ITCC-025

CLINICAL STUDY PROTOCOL

Study number: 2009-10

Protocol title:

INTERNATIONAL RANDOMIZED PHASE II TRIAL OF THE COMBINATION OF VINCRISTINE AND IRINOTECAN WITH OR WITHOUT TEMOZOLOMIDE (VI OR VIT) IN CHILDREN AND ADULTS WITH REFRACTORY OR RELAPSED RHABDOMYOSARCOMA

Study code : VIT-0910

EudraCT N° : 2010-023135-42

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Confidentiality

LIST OF PROTOCOL VERSIONS APPROVED BY REGULATORY AUTHORITIES

Last update: June 24, 2019

Version No	VHP No	VHP	FRANCE		ITALY		SPAIN		THE NETHERLANDS		UNITED KINGDOM	
			NCA	EC	Local CA	EC	NCA	EC	NCA	EC	NCA	EC
			ANSM (afssaps)	CPP Nord Ouest IV		Milano, Florencia, Genoa, Torino, Padova, Roma	AEMPS	Madrid, Barcelona, Tenerife, Valancia	CCMO	MEC	MHRA	NRES Committee South Central Oxford
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1.1b of 6 Dec 2011 : Amendment for NL (b)	*Not applicable*	*Not applicable*	*Not applicable*		*Not applicable*		*Not applicable*		*Not applicable*	**31 Oct 2011**	*Not applicable*	
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5.1 of June 24th 2019 including non-substantial amendment (i)	*Not applicable*	*Not applicable*	*Not applicable*	*Not applicable*								

NCA: National Competent Authority, EC: Ethic Committee

(a) Removal of pharmacogenetic study, trial site list update, clarifications requested by the NCRN, correction of typing errors, addition of formulae for calculation of creatinine clearance (Appendix 8)

(b) Funding arrangement for cefixime and temodal, drug management in The Netherlands (Appendix 11)

(C) Addition of Guidelines for administering temozolomide to patients in the United Kingdom who have difficulty swallowing temozolomide capsules (Appendix 12)

(d) Additional instructions about vincristine dose adjustments, and in case of bone marrow disease; clarification of SAE reporting; update of the study calendar; correction of typing errors

(e) information about hepatic toxicities occurring in patients treated with Temozolomide, revision of Temodal SmPC, revision of Helsinki declaration, update of staff contacts

(f) Addition of 40 extra patients with recurrent RMS, and non substantial modifications (changes in staff list, protocol clarifications)

(g) update of staff contact list (sponsor)

(h) addition of contraindications following update of irinotecan's SmPC, and non substantial modifications (changes in staff list, clarifications of biostatistical considerations, update of temozolomide and vincristine's SmPC without impact on patient's safety)

(g) removal of a withdrawal criterion; definition of the Last Visit of the Last Subject (LVLS) as the last VI/VIT administration + 6 months to have relevant data in terms of response after 2 cycles.

(i) removal of a withdrawal criterion: "Local therapy after 2nd cycle of study treatment", in line with Steering Committee recommendations to perform analysis on local treatment received after VI/VIT, in order to explain the much larger effect of VIT compared to VI on overall survival than progression-free survival ; and clarification of the Last Visit of the Last Subject (LVLS), defined as the last VI/VIT administration followed by 6 months to have relevant data in terms of response after 2 cycles

1 APPROBATION AND PROTOCOL SIGNATURE

Study code: VIT-0910

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	Date	Signature
Dr Anne-Sophie DEFACHELLES Pediatric Oncologist *Centre Oscar Lambret – Lille - France*		

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	Date	Signature
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The coordinating centre / coordinating investigator, on behalf of the sponsor, is responsible for submitting the application for an Ethics Committee opinion according to national and institutional guidelines (see Section 11.2.6. and 13.2.)

3. LIST OF TRIAL SITES

Will be attached to the protocol

Principal investigator / Site / Country

Protocol title: **International randomized phase II trial of the combination of Vincristine and Irinotecan with or without Temozolomide (VI or VIT) in children and adults with refractory or relapsed rhabdomyosarcoma**

Investigator name and address:

I have read the present protocol

I agree:

- To obtain approval of my Institution to lead the study in the establishment
- To maintain confidentiality regarding the contents of this protocol
- To conduct the study as outlined in the protocol and in compliance with GCP and with applicable regulatory requirements ;
- To provide the protocol and all drug information furnished to me by the sponsor, to all physicians responsible to me who participate in this study. I will discuss the material with them to assure that they are fully informed regarding the drug and the conduct of the study;
- To appropriately direct and assist the staff under my control, who will be involved in the study;
- To use the trial material only according to the instructions of the protocol;
- To permit monitoring, auditing and inspection;
- To inform patient and collect their consent before any selection procedure of the protocol
- To declare immediately Serious Adverse Events to the sponsor
- To complete and validate eCRF for each patient included in the study
- To retain the trial-related essential documents until the sponsor indicates that these documents are no longer needed and for a minimum period of 40 years.

Investigator signature: **Date:**

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4. SYNOPSIS

Will be attached to the protocol

5. INTRODUCTION AND STUDY RATIONALE

5.1. Study disease

Rhabdomyosarcoma (RMS) is a soft tissue sarcoma derived from muscle precursor cells. It is the commonest form of soft tissue sarcoma in children < 15yrs, accounting for around 4% of paediatric malignancies and with a peak incidence in young children < 5yrs. However, RMS can occur at all ages and overall 41% of cases occur in the adult population [Sultan 2009]. The pattern of disease changes with age, with alveolar and metastatic tumours commoner in older children/young people and pleomorphic RMS and not otherwise specified histologies commoner in adults. Adults are more likely to present with disease at unfavourable sites. The likely outcome in RMS depends on a number of risk factors at presentation including age, site, tumour size, histo-logy and presence of nodal or metastatic disease and initial treatment is now tailored according to risk.

Around 85% of children with RMS have localised disease at presentation. Within the SIOP experience the 3 yr event free survival of patients achieving complete local control is 64% and 36% of patients who relapse can be salvaged [Chisholm 2011]. Among patients experiencing relapse, the most frequent site of relapse is locoregional (76%) with only 15% of patients having an isolated metastatic recurrence [Chisholm 2010]. Survival after relapse is affected by several factors, the most important being the type of recurrence, previous radiotherapy, time of relapse and the initial tumour size [Chisholm 2010]. Survival after an isolated local relapse is around 50% at 3 years whereas it is only 13-14% at 3 years after a metastatic relapse [Dantonello 2008, Mattke 2009, Mazzolini 2005, Pappo 1999, Pappo 2001, Pappo 2007, Chisholm et al 2010]. This finding means that we urgently need new chemotherapy agents and/or targeted agents for systemic treatment of RMS. Another key factor is the ability to deliver good local therapy to locally relapsing tumours; where patients have previously received radiotherapy, local therapy may be limited to aggressive surgery. Surgical clearance may be aided by effective new systemic therapies justifying the use of volumetric response of the target lesions to the chemotherapy as the main evaluation criteria in the current study.

Most patients with relapsed rhabdomyosarcoma have measurable disease at local and/or metastatic sites at relapse. In this study we will test the new combination of vincristine, irinotecan and TMZ in RMS, using objective volumetric response after 2 cycles of treatment as our primary endpoint.

5.2. Irinotecan

Irinotecan is a camptothecin prodrug which is converted by endogenous carboxylesterases to the active topoisomerase I poison SN-38 [Masuda 1996]. In preclinical studies, irinotecan was highly active in vitro and in vivo against a broad spectrum of human and murine tumor cell lines. Substantial antitumor activity was observed in xenografts derived from pediatric tumors, including RMS, peripheral primitive neuroectodermal tumors as well as in RMS xenografts selected in vivo for resistance to vincristine, melphalan and topotecan [Hare 1997, Houghton 1993, Komuro 1994, Thompson 1997, Vassal 1996, Vassal 1997]. This preclinical activity can be optimized by protracted

administration on a 5 days x 2 schedule, in which drug is given for five consecutive days for two weeks in a row, thus prolonging the exposure of this S-phase-specific agent [Bomgaars 2001, Houghton 1995]. A protracted schedule also seems to be less myelotoxic than other regimens evaluated [Furman 1999, Gerrits 1997].

Two distinct patterns of diarrhea have been associated with irinotecan. Early-onset diarrhea typically occurs within 4 hour of administration, and is associated with the "cholinergic syndrome" consisting of cramping, flushing, and diaphoresis [Kawato 1993]. These symptoms occur in 9–27% of children receiving single large dosages of irinotecan [Bomgaars 2006, Vassal 2003, Vassal 2007], although its incidence is < 5% in patients treated with protracted schedules [Bisogno 2006, Furman 1999, Wagner 2007]. This syndrome results from direct inhibition of acetylcholinesterase by the terminal dipiperidino moiety in irinotecan [Harel 2005]. Early-onset diarrhea is preventable or readily reversible with atropine administration [Vassal 2007], and to date has not been dose-limiting.
In contrast, late-onset diarrhea usually develops during the second week of therapy, and can be dose-limiting regardless of the irinotecan schedule. In adults receiving single large dosages once every 1–3 weeks, irinotecan-associated diarrhea of any grade occurs in up to 80% of patients, with approximately 30% experiencing at least grade 3 diarrhea [Saltz 2000].

For children receiving 5 days x 2 intravenous irinotecan at the maximum tolerated dose of 20 mg/m²/day, irinotecan-associated diarrhea of any grade occurs in 73% of patients, with 10–18% having grade 3–4 diarrhea or abdominal pain [Bisogno 2006, Pappo 2007]**.** The mechanisms leading to late-onset diarrhea are complicated and not completely understood. It may be the result of active metabolite SN-38 present in the intestinal lumen inducing direct cytotoxic damage to the mucosa, resulting in secretory and exudative diarrhea symptoms [Saliba 1998]. Strategies to prevent diarrhea include the use of activated charcoal and/or prophylactic antibiotics during therapy with irinotecan [Furman 2006, Sergio 2008, Wagner 2008]. Cephalosporin prophylaxis is a safe and feasible way to help optimize use of protracted irinotecan in children, and can improve both dose intensity and drug exposure. Cefixime at 8 mg/kg/day (max 400 mg) is well tolerated and can be given once daily, starting up to 5 days before chemotherapy administration and continuing throughout the course of protracted irinotecan. In addition, it does not interfere with the pharmacokinetics of irinotecan [Furman 2006, Pappo 2007, Wagner 2007].
Four pediatric phase II studies were performed to determine the tumor response rate of a range of solid pediatric tumors to irinotecan as single agent. In addition to the response rate, the safety profile and pharmacokinetics of Irinotecan were assessed in three of them. Tumor response rate was the primary efficacy endpoint for these studies:

- Bisogno *et al* reported an overall response rate to irinotecan administered on a 5 days x2 schedule (20 mg/m²/day for 5 days a week, for 2 consecutive weeks) of 23% for a total of 32 heavily pre treated patients with sarcoma: 13 with peripheral primitive neuroectodermal tumor (PNET), 3 with desmoplasic small round cell tumor (DSRCT) and 2 with other STS. Overall response rates were 38% for peripheral PNET and 16% for RMS [Bisogno 2006].
- Bomgaars *et al* reported a specific response rate of 15.8% for patients with RMS receiving irinotecan 50 mg/m² IV for 5 days repeated every 3 weeks. Stable disease was noted for 47.1% of patients and this was seen with all tumor types [Bomgaars 2007].
- Vassal *et al* reported an overall response rate to irinotecan (at 600 mg/m² administered as a 60-minute infusion every 3 weeks) of 11.4% (2.9% complete responses, 8.5% partial responses) for a

total of 35 patients with refractory or relapsed RMS for which standard treatments have failed [Vassal 2007].

- Pappo *et al* have demonstrated that administration of Irinotecan using a low-dose protracted schedule (20 mg/m² intravenously over 60 minutes daily 5 d x 2 weeks) is highly effective when administered as window therapy in 19 pediatric patients with newly diagnosed metastatic RMS: 42% of children had a favourable response. However, the high progressive-disease rate prompted closure of this trial [Pappo 2007].

5.3. Combination of irinotecan with vincristine

After exposure to camptothecin analogues, many cell types arrest in S phase or G2-M phase. Thompson *et al* postulated that administration of topotecan followed by vincristine, that causes depolymerization of microtubules leading to mitotic arrest and death, might have a synergistic antitumor effect. They investigated the activity of this combination against a panel of childhood solid tumor xenografts representing childhood neuroblastoma, RMS or brain tumors: the therapeutic effect was greater than additive in most models of childhood solid tumors, and toxicity data suggest that this can be administered to mice with only moderate reduction in the dose levels for each agent [Thompson 1999].

Vincristine has demonstrated activity in several xenograft models of pediatrics tumors [Houghton 1984, Houghton 1987] and has an established role in the treatment of childhood cancers, in particular sarcomas.
Based on these observations, Pappo *et al* added vincristine (1.5 mg/m² at weeks 0, 1, 3 and 4) to Irinotecan (daily 5 d x 2 weeks) for patients with newly diagnosed metastatic RMS. This addition increased the window response rate (70% versus 42% with Irinotecan alone) and reduced the rate of progression (8% versus 32%) [Pappo 2007].

More recently, Mascarenhas *et al* reported the results of a randomized phase II window study of two schedules of irinotecan and vincristine in RMS at first relapse/disease progression.
Patients were randomized to one of two schedules of irinotecan-vincristine : A : irinotecan 20 mg/m^2 intravenously (IV) daily x 5d x 2w and vincristine 1.5 mg/m^2 IV on day 1 of weeks 1 and 2 versus B : irinotecan 50 mg/m^2 IV daily x 5d on week 1 and vincristine identical to A. There were no difference in the response rates (overall response 25% versus 37%, p=0.23), no unexpected toxicities or significant differences in toxicity between the two regimens. The shorter, more convenient CPT-11/VCR regimen is now being investigated in frontline Children's Oncology Group RMS clinical trials [Mascarenhas 2010].

5.4. Temozolomide

The mechanism of action of irinotecan - mainly S phase specific obstruction of DNA replication - supports its use combined with an alkylating agent as a strategy for increasing tumor-cell kill. Imidazotetrazine compounds (TZC) are alkylating agents with antitumor and antimetastatic potential. Dacarbazine, the first TZC to be utilized in cancer patients, was used for the treatment of malignant melanoma and, in combination regimens, for the treatment of sarcomas [Antman 1993, Zucali 2008].
TMZ is a second generation imidazotetrazine prodrug that is metabolized to the active metabolite monomethyl triazenoimidazole carboxamide (MTIC) [Stevens 1987]. This agent promotes

cytotoxicity primarily via O6-methylation of guanine, leading to base-pair mismatch and eventual inhibition of DNA replication, resulting in cell cycle arrest [Catapano 1987, Newlands 1997]. It has the advantages of excellent oral bioavailability, a favorable toxicity profile, and the ability to cross the blood–brain barrier. Recently, Diez *et al* demonstrated the exposure equivalence of a 90-min intravenous infusion with oral administration of TMZ. Intravenous administration of TMZ was well tolerated. In clinical practice, oral TMZ is administered using a variety of doses and schedules. Based on the data from this study and the known PK characteristics of TMZ, intravenous administration would result in an equivalent exposure compared with oral administration at any given dose and schedule [Diez 2009].

Preclinical studies demonstrate an antitumor effect in murine models of pediatrics solid tumors [Middlemas 2000]. TMZ has activity against adult and pediatric primary brain tumors as well as adult solid tumors with brain metastases, metastatic melanoma, and metastatic leiomyosarcoma [Anderson 2005, Nicholson 1998, Nicholson 2007, Rubie 2006, Ruggiero 2006, Verschuur 2004, Woll 1999]. However, data on the use of TMZ as a single agent in other pediatric malignancies are limited. De Sio *et al* investigated the use of TMZ as single agent in 52 relapsed or resistant pediatric tumors. They reported activity of TMZ in relapsed or resistant neuroblastoma patients and in a subset of patients with CNS tumors. TMZ did not induce any major response in other tumor types [De Sio 2006].

5.5. Combination of irinotecan with temozolomide

Although it is unclear exactly how the cytotoxicity of irinotecan is potentiated by TMZ, it may be related to TMZ -induced methylation of DNA causing localization and enhancement of topoisomerase I cleavage complexes allowing irinotecan to more effectively stabilize the DNA-enzyme complex and cause cytotoxicity after collision with advancing replication fork.
In addition to the single-agent activity and non-overlapping toxicity profiles (diarrhea versus myelosuppression), this combination is attractive because of significant therapeutic synergy demonstrated by Houghton *et al* [Houghton 2000] in preclinical experiments. They showed that the combination of non curative doses of each drug resulted in complete responses in xenograft models of neuroblastoma, rhabdomyosarcoma RMS, and glioblastoma multiforme. This occurred in tumors that were MGMT sufficient and mismatch repair (MMR) deficient, suggesting that the interaction between these agents may in part be independent of TMZ induced *O*6-methylation of guanine. This therapeutic synergy is greatest when TMZ is given before irinotecan, suggesting that TMZ potentiates the cytotoxic effects of irinotecan [Patel 2000].

This rationale has led to adult phase I and II trials of this combination in brain tumors [Gruber 2004] and solid tumors [Jones 2003].

A pediatric phase I trial has identified the MTD for TMZ to be 100mg/m²/day given x5 days combined with irinotecan 10 mg/m²/d given 5 days x 2 given in 28-day cycles. Despite these relatively low doses, clinically relevant SN-38 and MTIC exposures were achieved at the MTD and objective imaging responses were seen in over one-third of evaluable patients particularly for patients with neuroblastoma and Ewing sarcoma [Wagner 2004]. A phase II trial with this schedule is currently ongoing in children with relapsed medulloblastoma [Grill et al, ASCO 2009].

Kushner *et al* chose a 5-day plan of irinotecan 50 mg/m² (1-hour infusion) and TMZ 150 mg/m² (oral) every 3 to 4 weeks because of its convenience for patients. These courses of irinotecan and TMZ in a large series of heavily treated neuroblastoma patients had manageable adverse effects and no unexpected toxicities. The regimen was compatible with normal age-appropriate activities. Ease and rapidity of administration, plus little emetogenic effect, allowed outpatient treatment. When they occurred, gastrointestinal symptoms were generally self-limited, of short duration, or responsive to standard medications [Kushner 2006].

While TMZ has little clinical activity as a single agent against sarcomas, it may serve as a response modifier to potentiate the antitumor activity of irinotecan.
In a retrospective review, Wagner *et al* reported their clinical experience with TMZ and protracted irinotecan in patients with advanced Ewing sarcomas [Wagner 2007]. These patients received different doses of irinotecan and different lengths of treatment courses. The authors observed 1 complete, 3 partial and 3 minor responses in 14 evaluable patients with a median duration of 30 weeks. Another recent retrospective analysis builds on these observations, reporting an overall objective best response of 63% with the use of protracted irinotecan (20 mg/m²/day x5days x2weeks) in combination with TMZ (100mg/m²/dayx5days) for recurrent/ progressive Ewing sarcomas. It is notable that 5 (26%) of 19 evaluable patients achieved a complete response [Casey 2009].

5.6. Combination of irinotecan with vincristine and temozolomide

In a recent phase I trial, Wagner *et al* determined the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of orally administered irinotecan given on two different schedules together with TMZ and vincristine in children with refractory solid tumors, using cefixime to reduce irinotecan-associated diarrhea. The schedule A associated oral irinotecan daily for 5 days for 2 weeks (5 days x2), with vincristine 1.5 mg/m^2 on days 1 and 8 and TMZ 100 mg/m^2 on days 1-5. The schedule B associated oral irinotecan daily for 5 days for 1 week (5 days x1) with vincristine 1.5 mg/m^2 on day 1 and TMZ 100-150 mg/m^2 on days 1-5. Courses were repeated every 3 weeks. First-course and cumulative toxicity appeared worse with schedule A. The 5 days x1 schedule was well tolerated, with SN-38 exposures similar to those achieved with intravenous IRN at the dose of irinotecan 90 mg/m²/day. Activity on this and prior studies suggests a potential role for this association in sarcoma patients [Wagner 2009].
The current open-label, multicenter, randomized phase II study will evaluate the efficacy and tolerability of combination of TMZ with vincristine and irinotecan for 80 patients with refractory or recurrent RMS, and for 40 additional patients with reccurent RMS only (upon IDMC decision).
Given the results of Mascarenhas *et al* and of Wagner *et al* and because of its convenience for patients, we chose a 5-day plan of administration for irinotecan.
Depending on the results of this trial, the VIT combination could become a backbone chemotherapy in relapsed or refractory RMS, using three drugs of which two are not used in front line treatment. Further trials could be designed incorporating TMZ with new compounds such as targeted or antiangiogenic compounds, PARP inhibitors etc.

6. STUDY OBJECTIVES

6.1. Primary objectives

- To assess the rate of confirmed objective tumor response in patients with recurrent or refractory rhabdomyosarcoma in each treatment arm

6.2. Secondary objectives

- To describe the best overall response over the treatment duration, determine the duration of tumor response, progression-free survival (PFS), time to treatment failure and overall survival (OS) in each treatment arm.
- To assess safety and tolerability for each treatment arm.

6.3. Ancillary objective

- To estimate the relative treatment effect of VIT compared to VI in terms of objective response rate (ORR), PFS and OS (after amendment 5.0 July 2018).

7. STUDY DESIGN

7.1. Type of study

This is an international open-label, randomized, multicenter phase II study of VIT and VI for the treatment of 80 patients with recurrent or refractory RMS, and 40 additional patient with recurrent RMS only (upon IDMC decision). The study will evaluate the safety and efficacy of these combinations in patients with recurrent or refractory RMS.

The dose of vincristine will be 1.5 mg/m² or 0.05 mg/kg for patient ≤ 10 kg (maximum 2 mg) and will be administered by direct intravenous infusion on day 1 and 8 of each course, before irinotecan.

The dose of irinotecan will be 50 mg/m²/d. Irinotecan will be given intravenously infusion over 1 hour on days 1-5 of each course, one hour following the administration of TMZ.

In the absence of any contraindication (ie known allergies), treatment with oral cefixime 8 mg/kg once daily (maximum daily dose 400 mg) is recommended and will be started 2 days before chemotherapy until day 7 (see Appendix 11 for cefixime management in The Netherlands).

TMZ will be given according to the randomization. The starting dose of TMZ will be 125 mg/m²/d. The dose of TMZ will be escalated to 150 mg/m²/day at cycle 2 for patients who do not experience ≥ grade 3 toxicity of any kind. TMZ will be given orally, on an empty stomach, on days 1 through 5 of each course. The capsules must be swallowed whole with a glass of water. For young children and patients who have difficulty swallowing capsules, the full daily dose of TMZ capsules should be placed in 10-30 ml fruit juice or compote and administered after the capsules have been allowed to soften for 15-20 minutes.

Dose reductions and/or administration delays will be performed using specific predefined rules to accommodate individual patient tolerance of treatment and to maintain optimal dose intensity (section 8.3.5.).

7.2. End of study

If the study is not terminated for one of the reasons given in section 7.3., the main analysis will be performed when the end of treatment imaging on the last patient has been undertaken. The Last Visit of the Last Subject (LVLS) is defined as last VI/VIT administration + 6 months to have relevant data in terms of response after 2 cycles.
The final analysis of survival outcomes is planned 5 years after recruitment of the last patient.

7.3. Study discontinuation

Although the Investigator-Sponsor has every intention of completing the study, the Investigator-Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.
Reasons for terminating the study may include:
- Unexpected incidence of known AEs.
- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties in the recruitment of patients.

7.4. Inclusion criteria

Patients must satisfy all the following entry criteria before they are allowed to participate in the study.

TUMOR CHARACTERISTICS:

- Histologically or cytologically confirmed diagnosis of rhabdomyosarcoma (new biopsy recommended)
- Any Relapsed / progressive disease (in patients who have already presented a response to chemotherapy)

  OR
- Refractory disease (defined as progression after receiving chemotherapy without prior response)
- Patients must have measurable disease defined as lesions that can be measured in 3 dimensions by medical imaging techniques such as CT or MRI. Ascites, pleural fluid, bone marrow disease alone and lesions seen on Tc scintigraphy or PET scan only are not considered measurable.

PATIENT CHARACTERISTICS:

- Age > 6 months and ≤ 50 years
- Karnofsky performance status (PS) 70-100% (for patients > 12 years of age)
  OR Lansky Play Score 70-100 % (for patients ≤ 12 years of age)
- Life expectancy ≥ 12 weeks
- Adequate bone marrow function :
  - Absolute neutrophil count ≥ 1000/mm^3
  - Platelet count ≥ 100,000/mm^3 (transfusion independent)
  - Hemoglobin ≥ 8.5 g/dL (transfusion allowed)

    - In case of bone marrow disease:
        - Absolute neutrophil count ≥ 500/mm^3
        - Platelet count ≥ 75,000/mm^3
- Adequate renal function
    - Serum creatinine ≤ 1.5 X ULN for age
    - If serum creatinine > 1.5 ULN, creatinine clearance (or radioisotope GFR) must be ≥ 70 ml/min/1.73 m²
- Adequate hepatic function :
    - Total bilirubin ≤ 1.5 times upper limit of normal (ULN) for age, except if the patient is known to have Gilbert's syndrome
    - ALT and AST ≤ 2.5 X ULN for age
- Negative pregnancy test in females with childbearing potential
- Fertile patients must use effective contraception
- No active > grade 2 diarrhea or uncontrolled infection
- No other malignancy, including secondary malignancy
- Patient affiliated with a health insurance system. Applicable for French patients only
- Written informed consent of patient and/or parents/ guardians

PRIOR OR CONCURRENT THERAPY:

- More than 3 weeks since prior radiation therapy to the site of any progressive lesion that will be identified as a target lesion to measure tumor response
- At least 3 weeks since prior myelosuppressive therapy (6 weeks for nitrosourea, 2 weeks for vincristine, vinorelbine, vinblastine and low-dose cyclophosphamide)
- No concurrent enzyme-inducing anticonvulsants (EIAC), including phenytoin, phenobarbital, or carbamazepine
- No concurrent administration of any of the following : rifampicin, voriconazole, itraco-nazole, ketoconazole, aprepitant
- No prior irinotecan or temozolomide administration
- Prior administration of vincristine is allowed
- Concurrent palliative radiation therapy to sites allowed except for the main measurable target lesion
- Prior allo- or autologous SCT allowed

7.5. Exclusion criteria

- Inclusion criteria failure
- Concomitant anticancer treatment
- Know hypersensitivity to any component of study drugs or ingredients
- Pregnancy or breast feeding
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Neuromuscular disorders (e.g. Charcot-Marie Tooth disease)
- Uncontrolled intercurrent illness or active infection
- Unable for medical follow-up (geographic, social or mental reasons)

7.6. Life style guidelines

Patients with reproductive potential must agree to use effective contraception during the period of therapy. *Men should be advised not to father a child up to 6 months after receiving the last dose. Women of childbearing potential should be advised to use effective contraception to avoid pregnancy up to 6 months after the last dose of study treatment.*

7.7. Patient enrolment

According to the Good Clinical Practice (GCP) guidelines, all inclusion/exclusion criteria will be checked during the registration procedure. A registration number that further identifies the patient within the centre will be allocated to the patient.

The following procedures should be performed before completing the registration form:

- Informed consent leaflet should be signed by patient or the parents or legal representative of patient and the investigator before starting any study procedure ;
- All selection procedures should be performed as per protocol ;
- After patient registration, the patient identification number and treatment arm allocated will be retained within the study even if the patient is withdrawn from the study before the first study drug administration. New patients must always be allocated a new number.

The procedure for enrolling patients will be detailed for each participating centre. The TenAlea software program via internet will be the preferred system. It is possible to use a backup procedure by faxing the registration form to the following address:

Clinical Research Integrated Unit / Sponsor Unit
Centre Oscar Lambret – Lille - France
Tel: 33 (0)3 20 29 59 18 - Fax: 33 (0)3.20.29.58.96

7.8. Withdrawal from study treatment

Patients will be considered withdrawn from study for one of the following reasons:

- Progressive disease
- Global deterioration of health status
- Unacceptable toxicity (Noted on CRF adverse event page)
- Cycle of treatment delayed by more than 2 weeks
- Investigator decision
- At the request of the patient or a representative
- Lost to follow up
- Death of patient

This section only concerns treatment withdrawal, since the main statistical analysis will be performed on the intent to treat patient population. Follow-up visits are planned after "withdrawal from study treatment".

8. STUDY TREATMENT

Enrolment will take place after the patient or patient's parent or legal guardian have given written informed consent and eligibility has been established.
A patient identification number will be assigned, and this number will be retained for the patient throughout the duration of study participation. After the patient is enrolled, study treatment will be initiated as outlined in section 7.7.

8.1. Dispensing, storage of the investigational drug

In this clinical trial, vincristine, irinotecan and TMZ are all considered as Investigational Medicinal Products (IMPs). For the purposes of the protocol, the term "study medication" or "investigational agent" refers to the combination of vincristine, and irinotecan with or without TMZ.
The IMPs will be used from Normal Hospital Stock. In The Netherlands, neither TMZ, nor cefixim used as prophylactic treatment, are registered. This drugs will be considered as investigational medicinal products and will be provided as study medication (see Appendix 11 for TMZ and cefixime management in The Netherlands).

8.2. Drug supplies

The investigator/pharmacist must maintain an accurate record of the dispensing of the study drug in a standard drug accountability ledger, a copy of which must be sent to Sponsor at the end of the study.
An accurate record of the date and amount of study drug dispensed to each patient must be available for inspection at any time.

8.2.1. Vincristine

Vincristine is available commercially in 1mg/ml vials (1 mg, 2 mg, 5 mg vials with 10 ml diluent).
Reconstituted injection is stable for 14 days (2-8°C), refer to local guidelines.
Administration will be made by bolus injection taking care to avoid extravasion and must comply with guidance on administration of vinca alkaloids as per NPSA/2008/RRR004.

8.2.2. Irinotecan

The intravenous formulation of irinotecan (Irinotecan hydrochloride trihydrate) is available commercially in 20 mg/ml vials.
For intravenous administration, irinotecan should be diluted with 5% dextrose in water or 0.9% sodium chloride solution to a final concentration of 0.12-2.8 mg/ml and infused IV over 60 minutes. Nothing else should be added to the bag. The total administered dose of chemotherapy may be rounded up or down within a range not exceeding 5% of the actual calculated dose. After reconstitution, irinotecan is stable for 24 hours at room temperature and in ambient fluorescent lighting.
Drug handling precautions for cytotoxic drugs should be followed. Avoid contact or inhalation.

8.2.3. Temozolomide

TMZ, an imidazotetrazine derivative, is available commercially as capsules for oral administration. TMZ contains lactose. Each capsule will contain 5, 20, 100, 140, 180 or 250 mg of the active ingredient TMZ. TMZ must be stored protected from light. Do not store above 30°C.

If a capsule becomes damaged, avoid contact of powder contents with skin or mucous membrane. If contact does occur, wash the affected area. Capsules should not be chewed. Keep capsules out of reach and sight of children, preferably in a locked cupboard.

8.3. Summary of Products Characteristics

Investigators must refer to the informations contained in the country-specific applicable Summary of Products Characteristics (SPCs) of Marketing Authorized products for the management of patients, particularly with regard to contraindications, warnings and precautions for use, dose adjustments in case toxicity, monitoring of patients and prohibited drugs or drugs to use with caution.
Coordinating centres make available the official and updated versions of the SPCs for study drugs used in their respective territory.

9. TREATMENT ADMINISTRATION

9.1. Starting doses and schedules

ARM A		
D1 and D8 **Vincristine**	1.5 mg/m²/d – IV bolus (0.05 mg/kg for patient ≤ 10 kg)	3 weekly
D1 to D5 **Irinotecan**	50 mg/m²/d – IV over 1 hour	3 weekly
ARM B		
D1 to D5 **Temozolomide**	125 mg/m²/d - PO	3 weekly
D1 and D8 **Vincristine**	1.5 mg/m²/d – IV bolus (0.05 mg/kg for patient ≤ 10 kg)	3 weekly
D1 to D5 **Irinotecan**	50 mg/m²/d – IV over 1 hour	3 weekly

Vincristine: The dose of vincristine will be 1.5 mg/m² or 0.05 mg/kg for patient ≤ 10 kg (maximum 2.0 mg) and will be administered by direct intravenous infusion on day 1 and day 8 of each course, before irinotecan. Administration must comply with guidance on administration of vinca alkaloids as per NPSA/2008/RRR004.

Irinotecan: The dose of irinotecan will be 50 mg/m²/day. Irinotecan will be given intravenously infusion over 1 hour on days 1-5, one hour following the administration of TMZ.
In absence of contraindications (known allergies), **systematic treatment with oral cefixime 8 mg/kg once a day (maximum daily dose 400 mg) is recommended and will be started 2 days before chemotherapy until day 7** (see Appendix 11 for cefixime management in The Netherlands).

Temozolomide: will be given according to the randomization: The starting dose of TMZ will be 125 mg/m²/day. The dose of TMZ will be escalated to 150 mg/m²/day at cycle 2 for patients who do not experience ≥ grade 3 toxicity of any kind. The dose of TMZ should be rounded to the nearest 5 mg. TMZ will be given orally, on an empty stomach, prior to vincristine and irinotecan, on days 1-5 repeated every 3-weeks. If the patient vomits within 20 minutes after TMZ, the dose will be re-administered. The capsules must be swallowed whole with a glass of water. For young children and patients who have difficulty swallowing capsules, the full daily dose of TMZ capsules should be placed

in 10-30 ml fruit juice or compote and administered after the capsules have been allowed to soften for 15-20 minutes or according to normal local practice for patients in the United Kingdom (see Appendix 12).

Treatment will continue until disease progression, unacceptable toxicity or the patient's desire to discontinue therapy. Local treatment is allowed after 2 cycles.

Patients must have evidence of recovery from all prior cycle toxicity and the ANC must be > 1000/mm3 and platelets > 100 000/mm3 before receiving the next cycle of therapy. If initiation of the next treatment cycle is delayed by more than 2 weeks, the patients should be discontinued from the study.

In the absence of clinically progressive disease, patients should receive at least 2 cycles of VIT or VI prior to the first evaluation on study treatment.

9.2. Dosage adjustments

Patients should be carefully monitored for toxicity. After the initial treatment cycle, dose reductions and/or administration delays will be decided using specific predefined rules to accommodate individual tolerance of treatment and maintain optimal dose intensity. All toxicities will be graded according to version 4.0 of the NCI CTCAE. Doses are to be adjusted based on the most severe toxicity that the patient experiences related or possibly related to the study treatment between each cycle of treatment. For hematological toxicities, the guiding principle is that the full doses of both drugs will be administered only if toxicities have recovered to ANC ≥ 1000/mm3 or and platelet count ≥ 100 000/L, or ANC ≥ 500/mm3 or and platelet count ≥ 75 000/mm3 in case of bone marrow disease, by day 21 after the start of the cycle

9.2.1. Vincristine, Irinotecan and Temozolomide

Dose levels for dose adjustment

Starting dose	**Reduction (20%) dose level -1**	**Reduction (20%) dose level -2**
Temozolomide		
125 mg/m²/dx5 q 3 wks	100 mg/m²/dx5 q 3 wks	75 mg/m²/dx5 q 3 wks
150 mg/m²/dx5 q 3 wks	120 mg/m²/dx5 q 3 wks	90 mg/m²/dx5 q 3 wks
Irinotecan		
50 mg/m²/dx5 q 3 wks	40 mg/m²/dx5 q 3 wks	30 mg/m²/dx5 q 3 wks
	Reduction (50%) dose level -1	
Vincristine		
1.5 mg/m²/d (maximum 2mg) direct IV infusion at d1 and d8 q 3 wks (0.05 mg/kg for patient ≤ 10 kg)	0.75 mg/m² (maximum 1mg) direct IV infusion at d1 and d8 q 3 wks (0.025 mg/kg for patient ≤ 10 kg)	

Study treatment dose reduction or discontinuation

Arm A (VI)

Type of toxicity	Dose modification at first occurrence	Dose modification at second occurrence
• ANC < 1000/mm3 or • Platelet count < 100000/mm3 • But recovered on day 21 after the start of a cycle	• No dose modification	• No dose modification
• ANC < 1000/mm3 or • Platelet count < 100000/mm3 • But recovered between 22 to 28 after the start of a cycle	• Decrease irinotecan to dose level -1	• Decrease irinotecan to dose level –2
• ANC < 1000/mm3 or • Platelet count < 100000/mm3 • But recovered between 29 to 34 after the start of a cycle	• Decrease irinotecan to dose level-2	• Discontinue study treatment
• Grade 3 and 4 diarrhea despite maximum loperamide therapy	• Decrease Irinotecan dose to dose level -1 • If the same level of toxicity persists > 2 weeks despite suitable symptomatic treatment, discontinue study treatment • If diarrhea is ongoing on day 21, delay next cycle for up to 2 weeks until diarrhea resolves to $\leq$ grade 1 • If the diarrhea does not resolve after a 2-week delay, the patient should discontinue study treatment	• Decrease Irinotecan dose level -2 • If the same level of toxicity persists > 2 weeks despite suitable symptomatic treatment, discontinue study treatment • If diarrhea is ongoing on day 21, delay next cycle for up to 2 weeks until diarrhea resolves to $\leq$ grade 1 • If the diarrhea does not resolve after a 2-week delay, the patient should discontinue study treatment
• grade 3 or 4 peripheral neurotoxicity (including paresthesia, severe movement disorder, paralysis, etc) and paralytic ileus	• If grade 3 or 4 peripheral neurotoxicity occurs (including paresthesia, severe movement disorder, paralysis, etc) and paralytic ileus, one injection of vincristine should be omitted and restarted at a 50% dose	
• Other grade 3 non hematological toxicity *	• Decrease Irinotecan to level -1	• Discontinue study treatment
• Other grade 4 non hematological toxicity *	• Discontinue study treatment	• Not applicable

*For toxicities that are manageable or short-lived (i.e. grade 3-4 electrolyte abnormalities amenable to supplementation or grade 3 fatigue < 72 hours), the doses are not to be decreased.

Arm B (VIT)

Type of toxicity	Dose modification at first occurrence	Dose modification at second occurrence
• ANC < 1000/mm3 or • Platelet count < 100000/mm3 • But recovered on day 21 after the start of a cycle	• No dose modification	• No dose modification
• ANC < 1000/mm3 or • Platelet count < 100000/mm3 • But recovered between 22 to 28 after the start of a cycle	• Decrease temozolomide to dose level -1	• Decrease temozolomide to dose level -2 • Decrease irinotecan to dose level –1
• ANC < 1000/mm3 or • Platelet count < 100000/mm3 • But recovered between 29 to 34 after the start of a cycle	• Decrease temozolomide to dose level -1 • Decrease irinotecan to dose level-1	• Decrease temozolomide to dose level –2 • Decrease irinotecan to dose level -2
• ANC < 1000/mm3 or • Platelet count < 100000/mm3 • On day 34 after the start of the cycle	• Discontinue study treatment	• Not applicable
• Grade 3 and 4 diarrhea despite maximum loperamide therapy	• Decrease Irinotecan dose to dose level -1 • If the same level of toxicity persists > 2 weeks despite suitable symptomatic treatment, discontinue study treatment • If diarrhea is ongoing on day 21, delay next cycle for up to 2 weeks until diarrhea resolves to $\leq$ grade 1 • If the diarrhea does not resolve after a 2-week delay, the patient should discontinue study treatment	• Decrease Irinotecan dose level -2 • If the same level of toxicity persists > 2 weeks despite suitable symptomatic treatment, discontinue study treatment • If diarrhea is ongoing on day 21, delay next cycle for up to 2 weeks until diarrhea resolves to $\leq$ grade 1 • If the diarrhea does not resolve after a 2-week delay, the patient should discontinue study treatment
• grade 3 or 4 peripheral neurotoxicity (including paresthesia, severe movement disorder, paralysis, etc) and paralytic ileus	• If grade 3 or 4 peripheral neurotoxicity occurs (including paresthesia, severe movement disorder, paralysis, etc) and paralytic ileus, one injection of vincristine should be omitted and restarted at a 50% dose	
• Other grade 3 non hematological toxicity *	• Decrease both Irinotecan and Temozolomide to level -1	• Discontinue study treatment
• Other grade 4 non hematological toxicity *	• Discontinue study treatment	• Not applicable

*For toxicities that are manageable or short-lived (i.e. grade 3-4 electrolyte abnormalities amenable to supplementation or grade 3 fatigue < 72 hours), the doses are not to be decreased.

Considering that serious cases of liver injuries including some with fatal outcome have been reported with Temozolomide, in case of significant abnormalities of hepatic function, the benefits and risks to continue the treatment will have to be carefully examined by the investigator

9.3. Compliance

Vincristine and irinotecan will be administered intravenously. Information regarding the dates and doses of treatment administered will be recorded on the patient's medical record.
A pill count will be performed for temozolomide if dispensed for home use and documented on the pharmacy log.

9.4. Supportive concomitant therapy

9.4.1. Anti-emetics

The use of anti-emetic agents (e.g. ondansetron) for prophylaxis and treatment of nausea and vomiting is recommended. Further agents can be chosen in compliance with the conventional anti-emetic protocol at the center.

9.4.2. Anti-diarrhea medications

In the absence of any contraindications (ie known allergies), treatment with oral cefixime 8 mg/kg once a day (maximum daily dose 400 mg) is recommended and will be started 2 days before chemotherapy until day 7 (see Appendix 11 for cefixime management in The Netherlands).

Patients who have the onset of diarrhea during the irinotecan infusion or during the first 8 hours following the completion of infusion should receive a dose of atropine 0.02 mg/kg (maximum 0.25 mg) IV. Early onset diarrhea is usually preceded by diaphoresis, abdominal cramping and other cholinergic manifestations. Systematic prophylaxis is not recommended at the first cycle but is left to the investigator's judgment. Prophylactic treatment with atropine (0.02 mg/kg orally or IV, maximum 0.25mg) should be adopted before the next administration of irinotecan if the acute cholinergic symptoms including "early diarrhea" were severe during the prior cycle.
At the first sign of diarrhea starting > 8 hours after irinotecan administration, patients should begin intensive loperamide therapy. Each patient and/or patient's parent or legal guardian should be instructed to have anti-diarrheal medication readily available and begin treatment for diarrhea at the first episode of poorly formed or loose stools or earliest onset of bowel movements more frequent than normally expected for the patient. All patients and family members should receive written instructions for loperamide or racecadotril administration. Dosing is to be based on body weight. In addition, patients and family members should be instructed to contact their physician if any diarrhea occurs. Loperamide or racecadotril should be continued until a normal pattern of bowel movements returns.
Oral hydratation with large volumes of water and electrolytes should be prescribed during the whole diarrhea episode. Loperamide prophylaxis and treatment of diarrhea must be implemented according to local clinical practice.

9.4.3. Pneumocystis carinii pneumonitis prophylaxis

Patients may receive co-trimoxazole according to centre guidelines.

9.4.4. Growth factor

Prophylactic use of granulocyte colony stimulating factor (G-CSF) is not recommended during the trial, however G-CSF may be used for patients presenting severe infection with neutropenia and in subsequent cycles after infectious complications.

9.4.5. Concurrent therapy

Concurrent administration of Irinotecan with an inhibitor (eg ketoconazole) or inducer (eg rifampicin, carbamazepine, phenobarbital or phenytoin) of the cytochrome P 450 3A4 metabolic pathway may alter the metabolism of Irinotecan and should be avoided.

Concurrent administration of St. John's wort is contraindicated.

Live attenuated vaccines are contraindicated during VI/VIT therapy and until six months after the end of the treatment

Administration of Yellow fever vaccine shoud be avoided during VI/VIT treatment (risk of severe peripheral neuropathy when concomitant administration with vincristine)

10. TRIAL PROCEDURE

10.1. Pre-treatment investigations

The pre-treatment investigations will determine patient eligibility and staging. The pre-treatment investigations must be performed no more than 1 week before the planned start of chemotherapy, except for radiological investigations which must be completed no more than 14 days before the planned start.

Type of Assessment	Delay
• Information, written consent form	**To be obtained before all specific procedure of the study**
• Diagnosis, medical/oncology history and demographics : information on prior regimens, including dosing and duration of administration All clinical signs should be graded according to the NCI-CTC AEv4.0 (appendix 5)	Before inclusion
CLINICAL EXAM • Full physical examination • Height, weight , body surface • Vital signs : blood pressure after 5 min at rest, heart rate, temperature • Performance status (Lansky Play Score or Karnofsky Score – appendix 3-4)	To be completed < 7 days prior to the first study drug dose
LABORATORY TESTS* • Complete blood count : white count (WBC), hemoglobin (HGB), hematocrit (HCT), differential count and platelet count • Blood chemistry : glucose, urea, creatinine, total protein, albumin, Ca+, phosphorus and electrolytes (sodium, potassium, chloride and bicarbonate), AST, ALT, total bilirubin, alkaline phosphatase, LDH, GGT	To be completed < 7 days prior to the first study drug dose
PREGNANCY TEST* • Serum or urine pregnancy test	To be completed < 7 days prior to the first study drug dose
RADIOLOGICAL AND OTHER INVESTIGATIONS** • Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) of the primary site. Volume estimation should be attempted by providing the maximum sagital, coronal and axial diameters. • MRI: Intravenous gadolinium administration is mandatory for all MRI examinations (post-contrast T1-weighted sequences should ideally be performed with saturation). MRI is particularly mandatory for limb, head/neck, pelvic and paraspinal masses. MRI appears to be superior to CT scan in defining soft tissue extension. • CT scan: may be used for the assessment of thoracic or abdominal tumors. • Bone scan or FDG-PET Scan recommended	To be completed ≤ 14 days prior to the first study drug dose

• BM aspirates and trephine biopsies recommended mandatory in case of bone marrow disease	

** All blood sampling will be made after application of topical anaesthetic cream, where appropriate*
*** It is mandatory to evaluate treatment response with the same imaging technique (CT or MRI) particularly where measurement is required. All imaging data should be loaded the CDs onto the PACS system for later review.*

10.2. Trial Period

10.2.1 Treatment procedures for first two cycles

The following procedures must be performed prior to dosing with Temozolomide in combination with Vincristine and Irinotecan on the days indicated during weeks 1-6. Blood sampling will be made after application of topical anaesthetic cream, where appropriate.

Type of assessment	Delay for first 2 cycles (during weeks 1-6)
CLINICAL EXAM • Full physical examination • height, weight , body surface • Vital signs : blood pressure after 5 min at rest, heart rate, temperature • Performance status (Lansky Play Score or Karnofsky Score – appendix 3-4) • Assessment of adverse events according to the NCI-CTC AE v.4.0 (appendix 5) • Recording of concomitant medications	day 1
LABORATORY TESTS* • Complete blood count : white count (WBC), hemoglobin (HGB), hematocrit (HCT), differential count and platelet count • Serum chemistries : glucose, urea, creatinine, total protein, albumin, Ca+, phosphorus and electrolytes (sodium, potassium, chloride and bicarbonate), AST, ALT, total bilirubin, alkaline phosphatase, LDH, GGT	days 1, 8, 15 If aplasia, blood counts should be performed as clinically indicated
RADIOLOGICAL AND OTHER INVESTIGATIONS • Tumor assessments (CT scan and/or MRI) including measurement of target lesion and assessment of response to treatment should be loaded the CDs onto the PACS system for later review. • Bone scan or FDG-PET Scan** • BM aspirates and trephine biopsies**	Mandatory after cycle 2
STUDY TREATMENT • Administration of vincristine to patient, given intravenously prior the administration of Irinotecan on day 1 and day 8. • Administration of irinotecan to patient given by 60-intravenous infusion on days 1 through 5. • According to randomization, temozolomide will be given orally, on empty stomach, one hour prior to administration of irinotecan on days 1 through 5	

**Not necessary on day 1 of cycle 1 if screening blood draw performed within 7 days of the first treatment.*
***only repeated if clinically indicated or if initially involved or to confirm tumor response*

10.2.2 Treatment procedures for subsequent cycles

The following procedures must be performed prior to dosing with Temozolomide in combination with Vincristine and Irinotecan on the days indicated during weeks through all subsequent weeks that patient remains on study treatment (days 1, 8 and 15 based on 21 day cycles). Blood sampling will be made after application of topical anaesthetic cream, where appropriate.

Type of Assessment	Delay for subsequent cycles
CLINICAL EXAM • Full physical examination • height, weight , body surface • Vital signs : blood pressure after 5 min at rest, heart rate, temperature • Performance status (Lansky Play Score or Karnofsky Score – appendix 3-4) • Assessment of adverse events according to the NCI-CTC AE v.4.0 (appendix 5) • Recording of concomitant medications	day 1
LABORATORY TESTS • Complete blood count : white count (WBC), hemoglobin (HGB), hematocrit (HCT), differential count and platelet count	days 1, 8, 15. If aplasia, blood counts should be performed as clinically indicated
• Blood chemistry : glucose, creatinine, electrolytes (sodium, potassium, chloride and bicarbonate), AST, ALT, total and direct bilirubin, ASAT-ALAT, creatinine	day 1 if normal during cycles 1 and 2. If significantly abnormal during cycle 1 or 2, blood chemistry should be taken on days 1, 8 and 15 for all subsequent cycles after cycle 2
RADIOLOGICAL AND OTHER INVESTIGATIONS • Tumor assessments (CT scan and/or MRI) including measurement of target lesion and assessment of response to treatment should be loaded the CDs onto the PACS system for later review. • Bone scan or FDG-PET Scan* • BM aspirates and trephine biopsies*	Mandatory after completion of every two cycles (must assess at 5 weeks after cycle 2 for responding or stable disease)
STUDY TREATMENT • Administration of vincristine to patient, given intravenously prior the administration of Irinotecan on day 1 and day 8. • Administration of irinotecan to patient given by 60-intravenous infusion on days 1 through 5 • According to randomization, temozolomide will be given orally, on empty stomach, one hour prior to administration of irinotecan on days 1 through 5	

**only repeated if clinically indicated or if initially involved or to confirm tumor response*

10.2.3 End of study treatment / Withdrawal procedures

The duration of study participation is a maximum of 12 cycles. However, the continuation of treatment can be individually discussed with the investigator for patients who do not experience progression of disease after 12 cycles.

The following evaluation is performed 3 weeks after the last cycle of chemotherapy or at the end of study (see 7.2.).

Type of Assessment	Delay for End of Study treatment or Withrawal
CLINICAL EXAM • Full physical examination • height, weight, body surface • Vital signs : blood pressure after 5 min at rest, heart rate, temperature • Performance status (Lansky Play Score or Karnofsky Score – appendix 3-4) • Assessment of adverse events according to the NCI-CTC AE v.4.0 (appendix 5) • Recording of concomitant medications	To be performed 3 weeks after the last cycle of chemotherapy or at the end of study
LABORATORY TESTS • Complete blood count : white count (WBC), hemoglobin (HGB), hematocrit (HCT), differential count and platelet count • Serum chemistries : glucose, urea, creatinine, total protein, albumin, Ca+, phosphorus and electrolytes (sodium, potassium, chloride and bicarbonate), AST, ALT, total bilirubin, alkaline phosphatase, LDH, GGT	To be performed 3 weeks after the last cycle of chemotherapy or at the end of study
RADIOLOGICAL AND OTHER INVESTIGATIONS • Tumor assessments (CT scan and/or MRI) including measurement of target lesion and assessment of response to treatment should be loaded the CDs onto the PACS system for later review. • Bone scan or FDG-PET Scan* • BM aspirates and trephine biopsies*	Mandatory To be performed 3 weeks after the last cycle of chemotherapy or at the end of study, except documented previous disease progression

**only repeated if clinically indicated or if initially involved or to confirm tumor response*

10.2.4 Follow-up visit

Patients will be followed every 3 months for at least 2 years and then every 6 months during the subsequent 3 years or until death or lost to follow up until the date of the study cut-off, for the following:

- Patient status determination
- Tumour assessments including measurement of target lesion and assessment of response to treatment should be loaded the CDs onto the PACS system for later review.

11. OUTCOME MEASUREMENTS

11.1. Efficacy and treatment administration endpoints

11.1.1. Objective tumour response and progression

Measurements of all lesions should be recorded in metric units. All baseline evaluations should be performed as closely as possible to the treatment start, within 14 days of the beginning of the treatment if possible. The same radiological modality and technique (same sequence) for assessing disease at study entry is to be used for reassessment so that a direct comparison can be made to accurately evaluate disease response.

This study will use volumetric measurements of the primary tumour using an elliptical model (0.52 times the product of the 3 largest perpendicular diameters in the axial, coronal and sagittal plane) to assess response to neo adjuvant therapy. The RECIST 1.1 (Response Evaluation Criteria in Solid Tumours; *ref New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) European Journal of Cancer 45 (2009) 228–247)*) criteria will be used for assessment of the size of measurable metastases, including nodal metastases (see Section 10.1.3.).

Primary Tumour Response (Volumetric)

On the basis of previous reports showing that volumetric tumour measurements may be more accurate than bidirectional or unidirectional measurements for tumours measuring >35 cm^3, we will obtain volumetric measurements of the primary tumour using the formula for an ellipsoid model: volume 0.52 (antero-posterior diameter x transverse diameter x length) [Sohaib 2000, Prasad 2002].

Tumour volume (V) calculation:

a =length (in cm)

b = width (in cm) $V = \pi/6 \times a \times b \times c = 0.52 \times a \times b \times c$ in cm^3

c = thickness (in cm)

It is planned to also measure the maximum uni-dimensional measurement as suggested by the RECIST 1.1 guidelines (*European Journal of Cancer 2009; 45: 228-47*) and later compare the volume with uni-dimensional measurements in terms of tumour response. The maximum lesion diameter in any plane should be recorded as the longest tumour diameter and measurements may be taken from CT or MRI, but the maximum tumour measurement must always be in the same plane (axial, coronal or sagittal) even if this results in measuring the lesion at a different slice level or in a different orientation or vector compared with the baseline study.

A clinical assessment should be done at each visit in order to detect tumour progression at any point during treatment. This should be supplemented by radiological examination as appropriate.

RELATIONSHIP BETWEEN CHANGE IN SINGLE DIAMETER (RECIST), PRODUCT OF TWO DIAMETERS (WHO), AND THREE PERPENDICULAR DIAMETERS ("VOLUME")

Response	Diameter, 2R Decrease	Product,$(2R)^2$ Decrease	Volume, $4/3\pi R^3$ Decrease
	13%	24%	33%
	30%	50%	**65%**
	50%	75%	87%
Disease Progression	**Increase**	**Increase**	**Increase**
	12%	25%	40%
	20%	44%	**73%**
	25%	56%	95%
	30%	69%	120%

Response evaluation criteria (Volumetric)

Complete Response (CR)	Complete disappearance of all visible disease
Partial Response (PR>2/3)	≥ 65% reduction of tumour volume (volume response between 65-99%)
Minor Partial Response (PR<2/3)	Volume response between 34-64%
Stable Disease (SD)	No criteria for PR or PD
Progressive Disease (PD)	Any increase of more than 73% of any one target lesion/tumour volume or appearance of new lesions.

All responses must last at least 4 to 5 weeks without evidence of tumour progression or relapse.

Metastatic Disease Measurement

The RECIST 1.1 (*European Journal of Cancer 2009; 45: 228–47*) criteria will be used for assessment of the size of measurable metastases, including nodal metastases.

RECIST Methodology

Planes and techniques:

- CT: The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Lesions should be measured on the same window setting on each examination.
- MRI: Lesions must be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations.

Measurements:

DIAGNOSIS

- **Measurable lesion**: A lesion that can be accurately measured in at least 1 dimension with the longest diameter at least twice the thickness of the CT or MR slice with a minimum of 10 mm (for lymph nodes ≥15 mm shortest axis). This is defined as a "**target lesion**". The investigator will identify up to 5 target lesions total and up to 2 per organ to be followed for response. In general, the largest lesions representative of involved organs are selected to follow as target lesions. However, in some cases, the largest lesions may not be easily measured and are not suitable for follow-up because of their configuration. In these cases, identification of the largest most reproducible lesions is advised. Serial measurements of

target lesions are to be done with CT or MRI. The sum of the longest diameters of all target lesions will be calculated and reported as the measurable metastatic disease measurement.
Non target: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline and follow up.

- **Non-measurable:** All lesions that do not qualify as target lesions (all lesions whose largest diameter is less than twice the thickness of the CT or MRI slice, and all truly non-measurable disease such as bone lesions*, leptomeningeal disease, ascites, pleural/ pericardial effusions, lymphangitis cutis/pulmonis, and cystic lesions**).

Special note on lymph nodes:

Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

**Special note on bone lesions:*

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. All other bone lesions are considered non-measurable.

***Special note on cystic lesions:*

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

FOLLOW UP

- The same method of assessment is to be used to characterize each identified and reported lesion at baseline and during follow-up. Using the same plane of evaluation, the maximal diameter of each target lesion should always be measured at subsequent follow-up time points even if this results in measuring the lesion at a different slice level or in a different orientation or vector compared with the baseline study.

Metastatic Tumour Response

Target Lesions (RECIST):

- Complete Response (CR): Disappearance of all target lesions.
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameters of all target lesions, taking as reference the disease measurement done to confirm measurable disease at study enrolment.
- Progressive Disease (PD): At least a 20% increase in the sum of the longest diameters of all target lesions, taking as reference the smallest disease measurement recorded since the start of treatment. In addition to the relative increase of at least 20% the sum must also demonstrate an absolute increase of at least 5mm (*Note:* the appearance of one or more new lesions is also considered progression)

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started.

NOTES:

- *Lymph nodes* identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination) even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.
- *When lesions 'fragment'*, the individual lesion diameters should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'merged lesion'.
- *Target lesions that become too small to measure*: All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs it is important that a value be recorded in the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.
- *If a lesion disappears and reappears* at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. I.e. the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria.

Non-Target Lesions:

- Complete Response (CR): Disappearance of all non-measurable (non-target) lesions
- Stable Disease (SD): The persistence of non-measurable disease without the development of new foci of tumour involvement.
- Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions*

****Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).***

11.1.2. Overall Tumour Response (=Primary tumour and Metastatic lesions)

The overall response assessment takes into account the response in the primary tumour and metastases according to the criteria in the table below. The overall response assessment is shown in the last column, and depends on the assessments of the response in the primary tumour, target and non-target lesions, and the development of new lesions.

Primary Tumour	Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	CR	No	CR
CR	CR	Incomplete response/SD	No	PR
PR	PR	Non-PD	No	PR
Minor PR	Non-PD	Non-PD	No	Minor PR
SD	SD	Non-PD	No	SD
Any	PD	Any	Yes or No	PD
Any	Any	PD	Yes or No	PD
Any	Any	Any	Yes	PD

If a patient has not tumor evaluation due to clinical disease progression, it will be classified as a progressive disease.

11.1.3. Objective tumour response and progression

Primary efficacy endpoint

The primary efficacy endpoint is defined as the proportion of patients who had a documented complete or partial tumour response occurring after the first 2 cycles of treatment which must be confirmed by a follow-up objective tumour assessment obtained within 4-5 weeks after the initial documentation.

Secondary endpoints

Secondary efficacy endpoints are defined as follows:

- The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started) over the whole treatment duration. It must be confirmed by a follow-up objective tumour assessment obtained within 4-5 weeks after the initial documentation.
- Duration of tumour response: the time from first documentation of objective tumour response to the first objective or clinical documentation of progression
- Time to treatment failure: the time from the date of first treatment administration to the first documentation of tumour progression, discontinuation of study treatment before one year, or death, whichever occurs first
- Progression-free survival (PFS): the time from the date of first treatment administration to the date of first objective or clinical documentation of tumour progression or death due to any cause
- Overall survival (OS): the time from the date of first treatment administration to date of death

11.1. Safety assessments

Safety parameters include adverse events and haematology and blood chemistry assays. Safety evaluations will be performed as indicated in the Flowchart and will include characterization of the

frequency and severity of adverse events, complete blood cell counts with differential, serum chemistries and electrolytes, and change in weight and body surface area (BSA).

11.2.1. *Adverse event – definition*

- An **adverse event (AE)** is any adverse change from the patient's baseline condition, i.e. any subjective signs and symptoms, or change in a concomitant disease present at selection visit. This includes inter-current signs, symptoms, illness and significant deviations from baseline laboratory values, which may occur during the course of the clinical study, whether considered related to treatment or not.

All laboratory tests for which abnormal results are collected after study treatment initiation should be repeated until the values return to normal or to stable status. Abnormal results are defined as those falling outside the laboratory normal range that are clinically significant.

The frequency with which such checks should be made will be defined at the investigator's opinion depending on the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and the sponsor notified.

11.2.2. *Reporting of adverse events*

Any adverse or intercurrent event occurring during the study period, spontaneously reported by the patient or observed by others, and considered related to the study treatment will be recorded in the source documents as well as in the electronic Case Report Form (eCRF). The records will describe the nature (diagnosis, signs and symptoms), severity, date/time of onset, date/time of end, outcome and actions taken, and relationship to study treatment (according to the investigator's opinion).

Moreover, the investigator must assess for each adverse event recorded: its seriousness (see definition of "Serious Adverse Event" in section 11.2.3), its severity (intensity) according to **NCI-CTCAE v 4.0** (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf), its causal relationship with the study treatment or with any study-mandated procedure or activity.

The following events should be reported in the 'Adverse Events' section of the e-CRF:

- adverse events with the maximum grade per cycle (excepted grade 1 haematological events), meaning that if several adverse events of the same nature occur during the same cycle, but with a different grade, only event with the highest grade must be reported. An event that covers more than one cycle is recorded once in the database.

- all serious adverse events, of any grade

It is recommended to confirm the causal relationship of each non-serious or serious adverse event with the investigator, before updating database.

AEs already recorded and designated as "continuing", should be reviewed at each subsequent assessment. If resolved, the details in the eCRF are completed.

If any AE changes for the worse, in frequency of attacks/symptoms or in severity, a new record of the event must be started (i.e. distinct reports are required for differing frequencies and/or severity of the same event to enable comprehensive safety reports and later analysis).

11.2.3. *Serious adverse events – definition*

A serious adverse event (SAE) includes, but is not necessarily restricted to, any event which:

- Results in death (whatever may be the cause)
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires patient hospitalization or prolongation of existing hospitalization
- Is a congenital anomaly or birth defect
- Other events including cancer, over-dosage, pregnancy and any additional adverse experience or abnormal laboratory values occurring during the study period defined by the protocol as serious or which the investigator considers significant enough or that suggests a significant hazard, contraindication, side effect or precaution will be handled as a serious adverse event.

All deaths occurring while the patient is on study including deaths due to disease progression and deaths within 30 days of last administration of study drug should be notified as SAE.

11.2.4. *Reporting of Serious of adverse events*

A written agreement between the Coordinating Centre of each country and Sponsor should be obtained to clarify who is taking over the responsibility of informing competent authorities, ethics committees and investigators of this country to avoid double notification of safety information.
In the event of the occurrence of any SAE between signature of main informed consent form and the end of the 30-day follow up period after last treatment with study drug, irrespective of the treatment received by the subject, the Investigator is obliged to inform the Sponsor's designated Safety Desk immediately.

The investigator has to follow each SAE until its resolution and to transmit follow-up information as soon as available (detailed description and a final evaluation of the case, including copies of hospital reports, autopsy reports, or other relevant documents) to the Sponsor's Safety Desk.
The investigator has to answer to additional information requests by the Sponsor's Safety Desk or the monitor.

SAE notification to the Sponsor's Safety Desk by the Investigator is performed as follows:

	If SAE was **NOT** fatal nor life-threatening	If SAE was **fatal** or **life-threatening**	
		<u>During business hours</u> From Monday to Friday from 8:30 AM to 6:30 PM (French time), except from French bank holidays*	<u>Outside business hours</u> - Outside French bank holidays: From Monday to Friday from 6:30 PM to 8:30 AM (French time), on Saturdays and Sundays - At any time during French bank holidays*
Notification form	**LONG** SAE NOTIFICATION FORM <u>(duly signed and dated)</u>	**LONG** SAE NOTIFICATION FORM <u>(duly signed and dated)</u>	**SHORT** SAE NOTIFICATION FORM <u>(duly signed and dated)</u>
Instructions for transmission	Once completed, the form must be sent by e-mail to: **vigilanceEC@o-lambret.fr** (in case of any issue preventing the use of e-mails, the form may be sent by fax: 03.20.29.5**8**.96)	Once completed, the form must be sent by e-mail to: **vigilanceEC@o-lambret.fr** (in case of any issue preventing the use of e-mails, the form may be sent by fax: 03.20.29.5**8**.96) **AND** The sponsor must be informed by phone: **03 20 29 59 18** *(If no dedicated staff is available, the sponsor will give the investigator instructions to transmit the SAE to a hospital pharmacist.)* **If no sponsor staff answers the phone:** The form must be sent by e-mail to: **pharmaciens@o-lambret.fr** (in case of any issue preventing the use of e-mails, the form may be sent by fax: 03.20.29.5**9**.96) **AND** A hospital pharmacist must be warned by phone, *via* the central telephone desk of Centre Oscar Lambret: **03 20 29 59 59**	Once completed, the form must be sent by e-mail to: **vigilanceEC@o-lambret.fr** (in case of any issue preventing the use of e-mails, the form may be sent by fax: 03.20.29.5**8**.96) **AND** **pharmaciens@o-lambret.fr** (in case of any issue preventing the use of e-mails, the form may be sent by fax: 03.20.29.5**9**.96) **AND** The on-duty intern must be informed by phone: **03 20 29 59 29**

*** French bank holidays: January 1, Easter Monday, May 1, May 8, Ascension Day, Whit Monday, July 14, August 15, November 1, November 11, December 25**

11.2.5. *Pregnancies*

In the event of a pregnancy occurring during the course of the study, the female subject still under study therapy must be withdrawn from the study medication immediately. The Sponsor must be notified without delay via the Safety desk (as described in section 11.2.4 above). The same applies to pregnancies occurring within 6 months after the last administration of study treatment. The subject must be followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs.

In case a male subject fathers a child during the course of the study, the subject can continue study treatment but the Sponsor must be notified without delay. The same applies to pregnancies occurring within 6 months after the last administration of study treatment. The

child's mother must be followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs.

11.2.6. *Sponsor's responsibilities*

- Determination of expectedness/unexpectedness of Serious Adverse Reactions (SAR)

A Serious Adverse Reaction (SAR) is a SAE related to study treatment. A SAR will be considered as expected when already mentioned in the safety reference document(s) of study treatment. Nevertheless, all expected adverse reaction which differ on intensity, evolution or frequency will be considered as a Suspected Unexpected Serious Adverse Reactions (SUSAR).

- Recording of vigilance data and immediate reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR)

The sponsor will be responsible for the recording and updating of all vigilance data regarding the study.

The sponsor will also notify all Suspected Unexpected Serious Adverse Events to regulatory authorities (National Competent Authority and Ethic Committee) and inform all the investigators, in accordance with applicable laws and regulations.

Moreover, the sponsor transfers all relevant safety information to the Coordinating Centre of each country. He/she ensures that the responsible competent authorities, ethics committees and investigators participating within his/her country are informed of all SUSARs and all other relevant safety information in accordance with national legal requirements.

- Periodic Safety Reports

The Sponsor will prepare and submit appropriate periodic safety reports to regulatory authorities (National Competent Authority and Ethic Committee), in accordance with applicable laws, regulations and guidelines.

Periodic safety reports will be distributed via the Coordinating Investigators to responsible competent authorities and ethics committees in a timely manner.

12. STATISTICAL CONSIDERATIONS

12.1. Sample size

The primary endpoint of this clinical trial is response to treatment. The criteria for the evaluation of the primary endpoint is the objective response (success) rate.

Original study design (before amendment 4.0, in December 2015)

The maximum response rate for inefficacy is 20% (null hypothesis H0: $p0 \leq 0.20$). The minimum response rate for efficacy is 40% (alternative hypothesis H1: $p1 \geq 0.40$), for an expected difference of 20% (p1-p0).

Using an Optimum 2 stage Simon design (with α=0.10 and β=0.10), the first stage requires 17 eligible and evaluable patients in each arm. Decision rules with this design are applied to the VIT arm. In the first stage, if 3 patients or less among 17 patients in the VIT arm show a treatment success (17.6%), the trial should close prematurely and the experimental treatment be considered insufficiently active, that is to say with a success rate significantly less than 40%, which corresponds to a rejection of H1. If at least 4 patients among 17 patients in the VIT arm have a treatment

success, the second stage will continue to accrue 20 extra patients for a total of 37 patients in each arm. The same number of patients will be randomised to the VI arm which is used as the control arm.
At the end of the second stage, if 10 patients or less among 37 patients in the VIT arm have a treatment success, the treatment is considered insufficiently active, that is to say with a success rate significantly less than 40% (rejection of H1). If at least 11 patients among 37 patients show a treatment success, the treatment can be considered sufficiently active for further study in phase III. The success rate can be considered significantly greater than 20% (rejection of H0).
With this Optimum design, there is a 55% probability of early termination and the expected sample size under the null hypothesis is 26.02.
A total of 74 evaluable patients are required (37 per arm). Accounting for a 8% expected loss to follow-up rate (non evaluable), total accrual should reach **80** patients.
Patient recruitment will be interrupted between the two stages. Responses will be evaluated by central review once the first 17 evaluable patients of arms A and B have completed 2 cycles of treatment after which time a decision will be made to continue or not with the second stage. Inclusion interruption should last between 3 to 4 months.

Revised study design after amendment 4.0, in December 2015

IDMC reviewed the data analysis of the first 80 patients.
At that date, 80 patients (68 in the relapse status) had been enrolled with an annual accrual rate of 28 patients, which is higher than expected.
Based on the analysis, the IDMC considered that preliminary results indicate that more precision is needed, not only for the primary endpoint, but also for the secondary endpoints which will be used in planning the next phase III trial. They recommended that, in order to obtain a sufficient power to differentiate both arms and not to stop the European dynamic, the inclusion of a total of 120 patients (108 patients in the relapse status) in the VIT trial, should allow sufficient accuracy for choosing the standard arm: VI or VIT. The accrual of 40 extra patients should prolong the VIT trial one year.

The increase in the sample size is justified by the change in the statistical hypotheses since the IDMC recommended continuing the inclusion of only patients in relapse, refractory patients being no longer eligible for inclusion. Also, since the next trial will not be ready for another year, the extra patients in this trial should allow sufficient accuracy for choosing the standard arm in the next trial. The new design parameters are the following (p0=0.35, p1=0.55, a=0.10 and b=0.10) which lead to 47 evaluable patients. With 15% of lost follow-up (ineligible and non evaluable), 54 patients per arm should be included, for a **total of 108 randomized relapse patients**. Since 68 patients in relapse are already included, a total of **40 additional patients** in the relapse status should be included. With the new design parameters, if at least 22 patients among the 47 in the VIT arm show a treatment success, the treatment can be considered as sufficiently active. If 21 or less among 47 patients in the VIT arm have a treatment success, the treatment is considered insufficiently active.

Randomization 1:1 will be stratified for recurrent vs. refractory status and country for the first 80 patients. For the 40 additional patients in the relapse status, stratification by minimization will be performed for prior radiotherapy (yes vs no), country and recurrence (metastatic vs locoregional) according to the importance of these factors on the PFS curve.

12.2. Statistical analyses

The main analysis will be performed on the intent to treat principle, considering all patients included in the study. Patients who withdraw from the study will be accounted for up until the time they withdraw from the study. Secondary analyses will be performed on the per protocol population, that is eligible, evaluable and treated patients. Safety analyses will be performed on all treated patients.
Eligible patients are defined as patients who did not have a major violation of eligibility criteria (inclusion and exclusion criteria).
Treated patients are defined as patients who received at least one injection of the study treatment.
Evaluable patients for main objective (objective response at 2 cycles) are defined as patients who received at least 2 cycles of the study treatment and whose the tumor evaluation at 2 cycles was available.

The estimated difference in response rates between the two arms, will be presented with a 90% confidence interval. A Bayesian analysis of the final data will also be performed in which probabilities that one arm is better than the other will be given.

The risk / benefit ratio will be examined biannually by the IDMC on validated data. The sponsor may decide to temporarily halt recruitment to the trial if the rate of severe toxicities significantly exceeds 15%.
The decision rules for early termination are applied to the VIT arm as the VI arm is only used for controlling selection bias. However, at the end of the trial, if the VIT arm is considered sufficiently active, a phase III trial may be initiated. If the VIT arm is considered insufficiently active, this treatment strategy is rejected and other options should be considered. The cut points for acceptable and unacceptable response rates, obtained from the Optimum Simon design, will be used as guidelines for deciding whether VIT is worthy of further investigation; the response rate in the VI arm, the toxicity of the regimens and relevant external evidence will also be taken into consideration.
Categorical variables will be presented as frequencies and percentages. Continuous variables will be presented as means (standard deviation), and medians (range). The treatment groups will be compared for demographic and initial disease characteristics using Fisher's exact test for categorical variables and the non-parametric Wilcoxon test for continuous variables.
Response rates will be estimated in each treatment group along with a 90% confidence interval. Survival rates will be estimated according to the Kaplan-Meier method. Median survival times will be presented along with a 95% confidence interval. Correlations will be evaluated with the Spearman correlation coefficient.

After amendment 5.0 in July 2018

A comparison between arms VIT vs VI will be performed to estimate the relative effect of VIT compared to VI, for all efficacy and safety endpoints. Objective response rates will be compared using Mantel-Haenszel Chi 2 test adjusted for confounding factors (histological subtype: alveolar, including pure or alveolar component vs non alveolar; and disease status at study entry: metastatic relapse/progression vs localised disease). OS and PFS curves will be compared using stratified logrank tests. Hazard ratios will be estimated using Cox models controlling for confounding factors.
A future multi-arm multi-stage randomised phase II/III trial (FaR-RMS) plans comparing selected experimental arm(s) to control arm in the same setting. If the VI treatment is kept as a control arm and VIT as one of the experimental arms for the FaR-RMS trial, a joint analysis of both trials (VIT

and FaR-RMS) will be planned in order to provide efficacy results of VIT vs VI comparison (response rate, OS and PFS curves) on a larger sample of patients.

12.3. Data management

Data management will be performed by the Centre Oscar Lambret Methodology and Biostatistics Unit. A study-specific database will be created, tested and validated before data entry. This data base will be developed in collaborating with the "Data Treatment Center of the North-West Canceropole, authorized by INCa" using Capture System software (CLINSIGHT). This software program has been designed for the management of clinical studies, and meets the regulatory requirements associated with clinical trials. A data validation plan will be defined, providing a detailed description of the edit checks required for each variable, along with the list of obvious corrections allowed.

Individual pages of the Case Report Forms will be electronically entered into the database. At regular intervals, the data will be checked by the data management team using the error messages generated by the validation programs. Any obvious entry errors will be corrected by the data manager and sent to the investigating clinician for information. Other errors, omissions or inconsistencies will be stated on correction request forms that will be sent to the investigating physician for resolution. Once the Biostatistics Unit receives the response, the corrections will be added to the database.

The database will be locked after the interim and final quality control checks, and then exported to a statistical software package using an automated and validated procedure.

13. LEGAL AND ETHICAL ASPECTS

This study will be conducted in accordance with the ethical principles of the 1964 Helsinki declaration, revised in 2013 in Fortaleza, with the rules of Good Clinical Practice (GCP) defined by the International Conference on Harmonization (ICH-E6, 17/7/96). The clinical trial may not begin before approval of the Ethics Committees and authorization by competent authorities concerned is obtained.

13.1. Sponsorship

Centre Oscar Lambret – Lille (France) is sponsor of the international clinical trial VIT-0910 in the legal sense as defined by the Directive 2001/20/EC of the European Parliament and of the Council of 4th April 2001. The sponsor may delegate his duties for each participating country to an authorized coordinating centre/Institution (to be nominated by the national study coordinator) by written agreement (see Section 3).

The authorized institution will fulfill the transferred duties for the sponsor and warrants compliance with all statutory provisions relevant for the sponsor. The authorized institution will notify the sponsor of all duties required by the respective national regulation that were not transferred to the authorized institution. The authorized institution will fulfill these national required duties as required. In addition, all documents relevant for the trial master file will be provided. The sponsor may audit the authorized institution to ensure adherence to all legal requirements.

13.2. Coordinating centre's responsibilities

The Coordinating Investigator, on behalf of the sponsor, is responsible for the application for an EC/IRB approval according to national and institutional guidelines. Furthermore, the coordinating centre/Coordinating investigator will provide all authorized institutions of the participating countries with all documents required for an IEC/IRB approval according to local law and regulation. The authorized institutions will provide all further documents required by national law and for application at the responsible Ethics Committee.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.
Modifications to the study protocol will not be implemented by either the sponsor or the Coordinating Investigator without agreement by both parties.

13.3. Principal investigator's responsibilities

The principal investigator for each center concerned undertakes to manage the clinical trial in accordance with the protocol approved by IEC/IRB and competent authorities. The investigator must not make any modifications to the protocol without the sponsor's authorization and without the ethics committee and competent authorities' approving the proposed modifications.
The investigator is responsible:

- For providing the sponsor with his/her curriculum vitae, along with those of his/her co-investigators,
- For identifying the members of his/her team who are to take part in the trial and for defining their responsibilities,
- For initiating patient recruitment after receiving the sponsor's authorization,
- For making all necessary efforts to include the required number of patients, within the limits of the defined enrolment period.

Each investigator is responsible:

- For obtaining informed consent, personally dated and signed by the patient, prior to any trial specific selection procedure
- For regularly updating the electronic case report forms (eCRF) for each patient included in the trial and for providing the Clinical Research Associate (CRA) with direct access to the source documents to validate the eCRF data,
- For dating, correcting and signing any eCRF corrections for each patient included in the study,
- For welcoming regular visits from the CRA and, if applicable, those of auditors mandated by the sponsor, or by regulatory authority inspectors.

Any deviations from the protocol must be explained and documented by the investigator.
All documentation relative to the study (protocol, consent forms, eCRF, investigator's files, etc…) along with original documents (laboratory results, x-ray, consultation reports, clinical examinations reports, etc.) must be kept in a safe place and considered confidential. The investigator is responsible for data archiving in accordance with current legislation (see Section 12.3).

13.4. Amendments

Any significant change in the trial requires a protocol amendment. An investigator must not make any changes to the study without approval of the Sponsor, approval of ethics committee or sponsor, or authorization by the competent authorities except when necessary to eliminate apparent

immediate hazards to the patients. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, but the change must then be documented in an amendment, reported to the ethics committee and submitted to the appropriate competent authorities in the required time frame. Application for authorization and approval of all other substantial protocol amendments must follow the same process as the original protocol.
Substantial protocol amendments which are likely to have an impact on the treatment and/or safety of the participants or to modify the interpretation of the data or which are otherwise significant, are prepared by the Sponsor. The coordinating investigators are responsible for submitting application for authorization of an amendment to the competent authorities concerned and for the application of approval to IEC/IRB concerned according to national and institutional guidelines. Furthermore, the coordinating investigator will provide all authorized institutions of the participating countries with all essential documents required according to local law.

13.5. Patient information and informed consent form

Before signing the informed consent form the patient or the parents/ legal representatives must be informed about the disease, the treatment according to the clinical trial including estimated duration, randomization, possible effects of the treatment, the assessment required for the treatment and about alternative treatment options. The patients and/or their parents/legal representatives must have sufficient time to decide about trial participation and must have the opportunity to ask all questions they may have concerning the trial treatment before signing the consent form.
The signature of the legal representative is required for children and adolescents below legal age. Age-adapted informed assent forms for children and adolescents are provided and should be signed by underage patients. If an underage patient who is capable of forming an opinion and assessing the information refuses participation in the trial, this has to be considered by the investigator and, if appropriate, discussed with the principal investigator.
The informed consent form is documented on a standard form, written in non-technical language. A master version of each informed consent form is contained in Appendix 7. The consent forms will be translated and may be modified according to group or local requirements of each country. Modified versions must be submitted to the appropriate Ethics Committee for approval.

13.6. Withdrawal from the trial

The patient and/or their parents/legal representatives may withdraw from the clinical trial at any time by countermanding their informed consent without giving the reason for it. The patient and/or their parents/legal representatives are assured in writing on the informed consent form that withdrawal from the trial will not affect the medical treatment, but that medical treatment of the disease must be continued. Date of enrollment and date of and reason for (if provided) withdrawal are to be recorded in each case.
The patient and/or their parents/legal representatives must be informed that data stored up to this time will be used further if necessary to assess the effects of the treatment to be tested, to guarantee that the interests of the patients are not impaired, in accordance with regulatory requirements.

13.7. Patients Committee

This protocol will be reviewed by an independent patients committee, the UNAPECLE (Union Nationale des Associations de Parents d'Enfants atteints de Cancer ou de Leucémie - France) and the FCPRCC (Fédération des Comités de patients en recherché Clinique en cancérologie - France).

13.8. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be constituted in order to examine the risk / benefit ratio on validated data at regular intervals. The sponsor may decide to temporarily halt recruitment to the trial if the rate of severe toxicities significantly exceeds 15%.
It will meet at the end of each of the 2 study stages and at least x 1/year.

Pediatric Oncologist: Dr Myriam Ben-Arush De Haifa m_benarush@rambam.health.gov.il
Medical Oncologist: Dr Léo Mascarenhas; lmascarenhas@chla.usc.edu
Biostatistician: Sophie GOURGOU (Montpellier - France)

13.9. Blinded Central review

This part concerns primary objective.
To ensure an optimal radiological review, it is mandatory that each center regularly update database (e-CRF), indicating, for each patient treated:

- date and type of examination carried out with radiologist's conclusion,
- dates of cycles,
- when applicable, date and reason for treatment's discontinuation (progression, other treatment started ...)

A copy of all baseline radiologic examinations, and each subsequent tumor assessment (CT or MRI) must be sent regularly by research sites to Sponsor (in DICOM format, and identifiable with patient number) until tumor progression:

- through CR-Rom shipment to:

Alicia PROBST
DRCI Promotion - Centre Oscar Lambret
3 rue Frédéric Combemale – BP 307 – 59020 LILLE Cedex (France)

- or by using Sponsor's ETIAM address: promotionEC@relecture

The radiologic exams from the CDs will be uploaded onto a PACS system for image evaluation / interpretation and response assessment.
A radiology review committee comprising 3 radiologists will meet in order to assess the responses at the end of the first stage of Arms A and B and at the end of trial after the last patient has completed end of treatment imaging assessments:

- Dr Kieran Mc HUGH (UK)
- Dr Nathalie ROCOURT (FR)
- Dr Rick van RIJN (NL)
- Dr Giuseppina CALARESO (IT)

Data from review will be included in the trial-specific database.

13.10. Confidentiality

In accordance with the Public Health Code, the investigators and all individuals required to collaborate in the study shall be held to professional secrecy concerning, in particular, the nature of the products used, the study itself, the test patients and the results obtained. The investigator must ensure that his/her patients remain anonymous. The investigator shall keep a confidential patient identification list.

13.11. Declaration of the End of the Trial

The coordinating centre/coordinating investigator in each country, on behalf of the sponsor, is responsible for informing the ethics committees and competent authorities concerned of the regular or premature termination of the trial, according to national legal requirements.

13.12. Insurance

In general, if a subject is injured as a direct result of protocol defined treatment, reasonable and necessary medical treatment for the injury will be reimbursed by the insurance, if such expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. The authorized institutions of participating countries are responsible for providing insurance of indemnity in the respective country according to national law.
In the study patients are insured by BIOMEDIC-INSURE *(contract will be performed upon approval and before opening the study).* The insurance conditions are provided in the investigator site file.

13.13. Archiving

The archiving of all study relevant documents at the trial site, at the trial offices and the coordinating investigator's site will be handled according to the requirements of the ICH-GCP, the EU Commission Directive 2005/28/EC of 8th April 2005, national laws, and if possible, Ethical Considerations For Clinical Trials On Medicinal Products Conducted With The Paediatric Population, which recommends 40 years of archiving.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring

The authorized institutions are responsible for organizing adequate monitoring in the respective country. At least one initiation visit, one monitoring and one closing visit must be provided.

However, if frequent protocol violations, incomplete eCRFs, unanswered queries or other problems are encountered, focused monitoring visits may be performed.

On site monitoring visits include the checking of:

- Informed consent
- Inclusion and exclusion criteria
- Source data and CRFs , regarding the main efficacy and safety endpoints
- Abidance by ICH-GCP and national laws

Standard operating procedures for onsite monitoring are provided by the authorized institutions. A central review of the monitoring report will be provided by the sponsor. The authorized institutions are responsible for regular exchange of the monitoring reports.

14.2. Audits

The sponsor and his legal representatives reserve the right to audit selected trial sites in order to guarantee that the study is conducted in accordance with ICH-GCP. The auditor will be independent from the staff involved in the proceedings of this trial.

14.3. Inspections

According to the pertinent European legislation, inspections of trial sites may be performed by competent authorities during or after completion of the trial.

15. DATA OWNERSHIP AND PUBLICATION

At the end of the study, a report will be written by the sponsor, and then validated by the coordinating investigator (Dr. AS Defachelles) of trial VIT-0910. No publication or presentation of the results of this trial will be done without the permission of the sponsor.

All publications will make reference at a minimum to:

- Steering committee, the Coordinating Investigator of each country,
- All those having actively participated in the study. The order of co-authors will take into account the participation of the different trial investigators (number of eligible and evaluable patients).
- All those having contributed in a significant fashion to the progress of the study and publication process: the biostatistician, the manager of the Clinical Research Integrated Unit, and the sponsor.

In addition, any publication will include acknowledgements to:

- Senior trial coordinator
- Study Monitor,
- Pharmacist,
- Patients Committee,
- Nurse Research or Technicians Research in the trial sites,

The verification and agreement from the sponsor are required before any oral or poster communication.

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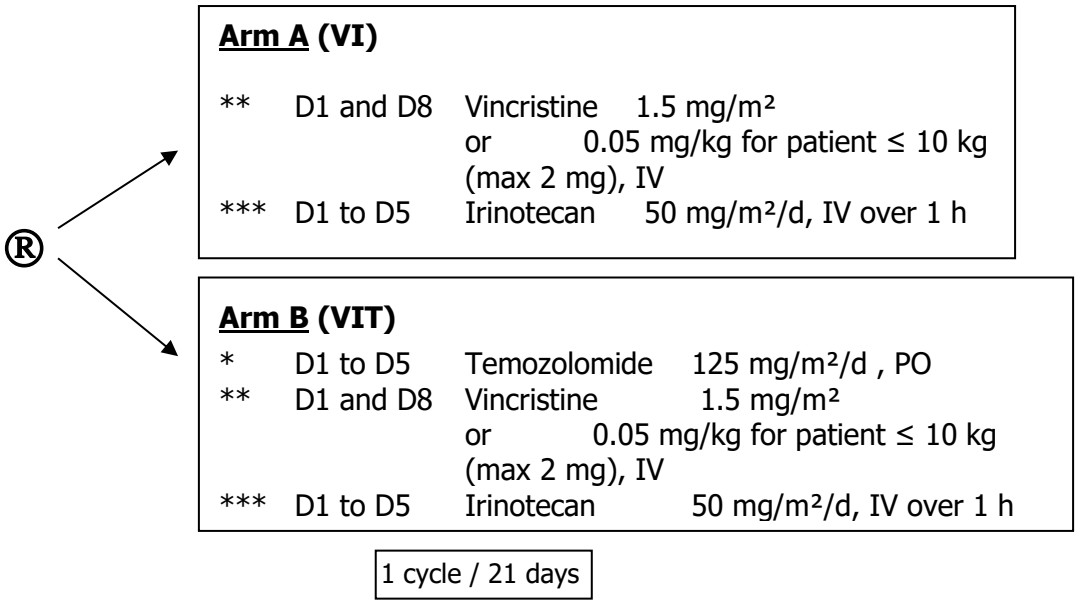
17. GLOSSARY AND ABBREVIATIONS

AE	Adverse Event
ARF	Additional Report Form
BSA	Body Surface Area
eCRF	Electronic Case Report Form
CR	Complete Response
CT	X-ray Computed Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSRCT	Desmoplasic Small Round Cell Tumor
DSUR	Development Safety Update Report
EFS	Event-free Survival
EIAC	Enzyme-Inducing Anticonvulsants
EpSSG	European Soft tissue Sarcoma Study Group
GCP	Good Clinical Practice
GSF-GETO	*Groupe Sarcome Français -Groupe d'Etudes des Tumeurs Osseuses*
G-CSF	Granulocyte colony stimulating factor
IDMC	Independent Data Monitoring Committee
ITCC	Innovative Therapies for Children with Cancer
MGMT	Methylguanine DNA methyltransferase
MMR	Mismatch Repair
MRI	Magnetic Resonance Imaging
MTIC	Metabolite monomethyl triazenoimidazole carboxamide
MTD	Maximum Tolerated Dose
OR	Objective Response
PET	Positron Emission Tomography
PNET	Primitive Neuroectodermal Tumor
PR	Partial Response
PS	Performance Status
RMS	Rhabdomyosarcoma
SAE	Serious Adverse Event
SCT	Stem Cell Transplantation
SD	Stable Disease
SFCE	*Société Française de Lutte contre les Cancers et Leucémies de l'Enfant et de l'Adolescent*
SIOP	*Société Internationale d'Oncologie Pédiatrique*
SNP	Single Nucleotide Polymorphism
STS	Soft Tissue Sarcoma
SUSAR	Serious Unexpected Suspected Adverse Reaction
TMZ	Temozolomide
ULN	Upper Limit of Normal
WHO	World Health Organization

18. APPENDIX

Appendix 1 – Scheme of the Study of treatment



Patients must have evidence of recovery from all prior cycle toxicity and the ANC must be > 1.0 x 10^9/L and platelets > 100 x 10^9/L before receiving additional therapy.
If initiation of the next treatment cycle is delayed by more than 2 weeks, the patients should be discontinued from the study.

Systematic treatment with oral cefixime 8 mg/kg once a day (max daily dose 400 mg) is recommended and will be started 2 days before chemotherapy until day 7 (see Appendix 11).
Repeated 3-weeks cycles until disease progression, unacceptable toxicity or the patient's desire to discontinue therapy

* The dose should be rounded off the nearest 5 mg. The dose will be escalated to 150 mg/m² at cycle 2 for patients who do not experience ≥ grade 3 toxicity (NCI-CTCAE v4.0). For patients who have difficulty to swallowing or young children, the daily dose of temozolomide capsules should be placed in 10-30 ml fruit juice or compote and administered after the capsules have been allowed to soften for 15-20 minutes. If the patient vomits within 20 minutes after TMZ, the dose will be re-administered.

** The dose will be 1.5 mg/m² or 0.05 mg/kg for patient ≤ 10 kg (max 2 mg), and will be administered by direct intravenous infusion on day 1 of each course, before irinotecan. Administration must comply with guidance on administration of vinca alkaloids as per NPSA/2008/RRR004.

*** The dose will be 50 mg/m² and will be administered by 60 min intravenous infusion one hour following the administration of temozolomide

Appendix 2 – Flowchart

	Inclusion **7 days < TTT**	**First 2 cycles** during weeks 1-6	**Subsequent cycles**	**End of study** (10)	**Follow-up** (11)
Information and consent form signed	X				
Diagnosis, medical/oncology history and demographics All clinical signs	X				
CLINICAL EXAM					
Full Physical examination, weight, height, body surface, performance status	X	X at day 1	X	X	X
Vital signs (body temperature, systolic and diastolic blood pressure sitting after 5 minutes rest, heart rate after 5 minutes rest, respiration rate)	X	X	X	X	
Concomitant treatment		X	X	X	
LABORATORY TESTS (1)					
Complete blood count	X	X (5,6)	X (5,6)	X	
ASAT, ALAT, total bilirubin, alkaline phosph, LDH, GGT	X	X (5)	X (8)	X	
Iono (Electrolytes), urea, creatinine, total protein, glucose, calcium, phosphate, albumin, chloride and bicarbonate	X	X (5)	X (8)	X	
Serum or urine pregnancy test, if applicable	X				
TUMOR ASSESSMENT (2)					
Computed Tomography (CT) scan or MRI of the primary site (3) Bone scan or FDG-PET Scan recommended BM aspirates, trephines biopsies recommended mandatory in case of bone marrow disease	X (4)	X (2,3,7)	X (2,3,9)	X (2,3)	X (2,3,12)
SAFETY ASSESSMENT					
Adverse events		X	X	X	X

(1) All blood sampling will be done after local application of topical anaesthetic cream, if applicable

(2) All imaging data should be stored in DICOM format for further review on CD-Rom

(3) Volume estimation should be attempted by providing the maximum sagittal, coronal and axial diameters. For MRI, intravenous gadolinium administration is mandatory for all MRI examinations (post-contrast T1-weighted sequences should ideally be performed with saturation). MRI is particularly recommended for

limb, head/neck, pelvis and paraspinal masses. MRI appears to be superior to CT scan in defining soft tissue extension. CT Scan could be performed for the assessment of thoracic or abdominal tumors.

(4) Within 14 days prior to the first study drug dose
(5) On days 1, 8 and 15
(6) If aplasia, blood counts should be performed as clinically indicated
(7) After cycle 2
(8) At day 1 if normal during cycles 1 and 2. If significantly abnormal during cycles 1 and 2, blood chemistry should be taken on days 1, 8 and 15 for all subsequent cycles after cycle 2
(9) After completion of every two cycles (must assess at 4-5 weeks after cycle 2 for responding or stable disease)
(10) 3 weeks after the last cycle of chemotherapy or at the end of study
(11) Every 3 months for at least 2 years and then every 6 months during the subsequent 3 years or until death or lost to follow-up until the date of the study cut-off
(12) Except previously documented progressive disease

Appendix 3 – Lansky scale

	Lansky scale	
Physical ability, work ability	Intense, without difficulty	**100%**
	Normal + moderate discomfort	**90%**
	Reduced	**80%**
Home activity	Normal, without assistance, but possible effort	**70%**
	Requires occasional help with personal needs	**60%**
	Minimal + occasional assistance	**50%**
Incapable of feeding self	Permanent assistance	**40%**
	Frequently bedridden	**30%**
	Bedridden	**20%**
	Moribund	**10%**

Appendix 4 – Karnofsky scale

Karnofsky Index	Description	ECOG Scale
Able to carry on normal activity; no special care is needed.		
100	Normal, no complaints, no evidence of disease.	0
90 80	Able to carry on normal activity, minor symptoms or signs of disease. Normal activity with effort, some signs or symptoms of disease.	1
Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.		
70	Cares for self, unable to carry on normal activity or to do work.	2
60 50	Requires occasional assistance from others, but able to care for most needs Requires considerable assistance from others and frequent medical care.	3
Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.		
40 30 20 10	Disabled, requires special care and assistance. Severely disabled, hospitalisation indicated, death not imminent. Very sick, hospitalisation necessary, active supportive treatment necessary. Moribund, fatal processes progressing rapidly.	4
0	Dead	5

Appendix 5 – Toxicity scale NCI-CTCAE Version 4.0

http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx

Appendix 7 – Parent and patient information and consent forms

These forms, in the language of each country, will be attached to the protocol

Appendix 8 – Formulae for calculation of creatinine clearance

Cockcroft and Gault formula

Men: $CrCl\ [ml/min] = \frac{(140-age) \times weight\ [kg] \times 1.23}{SeCr\ [\mu mol/l]}$

Women: $CrCl\ [ml/min] = \frac{(140-age) \times weight\ [kg] \times 1.04}{SeCr\ [\mu mol/l]}$

Schwartz formula

$CrCl\ [ml/min/1.73m^2] = \frac{F \times height\ [cm] \times 88.4}{SeCr\ [\mu mol/l]}$

Infants (< 1 year of age)	F = 0.45
Male, 1-16 years	F = 0.55
Female, 1-21 years	F = 0.55
Male, 16-21 years	F = 0.70

Wright formula

Jaffe Serum Creatinine without CK:

$GFR = \frac{(6580 - (38.8 \times age)) \times BSA \times (1 - (0.168 \times sex))}{SeCr\ [\mu mol/l]}$ sex: female = 1, male = 0

Enzymatic Serum Creatinine without CK:

$GFR = \frac{(6230 - (32.8 \times age)) \times BSA \times (1 - (0.23 \times sex))}{SeCr\ [\mu mol/l]}$ sex: female = 1, male = 0

Appendix 9 – Insurance

These forms, for each country, will be attached to the protocol

Appendix 10 – Helsinki declaration

This form will be attached to the protocol

Appendix 11 – Amendment for The Netherlands

This country-specific Amendment will be attached to the protocol

Appendix 12 – Direction for administering Temozolomide to patients who have difficulty swallowing capsules

This document will be attached to the protocol