
At the end of maintenance therapy, the response rate in the fotemustine group was higher than in the dacarbazine group: 15.2% versus 6.8%, p=0.043.

No difference between fotemustine and dacarbazine was observed in terms of:

- median duration of response: 5.8 months in the fotemustine group and 6.9 months in the dacarbazine group;
- median time to progression: 1.8 months in the fotemustine group and 1.9 months in the comparator group;
- time to occurrence of brain metastases in patients with no brain metastases on inclusion: 22.7 months in the fotemustine group and 7.2 months in the dacarbazine group (p=0.059);
- median overall survival (7.3 versus 5.6 months, p=0.067).
- quality of life evaluated using the QLQ-C30 questionnaire.

B) PRIMARY BRAIN TUMOURS INDICATION

Studies using fotemustine as a first-line or neoadjuvant treatment in experimental (off label) protocols in combination with radiotherapy ± other chemotherapies were not accepted. Similarly, the study that tested fotemustine in an experimental (off label) regimen in combination with bevacizumab will not be described in this document.

Studies using fotemustine before the introduction of the Stupp protocol

Before the Stupp protocol was marketed (standard treatment combining conformal radiotherapy at a dose of 60 Gy with concomitant daily oral temozolomide, followed by adjuvant treatment with temozolomide five days per month), the effects of fotemustine in the treatment of recurrent malignant gliomas were evaluated in several studies. The oldest have already been presented in the initial inclusion dossier for MUPHORAN. Six studies, including the most recent, are summarised in Table 5. Two of them[15,16] used fotemustine in experimental (off label) protocols and will therefore not be considered in this document.

Table 5: Studies using fotemustine in the treatment of recurrent malignant gliomas before the introduction of the Stupp protocol

Study	N	Treatment regimen for fotemustine	Population	% response (PR + SD)	Median duration of survival (pts responding to treatment, months)
Studies accepted					
Frenay et al., 1991	38	Standard	Recurrent malignant gliomas (including 21 GBM, 9 AA)	23%	9.2
Mousseau et al., 1996	34	Standard	Malignant gliomas without previous chemotherapy	70%	9.2
Malhaire et al., 1999	22	Standard	Recurrent malignant gliomas (including 19 GBM, 3 AA)	50%	9.4
Fazeny-Dörner et al., 2003	31	Standard combined with dacarbazine	Recurrent malignant gliomas after radiotherapy and previous chemotherapy (nitrosourea)	54.8%	10.4
Studies not accepted					
Khayat et al., 1994	*8*	*Intra-arterial*	*Recurrent malignant gliomas*	*12.5%*	-
Boiardi et al., 2001	*16*	*Increasing doses combined with procarbazine*	*Recurrent malignant gliomas after previous neurosurgery, radiotherapy and chemotherapy (nitrosourea)*	*50%*	*9.7 (overall survival)*

GBM: Glioblastoma
AA: anaplastic astrocytoma

Studies using fotemustine after the Stupp study, 2005[17]

A total of 8 studies examined the efficacy of fotemustine in the treatment of recurrent gliomas, of which 6 used experimental, off-label treatment protocols. Most of these studies were conducted in populations of patients who had relapsed after radiotherapy or were inoperable or after partial resection of the tumour(s). Depending on the study, the population of recruited patients had glioblastomas (grade IV) (the vast majority) and, to a lesser extent, grade III or low-grade (grades I and II) tumours.

[15] Khayat D, Giroux B, Berille J, Cour V, Gerard B, Sarkany M, et al. Fotemustine in the treatment of brain primary tumors and metastases. Cancer Invest 1994;12:414-20

[16] Boiardi A, Silvani A, Ciusani E, Watson A, Margison G, Berger E, et al. Fotemustine combined with procarbazine in recurrent malignant gliomas: A phase I study with evaluation of lymphocyte O-6 alkylguanine-DNA alkyltransferase activity. J Neuro Oncol 2001;52:149-56.

[17] Stupp R, Mason WP, Van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96

Only the results of studies that used fotemustine in a standard treatment regimen will be considered in this document (Scoccianti et al study, 2008[18] and Fabrini et al study, 2009[19]).

Table 6: Studies using fotemustine in the treatment of recurrent malignant gliomas after the introduction of the Stupp protocol

Study	N	Treatment regimen (fotemustine)	Population	Response rate (PR + SD)	Progression-free survival	Overall survival
Studies accepted						
Scoccianti et al., 2008 (non-comparative study)	27	Standard	GBM recurring after the Stupp protocol	48.1%	Median: 5.7 months At 6 months: 48.15%	Median after diagnosis: 21.1 months Median after fotemustine: 9.1 months
Fabrini et al., 2009 (non-comparative study)	50	Standard	GBM or AA recurring after the Stupp protocol	62%	Median: 6.1 months At 6 months: 51.5%	Median after diagnosis: 24.5 months Median after fotemustine: 8.1 months
Studies not accepted						
Silvani et al., 2008	*54*	*Combined fotemustine (not standard) + procarbazine*	*GBM recurring after temozolomide*	*64.9%*	*Median: 4.7 months* *At 6 months: 26.7%*	*Median after diagnosis: 20.8 months* *Median after treatment: 7.1 months*
Brandes et al., 2009	*43*	*Fotemustine 75 mg/m²*	*GBM progressing after the Stupp protocol*	*42%*	*Median: 1.7 months* *At 6 months: 20.9%*	*Median: 6 months*
Fabi et al., 2009	*40*	*Fotemustine 65 to 100 mg/m²*	*Pre-treated recurrent gliomas (including 14 GBM, 11 AA, 7 OA)*	*47.5%*	*Median: 4.0 months* *At 6 months: 27%*	*Median after fotemustine: 30 months*
Fabi et al., 2010	*40*	*Fotemustine 60 mg/m² every 3 weeks*	*Pre-treated recurrent or progressive gliomas (including 30 GBM, 6 AA, 4 AO)*	*52.5%*	*Median: 3.0 months* *At 6 months: 21%*	*Median after fotemustine: 6 months*
Addeo et al., 2011	*40*	*Fotemustine 80 mg/m² every 2 weeks*	*Pre-treated recurrent gliomas*	*65%*	*Median: 6.7 months* *At 6 months: 39%*	*Median after fotemustine: 11 months*
Gaviani et al ., 2013	*97/97*	*Fotemustine 80 mg/m² every 2 weeks*	*Pre-treated recurrent gliomas (including 58 GBM)*	*ND*	*Median: 3.7 months* *At 6 months: 56%*	*Median after fotemustine: 6.9 months*

GBM: glioblastoma
AA: anaplastic astrocytoma

In conclusion, despite a low level of evidence, fotemustine has proven efficacy in the treatment of recurrent malignant gliomas. In non-comparative studies using a standard regimen for administering fotemustine (dosage of 100 mg/m^2: 3 consecutive administrations one week apart,

[18] Scoccianti S, Detti B, Sardaro A, Iannalfi A, Meattini I, Leonulli BG, et al. Second-line chemotherapy with fotemustine in temozolomide-pretreated patients with relapsing glioblastoma: a single institution experience. Anticancer Drugs 2008;19:613-20.
[19] Fabrini MG, Silvano G, Lolli I, Perrone F, Marsella A, Scotti V, et al. A multi-institutional phase II study on second-line fotemustine chemotherapy in recurrent glioblastoma. J Neuro Oncol 2009;92:79-86.

followed by a treatment break of 4 to 5 weeks, then administration every 3 weeks), the response rates ranged from 48% to 62% and median survival ranged from 8.1 to 9.1 months after starting treatment with fotemustine, if studies conducted after the introduction of the Stupp protocol are taken into account.

No data from comparative studies are available in this indication.

09.2 Safety/Adverse effects

In metastatic melanoma

In the comparative pivotal study versus dacarbazine, myelosuppression was the most common event in both groups. In the fotemustine group, neutropenia was observed in 79 patients (71%) at grades 3 to 4 in 51% of patients. Two patients had febrile neutropenia. Thrombocytopenia was observed in 105 patients (94%) at grades 3 to 4 in 43% of patients. Grade 3 to 4 anaemia was rare. Myelosuppression mainly occurred during induction therapy, and very few exposed patients had grade 3 toxicity during maintenance therapy (one patient had neutropenia, two had thrombocytopenia). Myelosuppression was less common in the dacarbazine group than in the fotemustine group. Neutropenia was observed in 16 patients (14%) at grades 3 to 4 in 5.6%. Thrombocytopenia was observed in 64 patients (57%) at grades 3 to 4 in 6.3% of patients. Grade 3 to 4 anaemia remained rare.

In primary brain tumours

Myelosuppression was the main form of toxicity in the two non-comparative phase II studies (Scoccianti et al. study, 2008 and Fabrini et al. study, 2009): one grade 3 thrombocytopenia (8%), one grade 4 neutropenia (2%) and one grade 3 anaemia (2%).
In the Fabrini study, grade 3 thrombocytopenia was observed in 8%, grade 4 neutropenia in 2% and grade 3 anaemia in 2%.
In the Scoccianti study, the incidence of grade 3 thrombocytopenia was 11% and grade 4 leukopenia was 4% (neutropenia was not mentioned in the publication).

09.3 Usage/prescription data

The sales data for MUPHORAN in common dispensing units (UCD) from the GERS hospital database, up to the end of December 2013, are given below. A total of 4,198 UCD were sold over the period in question (moving 12-month total).

Proprietary medicinal product	UCD 12/2010	UCD 12/2011	UCD 12/2012	UCD 12/2013
MUPHORAN	5468	4583	4762	4198

09.4 Summary & discussion

In the indication “metastatic melanoma”, the results of the randomised trial comparing fotemustine to dacarbazine in 229 non-pre-treated adult patients with disseminated malignant melanoma showed that fotemustine had a superior response rate to dacarbazine at the end of maintenance therapy: 15.2% versus 6.8%, p=0.043.
No difference between fotemustine and dacarbazine was observed in terms of:

- median duration of response: 5.8 months in the fotemustine group and 6.9 months in the dacarbazine group;
- median time to progression: 1.8 months in the fotemustine group and 1.9 months in the comparator group;
- time to occurrence of brain metastases in patients with no brain metastases on inclusion: 22.7 months in the fotemustine group and 7.2 months in the dacarbazine group (p=0.059);
- median overall survival (7.3 versus 5.6 months, p=0.067);
- quality of life evaluated using the QLQ-C30 questionnaire.

In the indication “primary brain tumours”, two non-comparative phase II studies included a total of 77 patients with glioblastoma and anaplastic astrocytoma after standard treatment with the Stupp protocol (a protocol combining conformal radiotherapy at a dose of 60 Gy with concomitant daily oral temozolomide, followed by adjuvant treatment with temozolomide five days per month). They showed that, when fotemustine was administered at the marketing authorisation dosage (100 mg/m^2: 3 consecutive administrations one week apart, followed by a treatment break of 4 to 5 weeks, then administration every 3 weeks), the response rates ranged from 48% to 62% and median overall survival ranged from 8.1 to 9.1 months after starting treatment with fotemustine.

No data are available from comparative studies versus the other nitrosoureas with marketing authorisation in this indication.

The main forms of toxicity observed with fotemustine in both indications were thrombocytopenia and neutropenia.

09.5 Planned studies

No studies are currently in progress or planned.

010 THERAPEUTIC USE

A) Metastatic melanoma
Fotemustine’s role in the therapeutic strategy for metastatic melanoma is indicated by the INCa guidelines (INCa, 2013):

- In patients with brain metastases who are not BRAF gene mutation carriers, fotemustine monotherapy is the standard 1st-line chemotherapy.
- In patients with brain metastases who are BRAF gene mutation carriers:
  - In case of aggressive treatment failure on vemurafenib, fotemustine monotherapy is the standard chemotherapy;
  - If the response varies between different metastatic sites and vemurafenib is stopped, starting another monotherapy may be suggested; fotemustine is one of the treatment alternatives if local treatment is impossible;
  - In other treatment failure situations, monotherapy may be offered; fotemustine is one of the treatment alternatives.

- In patients without brain metastases who are not BRAF mutation carriers, fotemustine is recommended as 2nd-line therapy for unresectable metastatic melanoma in case of aggressive failure of 1st-line treatment (standard treatment: dacarbazine).

Note that the INCa guidelines were published before the marketing authorisation for first-line ipilimumab and are therefore not up-to-date on this particular point.

B) Primary brain tumours

The therapeutic strategy for high-grade (III and IV) malignant gliomas presented below comes from the ANOCEF (Association of French-Language Neuro-Oncologists) guidelines.[20]

Anaplastic gliomas (grade III)

1st-line therapy

Currently, treatment is not determined by histological type but by whether co-deletion of the chromosome arms 1p and 19q is present. Screening for 1p/19q co-deletion should be performed in grade III gliomas and is mainly seen in anaplastic oligodendrogliomas (60-80% of cases), anaplastic mixed gliomas (20-30% of cases) and very rarely in tumours classed as anaplastic astrocytomas (0-5% of cases). The finding of a 1p/19q co-deletion in a patient indicates a far better prognosis than in tumours without that co-deletion (median survival 3-5 times longer). Co-deletion seems to have both a true prognostic role (slower spontaneous progression of the tumour) and be predictive of a better response to treatments with radiotherapy and chemotherapy.
Consequently:

- In patients with a grade III glioma with 1p/19q co-deletion, a combination of radiotherapy and PCV chemotherapy (as adjuvant or neoadjuvant treatment) is the standard therapy.
- For patients with a grade III glioma (anaplastic astrocytomas and anaplastic oligodendroglial tumours) without 1p/19q co-deletion, there is no standard and radiotherapy is usually offered as the conventional treatment.

For adults with anaplastic gliomas (< 70 years and Karnofsky score ≥ 70) without 1p/19q co-deletion, the options are:

- radiotherapy alone (fractionated conformal radiotherapy)
- concomitant and adjuvant chemoradiotherapy following the Stupp protocol

For adults with anaplastic gliomas (≥ 70 years and Karnofsky score < 70), the treatment options are:

- radiotherapy alone (fractionated conformal radiotherapy)
- chemotherapy with temozolomide or nitrosoureas (BELUSTINE, IV carmustine or IV fotemustine)

In case of recurrence:

There is no standard treatment and the therapeutic strategy should always be discussed at a multidisciplinary team meeting. The treatment options will depend on the nature of the recurrence:

- multifocal or diffuse recurrence: chemotherapy, angiogenesis inhibitors, surgery for symptomatic lesions or palliative care
- focal recurrence:
  - if operable: excision +/- GLIADEL
  - if not operable: chemotherapy, angiogenesis inhibitors (bevacizumab), fractionated conformal radiotherapy, stereotactic re-irradiation or palliative care

  The chemotherapy options are temozolomide, nitrosoureas used alone (BELUSTINE, IV carmustine or IV fotemustine) or in combination as part of the PCV protocol (Carmustine, Procarbazine, Vincristine), platinum salts, etoposide, bevacizumab alone or in combination (off-label use, few data available).

[20] www.anocef.org/download.php?modele=anocef_referentiels (accessed 20 May 2014)

Glioblastoma (grade IV)

1st-line therapy

- Surgical excision
- Carmustine implants (GLIADEL): implanted by the neurosurgeon in the tumour excision cavity, if excision is complete or near-complete.
- Radiotherapy: radiotherapy should be started 4 to 6 weeks after the surgical procedure as long as the scalp has healed. It may be started early in case of biopsy.
- Chemotherapy:
  - Concomitant chemotherapy with radiotherapy (Stupp protocol, 2005), which combines conformal radiotherapy at a dose of 60 Gy and concomitant daily oral temozolomide, followed by adjuvant treatment with temozolomide 5 days per month
  - Adjuvant chemotherapy with temozolomide: this is started 4 weeks after chemoradiotherapy ends

Treatment of recurrence

- Repeat neurosurgery where possible
- Insertion of GLIADEL implants
- Re-irradiation
- 2^{nd}-line chemotherapy and targeted therapies
  - resume temozolomide
  - BELUSTINE (risk of pulmonary fibrosis)
  - IV carmustine (risk of pulmonary fibrosis, cumulative dose present)
  - IV fotemustine (well-documented hepatic toxicity, as with the other nitrosoureas)
  - PCV protocol
  - carboplatin + etoposide (impact on overall or progression-free survival not demonstrated) or carboplatin
  - bevacizumab (off label)

Fotemustine is suggested in the Association of French-Language Neuro-Oncologists (ANOCEF) guidelines:

- to treat anaplastic glioma (grade III) with multifocal or diffuse recurrence or inoperable focal recurrence. Nitrosoureas including fotemustine may be used alone or in combination as part of the PCV protocol (Carmustine, Procarbazine, Vincristine);
- to treat recurrent grade IV gliomas.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

A) Indication: melanoma

◗ Melanoma is a skin cancer with a strong metastatic potential which can, when advanced, be complicated by metastases and life-threatening in the short or medium term.

◗ This medicinal product is intended as specific curative therapy for melanoma.

◗ The efficacy/adverse effects ratio is modest.

◗ There is an alternative medicinal product.

◗ Public health benefit:
The public health burden of cutaneous melanomas and other skin cancers is moderate (approximately 160,000 DALYs). The burden represented by advanced melanomas (unresectable or metastatic) can be regarded as low.
Improving the management of patients with cancer is a public health need set out in the Cancer Plan 2009-2013.
In view of the available data, based on non-comparative studies and a single comparative study versus dacarbazine that showed a modest increase in response rate but no improvement in clinical criteria such as tumour progression or overall survival, the impact of the proprietary medicinal product MUPHORAN on morbidity/mortality and quality of life has not been established.
Consequently, it is not expected that the proprietary medicinal product MUPHORAN will benefit public health in this indication.

◗ This treatment should only be used when there are brain metastases, as second-line or first-line therapy.

Taking account of these points, the Committee considers that the actual benefit of MUPHORAN is substantial in the indication "metastatic melanoma".

B) Indication: primary brain tumours

◗ Primary malignant brain tumours are life-threatening, either immediately or as a result of complications.

◗ This medicinal product is intended as specific curative therapy for primary brain tumours.

◗ The efficacy/adverse effects ratio is modest.

◗ There are alternative medicinal products.

◗ Public health benefit:
High-grade malignant glioma is a serious, life-threatening clinical condition. Its public health burden may be regarded as low because of the small number of patients concerned.
In view of the current prognosis associated with usual management, there is a substantial therapeutic need in terms of public health.
The impact of the proprietary medicinal product MUPHORAN on the morbidity/mortality and quality of life of patients treated cannot be assessed, given shortcomings in the data available (non-comparative studies).
Consequently, it is not expected that the proprietary medicinal product MUPHORAN will benefit public health in this indication.

◗ This is a second-line treatment.

Taking account of these points, the Committee considers that the actual benefit of MUPHORAN is substantial in the indication "primary brain tumours".

011.2 Improvement in actual benefit (IAB)

Metastatic melanoma indication:
Taking into account:

- **the available data, based primarily on a comparative study versus dacarbazine that showed a modest increase in the overall response rate with no demonstrated improvement in clinical criteria such as time to progression or overall survival**

and

- **developments in the therapeutic strategy, with chemotherapy playing an increasingly limited role in favour of targeted therapies and immunotherapy,**

the Committee considers that MUPHORAN does not provide any improvement in actual benefit (level V, non-existent) in the management of metastatic melanoma.

Primary brain tumours indication:
As the data available are limited to non-comparative studies and there are no comparisons with the available treatments in this indication, the Committee considers that MUPHORAN does not provide any improvement in actual benefit (level V, non-existent) in the management of primary brain tumours.

011.3 Target population

Disseminated malignant melanoma (including brain metastases)
The target population for MUPHORAN in melanoma is made up of patients with unresectable disseminated melanomas, i.e. stage III and IV melanomas.
The partial prevalence of cutaneous melanoma calculated in late 2004 in France was 31,27 cases, of which 2,310 had metastases (stage IV) and 28,968 did not have metastases (TC opinion for YERVOY, 2011).
In 2012, the standardised incidences (per 100,000 patient-years) were 10.8 in men and 11.0 in women, i.e. a male/female ratio of 0.98. The standardised incidence of melanoma is increasing by 2.9% and 1.7% per year in men and women respectively.
Based on the hypothesis that the change in prevalence is equivalent to the change in gross incidence, the weighted mean increase in prevalence is 2.3% per year (INVS, 2013).
The prevalence of stage IV melanomas in late 2013 is estimated as 2,800 patients.
The exact prevalence of inoperable stage III melanoma is not known. In the MELODY study, the baseline sample consisted of 195 patients with stage IV and 23 patients with unresectable stage III on inclusion, a ratio of 11.8 between these two categories of patients.
On this basis, the number of patients with unresectable stage III melanoma is estimated at about 300 patients.
Note that the size of this population should be considered with regard to the BRAF mutation found in 40% to 60% of patients with advanced melanoma (CT opinion for YERVOY, 2011).
Therefore, the total number of patients with unresectable disseminated/metastatic melanoma can be estimated as 3,100.

Primary brain tumours
The population for MUPHORAN is patients with high-grade malignant gliomas (grade III and grade IV anaplastic glioblastomas, grade IV being glioblastomas):

- anaplastic gliomas (grade III) have an annual incidence of about 0.626 cases/100,000 inhabitants in adults[21] (Baldi, 2011), i.e. about 400 cases in France. The risk of relapse and recurrence with grade III gliomas is extremely high and it is almost inevitable that these aggressive tumours will progress in the majority of patients (http://www.mednet.ca/fr/report/tendances-actuelles-et-perspectives-davenir-dans.html);
- the number of histological cases of grade IV gliomas in France may be estimated as 2000 per year.[22] The recurrence rate is estimated to be 90%.[23]

Therefore, the population of patients with high-grade malignant gliomas (grades III and IV) may be estimated as 2,400 patients.

[21] Baldi I, Gruber A, Alioum A, Berteaud E, Lebailly P, Huchet A, Tourdias T, Kantor G, Maire JP, Vital A, Loiseau H, Gironde TSNC Registry Group: Descriptive epidemiology of CNS tumors in France: results from the Gironde Registry for the period 2000-2007. Neuro Oncol 2011;13:1370-8

[22] Zouaoui S, Rigau V, Mathieu-Daude H, Darlix A, Bessaoud F, Fabbro-Peray P, et al. French brain tumor database: general results on 40,000 cases, main current applications and future prospects. Neurochirurgie 2012;58:4-13

[23] Easaw JC, Mason WP, Perry J, Laperrière N, Eisenstat DD, Del Maestro R, Bélanger K, Fulton D, Macdonald D; Canadian Glioblastoma Recommendations Committee. Canadian recommendations for the treatment of recurrent or progressive glioblastoma multiforme. Curr Oncol 2011;18:126-36