CLINICAL TRIAL SUMMARY FOR LAYPERSONS

Identification of the clinical trial	
Title of the clinical trial	*Randomized Phase II Study comparing Vinblastine in combination with Nilotinib with Vinblastine alone in children, adolescents and young adults with low-grade glioma : an Innovative Therapies for Children with Cancer in Europe (ITCC) and SIOPE-Brain Tumor Group protocol - VINILO*
CSET number	*CSET 2012/1883*
EU CT number (CTIS)	*2012-003005-10*
Sponsor's name and adress	***Gustave Roussy*** *114 Rue Edouard Vaillant* *94805 Villejuif Cedex* *France*
Prinicpal Investigator's name	*Dr Jacques Grill* *Gustave Roussy*
General information about the clinical trial	
Main objectives of the trial	*Low-grade gliomas are the most common brain tumors in children.* *Standard treatment is surgery, but in a substantial number of cases, the tumor is inoperable and chemotherapy is proposed as first-line treatment.* *However, almost 50% of patients will recur within 5 years of first-line treatment.* *In these refractory or recurrent low-grade gliomas, a second-line chemotherapy-based treatment is recommended.* *Vinblastine is a validated and effective chemotherapy for low-grade gliomas, with almost 62% of patients still alive and progression-free 2 years after starting treatment.* *Vinblastine is also well tolerated.* *This trial was carried out to compare a new treatment strategy combining two drugs, Vinblastine and Nilotinib, with one of the strategies already validated which only includes Vinblastine.* *A first study has already assessed the toxicity of the combination of Nilotinib and Vinblastine in low-grade gliomas, and has established the most appropriate dose for each drug in the combination.* *The aim of this second study is to assess the efficacy of the combination, i.e. to determine whether the combination of Vinblastine and Nilotinib at the doses established in the first study is more or less effective than Vinblastine alone in low-grade gliomas in children, adolescents and young adults.*
Places and date of the trial	*The study was conducted at 37 centers in France, Spain, the United-Kingdom, Switzerland, Denmark and the Netherlands.* *Patients were included in the study between July 12, 2016 and April 25, 2019.*
Other information	*This is a **phase II** trial: it is carried out to determine the efficacy of a drug administered at a dose established in previous human toxicity studies.* *This is a **parallel group, two-arm** trial: patients could receive either the standard strategy (Vinblastine alone) or the experimental strategy (Vinblastine and Nilotinib).*

	*This is a **randomized** trial: study subjects were randomly assigned to one of the two treatment groups.* *This is an **open-label** study: participants and study team members were aware of the treatment being administered.* *No placebo was used.*

Participant population

Number of participants included in the trial

109 patients have been enrolled in the trial in 37 centers.:
- *France : 68*
- *EU,*
  United Kingdom 23
  Spain 8
  Netherlands 4
  Switzerland 3
  Denmark 3

Distribution by age group and sex

Variable		Total		Vinblastine alone		Vinblastine + Nilotinib	
		n	*%*	*n*	*%*	*n*	*%*
		109		53		56	
Age at study entry	< 3 years	24	22.0%	10	18.9%	14	25.0%
	3-6 years	31	28.4%	17	32.1%	14	25.0%
	7-9 years	24	22.0%	11	20.8%	13	23.2%
	> 10 year	30	27.5%	15	28.3%	15	26.8%
Gender	Male	47	43.1%	19	35.8%	28	50.0%
	Female	62	56.9%	34	64.2%	28	50.0%

Inclusion criteria

- Written informed consent signed by the patient or legal representative
- Age: 6 months to < 21 years of age at time of study entry.
- Diagnosis: one of the three conditions listed below:
• Refractory or recurrent low-grade glioma after at least one first-line therapy with pathological documentation in non NF1 patients.
• Refractory or recurrent low-grade glioma after at least one first-line therapy in NF1 patients, with or without pathological documentation.
• Low grade glioma at diagnosis in NF1 patients when the use of chemotherapy is considered for the treatment in case of threat to vision or unequivocal radiological tumor progression.
- Evaluable Disease on morphologic MRI
- Karnofsky performance status score ≥ 70% for patients > 12 years of age, or Lansky score ≥ 70% for patients ≤ 12 years of age, including patients with motor paresis due to disease.
- Life expectancy ≥ 3 months
- Administration of stable dose of steroids for at least one week.
- Adequate organ function (hematopoietic function, renal function, electrolytes levels,hepatic function, cardiac function, absence of peripheral neuropathy ≥ grade 2)
- Wash-out period of at least:
• 3 weeks in case of preliminary chemotherapy
• 6 weeks in case of nitrosourea-containing chemotherapy
• 2 weeks in the case of treatment with vincristine only
• 6 weeks in case of radiation therapy
- Possibility of receiving the therapeutic schedule as indicated in the protocol
- Patients with reproductive potential must use effective birth method control during their treatment and for up to 90 days after the last dose and have a negative pregnancy test ≤ 7 days before randomization.

Non-inclusion criteria

- Concomitant anti-tumor treatment
- Not recovered to < Grade 2 from the acute toxic effects of all prior chemotherapy, immunotherapy or radiotherapy
- Known intolerance or hypersensitivity to Vinblastine

	- Existence of another severe systemic disease *- Uncontrolled infections not responsive to antibiotics, antiviral medicines, or antifungal medicines* *- Any concurrent illness which in the opinion of the investigator may interfere with the treatment and evaluation of the patient* *- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of nilotinib* *- Simultaneous treatment with strong cytochromes P450 CYP3A4 inhibitors or with antiarrythmic drugs and other drugs known to prolong QT interval* *- Impaired cardiac function including any one of the following* *• Clinically significant resting brachycardia (< 50 beats per minute).* *• QTc > 450 msec on baseline ECG.* *• Other clinically significant uncontrolled heart disease (e.g. unstable angina)* *• History of or presence of clinically significant ventricular or atrial* *- Positive test for Hepatitis B virus surface antigen*
Drugs under study	
Description of the experimental treatments used	***Vinblastine** is an intravenous chemotherapy already marketed and validated for the treatment of many childhood and adult cancers. It acts directly on tumor cells, preventing them from multiplying, and also limits the growth of blood vessels that feed the tumor.* ***Nilotinib** is a tablet-form drug already marketed and validated for the treatment of chronic myeloid leukemia, a form of blood cancer, where it works by blocking a protein produced by leukemia cells called "Bcr-Abl", which enables them to multiply uncontrollably. This drug is also able to block the functioning of several other proteins, including "c-Kit" and "PDGF receptors". Blocking "PDGF receptors", which are located on low-grade glioma tumour cells and the vessel cells that feed them, could help to control the growth of low-grade gliomas. Blocking "c-Kit" disrupts the environment of low-grade glioma tumour cells, and could thus indirectly disrupt tumour cell function.* *In the standard treatment group, Vinblastine was administered intravenously every week.* *In the dual therapy group, Vinblastine was administered intravenously every week, and Nilotinib was administered orally twice daily, every day.* *In this trial, treatments were administered for a maximum of 1 year. Treatment was stopped earlier in the event of progression or unacceptable toxicity.*
Observed side effects	
Description of side effects and their frequency	*Only a few mild side effects were reported. Only three patients had to stop treatment for toxicity, two in the vinblastine+nilotinib arm and one in the vinblastine only arm. In the combined treatment, most frequent side effects were skin rash, flu-like symptoms, fatigue, liver enzyme increase, mild anemia and leucopenia and nausea and vomiting. In the vinblastine only the same side effects were reported except for liver enzyme increase and skin rash.*
Results	
Overall Clinical Trial Results	*After the inclusion of 109 patients (69 with optic pathway gliomas, 37 with neurofibromatosis type 1) in six countries, the inclusions were stopped before the planned term because the second interim analysis showed a significant difference in progression-free survival (PFS) between the two arms. With a median follow-up of 39 months (95%CI 35-42), the median PFS in the vinblastine arm 15 months (95%CI 11-not reached) while it was significantly lower in the vinblastine+nilotinib arm 8 months (95%CI 5-27). This difference was also observed in the subpopulation of NF1 patients treated mostly at diagnosis with a HR of 1.90 (95%CI 1.06-3.40). Overall survival was not affected by the treatment received.*

Comments on the results of the clinical trial	*The addition of nilotinib did not improve progression-free survival of patients with recurrent low-grade gliomas in case of decrease of the overall dose of vinblastine. This suggest a dose-effect of vinblastine in its efficacy against low-grade gliomas.*
Other information	
Indication of any planned follow-up clinical trials	NA
Additional Information	*European Union clinical trials registry : https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-003005-10* *United States clinical trials registry : https://clinicaltrials.gov/study/NCT01884922*